Evaluation of the efficacy, safety and tolerability of herbal medicine for management of the behavioural and psychological symptoms of dementia

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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For candidates submitting a thesis

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and, ethics procedures and guidelines have been followed.

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Table of Contents

Declaration II
Acknowledgements III
Table of Contents IV
List of Figures XIII
List of Tables XIV
List of Appendices XVII
Publications XX
Abbreviations used in the text XXI
Summary XXIV

1 CHAPTER ONE INTRODUCTION .......................................................................................................................................................................................... 1

1.1 Background ............................................................................................................................................................................................................................................. 1

1.1.1 The classification of the dementias ................................................................................................................................................................................. 1

1.1.2 Behavioural and Psychological Symptoms of Dementia (BPSD) ...................................................................................................................... 3

1.1.3 Aetiologies and Pathologies of dementia, NCDs and BPSD ................................................................................................................................. 4

1.1.4 Prevalence and Impact of dementia and BPSD ....................................................................................................................................................... 6

1.1.5 Diagnosis and assessment of dementia and NCDs, and BPSD ........................................................................................................................... 8

1.1.6 Diagnosis and assessment of BPSD ...................................................................................................................................................................... 11

1.1.7 Grouping of BPSD into subsyndromes ................................................................................................................................................................. 14

1.1.8 Agitation ......................................................................................................................................................................................................................... 15

1.2 Current therapies for dementia and NCDs .................................................................................................................................................................. 16

1.3 Current therapies for BPSD .................................................................................................................................................................................................. 17

1.3.1 Pharmacological interventions for BPSD ............................................................................................................................................................... 17

1.3.2 Specific pharmacological recommendations for other NCD types .................................................................................................................... 20

1.3.3 Other treatments for managing BPSD .............................................................................................................................................................. 20

1.3.4 Non-pharmacological interventions for managing BPSD ................................................................................................................................... 21

1.4 Need for new interventions .................................................................................................................................................................................................. 21

1.4.1 Emerging disease modifying therapies for NCDs .............................................................................................................................................. 21

1.4.2 Interventions for preventing or delaying the onset of dementia and NCDs ................................................................................................. 22
### Table of Contents

1.4.3 Nutrition, diet and lifestyle for prevention, risk reduction and/or management of NCDs 22

1.5 Rationale for this research and its significance ................................................................. 23

1.5.1 Combining multiple herbs into herbal formulae .......................................................... 24

1.6 Aims ................................................................................................................................. 25

1.7 Outline of the project ...................................................................................................... 26

1.8 Research questions ........................................................................................................ 30

2 CHAPTER TWO LITERATURE REVIEW OF HERBAL MEDICINE FOR DEMENTIA AND BPSD .......... 31

2.1 Introduction .................................................................................................................... 31

2.2 Use of single herbs and their standardised extracts for dementia, NCDs and BPSD .......... 31

2.2.2 Ginkgo biloba leaf ........................................................................................................ 31

2.2.3 Panax ginseng ............................................................................................................. 35

2.2.4 Melissa officinalis ........................................................................................................ 36

2.2.5 Angelica archangelica ................................................................................................. 36

2.2.6 Huperzine A ............................................................................................................... 36

2.2.7 Actions of HMs in the treatment of dementia and its associated symptoms ............... 37

2.3 Chinese medicine (CM), dementia, NCDs and BPSD .................................................... 39

2.3.1 Treatment of ‘mental’ disorders with herbs: .............................................................. 39

2.3.2 Contemporary practice of traditional Chinese herbal medicine ................................. 39

2.3.3 Syndrome differentiation and treatment of AD ......................................................... 41

2.3.4 Chinese medicine and BPSD .................................................................................... 42

2.4 Kampo ........................................................................................................................... 44

2.5 Considerations when prescribing HMs ......................................................................... 45

3 CHAPTER THREE METHODOLOGY FOR THE SYSTEMATIC REVIEW OF CLINICAL TRIALS AND THE ANALYSIS OF CLASSICAL CHINESE MEDICAL LITERATURE ......................................................... 46

3.1 Introduction .................................................................................................................... 46

3.2 SR of clinical trials of HMs for BPSD ........................................................................... 46

3.2.1 Search strategies and identification of studies ......................................................... 46
3.2.2 Criteria for considering studies for inclusion ................................................................. 48
3.2.3 Data extraction (selection and coding) ...................................................................... 49
3.2.4 Risk of bias (quality) assessment .............................................................................. 50
3.2.5 Data analyses and syntheses .................................................................................... 51
3.2.6 Qualitative synthesis ............................................................................................... 53
3.2.7 Methods for investigation of clinically meaningful change of total NPI scores ....... 53
3.3 Data mining and analyses of classical Chinese medical literature .............................. 53
3.3.1 Search strategies ..................................................................................................... 53
3.3.2 Identification of search terms related to the 12 NPI domains .................................. 54
3.3.3 Data extraction and management ......................................................................... 54
3.3.4 Data coding and scoring system ............................................................................... 54
3.3.5 Data analyses ........................................................................................................ 54

4 CHAPTER FOUR HERBAL MEDICINE FOR MANAGEMENT OF THE BEHAVIOURAL AND
PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS .... 56
4.1 Abstract .................................................................................................................... 56
4.2 Introduction .............................................................................................................. 56
4.3 Methods .................................................................................................................. 57
4.4 Results ................................................................................................................... 58
4.4.1 Risk of Bias .......................................................................................................... 65
4.4.2 Results of Meta-analysis ...................................................................................... 66
4.4.3 Numbers of Dropouts ......................................................................................... 87
4.4.4 Numbers and types of adverse events ................................................................. 89
4.5 Discussion .............................................................................................................. 94
4.5.1 How the HMs might work ................................................................................... 96
4.5.2 Limitations to this systematic review ................................................................. 97
4.6 Conclusions from this systematic review .............................................................. 98

5 CHAPTER FIVE ANALYSIS OF THE CLASSICAL CHINESE MEDICAL LITERATURE OF HERBS USED
FOR THE TREATMENT OF SYMPTOMS RELATED TO BPSD .................................................. 99
5.1 Introduction .......................................................................................................................... 99
5.2 Methods ................................................................................................................................ 99
5.3 Results of the analysis ........................................................................................................... 99
  5.3.1 Subgroup analysis – Numbers of citations according to each symptom of the Neuropsychiatric Inventory (NPI) ............................................................................................... 102
  5.3.2 Comparison of the ranked lists ................................................................................... 103
  5.3.3 Ranking of herbs for symptoms analogous to dementia with agitation/aggression .. 104
  5.3.4 Modified rank method ................................................................................................ 106
  5.3.5 Traditional use in China and scientific research on the top ranked herbs for dementia with agitation .............................................................................................................................. 108
5.4 Summary of the herbs for agitation/aggression in the classical literature ......................... 116
5.5 Discussion of the classical literature analysis ..................................................................... 116

6 CHAPTER SIX PUTATIVE MECHANISMS OF THE HERBAL MEDICINES CURRENTLY USED FOR MANAGEMENT OF BPSD ..................................................................................................................... 120
  6.1 Introduction ........................................................................................................................ 120
  6.2 Ginkgo biloba (leaf) ............................................................................................................. 120
    6.2.1 Overview of the experimental studies of G. biloba from the 1980s to 1990s............ 120
    6.2.2 Overview of Ginkgo reviews ....................................................................................... 121
    6.2.3 Overview of activities of G. biloba of relevance to BPSD ............................................ 126
    6.2.4 Effects of G. biloba on pathological models related to BPSD ..................................... 132
  6.3 Yokukansan mechanisms and activities in experimental studies ..................................... 139
    6.3.1 Uncaria rhyynchophylla .............................................................................................. 140
    6.3.2 Poria cocos (sclerotium) (fu ling) ................................................................................ 144
    6.3.3 Glycyrrhiza uralensis ................................................................................................. 145
    6.3.4 Atractylodes lancea (rhizome) ................................................................................... 148
    6.3.5 Angelica species including A. acutiloba, A. archangelica, A. sinensis ......................... 149
    6.3.6 Bupleurum species, including B. falcatum and B. chinense....................................... 154
    6.3.7 Cnidium officinale / Cnidium officinale Makino and Ligusticum chuanxiong [Syn. Ligusticum wallichii] ............................................................................................................................... 154
6.4 Discussion of the experimental literature ................................................................. 155
6.5 Conclusions from this review ................................................................................... 157

7 CHAPTER SEVEN VARIATION IN PLACEBO EFFECT SIZE IN CLINICAL TRIALS OF THE BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS... 158

7.1 Abstract ...................................................................................................................... 158
7.2 Introduction ............................................................................................................... 158

7.2.1 Behavioral and psychological symptoms of dementia (BPSD) ......................... 160
7.2.2 The Neuropsychiatric Inventory (NPI) ................................................................. 160

7.3 Methods ..................................................................................................................... 161

7.3.1 Inclusion criteria .................................................................................................. 161
7.3.2 Exclusion criteria ................................................................................................. 161
7.3.3 Risk of bias ........................................................................................................... 162
7.3.4 Statistical methods .............................................................................................. 162

7.4 Results: ...................................................................................................................... 162

7.4.1 Risk of Bias ........................................................................................................... 166
7.4.2 Results of meta-analysis ....................................................................................... 167
7.4.3 Subgroup meta-analysis: ...................................................................................... 172
7.4.4 Meta-regression analysis: ..................................................................................... 173
7.4.5 Comparison of baseline versus EoT within active treatment groups ................ 173
7.4.6 Comparison of active treatment groups versus placebo control groups at EoT ... 174
7.4.7 Baseline characteristics and dropouts analysis: .................................................. 176

7.5 Discussion of this study on placebo effect sizes in BPSD .......................................... 177

7.6 Summary of Chapter Seven ..................................................................................... 180

7.6.1 Implications of the variation in placebo effect sizes ........................................... 181
7.6.2 Limitations of this review .................................................................................... 181

7.7 Conclusions from this systematic review ................................................................. 181
CHAPTER EIGHT  A CLINICAL TRIAL PROTOCOL FOR A TESTING HERBAL MEDICINE
INTERVENTION FOR MANAGEMENT OF THE COGNITIVE, BEHAVIOURAL AND PSYCHOLOGICAL
SYMPTOMS OF DEMENTIA.......................................................................................................................... 183

8.1 Introduction ........................................................................................................................................... 183

8.1.1 Rationale for testing the combination of Yokukansan and EGb 761® for BPSD ................. 183

8.1.2 Safety assessment and monitoring of known and potential adverse effects associated
with the HMs................................................................................................................................................... 186

8.1.3 Known and potential adverse effects associated with EGb 761® and Yokukansan .... 186

8.1.4 Design of the proposed clinical trial ......................................................................................... 193

8.2 Objectives of this clinical trial ............................................................................................................. 194

8.3 Trial registration and compliance with relevant Codes ........................................................................ 194

8.4 Participants ........................................................................................................................................... 195

8.4.1 Minimising trial-related risks to participants................................................................................. 195

8.4.2 Determining mild to moderate severity of cognitive symptoms................................................... 196

8.4.3 Age of participants ......................................................................................................................... 196

8.4.4 BPSD symptoms .............................................................................................................................. 196

8.4.5 Inclusion criteria of the participant with BPSD ............................................................................ 196

8.4.6 Exclusion criteria of the participant with BPSD .......................................................................... 198

8.4.7 The caregiver as a secondary participant ..................................................................................... 199

8.4.8 Dropout and sample size calculation ............................................................................................... 200

8.5 Recruitment procedure ......................................................................................................................... 202

8.5.1 Setting and participant source ......................................................................................................... 202

8.5.2 Advertising ........................................................................................................................................ 202

8.5.3 Screening .......................................................................................................................................... 203

8.6 Informed consent ................................................................................................................................ 203

8.6.1 Compliance with Australian laws .................................................................................................. 204

8.6.2 Assessment of decision making capacity ...................................................................................... 204

8.6.3 Advanced consent option ................................................................................................................. 204
8.10 Data collection and analyses

8.10.1 Case report forms (CRFs)

8.10.2 Data safety monitoring board

8.10.3 Access to source data and documents

8.10.4 Data Quality Control and Quality Assurance

8.10.5 Data Handling and Record Keeping

8.10.6 Data analysis

8.10.7 Secondary and subgroup analysis

8.10.8 Data storage and security

8.10.9 Anticipated Outcomes of the study

8.11 Discussion of this clinical trial protocol

8.11.1 Strengths of this study

8.11.2 Limitations of this study

8.11.3 Transferability and generalisability of the study results

8.12 Implications and conclusions from this clinical trial protocol

9 CHAPTER NINE SUMMARY OF ALL EVIDENCE, GENERAL DISCUSSION AND FUTURE DIRECTIONS

9.1 Summary

9.2 Synthesis of findings

9.3 Research questions and main results

9.3.1 What is the current clinical trial evidence for the use of HMs for management of BPSD?

9.3.2 Which herbs and herbal formulae were used for memory impairment and symptoms consistent with BPSD in the classical Chinese medical literature?

9.3.3 What is the experimental evidence for mechanisms of action of HMs for management of BPSD?

9.3.4 Which herbs and combinations of herbs showed the greatest promise of efficacy, tolerability and safety for BPSD?
9.3.5 Which of these herbs show potential for use in clinical trials, and what is a suitable HM intervention for management of cognitive symptoms and BPSD? 236

9.3.6 How is this formula likely to work? 236

9.3.7 How could the effects of these herbs be measured? 237

9.3.8 What are the issues in clinical trial design of HMs for BPSD? 237

9.3.9 What is an appropriate and ethical design of a clinical trial of the HM to assess its effects on BPSD and cognitive symptoms? 237

9.4 Strengths and innovative aspects of the project 238

9.5 Limitations of the project 238

9.6 Implications for clinical practice 239

9.7 Future research directions 240

9.8 General conclusions in relation to the research questions 240

10 REFERENCES 242

11 APPENDICES 293
List of Figures

Figure 1.1: Old and new terminology regarding progression of age-related cognitive decline 2
Figure 1.2: BPSD in relation to severity of cognitive impairment 4
Figure 1.3: Prevalence of dementia with age 7
Figure 1.4: Flow diagram showing the thesis structure and sequence 29
Figure 4.1: Flow diagram of search and selection process of studies of herbal medicines for BPSD 59
Figure 4.2: Forest plot of total NPI scores at end of treatment for studies of herbal medicines for BPSD (MD; RE) 68
Figure 4.3: Forest plot of total NPI scores at end of treatment for studies of herbal medicines for BPSD (SMD; RE) 69
Figure 4.4: Forest plot of total NPI-Q scores 73
Figure 4.5: Forest plot of BEHAVE-AD scores 86
Figure 5.1: Overlap of the herb ingredients of Yokukansan, Gui pi tang and Tian wang bu xin dan 117
Figure 7.1: Flow diagram of search and selection process for randomised, placebo-controlled, oral interventions for management of BPSD 163
Figure 7.2: Total NPI effect sizes of placebo groups, in chronological order according to year of publication 167
Figure 7.3: Effect sizes within active treatment groups of all included studies, in chronological order according to year of publication 174
Figure 7.4: Results of meta-analysis at end of treatment for active treatment vs placebo for all included studies, in chronological order according to publication year 175
List of Tables

Table 4.1: Search terms used for PubMed for identifying clinical trials and reviews of herbal medicines for BPSD 57
Table 4.2: Characteristics of included studies of herbal medicine for BPSD 59
Table 4.3: Ingredients of the HM interventions used in the included studies 63
Table 4.4: Risk of bias assessments for included studies 66
Table 4.5: Meta-analysis results for Egb 761® studies at end of treatment and change within treatment groups 70
Table 4.6: Meta-analysis results for studies of extracts of Panax ginseng and Curcuma longa at end of treatment and change within treatment groups 71
Table 4.7: Details of NPI versions, NPI inclusion criteria and availability of NPI domain data in studies which reported NPI domain scores 73
Table 4.8: Meta-analysis results for Yokukansan and YKCH studies at end of treatment and change within treatment groups 74
Table 4.9: Results of meta-analysis of NPI domain scores 76
Table 4.10: Results of meta-analysis of NPI-Q domain scores 82
Table 4.11: Meta-analysis results for the other HM studies at end of treatment and change within treatment groups 83
Table 4.12: Numbers of dropouts from the included studies 87
Table 4.13: Numbers of reported adverse events from the included studies 89
Table 4.14: Details of the reported adverse events from the included studies testing Egb 761® 91
Table 4.15: Details of the adverse events reported in the studies testing Yokukansan or YKCH 91
Table 4.16: Details of the adverse events reported in the studies testing other HM interventions including P. ginseng and Curcuma longa 93
Table 5.1: Frequency of citations by search term variables for the total BPSD dataset 99
Table 5.2: Frequency of citation by dynasty 100
Table 5.3: Sources of the citations of herbs for symptoms analogous to dementia with BPSD 100
Table 5.4: Most common formulas cited in the total BPSD dataset 101
Table 5.5: Frequency ranking of all herbs according to total numbers of citations 102
Table 5.6: Total numbers of citations of all herbs for all 12 NPI symptom domains 103
Table 8.10: Checklist of assessments to be undertaken at each visit  218
Table 8.11: Limitations of previous AD intervention trials and strategies to overcome these  224
List of Appendices

Appendix Forest Plot 1: Effect sizes within treatment groups of all included studies, in chronological order by publication year

Appendix Forest Plot 2: Effect sizes within treatment groups of all included studies, in chronological order by publication year

Appendix Forest Plot 3: Results of meta-analysis at end of treatment (EoT) for active treatment vs placebo for all included studies, in chronological order by publication year

Appendix Forest Plot 4: Results of meta-analysis at end of treatment (EoT) for active treatment versus placebo for all included studies, in chronological order by publication year

Appendix Forest Plot 5: Results of risk ratio meta-analysis for numbers of dropouts at end of treatment (EoT) for active treatment versus placebo control for all included studies, in chronological order by publication year

Appendix Forest Plot 6: Results of meta-analysis for placebo groups at baseline vs End of treatment subgroup analysis: studies funded by manufacturer only

Appendix Table 1: Results of meta-analysis for single study of NPI-Q scores

Appendix Table 2: Results of meta-analysis of changes from baseline to end of treatment in total NPI scores in active treatment groups of studies testing oral interventions for management of BPSD

Appendix Table 3: Results of meta-analysis at end of treatment (EoT) in total NPI scores in active treatment groups versus placebo control groups of studies testing oral interventions for management of BPSD

Appendix Table 4: Combined n participants, mean, and SD baseline NPI scores from multiple groups for all 25 included studies, in groups according to year of publication

Appendix Table 5: Combined n participants, mean, and SD baseline NPI scores from multiple placebo groups, Group 1 studies

Appendix Table 6: Combined n participants, mean, and SD baseline NPI scores from multiple placebo groups for included Group 2 studies

Appendix Table 7: Combined n participants, mean, and SD baseline ages of participants from multiple placebo groups for all 25 included studies, published from 2000 – 2015

Appendix Table 8: Combined n participants, mean, and SD baseline ages of participants from multiple placebo groups for included Group 1 studies

Appendix Table 9: Combined n participants, mean, and SD baseline ages of participants from multiple placebo groups for included Group 2 studies

Appendix Table 10: Numbers and proportions of dropouts in placebo groups of studies testing oral interventions for management of BPSD
Appendix Table 11: Methods of treatment of missing data; and reporting of NPI scores for the included studies

Appendix Table 12: Summary of results for changes in placebo and active groups (baseline versus end of treatment)

Appendix Meta-regression 1: WMD within placebo groups by year of publication; all 25 studies

Appendix Meta-regression 2: WMD within placebo groups by year of publication; Group 1 studies

Appendix Meta-regression 3: WMD within placebo groups by year of publication; Group 2 studies

Appendix Meta-regression 4: WMD within placebo groups by year of publication; 20 to 26 weeks duration studies

Appendix Meta-regression 5: WMD within placebo groups by year of publication; 20 to 26 weeks duration studies; Group 1

Appendix, Meta-regression 6: WMD within placebo groups by year of publication; 20 to 26 weeks duration studies; Group 2 (published 2009-2015).

Appendix, Meta-regression 7: WMD within placebo groups by treatment duration (weeks); all 25 studies.

Appendix, Meta-regression 8: WMD within placebo groups by treatment duration (weeks); Group 1 studies

Appendix Meta-regression 9: WMD within placebo groups by treatment duration (weeks); Group 2 studies

Appendix, Meta-regression 10: WMD within placebo groups by total sample size at baseline in both Treatment and Control groups; all 25 studies

Appendix Meta-regression 11: WMD within placebo groups by mean total baseline NPI score; all 25 studies

Appendix, Meta-regression 12: WMD within placebo groups by mean total baseline NPI score; Group 1 studies

Appendix, Meta-regression 13: WMD within placebo groups by mean total baseline NPI score; Group 2 studies

Appendix, Meta-regression 14: WMD within active treatment groups by year of publication; all 25 studies

Appendix, Meta-regression 15: WMD within active treatment groups by year of publication; 20 to 26 weeks duration studies; of all 25 studies

Appendix, Meta-regression 16: WMD within active treatment groups by treatment duration (weeks); all 25 studies
Appendix, Meta-regression 17: WMD within active treatment groups by total sample size at baseline in both treatment and control groups; all 25 studies.

Appendix, Meta-regression 18: WMD for TvsC at end of treatment by year of publication; all 25 studies

Appendix, Meta-regression 19: WMD for TvsC at end of treatment by year of publication; Group 1 studies

Appendix, Meta-regression 20: WMD for TvsC at end of treatment by year of publication; Group 2 studies

Appendix, Meta-regression 21: WMD for TvsC at end of treatment by year of publication; 20 to 26 weeks duration studies (published 2000-2015)
Publications

Thesis related:


Additional papers:


Abbreviations used in the text:

AChEI: Acetylcholinesterase inhibitor
AD: Alzheimer’s disease
ADAS: Alzheimer’s disease Assessment Scale
ADAS-cog: Alzheimer’s Disease Assessment Scale-cognitive section
ADAS-noncog: ADAS-noncognitive section
ADL: Activities of Daily Living
AE: Adverse event
APOE: Apolipoprotein E
APP: Amyloid precursor protein
B: baseline
BBB: Blood-brain-barrier
BEHAVE-AD: Behavioral Pathology in Alzheimer’s disease Rating Scale
BPSD: behavioural and psychological symptoms of dementia
BSHTF: Bu shen hua tan fang
BSHTT: Bu shen hua tan tang
BSTLT: Bu shen tong luo tang
bvFTD: behavioural variant fronto-temporal dementia
C: Control group
CDR: Clinical Dementia Rating scale
CERAD-BRSD: Consortium to Establish a Registry for Alzheimer’s Disease-Behavior Rating Scale for Dementia
CI: Confidence interval
CM: Chinese Medicine
CMAI: Cohen-Mansfield Agitation Inventory
CNS: Central nervous system
CSF: Cerebro-spinal fluid
CT: Computed Tomography
DEMQOL: Dementia quality of life
DSM: Diagnostic and Statistical Manual of Mental Disorders
EGb 761®: Extract of Ginkgo biloba leaf 761
EPS: Extra pyramidal symptoms
EoT: End of treatment
FDA: Food and Drug Administration
FTD: Fronto-temporal dementia
FZS: Fu zhi san
HM: Herbal medicine
GDS: Geriatric Depression Scale
GERRI: Geriatric Evaluation by Relative’s Rating Instrument
I²: Index of heterogeneity
IADL: Instrumental activities of daily living
ICD: International Statistical Classification of Diseases and Related Health Problems
IL: Interleukin
LBD: Lewy body dementia/ Lewy body disease
MADRS: Montgomery Asberg Depression Rating Scale
MAO: Monoamine oxidase
MCI: Mild Cognitive Impairment
MD: Mean difference
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
MRI: Magnetic Resonance Imaging
NCD: Neurocognitive disorder
NICE: National Institute of Health and Care Excellence
NLKL: Nao ling ke li
NMDA: N-methyl-D-aspartate
NPI: Neuropsychiatric Inventory
NPI-NH: NPI nursing home version
NPI-Q: NPI Questionnaire version
NSAIDs: Non-steroidal anti-inflammatory drugs
NYT: Ninjin’yoeito (Chinese: Ren shen yang rong tang)
PAF: Platelet activating factor
PANSS: Positive and Negative Syndrome Scale
PD: Parkinson’s disease
PDD: Parkinson’s disease dementia
PICOS: Participant, intervention, comparator/control, outcome, study design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUFA: Polyunsaturated fatty acid
RCT: Randomised controlled trial
RE: Random effects
RoB: Risk of bias
ROS: Reactive oxygen species
SAE: Severe adverse event
SD: Standard deviation
SKT: Syndrom-Kurz Test / Short Cognitive Performance Test
SMD: Standardised mean difference
SOD: Superoxide dismutase
SR: Systematic review
SSRI: Selective serotonin reuptake inhibitor
SZL: Shen zhi ling
T: Treatment group
Tg: Transgenic
TQHXT: Tong qiao huo xue tang
TTL: Terpene trilactone
TXLJN: Tong xin luo jiao nan
VaD: Vascular dementia
YKCH: Yokukansan-ka-chimpi-hange (Chinese: Yi gan san jia chen pi ban xia)
YKS: Yokukansan (Chinese: Yi gan san)
YSHZ: Yi shen hua zhuo
ZBDHT: Zhi bai di huang tang
ZBI: Zarit caregiver burden inventory
ZHYD: Zhong Hua Yi Dian
ZYFJDCD: Zhong Yi Fang Ji Da Ci Dian

Chinese herb names are written in pinyin in lower case, italised. Chinese herbal formula names are in pinyin, lower case, italicised with the first letter of the name in upper case. Chinese classical book names are in pinyin, lower case, italicized, with the first letter of each word in upper case.
Summary

Dementia involves a gradual loss of memory and cognitive skills. Over 50% of people with dementia also suffer from the behavioural and psychological symptoms of dementia (BPSD). BPSD refer to disturbed perception, thought content and mood associated with dementia, and include psychosis, agitation, aggression, irritability, depression, anxiety and abnormal motor activity. BPSD can have a negative impact on the progression of Alzheimer’s disease and related disorders and are associated with a greater level of caregiver distress.

Currently recommended pharmacological treatments for dementia, including acetylcholinesterase inhibitors and memantine, focus on relieving cognitive symptoms, while BPSD are managed according to the presenting symptoms. Guidelines recommend non-pharmacological approaches for BPSD but selective serotonin reuptake inhibitors, analgesics and second generation antipsychotics may be used when other approaches fail. Pharmacological treatments for BPSD have limited benefit and safe prescribing is difficult as some may produce severe adverse effects and may worsen cognitive symptoms. Consequently, there is a pressing need for new approaches to BPSD management.

Multiple clinical studies have reported that herbal medicines (HMs), such as Ginkgo biloba leaf extract, can alleviate BPSD as well as improve cognition in dementia. The present project aimed to determine the current state of evidence for HMs and propose future directions for the development of plant-based therapeutics for managing BPSD.

Both historical use and contemporary clinical trials provide evidence for the use of herbs for management of memory impairment, cognitive symptoms of dementia and BPSD. Based on these findings, there is potential for identifying effective herbal interventions that could be fast-tracked into clinical use for this unmet need. Identification of useful compounds and their possible mechanisms of action may contribute to development of new therapeutic approaches and/or drug discovery. Notably, the acetylcholinesterase inhibitors galantamine and rivastigmine were discovered from plant-derived compounds.

The objectives of this project were to assess the current state of evidence and its limitations regarding the efficacy, safety and tolerability of HMs for BPSD by systematically reviewing and analysing the results of clinical trials and the classical Chinese medicine literature on BPSD; identify any HMs that show potential benefit for BPSD; based on the best available evidence, select a herbal intervention suitable for further clinical investigation; and design a rigorous randomised controlled trial (RCT) to test the intervention that addresses the limitations of previous clinical studies.
The comprehensive systematic review and meta-analysis included 31 controlled clinical trials testing 19 different HMs. Meta-analysis of well-designed, placebo-controlled studies indicated that the *G. biloba* leaf extract EGb 761® was safe and well-tolerated. Significant and clinically meaningful improvements in BPSD and cognition were detected at 24 weeks. However, independently funded studies of *G. biloba* leaf extract are needed to confirm these findings. Meta-analysis of randomised, comparative effectiveness studies of the Japanese multi-herb formula *Yokukansan* (Chinese: *Yi gan san*) showed no significant differences on BPSD outcomes when compared to standard pharmacotherapies used in Japan for BPSD management and superiority to no treatment. However, the only placebo-controlled study of *Yokukansan* for BPSD did not find any difference in BPSD outcomes at the end of four weeks treatment. Important limitations were identified in this trial which could have resulted in a false negative. These included its short duration, relatively small sample size, large improvement in the placebo group, and the use of a simplified outcome measure which could be less likely to detect changes in symptoms. Overall, the clinical evidence for *Yokukansan* suggested improvements in BPSD, notably in the clinically important symptoms of irritability/lability and agitation/aggression. An issue identified with *Yokukansan* was the increased risk of liquorice-induced hypokalaemia, which requires monitoring. Lack of replication and methodological issues in the studies testing other HMs precluded any conclusions for these other interventions.

The classical Chinese medical literature was evaluated using the *Zhong Hua Yi Dian* database, using similar methods to a previous study which evaluated the herbs used for treatment of the cognitive symptoms of dementia. No specific term in the literature corresponded with BPSD, although terms for specific symptoms such as anxiety, depression and agitation were frequently mentioned in conjunction with terms for memory impairment. Some of the HMs described in the classical Chinese medical literature for treatment of memory impairments with mood and behavioural symptoms had also been tested in the clinical trial literature, including *Glycyrrhiza uralensis*, *Porzia cocos* and *Angelica* species, which are ingredients of *Yokukansan*, but the most frequently cited herbs in the classical literature were generally not the same as the frequently tested HMs in clinical trials.

The *in vitro* and *in vivo* literature showed evidence of relevance to treatment of BPSD for *G. biloba*, *Yokukansan* and their constituent compounds. For both these HMs, animal studies have reported anti-aggression-like, antidepressant-like, anxiolytic-like effects as well as benefits on abnormal motor activities and reduction in cognitive impairments and mental stress. Important activities of *G. biloba* leaf and *Yokukansan* of relevance to BPSD include modulation of neurotransmission, neuroendocrine regulation and antioxidant effects.
The issue of wide variation in placebo effect sizes in BPSD studies was explored through meta-analysis of placebo data. Results showed that placebo effect sizes for BPSD have increased over time. Proposed new studies may therefore require larger sample sizes in order to be adequately powered.

Based on the available evidence, it appears that EGB 761® provides small improvements in cognitive symptoms and reduces BPSD while Yokukansan can improve BPSD but not cognition, although it does not appear to have any negative effect on cognition. Both HMs are available commercially, are well characterised and are in widespread use but their combination has not been tested in a clinical trial. Notably, most studies of EGB 761® were conducted in Europe or Russia while Yokukansan was tested in Japan. Therefore, it was proposed that the combination of EGB 761® and Yokukansan at conservative dosages should be tested through an adequately powered, randomised, placebo-controlled clinical trial.

A clinical trial protocol was designed which utilised validated diagnostic criteria and assessments relevant to an older population with BPSD, including assessments of caregiver distress associated with BPSD. Issues relating to informed consent from participants and their caregivers were addressed. Safety was an important consideration and was addressed through inclusion and exclusion criteria, careful monitoring of adverse events and strategies to reduce the risk of liquorice-induced hypokalaemia.

The results of the RCT would provide useful data on the safety, tolerability and efficacy of this combined intervention in an Australian population with BPSD. The results would assist with clinical decision-making in the management of BPSD.
1 CHAPTER ONE INTRODUCTION

1.1 Background

1.1.1 The classification of the dementias

Dementia was described in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) as a range of symptoms involving memory impairment and at least one of four other cognitive deficits: aphasia (impairment of language skills), apraxia (impaired ability to execute learned purposeful movements including speech), agnosia (impaired ability to recognise familiar people, items, smells) and disturbance in executive functioning (management of cognitive processes including problem solving and reasoning). These symptoms could be due to the direct effects of a medical condition, the persisting effects of a substance, or multiple aetiologies (American Psychiatric Association, 2000).

The *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition (DSM-5) (American Psychiatric Association, 2013) has subsumed the terms ‘Dementia’, ‘Delirium’, ‘Amnestic’, and ‘Other Cognitive Disorders’ into ‘Neurocognitive Disorders’ (NCDs) in order to allow for more specific diagnoses of these conditions due to recent advances in brain imaging, neuroscience and neuropsychology (American Psychiatric Association, 2013). NCDs are defined as disorders whose core features are cognitive and not present since early life, therefore NCDs result in ‘a decline from a previously attained level of functioning’ (American Psychiatric Association, 2013).

Mild Cognitive Impairment (MCI) has been used to describe a heterogeneous disorder which originally referred to a transitional stage between normal ageing and dementia. The presence of MCI was associated with an increased risk of dementia (Petersen 1999). However, not all cases of MCI transition to dementia (Visser et al., 2006; Mitchell & Shiri-Feshki 2009). MCI was not included in the DSM-IV-TR. The DSM-5 uses the terms ‘Major’ and ‘Mild’ NCDs, allowing for broader diagnoses of NCDs along a spectrum of cognitive and functional decline. In general, Major NCD corresponds to the same level of severity as dementia whereas Mild NCD corresponds to the level of severity as MCI.
The DSM-5 types of NCDs are: NCD due to Alzheimer’s disease (AD); vascular NCD; NCD with Lewy bodies; NCD due to Parkinson’s disease; frontotemporal NCD; NCD due to traumatic brain injury; NCD due to HIV infection; substance/medication-induced NCD; NCD due to Huntington’s disease; NCD due to prion disease; NCD due to another medical condition; NCD due to multiple aetiologies; and unspecified NCD (American Psychiatric Association, 2013).

The DSM-IV-TR had also listed the different dementia types according to their presumed aetiologies, including Dementia of the Alzheimer’s Type, Vascular Dementia, Dementia due to Other Medical Conditions including Human immunodeficiency virus (HIV), head trauma, Parkinson’s disease and Huntington’s disease, followed by Substance-Induced Persisting Dementia, Dementia due to Multiple Aetiologies, and Dementia Not Otherwise Specified (American Psychiatric Association, 2000).

This project focussed on the symptoms which can be present in the chronic, degenerative NCDs that generally occur in older people. The most common of these is believed to be NCD due to Alzheimer’s disease (AD). Vascular NCD, NCD with Lewy bodies, NCD due to Parkinson’s disease (PD) and frontotemporal NCD are also considered common age-related NCDs, although frontotemporal NCD can occur more commonly in younger people. Delirium, which the DSM-IV-TR defined as ‘a disturbance of consciousness and a change in cognition that develop over a short period of time’ (American Psychiatric Association, 2000) and ‘amnestic disorder’, which was defined as ‘memory impairment in the absence of other significant accompanying cognitive impairments’ (American Psychiatric Association, 2000) were not within the scope of this project. Both terms ‘dementia’ and ‘NCD’ are used throughout this thesis, as well as ‘MCI’, depending on which term best applied in the given context.
1.1.2 Behavioural and Psychological Symptoms of Dementia (BPSD)

Behavioural and Psychological Symptoms of Dementia (BPSD) refer to a range of additional symptoms that may occur in people with dementia, as defined by the International Psychogeriatric Association Consensus Group in 1996 (Finkel et al., 1996). BPSD include agitation, aberrant motor behaviour (excessive motor activity such as fidgeting and pacing), anxiety, elation, irritability, depression, apathy, disinhibition, delusions, hallucinations and changes in sleep or appetite (Cerejeira et al., 2012). The term ‘neuropsychiatric symptoms’ is more commonly used in the United States and can refer to the same symptoms (Cerejeira et al., 2012), although this term is not specific to dementia. Frisoni et al. (1999) found that 50% of people with BPSD have at least four of the above symptoms simultaneously.

The behavioural symptoms can also involve wandering, catastrophic reactions (severe overreactions to non-threatening situations), intrusiveness, negativism (refusal to do what is expected or tendency to do the opposite), sexual disinhibition, hoarding, screaming, cursing and shadowing (closely following the caregiver), while the psychological symptoms can involve psychosis and other mood changes (Purandare et al., 2000).

BPSD have not been included in the DSM-5 or The Merck Manual of Diagnosis and Therapy, 19th Edition (Porter, 2011) as defining criteria of dementia or NCDs. The defining criteria for dementia are its cognitive features, although BPSD frequently occur (Finkel et al., 1996) and are believed to be an integral part of these disorders (Purandare et al., 2000). The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) includes ‘Unspecified dementia with behavioural disturbance’, which includes aggressive, combative and violent behaviours consistent with BPSD (World Health Organization, 2018).

Reisberg et al. (1982) reported that mood changes are less constant features of AD than the cognitive and daily functioning changes. Cohen-Mansfield (1999) also stated that BPSD do not necessarily progress uniformly from person to person. However, severity of BPSD and cognitive decline are weakly correlated (McKeith & Cummings, 2005). Lovheim et al. (2008) found that the relationships were non-linear, with higher prevalence in the middle stages of dementia, except for apathy/passiveness, which increased almost linearly with severity of cognitive decline. The other BPSD declined in severe cognitive impairment and were most prevalent at the middle stages of cognitive impairment (Lovheim et al., 2008).
1.1.3 Aetiologies and Pathologies of dementia, NCDs and BPSD

The aetiologies of dementias and NCDs are complex and multifactorial. Multiple dementia types often coexist. Cognitive disorders are characterised by disrupted interactions of a variety of neurotransmitters and receptors (Levin, 2006). Atrophy in the cortex and hippocampus is considered the best determinant of age-related cognitive decline (Fotuhi et al., 2009). This can result from a combination of pathologies including AD, vascular lesions, Lewy bodies and inflammation (Fotuhi et al., 2009). Current research indicates that emotion and cognition are integrated in the brain (Pessoa, 2015), and that although ‘emotion’ and ‘cognition’ may be used as labels of certain behaviours, they ‘will not map cleanly into compartmentalised pieces of the brain’ (Pessoa, 2015). BPSD are likely to result from a combination of biological, psychological and social factors (Cerejeira et al., 2012) but the pathological changes to the brain due to the NCD are the primary causes of the clinical manifestations of BPSD (Cerejeira et al., 2012).

AD involves progressive memory loss plus cognitive and personality changes (Parker, 2014). According to the amyloid cascade hypothesis, deposition of beta-amyloid plaques is postulated to be an initial event in the multifactorial pathogenesis (Parker, 2014). Hyperphosphorylation of the tau protein, which causes its misfolding and aggregation, may also be involved (Tenreiro et al., 2014). However, the pathological changes can occur in asymptomatic people (Hachinski, 2014).
Ischemic, hypoperfusive or haemorrhagic brain lesions can cause vascular NCD (Liu, 2008). The risk of NCD/dementia is approximately doubled if there is vascular pathology (Hachinski, 2014). The diagnoses of ‘pure’ vascular dementia (VaD) (or vascular NCD) or ‘pure’ NCD due to AD have been debated (Fotuhi et al., 2009) mainly due to findings that mixed dementia pathologies are common. Certain combinations such as AD plus infarcts are more closely associated with dementia than individual lesions (Fotuhi et al., 2009). Strokes can amplify the effects of and precipitate AD (Hachinski, 2014). Lopez et al. (2014) found that beta-amyloid deposition, hippocampal atrophy and white matter lesions were highly prevalent in cognitively normal older people and those with MCI. A combination of at least two of these features was a strong predictor of dementia (Lopez et al., 2014). Hypertension and inflammation, and interactions of the two, are increasingly being recognised for their roles in the pathogenesis and progression of AD (Nelson et al., 2014).

Lewy bodies are abnormal masses primarily composed of the protein alpha-synuclein. Lewy body dementia (LBD) can refer to NCD due to PD or NCD with Lewy bodies. Both have the same pathology and progression. A diagnosis of PD is made if motor symptoms are the primary feature. If motor and cognitive symptoms appear together, or cognitive symptoms appear first, the diagnosis will be LBD or NCD with Lewy bodies. A combination of AD and vascular pathologies, along with the presence of Lewy bodies and inflammation, appear more likely to result in age-related cognitive decline (Fotuhi et al., 2009). The aggregation and disposition of misfolded proteins are believed to be a common pathogenesis mechanism for AD, PD, LBD, stroke and depression (Bai et al., 2014).

Frontotemporal NCD involves progressive atrophy of the frontal and/or temporal lobes. It is a common early-onset NCD (Clark et al., 2015). Frontotemporal NCD is clinically and pathologically heterogeneous (Banks & Weintraub, 2008). Symptoms may depend on the locations of neurodegeneration. Neuropathological findings vary and various tauopathies or proteinopathy are detected (D’Alton & Lewis, 2014), including Pick’s disease tauopathy (Josephs et al., 2009).

1.1.3.1 Prominent BPSD according to NCD type and subtype

BPSD are largely related to specific anatomical and pathological changes in the brain that occur with the different NCD types and subtypes (McKeith & Cummings, 2005). Prominent behavioural and psychological symptoms of AD are apathy, agitation, depression, anxiety, delusions and irritability, with hallucinations and euphoria being less prominent (McKeith & Cummings, 2005). Purandare et al. (2000) reported that previous studies had not found any significant associations between Apolipoprotein E (APOE) dementia subjects and BPSD. A review of 25 studies concluded that the association of APOE genotypes with BPSD in AD was unclear (Panza et al., 2012). However, Christie et al. (2012) reported that hallucinations were significantly more likely to occur in participants with
probable AD with no APOE4 alleles compared to those with two E4 alleles. No associations were detected between presence of delusions, aberrant motor behaviour or agitation and the number of APOE4 alleles. These findings support the hypothesis that specific BPSD may be associated with the APOE allele (Christie et al., 2012).

Behavioural and personality changes are a key symptom of behavioural variant FTD (bvFTD). In particular, behavioural changes which may be mistaken as depression, plus disinhibition, are commonly observed (Alzheimer’s Association, n.d.). Apathy, elation, repetitive behaviours and eating disturbances are also prominent (McKeith & Cummings, 2005). Banks et al. (2008) found an increasing overlap of behavioural symptoms in different subtypes of FTD with longer duration of disease. Leger and Banks (2014) found that of 149 patients clinically diagnosed with bvFTD, 20.5% had primarily AD pathology. Hallucinations, delusions or agitation were more common in the participants with AD pathology, while anxiety, elation, apathy, disinhibition, motor changes and night-time behavioural disturbances were more common in those with clinically diagnosed bvFTD (Leger & Banks, 2014). In addition, participants were further divided into those with tauopathies and those with no tauopathies detected. Participants with FTD pathology and tau negative pathology were more likely to exhibit delusions, depression and appetite and eating changes (Leger & Banks, 2014).

1.1.3.2 Other possible causes of BPSD
Clinical manifestation of BPSD may be associated with other factors in addition to NCD types and subtypes. For example, physical aggression is more common in men with severe dementia, and passive aggressive behaviours are reported to be more common in women with mild to moderate dementia (Purandare et al., 2000). Environmental factors including living conditions may play a substantial role in the manifestation of BPSD. Kasai et al. (2014) found nursing home residents in Japan had fewer symptoms of dementia than community residents, according to assessments of aggressiveness, affective disturbances, and anxieties and phobias. Kolanowski et al. (2017) reported that each BPSD symptom had its own set of determinants, and that these determinants commonly overlapped across several symptoms. The main determinants identified were neurodegeneration, type of dementia, severity of cognitive impairments and declining functional abilities, and to a lesser extent caregiver distress and communication difficulties (Kolanowski et al., 2017).

1.1.4 Prevalence and Impact of dementia and BPSD
Dementia is estimated to affect 35 million people worldwide (Prince, 2013). The prevalence and incidence of dementia and lifetime risk of age-related NCDs is expected to increase globally, including in developing countries, due to a projected rise in the aged population (Ferri et al., 2005;
Prince et al., 2008; Kalaria et al., 2008). A Delphi consensus study in 2005 estimated that 24.3 million people had dementia worldwide and predicted the number of people with dementia would double every 20 years to 42.3 million by 2020 and to 81.1 million by 2040 (Ferri et al., 2005). In Australia in 2011, almost one in ten Australians aged 65 and over had dementia, and three in ten Australians aged 85 and over had dementia (Alzheimer’s Australia, 2016). In China, the estimated number of people with dementia in 1990 was 3.68 million (CI 2.22-5.14) and 9.19 million (CI 5.92-12.48) in 2010 (Chan et al., 2013). A systematic review (SR) suggested that the prevalence of dementia in Japan has increased, possibly due to an ageing population. This study indicated prevalence rates for all types of dementia in Japan ranged from 2.9% to 12.5% (Okamura et al., 2013).

More than 50% of people with dementia experience BPSD (Hersch & Falzgraf, 2007) and it has been estimated that up to 90% of people with dementia will experience BPSD (Cerejeira et al., 2012). BPSD are estimated to affect 35-85% of people in early stages of cognitive impairment (Monastero et al., 2009; Cerejeira et al., 2012), while about two thirds of people in moderate to severe stages of AD are reported to demonstrate BPSD (Lawlor, 2002). A SR which included studies from any country reported that 58% of residents in aged care facilities had dementia and, of those, 78% had BPSD (Seitz et al., 2010).

BPSD can have a profound impact on people with NCDs and their communities. Beeri et al. (2002) found that BPSD accounted for 30% of care costs of community dwelling people with dementia. BPSD may be associated with faster disease progression (Rabins et al., 2013) as well as having negative impacts on the health, quality of life, and ability to earn an income for caregivers (Kales et al., 2014). BPSD are recognised as a main determinant of caregiver burden (Rosdinom et al., 2013) and can cause distress to people with NCDs, leading to higher institutionalisation numbers (Cerejeira et al., 2012).
1.1.5 Diagnosis and assessment of dementia and NCDs, and BPSD

Dementia and NCDs are primarily diagnosed and assessed through clinical evaluation. This generally involves interviews with the patient and a reliable family member or caregiver, often including cognitive assessment questionnaires and assessments of ability to undertake daily activities. Many authors have agreed that assessments should be comprehensive and evaluate changes in function and behaviour in addition to cognition. Of the numerous cognitive assessment measures available, the Mini-Mental State Examination (MMSE); the Alzheimer’s Disease Assessment Scale – cognitive section (ADAS-cog) and the Short Cognitive Performance Test (SKT) are commonly used in research of herbal medicines (HMs) for dementia.

1.1.5.1 MMSE

The MMSE is the most well-known and commonly used short screening tool for measuring cognitive impairment in clinical and research settings (Burns, 2005; Arevalo-Rodriguez et al., 2015). It was originally designed as a fast and practical method for grading cognitive function, which could be applied to people with dementia or delirium who may only cooperate for a short time (Folstein et al., 1975). It is accepted as a measure of efficacy of pharmaceutical interventions, and its widespread use is confirmed by surveys (Mitchell, 2013). The MMSE is used for assessment of NCDs due to AD, VaD, LBD, PD and other cognitive disorders. Internal consistency has been found to be moderate and test-retest reliability good according to an update on its diagnostic validity for cognitive disorders (Mitchell, 2013). The tool comprises a brief questionnaire that includes questions about orientation to time and place, attention and calculation, recall of three words (e.g. ball, flag, tree), language, and visual construction. It is scored by an assessor who questions the patient. The number of correct responses is added to derive the total score.

The maximum score is 30, which indicates normal cognition. MMSE scores correlate with severity of cognitive decline but generally do not solely define a diagnosis of dementia or Major NCD. There is variation in different guidelines for interpreting MMSE scores. For example, the original instructions used by Folstein, Folstein and McHugh were: ‘23 to 30 equals Normal; 19 to 23 equals Borderline; less than 19 equals Impaired’ (Folstein et al., 1975), while the former UK Standing Medical Advisory Committee (SMAC) guidelines from 1998 interpreted an MMSE score of between 10 and 26 as indicating mild to moderate AD, based on the published studies at that time. Often a score of less than 24 is interpreted as indicating probable dementia and scores between 24 and 27 may correspond to MCI/Mild NCDs (Friedman et al., 2012). A score of 23/30 is sometimes recommended as a cut-off score for dementia (Mitchell, 2013). Folstein et al. (1975) recommended a cut-off of less than 24 as significant in people with at least eight years of education (Mitchell, 2013). Others avoid
using MMSE cut-off scores for diagnosis of cognitive decline (Tombaugh & McIntyre, 1992). O’Connor et al. (1989) found that 86% of respondents who were judged to have disorders consistent with dementia or delirium scored 23 or less, and 92% of those judged to be cognitively intact scored 24 or more. This team recommended that MMSE scores should not be used for diagnoses, but that low scorers required further investigation (O’Connor et al., 1989). Guidelines from the UK National Institute for Health and Care Excellence (NICE) guidance have indicated that AD severity is frequently defined by the following MMSE scores:

- 21 – 26: mild AD
- 10 – 20: moderate AD
- 10 – 14: moderately severe AD
- Less than 10: severe AD (NICE, n.d.)

It has been shown that MMSE scores decrease with age in the general population, and that this decrease is greater in people with fewer years of formal education. Some have proposed age and education-corrected cut-off scores (Hodges, 2007) although others have argued that as age and education are important risk factors for dementia, use of corrected scores should be avoided as the effects of age and education are not benign (Minati et al., 2009).

Schmand et al. (1995) investigated the distribution of MMSE change scores after one year in a sample of healthy participants aged 65 to 84. The distribution of change scores ranged from -nine to +five. The authors proposed that based on these results, a cognitively intact patient at baseline must have a deterioration of more than five points after one year to be considered as requiring further investigation for a possible diagnosis of genuine cognitive decline. Previous studies by van Belle et al. (1990) in participants with AD, and Mitrushina and Satz (1991) in healthy, highly educated participants, had also recommended that a reduction of more than five points was required for cognitive decline to be considered significant. Mitrushina and Satz (1991) found that a change of more than five points over a two-year period was associated with a neurological disorder.

Byrne et al. (2000) argued that although it is appropriate for a dementia specialist to use the MMSE to inform clinical judgement of treatment efficacy, it should not necessarily be used as a means to quantify treatment response. Few recommendations were identified on MMSE scores required to indicate clinically meaningful change in a clinical trial setting. Burback et al. (1999) determined a minimal clinically important difference of 3.72 points (95% CI; 3.50-3.95) after surveying 476 neurologists and 111 geriatricians. A criticism of MMSE testing has been that studies have reported higher scores on retest, likely due to practice effects (Tombaugh & McIntyre, 1992) and that some patients may rehearse answers given on previous MMSE testing to prepare for their next assessment.
There are criticisms of the use of MMSE for clinical diagnosis as well as for measuring efficacy of interventions, yet it remains the commonly used measure.

1.1.5.2 Alzheimer’s Disease Assessment Scale (ADAS)
The ADAS (Rosen et al., 1984) was designed to assess all major cognitive, behavioural and psychological symptoms associated with AD, and to be sensitive to change in these symptoms in order to measure the efficacy of interventions for treatment of AD. It contains cognitive and noncognitive subscales and is commonly used in clinical trials of HM for AD (Lezak, 2012). The cognitive subscale (ADAS-cog) was the primary cognitive outcome measure in clinical trials of tacrine for treatment of AD (Davis et al., 1992). This study resulted in approval of tacrine as the first pharmacological treatment for AD by the US FDA (Lezak, 2012). The ADAS total score is calculated according to the number of errors. Scores range from zero, indicating good cognitive function and no BPSD, to 120, indicating greatest impairment (Hodges, 2007). Scores for ADAS-cog range from zero to 70. The ADAS-cog and ADAS-noncog scores are often reported separately (see below for ADAS-noncog).

There has been concern that in general the major clinical scales used to assess cognitive function in NCDs are not suitable for clinical studies, and that they do not adequately reflect the level of cognitive ability of the participants, leading to problems with current research into treatments for NCDs (Wesnes & Edgar, 2014). It has been proposed that any meaningful measure of change in intervention studies must include assessment of efficacy informed by both cognitive and functional outcomes (Byrne et al., 2000).

1.1.5.3 Short Cognitive Performance Test or Syndrom Kurztest (SKT)
The SKT is a German assessment scale for quantifying memory and attention deficits, used in people with varying degrees of cognitive decline. The total SKT score has a range of 0 to 27. Higher scores indicate more severe cognitive impairment.

1.1.5.4 Other outcome measures:
Robert et al. (2010) identified 17 Activities of daily living (ADL) instruments which test self-maintenance skills such as walking and dressing. Instrumental activities of daily living (IADL) scales measure more complex tasks including cooking and handling finances. ADL and IADL may be assessed by direct observation of a patient’s behaviour or by questioning a caregiver (Lezak, 2012).

1.1.5.5 Other methods of dementia diagnosis (laboratory, imaging)
Biochemical, neuroimaging, electrophysiological and neuropsychological markers can assist with diagnosing and tracking AD at early stages (Drago et al., 2011; O’Bryant et al., 2014). These methods
for facilitating diagnosis include beta-amyloid deposition measured by cerebro-spinal fluid (CSF) concentrations of beta-amyloid. Other biomarkers that are under current research show potential to assist with diagnoses of AD (O’Bryant et al., 2014). Examination of CSF for markers of beta-amyloid plaques, tau pathology, oxidative stress, neuroinflammation, synaptic and neuronal losses and astrogliosis may assist with monitoring disease progression (Drago et al., 2011). Structural imaging including magnetic resonance imaging (MRI) and computed tomography (CT) can assist with diagnosis of dementia subtypes (Kuruvilla et al., 2014). Alachkar (2014) conducted an audit of 75 patients of a memory clinic and found that the diagnosis of dementia type was changed after neuroimaging in 45% of cases who had previously received a clinical diagnosis based on MMSE and other interview-based scales. The most common changes were from AD or VaD to a mixed-type dementia.

MMSE scores, along with ADAS-cog and ADL outcomes, have been found to correlate with whole brain atrophy and ventricular enlargement in AD (Ridha et al., 2008). However, Cummings (2009) reported that the relationship between changes in CSF beta-amyloid or tau/p-tau levels and cognitive function, as determined by MMSE, ADAS-cog or Clinical Dementia Rating scale (CDR), has not been successfully demonstrated in clinical trials of AD. A Cochrane review (Ritchie et al., 2014) found that measurement of beta-amyloid in CSF lacked accuracy to identify people with MCI who would progress to dementia.

1.1.6 Diagnosis and assessment of BPSD

Assessment of BPSD should include interviews with the person with BPSD and the primary caregiver or person who spends most time with that person. The decision to determine whether a person is experiencing BPSD can be subjective and may partly depend on the caregiver’s ability to tolerate that behaviour, as well as other external factors (Porter, 2011). For example, age, education, mood and working conditions of the caregiver may affect the reported severity of BPSD (Sink et al., 2006, Cerejeira et al., 2012). Some BPSD have been found to be associated with specific characteristics of the caregiver. For example, angry behaviour is associated with caregiver depression, and apathy is associated with a deterioration of the relationship between the person with BPSD and the caregiver (Ornstein & Gaugler, 2012).

Depression, like other mood disturbances, may co-exist with NCDs with or without being directly related, or may be due to the same pathological cause as the NCD. Depression may also lead to reversible cognitive impairments which are sometimes mistaken as NCDs (Purandare et al., 2000). The first clinical manifestation of dementia is sometimes depression (Porter, 2011).
BEHAVE-AD was the first validated clinical assessment scale for rating BPSD in people with AD (Reisberg et al., 1987; Cerejeira et al., 2012). It involves a series of questions asked by a clinician to an informed caregiver. The Neuropsychiatric Inventory (NPI) is more commonly used than BEHAVE-AD and also involves an interview with the caregiver. Both BEHAVE-AD and NPI are used to capture treatment-related behavioural changes in people receiving drug interventions for BPSD (Cummings 1997). The Cohen-Mansfield Agitation Inventory (CMAI) is used for characterisation and classification of physically and verbally aggressive behaviours. The Consortium to Establish a Registry for Alzheimer’s Disease-Behavior Rating Scale for Dementia (CERAD-BRSD) measures 46 items grouped into six domains of behavioural disturbances (CERAD, 1986). Jeon et al. (2011) reviewed all published instruments for BPSD and recommended the NPI and BEHAVE-AD as most appropriate for both clinical practice and research. The CERAD-BRSD was recommended for research in an Australian context due to its comprehensiveness and highly rated psychometric properties, but required longer administration times and higher cost (Jeon et al., 2011).

Depression scales including the Hamilton Depression Rating Scale (HAM-D) and the Geriatric Depression Scale (GDS) are sometimes used to detect depression, but many researchers have found that use of these traditional scales is problematic in AD, as depression associated with AD is different to other depressive disorders (Minati et al., 2009).

1.1.6.1 Neuropsychiatric Inventory (NPI)

The NPI is commonly used in dementia trials (Connor et al., 2008). It is administered as an interview with an informed caregiver who is knowledgeable about the patient’s daytime and night-time behaviours. It includes the following 12 domains: A: Delusions; B: Hallucinations; C: Agitation/Aggression; D: Depression/Dysphoria; E: Anxiety; F: Elation/Euphoria; G: Apathy/Indifference; H: Disinhibition; I: Irritability/Lability; J: Aberrant motor behaviour; J: Sleep and night-time behaviour disorders; K: Appetite and Eating disorders. An initial screening question is used to determine whether the behaviour of each domain is present. If a domain is not present the assessor will not score that domain but move to the next. If the symptom is present, a series of yes/no questions will follow (Connor et al., 2008). Each domain score is calculated by multiplying frequency and severity. The total score is obtained by adding the scores for each of the 12 items. The maximum score for the 12 item NPI-12 is 144. A high score indicates severe BPSD. The original publication of the NPI did not include domains K or L and these two symptoms are not always included in the total NPI score. The NPI is reported to be stable, valid and reliable across countries (Lai, 2014). Some researchers recommend avoiding the use of cut-off scores to categorise BPSD severity, but one proposed interpretation is as follows:
Limitations and issues of the NPI

The scores of each NPI domain are non-continuous as they are a result of multiplying frequency (1 to 4) and severity (1 to 3). There are no multiples of five, seven or eleven. Mega et al. (1996) advised that parametric analysis methods may be problematic as scores may not be normally distributed. Connor et al. (2008) found that measurement biases may be introduced into clinical trials due to variability in the way the NPI is administered in clinical trials and proposed a set of specific recommendations to improve intra-rater variability and inter-rater reliability (Connor et al., 2008). Lai (2014) also argued that detection bias can occur as behaviours can potentially be attributed as neuropsychiatric symptoms that were due to another cause, and that recall bias is possible as scoring relies on caregivers’ recollections. Lai (2014) also pointed out that NPI scores may not be in accordance with patients’ self-reporting. In addition, the NPI’s sensitivity to change has not been established for all NCDs. Robert et al. (2009) proposed that new criteria should be applied for assessment of apathy in dementia patients, as it is the most frequent BPSD in AD.

1.1.6.2 ADAS-noncog

Scores for ADAS-noncog range from 0 to 50, including ten sub-items each scored on a scale of 0 to 5. It consists of ten items covering concentration, motor disturbances (tremors, pacing and motor restlessness), appetite change, mood disturbance (tearfulness and depressed mood), behavioural disturbance (‘uncooperativeness’), and psychotic symptoms (delusions and hallucinations). Assessments are based on an interview with a caregiver/informant and direct observation of the person with BPSD by the clinician (Rush et al., 2008). Rosen et al. (1984) reported that the correlation coefficients for test-retest scores of measures of cognitive function were better than for measures of BPSD. For ADAS-cog test-retest scores were 0.918 while for ADAS-noncog, only 0.588.

1.1.6.3 Behavioral Pathology in Alzheimer’s Disease Rating Scale (BEHAVE-AD)

The BEHAVE-AD (Reisberg et al., 1987) was designed to measure behavioural symptoms in AD by separating the behavioural disturbance symptoms from cognitive and functional symptoms (Reisberg et al., 2014). It involves an interview with a knowledgeable caregiver or informant, in addition to briefly observing the patient. It consists of the following seven categories:

1. Paranoid and delusional ideation (7 items)
2. Hallucinations (5 items)
3. Activity disturbances (3 items)
4. Aggressiveness (3 items)
5. Diurnal rhythm disturbances (1 item)
6. Affective disturbances (2 items)
7. Anxieties and phobias (4 items) (Rush et al., 2008)

Scores can range from 0 to 75, with higher scores indicating more severe BPSD. Similarly to the NPI, BEHAVE-AD rates the severity of each symptom on a scale from 0, indicating the symptom is not present, to 4, indicating the symptom is severe and not tolerable to the caregiver, and also rates the impact of the behavioural disturbances on caregivers (Lezak, 2012). According to Reisberg et al. (2014) BEHAVE-AD was designed to assess behavioural disturbances in people with AD which were potentially modifiable by pharmacological interventions, whereas the NPI assesses BPSD more broadly and is not specific to any dementia type or subtype. BEHAVE-AD is considered a valid, reliable and sensitive tool to measure change in symptoms, and therefore suitable for use in intervention studies (Reisberg et al., 2014; Rush et al., 2008; Lezak, 2012).

1.1.6.4 Other assessment scales for specific dementia types and subtypes:
Many validated measures have been designed which focus on assessing symptoms specific to certain dementia types or subtypes. For example, ADAS is commonly used for AD. Diehl et al. (2005) reported that the MMSE in addition to the language subsets of the Consortium to Establish a Registry for Alzheimer’s Disease-Neuropsychological Assessment Battery (CERAD-NAB) were useful for differentiating between early stage FTD, semantic dementia and AD. Barsuglia et al. (2014) proposed a scale to measure social impairment in bvFTD, the Socioemotional Dysfunction Scale (SDS). The authors reported that the SDS assisted with differentiating bvFTD with early onset AD, so could be useful for providing accurate diagnosis (Barsuglia et al., 2014).

1.1.7 Grouping of BPSD into subsyndromes
Aalten et al. (2003) performed a factor analysis of the NPI. The main finding reported was the presence of three subsyndromes of ‘mood/apathy’, ‘psychosis’ and ‘hyperactive behaviour’. ‘Mood/apathy’ was the most common subsyndrome in 199 community-dwelling dementia patients and often co-occurred with ‘hyperactivity’, while ‘psychosis’ was less prevalent except in severe BPSD (Aalten et al., 2003). This team also found that the presence of aberrant motor behaviour, anxiety and night-time behaviour disturbances appeared dependent on the severity of the NCD, whereas the presence of the other nine domain symptoms were consistent regardless of disease severity. Aalten et al. (2003) also argued that interventions may be more effective when targeting subsyndromes instead of targeting individual symptoms.
The European Alzheimer Disease Consortium proposed that four subsyndromes of hyperactivity, psychosis, affective symptoms and apathy were present in AD (Aalten et al., 2007). Van der Linde et al. (2014) agreed that studying correlated symptom groups may lead to better findings regarding aetiologies and potential treatments of different BPSD. Affective symptoms, psychosis, hyperactivity and euphoria were the suggested groups, while apathy, eating disturbances, night-time behaviour disturbances, disinhibition and aberrant motor activity did not show consistent results for grouping (van der Linde et al., 2014).

1.1.8 Agitation

Agitation is an important indicator of discomfort (Cohen-Mansfield, 2004), characterised as disruptive motor or vocal activity, and is common across all the NCDs (American Psychiatric Association, 2013). According to Ballard et al. (2016) agitation is the most frequent and disturbing behavioural and psychological symptom in nursing home or residential care residents and in people with severe dementia. Agitation was reported to affect almost half of people with AD during a one month period (Ryu, 2005; Okura, 2010). Koss et al. (1997) found that severity of agitation did not relate linearly to the progression of cognitive decline. Later studies including Lovheim et al. (2008) have shown similar results.

Ballard (2007) defined agitation as ‘a syndrome characterised by excessive motor activity and a feeling of inner tension, with a cluster of related symptoms including anxiety and irritability, motor restlessness and abnormal vocalisation (e.g. shouting).’ Ballard (2007) reported that agitation occurs in approximately 20% of community dwelling people with AD in contact with clinical services, and in 40 to 60% to people with AD living in care facilities. Ballard (2007) also reported that agitation can be persistent. Cohen-Mansfield et al. (2014) found that improved levels of agitation during a nonpharmacological intervention trial correlated significantly with increased levels of cognitive function in nursing home residents with severe dementia and agitation.

Severity and prevalence of agitation compared to severity of cognitive decline

Cohen-Mansfield et al. (1990) reported that agitated verbal behavioural disturbances were significantly related to depressed mood, cognitive impairment, pain and sleep disturbances. Van der Mussele et al. (2015) found that people with MCI and agitation had more severe behavioural symptoms than Alzheimer’s dementia participants without agitation. This study reported the prevalence of agitation in Alzheimer’s dementia was 76%. As proposed by van der Mussele et al. (2015) the management of agitation may assist indirectly with managing other associated symptoms, as well as assist with reducing caregiver distress.
The NPI-C Agitation/Aggression domain tests for the presence of this symptom by asking the caregiver whether the person has ‘periods when he/she refuses to cooperate or won’t let people help him/her’, and whether the person is ‘hard to handle’ (Cummings, 1997). Cohen-Mansfield and Billig (1986) defined agitation as ‘inappropriate verbal, vocal or motor activity that is not judged by an outside observer to result directly from the need or confusion of the individual (Cohen-Mansfield & Libbin, 2004). Cohen-Mansfield and others classify agitation into verbal or physical types, and aggressive or non-aggressive types (Cohen-Mansfield & Libbin, 2004). Studies of the CMAI have identified four factors: aggressive agitation, physically nonaggressive agitation, verbally agitated behaviour, and hiding and hoarding behaviour (Whall et al., 2013).

Cohen-Mansfield’s ‘syndromes of agitation’ include:

1. Physically non-aggressive (inappropriate dressing or disrobing, inappropriate eating or drinking, exit-seeking behaviours, handling things inappropriately, hiding things, hoarding, pacing, repetitious mannerisms, restlessness)
2. physically aggressive (biting, grabbing, hitting, hurting oneself or others, falling intentionally, kicking, physical sexual advances, pushing, scratching, spitting, tearing things, throwing things)
3. verbally non-aggressive (attention-seeking behaviours, complaining, negativism, repetitive sentences or questions)
4. verbally aggressive (cursing, making strange noises, screaming, verbal sexual advances)
(Cohen-Mansfield, 2008)

1.2 Current therapies for dementia and NCDs
There are currently few effective treatment options for NCDs, but potential preventative measures are increasingly being acknowledged (Nelson, 2014) and disease modifying interventions are a focus of current research (Parker, 2014; Montoliu-Gaya 2015).

At present, acetylcholinesterase inhibitors (AChEIs), including donepezil, galantamine and rivastigmine, are first line treatments for management of cognitive symptoms of AD, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine was reported in a meta-analysis of RCTs as being well-tolerated and significantly better than placebo for moderate to severe AD (Winblad et al., 2007). A SR of RCTs concluded that AChEIs for MCI did not delay the onset of dementia (Raschetti et al., 2007), although a more recent randomised trial of 332 participants found that donepezil reduced basal forebrain atrophy progression in prodromal AD (Cavedo et al., 2017). Piracetam (naofukang), the nootropic, has been used as a control intervention in Chinese clinical trials of
Herbal medicines for NCDs. It was previously found to be effective for improving cognitive symptoms in AD and other dementias (Waegemans et al., 2002), but a Cochrane review reported a lack of consistent evidence to support its use for dementia or cognitive impairment (Flicker et al., 2012).

1.3 **Current therapies for BPSD**

Current therapies aim to manage BPSD but do not stop or reverse progression of the underlying NCD. A combination of interventions may be required to adequately treat BPSD (McKeith & Cummings, 2005). Non-pharmacological interventions are recommended as first-line treatments; combined with careful administration of pharmacological treatments for severe BPSD (Cerejeira et al., 2012).

### 1.3.1 Pharmacological interventions for BPSD

Popp and Arlt (2011) reported that mood disturbances, psychosis, apathy, hyperactivity and disturbance of circadian rhythm may be targeted by pharmacological treatments. Cummings (2008) found that many RCTs and open label studies have shown beneficial behavioural outcomes associated with pharmacological treatments for management of dementia symptoms.

A SR and meta-analysis by Wang et al. (2014) of pharmacological treatment of neuropsychiatric symptoms in AD investigated antipsychotics, antidepressants, benzodiazepines/anxiolytics, mood stabilisers and the cognitive enhancers - AChEIs and NMDA receptor modulators. Very few trials on typical antipsychotics, antidepressants and mood stabilisers for BPSD were found. In addition, analgesics are sometimes used to reduce BPSD in nursing home residents with AD (Husebo et al., 2011).

#### 1.3.1.1 Antipsychotics

First generation (typical) antipsychotics, including haloperidol, can be effective in mild cases of psychosis but often cannot be tolerated in large doses or long-term in older people as they can produce severe adverse effects. The use of antipsychotics for BPSD is off-label, according to Azermai (2015), although there is evidence of modest efficacy to support their use for aggression and psychosis, and they are considered the ‘best short-term pharmacological option for severe and persistent symptoms of dementia-related aggression/agitation’ (Azermai et al., 2015). An important adverse effect of antipsychotics is uncontrolled body movements, such as dyskinesias, which are collectively known as extrapyramidal symptoms (EPS). EPS are due to blockage or depletion of dopamine in the basal ganglia (Blair & Dauner, 1992). EPS are classified as either acute or tardive (symptoms appearing later) and also include Parkinsonism (rigidity, tremor and bradykinesia), akinesia, akathisia (motor restlessness), neuroleptic malignant syndrome, acute dyskinesias and
dystonic reactions (Blair & Dauner, 1992). Dopamine D2 receptor antagonist drugs are reportedly the most common cause of EPS (Pierre, 2005). EPS have a significant impact on adherence and tolerability to antipsychotic therapy and on daily function (Pierre, 2005). Tardive dyskinesia is chronic and characterised by irregular, repetitive, involuntary, jerky movements, mainly affecting the lower face and distal extremities (Pierre, 2005). Older people, especially women, have a higher risk of developing tardive dyskinesia, which is often incurable (Saltz et al., 2004).

Second generation (atypical) antipsychotics, including aripiprazole, olanzapine and risperidone, pose less risk of producing EPS. They have shown some efficacy for aggression, psychosis and agitation but can lead to increased mortality in older people, partly due to increased risk of stroke (Schneider et al., 2006; Tampi et al., 2009). Schneider et al. (2006) found that common adverse effects of atypical antipsychotics were somnolence, urinary tract infection or incontinence from all drugs reviewed, and EPS or abnormal gait with risperidone or olanzapine. Also, cognitive function worsened with these drugs. There has been concern about inappropriate use of antipsychotics for BPSD in residential care facilities (Looi & Macfarlane, 2014). As the risk of adverse effects is high, some studies have investigated the effects of discontinuation of the use of antipsychotics. A Cochrane review (Declercq et al., 2013) concluded that many older people with AD and BPSD can be withdrawn from chronic antipsychotic administration, although withdrawal might not be recommended for severe cases of psychosis at baseline. Reeve (2014) and Scott (2014) have also argued that deprescribing antipsychotics may lead to significantly better outcomes for older people.

1.3.1.2 Antidepressants
Reduction of serotonergic function may be related to the genesis of BPSD (Martinon-Torres et al., 2004). A Cochrane review (Seitz et al., 2011) concluded that the Selective Serotonin Reuptake Inhibitors (SSRIs) sertraline and citalopram were associated with reduced agitation in two studies and that SSRIs, including the compound drug trazodone, were better tolerated than typical or atypical antipsychotics. Trazodone was found to have a low rate of adverse events but no benefit was found for BPSD in AD, according to Martinon-Torres et al., (2004). Cognitive function in AD also worsened significantly in the trazodone group at end of treatment compared to the placebo group. In addition, there was a lack of data to support its use for BPSD in Frontotemporal NCD (Martinon-Torres et al., 2004). According to Porter (2011), antidepressants should only be prescribed if there are depressive symptoms. Wang et al. (2014) found antidepressants did not improve total NPI scores in a meta-analysis of two placebo-controlled RCTs.
1.3.1.3 Benzodiazepines/Anxiolytics

Benzodiazepines enhance the effect of GABA at the GABA<sub>A</sub> receptor, which leads to sedative, anxiolytic, muscle relaxant and other effects. This class of drugs is used to manage anxiety, insomnia, agitation and irritability but is associated with excessive sedation, increased risk of falls and confusion (Purandare et al., 2000). In order to avoid dependency or tolerance, benzodiazepines should only be prescribed for short periods (Barker et al., 2004). McKeith and Cummings (2005) advised against use of benzodiazepines in people with dementia. Withdrawal from long-term use of benzodiazepines has been shown to improve mental and physical health (Barker et al., 2004). A meta-analysis of cognitive effects of long-term benzodiazepine use (not for BPSD) found moderate to large effect sizes across 12 different categories of cognition, indicating significant worsening of cognitive function (Barker et al., 2006). Consequently, other approaches to the management of BPSD are being sought (Cerejeira et al., 2012). Benzodiazepines may be prescribed for acute agitation or agitation with anxiety in BPSD (Cerejeira et al., 2012; Azermai et al., 2012).

1.3.1.4 Anticonvulsant mood stabilisers

Anticonvulsant mood stabilisers, including valproic acid, gabapentin, lamotrigine, topiramate and carbamazepine, may enable antipsychotic dosage to be reduced (Cerejeira et al., 2012). However, they are not recommended for routine use in managing BPSD (Cerejeira et al., 2012). Carbamazepine, the anticonvulsant with a tricyclic structure, may reduce agitation, impulsivity and lability in psychiatric illness and has been a focus of research attention for BPSD (Tampi et al., 2009). A systematic review by Wang et al. (2014) found few trials and stated that no convincing conclusions could be drawn.

1.3.1.5 Analgesics

Pain control reduced BPSD in nursing home residents with AD (Husebo et al., 2011). Participants received paracetamol, morphine, buprenorphine transdermal patch or pregabaline on a daily, individualised basis. Cognition and ADL scores were unchanged but CMAI and NPI-NH aggression scores were improved. A Cochrane review has examined use of opioids to treat agitation in dementia (Brown et al., 2015). There was a lack of data to determine whether opioids relieve or exacerbate dementia-related agitation.

1.3.1.6 Cognitive enhancers for BPSD

Cognitive enhancers may also be prescribed to manage BPSD. AChEIs were reported to improve apathy and affective symptoms (McKeith & Cummings, 2005). Cummings et al. (2006) reported that donepezil appeared to reduce mood disturbances and delusions in people with AD and severe BPSD. Miller (2007) proposed that AChEIs and memantine may be prescribed as an alternative or adjunct
to antipsychotics for the treatment of moderate to severe BPSD in AD, after reviewing double-blind, placebo-controlled trials which used NPI to assess changes. A meta-analysis of double-blinded RCTs of AChEIs on behavioural and psychological symptoms of AD concluded that AChEIs led to a statistically significant reduction in BPSD, but the clinical relevance was not determined (Campbell et al., 2008). Donepezil improved NPI, MMSE and ZBI scores in mild to moderate AD (Carrasco et al., 2011). A meta-analysis of total NPI scores showed that AChEIs improved BPSD in AD but with a high number of dropouts due to adverse effects (Wang et al., 2014). A galantamine subgroup of the same meta-analysis showed significant improvements in BPSD. An earlier Cochrane review by Loy and Schneider (2006) indicated that galantamine for mild to moderate AD led to significantly improved or unchanged scores using global rating scales, although it was associated with an increased death rate and its long-term use had not been adequately tested. Wang et al. (2014) found memantine did not improve total NPI scores in AD, reporting high heterogeneity of included studies. Yaffe et al. (2014) reported that results of small trials suggested that AChEIs might improve sleep quality in AD but potential side effects may outweigh benefits. Popp and Arlt (2011) advised that AChEIs and memantine may not be effective enough in severe cases of BPSD and that additional drugs may be needed. Manabe et al. (2015) reported that increased dosage of donepezil improved NPI scores in people with LBD, in an open-label study of 24 participants. The biggest change was detected in hallucinations scores, which changed from mean 8.23 at baseline to mean 2.85 at week 4.

1.3.2 Specific pharmacological recommendations for other NCD types

A SR of interventions for non-motor symptoms of PD included clinical trials testing rivastigmine for apathy and donepezil, pimavanserin or olanzapine for psychosis (Schrag et al., 2015).

Although SSRIs or SNRIs may be useful for treatment of depression in some people with frontotemporal NCD, there is currently no definitive treatment for frontotemporal NCD, as AChEIs, antipsychotics and memantine have been found to be ineffective (D’Alton & Lewis, 2014).

1.3.3 Other treatments for managing BPSD

As discussed and reviewed in detail in subsequent chapters of this thesis, HMs and their standardised extracts are sometimes used for management of BPSD. In particular, the standardised extract of Ginkgo biloba leaf, Egb 761®, and Yokukansan, a Japanese kampo formula which contains seven commonly used herbs, have received substantial research attention for their effects on symptoms of NCDs.

A SR of aromatherapy for BPSD concluded that aromatherapy had positive effects on reducing BPSD, but that better designed RCTs were needed before recommendations could be made (Fung et al.,
Lavender species and Melissa officinalis have been reported to reduce anxiety, agitation and sleep disturbances in people with NCDs, and were reported to be safe, although increased agitation was observed in people with Major NCD with Lewy bodies (Fung et al., 2012).

1.3.4 Non-pharmacological interventions for managing BPSD

Non-pharmacological interventions include design of environments which aim to create constant, familiar, non-stressful settings; psychological-behavioural interventions including cognitive rehabilitation programs; and functional analysis-based interventions, which were reported in a Cochrane review to have potential benefit for challenging behaviours in dementia (Moniz-Cook et al., 2012). Enjoyable activities such as pet therapy, horticultural therapy and art therapy are also implemented. A Cochrane review showed no strong evidence for or against music therapy for dementia (Vink et al., 2011). Bright light therapy for sleep disturbances has been tested but a Cochrane review reported insufficient evidence to recommend this intervention for people with dementia (Forbes et al., 2014). Caregiver support and education are also important, as increased caregiver distress may lead to worsening of BPSD. Exercise programs for people with major NCDs have been shown to improve mood as well as functional ability (Azermai et al., 2015).

1.4 Need for new interventions

Current therapies are aimed to manage symptoms but cannot stop or reverse the disease process. There is a need for new treatments, especially for management of persistent symptoms, as well as a need for new therapeutics that may target underlying causes of NCDs and BPSD.

1.4.1 Emerging disease modifying therapies for NCDs:

Secretase modulators, inhibitors of beta-amyloid aggregation, immunotherapy, inhibitors of tau phosphorylation, delivery of nerve growth factor and other therapies are under current research (Minati et al., 2009). Beta-amyloid therapy involves active and passive immunisations against beta-amyloid. Based on the amyloid cascade hypothesis, this therapy might prevent the downstream pathogenesis of the disease (Lambracht-Washington & Rosenberg, 2013). However, clinical trials have not yet resulted in positive outcomes and research is ongoing.

Tropisetron, the serotonin 5-HT3 receptor antagonist, is a well-tolerated drug prescribed for chemotherapy-induced nausea and vomiting (Hashimoto, 2014). Recent studies have shown that tropisetron bound to alpha7 nAChR has a crucial role on beta-amyloid deposition and inflammation in the brain (Hashimoto, 2014). Tropisetron was also superior to memantine and donepezil for improving memory in AD. Tropisetron has recently become of interest for its potential to prevent or delay onset of dementia (Hashimoto, 2014).
1.4.2 Interventions for preventing or delaying the onset of dementia and NCDs

Interventions to prevent stroke, including physical activity, aspirin, statins and non-steroidal anti-inflammatory drugs (NSAIDs) may delay onset of some dementias (Hachinski, 2014). A two-year RCT found that a combined intervention of diet, exercise, cognitive training and monitoring to reduce vascular risk factors resulted in an improvement or maintaining of cognitive function in at risk older participants in Finland (Ngandu et al., 2015). Holmgren et al. (2014) investigated the role of neuroinflammation in 94 people with BPSD. Analysis of cytokine levels in CSF samples indicated a relationship between neuroinflammation and BPSD in AD and that anti-inflammatory signalling by Interleukin-10 (IL-10) was beneficial for mental health.

1.4.3 Nutrition, diet and lifestyle for prevention, risk reduction and/or management of NCDs

Nutrition and diet may play a role in the development and progression of NCDs. Preventative dietary interventions that are receiving research attention include calorie restriction and Mediterranean diets (Sarri et al., 2004; Martinez-Lapiscina et al., 2013; Morris et al., 2015). Restricting calorie intake has been shown to protect against neuronal loss in animal models of AD and PD (Srivastava & Haigis, 2011). Dhurandar et al. (2013) found that hunger alone, induced by a ghrelin agonist, improved cognition and reduced beta-amyloid deposition in a mouse model of AD. However, a large scale retrospective cohort study of two million people over two decades found that being underweight in middle age and old age carried an increased risk of developing dementia over two decades, and that very obese people had a lower dementia risk than people of a healthy weight (Qizilbash et al., 2015).

A Mediterranean-style diet intervention supplemented with nuts and extra virgin olive oil appeared to improve cognition, compared to a low fat diet, in a 6.5 year study of 522 participants with high vascular risk at baseline (Martinez-Lapiscina et al., 2013). Morris et al. (2015) found that a Mediterranean-style diet which emphasised dietary components and servings was associated with reduced incidence of AD in 923 participants in the US over an average of 4.5 years.

Dietary omega-3 polyunsaturated fatty acids (PUFAs) have been the subject of numerous studies. Older French community dwellers who regularly consumed fish had fewer depressive symptoms and scored higher on the MMSE (Barberger-Gateau et al., 2005). Carrie et al. (2009) found evidence to support the belief that regular consumption of omega-3 PUFAs from seafood prevents cognitive decline due to ageing. Omega-3 PUFAs are also reported to have effects on dopaminergic and serotonergic systems so may be involved with some BPSD. A meta-analysis indicated that omega-3 PUFAs play an important role in the pathophysiology of dementia (Lin et al., 2011).

A meta-analysis of dietary intakes of vitamins E, C and beta-carotene (Li et al., 2012) found that dietary intake of these antioxidants was associated with lowered risk of AD. However, a Cochrane
review concluded that Vitamin E should not be used for treatment of MCI and dementia due to AD (Farina et al., 2012). Littlejohns et al. (2014) found a significant increased risk of AD and all-cause dementia associated with vitamin D deficiency. Excessive copper and iron levels are associated with cognitive decline. Some studies have found increased levels of AD in areas with higher aluminium concentrations in tap water, but its role in NCDs is not known (Barnard et al., 2014).

Ensuring adequate nutrition and hydration can be a concern in people with dementia, partly due to pathological changes in appetite and eating. No specific nutrient supplements are currently recommended (Scheltens, 2009). Overall, there is evidence that diet can play a role in risk reduction of developing Major NCD due to AD. However, there is a lack of evidence for prevention.

1.5 Rationale for this research and its significance

Dealing with BPSD is complex and difficult. There is currently no adequate pharmacological intervention for management of long-term or severe BPSD. Antipsychotics or benzodiazepines may provide short-term benefit in management of some symptoms, but the adverse effects are potentially severe and even fatal, including EPS and increased risk of falls (Purandare et al., 2000; Azermai et al., 2015). Some of these drugs are also associated with worsening of cognitive symptoms (Cerejeira et al., 2012; Barker et al., 2004). There is an urgent and growing need for efficacious and safe interventions. Most research on NCDs has focussed on the cognitive symptoms although BPSD are commonly seen in these disorders and it is likely that the BPSD are due to the same pathological processes as the cognitive impairments (McKeith & Cummings, 2005). Consequently, there is a need for research into interventions for managing cognitive symptoms and BPSD (McKeith & Cummings, 2005; Cerejeira et al., 2012).

As explored in detail in the next chapters of this thesis, HMs may hold potential as sources of ideas for new interventions for the effective management of cognitive symptoms and BPSD. Both historical use and clinical trials provide evidence for the use of single plant-based medicines and multi-ingredient herbal formulae in managing these symptoms. Clinical trials of standardised HMs indicate that certain BPSD can be controlled, at least in the short-term, without producing or further aggravating EPS (Teranishi et al., 2013; Ihl et al., 2013). However, it is likely that more effective combinations could be developed.

Many HMs used for dementia have long histories of use in humans and have been tested in clinical trials, so there is the potential for such multi-herb combinations to be fast-tracked into clinical use. It is also possible that certain compounds or combinations of compounds within the single and multi-herb formulations used for BPSD may be primarily responsible for the clinical effects. Identification
of these compounds and their possible mechanisms of action have the potential to contribute to drug discovery for AD and for cognition and BPSD. Recent experimental studies of natural products have resulted in encouraging findings regarding new compounds for treating symptoms of depressed mood as well as potential disease modifying compounds (Carhart-Harris et al., 2016; Moon et al., 2017; Meineck et al., 2017).

Results of clinical and experimental studies suggest that HMs may play a role in the development of pharmaceutical interventions for management of BPSD (Yi et al., 2017). Of the currently used pharmaceutical drugs for NCDs, galantamine can be derived from the bulbs of Galanthus, Lycoris, Narcissus, Leucojum and other species in the Amaryllidaceae family, and rivastigmine is a synthetic derivative of phystostigmine from the Calabar bean (Physostigma venenosum) (Calcul et al., 2012).

HMs for NCDs have become a research focus in the search for alternative approaches to the management of cognitive symptoms, and/or slowing of cognitive decline (Kanba & Richelson, 1999; dos Santos-Neto et al., 2006; May et al., 2009a; May et al., 2009b; Jiang et al., 2017; Takayama & Iwasaki, 2017; Xu et al., 2018). This may be partly due to new interest in HM literature, driven by a paucity of candidates for drug discovery and the availability of new technologies for bioprospecting (Rausser & Small, 2011; Sucher, 2013; Dey et al., 2017).

Clinical trials have shown some evidence of HMs for the management of BPSD (Iwasaki et al., 2004; Herrschaft et al., 2011). As reviewed and discussed in more detail in Chapter Two and investigated by meta-analysis in Chapter Four, there is evidence to support further investigation of HMs for improving some symptoms, including agitation/aggression and irritability, compared to usual care. Results of these studies generally show HMs are well-tolerated.

1.5.1 Combining multiple herbs into herbal formulae

As mixtures of drugs may be more effective than a single drug for some multifactorial conditions, some researchers have shown interest in herbal formulae as a source of discovery of combination therapies. Much of the focus of HM research has been on single active ingredients. However, there has recently been a shift towards the investigation of drug therapies with multiple compounds (Sucher 2013; Dey et al., 2017). Wink (2008) stated that many complex HM mixtures have clear biological activities. These complex mixtures of secondary compounds in plants have evolved to provide chemical defences that are effective against microbial pathogens, viruses and attack by herbivores. Howes and Perry (2011) proposed that phytochemicals’ effects on mood, memory and other complex cerebral functions may be due to these chemicals targeting the nervous system in order to attract pollinators or deter predators.
There has been greater research focus on cognitive symptoms compared to BPSD, but assessment of BPSD has been included in several clinical studies of HMs for NCDs (see Chapters Two and Four). Fabricant and Farnsworth (2001) reported that an ethnobiological approach to drug discovery has been more successful than random screening of botanical specimens. The classical Chinese medical literature provides numerous references to plants and other substances that were recommended for improving memory and treating forgetfulness associated with older age, as well as for treating agitation, insomnia, depression, mania and withdrawal, and other neuropsychological symptoms (May et al., 2014). Helmstadter and Staiger (2014) argued that carefully evaluated traditional use of HMs can play a role in rational drug design and development. Consistent uses over multiple generations, plus traditions that continue in the present, are important considerations when identifying traditional medicines as potential candidates for further research.

The practice in China has been to combine herbs into formulae with multiple ingredients (May et al., 2014). Herbal formulae have been documented in the classical Chinese medical literature since before 168 BCE (Goldschmidt, 2009; Sucher, 2013). The Zhong Yi Fang Ji Da Ci Dian (ZYFJDCD) contains approximately 97,000 individual entries, which each refer to at least one formula. The Zhong Hua Yi Dian (ZHYD) (Encyclopaedia of Chinese medicine) is a CD-Rom which contains the full text of 1,000 books. May (2009) developed methods for extracting, evaluating and interpreting data from the Chinese classical medical literature. These methods were applied to disorders which correspond to dementia and memory loss. The terms chi dai and jian wang correspond with the modern Chinese medicine terms for dementia and forgetfulness, respectively (May et al., 2016). Within this Chinese literature relating to dementia, the systematic application of search terms which correspond to BPSD terminology could provide leads for further research into natural products with potential for alleviating BPSD. For example, Kai xin san (Open the Mind Powder) is a formula of four herbs that was originally described during the Tang Dynasty circa 652CE in Bei Ji Qian Jin Yao Fang, as a treatment for ‘desolation, moodiness and forgetfulness’ (Dang et al., 2009).

1.6 Aims

This project aimed to form an original and worthwhile contribution towards the development of pharmacological interventions for management of cognitive, behavioural and psychological symptoms of dementia, by building on previous research into HMs for cognitive decline and forming part of a collaborative research team focussed on HM for NCDs.

The main aims of the project were:
1. to review the literature on BPSD including classifications, assessments, aetiology, pathogeneses, currently available treatment options and proposed worthwhile areas of investigation;
2. to review the literature on traditional medicines and natural products research for treatment of cognitive, behavioural and psychological symptoms of dementia;
3. to devise and describe methods to undertake specific studies to analyse the evidence on efficacy, safety and tolerability of HMs for BPSD;
4. to undertake meta-analysis of data from clinical trials of HMs for dementia and BPSD. Outcome measures of interest included assessments of BPSD and cognition. This project included efficacy and safety from clinical studies and also a summary of the current knowledge of active ingredients which may hold potential for drug discovery. This led to identification of gaps in knowledge for future research.
5. to undertake analyses of classical Chinese medical literature entries relating to the use of herbs for memory disorders accompanied by neuropsychiatric symptoms including hallucinations, anxiety, depression, agitation and sleep disorders;
6. select herbs and combinations of herbs that show potential for further research based on the results of meta-analyses and analyses of the classical literature; and to investigate possible mechanisms of the compounds contained in the selected herbs and explore their relevance to BPSD. Possible interactions of multiple compounds were considered to assist in the proposal of a multiple component herbal formula for clinical use.
7. to explore the issue of increasing placebo effect sizes over time in clinical trials of BPSD, and propose methods to reduce the possibility of false negative results of a trial due to this possibility;
8. to propose a novel HM intervention that is specifically targeted for cognitive symptoms and BPSD and to design an ethical and rigorous clinical trial that is suitable for testing the proposed herbal formula to evaluate its effects on cognitive symptoms and BPSD. The design process explored suitability of participant groups including issues relating to vulnerable people with cognitive and neuropsychiatric symptoms. In addition, the design examined suitable approaches to measuring outcomes relating to cognition and behaviour as well as physiological changes. The conduct of the clinical trial itself was not in the scope of this PhD.
9. to summarise and discuss the findings and propose areas of future research based on these.

1.7 Outline of the project

Chapter Two: A narrative review and background of the contemporary and historical use of HMs related to BPSD.
Chapter Three: Methods of the systematic review of clinical trials and the analysis of the classical Chinese medical literature.

Chapter Four: SR and meta-analysis of HM for cognitive symptoms and BPSD. The meta-analysis of outcomes of clinical trials facilitated the selection of herbal interventions for further consideration. This chapter is modified from the publication:


Role: developed the study design and search queries, conducted the database searches, screened the studies and extracted data, assessed risk of bias, conducted meta-analysis, wrote the article, with collaboration from the co-authors and others mentioned in the acknowledgements.

Chapter Five: Analyses of herbs in the Chinese medicine classical literature that were used for memory impairment and BPSD. These analyses provided herbs that showed evidence of historical use for cognitive symptoms and BPSD. Data convergences between the results from Chapters Four and Five were used to inform the selection of herbs and herbal formula for further consideration.

Chapter Six: Investigation of the literature on the possible mechanisms of the selected herbs in relation to cognitive symptoms and BPSD. This involved identification of the known active ingredients in the herbs and an examination of the in-vitro and in-vivo studies of herb extracts and their constituent compounds. This further focussed the project on the herbs and herbal combinations that showed greatest promise of efficacy in cognitive symptoms and BPSD.

Chapter Seven: Investigation of issues related to clinical trial design for HMs for people with BPSD, and proposals to resolve any important issues identified.


Role: initiated the study, developed the study design and search queries, conducted the database searches, screened the studies and extracted data, assessed risk of bias, conducted meta-analysis,
wrote the article, with collaboration from the co-authors and others mentioned in the acknowledgements.

Chapter Eight: Design or selection of a HM intervention for cognitive symptoms and BPSD. The findings of the previous sections were synthesised to select a HM intervention that showed suitability for use in a clinical trial taking into account issues of quality, efficacy, safety, tolerability, acceptability, mechanisms, dosage and duration of use. This chapter also details the design of a clinical trial protocol. The trial type and participant group were in accordance with the specific therapeutic focus of the intervention.

The structure and sequence of this thesis are presented in the following flow diagram:
Chapter One
Introduction to dementia, BPSD and NCDs, including rationale and aims of the research

Chapter Two
Herbal medicines for dementia, BPSD and NCDs

Chapter Three
Methodology

Chapter Four
Systematic review and meta-analysis of clinical trials testing herbal medicines for BPSD

Chapter Five
Analysis of the classical Chinese medical literature of herbs for symptoms analogous to BPSD

Chapter Six
Review of experimental studies of herbs for BPSD

Chapter Seven
Investigation of issues in clinical trial design in BPSD; a systematic review and meta-analysis of variation in placebo effect size

Chapter Eight
Data synthesis and design of a clinical trial protocol for testing a herbal intervention for management of BPSD

Chapter Nine
Discussion, conclusions and further directions

Additional journal articles associated with this thesis:

Role: assisted with development of the study design and search queries, conducting the database searches, screening the studies and extracting data, editing and contributing the article, with collaboration from the first two authors, co-authors and others mentioned in the acknowledgements.

Role: assisted with development of the study design and search queries, conducting the database searches, screening the studies and extracting data, assessing risk of bias, conducting meta-analysis, preparing graphic materials, co-authoring and editing the article, with collaboration from the first two authors, other co-authors and others mentioned in the acknowledgements.

**Figure 1.4: Flow diagram showing thesis structure and sequence**

1.8 **Research questions**

1. What is the current clinical trial evidence for the use of HMs for management of BPSD? (Chapters Two and Four)

2. Which herbs and herbal formulae were used for memory impairment and symptoms consistent with BPSD in the classical Chinese medical literature? (Chapter Five)

3. What is the experimental evidence for effects on animal models and mechanisms of action of HMs for management of BPSD? (Chapter Six)

4. Which herbs and combinations of herbs showed the greatest promise of efficacy, safety and tolerability for BPSD? (Chapters Four and Six)

5. Which of these herbs show potential for use in clinical trials, and what is a suitable HM intervention for management of cognitive symptoms and BPSD? (Chapters Four, Six and Eight)

6. How is this formula likely to work? (Chapters Six and Eight)

7. How could the effects of these herbs be measured? (Chapter Eight)

8. What are the issues in clinical trial design of HMs for BPSD? (Chapters Seven and Eight)

9. What is an appropriate and ethical design of a clinical trial of the herbal intervention to assess its effects on cognitive symptoms and BPSD? (Chapter Eight)
CHAPTER TWO LITERATURE REVIEW OF HERBAL MEDICINE FOR DEMENTIA AND BPSD

2.1 Introduction

This chapter reviews the literature, including clinical studies of herbal medicines (HMs), for dementia and BPSD. As outlined in the previous chapter, careful evaluation of the existing literature regarding HMs for treating symptoms of dementia may assist with identification and future development of effective treatments. The classical Chinese medical literature shows a long history of addressing multiple specific symptoms, e.g. memory impairment with depression, with multiple herbs combined into formulae. This literature also indicates a long history of addressing both ‘mental’ and ‘physical’ conditions with HMs, rather than distinguishing between the two, and this strategy has continued in current practice of traditional medicine in China and Japan. This chapter outlines premodern use of HM in China for conditions analogous to age-related NCDs due to AD and BPSD, as well as contemporary use of HMs for AD and BPSD in China according to textbooks and clinical guidelines. Traditional Chinese and Japanese clinical reasoning processes regarding treatment of symptoms of dementia with HMs are described. Contemporary research of multiple-component Chinese herbal formulae and kampo formulae for BPSD are reviewed and possible mechanisms outlined. These mechanisms are explored in detail in Chapter Six. Finally, current issues of complementary medicine and HM research and their implications for this project are summarised.

2.2 Use of single herbs and their standardised extracts for dementia, NCDs and BPSD

A number of single herbs have been investigated in clinical studies for their effects on dementia, NCDs and BPSD. The results of systematic searches of biomedical databases, as described in Chapter Four, indicate that Ginkgo biloba has been studied extensively for treatment of BPSD, and that four other single herbs have received considerable research attention for treatment of BPSD including Panax ginseng, Melissa officinalis, Angelica archangelica, and Huperzine A which is extracted from Huperzia serrata.

2.2.1 Ginkgo biloba leaf

Although the G. biloba tree is believed to be native to China, use of its leaves, yin xing ye or bai guo ye, is only briefly mentioned in the classical Chinese medical literature. The nuts of G. biloba have a longer history of use as a food and medicinal herb in China, mainly used medicinally for treatment of lung conditions. According to Bensky et al. (2004), the current medicinal interest in the use of G. biloba leaves ‘was introduced to Chinese medicine from the West’. Bensky et al. (2004) cited the 16th Century Ben Cao Pin Hue Jing Yao (Essentials of Materia Medica Distinctions), by Liu Wen-Tai, as the first text to describe the use of G. biloba leaves for medicinal purposes. This text contained a formula...
to ‘stop dysenteric disorder’ which contained *G. biloba* leaf (Bensky et al., 2004). According to the current Chinese medicine Materia Medica, *yin xing ye* is reported to ‘calm wheezing, stop cough and treat a stifling sensation in the chest and chest pain, as well as invigorate the blood and stop pain’ (Bensky et al., 2004). No record was identified of medicinal use of *yin xing ye* for cognition, memory or behavioural disturbances in the classical Chinese medical literature.

The *G. biloba* tree may have first been described to the West around 1700 CE (Foster, 1990). According to DeFeudis (2003) its leaf extracts were introduced into clinical practice in Germany in 1965, and effects on cerebral blood flow disturbances and cerebral atherosclerosis were first published in 1965-66 (DeFeudis, 2003). The standardised extract of *G. biloba* leaf, EGb 761®, has been described as ‘one of the most commonly used herbal medicines in the world’ (DeFeudis, 2003). Its use for improving cognitive function in NCDs including AD and VaD has been the subject of numerous experiments and reviews, with inconsistent results. It has also been tested for its effects on BPSD using the NPI, Geriatric Evaluation by Relative’s Rating Instrument (GERRI) and Geriatric Depression Scale (GDS) as outcome measures, as discussed and reviewed in Chapter Four.

Ernst and Pittler (1999) conducted a systematic review (SR) of double-blind, placebo-controlled trials of *G. biloba* for dementia. Of the nine studies included in the review, a study by Le Bars et al. (1997) was suggested to be ‘the most convincing’. Le Bars et al. (1997) conducted a large-scale RCT of EGb 761® for treatment of participants with moderate to severe AD or VaD. At the end of treatment (EoT) (week 52), better scores were observed in the EGb 761® group compared to the placebo group in ADAS-cog and GERRI, which included caregiver assessments of mood as well as cognitive and social function. However, EGb 761® did not affect global change measures. Le Bars et al. (1997) concluded that EGb 761® was safe and that administration led to noticeable improvements in cognitive and social functioning in participants with dementia. Results of Ernst and Pittler’s (1999) review indicated that *G. biloba* leaf extract was superior to placebo and that benefits were slightly greater in participants diagnosed with AD compared to those diagnosed with VaD. Few and generally mild adverse effects were reported. Ernst and Pittler (1999) postulated that the whole plant extract may exert more powerful effects than single subfractions.

A Cochrane review and its updates on *G. biloba* for cognitive impairment and dementia (Birks & Grimley-Evans, 2002; Birks & Grimley-Evans, 2007; Birks & Grimley-Evans, 2009) described *G. biloba* as safe but that evidence of having benefit for treatment of acquired cognitive impairment, including dementia, was inconsistent and unreliable. Results of 36 trials were included, of which nine were considered to be of an adequate duration, size and standard. A subgroup analysis of AD participants
did not show consistent benefit beyond placebo. These authors recommended that future studies should include assessments of effects of EGb 761® on BPSD (Birks & Grimley Evans, 2009).

Ernst (2005) investigated whether *G. biloba* increases the risk of bleeding by conducting a SR of case reports. It was noted that modern reference texts and reviews had often stated that *G. biloba* may cause bleeding due to its inhibitory effects on platelet aggregation, and that this could lead to important adverse effects in older people (Ernst, 2005). After reviewing 12 case reports it was concluded that the causality of this association was unlikely but that continued monitoring of at risk patients was advised (Ernst, 2005).

A six-year placebo-controlled RCT of 3,069 participants, funded by the US National Center for Complementary and Integrative Health, found that EGb 761® was not effective for lowering the incidence of AD and dementia in older people, or for slowing cognitive decline in participants with MCI (DeKosky et al., 2008). Participants were aged 75 years or over and had normal cognitive function at baseline. Adverse effects and dropouts were similar whether taking EGb 761® or placebo.

More recently, EGb 761® has been tested for its effects on BPSD using NPI. These studies were conducted by the pharmaceutical company which has manufactured a commercial product containing EGb 761® since 1965 (Wagner & Ulricj-Merzenich, 2013). Scripnikov et al. (2007) reported that EGb 761® was superior to placebo for improving NPI scores for depression/dysphoria, anxiety, apathy/indifference, irritability and sleep/night-time behaviour disturbances, in a secondary analysis of a 22 week RCT. Napryeyenko et al. (2009) analysed effects of EGb 761® on NPI scores by dementia type, based on results of the previous RCT by the same group (Napryeyenko et al., 2007). Results indicated that EGb 761® was equally efficacious and safe for AD and VaD. Weinmann et al. (2010) found no consistent results for BPSD in a systematic review and meta-analysis of *G. biloba* for AD, VaD and mixed dementia, which included cognitive, ADL, QoL and adverse effects. Included studies with BPSD outcomes included four which used NPI, three which used the Hamilton Depression Rating Scale (HAM-D), one which used GDS and one which used the Montgomery Asberg Depression Rating Scale (MADRS). Bachinskaya et al. (2011) conducted secondary analyses of findings of the RCT by Ihl et al. (2011). The secondary analyses concluded that EGb 761® was safe and alleviated BPSD in people with mild to moderate dementia, as well as improved wellbeing of caregivers, based on analyses of NPI caregiver distress scores.

A SR of RCTs of EGb 761® for dementia with BPSD concluded that cognitive and behavioural symptoms were significantly improved, with a similar effect size as cholinesterase inhibitors (Ihl, 2013). This review covered four RCTs which had tested EGb 761® for BPSD (Napryeyenko et al.,
Inclusion criteria were probable AD, or possible AD with cardiovascular disease (CVD), or probable VaD in studies by Napryeyenko, Ihl and Herrschaft, and probable AD for the study by Yancheva et al. Two studies were conducted in Ukraine, one in Bulgaria and Herrschaft et al. conducted a multi-centre study in Belarus, Moldova and the Russian Federation. All studies involved the same intervention: 240mg per day Egb 761®, although Yancheva et al., (2009) conducted a three-armed study testing Egb 761® plus donepezil compared to donepezil plus placebo or Egb 761® plus placebo, using a double dummy method. Ihl (2013) concluded that Egb 761® is safe and that compared to placebo, Egb 761® reduced impairment of cognitive functioning, BPSD, ADL and QoL of participants with mild to moderate age-related dementia, reduced caregiver distress, and improved distress due to concurrent neurosensory symptoms associated with old age and dementia, including dizziness and tinnitus. The effect size for improvement of cognitive and behavioural symptoms was concluded to be similar to cholinesterase inhibitors (Ihl, 2013). This review and its four included studies were funded by the same manufacturer (Schwabe Pharmaceuticals). As pointed out by McCarney et al. (2008) studies funded by the pharmaceutical industry often report larger effect sizes than independently funded studies.

Jiang et al. (2013) conducted a SR and meta-analysis of G. biloba extract on cognition and daily functioning in dementia. This review included placebo-controlled RCTs lasting a minimum of 22 weeks. Results of nine studies were pooled. The authors reported several potential biases in the original clinical studies as well as heterogeneity considerable enough to deter the reviewers from drawing firm conclusions about the overall benefits. They did conclude, however, that G. biloba extract may be effective in people under 75 with dementia but that larger, well designed, longer duration RCTs were required. Montes et al. (2015) reviewed experimental and clinical studies of Egb 761® for use in psychiatric disorders, which included depression, anxiety, schizophrenia as well as dementia with comorbid psychiatric disorders. It was concluded that multiple components of Egb 761® act synergistically to combat several pathophysiological mechanisms of psychiatric disorders (Montes et al., 2015).

Von Gunten et al. (2015) conducted a SR and meta-analysis of RCTs of Egb 761® for BPSD. This review included a responder analysis which determined clinically meaningful change scores for ADAS-cog (four points); SKT (three points) and total NPI (four points). Subgroup analyses showed statistically significant superiority of Egb 761® compared to placebo for almost all measures of all three diagnostic groups, which included probable AD, probable VaD and mixed dementia. Improvements were detected in total SKT scores, total NPI scores, NPI caregiver distress scores, ADL
scores and Clinical Global Assessment for all three dementia types, and in DEMQOL-Proxy scores and quality of life scores for probable AD and mixed types, but not for the probable VaD subgroup. Adverse events (AEs) and serious adverse events (SAEs) were reported as 821 AE in 479 participants receiving EGb 761® compared to 998 AE in 488 participants receiving placebo; and 18 SAE in 18 participants receiving EGb 761® compared to 22 SAE in 20 participants receiving placebo (von Gunten et al., 2015). Kasper (2015) conducted a meta-analysis of EGb 761® versus placebo studies using NPI total and NPI-D (caregiver distress due to BPSD) scores. Results indicated EGb 761® was superior to placebo for improvements in both outcomes. A SR and meta-analysis of RCTs investigated G. biloba for MCI and AD (Yang et al., 2016), including 21 trials involving 2,608 participants. G. biloba in addition to conventional medicine was superior to conventional medicine alone for improving MMSE scores in 24-week studies of participants with AD or MCI (Yang et al., 2016). AEs of G. biloba were considered ‘mild’. The authors concluded that results should be interpreted with caution due to inconsistent findings of individual trials and methodological weaknesses of many included studies (Yang et al., 2015). BPSD were not included in this review.

As discussed further in Chapter Four, controlled clinical studies and reviews have reported that EGb 761® can assist with alleviation of BPSD. However, large scale, independent studies are required before strong conclusions may be drawn. EGb 761® does not appear to prevent, delay or reverse NCDs.

2.2.3 Panax ginseng

P. ginseng (ren shen) is one of few herbs that have historically been prescribed as a single herb in China, although it is also often added to multiple-component formulae. In China, P. ginseng has been prescribed for a range of conditions including lung diseases as well as for symptoms analogous to poor cognition and BPSD. The Shen Nong Ben Cao Jing (The Divine Farmer’s Materia Medica) stated that P. ginseng ‘quiets the essence spirit, settles the ethereal and corporeal souls, checks fright palpitations, eliminates evil qi, brightens the eyes, opens the heart and sharpens the wits’ (Yang, 1998). Current use of P. ginseng includes Chronic Obstructive Pulmonary Disease (COPD) as well as improving cognition and memory (Xuedong et al., 2011). A prospective study of COPD and the risk for MCI (Singh et al., 2014) found that people diagnosed with COPD had an increased incidence of developing MCI.

ADAS-noncog has been used to assess effects of P. ginseng on BPSD in at least two small, open-label studies (Heo et al., 2008; Lee et al., 2008). As reviewed and discussed further in Chapter Four, results indicated no significant difference in BPSD between P. ginseng and usual care groups after 12 weeks. Improvements were detected in MMSE and ADAS-cog scores at four weeks and 12 weeks in the P.
ginseng group compared to control, but after discontinuation of the intervention there was no significant difference between groups by the week 24 follow up assessment (Lee et al., 2008). Korean red ginseng showed cognitive benefits which were sustained for two years in AD patients, in a 24-week randomised open label study (Heo et al., 2011). However, BPSD were not assessed. A systematic review and meta-analysis of RCTs testing P. ginseng for AD identified four RCTs involving 259 participants (Wang et al., 2016). The authors found that the included studies had small sample sizes, poor methodological qualities and lack of placebo control. As a result, no conclusions were made about effects of P. ginseng on AD (Wang et al., 2016).

### 2.2.4 Melissa officinalis

A clinical study investigated effects of M. officinalis extract on cognitive symptoms and clinical dementia rating on people with AD in Iran and included presence of agitation as an adverse effect (Akhondzadeh et al., 2003). It was reported that at EoT there was only one participant with agitation in the M. officinalis extract group, compared to six in the placebo group. Based on this study, M. officinalis has been reported to improve cognitive function and reduce agitation in people with mild to moderate AD, in two reviews of HMs for AD (Akhondzadeh et al., 2006; Dos Santos-Neto et al., 2006). M. officinalis administered by aromatherapy was reported to improve agitation in a double-blind, placebo-controlled RCT (Burns et al., 2011).

### 2.2.5 Angelica archangelica

A prospective, open-label study of A. archangelica extract with ferulic acid reportedly led to improved total NPI scores in 19 of 20 participants with FTD or LBD after four weeks (Kimura et al., 2011). Significant reductions in delusions, hallucinations, agitation/aggression, anxiety, apathy, irritability and aberrant motor behaviour scores were detected.

### 2.2.6 Huperzine A

Huperzine A has received substantial research attention for treatment of dementia and NCDs, but effects on BPSD have not yet been tested in a clinical setting, according to results of database searches described in Chapter Four. Huperzine A has been shown to have anti-acetylcholinesterase activities (Hao et al., 2009). A Cochrane review of clinical trials reported that Huperzine A showed no obvious adverse effects for people with AD but that the included trials were of poor methodological quality so no conclusions could be made about reported benefits for dementia (Li et al., 2008). A SR and meta-analysis of RCTs (Yang et al., 2013) concluded that Huperzine A appeared to be an effective drug for people with AD for improvements in ADL, global clinical assessment and cognitive function, but that the included trials were generally of poor methodological quality. Another meta-analysis of placebo-controlled RCTs of Huperzine A for AD and VaD found that Huperzine A could
significantly improve MMSE and ADL scores in AD and VaD subjects and that it was well-tolerated (Xing et al., 2014).

2.2.7 **Actions of HMs in the treatment of dementia and its associated symptoms**

Cummings (2008) argued that a number of exploitable critical steps could offer opportunities for treatment of AD, including intervention at the level of beta-amyloid processing, tau hyperphosphorylation, inflammation, excitotoxicity or apoptosis. Most recent pharmacological research on AD has focussed on generation of beta-amyloid plaques and their clearance from the brain with the aim of prevention of these changes to the brain before symptoms start to occur (Popp & Arlt, 2011; Parker, 2014). This strategy is dependent on new technologies for earlier detection of pathological changes in the hope that this may allow for better therapeutic windows.

Some of the targets of relevance to drug development for cognition and BPSD are the same as those for AD. AChEIs can improve cholinergic transmission. Most of the currently used cognitive enhancer drugs are AChEIs. One approach to drug development has been the identification of novel AChEIs. Huperzine A, *Bacopa monnieri*, *Angelica* species and other plants have shown anti-acetylcholinesterase actions (Orhan, 2012).

Interventions that affect beta-amyloid processing could offer opportunities. Uncaric acid A-D, from *Uncaria rhynchophylla*, was found to inhibit beta-amyloid aggregation (Fujiwara et al., 2011). Compounds derived from other plants used in Chinese medicine, including *Polygala tenuifolia*, have shown beta-amyloid secretase inhibitory activity (Orhan, 2012). Another possibility is targeting the development of neurofibrillary tangles through inhibition of tau protein hyperphosphorylation (Salloway et al., 2008). Herbs that have shown activity include *Salvia miltiorrhiza* and *Panax ginseng* (Calcul et al., 2012).

Other mechanisms that could be targeted include inflammation mediated by microglia and astrocytes (Wang et al., 2014). Holmgren et al. (2014) investigated the role of neuroinflammation in 94 BPSD patients. Analysis of cytokine levels in CSF samples indicated a relationship between neuroinflammation and BPSD in AD (Holmgren et al., 2014).

Serotonergic neurotransmission is known to be reduced in AD (Seitz et al., 2010) which may be related to depression and other BPSD (Martinon-Torres et al., 2004). Geissoschizine methyl ether, found in *U. rhynchophylla*, has high blood-brain barrier permeability and antipsychotic-like properties. It is a serotonin1A receptor agonist and serotonin, antagonist (Ueda et al., 2011).

In the case of plants such as *U. rhynchophylla*, which contain multiple compounds with multiple activities of relevance to AD and BPSD, these compounds may have synergistic effects to provide
protection (de Caires & Steenkamp, 2010). Therefore, approaches to the analysis of the likely mechanisms of these herbs need to take the multiple-compound, multiple-target approach.

Pahnke et al. (2014) reported that a common mechanism may modulate depression and neurodegenerative diseases in the elderly. This team proposed that *Hypericum perforatum* (St John’s Wort) directly activated ABC transporters, which may suggest that treatment of depression in elderly participants with *H. perforatum* may target a mechanism that is involved with depression as well as storage and clearance of beta-amyloid at the blood-brain barrier.

There is some evidence to suggest that anti-inflammatory and anti-oxidant drugs can improve cognitive function and reduce risk of age-related NCDs (Fotuhi et al., 2009). Polyphenolic compounds, especially those found in berries and grape skins, including resveratrol, have received attention mainly for their anti-oxidant and anti-inflammatory effects. There is some evidence to support activities of wine or grape juice polyphenols as protecting against dementia (Howes & Perry, 2011). Green tea (*Camellia sinensis* Kuntze) contains epigallocatechin, a phenolic compound with neuroprotective effects (Howes & Perry, 2011). Noguchi-Shinohara et al. (2014) conducted a population based prospective study of Japanese residents aged over 60 years, to investigate cognitive decline in relation to consumption of green tea, coffee and black tea. No association was found between consumption of black tea or coffee and incidence of NCDs, but consumption of green tea was found to be significantly associated with reduced risk of cognitive decline. Holmgren et al. (2014) investigated the role of neuroinflammation in 94 people with BPSD. Analysis of cytokine levels in CSF samples indicated a relationship between neuroinflammation and BPSD in AD and that anti-inflammatory signalling by Interleukin-10 (IL-10) was beneficial for mental health.

Cognitive disorders are characterised by disrupted interactions of a variety of neurotransmitters and receptors (Levin, 2006). Serotonergic neurotransmission is known to be reduced in AD which may be related to depression and other BPSD (Lanctot, 2001). Reduction of serotonergic function may be related to the genesis of BPSD (Martinon-Torres, 2004). Popp and Arlt (2011) reported that mood disturbances, psychosis, apathy, hyperactivity and disturbance of circadian rhythm may potentially be targeted by psychopharmacological treatment.

As discussed by Hugel et al. (2012), in the investigation of oral HMs for dementia, these firstly require the identification and quantification of bioactive plant metabolites. The degree to which these active compounds become available to the brain also needs to be determined. In addition, consistency and stability of these compounds must be ensured if the product’s efficacy and safety for management of cognitive symptoms and BPSD are to be established.
2.3 Chinese medicine (CM), dementia, NCDs and BPSD

This section details Chinese approaches to treatment of dementia and BPSD using HMs.

2.3.1 Treatment of ‘mental’ disorders with herbs:

Mind-body dualism, the view that mind and body are essentially separate entities (Mehta, 2011) is said to have heavily influenced the field of medicine in the West since at least Descartes’ version from the 17th century (Mehta, 2011). Historically, diseases have also often been believed to be caused by nonmaterial forces such as wrongdoings (Mehta, 2011) according to religious beliefs. There is now strong evidence that cognitive processes have physical bases in the brain (Dehaene et al., 2001), as do emotional processes (Pessoa, 2015).

As pointed out by Willmont (1998), conditions that, until recently, may have been considered purely ‘mental’ disorders in the West, have been treated with the same approach as ‘material’ or ‘physical’ disorders according to traditional medicine in China. Willmont (1998) provided an example by referencing the early English language text, Mental Dysfunction as Treated by Traditional Chinese Medicine, (Cheung et al., 1981). Cheung et al. discussed 11 ‘mental’ disorders including schizophrenia, hysteria, insomnia, forgetfulness, somnolence and others. All were treated as physical disorders although some may have been considered ‘mental’ according to Western thought at that time (Willmont, 1998). For example, Cheung et al. (1981) instructed that forgetfulness was usually due to ‘inadequacy of Heart and Spleen’ and ‘deficiency and degeneration of Kidney essence.’

2.3.2 Contemporary practice of traditional Chinese herbal medicine

There is a growing interest in the investigation of traditional HMs of China to assist with development of contemporary drugs of global relevance (Wagner & Ulrich-Merzenich, 2013).

Historically, CM represents a heterogeneous range of beliefs and practices. The traditional medicine currently practiced in China is partly the result of decisions made in the 1950s to attempt to standardise some of these (Unschuld, 1985). Current traditional use of herbs in China reflects documented observations of therapeutic effects and suitable dosages, as well as the application of clinical reasoning processes according to traditional views about aetiologies and pathogeneses of diseases. CM syndrome differentiation is the typical method used to guide the choice of HM treatment in current practice.

In CM, syndrome differentiation is the analysis of information about a patient, collected by the four main diagnostic procedures of observation, listening and smelling, questioning and palpation. According to the syndrome differentiation reasoning, each patient should receive a personalised prescription based on their presenting signs and symptoms, even if the medical diagnosis is the same.
as another patient. The syndrome is used as the basis for developing a treatment strategy. For example, a patient with a diagnosis of Major NCD due to AD who presented with a pale tongue, weak pulse and apathy as a predominant symptom would receive a different prescription than a patient with Major NCD due to AD who presented with a red tongue, forceful pulse and predominant irritability. The prescription may be modified on each visit, depending on changes to the presenting signs and symptoms. In contemporary practice of Chinese herbal medicine, a clinician may prescribe a personalised herbal formula or standard formula for a specific syndrome, medical diagnosis or symptom. Sometimes a CM syndrome closely resembles a medical diagnosis.

Researchers have conducted clinical trials to test syndrome differentiation with mixed results. Bensoussan et al. (1998) compared individualised Chinese herbal formulae, a standard Chinese herbal formula, or placebo for treatment of irritable bowel syndrome, in a double-blind RCT. Results indicated that both the individualised formulae and the standard formula were moderately superior to placebo but the individualised formulae were not more effective than the standard formula at end of treatment (16 weeks). However, at 14 weeks follow-up, participants in the individualised treatment group had maintained more substantial improvement compared to participants in the standard formula group.

Contemporary CM guidelines are structured according to treatment of a medical diagnosis. Typically there is a description of the medical condition and a section on the aetiologies and pathogeneses according to CM views, followed by a section on syndrome differentiation. Characteristic signs and symptoms for each syndrome are listed, followed by standard herbal formulae recommendations for each of the syndromes. These are often followed by suggestions for modifications to each standard formula according to the presence or absence of other signs and symptoms. The modifications typically involve adding a particular herb or group of herbs if a particular symptom or sign is prominent. Descriptions of signs and symptoms for each syndrome typically include some that are specific to the medical condition, plus others that are common to that syndrome and present in many medical conditions. For example, according to Flaws and Lake (2001) ‘senile dementia with kidney essence insufficiency’ syndrome involves the common dementia symptoms of ‘difficulty thinking’ and ‘impaired memory’ as well as common characteristics of this syndrome, including ‘tinnitus’ and ‘low back and knee soreness and weakness’.

In contemporary practice of CM, a medical condition typically corresponds with one or more possible CM syndromes. Each syndrome will have a recommended key formula which is designed to address the medical diagnosis and the typical symptoms of the syndrome. A herbal formula will be
chosen and modified according to the medical diagnosis, presenting signs and symptoms, as well as constitutional characteristics of the individual.

2.3.3 Syndrome differentiation and treatment of AD

Based on previous standards, expert consensus meetings and results of Delphi method judgements, seven CM syndrome differentiation guidelines for AD were formed in the Chinese Guidelines for the Diagnosis and Treatment of Alzheimer’s Disease (2012). The syndromes are:

1. ‘Sea of Marrow deficiency’
2. ‘Spleen and Kidney deficiency’
3. ‘Qi and Blood deficiency’
4. ‘Turbid Phlegm obstructing the Orifices’
5. ‘Blood stasis obstructing the Brain Collaterals’
6. ‘Heart and Liver Fire’
7. ‘Endogenous Toxins damaging the Brain Collaterals’

Each syndrome is associated with certain signs and symptoms, which are listed in the guidelines. For example, a person with ‘Sea of Marrow deficiency’ might present with memory loss, fatigue, loosening of teeth, hair loss, lower back weakness and pain, difficulty walking, inarticulate speech, poor orientation, inability to do simple arithmetic calculations, and in severe cases agnosia or apraxia (translated in Xue & Lu, 2018). Conversely, a person with ‘Heart and Liver fire’ could present with amnesia, cognitive impairment, a self-centred outlook, irritability, headaches, muscular twitches and red complexion (Xue & Lu, 2018). A treatment principle and key formula are recommended for each syndrome, with analyses to explain how the herbs in the formula are said to address the syndrome. Three descriptions of symptoms correspond to BPSD. Apathy is listed as a symptom of ‘Qi and Blood deficiency,’ as well as ‘Blood stasis obstructing the Brain Collaterals’. Irritability is listed as a symptom of ‘Heart and Liver Fire syndrome’. The treatment principles and analyses of herbs typically involve combinations of herbs acting to address the syndrome, rather than addressing the BPSD. For example, modified Gui pi tang is recommended for ‘Qi and Blood deficiency’. The treatment principle is to ‘tonify Qi, invigorate the Spleen, nourish Blood and tranquilise the mind’. Twelve herbs are included to address these principles: Huang qi is said to ‘tonify Qi and invigorate the Spleen’; long yan rou is said to ‘nourish Blood and tranquilise the mind’; ren shen and bai zhu also ‘tonify Qi and invigorate the Spleen’; dang gui and long yan rou ‘generate Blood’; suan zao ren, fu ling and yuan zhi ‘tranquilise the mind’; mu xiang ‘regulates Qi and invigorates the Spleen’ to prevent the tonifying herbs from causing ‘fullness to the Stomach’; sheng
jiang and da zao ‘regulate the Spleen and Stomach’, and zhi gan cao ‘regulates the Middle-Jiao’ and also ‘moderates effects of the other herbs’.

In addition, three single herb interventions are recommended for treatment of AD. Ren shen porridge is recommended to ‘powerfully tonify Qi, tranquilise the mind and benefit cognitive function’. Ci wu jia powder is recommended to ‘tonify Qi, invigorate the Spleen, tonify the Kidney and calm the mind’. Jiao gu lan powder is recommended to ‘nourish the Heart and tranquilise the mind’.

2.3.4 Chinese medicine and BPSD

A search of key Chinese language Chinese medicine textbooks and monographs was conducted to investigate Chinese medicine theories and approaches to BPSD. This included the standard textbook used in Chinese medicine education, the Teaching Material Internal Medicine of Traditional Chinese Medicine (2012). No exact description of BPSD was found, presumably as BPSD is a relatively new concept globally. According to syndrome differentiation, the Chinese concepts of ‘Blood stasis’, ‘Phlegm’, ‘Liver depression’, ‘Liver Fire’ and ‘deficiency of Zang Fu organs’ could be potential causes of BPSD. In general, limited information was found on BPSD or specific NPI symptoms in NCDs in the modern Chinese texts. However, there were occasional key formulae for AD with modifications for common symptoms including insomnia or anxiety.

Currently in China, clinicians working within the Neurology department at Guangdong Provincial Hospital of Chinese medicine, Guangdong Provincial Academy of Chinese Medical Sciences and The Second Clinical College, Guangzhou University of Chinese Medicine, Guangzhou, refer to Chinese Guidelines for the Diagnosis and Treatment of AD and Other Dementias (2010), Evidence-based Guidelines of Clinical Practice in Chinese Medicine – Internal Medicin’ (2012) and other similar guidelines for recommendations on treatment of NCDs. BPSD may be considered as secondary symptoms. These guidelines provide instructions for prescribing ‘Western’ pharmacological interventions for management of BPSD, as well as occasional descriptions about CM conjecture relating to aetiologies and pathogeneses of BPSD.

2.3.4.1 Chinese medicine strategies for choosing herbs for BPSD

A convenience sample of four modern English language text books and clinical manuals of CM were searched and evaluated for entries of HMs for BPSD. The texts were Traditional Chinese Treatment for Senile Diseases (Geng et al., 1997); Chinese Medical Psychiatry (Flaws & Lake, 2001); Chinese Herbal Therapy: A Guide to its Principles and Practice (Kuwaki, 1990); and Mental Dysfunction as Treated by Traditional Chinese Medicine, (Cheung et al., 1981).
Strategies for choosing herbs for BPSD were investigated. No entries were identified of herbs recommended to be taken individually for treatment of symptoms that correspond to contemporary definitions of specific BPSD.

Three strategies were identified for recommending herbs for treatment of BPSD, as follows.

1. The text describes a combination of herbs in a formula. The formula is recommended to treat a CM syndrome, described as a combination of symptoms. One or more symptom is analogous to one or more BPSD. This was the most common finding. For example, the main symptoms of the ‘Qi and Blood deficiency pattern’ (Flaws & Lake, 2001) included ‘insomnia and profuse dreams’, which may correspond to NPI-K: Sleep and Night-time Behaviour Disorders; as well as ‘decreased eating and drinking’ which may correspond to NPI-L: Appetite/Eating changes. The recommended formula for this syndrome is *Gui pi tang*, with 13 ingredients. The analysis of this formula states that four of the herbs, *long yan rou, dang gui, da zao* and *yuan zhi* all ‘quiet the spirit’. This may be analogous to having a sedative effect. There is no direct description of a specific herb treating ‘decreased eating and drinking’, although the analysis of the overall formula may suggest that this symptom is addressed by the combination of ingredients working together, yet this is not explicitly stated. For example, *huang qi, dang shen, bai zhu, fu ling* and *zhi gan cao* all are said to ‘fortify the spleen and boost the qi’ which typically would treat fullness and poor appetite associated with ‘Spleen deficiency’, while *mu xiang* ‘rectifies the qi and harmonises the Liver and Spleen’, which may correspond to treatment of poor appetite, nausea and distension in the epigastrium and abdomen. In addition, *da zao* and *sheng jiang* are said to ‘help supplement the qi’ which suggests these herbs assist with treatment of poor appetite caused by ‘qi deficiency’, as well as other symptoms. Similarly, Kuwaki (1990) recommended that *Gui pi tang* is indicated for treatment of ‘insomnia, memory loss, anaemia and various conditions of bleeding in individuals with constitutions manifesting gastrointestinal weakness’.

2. The text recommends modifications to key formulae according to additional symptoms that correspond to BPSD. Geng et al. (1997) contains a chapter on ‘senile dementia’ which describes nine common syndromes. The descriptions include symptoms analogous to some BPSD, as well as other common descriptions used in CM syndrome differentiation such as appearance of the tongue and characteristics of the radial artery pulse. The modifications also include descriptions analogous to specific BPSD, with recommendations of specific changes to the formula if a particular symptom is present. For example, in ‘senile dementia
with deficiency of Heart and Spleen’, if ‘melancholia and crying’ are prominent, *he huan hua* and/or *mei gui hua* may be added to the key formula of modified *Bao yuan tang*.

Flaws and Lake (2001) described eight syndromes of ‘senile dementia’, their corresponding treatment principles, key formulae and analyses or explanations of each herb in each formula. As with Geng et al. (1997), there were specific recommendations of herbs to be added to a key formula for symptoms corresponding to individual BPSD. For example, under the category of ‘yin vacuity-internal heat pattern’, the addition of *suan zao ren* and *bai zi ren* is recommended if insomnia is prominent, and the addition of *long gu*, *mu li* and *ci shi* is recommended if agitation and restlessness are prominent. Kuwaki (1990) recommended the addition of *chai hu* and *zhi zi* to *Gui pi tang* if there is ‘heat in the upper body’ which may manifest as ‘fidgeting’ (Kuwaki, 1990). ‘Fidgeting’ may correspond with NPI-J: Aberrant motor behaviour.

3. The term does not directly correspond to BPSD. It is unclear whether an interpretation of BPSD should be inferred as the term is ambiguous or could correspond to multiple symptoms. For example, under the ‘Yin Vacuity-Internal Heat’ syndrome (Flaws & Lake, 2001), it was recommended to add *di long*, *tian ma* and *gou teng* ‘if yin vacuity and heat engender internally stirring of wind’. The clinical manifestations of ‘internal wind’ may correspond to BPSD such as aberrant motor activity, but can also refer to dizziness, vertigo, numbness, convulsions, unconsciousness, opisthotonos, hemiplegia and deviation of the mouth (Maciocia & Su, 2005) which are not BPSD.

2.4 **Kampo**

CM is understood to have been introduced to Japan along with Buddhism during the Sui (581 – 618 CE) and Tang (618 – 907 CE) dynasties (Kuwaki, 1990). ‘Japanised Chinese herbal medicine’ is understood to have been largely influenced by the Dosan School of Medicine during the Ming dynasty (1368 – 1644 CE) (Muromachi period in Japan: circa 1336 – 1573 CE) (Kuwaki, 1990). This Japanese style of Chinese herbal medicine based diagnoses and treatments on the Chinese texts *Shang Han Lun* and *Jin Gui Yao Lue* by Zhang Zhong Jing (150 – 219 CE) (Kuwaki, 1990). The Edo period of Japan (1603 – 1868 CE) was characterised by isolationist foreign policies as well as economic prosperity. During this period CM continued to develop in China into the late Ming dynasty (1368 – 1644) and early Qing dynasty (1644 – 1912), while the Japanised Chinese herbal medicine, or kampo, developed independently and concurrently in Japan, as communication of medical texts and trade of herbs between China and Japan were prohibited (Kuwaki, 1990).
Kampo was the predominant form of medicine in Japan for over 1500 years, until after the Meiji Restoration in 1868, which led to modernisation in Japan, including the implementation of the German medical system to replace kampo from the official Japanese medical education system (Terasawa, 2004). During the Meiji period (1868 – 1912) the practice of kampo declined and the legal status of kampo practitioners as medical doctors was removed in 1883 (Shibata, 1997). However, in the twentieth century, research of kampo formulae as potential sources of modern drugs became popular at Japanese universities (Shibata, 1997).

Terasawa (2004) put forward that kampo was similar to the Chinese herbal medicine practiced in China until approximately 300 years ago. During the Edo period (1603 – 1867) a widespread nationalistic movement influenced Japanese scholars of the time to reject the ‘then authoritative neo-Confucian interpretation’ of Confucian philosophy and apply a more positivistic approach to herbal prescriptions (Terasawa, 2004).

Kampo products have been approved for coverage by the Japanese national health insurance since the 1970s (Shibata, 1997). Extracts of these herbal formulae from the classical texts are regulated as pharmaceutical preparations in Japan. A substantial amount of research on HMs for BPSD has been conducted in Japan and typically involves these kampo preparations. Since at least the 1990s, Japanese researchers have investigated use of kampo formulae for chronic, degenerative conditions, including age-related conditions (Shibata, 1997). As it is often agreed that standardised kampo formulae cause few adverse effects, they have been an area of research interest for long-term use in older people who may be unable to tolerate some pharmacotherapies (Shibata, 1997). Contemporary clinical studies of kampo typically focus on prescribing standardised herbal formulae for specific medical diagnoses. For example, clinical studies of HMs for BPSD, as reviewed below and in Chapter Four, involved recruitment of participants with BPSD. Details of Chinese medicine syndrome differentiation were not reported in any included Japanese study.

2.5 Considerations when prescribing HMs

Not all herbs are acceptable in all countries/regions. Some of the herbs identified in the literature may no longer be in use, may be toxic, or be prohibited or restricted under the provisions of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES). Researchers and consumers must obey the relevant legal regulations. In Australia these include Guidelines for safe Chinese herbal medicine practice set by the Chinese Medicine Board of Australia and Standard for the Uniform Scheduling of Drugs and Poisons (SUSDP) set by the States or Commonwealth.
CHAPTER THREE  METHODOLOGY FOR THE SYSTEMATIC REVIEW OF CLINICAL TRIALS AND THE ANALYSIS OF CLASSICAL CHINESE MEDICAL LITERATURE

3.1  Introduction

This project aimed to summarise and critically evaluate the available evidence from contemporary clinical trial research literature and the classical Chinese medical literature, regarding the effects of HMs for the management of BPSD. This chapter details general methods for conducting the first two studies:

1. a systematic review (SR) and meta-analyses of clinical trials;
2. text mining and analyses of classical Chinese medical literature

3.2  SR of clinical trials of HMs for BPSD

A SR and meta-analysis of clinical trials testing HMs for BPSD was conducted with methods in accordance with the *Cochrane Handbook of Systematic Reviews for Interventions* (Cochrane Handbook) (Higgins & Greene, 2011).

The protocol of this review was registered with the PROSPERO International prospective register of systematic reviews (registration number: PROSPERO 2015:CRD42015020329).

3.2.1  Search strategies and identification of studies

This study involved searches of major English, Chinese and Japanese biomedical databases. Wu et al. (2013) argued that SRs of Chinese medicine should include searches of non-English biomedical databases, as failure to do so may cause selection bias due to the possibility of missing relevant studies. Cohen et al. (2015) reported that the five major Chinese biomedical databases index approximately 2,500 journals and that less than six percent of these are indexed in Medline. Cohen et al. (2015) recommended collaborative efforts to better incorporate Chinese resources in systematic reviews. Including a search of a Japanese literature database has been recommended for topics investigated in Japanese research studies (Kojimahara et al., 2015). Ichushi-Web, the web version of *Igaku chuo zasshi*, is a database of Japanese biomedical literature from the past 110 years. Its number of citations exceeds nine million (Kojimahara et al., 2015). The Japan Science and Technology Information Aggregator, Electronic (J-STAGE), is an electronic database of Japanese scholarly journals developed by the Japan Science and Technology Corporation in 1999 (JST Information, 2016).
3.2.1.1 **Searches of English language databases**

An online search of five English language databases was undertaken. This search involved a broad scope including Chinese medicine and herbal medicine for NCDs. The databases were PubMed, Embase, Allied and Complementary Medicine Database (AMED), Cochrane Register of Controlled Trials, and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The following search query was used for searching for clinical studies testing effects of HMs for NCDs:

(Traditional Chinese Medicine OR Chinese Traditional Medicine OR Chinese Herbal Drugs OR Chinese Drugs, Plant OR Medicine, Traditional OR Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR Medicine, Kampo OR Kanpo OR TCM OR Medicine, Ayurvedic OR Phytotherapy OR Herbology OR Plants, Medicinal OR Plant Preparation OR Plant Extract OR Plants, Medicine OR Materia Medica OR Single Prescription OR Chinese Medicine Herb OR Herbal Medicine OR Herbs intervention) AND (dementia OR dement* OR cognitive OR neurocognitive OR BPSD OR NCD OR amnestic OR amnesia OR memory OR AAMI OR Alzheimer OR beta-amyloid OR "amyloid beta" OR CADASIL OR Chmp2b OR MCI OR DLB OR lewy bod* OR "pick disease" OR "pick's disease" OR "pick presenile dementia" OR "picks disease" OR SVD OR FTDP-17).

3.2.1.2 **Searches of Chinese language databases**

A similar search was conducted by collaborators at Guangzhou University of Traditional Chinese Medicine, using Chinese language databases. Chinese databases included The Chinese Biomedical database (CBM), VIP Chinese Science and Technique Journals Database, China National Knowledge Infrastructure (CNKI), Chinese Medical Current Content (CMCC) and Wanfang database (Chinese medicine premier).

3.2.1.3 **Searches of Japanese language databases**

Searches were conducted of J-STAGE and Ichushi web.

The J-Stage search query was as follows:

Full Text: 漢方 AND 痴呆 OR Full Text: 漢方 AND 認知症

3.2.1.4 **Additional searches:**

Clinical trial registries (UMIN and ALOIS) and reference lists of relevant papers were searched. Pharmaceutical companies (Schwabe Pharmaceuticals; Tsumura Japan) and corresponding authors were contacted for unpublished data.
3.2.2 Criteria for considering studies for inclusion

Titles and abstracts were screened independently and full texts of potentially relevant papers obtained. The PICOS process (Participant, Intervention, Comparator, Outcome, Study design) was followed to determine studies for inclusion, as follows:

3.2.2.1 Participants

People diagnosed with probable dementia or neurocognitive disorders (NCDs) were included. No restriction was placed on stage or severity so mild NCDs consistent with early stage dementia or MCI were included. People diagnosed with cognitive impairment due to depression, delirium, disorders with acute onset or reversible conditions were excluded.

3.2.2.2 Intervention(s)

Interventions composed of HMs (defined as medicines composed of natural products of plant, animal or mineral origin) administered orally were included. Interventions comprised single or multiple natural products. Synthetic compounds or isolated chemical compounds, homoeopathic preparations, foods and nutritional supplements were excluded. Aromatherapy studies were excluded.

3.2.2.3 Comparator(s)/ control

Included studies compared HMs versus placebo, no treatment or specific pharmacological treatment. Integrative medicine interventions involving HMs plus pharmacotherapy versus the same pharmacotherapy were included. Studies that compared a HM with a non-pharmacological therapy or a different HM were excluded.

3.2.2.4 Outcomes

Included studies assessed changes in BPSD using measures designed specifically for this purpose; e.g. the Neuropsychiatric Inventory (NPI), Alzheimer’s disease Assessment Scale-noncognitive section (ADAS-noncog), Cohen-Mansfield Agitation Inventory (CMAI) and the Behavioural Pathology in Alzheimer’s Disease Scale (BEHAVE-AD). Studies which used outcome measures designed to assess mood and behavioural changes in cognitively intact people, e.g. the Geriatric Depression Scale and the Hamilton Dementia Rating Scale, were excluded.

Secondary outcomes included those measuring cognitive function as assessed by the Mini-Mental State Examination (MMSE), ADAS-cognitive section (ADAS-cog), Short Cognitive Performance Test (SKT) or other internationally recognised scales. Secondary outcomes also included caregiver distress as measured by NPI-D caregiver distress due to neuropsychiatric symptoms scale, Zarit Caregiver...
Burden Inventory (ZBI), Zung self-rating depression scale; Activities of Daily Living as measured by Barthel Index (BI) and Functional Independence Measure (FIM).

Secondary outcomes also included safety and tolerability data including: adverse effects and adverse events (AEs) associated with HM interventions and control interventions, and AEs of HMs combined with or versus pharmacotherapies (PTs); plus total numbers of dropouts due to any cause.

3.2.2.5 Study design

Prospective, randomised and non-randomised controlled trials, including crossover and open-label trials were included in the quantitative synthesis.

Evaluation of non-randomised studies was conducted according to guidelines in the Cochrane Handbook, Chapter 13 (Higgins & Green, 2013). Causal inferences of efficacy were primarily made from results of randomised studies. Safety, risk of associated AEs and effects of long term use were to be informed by data from non-randomised studies. The rationale for including non-randomised studies, based on the Cochrane Handbook Chapter 13.1.2, was:

- to examine the case for designing and conducting a RCT on HM for BPSD, by providing an explicit evaluation of the weaknesses of available NRS. The findings may help to inform a suitable RCT design.
- to examine the evidence of effects (benefit or harm) that may not have been adequately addressed in the existing randomised trials, including long-term and rare outcomes, or unexpected outcomes.

As advised in the Cochrane Handbook, Chapter 13, caution must be taken when including NRS, as ‘adding non-randomised to randomised evidence may change an imprecise but unbiased estimate to a precise but biased estimate, i.e. an exchange of undesirable uncertainty for unacceptable error.’

The review primarily used data from RCTs when drawing any potential generalisations about causal effects, but results of NRS were included in case of additional findings of importance.

3.2.3 Data extraction (selection and coding)

For studies that satisfied the inclusion criteria, data from English and Japanese and some Chinese studies were extracted into an Excel spreadsheet by AJH, with assistance from George Shengxi Zhang, Jason Jingjie Yu, Kevin Kaiyi Wang, and online software for translating simplified Chinese to English. Data from other Chinese studies were extracted by Lin Dong, Mei Feng or George Shengxi Zhang. Extracted data included: author(s), publication year, country, trial design, duration, follow-up period(s), diagnosis at baseline, number of participants, number of dropouts, age of participants,
details of herbal medicine intervention, baseline, end of treatment, interim and end of follow-up scores of outcome measures, AEs and dropouts. Data were checked by a second reviewer (Lin Dong) and any discrepancies were resolved by discussion with mediation by a third reviewer (Brian May). Attempts were made to contact corresponding authors regarding missing data or other clarification. If attempts to obtain missing data were unsuccessful, scores were approximated from graphs or change scores where possible.

3.2.3.1 Approximation of data from graphs
Data that were represented clearly in bar or line graphs were obtained by enlarging the graph to a scale where scores could be measured with a scale ruler. If the graph was unclear, inaccurate when compared to reported scores, or difficult to obtain measurements from, for example if the original graph size was very small, data were excluded.

3.2.3.2 Approximation of data from change scores
Where baseline and change mean (standard deviation) scores were reported, the end of treatment score was calculated by adding or subtracting the mean change score from the mean baseline score, then substituting the baseline standard deviation as the end of treatment standard deviation.

3.2.4 Risk of bias (quality) assessment
The Cochrane Collaboration’s tool for assessing risk of bias (RoB) in randomised trials was used independently by two investigators (AJH, Lin Dong). George Shengxi Zhang assisted with Chinese language RoB assessments and Brian May with Japanese RoB assessments. An assessment of high, low or unclear risk of bias was recorded for random sequence generation, allocation concealment, blinding of participants, blinding of caregivers, blinding of personnel, blinding of outcome assessors, incomplete outcome data and selective outcome reporting. Evaluation of non-randomised studies was conducted using the same tool as the randomised studies, as well as according to guidelines in the Cochrane Handbook, Chapter 13. Disagreements were resolved by a third reviewer (Yuan Ming Di). The use of A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI) (Sterne et al., 2014) was initially considered, but it was decided not to use this new tool as it was still in its initial version and likely to undergo updating. In addition, only one non-randomised study was included and it did not seem that any benefit would be likely from the assessment of one study with the new tool, as its results were analysed and presented separately to the randomised studies.
3.2.5 *Data analyses and syntheses*

3.2.5.1 *Meta-analyses using Review Manager 5.3*

Review Manager 5.3 was used to analyse data, with methods in accord with the Cochrane Handbook. Meta-analyses were based on published aggregate data and additional data obtained from corresponding authors. Mean differences (MD) or standardised mean differences (SMD) were calculated for continuous data with 95% confidence intervals (CI). A Random effects model (RE) was applied.

3.2.5.1.1 Grouping of included studies

Studies were divided into three main categories:

1. HM versus inactive controls;
2. HM versus active control interventions (conventional pharmacotherapies);
3. HM plus pharmacotherapy versus the same pharmacotherapy.

Within these main groups, data were pooled firstly by outcome measure, with subgroups for different comparators. When studies employed three arms, these arms were allocated to the relevant groups. Randomised and non-randomised trials were analysed separately.

3.2.5.1.2 Testing for publication bias

Possibility of publication bias was to be tested using funnel plots. Where appropriate, Egger’s test was to be conducted using STATA statistical software to determine whether funnel plots are symmetrical. However, all groups had less than ten studies, so were not suitable for analyses using funnel plots.

3.2.5.1.3 Analyses of data at multiple time points

Differences between and within groups at the end of the treatment phase and at any reported interim and follow-up were investigated. Where possible, changes in scores at follow-up time measurement points were to be investigated using meta-analyses, using the same methods as for end of treatment (EoT) analyses, described above.

3.2.5.1.4 Four comparisons:

Meta-analyses were conducted of four comparisons:

1. Treatment versus Control baseline scores;
2. Treatment versus Control EoT scores;
3. Treatment baseline versus EoT scores; and
4. Control baseline versus EoT scores.
If a baseline imbalance was found, this was taken into consideration when interpreting EoT score comparisons. Similarly, effect size or lack thereof in the baseline versus EoT comparisons were considered when interpreting results.

For non-randomised studies, baseline characteristics and scores in the treatment and control groups were first checked for baseline imbalance. If there was no significant baseline imbalance, study data were analysed.

3.2.5.2 Strategies for specific types of data analyses

Strategies for specific types of data analyses are shown in this section:

3.2.5.2.1 Scores of zero (0)

Studies with a score of zero (0) or with a standard deviation of zero (0) were not included in analysis of that outcome of continuous data but were taken into consideration when interpreting results. The score of zero (0) was not changed to a score of 0.5, although this has been recommended by the Cochrane Collaboration (Higgins, 2011).

3.2.5.2.2 Analyses of three-armed studies

Each arm was analysed independently and data were not merged. For example, Teranishi et al. (2013) compared Yokukansan with fluvoxamine and risperidone in a three-armed head-to-head comparative study. The fluvoxamine versus Yokukansan comparison was analysed separately to the risperidone versus Yokukansan comparison, rather than merging the fluvoxamine and risperidone data. The fluvoxamine and risperidone groups were not pooled as they are different types of drugs with different mechanisms and different expected therapeutic outcomes. When pooling data the N value of the comparator analysed twice (the Yokukansan group data) was halved to avoid inflating N.

Similarly, Heo et al. (2008) conducted a three-armed study comparing low dose $P. ginseng$ (4.5g per day), high dose $P. ginseng$ (9g per day) and no ginseng in addition to continuing dementia medications unchanged. As it was unclear whether the low dose was considered a placebo or a therapeutic dose, scores were not merged.

3.2.5.2.3 Analyses of cross-over studies

Cross-over study data were included for time period I and excluded for time period II. This was to avoid the possibility of a carry-over effect in the group which had taken HM in time period I.
3.2.5.2.4 Analyses of subgroups or subsets
Explorations of subgroups included: BPSD domain, severity of symptoms at baseline, trial duration, type of comparator, ingredients of herbal intervention, and methodological factors (whether the study was randomised).

3.2.5.2.5 Analyses of numbers of participants with NPI domain symptoms at baseline versus total numbers of participants
Some studies reported numbers of participants with each NPI domain symptom present at baseline. For studies which did not report these numbers, e.g. Iwasaki et al. (2005), it was assumed that all participants had all domain symptoms present at baseline. For studies which did report these numbers, e.g. Mizukami et al. (2009), this was considered a subgroup. These analyses were compared with analyses which used total numbers of participants.

3.2.6 Qualitative synthesis
Qualitative and non-numerical outcomes were included in qualitative synthesis.

3.2.7 Methods for investigation of clinically meaningful change of total NPI scores
Investigations of baseline versus end of treatment effect sizes were undertaken to judge effect size and clinically meaningful change of total NPI scores. Methods for these investigations are shown in Chapter Four.

3.3 Data mining and analyses of classical Chinese medical literature
The methods used in this study are adapted from methods devised by May (2009) and May et al. (2012a, 2013, 2014) for investigation of classical Chinese medical literature for dementia and related disorders.

3.3.1 Search strategies
Searches of classical Chinese medical literature were previously conducted using the database software Zhong Hua Yi Dian (ZHYD) (Encyclopaedia of Traditional Chinese Medicine). ZHYD is a CD of the full texts of 1,000 classical medical books spanning 2000 years of medical history from the second century BCE until the early 20th century. It is the largest single collection of Chinese medical books and is representative of the breadth and scope of the pre-modern Chinese medical literature (May et al., 2012b, 2012c).

Searches were conducted for terms analogous to memory impairment, cognitive decline and dementia. These terms included chi dai 痴呆 (dementia), jian wang 健忘 (forgetfulness) and others.
These searches resulted in a large dataset of citations that referred to descriptions of age-related memory loss and provided HM interventions used to treat these symptoms. Results of these searches were analysed using SPSS. The dataset was analysed to investigate records of terms analogous to the 12 symptom domains of the NPI.

3.3.2 Identification of search terms related to the 12 NPI domains

Search terms for the NPI domains were identified informed by the Chinese version of the NPI and a workshop held at RMIT involving four native Chinese-speaking and three native English speaking Chinese medicine research students. The main terms chosen were:

NPI-A: Delusions: *wang xiang* 妄想
NPI-B: Hallucinations: *huan jue* 幻覺
NPI-C: Agitation/aggression: *fan zao/gong xing wei* 煩躁/攻擊行為
NPI-D: Depression/dysphoria: *yi yu/qing xu di luo* 抑鬱/情緒低落
NPI-E: Anxiety: *jiao lu* 焦慮
NPI-F: Euphoria: *qing xu gao zhang/xin kuai* 情緒高漲/欣快
NPI-G: Apathy/indifference: *qing xu dan mo/leng mo* 情緒淡漠/冷漠
NPI-H: Disinhibition: *yi zhi jie chu* 抑制解除
NPI-I: Irritability/lability: *yi nu/qing xu bo dong* 易怒/情緒波動
NPI-J: Aberrant motor activity: *yi chang de dong zuo xing wei* 異常的動作行為
NPI-K: Sleep and night-time behaviour disturbances: *shui mian* 睡眠
NPI-L: Appetite and eating behaviour disturbances: *shi yu huo yin shi shi tiao* 食慾或飲食失調

Chinese terms found in the classical literature that were synonymous with the above modern Chinese terms were identified and scored according to the appropriate NPI category.

3.3.3 Data extraction and management

Data were extracted to Excel for the books, publication year, book type (including formulary, *Materia Medica*, and others), symptoms and signs, formula, and formula ingredients.

3.3.4 Data coding and scoring system

Data were coded for the search terms, cognitive symptoms and BPSD symptoms (based on the above NPI categories) by Su-yueh Chang and Iris Wenyu Zhou with mediation by Brian May, according to the methods used in May et al. (2012), May et al. (2014) and May et al. (2016).

3.3.5 Data analyses

Data were analysed using SPSS to identify specified subgroups of citations and identify which herbs and formulae showed histories of use for BPSD.

Proposed investigations included:

1) Frequencies of terms analogous to BPSD vocabulary
2) Herbs most frequently recommended for BPSD
3) Changes in use over time

4) Comparison of the descriptions of dementia compared to contemporary definitions

5) Comparison of frequencies of herbs mentioned in the classical literature with herbs used in the clinical trials included in Chapter Four
CHAPTER FOUR  HERBAL MEDICINE FOR MANAGEMENT OF THE BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

4.1 Abstract
Management of the behavioural and psychological symptoms of dementia (BPSD) remains a challenge worldwide. Herbal medicines (HMs) may play a role in the development of new interventions. To determine effects of HMs for BPSD management, meta-analysis was conducted of 31 controlled trials (3,613 participants). Frequently tested HMs were the Ginkgo biloba leaf extract EGb 761® (seven studies) and the multi-ingredient formula Yokukansan (eight studies). Sixteen studies tested other HMs. Improvements were detected in Neuropsychiatric Inventory scores in EGb 761® groups compared to placebo (MD -3.46 [-5.94, -0.98]; I²=93%; n=1,757) and Yokukansan groups compared to no treatment (SMD -0.53 [-0.86, -0.21]; I²=0%; n=150). Cognitive scores were improved in EGb 761® groups while Yokukansan did not appear to affect cognitive function. Of the other HMs, there were improvements in BPSD and cognitive outcomes in two of four placebo-controlled studies. EGb 761® and Yokukansan appeared safe and well-tolerated. Adverse effects and dropouts were not reported consistently for the other HMs. Weaknesses of these included short durations, small sample sizes, lack of blinding and other risks of bias. Well-designed studies are needed to further investigate the reported effects of these interventions on BPSD.

4.2 Introduction
Other systematic reviews of HMs for AD and other age-related Neurocognitive disorders (NCDs) have focussed on cognitive function and ADL outcomes (Fu & Li, 2011; May et al., 2009a; May et al., 2009b; Yang et al., 2016; Wang et al., 2016; Zeng et al., 2015; Brondino et al., 2014; Dong et al., 2016; Xu et al., 2018). No reviews were found that encompassed a broad scope of HMs specifically in relation to effects on BPSD.

This systematic review aims to: 1. determine which, if any, HMs are efficacious and safe for BPSD, without adversely affecting cognitive symptoms; 2. investigate the effects of these HMs on individual symptoms of the NPI; and 3. identify HMs which show promise for further investigation.

Previous researchers have identified that the reporting quality of SRs of some complementary medicines was in need of improvement, as it did not always meet the standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liu et al., 2014). The present review was conducted in accordance with this statement.
4.3 Methods

A systematic review and meta-analysis of clinical trials testing HMs for management of BPSD was conducted with methods as detailed in Chapter Three.

Three groups of search terms were used: 1. Disorder: dementia and related terms; 2. Intervention: herbal medicine, Chinese medicine and related terms; and 3. Study type: clinical trial and related terms (Table 4.1).

Table 4.1: Search terms used for PubMed for identifying clinical trials and reviews of herbal medicines for BPSD.

<table>
<thead>
<tr>
<th>Category</th>
<th>Search terms</th>
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<tbody>
<tr>
<td>Condition</td>
<td>Dementia OR dement* OR cognitive OR neurocognitive OR BPSD OR NCD OR amnestic OR amnesia OR memory OR AAMI OR Alzheimer OR beta-amyloid OR &quot;amyloid beta&quot; OR CADASIL OR Chmp2b OR MCI OR DLB OR lewy bod* OR &quot;pick disease&quot; OR &quot;pick's disease&quot; OR &quot;pick presenile dementia&quot; OR &quot;picks disease&quot; OR SVD OR FTDP-17</td>
</tr>
<tr>
<td>Intervention</td>
<td>HM Plant OR Medicine, Traditional OR Ethnopharmacology OR Ethnomedicine OR Ethnobotany OR Medicine, Kampo OR Kanpo OR TCM OR Medicine, Ayurvedic OR Phytotherapy OR Herbology OR Plants, Medicinal OR Plant Preparation OR Plant Extract OR Plants, Medicine OR Materia Medica OR Single Prescription OR Traditional Chinese Medicine OR Chinese Traditional Medicine OR Chinese Herbal Drugs OR Chinese Drugs OR Chinese Medicine Herb OR Herbal Medicine OR Herbs</td>
</tr>
<tr>
<td>Study design</td>
<td>Review &quot;Systematic&quot;[sb]</td>
</tr>
<tr>
<td>Other studies</td>
<td>&quot;cohort studies&quot;[mesh] OR &quot;case-control studies&quot;[mesh] OR &quot;comparative study&quot;[pt] OR &quot;risk factors&quot;[mesh] OR &quot;cohort&quot;[tw] OR &quot;compared&quot;[tw] OR &quot;groups&quot;[tw] OR &quot;case control&quot;[tw] OR &quot;multivariate&quot;[tw] OR &quot;case series&quot;[tw]</td>
</tr>
</tbody>
</table>

AAMI: age associated memory impairment; BPSD: behavioural and psychological symptoms of dementia; CCT: Controlled clinical trial; CM: Chinese medicine; DLB: Lewy body dementia; FTDP-17: frontotemporal dementia P-17; MCI: mild cognitive impairment; NCD: Neurocognitive disorder; RCT: randomised controlled trial; SVD: subcortical vascular dementia; TCM: traditional Chinese medicine

Results were downloaded to Endnote libraries and combined. Clinical trial registries and reference lists of review articles and clinical studies were searched for additional papers. The following clinical trial registries were searched: 1. University hospital Medical Information Network (UMIN) Center; 2. ALOIS (The Cochrane Dementia and Cognitive Improvement Group register of dementia studies).

We included controlled studies that tested effects of HMs on participants diagnosed with probable dementia or NCDs, including early stage NCDs. Studies could be randomised or not randomised. Included HM interventions were orally administered herbal and traditional medicines. Forms could include extracts or mixtures of single or multiple substances. Studies testing single purified compounds and products for injection were excluded.
Control interventions included placebo, usual care, no treatment or pharmacotherapy. Integrative treatments involving HM plus pharmacotherapy versus the same pharmacotherapy were also included. Studies that compared HM with a non-pharmacotherapy or a different HM were excluded. Included studies assessed changes in BPSD using at least one multi-domain evaluation scale designed for assessing mood and behavioural changes in people with dementia; i.e. NPI, ADAS-noncog, or BEHAVE-AD. Secondary outcomes included measures of cognitive function as assessed by the MMSE, ADAS-cog or SKT; plus safety and tolerability assessed by numbers of reported adverse events (AEs) and dropouts.

Data were extracted using pre-designed data collection forms. Pharmaceutical companies and corresponding authors were contacted for missing data. Risk of bias was assessed by two reviewers independently (AJ Hyde and L Dong) with assistance from GS Zhang for Chinese and BH May for Japanese language studies. Mediation was by YM Di.

Meta-analysis was conducted using RevMan 5.3, based on published aggregate data and additional data obtained from corresponding authors. All studies were tested for baseline imbalance by generating forest plots of baseline data. Randomised and non-randomised studies were analysed separately. Mean Differences (MD) were calculated for continuous data with 95% confidence intervals (CI), except for meta-analyses that combined data for the NPI-10 and the NPI-12. For these, Standardised Mean Differences (SMD) were calculated. Data for NPI-Q were analysed separately. Random effects (RE) models were adopted due to the likelihood of heterogeneity between studies.

4.4 Results
Searches of databases and reference lists located 22,203 potentially relevant references. Searches of clinical trial registries did not result in any additional studies. Following screening and full text assessment, 31 studies were included (see Figure 4.1).
Records identified through Chinese database searches (n = 12,989)

Records identified through English database searches (n = 21,373)

Records identified through Japanese database searches (n = 1,004)

Records identified through other sources (n = 4)

Records after duplicates removed (n = 22,203)

Not a clinical study of HM for NCDs in humans (n = 19,914)

Records after screening titles and abstracts (n = 2,289)

Excluded based on full text: Not a prospective clinical study of HM related to BPSD (n = 2,199)

Clinical studies related to HM for BPSD (n = 90)

Excluded with reasons (n = 59)
- Uncontrolled study (n = 22)
- Duplicate literature (n = 5)
- Not specified outcomes (n = 30)
- No usable data (n = 2)

Studies included in quantitative synthesis (meta-analysis) (n = 31)

Figure 4.1: Flow diagram of search and selection process for studies of herbal medicines for BPSD

HM: herbal medicine; NCDs: Neurocognitive disorders

Studies were conducted in China (10), Japan (10), South Korea (3), Ukraine (2), Germany (1), United States (1), Bulgaria (2) Russian Federation (1) and a multi-centre study was conducted in Belarus, Moldova and the Russian Federation. These included 3,613 participants with 1,832 in treatment groups and 1,781 in control groups (see Table 4.2).

Table 4.2: Characteristics of included studies of herbal medicine for BPSD

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study name; location; language of publication; duration</th>
<th>Diagnosis for inclusion; No. participants at baseline</th>
<th>Treatment (T)</th>
<th>Control (C)</th>
<th>Outcome measures included in this review</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bi 2011; China; English; 12wks</td>
<td>AD; 25</td>
<td>Fu zhi san (FZS) 10g daily</td>
<td>Placebo 10g daily</td>
<td>Total NPI, ADAS-cog</td>
</tr>
<tr>
<td>2</td>
<td>Chen 2013; China; Chinese; 4wks</td>
<td>AD or VaD; 60</td>
<td>Nao ling ke li (NLKL) 1 dose 3 times daily</td>
<td>Risperidone NS</td>
<td>BEHAVE-AD</td>
</tr>
<tr>
<td>3</td>
<td>Cheng 2013; China; Chinese;</td>
<td>AD; 36</td>
<td>Yang xue qing nao (YXQN) + donepezil</td>
<td>Donepezil 10mg daily</td>
<td>Total NPI; MMSE</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study name; location; language of publication; duration</td>
<td>Diagnosis for inclusion; No. participants at baseline</td>
<td>Treatment (T)</td>
<td>Control (C)</td>
<td>Outcome measures included in this review</td>
</tr>
<tr>
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</tr>
<tr>
<td>12wks</td>
<td></td>
<td></td>
<td>10mg daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Furuhashi 2011; Japan; English; 4wks</td>
<td>AD and BPSD; 38</td>
<td>YKS 7.5g daily</td>
<td>Risperidone 4mg daily</td>
<td>Total NPI, MMSE, CMAI, frequency of EPS, AEs</td>
</tr>
<tr>
<td>5</td>
<td>Furukawa 2015; Japan; English; 4wks + 8wks safety assessment</td>
<td>AD and BPSD; 145</td>
<td>YKS 5-7.5g daily; rescue medication and nonPT allowed</td>
<td>Placebo 5-7.5g daily; rescue medication and nonPT allowed</td>
<td>Total NPI-Q and domains; MMSE, dose of rescue drug, safety assessments by wk 12</td>
</tr>
<tr>
<td>6</td>
<td>Gavrilova 2014; Russian Federation; English; 24wks</td>
<td>MCI and NPS; 160</td>
<td>EGB 761 240mg daily</td>
<td>Placebo 240mg daily</td>
<td>Total NPI-12</td>
</tr>
<tr>
<td>7</td>
<td>Guo 2011; China; Chinese; 4wks</td>
<td>AD; 60</td>
<td>Zhi bai di huang tang (ZBDHT) 1 dose twice daily + donepezil 5mg daily</td>
<td>Donepezil 5mg daily</td>
<td>BEHAVE-AD, MMSE</td>
</tr>
<tr>
<td>8</td>
<td>Guo 2013; China; Chinese; 12wks</td>
<td>AD and BPSD; 127</td>
<td>Bu shen hua tan fang (BSHTF) + donepezil NS</td>
<td>Donepezil NS</td>
<td>BEHAVE-AD</td>
</tr>
<tr>
<td>9</td>
<td>Hamazaki-Fujita 2013; Japan; Japanese; 4wks</td>
<td>any age-related cognitive decline; and ≥1 of other symptoms; 41</td>
<td>Yokukansan-ka-chimphange (YKCH) 7.5g daily</td>
<td>'no test drug'</td>
<td>Total NPI, MMSE, ADAS-J cog</td>
</tr>
<tr>
<td>10</td>
<td>Hao 2006; China; Chinese; 6mths</td>
<td>VaD; 100</td>
<td>Tong xin luo jiao nan (TXLJN) 9 capsules daily</td>
<td>Piracetam 1.8g daily</td>
<td>Total NPI, MMSE</td>
</tr>
<tr>
<td>11</td>
<td>Heo 2008 &amp; 2011; South Korea; English; 12wks</td>
<td>AD; 61</td>
<td>Korean Red Ginseng T1: 9g daily + meds; T2: 4.5g daily + meds</td>
<td>meds as taken before randomisation</td>
<td>ADAS-noncog, ADAS-cog, ADAS total, MMSE</td>
</tr>
<tr>
<td>12</td>
<td>Heo 2012; South Korea; English; 12wks EoT, 24wks FU</td>
<td>AD; 40</td>
<td>Heat processed ginseng; T1:1.5g, T2:3g, T3:4.5g daily + conservative and supportive therapies</td>
<td>Conservative and supportive therapies</td>
<td>ADAS-noncog, ADAS-cog, MMSE</td>
</tr>
<tr>
<td>13</td>
<td>Herrschaft 2012; Republics of Belarus, Moldova &amp; Russian Federation; English; 24wks</td>
<td>AD or VaD, and BPSD; 410</td>
<td>EGB 761 240mg daily</td>
<td>Placebo 240mg daily</td>
<td>Total NPI-12, total SKT, 11 point box scale dizziness; 11 point box scale tinnitus</td>
</tr>
<tr>
<td>14</td>
<td>Hu 2015; China; Chinese; 24wks</td>
<td>AD; 80</td>
<td>Bu shen tong luo tang (BSTLT) 1 dose twice daily + donepezil 10mg daily + piracetam</td>
<td>Donepezil 10mg daily + piracetam 2.4g daily</td>
<td>Total NPI, MMSE, ADAS-cog</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study name; location; language of publication; duration</td>
<td>Diagnosis for inclusion; No. participants at baseline</td>
<td>Treatment (T)</td>
<td>Control (C)</td>
<td>Outcome measures included in this review</td>
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</tr>
<tr>
<td>15</td>
<td>Ihl 2011; Ukraine; English; 24wks</td>
<td>AD, VaD or mixed, with BPSD; 410</td>
<td>Egb 761 240mg daily</td>
<td>Placebo 240mg daily</td>
<td>Total NPI-12; NPI-12-D, total SKT, 11 point box scale tinnitus; 11 point box scale dizziness</td>
</tr>
<tr>
<td>16</td>
<td>Iwasaki 2005a; Japan; English; 4wks</td>
<td>dementia and BPSD; 52</td>
<td>YKS 7.5g daily + rescue medication allowed</td>
<td>'Drug free' + rescue medication allowed</td>
<td>Total NPI-12 and domains, MMSE, frequency of EPS, other AEs</td>
</tr>
<tr>
<td>17</td>
<td>Kudoh 2015; Japan; English; 24mths</td>
<td>AD; 23</td>
<td>Ninjin'yoeito (NYT) 7.5g daily + donepezil 5mg daily</td>
<td>Donepezil 5mg daily</td>
<td>Total NPI and domains, MMSE, ADAS-cog</td>
</tr>
<tr>
<td>18</td>
<td>Lee 2008; South Korea; English; 12wks</td>
<td>AD; 97</td>
<td>Korean white ginseng 4.5g daily</td>
<td>no treatment</td>
<td>ADAS-noncog, ADAS-cog, ADAS total, MMSE</td>
</tr>
<tr>
<td>19</td>
<td>Maurer 1997; Germany; English; 12wks</td>
<td>AD; 20</td>
<td>Egb 761 240mg daily</td>
<td>Placebo 240mg daily</td>
<td>ADAS-noncog, ADAS-cog, total SKT</td>
</tr>
<tr>
<td>20</td>
<td>Miao 2009; China; Chinese; 8wks</td>
<td>VaD; 116</td>
<td>Bu shen hua tan tang (BSHTT) 1 dose 3 times daily</td>
<td>Nimodipine 60mg daily + piracetam 2.4g daily</td>
<td>BEHAVE-AD</td>
</tr>
<tr>
<td>21</td>
<td>Mizukami 2009; Japan; English; 4wks + 4wks crossover</td>
<td>dementia and BPSD; 106</td>
<td>YKS 7.5g daily</td>
<td>no treatment</td>
<td>Total NPI-10 and domains, MMSE</td>
</tr>
<tr>
<td>22</td>
<td>Monji 2009; Japan; English; 12wks</td>
<td>AD and BPSD; 15</td>
<td>YKS 7.5g daily + flexibly dosed sulpiride (max 50mg daily)</td>
<td>Sulpiride flexibly dosed (max 50mg daily)</td>
<td>Total NPI, MMSE, sulpiride dose</td>
</tr>
<tr>
<td>23</td>
<td>Napryeyenko 2007; Ukraine; English; 22wks</td>
<td>AD, AD with CVD, VaD, with BPSD; 400</td>
<td>Egb 761 240mg daily</td>
<td>Placebo 240mg daily</td>
<td>Total NPI-12, NPI-12-D, total SKT, tinnitus; dizziness</td>
</tr>
<tr>
<td>24</td>
<td>Nikolova 2013; Bulgaria; Bulgarian (English translation available from authors); 22wks</td>
<td>AD, AD with CVD, VaD, with BPSD; 408</td>
<td>Egb 761 240mg daily</td>
<td>Placebo 240mg daily</td>
<td>Total NPI-12, NPI-12-D, total SKT, tinnitus; dizziness</td>
</tr>
<tr>
<td>25</td>
<td>Okahara 2010; Japan; English; 4wks</td>
<td>AD including mixed and BPSD; 63</td>
<td>YKS 7.5g daily + donepezil 'at a fixed dose' NS + rescue medication allowed</td>
<td>Donepezil 'at a fixed dose' NS + rescue medication allowed</td>
<td>Total NPI, MMSE</td>
</tr>
<tr>
<td>26</td>
<td>Pan 2014; China; English; 20wks EoT, 25wks FU + measurement at 10wks</td>
<td>AD and BPSD; 98</td>
<td>Shen zhi ling (SZL) oral liquid 1.5g daily + medsa</td>
<td>Placebo +medsd</td>
<td>NPI-12 domain scores (not totals), BEHAVE-AD subcategories (not totals), MMSE, dosages of concomitant medications</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study name; location; language of publication; duration</td>
<td>Diagnosis for inclusion; No. participants at baseline</td>
<td>Treatment (T)*</td>
<td>Control (C)</td>
<td>Outcome measures included in this review</td>
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</tr>
<tr>
<td>27</td>
<td>Pu 2014; China; Chinese; 8wks</td>
<td>AD and agitation; 70</td>
<td>Tong qiao huo xue tang (TQHXT) 1 dose twice daily</td>
<td>oxcarbazepine 300-600mg daily</td>
<td>BEHAVE-AD, MMSE</td>
</tr>
<tr>
<td>28</td>
<td>Ringman 2012; US; English; 24wks</td>
<td>AD; 36</td>
<td>Curcumin C3 Complex® (CC) T1: 2g daily; T2: 4g daily + meds*</td>
<td>Placebo 2g daily + meds*</td>
<td>Total NPI-10, MMSE, ADAS-cog, AEs</td>
</tr>
<tr>
<td>29</td>
<td>Teranishi 2013; Japan; English; 8wks</td>
<td>dementia and BPSD; 76</td>
<td>YKS flexibly dosed 2.5-7.5g daily</td>
<td>C1: risperidone 0.5-2mg daily; C2: fluvoxamine 25-100mg daily</td>
<td>Total NPI-NH and domains, MMSE, AEs</td>
</tr>
<tr>
<td>30</td>
<td>Yancheva 2009; Bulgaria; English; 22wks</td>
<td>AD and BPSD; 96</td>
<td>T1: Egb 761 240mg daily + placebo initially 5mg, after 4wks 10mg daily; T2: placebo 240mg daily + donepezil initially 5mg, after 4wks 10mg daily</td>
<td>Placebo 240mg daily + donepezil initially 5mg daily, after 4wks 10mg daily</td>
<td>Total NPI-12; total SKT; tinnitus; dizziness,</td>
</tr>
<tr>
<td>31</td>
<td>Zhang 2015; China; English; 24wks EoT; 48wks FU</td>
<td>AD; 144</td>
<td>Yi shen hua zhuo (YSHZ) decoction 100mL daily + placebo 5mg daily</td>
<td>Donepezil 5mg daily + placebo 100mL daily</td>
<td>Total NPI, MMSE, ADAS-cog</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; ADAS: Alzheimer’s disease Assessment Scale; ADAS-cog: ADAS-cognitive section; ADAS-J-cog: ADAS-cog Japanese version; ADAS-noncog: ADAS-noncognitive section; AE: adverse effect; BEHAVE-AD: Behavioural Pathology in Alzheimer’s disease Scale; BPSD: Behavioural and psychological symptoms of dementia; CMAI: Cohen-Mansfield Agitation Inventory; CVD: cerebrovascular disease; Egb 761: Extract of Ginkgo biloba leaf 761; EoT: end of treatment; FU: follow-up; MMSE: Mini-Mental State Examination; nonPT: non-pharmacotherapy (non-pharmacological interventions for management of BPSD); NPI: Neuropsychiatric Inventory; NPI-Q: NPI Questionnaire version; NPI-NH: NPI Nursing Home version; NS: not specified; SKT: Short Cognitive Performance Test; US: United States; YKS: yokukansan; VaD: vascular dementia;

*See Supplementary Material, Table S2 for full species names

b Hamazaki-Fujita 2013: other symptoms included weak gastrointestinal function, easy-fatigability, short-temperedness, irritation, insomnia
c Heo 2008 & 2011: study was originally published in 2008 and republished in 2011; all participants continued to take either donepezil 5-10mg, galantamine 16-24mg, memantine 20mg or rivastigmine 6-12mg daily, as taken before randomisation
d Pan 2014: all participants continued to take other dementia medications unchanged (Huperzine A, aniracetam, memantine, donepezil, rivastigmine or galantamine, as previously prescribed)
e Ringman 2012: all participants could continue to take acetylcholinesterase inhibitors or memantine if taken at stable dose for 1 month prior to enrollment, and vitamins E and C were allowed.

Seven studies tested Egb 761®; three tested extracts of Panax ginseng C.A. Mey; one tested an extract of Curcuma longa L.; and eight tested Yokukansan or the modified version Yokukansan-ka-chimpihange (YKCH). All Egb 761® studies tested the recommended daily dose of 240mg. All Yokukansan studies tested the recommended daily dose of 7.5g, although 5mg was generally allowed at the discretion of the trial investigators. An additional 12 studies tested 12 different multi-
ingredient formulae, in which the most frequently used ingredients were: Acorus gramineus Soland. or A. tatarinowii Schott. (shi chang pu) in 7 studies; Polygala tenuifolia Willd., or P. sibirica L. (yuan zhi) in 6 studies; Rehmannia glutinosa Libosch. (shu di, sheng di) in 5 studies; Ligusticum chuanxiong Hort. (chuan xiong) in 5 studies; Panax ginseng C.A. Mey. (ren shen) and Poria cocos (Schw.) Wolf (fu ling) each in 4 studies (see Tables 4.2 and 4.3).

### Table 4.3: Ingredients of the HM interventions used in the included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study name</th>
<th>HM intervention; manufacturer</th>
<th>Ingredients of HMs: Latin binomial (Chinese name in pinyin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGb 761* intervention</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6, 13, 15, 19, 23, 24, 30</td>
<td>Gavrilova 2014; Herrschaft 2012; Ihl 2011; Maurer 1997; Napryeyenko 2007; Nikolova 2013; Yancheva 2009</td>
<td>EGb 761*; Dr. Willmar Schwabe GmbH &amp; Co. KG Pharmaceuticals, Germany.</td>
<td>dry extract of G. biloba leaves</td>
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<td>Yokukansan interventions</td>
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<td>Yokukansan-ka-chimpihange (YKCH) [Chinese: yi gan san jia chen pi ban xia]; granulated extract KB-83, Kracie Pharma Ltd., Japan</td>
<td>Uncaria rhynchophylla (gou teng); Angelica acutiloba (dong dang gui); Poria cocos (fu ling); Bupleurum falcatum (chai hu); Cnidium officinale (xiong qiong); Atractylodes lancea (bai zhu); Glycyrrhiza uralensis (gan cao); Citrus unshiu or C. reticulata (chen pi), Pinellia ternata (ban xia).</td>
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<td>Furuhashi 2011; Furukawa 2015; Iwasaki 2005; Mizukami 2009; Monji 2009; Okahara 2010; Teranishi 2013</td>
<td>Yokukansan (YKS); TJ-54, Tsumura, Japan.</td>
<td>Uncaria rhynchophylla (gou teng); Angelica acutiloba (dong dang gui); Poria cocos (fu ling); Bupleurum falcatum (chai hu); Cnidium officinale (xiong qiong); Atractylodes lancea (bai zhu) and Glycyrrhiza uralensis (gan cao)</td>
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<td>Panax ginseng (ren shen), Scutellaria baicalensis (huang qin), Acorus gramineus or A. tatarinowii (shi chang pu), Glycyrrhiza uralensis (gan cao)</td>
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<td>Chen 2013</td>
<td>Nao ling ke li (NLKL) granules; 2nd Chinese Medicine Hospital of Guangdong Province, China</td>
<td>Cistanche deserticola or C. tubulosa (rou cong long), Epimedium spp. (xian ling pi), Astragalus membranaceus (huang qi), Codonopsis pilosula or C. tangshen (dang shen), Ligusticum chuanxiong (chuan xiong), Panax notoginseng (tian qi), Salvia miltiorrhiza (dan shen), Acorus gramineus or A. tatarinowii (shi chang pu), Polygala tenuifolia or P. sibirica (yuan zhi), Pheretima spp. (di long), Bombyx mori with Beauveria bassiana (jiang can), Buthus martensii (quan xie)</td>
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<td>Yang xue qing nao ke li (YXQN); NS</td>
<td>Angelica sinensis (dang gui), Ligusticum chuanxiong (chuan xiong), Cassia obtusifolia or C. tora (jue ming zi), Hyriopsis cumingii or Cristaria plicata or Pteria martensii (zhen zhu mu), Rehmannia glutinosa (shu di huang), ‘and other components’</td>
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<td><em>Bu shen hua tan fang</em>; (BSHTF) a.k.a. ‘compound sea cucumber capsule’; Zhejiang Hacon Pharmaceutical Co. Ltd., China</td>
<td><em>Laticauda semifasciata</em> (hai she), <em>Holothuria leucospilota</em> (hai shen), <em>Polygala tenuifolia</em> or <em>P. sibirica</em> (yuan zhi), <em>Acorus gramineus</em> or <em>A. tatarinowii</em> (shi chang pu); ‘and other components’</td>
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<td><em>Tong xin luo jiao nan</em> (TXLJN), capsules; Shijiazhuang Yiling Pharmaceutical Co. Ltd., China</td>
<td><em>Panax ginseng</em> (ren shen), <em>Whitmania</em> or <em>Hirudo</em> spp. (shui zhi), <em>Buthus martensii</em> (quan xie), <em>Eupolyphaga sinensis</em> or <em>Steleophaga plancyi</em> (tu bie chong), <em>Scolopendra subspinipes</em> (wu gong), <em>Cryptotympana postulata</em> (chan tui), <em>Saussurea lappa</em> (zha kui), <em>Borneol</em> (bing pian), <em>Santalum album</em> (tan xiang), <em>Dalbergia odorifera</em> (jiang xiang), <em>Boswellia</em> spp. (ru xiang), <em>Zizyphus jujuba</em> (suan zao ren)</td>
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<td>Korean red ginseng; Korea Ginseng Corporation, Korea</td>
<td><em>Panax ginseng</em> (ren shen): Korean Red Ginseng (powder capsule, 6 year old root)</td>
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<td>Heat processed ginseng; Sun ginseng SG-135; Ginseng Science Inc., Korea</td>
<td><em>Panax ginseng</em> (ren shen): heat processed ginseng (powder capsule)</td>
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<td>14</td>
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<td><em>Bu shen tong luo tang</em> (BSTLT); individualised decoctions according to syndrome differentiation, Puren Hospital of Wuhan City, China</td>
<td><em>Polygonatum</em> spp. (huang jing), <em>Rehmannia glutinosa</em> (shu di huang), <em>Cuscuta chinensis</em> (tu si zil), <em>Panax ginseng</em> (ren shen), <em>Salvia miltiorrhiza</em> (dan shan), <em>Panax notoginseng</em> (san qi fen), <em>Polygala tenuifolia</em> or <em>P. sibirica</em> (yuan zhi), <em>Ligusticum chaixiang</em> (chu xian qi), <em>Citrus reticulata</em> (chen pi), <em>Ginkgo biloba</em> (yin xing ye)</td>
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<td>18</td>
<td>Lee 2008</td>
<td><em>P. ginseng</em>; Korean white ginseng powder capsules; Nonghyup Co, South Korea</td>
<td><em>Panax ginseng</em> (ren shen): roots from Hongcheon and Heongsung provinces in South Korea</td>
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<td>20</td>
<td>Miao 2009</td>
<td><em>Bu shen hua tan tang</em> (BSHTT); decoctions prepared on site at affiliated Hospital of Shanxi Chinese medicine College or Bai He County hospital of</td>
<td><em>Rehmannia glutinosa</em> (shu di huang), <em>Cornus officinalis</em> (shou di huang), <em>Ophiopogon japonicus</em> (mai men dong), <em>Cistanche deserticola</em> or <em>C. tubulosa</em> (rou cong rong), <em>Acorus gramineus</em> or <em>A. tatarinowii</em> (shi chang pu), <em>Cortus cocos</em> (fu ling), <em>Schisandra chinensis</em> (wu wei zi), synthetic bezoar (ren gong niu huang), <em>Gleditsia sinensis</em> (zao jia), <em>Polygala tenuifolia</em> or <em>P. sibirica</em> (yuan...</td>
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<td>Ingredients of HMs: Latin binomial (Chinese name in pinyin)</td>
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<td>26</td>
<td>Pan 2014</td>
<td>Shen zhi ling (SZL) oral liquid; Shandong Wohua Pharmaceuticals Co. Ltd., China</td>
<td>Codonopsis pilosula (dang shen), Cinnamomum cassia (gui zhi), Paeonia lactiflora (bai shao), honey-fried Glycyrrhiza uralensis (zhi gan cao), Poria cocos (fu ling / fu shen), Zingiber officinale (sheng jiang), Polygala tenuifolia or P. sibirica (yuan zhi), Acorus gramineus or A. tatarinowii (shi chang pu), fossilized bone (long gu), Ostrea spp. (mu li)</td>
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<tr>
<td>27</td>
<td>Pu 2014</td>
<td>Tong qiao huo xue tang (TQHXT); decoctions prepared on site at Kang Ci Hospital of Jiaxing, Jiaxing, China</td>
<td>Prunus persica or P. davidiana (tao ren), Carthamus tinctorius (hong hua), Paeonia lactiflora or P. veitchii (chi shao), Ligusticum chuanxiong (chuan xiong), Moschus berezovskii or M. sifanicus or M. moschiferus (she xiang), Allium fistulosum (lao cong gen), Zingiber officinale (sheng jiang), Zizyphus jujuba (da zao), Acorus gramineus or A. tatarinowii (shi chang pu)</td>
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<tr>
<td>28</td>
<td>Ringman 2012</td>
<td>Curcumin C3 Complex® (CCC) capsules; Sabinsa Corporation, New Jersey, United States</td>
<td>Powdered plant extract of Curcuma longa rhizomes; containing curcumin, demethoxycurcumin and bisdemethoxycurcumin</td>
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<td>31</td>
<td>Zhang 2015</td>
<td>Yi shen hua zhuo (YSHZ) decoction; Shenzhen Sanjiu Modern Chinese Medicine limited Company, China</td>
<td>Epimedium spp. (yin yang huo), Ligustrum lucidum (nu zhen zi), Psoralea corylifolia (bu gu zhi), Polygonum multiflorum (he shou wu), Astragalus membranaceus (huang qi), Ligusticum chuanxiong (chuan xiong), Acorus gramineus or A. tatarinowii (shi chang pu)</td>
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</table>

HM: herbal medicine

4.4.1 Risk of Bias

Risk of bias judgements are provided in Table 4.4. Thirty of the 31 studies claimed to be randomised. One study indicated it was not randomised (Kudoh et al., 2015). Fifteen RCTs stated an adequate method of random sequence generation, so were judged as ‘low’ risk of bias for this category. The other 15 RCTs were judged as ‘unclear’ risk as methods were not described. Nine placebo-controlled studies were judged ‘low’ risk of bias for blinding of participants, blinding of caregivers, blinding of the personnel who provided the treatment and blinding of outcome assessors. All EGb 761® studies except Maurer et al. (1997) were judged ‘low’ risk of bias in all categories. Of the Yokukansan studies, only Furukawa et al. (2015) was placebo-controlled. The other Yokukansan studies were judged as ‘high’ risk of bias for blinding of participants and caregivers. Two Yokukansan studies reported blinding of outcome assessors so were judged ‘low’ risk for this domain.
<table>
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</table>


No group had ten studies or greater, so risk of publication bias could not be assessed. All EGB 761® studies were funded by the manufacturer and all studies of Yokukansan or YKCH were supplied these formulations by the manufacturers.

### 4.4.2 Results of Meta-analysis

Results are presented as four groups of HM interventions: 1. EGB 761®; 2. Extracts of single herbs *P. ginseng* and *C. longa*; 3. Yokukansan or YKCH; 4. Other multi-ingredient formulae. Meta-analysis was performed for the following comparisons: 1. HM versus inactive controls; 2. HM versus pharmacotherapy; and 3. HM plus pharmacotherapy versus the same pharmacotherapy. Results for BPSD outcomes are presented first, followed by results for cognitive outcomes. Pharmacotherapies
included the acetylcholinesterase inhibitor donepezil, the SSRI fluvoxamine, the atypical antipsychotics risperidone and sulpiride, the nootropic piracetam, the calcium channel blocker nimodipine and the anticonvulsant oxcarbazepine.

Data are presented at end of treatment (EoT) between groups. In addition, within group comparisons, i.e. baseline versus EoT, are provided for the treatment groups as measures of effect size.
Figure 4.2: Forest plot of total NPI scores at end of treatment for studies of herbal medicines for BPSD (MD, RE)

EGb 761: Extract of Ginkgo biloba leaf 761; HM: herbal medicine; YKCH: Yokukansan-ka-chimpi-hange; YKS: Yokukansan

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<th>Study or Subgroup</th>
<th>HM EoT Mean</th>
<th>Control EoT Mean</th>
<th>Mean Difference IV, Random, 95% CI</th>
<th>Mean Difference IV, Random, 95% CI</th>
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<tr>
<td>1.1.1 EGb 761 vs placebo</td>
<td>4.5, 3.5</td>
<td>6.0, 6.1</td>
<td>9.7, 20.8%</td>
<td>-1.60 [-2.72, -0.48]</td>
</tr>
<tr>
<td>Garriola 2014</td>
<td>12.2, 6.9</td>
<td>200, 14.6</td>
<td>202, 20.5%</td>
<td>-2.40 [-3.70, -1.10]</td>
</tr>
<tr>
<td>Herrschafi 2012</td>
<td>13.2, 8.1</td>
<td>202, 17</td>
<td>202, 19.9%</td>
<td>-3.80 [-5.36, -2.21]</td>
</tr>
<tr>
<td>In 2011</td>
<td>14.8, 9.5</td>
<td>198, 24</td>
<td>197, 19.2%</td>
<td>-0.20 [-1.11, -0.29]</td>
</tr>
<tr>
<td>Nagaoka 2007</td>
<td>13.2, 9.5</td>
<td>196, 13.8</td>
<td>201, 19.5%</td>
<td>-0.55 [-2.34, 1.24]</td>
</tr>
<tr>
<td>Nikova 2013</td>
<td>876</td>
<td></td>
<td>876</td>
<td>-3.46 [-5.94, -0.98]</td>
</tr>
</tbody>
</table>

Test for overall effect: Z = 2.74 (P = 0.006)

Heterogeneity: Tau² = 7.35, Chi² = 55.21, df = 4 (P = 0.00001); I² = 93%

1.1.2 EGb 761 vs donepezil

Yancheva 2009 T1  | 12.5, 7.1   | 30, 13.9         | 9.7, 29.0%                         | -1.40 [-5.75, 2.95]               |

Subtotal (95% CI): 30, 29, 100.0% -1.40 [-8.75, 2.95]

Heterogeneity: Not applicable

Test for overall effect: Z = 0.63 (P = 0.53)

1.1.3 EGb 761 + donepezil vs donepezil

Yancheva 2009 T2 IM | 12.1, 8     | 29, 13.9         | 9.7, 29.0%                         | -1.60 [-6.38, 2.78]               |

Subtotal (95% CI): 29, 29, 100.0% -1.60 [-6.38, 2.78]

Heterogeneity: Not applicable

Test for overall effect: Z = 0.77 (P = 0.44)

1.1.4 Curcumina longa extract + meds vs meds

Rimman 2012       | 8.84, 11.45 | 19, 10.3         | 14.3, 11, 100.0%                   | -1.46 [-11.36, 8.44]               |

Subtotal (95% CI): 19, 11, 100.0% -1.46 [-11.36, 8.44]

Heterogeneity: Not applicable

Test for overall effect: Z = 0.29 (P = 0.77)

1.1.5 YKS and YKCH vs inactive control

Fujita 2013       | 0.9, 3.4    | 17, 0.9          | 2.2, 21, 42.3%                     | 0.00 [-1.87, 1.87]                |

Iwashita 2005     | 19.5, 15.6  | 27, 31           | 20.8, 25, 25.6%                    | -1.50 [-21.06, -1.44]             |

Mizumoto 2010     | 19.7, 14.7  | 48, 26.6         | 50, 32%, 32.2%                     | -8.90 [-16.01, -1.79]             |

Subtotal (95% CI): 92, 96, 100.0% -5.80 [-13.75, 2.14]

Heterogeneity: Tau² = 37.96, Chi² = 10.02, df = 2 (P = 0.007); I² = 80%

Test for overall effect: Z = 1.43 (P = 0.15)

1.1.6 YKS vs pharmacotherapy

Furusashi 2011    | 26.1, 7.7   | 18, 26.3         | 5.4, 20, 63.4%                     | -0.20 [-4.47, 4.07]               |

Tanetani 2013 merged | 15.10     | 26, 15.28       | 13.56, 50, 36.6%                   | -0.28 [-5.90, 5.34]               |

Subtotal (95% CI): 44, 70, 100.0% -0.23 [-3.63, 3.17]

Heterogeneity: Tau² = 0.00, Chi² = 0.00, df = 1 (P = 0.98); I² = 0%

Test for overall effect: Z = 0.13 (P = 0.09)

1.1.7 YKS + pharmacotherapy vs pharmacotherapy

Mori 2009         | 18, 19      | 10, 18           | 5, 4, 23.5%                        | 0.00 [-12.75, 12.75]              |

Okahara 2010      | 15.1, 13.4  | 29, 20.5         | 14.8, 32, 76.5%                    | -0.40 [-12.48, 1.68]              |

Subtotal (95% CI): 39, 39, 100.0% -4.13 [-18.32, 2.08]

Heterogeneity: Tau² = 0.00, Chi² = 0.53, df = 1 (P = 0.47); I² = 0%

Test for overall effect: Z = 1.31 (P = 0.19)

1.1.8 Other multi-herb formulas vs placebo

BI 2011           | 16.83, 4.82 | 12, 20.5         | 6.5, 10, 100.0%                    | -3.67 [-8.53, 1.18]               |

Subtotal (95% CI): 12, 10, 100.0% -3.67 [-8.53, 1.18]

Heterogeneity: Not applicable

Test for overall effect: Z = 1.48 (P = 0.14)

1.1.9 Other multi-herb formulas vs pharmacotherapy

Hsu 2006          | 30.63, 5.25 | 50, 38.52        | 2.02, 50, 49.5%                    | -7.89 [-9.52, -6.26]              |

Zhang 2015        | 0.88, 1.34  | 56, 1.22         | 1.99, 55, 50.5%                    | -0.54 [-1.17, 0.08]               |

Subtotal (95% CI): 108, 105, 100.0% -4.17 [-11.38, 3.03]

Heterogeneity: Tau² = 26.61, Chi² = 68.04, df = 1 (P < 0.00001); I² = 99%

Test for overall effect: Z = 1.14 (P = 0.26)

1.1.10 Other multi-herb formulas + pharmacotherapy vs pharmacotherapy

Cheng 2013        | 12.67, 6.35 | 18, 15.11        | 7.42, 18, 9.7%                     | -2.44 [-6.95, 2.07]               |

Hu 2015           | 14.09, 1.32 | 40, 17.45        | 3.62, 40, 90.3%                    | -3.36 [-4.84, 1.88]               |

Subtotal (95% CI): 58, 58, 100.0% -3.27 [-4.68, -1.86]

Heterogeneity: Tau² = 0.00, Chi² = 0.14, df = 1 (P = 0.70); I² = 0%

Test for overall effect: Z = 4.56 (P < 0.00001)

Test for subroumes differences: Chi² = 4.47, df = 9 (P = 0.88), I² = 0%
69

Figure 4.3: Forest plot of total NPI scores (SMD; RE)

EGb 761: Extract of Ginkgo biloba leaf 761; HM: herbal medicine; YKCH: Yokukansan-ka-chimpi-hange; YKS: Yokukansan

1. EGb 761® (7 RCTs)

Six studies tested EGb 761® using NPI-12 and one used ADAS-noncog. Meta-analysis results are shown in Figure 4.2, Figure 4.3 and Table 4.5. For NPI-12 (1,757 participants), EGb 761® was superior to placebo at EoT (MD -3.46 [-5.94, -0.98] I² 93%, 5 RCTs), and there was a significant improvement within the EGb 761® group. EGb 761® was not superior to placebo in the small study which used ADAS-noncog (Maurer et al., 1997). In the single comparison with pharmacotherapy, EGb 761® plus placebo was neither superior nor inferior to donepezil plus placebo on NPI 12 and adding EGb 761® to donepezil did not improve the result (Yancheva et al., 2009).
Of the cognitive outcomes, the pooled result of SKT scores (1,733 participants) showed significant improvements in the EGB 761® groups compared to placebo at EoT (MD - 2.32 [-3.74, -0.90] I² 90%, five RCTs). In the single study that used ADAS-cog, EGB 761® was not superior to placebo (Maurer et al., 1997). In comparison with donepezil there was no difference in SKT results between groups and there was no additional benefit for combining EGB 761® and donepezil (Yancheva et al., 2009).

Table 4.5: Meta-analysis results for EGB 761® studies at end of treatment and change within treatment groups

<table>
<thead>
<tr>
<th>Comparison</th>
<th>n studies (n participants at EoT: T, C); duration; [study ID]</th>
<th>T vs C at EoT; RE; I²</th>
<th>T group change (baseline vs EoT); RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPI-12 (total scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGB 761® vs placebo</td>
<td>5 (876,881); 22–24wks; [6,13,15,23,24]</td>
<td>MD -3.46 [-5.94, -0.98] *; 93%</td>
<td>MD -5.06 [-6.61, -3.51] *; 81%</td>
</tr>
<tr>
<td>EGB 761® vs placebo; exclude MCI</td>
<td>4 (796,802); 22 – 24wks; [13,15,23,24]</td>
<td>MD -3.96 [-7.19, -0.73] *; 94%</td>
<td>MD -4.49 [-5.79, -3.18] *; 60%</td>
</tr>
<tr>
<td>EGB 761® + placebo vs donepezil + placebo</td>
<td>1 (30,29); 22wks; [30]</td>
<td>MD -1.40 [-5.75, 2.95]</td>
<td>MD -6.40 [-9.96, -2.84] *</td>
</tr>
<tr>
<td>EGB 761® + donepezil vs placebo + donepezil</td>
<td>1 (31,32); 22wks; [30]</td>
<td>MD -1.00 [-3.13, 1.13]</td>
<td>MD -3.50 [-5.69, -1.31] *</td>
</tr>
<tr>
<td><strong>ADAS-noncog (total scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGB 761® vs placebo</td>
<td>1 (9,9); 12wks; [19]</td>
<td>MD -1.11 [-6.38, 4.16]</td>
<td>MD -1.78 [-5.01, 1.45]</td>
</tr>
<tr>
<td><strong>ADAS-cog</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGB 761® vs placebo</td>
<td>1 (9,9); 12wks; [19]</td>
<td>MD -5.80 [-19.82, 8.22]</td>
<td>MD -0.88 [-13.31, 11.55]</td>
</tr>
<tr>
<td><strong>SKT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGB 761® vs placebo</td>
<td>5 (805,811); 12 – 24wks; [13,15,19,23,24]</td>
<td>MD -2.32 [-3.74, -0.90] *; 90%</td>
<td>MD -2.26 [-2.97, -1.55] *; 63%</td>
</tr>
<tr>
<td>EGB 761® + placebo vs donepezil + placebo</td>
<td>1 (30,32); 22wks; [30]</td>
<td>MD -1.00 [-3.22, 1.22]</td>
<td>MD -2.27 [-3.30, -1.23] *; 81%</td>
</tr>
<tr>
<td>EGB 761® + donepezil vs placebo + donepezil</td>
<td>1 (31,32); 22wks; [30]</td>
<td>MD -1.00 [-3.13, 1.13]</td>
<td>MD -3.50 [-5.69, -1.31] *</td>
</tr>
</tbody>
</table>

ADAS-cog: Alzheimer’s disease Assessment Scale-cognitive section; ADAS-noncog: Alzheimer’s disease Assessment Scale-noncognitive section C: control group; EGB 761: Extract of Ginkgo biloba leaf 761; EoT: end of treatment; I²: Index of heterogeneity; MCI: mild cognitive impairment; MD: mean difference; NPI-12: Neuropsychiatric Inventory 12 item version; RE: random effects model; SKT: Short Cognitive Performance Test T: treatment group

*significant (p<0.05)

excluding study of participants with mild cognitive impairment (Gavrilova et al., 2014)

2. Extracts of the single herbs Panax ginseng and Curcuma longa (4 RCTs)

One RCT used NPI-12 (30 participants) to assess the effects of C. longa extract (CCC) (Ringman et al., 2012). Combining C. longa extract with dementia medications did not improve NPI scores after 24 weeks. Results of meta-analysis are shown in Table 4.6.
Table 4.6: Meta-analysis results for studies of extracts of Panax ginseng and Curcuma longa at end of treatment and change within treatment groups

<table>
<thead>
<tr>
<th>Comparison</th>
<th>n studies (n participants at EoT: T, C); duration; [study ID]</th>
<th>T vs C at EoT; RE; I²</th>
<th>Treatment group Baseline vs EoT; RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPI-12 (total scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Curcuma + meds vs placebo + meds</td>
<td>1 (19,11); 24wks; [28]</td>
<td>MD -1.46 [-11.36, 8.44]</td>
<td>MD -1.46 [-8.93, 6.01]</td>
</tr>
<tr>
<td><strong>ADAS-noncog</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginseng (4.5g/d) + UC vs UC</td>
<td>1 (50,32); 4wks interim; [18]; 2 (56,38); 12wks EoT &amp; 24wks FU; [12,18]</td>
<td>4wks: MD -2.59 [-4.61, -0.57]*; 12wks: MD -0.55 [-2.41, 1.32]; 0% 24wks: MD -1.30 [-3.17, 0.58]; 0%</td>
<td>4wks: MD -2.90 [-4.60, -1.20]<em>; 12wks: MD -4.21 [-8.15, -0.27]</em>; 52%; 24wks: MD -4.76 [-8.77, -0.74]*; 47%</td>
</tr>
<tr>
<td>Ginseng Low dose (4.5g/d), High dose (9g/d) + meds vs meds</td>
<td>1 Low (13,28); 12wks; High (13,28); 12wks; [11]</td>
<td>Low MD -1.36 [-3.55, 0.83];# High MD -0.87 [-2.85, 1.11]#</td>
<td>Low MD -0.78 [-3.00, 1.44]; High MD -0.49 [-2.76, 1.78]</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginseng (4.5g/d) + UC vs UC</td>
<td>2 (64,45); 12wks EoT, 24wks FU; [12,18]</td>
<td>12wks: MD 1.47 [-0.05, 2.99]; 0% 24wks: MD -0.91 [-2.44, 0.62]; 0%</td>
<td>12wks: MD 2.55 [-0.69, 5.79]; 29%; 24wks: MD 0.62 [-0.75, 1.98]; 0%</td>
</tr>
<tr>
<td>Ginseng Low dose (4.5g/d), High dose (9g/d) + meds vs meds</td>
<td>1 Low (15,31); High (15,31); 12wks; [11]</td>
<td>Low MD 2.71 [0.32, 5.10]#; High MD 2.16 [-1.75, 6.07]</td>
<td>Low MD 1.48 [-1.29, 4.25]; High MD 1.57 [-3.37, 6.51]</td>
</tr>
<tr>
<td>Curcuma (4g/day) + meds vs placebo + meds</td>
<td>1 (19,11); 24wks; [28]</td>
<td>MD -2.94 [-4.97, -0.91]*</td>
<td>MD -2.34 [-4.35, -0.33]*</td>
</tr>
<tr>
<td><strong>ADAS-cog</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ginseng (4.5g/d) + UC vs UC</td>
<td>2 (56,38); 12wks EoT, 24wks FU; [12,18]</td>
<td>12wks: MD -1.74 [-5.58, 2.09]; 0% 24wks FU: MD 2.25 [-1.60, 6.09]; 0%</td>
<td>12wks: MD -3.60 [-7.07, -0.13]*; 0% 24wks FU: MD -1.90 [-10.18, 6.38]; 0%</td>
</tr>
<tr>
<td>Ginseng Low dose (4.5g/d), High dose (9g/d) + meds vs meds</td>
<td>1 Low (15,31); High (15,31); 12wks; [11]</td>
<td>Low MD -2.21 [-7.58, 3.16]; High MD -0.34 [-8.14, 7.46]</td>
<td>Low MD -1.85 [-7.40, 3.70]; High MD -3.29 [-11.67, 5.09]</td>
</tr>
<tr>
<td>Curcuma + meds vs placebo + meds</td>
<td>1 (19,11); 24wks; [28]</td>
<td>MD 4.27 [-1.48, 10.02]</td>
<td>MD 4.57 [0.02, 9.12]*</td>
</tr>
</tbody>
</table>

ADAS-cog: Alzheimer’s disease Assessment Scale-cognitive section; ADAS-noncog: Alzheimer’s disease Assessment Scale-noncognitive section; C: control group; Curcuma: Curcumin C3 Complex (Curcuma longa extract); EoT: end of treatment; FU: follow-up; g/d: grams per day; Ginseng: Panax ginseng extract; High: high dose group; I²: Index of heterogeneity; Low: low dose group; MD: mean difference; MMSE: Mini-Mental State Examination; n: number; NPI: Neuropsychiatric Inventory; RE: random effects model; T: treatment group; UC: supportive and conservative usual care; wks: weeks
#baseline imbalance (removed from pool); *significant,
a Ringman 2012: all participants could continue to take acetylcholinesterase inhibitors or memantine if taken at stable dose for 1 month prior to enrollment, and vitamins E and C were allowed.
b merged data for 2g and 4g per day treatment groups.
c Heo 2008: all participants continued to take either donepezil 5-10mg, galantamine 16-24mg, memantine 20mg or rivastigmine 6-12mg daily, as taken before randomisation.
For ADAS-noncog, *P. ginseng* plus usual care appeared superior to usual care after four weeks but not at 12 weeks EoT or at follow-up (24 weeks) (94 participants). In the study of *P. ginseng* plus AD medications (Heo et al., 2008) (54 participants) there was baseline imbalance between groups which confounded the comparison but there was no significant change within either the treatment or control groups (see Figure 4.3).

![Figure 4.3: Forest plot of ADAS-noncog scores for the single herb intervention studies (MD; RE; 95% CI)](image)

For MMSE, no significant differences were detected between *P. ginseng* and usual care at 12 weeks (EoT) or 24 weeks (follow-up). In Heo et al. (2008) there was no difference between the high dose *P. ginseng* group plus usual dementia medication and the dementia medication control group but there was a benefit for the low dose *P. ginseng* group. For *C. longa* extract plus usual dementia medication, there was significant worsening of MMSE scores within both the high dose and low dose (4g and 2g per day) *C. longa* extract treatment groups after 24 weeks and no significant change within the control group.

For ADAS-cog, no benefit was detected for adding *P. ginseng* to an existing dementia medication regime (Heo et al., 2008). There was significant decline within the pooled *C. longa* extract groups but not within the control group after 24 weeks, and no significant difference between groups.

### 3. Yokukansan and YKCH (8 RCTs)

Seven studies tested Yokukansan and one tested YKCH using NPI-10 or NPI-12, and one additional study used NPI-Q, as detailed in Table 4.7.
Table 4.7: Details of NPI versions, NPI inclusion criteria and availability of NPI domain data in studies which reported NPI domain scores

<table>
<thead>
<tr>
<th>Study ID; duration; intervention; design; diagnosis; BPSD inclusion criteria</th>
<th>NPI version; How is NPI domain baseline and EoT data reported?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furukawa 2015; 4wks; YKS vs placebo; RCT; AD and BPSD; with sum of NPI-Q subcategories for ‘agitation/aggression’ and ‘irritability/lability’&gt;2</td>
<td>NPI-Q; Mean (SD) scores shown on bar graph; numbers of participants with symptom present not reported</td>
</tr>
<tr>
<td>Iwasaki 2005a; 4wks; YKS vs ‘drug free’ + rescue medication if required; RCT; AD, VaD, AD with CVD or LBD, all with BPSD; NPI more than 6 on at least 1 of the ‘delusion, hallucination, violent behaviour or apathy subscales’</td>
<td>NPI-12; Mean (SD) scores shown on bar graph; numbers of participants with symptoms present not reported</td>
</tr>
<tr>
<td>Kudoh 2015; 24months; NYT + donepezil vs donepezil; NRS; AD; BPSD not required</td>
<td>NPI-10; Mean (SD) scores reported in table; numbers of participants with symptoms present not reported</td>
</tr>
<tr>
<td>Mizukami 2009; 4wks; YKS vs no treatment; RCT (crossover); BPSD; NPI score of at least 6 for at least 1 of the 10 domains at baseline</td>
<td>NPI-10; Mean (SD) scores reported in table; numbers of participants with symptoms at baseline and EoT shown in table</td>
</tr>
<tr>
<td>Okahara 2010; 4wks; YKS + donepezil vs donepezil, + risperidone allowed as a rescue drug in both groups; RCT; AD including mixed type, and BPSD; NPI score of at least 4 for at least 1 of the 10 domains at baseline</td>
<td>NPI-10, Mean (SD) scores reported in table; numbers of participants with symptoms present at baseline shown in table</td>
</tr>
<tr>
<td>Pan 2014; 10wks interim, 20wks EoT, 25wks FU; SZL oral liquid vs placebo; RCT; AD and BPSD; Not stated how BPSD was determined at baseline</td>
<td>NPI-12 mean (SD) domain scores shown on table; nos with symptoms present at baseline not reported</td>
</tr>
<tr>
<td>Teranishi 2013; 8wks; YKS vs risperidone vs fluvoxamine; RCT; AD, VaD or LBD, and BPSD; NPI-NH score of &gt;4 for at least 1 of 12 domains at baseline</td>
<td>12 item NPI-NH; Mean (SD) scores reported in table; numbers of participants with symptoms present not reported</td>
</tr>
<tr>
<td>Zhang 2015; 24wks EoT, 48wks FU; YSHZ decoction + placebo vs donepezil + placebo; RCT; AD; BPSD not required</td>
<td>NPI-12; domain scores not reported but received mean (SD) scores for 12 NPI domains from author June 2015; numbers of participants with symptoms present not reported</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; BPSD: behavioural and psychological symptoms of dementia; CVD: cerebrovascular disease; FU: follow up; LBD: Lewy Body dementia; NPI: Neuropsychiatric Inventory; NPI-NH: NPI Nursing Home version; NPI-Q: NPI Questionnaire version; NRS: non-randomised study; NYT: Ninjin’yoeito; RCT: randomised controlled trial; SD: standard deviation; SZL: Shen zhi ling; VaD: vascular dementia; wks: weeks; YKS: Yokukansan; YSHZ: Yi shen hua zhuo

Meta-analysis results are shown in Figure 4.2, Table 4.8 and Figures 4.4, 4.x and 4.x.

**Figure 4.4: Forest plot of total NPI-Q scores**

(MD; RE, 95% CI)

Using NPI-10 or NPI-12 (188 participants), Yokukansan / YKCH were superior to no treatment (SMD -0.42 [-0.73, -0.10] I² 12%, 3 RCTs). For NPI-Q (137 participants), Yokukansan was not superior to...
placebo (MD -0.20 [-1.83, 1.43], 1 RCT), but significant improvements were detected in both the Yokukansan and placebo groups.

### Table 4.8: Meta-analysis results for Yokukansan and YKCH studies at end of treatment and change within treatment groups

<table>
<thead>
<tr>
<th>Outcome, Comparison</th>
<th>n studies (n participants at EoT: T, C); duration; [study ID]</th>
<th>T vs C at EoT; RE; I²</th>
<th>Treatment group Baseline vs EoT; RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPI 10/12 (total scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>2 (75,75); 4wks; [16,21]</td>
<td>SMD -0.53 [-0.86, -0.21]**; 0%</td>
<td>SMD -0.70 [-1.51, 0.11]; 82%</td>
</tr>
<tr>
<td>YKCH vs no treatment</td>
<td>1 (17,21); 4wks; [9]</td>
<td>MD 0.00 [-1.87, 1.87]</td>
<td>MD 0.50 [-1.20, 2.20]</td>
</tr>
<tr>
<td>Total: YKS/YKCH vs no treatment</td>
<td>3 (92,96); 4wks; [9,16,21]</td>
<td>SMD -0.42 [-0.73, -0.10]**; 12%</td>
<td>SMD -0.43 [-1.11, 0.26]; 80%</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); 8wks; [29]</td>
<td>MD 2.16 [-5.12, 9.44]</td>
<td>MD -7.73 [-14.56, -0.90]**</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>2 (44,45); 4–8wks; [4,29]</td>
<td>SMD -0.15 [-0.57, 0.27]; 0%</td>
<td>SMD -0.98 [-1.79, -0.16]**; 68%</td>
</tr>
<tr>
<td>Total: YKS vs pharmacotherapy</td>
<td>2 studies, 3 groups (44,70); 4–8wks; [4,29]</td>
<td>SMD -0.02 [-0.40, 0.36]; 0%</td>
<td>SMD -0.98 [-1.79, -0.16]**; 68%</td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil</td>
<td>1 (29,32); 4wks; [25]</td>
<td>MD -5.40 [-12.48, 1.68]</td>
<td>MD -7.20 [-13.33, -1.07]**</td>
</tr>
<tr>
<td>YKS + sulpiride vs sulpiride</td>
<td>1 (10,4); 12wks; [22]</td>
<td>MD 0.00 [-12.75, 12.75]</td>
<td>MD -8.70 [-23.98, 6.58]</td>
</tr>
<tr>
<td>Total: YKS + pharmacotherapy vs pharmacotherapy</td>
<td>2 (39,36); 4–12wks; [22,25]</td>
<td>SMD -0.32 [-0.78, 0.15]; 0%</td>
<td>SMD -0.56 [-1.01, -0.11]**; 0%</td>
</tr>
<tr>
<td><strong>NPI-Q (total scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs placebo</td>
<td>1 (72,65); 4wks; [5]</td>
<td>MD -0.20 [-1.83, 1.43]</td>
<td>MD -2.30 [-3.68, -0.92]**</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs placebo</td>
<td>1 (72,64); 4wks; [5]</td>
<td>MD 0.40 [-1.13, 1.93]</td>
<td>MD 0.40 [-0.97, 1.77]</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>2 (75,75); 4wks; [16,21]</td>
<td>MD 0.20 [-2.24, 2.63]; 0%</td>
<td>MD -0.57 [-3.08, 1.93]; 0%</td>
</tr>
<tr>
<td>YKCH vs no treatment</td>
<td>1 (17,21); 4wks; [9]</td>
<td>MD 0.50 [-1.97, 2.97]</td>
<td>MD 0.80 [-2.16, 3.76]</td>
</tr>
<tr>
<td>Total: YKS/YKCH vs no treatment</td>
<td>3 (92,96); 4wks; [9,16,21]</td>
<td>MD 0.35 [-1.39, 2.08]; 0%</td>
<td>MD -0.00 [-1.91, 1.91]; 0%</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); 8wks; [29]</td>
<td>MD 0.63 [-2.17, 3.43]</td>
<td>MD -0.07 [-2.47, 2.33]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>2 (44,45); 4–8wks; [4,29]</td>
<td>MD 0.67 [-0.95, 2.29]; 0%</td>
<td>MD 0.02 [-1.59, 1.64]; 0%</td>
</tr>
<tr>
<td>Total: YKS vs pharmacotherapy</td>
<td>2 studies, 3 groups (44,70); 4–8wks; [4,29]</td>
<td>MD 0.68 [-0.83, 2.20]; 0%</td>
<td>MD 0.02 [-1.59, 1.64]; 0%</td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil</td>
<td>1 (29,32); 4wks; [25]</td>
<td>MD -0.20 [-3.04, 2.64]</td>
<td>MD 0.00 [-2.68, 2.68]</td>
</tr>
<tr>
<td>YKS + sulpiride vs sulpiride</td>
<td>1 (10,4); 12wks; [22]</td>
<td>MD 1.50 [-2.95, 5.95]</td>
<td>MD -1.10 [-5.57, 3.37]</td>
</tr>
<tr>
<td>Total: YKS + pharmacotherapy vs pharmacotherapy</td>
<td>2 (39,36); 4–12wks; [22,25]</td>
<td>MD 0.29 [-2.10, 2.68]; 0%</td>
<td>MD -0.29 [-2.59, 2.01]; 0%</td>
</tr>
<tr>
<td><strong>ADAS-cog</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>YKCH vs no treatment</td>
<td>1 (17,21); 4wks; [9]</td>
<td>MD -1.02 [-5.99, 3.95]</td>
<td>MD -2.90 [-9.11, 3.31]</td>
</tr>
</tbody>
</table>

ADAS-cog: Alzheimer’s disease Assessment Scale-cognitive section; C: control group; EoT: end of treatment; FU: follow up; I²: Index of heterogeneity; MD: mean difference; MMSE: Mini-Mental State Examination; NPI: 74
Neuropsychiatric Inventory; NPI-Q: NPI Questionnaire version; RE: random effects model; SMD: standardised mean difference; T: treatment group; YKCH: Yokukansan-ka-chimpilhange; YKS: Yokukansan
*significant
Note: SMD was used when scores of NPI-10 and NPI-12 were pooled and when it was unclear whether NPI-10 or NPI-12 were used in pooled studies.

For the individual domains of NPI, four Yokukansan studies reported domain scores for NPI 10/12 and one reported these for NPI-Q (Tables 4.9 and 4.10).
Table 4.9: Results of meta-analyses of NPI domain scores

<table>
<thead>
<tr>
<th>Comparison</th>
<th>n studies (n participants)</th>
<th>EoT; MD, RE; $I^2$</th>
<th>T Baseline vs EoT; MD, RE; $I^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPI-A: DELUSIONS; HM vs inactive controls</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-1.65 [-3.36, 0.06]</td>
<td>-0.85 [-2.43, 0.73]</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>-3.90 [-5.48, -2.32]*</td>
<td>-3.00 [-4.11, -1.89]*</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>-2.80 [-5.00, -0.60]*; 72%</td>
<td>-2.00 [-4.10, 0.10]; 79%</td>
</tr>
<tr>
<td><strong>HM vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); [31]</td>
<td>0.03 [-0.06, 0.13]</td>
<td>0.03 [-0.07, 0.12]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>1.00 [-0.44, 2.44]</td>
<td>-0.61 [-2.46, 1.24]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>0.80 [-0.52, 2.12]</td>
<td>-0.61 [-2.46, 1.24]</td>
</tr>
<tr>
<td><strong>HM + pharmacotherapy vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil</td>
<td>1 (29,32); [25]</td>
<td>-3.00 [-4.35, -1.65]*</td>
<td>-1.50 [-2.63, -0.37]*</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS*</td>
<td>1 (12,11); [17]</td>
<td>-0.20 [-1.23, 0.83]</td>
<td>0.50 [-0.50, 1.50]</td>
</tr>
<tr>
<td>SZL + meds vs placebo plus meds</td>
<td>1 (45,46); [26]</td>
<td>10w -0.24 [-0.48, 0.00]; 20w -0.38 [-0.76, 0.00]; 25w -0.55 [-1.10, 0.00]</td>
<td>10w 0.04 [-0.21, 0.29]; 20w 0.21 [-0.10, 0.52]; 25w 0.32 [-0.02, 0.66]</td>
</tr>
<tr>
<td><strong>NPI-B: HALLUCINATIONS; HM vs inactive controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-1.50 [-3.56, 0.06]</td>
<td>-2.40 [-5.52, -0.58]*</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>-2.70 [-4.23, -1.17]*</td>
<td>-2.00 [-2.83, -1.17]*</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>-1.30 [-4.14, 1.54]; 82%</td>
<td>-2.10 [-2.88, -1.32]*; 0%</td>
</tr>
<tr>
<td><strong>HM vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); [31]</td>
<td>-0.00 [-0.05, 0.05]</td>
<td>-0.01 [-0.06, 0.04]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>-0.02 [-0.85, 0.81]</td>
<td>0.07 [-0.79, 0.93]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>-0.38 [-1.25, 0.49]</td>
<td>0.07 [-0.79, 0.93]</td>
</tr>
<tr>
<td><strong>HM + pharmacotherapy vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil</td>
<td>1 (29,32); [25]</td>
<td>-3.00 [-4.24, -1.76]*</td>
<td>-0.90 [-1.80, 0.00]</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS*</td>
<td>1 (12,11); [17]</td>
<td>24m-0.10 [-1.05, 0.85]</td>
<td>24m 0.00 [-0.84, 0.84]</td>
</tr>
<tr>
<td>SZL + meds vs placebo plus meds</td>
<td>1 (45,46); [26]</td>
<td>10w -0.20 [-0.67, 0.27]; 20w -0.41 [-0.89, 0.07]; 25w -0.68 [-1.21, -0.15]*</td>
<td>10w 0.03 [-0.44, 0.50]; 20w0.10 [-0.22, 0.42]; 25w 0.19 [-0.11, 0.49]</td>
</tr>
<tr>
<td><strong>NPI-C: AGITATION/AGGRESSION; HM vs inactive controls</strong></td>
<td></td>
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</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-1.50 [-3.56, 0.56]</td>
<td>-2.40 [-5.50, -0.30]*</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>-1.80 [-3.25, -0.35]*</td>
<td>-2.00 [-3.22, -0.78]*</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>-1.70 [-2.88, -0.52]; 0% *</td>
<td>-2.10 [-3.15, -1.05]*; 0%</td>
</tr>
<tr>
<td>Comparison</td>
<td>n studies (n participants)</td>
<td>EoT; MD, RE; I²</td>
<td>T Baseline vs EoT; MD, RE; I²</td>
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<tr>
<td>------------</td>
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<tr>
<td>HM vs pharmacotherapy</td>
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</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); [31]</td>
<td>-0.04 [-0.11, 0.03]</td>
<td>-0.01 [-0.06, 0.04]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>0.68 [-1.28, 2.64]</td>
<td>-1.04 [-3.11, 1.03]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>-0.08 [-2.06, 1.90]</td>
<td>-1.04 [-3.11, 1.03]</td>
</tr>
<tr>
<td>HM + pharmacotherapy vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil RCT</td>
<td>1 (29,32); [25]</td>
<td>-1.40 [-2.73, -0.07]*</td>
<td>-1.50 [-2.92, -0.08]*</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS</td>
<td>1 (12,11); [17]</td>
<td>24m 0.10 [-0.55, 0.75]</td>
<td>24m 0.20 [-0.44, 0.84]</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds</td>
<td>1 (45,46); [26]</td>
<td>10w -1.03 [-1.41, -0.65]<em>; 20w -1.20 [-1.61, -0.79]</em>; 25w -1.08 [-1.67, -0.49]*</td>
<td>10w 0.13 [-0.26, 0.52]; 20w 0.96 [0.55, 1.37]<em>; 25w 1.57 [1.09, 2.05]</em></td>
</tr>
<tr>
<td>NPI-D: DEPRESSION/DYSPHORIA; HM vs inactive controls</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-3.20 [-4.98, -1.42]*</td>
<td>2.40 [1.15, 3.65]* (decline)</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>-3.10 [-4.53, -1.67]*</td>
<td>-1.40 [-2.43, -0.37]*</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>-3.14 [-4.25, -2.03]; 0%.*</td>
<td>0.48 [-3.24, 4.21]; 95%</td>
</tr>
<tr>
<td>HM vs pharmacotherapy</td>
<td></td>
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</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); [31]</td>
<td>-0.17 [-0.39, 0.05]</td>
<td>-0.22 [-0.47, 0.03]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>0.14 [-0.56, 0.84]</td>
<td>-0.16 [-1.11, 0.79]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>0.02 [-0.78, 0.82]</td>
<td>-0.16 [-1.11, 0.79]</td>
</tr>
<tr>
<td>HM + pharmacotherapy vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil RCT</td>
<td>1 (29,32); [25]</td>
<td>-0.10 [-1.43, 1.23]</td>
<td>-1.20 [-2.44, 0.04]</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS</td>
<td>1 (12,11); [17]</td>
<td>-1.40 [-2.24, -0.56]*</td>
<td>-1.50 [-2.46, -0.54]*</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds</td>
<td>1 (45,46); [26]</td>
<td>10w 0.07 [-0.29, 0.43]; 20w -0.10 [-0.53, 0.33]; 25w -0.09 [-0.54, 0.36]</td>
<td>10w 0.05 [-0.33, 0.43]; 20w -0.02 [-0.34, 0.30]; 25w 0.16 [-0.29, 0.61]</td>
</tr>
<tr>
<td>NPI-E: ANXIETY; HM vs inactive controls</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>0.00 [-1.56, 1.56]</td>
<td>-1.50 [-3.32, 0.32]</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>0.00 [-1.44, 1.44]</td>
<td>-1.80 [-3.03, -0.57]*</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>0.00 [-1.06, 1.06]; 0%.*</td>
<td>-1.71 [-2.72, -0.69]; 0%</td>
</tr>
<tr>
<td>HM vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); [31]</td>
<td>-0.15 [-0.34, 0.04]</td>
<td>-0.21 [-0.41, -0.01]*</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>0.16 [-1.60, 1.92]</td>
<td>-0.58 [-2.27, 1.11]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>0.64 [-0.97, 2.25]</td>
<td>-0.58 [-2.27, 1.11]</td>
</tr>
<tr>
<td>HM + pharmacotherapy vs pharmacotherapy</td>
<td></td>
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</tr>
</tbody>
</table>

77
<table>
<thead>
<tr>
<th>Comparison</th>
<th>n studies (n participants)</th>
<th>EoT; MD, RE; I²</th>
<th>T Baseline vs EoT; MD, RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>YKS + donepezil vs donepezil RCT</td>
<td>1 (29,32); [25]</td>
<td>-1.70 [-3.03, -0.37]*</td>
<td>-2.10 [-3.29, -0.91]*</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS</td>
<td>1 (12,11); [17]</td>
<td>6m -0.90 [-1.82, 0.02]; 12m -0.10 [-1.05, 0.85]; 24m -0.80 [-1.75, 0.15]</td>
<td>24m -0.10 [-0.94, 0.74]</td>
</tr>
<tr>
<td>SZL + meds vs placebo plus meds</td>
<td>1 (45,46); [26]</td>
<td>10w -0.04 [-0.42, 0.34]; 20w -0.03 [-0.48, 0.42]; 25w -0.12 [-0.75, 0.51]</td>
<td>10w 0.04 [-0.31, 0.39]; 20w 0.09 [-0.30, 0.48]; 25w 0.05 [-0.47, 0.57]</td>
</tr>
<tr>
<td>NPI-F: EUPHORIA/ELATION; HM vs inactive controls</td>
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<td></td>
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</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-0.40 [-2.19, 1.39]</td>
<td>-0.70 [-2.69, 1.29]</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>0.70 [-0.69, 2.09]</td>
<td>0.00 [-1.14, 1.14]</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>0.29 [-0.81, 1.38]; 0%</td>
<td>-0.17 [-1.16, 0.81]; 0%</td>
</tr>
<tr>
<td>HM vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>0.11 [-0.50, 0.72]</td>
<td>-0.11 [-0.87, 0.65]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>-0.01 [-0.60, 0.58]</td>
<td>-0.11 [-0.87, 0.65]</td>
</tr>
<tr>
<td>HM + pharmacotherapy vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil RCT</td>
<td>1 (29,32); [25]</td>
<td>2.00 [0.39, 3.61]*#</td>
<td>-2.70 [-4.38, -1.02]*</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS</td>
<td>1 (12,11); [17]</td>
<td>6m 0.70 [0.29, 1.11]<em>; 12m 0.70 [0.13, 1.27]</em>; 18m 0.70 [-0.04, 1.44]<em>; 24m 1.00 [0.43, 1.57]</em> (decline)</td>
<td>6m 0.70 [0.21, 1.19]<em>; 12m 0.70 [0.14, 1.26]</em>; 18m 0.90 [0.30, 1.50]<em>; 24m 0.90 [0.30, 1.50]</em> (no change between 18 and 24months).</td>
</tr>
<tr>
<td>SZL + meds vs placebo plus meds</td>
<td>1 (45,46); [26]</td>
<td>10w 0.01 [-0.30, 0.32]; 20w -0.05 [-0.32, 0.22]; 25w -0.02 [-0.30, 0.26]</td>
<td>10w 0.10 [-0.22, 0.42]; 20w 0.12 [-0.13, 0.37]; 25w0.18 [-0.03, 0.39].</td>
</tr>
<tr>
<td>NPI-G: APATHY HM vs inactive controls</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>0.30 [-1.67, 2.27]</td>
<td>-1.60 [-3.61, 0.41]</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>-0.30 [-1.78, 1.18]</td>
<td>-0.70 [-1.97, 0.57]</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>-0.08 [-1.27, 1.10]; 0%</td>
<td>-0.96 [-2.03, 0.12]; 0%</td>
</tr>
<tr>
<td>HM vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); [31]</td>
<td>-0.07 [-0.32, 0.17]</td>
<td>-0.12 [-0.39, 0.14]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>-0.14 [-1.14, 0.86]</td>
<td>-1.07 [-2.39, 0.25]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>-1.02 [-2.48, 0.44]</td>
<td>-1.07 [-2.39, 0.25]</td>
</tr>
<tr>
<td>Comparison</td>
<td>n studies (n participants)</td>
<td>EoT; MD, RE; I²</td>
<td>T Baseline vs EoT; MD, RE; I²</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------</td>
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</tr>
<tr>
<td><strong>HM + pharmacotherapy vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil RCT</td>
<td>1 (29,32); [25]</td>
<td>-1.00 [-2.38, 0.38]#</td>
<td>-1.50 [-2.48, -0.52]</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS</td>
<td>1 (12,11); [17]</td>
<td>24m 0.00 [-0.49, 0.49]</td>
<td>24m 0.00 [-0.48, 0.48]</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds</td>
<td>1 (45,46); [26]</td>
<td>10w -0.04 [-0.38, 0.30];</td>
<td>10w -0.02 [-0.34, 0.30]; 20w 0.12 [-0.22, 0.46]; 25w 0.04 [-0.26, 0.34];</td>
</tr>
<tr>
<td><strong>NPI-H: DISINHIBITION; HM vs inactive controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-0.30 [-2.34, 1.74]</td>
<td>-1.60 [-3.72, 0.52]</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>1.10 [-0.74, 2.94]</td>
<td>-0.70 [-2.26, 0.85]</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>0.47 [-0.89, 1.84]; 0%.</td>
<td>-1.02 [-2.27, 0.24]; 0%.</td>
</tr>
<tr>
<td><strong>HM vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>-0.74 [-2.05, 0.57]</td>
<td>-1.12 [-2.63, 0.39]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>0.06 [-0.83, 0.95]</td>
<td>-1.12 [-2.63, 0.39]</td>
</tr>
<tr>
<td><strong>HM + pharmacotherapy vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil RCT</td>
<td>1 (29,32); [25]</td>
<td>-1.00 [-2.51, 0.51]</td>
<td>-1.30 [-2.84, 0.24]</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS</td>
<td>1 (12,11); [17]</td>
<td>24m 0.00 [-0.49, 0.49]</td>
<td>24m 0.10 [-0.42, 0.62]</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds</td>
<td>1 (45,46); [26]</td>
<td>10w -0.15 [-0.34, 0.04];</td>
<td>10w 0.02 [-0.18, 0.22]; 20w -0.16 [-0.42, 0.10]; 25w -0.04 [-0.31, 0.23];</td>
</tr>
<tr>
<td><strong>NPI-I: IRRITABILITY/LABILITY; HM vs inactive controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-0.70 [-2.72, 1.32]</td>
<td>-2.60 [-4.89, -0.31]*</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>-1.70 [-3.21, -0.19]*</td>
<td>-1.70 [-3.08, -0.32]*</td>
</tr>
<tr>
<td>Total YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>-1.34 [-2.55, -0.13]*; 0%.</td>
<td>-1.94 [-3.12, -0.76]*; 0%.</td>
</tr>
<tr>
<td><strong>HM vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); [31]</td>
<td>-0.08 [-0.22, 0.06]</td>
<td>-0.18 [-0.41, 0.05]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>-0.74 [-2.63, 1.15]</td>
<td>-1.04 [-3.08, 1.00]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>-0.78 [-2.76, 1.20]</td>
<td>-1.04 [-3.08, 1.00]</td>
</tr>
<tr>
<td><strong>HM + pharmacotherapy vs pharmacotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil RCT</td>
<td>1 (29,32); [25]</td>
<td>-2.30 [-3.71, -0.89]</td>
<td>-2.00 [-3.52, -0.48]</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS</td>
<td>1 (12,11); [17]</td>
<td>24m 0.10 [-0.79, 0.99]</td>
<td>24m 0.00 [-0.72, 0.72].</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds</td>
<td>1 (45,46); [26]</td>
<td>10w -0.88 [-1.16, -0.60]*;</td>
<td>10w 0.03 [-0.29, 0.35]; 20w -0.23 [-0.56, 0.10]; 25w -0.26 [-0.48, -0.04]*;</td>
</tr>
</tbody>
</table>

79
<table>
<thead>
<tr>
<th>Comparison</th>
<th>n studies (n participants EoT T,C); [study ID]</th>
<th>EoT; MD, RE; I²</th>
<th>T Baseline vs EoT; MD, RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI-J: ABERRANT MOTOR BEHAVIOUR; HM vs inactive controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-3.80 [-6.27, -1.33]</td>
<td>-1.10 [-3.43, 1.23]</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (45,43); [21]</td>
<td>0.80 [-0.92, 2.52]</td>
<td>-0.50 [-1.94, 0.94]</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>2 (72,68); [16,21]</td>
<td>-1.41 [-5.92, 3.09]; 89%</td>
<td>-0.67 [-1.89, 0.56]; 0%</td>
</tr>
<tr>
<td>HM vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); [31]</td>
<td>-0.00 [-0.10, 0.09]</td>
<td>0.02 [-0.06, 0.11]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>1.65 [-0.25, 3.55]</td>
<td>-0.85 [-3.15, 1.45]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>0.09 [-2.14, 2.32]</td>
<td>-0.85 [-3.15, 1.45]</td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil RCT</td>
<td>1 (29,32); [25]</td>
<td>0.80 [-1.20, 2.80]</td>
<td>-2.50 [-4.71, -0.29]</td>
</tr>
<tr>
<td>HM + pharmacotherapy vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-1.40 [-3.63, 0.83]</td>
<td>-2.10 [-4.19, -0.01]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>0.81 [-0.36, 1.98]</td>
<td>-1.39 [-2.99, 0.21]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>-0.47 [-1.90, 0.96]</td>
<td>-1.39 [-2.99, 0.21]</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds DRS</td>
<td>1 (45,46); [26]</td>
<td>10w -0.36 [-0.66, -0.06]<em>; 20w -0.86 [-1.34, -0.38]</em>; 25w -1.02 [-1.44, -0.60]*</td>
<td>10w -0.01 [-0.31, 0.29]; 20w -0.02 [-0.40, 0.36]; 25w 0.03 [-0.32, 0.38]</td>
</tr>
<tr>
<td>NPI-K: SLEEP AND NIGHT-TIME BEHAVIOUR CHANGE; HM vs inactive controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-1.40 [-3.63, 0.83]</td>
<td>-2.10 [-4.19, -0.01]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>0.81 [-0.36, 1.98]</td>
<td>-1.39 [-2.99, 0.21]</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>0.09 [-2.14, 2.32]</td>
<td>-0.85 [-3.15, 1.45]</td>
</tr>
<tr>
<td>HM + pharmacotherapy vs pharmacotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>1 (27,25); [16]</td>
<td>-0.90 [-3.05, 1.25];</td>
<td>-0.30 [-2.30, 1.70]</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>1 (26,25); [29]</td>
<td>0.01 [-0.20, 0.22];</td>
<td>0.00 [-0.26, 0.34];</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>1 (26,25); [29]</td>
<td>20w 0.01 [-0.20, 0.22];</td>
<td>20w 0.10 [-0.10, 0.30];</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds DRS</td>
<td>1 (45,46); [26]</td>
<td>10w -0.16 [-0.43, 0.11]; 20w 0.21 [-0.02, 0.44]</td>
<td>10w 0.04 [-0.26, 0.34]; 20w 0.16 [-0.08, 0.40]</td>
</tr>
</tbody>
</table>

C: control group; Baseline vs EoT: baseline versus end of treatment; EoT: end of treatment; MD: mean difference; HM: herbal medicine; meds: all participants could continue to take dementia medications, as prescribed and taken before trial commencement; NPI: Neuropsychiatric Inventory; NRS: non-randomised study; NYT: Ninjin’yoetito; RCT: randomised controlled trial; RE: random effects model; SZL: shen zhi ling; T: treatment Group; YKS: yokukansan; YSHZ: yi shen hua zhuo
*baseline imbalance between groups; * significant (p<0.05)
a all studies are RCTs except for NYT+ donepezil vs donepezil (Kudoh 2015, study ID [17])

All these studies specified BPSD as an inclusion criterion. Furukawa et al. (2015) required at least one of agitation/aggression or irritability/lability, and Iwasaki et al. (2005) required at least one of delusions, hallucinations, ‘violent behaviour’ (i.e. agitation/aggression) or apathy.
Due to differences in study designs, only the results of the *Yokukansan* studies by Iwasaki et al. (2005) and Mizukami et al. (2009) were suitable for pooling. When compared to no treatment (140 participants), improvements were detected after four weeks in the *Yokukansan* group for delusional symptoms (MD -2.80 [-5.00, -0.60] I² 72%); depression/dysphoria (MD -3.14 [-4.25, -2.03] I² 0%); irritability/lability (MD -1.34 [-2.55, -0.13] I² 0%) and agitation/aggression (MD -1.70 [-2.88, -0.52] I² 0%); but not for other NPI domains. Based on the one small study of participants with severe BPSD (77 participants), *Yokukansan* was not different to fluvoxamine or risperidone with no changes in either group for any domain (Teranishi et al., 2013). When combined with donepezil in a single study (61 participants), *Yokukansan* produced significant reductions in delusions (MD -3.00 [-4.35, -1.65]), hallucinations (MD -3.00 [-4.24, -1.76]), agitation/aggression (MD -1.40 [-2.73, -0.07]) and anxiety (MD -1.70 [-3.03, -0.37]) (Okahara et al., 2010).

For the 12 NPI-Q domains (137 participants), after four weeks there were no significant differences between *Yokukansan* and placebo for any domain, but significant improvements were detected within the *Yokukansan* group for agitation/aggression and irritability/lability (Furukawa et al., 2015) (Table 4.10).

For MMSE, no significant differences were detected between *Yokukansan* and placebo in one study (137 participants) and there were no significant changes within either group (Furukawa et al., 2015). Compared to no treatment (188 participants), *Yokukansan*/YKCH did not improve MMSE scores after four weeks of treatment (MD 0.35 [-1.39, 2.08] I² 0%, 3 RCTs). For the comparisons with pharmacotherapies (114 participants), no significant differences were detected between *Yokukansan* and fluvoxamine or risperidone. No differences were evident for adding *Yokukansan* to
donepezil or sulpiride, when compared to these single pharmacotherapies (75 participants) (Okahara et al., 2010; Monji et al., 2009) (Table 4.7).

4. Other HMs (11 RCTs, 1 non-randomised study)

For total NPI, five RCTs and one non-randomised study tested multi-ingredient formulae (Table 4.2). Studies were not suitable for pooling due to differences in interventions, trial design and baseline imbalance. Results of meta-analysis are shown in Figure 4.2, Table 4.11, and Figures 4.8 to 4.12. No difference was detected between FZS and placebo. YSHZ plus placebo was not significantly different to donepezil plus placebo but there was a small improvement within the YSHZ group. TXLJN appeared significantly superior to piracetam, but a baseline imbalance in NPI scores was detected. YXQN showed no additional benefit when combined with donepezil. In the single non-randomised study which added NYT to donepezil (23 participants), no significant differences between groups were detected at any time-point for two years.

Table 4.11: Meta-analysis results for the other HM studies at end of treatment and change within treatment groups.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>n studies (n participants at EoT: T, C); duration; [study ID]</th>
<th>T vs C at EoT; RE; $I^2$</th>
<th>Treatment group Baseline vs EoT; RE; $I^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPI 10/12 (total scores)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FZS vs placebo</td>
<td>1 (12,10); 12wks; [1]</td>
<td>MD -3.67 [-8.53, 1.19]</td>
<td>MD -2.67 [-6.48, 1.14]</td>
</tr>
<tr>
<td>YSHZ decoction + placebo vs donepezil + placeboa</td>
<td>1 (58,55); 24wks EoT; 1 (54,50); 48wks FU; [31]</td>
<td>24wks: MD -0.54 [-1.17, 0.09]; 48wks: MD -0.57 [-1.35, 0.21]</td>
<td>24wks: MD -0.82 [-1.59, -0.05]<em>; 48wks: MD -0.87 [-1.73, -0.01]</em></td>
</tr>
<tr>
<td>TXLJN vs piracetam</td>
<td>1 (50,50); 24wks; [10]</td>
<td>MD -7.89 [-9.52, -6.26]*#</td>
<td>MD -11.10 [-12.77, -9.43]*</td>
</tr>
<tr>
<td>YXQN + donepezil vs donepezilb</td>
<td>1 (18,18); 12wks; [3]</td>
<td>MD -2.44 [-6.95, 2.07]</td>
<td>MD -13.77 [-19.11, -8.43]*</td>
</tr>
<tr>
<td>BSTLT + donepezil + piracetam vs donepezil + piracetamb</td>
<td>1 (40,40); 24wks; [14]</td>
<td>MD -3.36 [-4.84, -1.88]*</td>
<td>MD -10.37 [-12.01, -8.73]*</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil (non-randomised study)</td>
<td>1 (12,11); 96wks EoT; [17]</td>
<td>24wks:MD -3.00 [-6.14, 0.14]; 48wks: MD -1.50 [-5.51, 2.51]; 72wks: MD -1.20 [-5.20, 2.80]; 96wks: MD -1.50 [-5.14, 2.14]</td>
<td>24wks: MD -2.10 [-5.14, 0.94]; 48wks: MD -1.20 [-5.04, 2.64]; 72wks: MD 0.40 [-3.24, 4.04]; 96wks: MD 0.10 [-3.62, 3.82]</td>
</tr>
<tr>
<td><strong>BEHAVE-AD</strong></td>
<td></td>
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</tr>
<tr>
<td>NLKL granules vs risperidone</td>
<td>1 (30,30); 4wks; [2]</td>
<td>MD 0.20 [-3.17, 3.57]</td>
<td>MD -9.10 [-12.60, -5.60]*</td>
</tr>
<tr>
<td>TQHXT vs oxcarbazepine</td>
<td>1 (35,35); 8wks; [27]</td>
<td>MD -2.34 [-4.15, -0.53]*</td>
<td>MD -10.95 [-13.43, -8.47]*</td>
</tr>
<tr>
<td>Comparison</td>
<td>n studies (n participants at EoT; T, C); duration; [study ID]</td>
<td>T vs C at EoT; RE; I²</td>
<td>Treatment group Baseline vs EoT; RE; I²</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-----------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>BSHTT vs nimodipine + piracetam</td>
<td>1 (59,57); 8wks; [20]</td>
<td>MD -1.97 [-4.15, 0.21]</td>
<td>MD -2.94 [-5.21, -0.67]*</td>
</tr>
<tr>
<td>Total: HM vs pharmacotherapy</td>
<td>3 (124,122); 4-8 wks; [2,20,27]</td>
<td>MD -1.84 [-3.13, -0.55]*</td>
<td>MD -7.61 [-12.94, -2.28]*; 91%</td>
</tr>
<tr>
<td>ZBDHT + donepezil vs donepezil</td>
<td>1 (30,30); 4wks; [7]</td>
<td>MD -2.70 [-4.39, -1.01]*</td>
<td>MD -6.50 [-7.90, -5.10]*</td>
</tr>
<tr>
<td>BSHTF + donepezil vs donepezil</td>
<td>1 (62,65); 12wks; [8]</td>
<td>MD -1.10 [-2.17, -0.03]*</td>
<td>MD -5.60 [-6.67, -4.53]*</td>
</tr>
<tr>
<td>Total RCTs HM + donepezil vs donepezil</td>
<td>2 (92,95); 4-12wks; [7,8]</td>
<td>MD -1.76 [-3.30, -0.22]*</td>
<td>MD -5.93 [-6.78, -5.08]*; 0%</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); 12wks interim, 24wks EoT, 48wks FU; [31]</td>
<td>12wks: MD 0.64 [-0.84, 2.12]; 24wks: MD 1.14 [-0.40, 2.68]; 48wks: MD 1.77 [0.16, 3.38]*</td>
<td>12wks MD 1.29 [-0.21, 2.79]; 24wks MD 2.18 [0.59, 3.77]<em>; 48wks MD 1.88 [0.30, 3.46]</em></td>
</tr>
<tr>
<td>TXLJN vs piracetam</td>
<td>1 (50,50); 6mths; [10]</td>
<td>MD 1.49 [-0.53, 3.51]*</td>
<td>MD 4.89 [3.02, 6.76]*</td>
</tr>
<tr>
<td>TQHXT vs oxcarbazepine</td>
<td>1 (35,35); 8wks; [27]</td>
<td>MD 2.62 [0.38, 4.86]*</td>
<td>MD 2.23 [-0.03, 4.49]</td>
</tr>
<tr>
<td>Total: HM vs pharmacotherapy (no baseline imbalance)</td>
<td>2 (93,90); 8-24wks; [27,31]</td>
<td>MD 1.71 [0.30, 3.11]*; 0%</td>
<td>MD 2.20 [0.89, 3.50]*; 0%</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds c</td>
<td>1 (45,46); 10wks interim, 20wks EoT, 25wks FU; [26]</td>
<td>10wks: MD -0.40 [-1.60, 0.80]; 20wks: MD -0.07 [-1.28, 1.14]; 25wks: MD 0.60 [-0.33, 1.53]*</td>
<td>10wks: MD -0.50 [-1.55, 0.55]; 20wks: MD -1.40 [-2.25, -0.55]<em>; 25wks: MD -1.60 [-2.30, -0.90]</em></td>
</tr>
<tr>
<td>YXQN + donepezil vs donepezil</td>
<td>1 (18,18); 12wks; [3]</td>
<td>MD -1.46 [-4.46, 1.54]*</td>
<td>MD 2.85 [0.19, 5.51]*</td>
</tr>
<tr>
<td>ZBDHT + donepezil vs donepezil</td>
<td>1 (30,30); 4wks; [7]</td>
<td>MD 0.47 [-0.82, 1.76]</td>
<td>MD 1.64 [0.30, 2.98]*</td>
</tr>
<tr>
<td>BSTLT + donepezil + piracetam vs donepezil + piracetam</td>
<td>1 (40,40); 24wks; [14]</td>
<td>MD 4.15 [2.49, 5.81]*</td>
<td>MD 8.51 [7.04, 9.98]*</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil (non-randomised study)</td>
<td>1 (12,11); 24months; [17]</td>
<td>MD 0.22 [-1.62, 2.06]</td>
<td>MD 0.08 [-1.45, 1.61]</td>
</tr>
<tr>
<td><strong>ADAS-cog</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FZS vs placebo</td>
<td>1 (12,10); 12wks; [1]</td>
<td>MD -2.00 [-6.67, 2.67]</td>
<td>MD -0.58 [-5.35, 4.19]</td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>1 (58,55); 12 wks, 24wks (EoT); 48wks FU; [31]</td>
<td>12wks MD -3.38 [-6.32, -0.44]<em>; 24wks MD -4.06 [-7.11, -1.01]</em>; 48wks MD -5.51 [-9.08, -1.94]*</td>
<td>12wks MD -1.40 [-4.42, 1.62]; 24wks MD -3.85 [-6.94, -0.76]*; 48wks (no data)</td>
</tr>
<tr>
<td>BSTLT + donepezil + piracetam vs donepezil +</td>
<td>1 (40,40); 24wks; [14]</td>
<td>MD -11.77 [-14.75, -8.79]*</td>
<td>MD -28.79 [-32.02, -25.56]*</td>
</tr>
<tr>
<td>Comparison</td>
<td>n studies (n participants at EoT: T, C); duration; [study ID]</td>
<td>T vs C at EoT; RE; ( I^2 )</td>
<td>Treatment group Baseline vs EoT; RE; ( I^2 )</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------</td>
<td>-----------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>piracetam</td>
<td>NYT + donepezil vs donepezil (non-randomised study) 1 (12,11); 24months; [17]</td>
<td>MD -6.00 [-9.55, -2.45]*</td>
<td>MD -4.70 [-8.17, -1.23]*</td>
</tr>
</tbody>
</table>

ADAS-cog: Alzheimer’s disease Assessment Scale-cognitive section; ADAS-noncog: Alzheimer’s disease Assessment Scale-noncognitive section; BEHAVE-AD: Behavioural Pathology in Alzheimer’s disease Scale; BSHTF: Bu shen hua tan fang; BSHTT: Bu shen hua tan tang; BSTLT: Bu shen tong luo tang; C: control group; EoT: end of treatment; FU: follow-up; FZS: fu zhi san; HM: Herbal medicine; \( I^2 \): Index of heterogeneity; MD: Mean Difference; MMSE: Mini-Mental State Examination; meds: all participants could continue to take dementia medications, as prescribed and taken before trial commencement; n: number; NLKL: Nao ling ke li; NPI: Neuropsychiatric Inventory; NYT: Ninjin’yoeito; RCT: randomised controlled trial; RE: random effects model; RoB: risk of bias; SMD: standardised mean difference; SZL: Shen zhi ling; T: treatment group; TQHXT: Tong qiao huo xue tang; TXLJN: Tong xin luo jiao nan; UC: supportive and conservative usual care; wks: weeks; YSHZ: Yi shen hua zhuo; YXQN: Yang xue qing nao; ZBDHT: Zhi bai di huang tang

#baseline imbalance (removed from pool); *significant,

Note: SMD was used when scores of NPI 10 and NPI 12 were pooled and when it was unclear whether NPI 10 or NPI 12 was used in the study.

* BPSD not required as inclusion criteria

b study judged mainly ‘unclear’ or ‘high’ risk of bias

\(^{\dagger}\) Pan et al. (2014): all participants continued to take other dementia medications unchanged (Huperzine A, aniracetam, memantine, donepezil, rivastigmine or galantamine, as previously prescribed)

NPI domain scores were reported in three studies of multi-ingredient formulae but one of these did not report NPI total scores (Pan et al., 2014). It was unclear whether all participants in these studies had BPSD at baseline. For YSHZ versus donepezil, there were no changes in either group for any of the domains (Zhang et al., 2015) but BPSD were barely present at baseline. SZL plus dementia medications (Pan et al., 2014) were superior to placebo plus medications for hallucinations, agitation/aggression, irritability/lability, aberrant motor behaviour, and sleep and night-time behaviour disturbances at 25 weeks. In the non-randomised study (Kudoh et al., 2015), NYT plus donepezil showed an increase in euphoria/elation and a decrease in depression/dysphoria compared to donepezil after two years but no changes in other domains (Table 4.11).

Five studies assessed changes in BPSD using BEHAVE-AD (433 participants). All tested different Chinese multi-ingredient formulae (Table 4.2). One study reported that BPSD were required for inclusion (Guo et al., 2013) and one required AD with agitation (Pu et al., 2014). The pool of three studies of comparisons with pharmacotherapy (246 participants) showed a significant difference in favour of HM (MD -7.61 [-12.94, -2.28]; \( I^2 \) 91%) but there was considerable heterogeneity and the reported magnitude of change in two of the studies was unusually large (Chen & Gao, 2013; Pu et al., 2014). For the two studies that combined HMs with donepezil (Guo et al., 2011; Guo et al., 2013), results favoured the HM plus donepezil group at EoT (MD -1.76 [-3.30, -0.22]; \( I^2 \) 59%) (Table 4.11; Figure 4.5).
Seven RCTs and one non-randomised study used MMSE to assess changes in cognitive symptoms. For YSHZ plus placebo versus donepezil plus placebo there was a significant difference between groups favouring YSHZ at 48 weeks (follow-up) but not at other measurement points (MD 1.77 [0.16, 3.38]). However, the changes were small and participants had mild symptoms at baseline. Pu et al. (2014) found a non-significant worsening of cognitive function in the oxcarbazepine group compared to a non-significant improvement in the TQHXT group, resulting in a significant difference between groups at EoT. There was no additional benefit for adding ZBDHT or YXQN to donepezil but for YXQN there was a non-significant baseline imbalance favouring the donepezil monotherapy (Guo et al., 2011; Cheng & Zang, 2013). In Hu et al. (2015), the combination of BSTLT plus donepezil and piracetam showed a large benefit at 24 weeks (MD 4.15 [2.49, 5.81]). For SZL there were significant increases in MMSE scores within the SZL group but the comparison with the AD medication group was marred by a baseline imbalance (Pan et al., 2014). No differences in MMSE were evident for adding NYT to donepezil compared to donepezil (Kudoh et al., 2015) (Table 4.11).

Three studies used ADAS-cog to assess comparisons with placebo, no treatment or usual care (116 participants). There were no significant changes in any group. A significant difference in ADAS-cog was detected favouring YSHZ compared to donepezil at 12 weeks, 24 weeks (EoT) and 48 weeks (follow-up) (113 participants). However, a non-significant baseline imbalance was detected favouring the YSHZ group which is likely to have confounded this result. Nevertheless, there was a significant improvement within the YSHZ group at 24 weeks. For NYT combined with donepezil (23 participants), there was a significant difference between groups favouring NYT at 24 months (MD -6.00 [-9.55, -2.45], 1 non-randomised study) (Kudoh et al., 2015).

---

**Table 4.11:** Comparison of MMSE scores between YSHZ and donepezil

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen 2013</td>
<td>7.2</td>
<td>6.6</td>
<td>30</td>
<td>7</td>
<td>6.8</td>
<td>20</td>
<td>14.0%</td>
<td>0.20 [-3.17, 3.57]</td>
</tr>
<tr>
<td>Mao 2003</td>
<td>9.33</td>
<td>5.74</td>
<td>59</td>
<td>11.8</td>
<td>5.22</td>
<td>57</td>
<td>34.9%</td>
<td>-1.97 [4.16, 0.21]</td>
</tr>
<tr>
<td>Pu 2014</td>
<td>6.36</td>
<td>4.01</td>
<td>25</td>
<td>8.19</td>
<td>2.73</td>
<td>25</td>
<td>50.4%</td>
<td>-2.34 [4.16, -0.52]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>124</td>
<td>122</td>
<td>100.0%</td>
<td>122</td>
<td>100.0%</td>
<td>100.0%</td>
<td>122</td>
<td>-1.84 [-3.13, -0.55]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00, Q(1, df = 2) = 0.42, p = 0.81; I² = 0%

Test for overall effect: Z = 2.80 (p = 0.005)

Test for subgroup differences: Q(1, df = 1) = 0.24, p = 0.62; I² = 0%

---

**Figure 4.5:** Forest plot of BEHAVE-AD scores (MD; RE; 95% CI)
4.4.3  **Numbers of Dropouts**

Based on numbers of dropouts, the HMs were as well-tolerated as inactive or active controls. Adding HMs to pharmacotherapies did not change the numbers of dropouts although there were slightly more dropouts in the *C. longa* extract groups compared to placebo, as shown in Table 4.12.

**Table 4.12: Numbers of dropouts from included studies**

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Study name; duration</th>
<th>Total n participants at baseline (T,C)</th>
<th>T n dropouts</th>
<th>C n dropouts</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGb 761® vs placebo</td>
<td>Gavrilova 2014; 24wks</td>
<td>(80,80)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>EGb 761® vs placebo</td>
<td>Herrschaft 2012; 24wks</td>
<td>(205, 205)</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>EGb 761® vs placebo</td>
<td>Ihl 2011; 24wks</td>
<td>(206, 204)</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>EGb 761® vs placebo</td>
<td>Maurer 1997; 12wks</td>
<td>(10,10)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>EGb 761® vs placebo</td>
<td>Napryeyenko 2007; 22wks</td>
<td>(200, 200)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>EGb 761® vs placebo</td>
<td>Nikolova 2013; 22wks</td>
<td>(203, 205)</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td><strong>Subtotal EGb 761® vs placebo</strong></td>
<td>6 studies; 12 – 24wks</td>
<td>(904,904)</td>
<td>37 (4.1%)</td>
<td>30 (3.3%)</td>
</tr>
<tr>
<td>Fu Zhi San vs placebo</td>
<td>Bi 2011; 12wks</td>
<td>(13,12)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>YKS vs placebo</td>
<td>Furukawa 2015; 4wks</td>
<td>(74,70)</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>Hamazaki-Fujita 2013; 4wks</td>
<td>(17,21)</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>Iwasaki 2005a; 4wks</td>
<td>(27,25)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>Mizukami 2009; 4wks</td>
<td>(54,52)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Subtotal YKS or YKSCH vs no treatment</strong></td>
<td>4 studies; 4wks</td>
<td>(172,168)</td>
<td>6 (3.4%)</td>
<td>7 (4.2%)</td>
</tr>
<tr>
<td>Ginseng plus UC vs UC</td>
<td>Lee 2008; 12wks</td>
<td>(58,39)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Ginseng plus UC vs UC</td>
<td>Heo 2012; 12wks</td>
<td>(10,10)*</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total HM vs inactive</strong></td>
<td>11 studies; 4wks – 24wks</td>
<td>(954, 928)</td>
<td>50 (5.2%)</td>
<td>48 (5.2%)</td>
</tr>
<tr>
<td>EGb 761® + placebo vs donepezil + placebo</td>
<td>Yancheva 2009; 22wks</td>
<td>(31,33)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>Zhang 2015; 24wks</td>
<td>(72,72)</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>Teranishi 2013; 8wks</td>
<td>(26,25)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>Furuhashi 2011; 4wks</td>
<td>(18,20)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>Teranishi 2013; 8wks</td>
<td>(26,25)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><strong>Subtotal YKS vs active control</strong></td>
<td>2 studies, 3 groups; 4 – 8wks</td>
<td>(44,70)</td>
<td>1 (2%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>NLKL vs risperidone</td>
<td>Chen 2013; 4wks</td>
<td>(30,30)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TXLJN vs piracetam</td>
<td>Hao 2006; 24wks</td>
<td>(50,50)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BSHTT vs nimodipine + piracetam</td>
<td>Miao 2009; 8wks</td>
<td>(59,57)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TQHXT vs oxcarbazepine</td>
<td>Pu 2014; 8wks</td>
<td>(35,35)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total HM vs pharmacotherapy</strong></td>
<td>4wks – 24wks</td>
<td>(347, 347)</td>
<td>21 (6.1%)</td>
<td>31 (8.9%)</td>
</tr>
<tr>
<td><strong>Total HM vs PT (excluding studies judged ‘unclear’ risk of selective reporting bias)</strong></td>
<td>4wks – 24wks</td>
<td>(173, 175)</td>
<td>21 (12.1%)</td>
<td>31 (17.7%)</td>
</tr>
<tr>
<td>EGb 761® + donepezil vs donepezil + placebo</td>
<td>Yancheva 2009 T2; 22wks</td>
<td>(32,33)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil</td>
<td>Okahara 2010; 4wks</td>
<td>(30,33)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Comparator</td>
<td>Study name; duration</td>
<td>Total n participants at baseline (T,C)</td>
<td>T n dropouts</td>
<td>C n dropouts</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------</td>
<td>----------------------------------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil NRS</td>
<td>Kudoh 2015; 24m</td>
<td>(12,11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>YXQN + donepezil vs donepezil</td>
<td>Cheng 2013; 12wks</td>
<td>(18,18)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ZBDHT + donepezil vs donepezil</td>
<td>Guo 2011b; 4wks</td>
<td>(30,30)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BSHTF + donepezil vs donepezil</td>
<td>Guo 2013; 12wks</td>
<td>(62,65)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BSTLT + donepezil + piracetam vs donepezil + piracetam</td>
<td>Hu 2015; 24wks</td>
<td>(40,40)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>YKS + sulpiride vs sulpiride</td>
<td>Monji 2009; 12wks</td>
<td>(10,5)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds</td>
<td>Pan 2014; 20wks</td>
<td>(45,46)</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Ginseng + meds vs meds (L=low dose; H=high dose)</td>
<td>Heo 2008; 12wks</td>
<td>L: (15,31); H: (15,31)</td>
<td>L: 2; H: 2</td>
<td>3</td>
</tr>
<tr>
<td>CCC + meds vs placebo + meds</td>
<td>Ringman 2012; 24wks</td>
<td>L: (12,12); H: (12,12)</td>
<td>L: 3; H: 2</td>
<td>1</td>
</tr>
<tr>
<td>Total HM + PT vs PT</td>
<td>4 - 96wks</td>
<td>(333, 324)</td>
<td>16 (4.8%)</td>
<td>12 (3.7%)</td>
</tr>
<tr>
<td>Total HM + PT vs PT (excluding studies judged ‘unclear’ for selective outcome reporting bias)</td>
<td>4 - 96wks</td>
<td>(183, 171)</td>
<td>16 (8.7%)</td>
<td>12 (7.0%)</td>
</tr>
</tbody>
</table>

BSHTF: Bu shen hua tan fang; BSHTT: Bu shen hua tan tang; BSTLT: Bu shen tong luo tang; C: control group; CCC: Curcumin C3 Complex; EGb 761: Extract of Ginkgo biloba leaf 761; H: high dose group; HM: herbal medicine; L: low dose group; NLKL: Nao ling ke li; NYT: Ninjin’yoeito; PT: pharmacotherapy; T: treatment Group; TQHXT: Tong qiao huo xue tang; TXLJN: Tong xin luo jiao nan; SZL: Shen zhi ling; UC: usual care; YKS: Yokukansan; YKCH: Yokukansan-ka-chimpihange; YSHZ: Yi shen hua zhuo; YXQN: Yang xue qing niao; ZBDHT: Zhi bai di huang tang

* excluding low dose P. ginseng groups
4.4.4 Numbers and types of adverse events

More AEs were reported in both inactive and active control groups, compared to the HM groups or HM plus pharmacotherapy groups, as shown in Table 4.13. AEs were reported clearly in the EGb 761® studies. Spontaneous bleeding has been reported to be an AE of G. biloba (Posadzki et al., 2013) but no cases were reported in participants taking EGb 761® for up to 24 weeks in the BPSD studies and there were no serious AEs (SAEs) judged as related to EGb 761®. Diarrhoea and black stools consistent with melaena were observed in two participants in the low dose C. longa extract group, resulting in withdrawal from the study, although there was no conclusive evidence of gastrointestinal haemorrhage or haemodynamic compromise (Ringman et al., 2012). In the three studies of P. ginseng, there were no differences between groups in numbers of AEs and there were no SAEs, as shown in Tables 4.14(b) and 4.12(c).

Table 4.13: Numbers of reported adverse events from included studies

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Study name; duration</th>
<th>n participants baseline (T,C)</th>
<th>T no of AE</th>
<th>C no of AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGb 761 vs placebo</td>
<td>Gavrilova 2014; 24wks</td>
<td>(80,80)</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td>EGb 761 vs placebo</td>
<td>Herrschaft 2012; 24wks</td>
<td>(205,205)</td>
<td>45</td>
<td>57</td>
</tr>
<tr>
<td>EGb 761 vs placebo</td>
<td>Ihl 2011; 24wks</td>
<td>(206,204)</td>
<td>257</td>
<td>261</td>
</tr>
<tr>
<td>EGb 761 vs placebo</td>
<td>Maurer 1997; 12wks</td>
<td>(9,9)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>EGb 761 vs placebo</td>
<td>Napryeyenko 2007; 22wks</td>
<td>(200,200)</td>
<td>302</td>
<td>481</td>
</tr>
<tr>
<td>EGb 761 vs placebo</td>
<td>Nikolova 2013; 22wks</td>
<td>(196,201)</td>
<td>145</td>
<td>130</td>
</tr>
<tr>
<td>Total EGb 761 vs placebo</td>
<td>12 – 24wks</td>
<td>(896,899)</td>
<td>786 (87.7%)</td>
<td>975 (108.5%)</td>
</tr>
<tr>
<td>FZS vs placebo</td>
<td>Bi 2011; 12wks</td>
<td>(13,12)</td>
<td>unclear</td>
<td>unclear</td>
</tr>
<tr>
<td>YKS vs placebo</td>
<td>Furukawa 2015; 4wks</td>
<td>(75,70)</td>
<td>unclear</td>
<td>unclear</td>
</tr>
<tr>
<td>YKSCH vs no treatment</td>
<td>Hamazaki-Fujita 2013; 4wks</td>
<td>(17,21)</td>
<td>unclear</td>
<td>unclear</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>Iwasaki 2005a; 4wks</td>
<td>(27,25)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>YKS vs no treatment</td>
<td>Mizukami 2009; 4wks</td>
<td>(54,52)</td>
<td>unclear</td>
<td>unclear</td>
</tr>
<tr>
<td>Ginseng + UC vs UC</td>
<td>Lee 2008; 12wks</td>
<td>(58,39)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Ginseng + UC vs UC</td>
<td>Heo 2012; 12wks</td>
<td>(10,10)a</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total HM vs inactive</td>
<td>4 - 24wks</td>
<td>(880,858)</td>
<td>652 (74.1%)</td>
<td>855 (99.7%)</td>
</tr>
<tr>
<td>Total HM vs inactive; excluding ‘unclear’ AEs studies</td>
<td>4 - 24wks</td>
<td>(786, 763)</td>
<td>652 (83.0%)</td>
<td>855 (112.1%)</td>
</tr>
<tr>
<td>EGb 761 + placebo vs donepezil + placebo</td>
<td>Yancheva 2009; 22wks</td>
<td>(31,33)</td>
<td>27</td>
<td>51</td>
</tr>
<tr>
<td>YSHZ + placebo vs donepezil + placebo</td>
<td>Zhang 2015; 24wks</td>
<td>(72,72)</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>YKS vs fluvoxamine</td>
<td>Teranishi 2013; 8wks</td>
<td>(26,25)</td>
<td>19</td>
<td>21</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>Furuhashi 2011; 4wks</td>
<td>(18,20)</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>YKS vs risperidone</td>
<td>Teranishi 2013; 8wks</td>
<td>(26,25)</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Subtotal YKS vs active</td>
<td>2 studies; 3 groups; 4 – 8wks</td>
<td>(44,70)</td>
<td>37 (84%)</td>
<td>63 (90%)</td>
</tr>
<tr>
<td>HM vs risperidone</td>
<td>Chen 2013; 4wks</td>
<td>(30,30)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>TXLJN vs piracetam</td>
<td>Hao 2006; 24wks</td>
<td>(50,50)</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>BSHTT vs nimopidine</td>
<td>Miao 2009; 8wks</td>
<td>(60,60)</td>
<td>None reported</td>
<td>None reported</td>
</tr>
</tbody>
</table>
### Comparator Study name; duration n participants baseline (T,C) T no of AE C no of AE

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Study name; duration</th>
<th>n participants baseline (T,C)</th>
<th>T no of AE</th>
<th>C no of AE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TQHXT vs oxcarbazepine</td>
<td>Pu 2014; 8wks</td>
<td>(35,35)</td>
<td>8</td>
<td>23</td>
</tr>
<tr>
<td>Total HM vs active</td>
<td>6 studies; 7 groups; 4–24wks</td>
<td>(348,350)</td>
<td>105 (30.2%)</td>
<td>155 (44.3%)</td>
</tr>
<tr>
<td>EGb 761 + donepezil vs placebo + donepezil</td>
<td>Yancheva 2009 T2; 22wks</td>
<td>(32,33)</td>
<td>29</td>
<td>51</td>
</tr>
<tr>
<td>YKS + donepezil vs donepezil</td>
<td>Okahara 2010; 4wks</td>
<td>(30,33)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NYT + donepezil vs donepezil</td>
<td>Kudoh 2015; 96wks</td>
<td>(12,11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>YKQXN + donepezil vs donepezil</td>
<td>Cheng 2011; 12wks</td>
<td>(18,18)</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>ZBDHT + donepezil vs donepezil</td>
<td>Guo 2011b; 4wks</td>
<td>(30,30)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>BSHTF + donepezil vs donepezil</td>
<td>Guo 2013; 12wks</td>
<td>(62,65)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BSTLT + donepezil + piracetam vs donepezil + piracetam</td>
<td>Hu 2015; 24wks</td>
<td>(40,40)</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>YKS + sulpiride vs sulpiride</td>
<td>Monji 2009; 12wks</td>
<td>(10,5)</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>SZL + meds vs placebo + meds</td>
<td>Pan 2014; 20wks</td>
<td>(45,46)</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ginseng + meds vs meds</td>
<td>Heo 2008; 12wks</td>
<td>Low dose:(15,31); High dose:(15,31)</td>
<td>L: 2; H: 2</td>
<td>3</td>
</tr>
<tr>
<td>CCC + meds vs placebo + meds</td>
<td>Ringman 2012; 24wks</td>
<td>L: (12,12); H: (12,12)</td>
<td>L&amp;H: 100% of participants had AEs</td>
<td>91.7% of participants had AEs</td>
</tr>
<tr>
<td>Total HM + PT vs PT (excluding Ringman 2012 as only percentages reported)</td>
<td>4 - 96wks</td>
<td>(309, 343)</td>
<td>42 (13.6%)</td>
<td>60 (17.5%)</td>
</tr>
</tbody>
</table>

BSHTF: Bu shen hua tan fang; C: control Group; CCC: Curcumin C3 Complex; EGb 761: Extract of Ginkgo biloba leaf 761; FZS: Fu zhi san; H: high dose group; HM: herbal medicine; L: low dose group; meds: all participants could continue to take dementia medications, as prescribed and taken before trial commencement; NYT: Ninjin’yoeto; PT: pharmacotherapy; T: treatment group; TXLJN: Tong xin luo jiao nan; SZL: Shen zhi ling; UC: usual care; YKS: Yokukansan; YKCH: Yokukansan-ka-chimpi-hange; YSHZ: Yi shen hua zhua; ZBDHT: Zhi bai di huang tang

*excluding low dose P. ginseng groups*

For Yokukansan and YKCH, AE reporting was unclear in three of the eight studies. Hypokalaemia was reported in four participants in two studies. This was monitored and managed. Other AEs included gastrointestinal symptoms and sedation. In the 12 studies of other HM formulae, AEs were not reported clearly in five studies. In the three placebo-controlled studies of HM formulae (Bi et al., 2011; Pan et al., 2014; Zhang et al., 2015) there were two SAEs (cerebral infarctions) but these were not thought to be related to the interventions. Of all included studies, 11 SAEs were reported but these were not apparently related to the interventions, as described in Tables 4.14 to 4.16.
Table 4.14: Details of reported adverse events from included studies testing EGb 761®

<table>
<thead>
<tr>
<th>Study name; comparator; duration; total n participants</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gavrilova 2014; placebo; 24wks; 160</td>
<td>T: 37; C:46; headache: T6, C9; increased blood pressure: T6, C7; respiratory tract infection: T7, C3; dyspepsia/epigastric discomfort: T4, C1; no SAEs in either group.</td>
</tr>
<tr>
<td>Herrschaft 2012; placebo; 24wks; 410</td>
<td>SAE: T: 3; C: 1, T: 1 lethal cardiac arrest due to chronic heart failure in a participant suffering from multiple illnesses, 1 lethal ischaemic infarction in a patient with a history of diabetes mellitus, hypertension, atherosclerosis, myocardial infarction and previous stroke, 1 transitory ischaemic attack in a participant with insufficiently controlled arterial hypertension; T: 45; C: 57; NS, but most common AE was headache.</td>
</tr>
<tr>
<td>Ihl 2011; placebo; 24wks; 410</td>
<td>SAE: T: 2, C: 2, T: 1 ischaemic stroke, 1 stage IV lung cancer; C: 1 ischaemic stroke, 1 rapid deterioration of intellectual and motor function. SAEs were considered unrelated to study medication; AE: T: 255 AE for 139 participants; C: 261 AE for 141 patients; headache: T43, C38; respiratory tract infection: T27, C20; blood pressure increased, hypertension: T22, C21; dizziness: T19, C23; Diarrhoea: T9; C13; Angina pectoris: T6, C12; Tinnitus: T2, C15</td>
</tr>
<tr>
<td>Maurer 1997; placebo; 12wks; 20</td>
<td>‘No adverse events were reported during the study’. AEs not reported.</td>
</tr>
<tr>
<td>Napryeyenko 2007; placebo; 22wks; 400</td>
<td>T: 302 AEs in 166 participants; 7 nonfatal SAE in 7 patients; headache: 49; angina pectoris: 20; dizziness: 12; back pain: 12; diarrhoea: 18; tinnitus: 9; cough: 14; influenza: 14; hypertensive crisis: 10; URTI: 10; blood pressure increased: 4; C: 178 patients reported 481 AEs; 13 nonfatal SAE in 11 patients; headache: 85; angina pectoris: 35; dizziness: 36; back pain: 22; diarrhoea: 16; tinnitus: 18; cough: 11; influenza: 11; hypertensive crisis: 12; URTI: 10; blood pressure increased: 13; No bleeding in either group</td>
</tr>
<tr>
<td>Nikolova 2013; placebo; 22wks; 397</td>
<td>T: 6 SAE in 6 participants; 145 AEs in 83 participants; NS; C: 6 SAE in 6 participants; 130 AE in 87 participants; NS. SAE judged as potentially related to EGb 761.</td>
</tr>
<tr>
<td>Yancheva 2009; placebo + donepezil; 22wks; 96</td>
<td>T1: 1 SAE: (1 rapid and severe physical and mental deterioration due to incompletely understood somatic disease, judged as unrelated to study drug (EGb 761); 26 AE in 10 participants; T2:29 AEs in 18 participants; C: 51 AEs in 24 participants. Headache: T1 2; T2 3, C 6; insomnia: T1: 4; T2: 2; C: 4; diarrhoea: T1: 1; T2: 0; C: 5; fatigue: T1: 1; T2: 2; C: 3</td>
</tr>
</tbody>
</table>

AE: adverse event; C: control group; n: number; EGb 761: Extract of Ginkgo biloba leaf 761; n: number; NS: not specified; SAE: serious adverse event; T: treatment group; URTI: upper respiratory tract infection; wks: weeks

Table 4.15: Details of adverse events reported in included studies testing Yokukansan or YKCH

<table>
<thead>
<tr>
<th>Study name; comparator; duration; total n participants</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hamazaki-Fujita 2013; no treatment; 4wks; 41</td>
<td>2; vomiting, hypertension</td>
</tr>
<tr>
<td>Furuhashi 2011; risperidone; 4wks; 38</td>
<td>T:1 (0 constipation, 0 somnolence, 1 diarrhoea); C: 3 (2 constipation, 1 somnolence, 0 diarrhoea); EPS not observed in either group; no clinically meaningful changes in vital signs, laboratory data or ECG in either group</td>
</tr>
<tr>
<td>Furukawa 2015; placebo; 4wks; 145</td>
<td>T: 3 hypokalaemia; C: 0 hypokalaemia</td>
</tr>
<tr>
<td>Iwasaki 2005a; no treatment + tiapride hydrochloride if required; 4wks; 52</td>
<td>None but 2 oversedated after continuing YKS after trial finished; resolved when dosage reduced from 4.5 to 3.0g/ day</td>
</tr>
<tr>
<td>Mizukami 2009; no</td>
<td>SAE: 0; Total: 6 AEs. 3 gastrointestinal symptoms (vomiting/diarrhoea, epigastric</td>
</tr>
</tbody>
</table>

91
<table>
<thead>
<tr>
<th>Study Year</th>
<th>Intervention</th>
<th>Duration</th>
<th>AE Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monji 2009</td>
<td>Sulpiride</td>
<td>12wks</td>
<td>2 hypokalaemia; 1 EPS (no SAE observed); C: 1 oedema - dropped out</td>
</tr>
<tr>
<td>Okahara 2010</td>
<td>Donepezil hydrochloride</td>
<td>4wks</td>
<td>None observed</td>
</tr>
<tr>
<td>Teranishi 2013</td>
<td>C1: Risperidone; C2: Fluvoxamine</td>
<td>8wks</td>
<td>80 AEs including 11 SAEs (T: 5, C: 6). All AEs T: 19 total (1 fracture on day of entry, 1 head injury, 1 fall with contusion, 15 constipation, 1 fatigue, 2 insomnia); C: 43 total (1 fall with contusion, 1 oversedation, 1 swallowing difficulty, 1 stridor (abnormal breathing sound), 1 sudden death (cardiac infarct), 42 constipation, 5 muscle rigidity, 4 sialorrhoea (excessive drooling), 4 sedation, 3 fatigue, 1 insomnia; + (1 hallucination and delusion, 1 refusal to eat, 1 fall with contusion, 1 muscle rigidity. 4 dropouts due to AEs. AEs not considered related to interventions)</td>
</tr>
</tbody>
</table>

AE: adverse event; C: control group; ECG: electrocardiogram; EPS: extrapyramidal symptoms; SAE: serious adverse event; T: treatment group; tx: treatment period; wks: weeks; YKS: Yokukansan; YKCH: Yokukansan-ka-chimpihange
Table 4.16: Details of adverse events reported in the studies testing other HM interventions including *Ginseng* and *Curcuma*

<table>
<thead>
<tr>
<th>Study name; comparator; duration; total n participants</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bi 2011; placebo; 12wks; 25</td>
<td>Lab tests in normal ranges (including Liv/Kid function) 1 nausea, 1 constipation, C: 1 dropout due to medical condition, T: 1 dropout started donepezil instead</td>
</tr>
<tr>
<td>Chen 2013; risperidone; 4wks; 60</td>
<td>T: 2 insomnia, 1 constipation; C: 3 drowsiness, 6 insomnia, 4 headache, 15 dry mouth, 1 constipation, 4 EPS</td>
</tr>
<tr>
<td>Cheng 2013; donepezil; 12wks; 36</td>
<td>T: 1 over sedation, 1 diarrhoea; C: 2 diarrhoea, 1 insomnia, 1 urinary incontinence</td>
</tr>
<tr>
<td>Guo 2011b; donepezil; 4wks; 60</td>
<td>T: 2 nausea, 1 diarrhoea; C: 1 nausea</td>
</tr>
<tr>
<td>Guo 2013; donepezil; 12wks; 127</td>
<td>None observed</td>
</tr>
<tr>
<td>Hao 2006; piracetam; 6mths; 100</td>
<td>T: 7 stomach discomfort, nausea, anorexia; C: 9 nausea, anorexia</td>
</tr>
<tr>
<td>Heo 2008; continue same meds as before randomisation; 12wks; 61</td>
<td>T1: 2 nausea; T2: 2 feeling feverish; C: 1 nausea, 1 diarrhoea, 1 headache; all 7 who reported AEs withdrew from study (but were included in data analysis)</td>
</tr>
<tr>
<td>Heo 2012; conservative and supportive therapies; 12wks; 40</td>
<td>SAE: 0; all who reported AE withdrew from the study (4 from each group of 10); AE included urticaria, headache, palpitation, nausea, irritability; NS which groups but urticaria, headache, palpitation and irritability noted in <em>P. ginseng</em> groups and headache and nausea in control group</td>
</tr>
<tr>
<td>Hu 2015; donepezil + piracetam; 24wks; 80</td>
<td>None reported</td>
</tr>
<tr>
<td>Kudoh 2015; donepezil; 24mths; 23</td>
<td>None reported</td>
</tr>
<tr>
<td>Lee 2008; no treatment; 12wks; 97</td>
<td>T: 7, 2 heat sense; 1 dizziness, 1 nausea, 1 anorexia, 1 diarrhoea, 1 headache; C: 6, 3 diarrhoea, 1 headache, 1 dizziness, 1 anorexia</td>
</tr>
<tr>
<td>Miao 2009; nimopidine; 8wks; 120</td>
<td>None reported</td>
</tr>
<tr>
<td>Pan 2014; placebo + meds; 20wks EoT, 25wks FU; 98</td>
<td>SAE: 0; AE: dropouts due to bitter taste: T:2/C:0; dropouts due to conflict with other HM prescribed for concomitant diseases: T:2, C:3; no other adverse changes</td>
</tr>
<tr>
<td>Pu 2014; oxcarbazepine; 8wks; 70</td>
<td>T: 2 excessive sedation, 2 dizziness, 1 cognitive impairment, 3 constipation; C: 10 excessive sedation, 4 dizziness, 8 cognitive impairment, 1 constipation.</td>
</tr>
<tr>
<td>Ringman 2012; 24wks EoT+24wks open label</td>
<td>SAE: 0; AEs leading to dropouts: T1: 2 gastrointestinal symptoms of black stools consistent with melena and diarrhoea; 1 difficulty swallowing pills; T2: 1 diarrhoea; 1 difficulty swallowing pills; C: 1 worsened memory; open label phase: 1 deterioration of AD symptoms; 1 weight loss and low haematocrit; other AEs: T1: 6% of visits diarrhoea; T2: 8% diarrhoea; C: 4% diarrhoea; T1: 9% joint pain; T2: 5% joint pain; C: 15% joint pain.</td>
</tr>
<tr>
<td>Zhang 2015; donepezil; 24wks EoT, 48wks FU; 144</td>
<td>T: 1 cerebral infarction; 1 catching cold; 1 abnormal liver function test; 1 arthralgia; 1 constipation; C: 2 diarrhoea; 1 cerebral infarction; 1 catching cold; 1 abnormal liver function test; 1 insomnia</td>
</tr>
</tbody>
</table>

AD: Alzheimer’s disease; AE: adverse event; C: control group; EPS: extrapyramidal symptoms; FU: follow-up; meds: all participants could continue to take dementia medications, as prescribed and taken before trial commencement; NS: not specified; SAE: serious adverse event; T: treatment group; tx: treatment; wks: weeks;
4.5 Discussion

The EGb 761® studies had the largest sample sizes, consistently longer treatment durations and lower risk of bias. Results suggested EGb 761® was superior to placebo for improvements in BPSD. When added to donepezil, EGb 761® did not provide any additional benefit but this was based on one small study. EGb 761® was well-tolerated with no evidence of increased spontaneous bleeding or other AEs. Data were not available to enable assessment of which NPI domains showed significant improvements. However, Nacu and Hoerr (2016) reported that the largest improvements within the EGb 761® group in the RCT by Herrschaft et al. (2012) were in NPI domains with high severity at baseline, namely anxiety, apathy/indifference and sleep and night-time behavioural disturbances. There were also reductions in caregiver distress related to depression/dysphoria, anxiety, apathy/indifference, aberrant motor behaviour, and sleep and night-time behaviour disturbances.

For cognitive function based on SKT scores, positive results were detected for EGb 761® compared to placebo. In addition, Brondino et al. (2013) found sufficient evidence to support use of G. biloba for cognitive symptoms and ADL in people with dementia. Ihl (2013) found improvements in cognition and BPSD were comparable to those of cholinesterase inhibitors in four studies of EGb 761® for people with BPSD.

In two of the three studies of P. ginseng there was evidence of improvement in ADAS-noncog and MMSE scores within groups (Lee et al., 2008; Heo et al., 2012) but there were no changes in the other study (Heo et al., 2008). Different P. ginseng preparations were used and studies were small and unblinded, so it remains unclear whether P. ginseng supplementation affects BPSD. There was no evidence of improvement in NPI, ADAS-cog or MMSE in the C. longa extract study. This study was placebo-controlled and judged ‘low’ risk of bias in all domains but the sample size was small (36 participants at baseline) and low plasma curcumin measurements of participants indicated limited bioavailability of active ingredients (Ringman et al., 2012).

Results for Yokukansan compared to no treatment indicated improvements in total NPI scores and in delusions, depression/dysphoria, irritability/lability and agitation. Results for the only placebo-controlled Yokukansan study suggested no significant differences between groups for NPI-Q in any of the 12 domains. NPI-Q scores improved in both groups and there were significant improvements in agitation/aggression and irritability/lability within the Yokukansan group (Table 4.10). Furukawa et al. (2015) suggested that since the NPI-Q is a brief version of the NPI-12 which only assesses symptom severity, it may be less sensitive to detect subtle changes in symptoms and may not be suitable for distinguishing specific and nonspecific effects of interventions. In comparison to fluvoxamine or risperidone, there were no significant changes in total NPI scores or in any domains
within and between groups. In combination with donepezil there was no additional benefit on total NPI but there were improvements in delusions, hallucinations, agitation/aggression and anxiety.

Overall, the results for Yokukansan suggested effects on certain NPI symptoms. There was no change in MMSE so the reported benefits on BPSD were unlikely due to improvements in cognition. However, due to small sample sizes and short trial durations, no firm conclusions could be drawn about the effects of Yokukansan. It is unclear whether statistical regression to the mean or other non-specific effects played a role in these results. Yokukansan appears well-tolerated although caution needs to be taken to avoid hypokalaemia.

Yi gan san was first described circa 1555 in the classic text of CM for paediatric conditions, Bao Ying Cuo Yao (Essentials of Infant Care). This formula was prescribed to children with restlessness, sleep disturbance and agitation. Yi gan san is still prescribed for this purpose. Hara (1984) published a clinical study on effects of Yokukansan on emotional symptoms in the aged. Following this its use for treatment of BPSD became more widespread.

Of the 12 studies of other HM formulae, three used placebo controls. Zhang et al. (2015), which was judged ‘low’ risk of bias in all domains, found YSHZ improved total NPI and MMSE scores and was not inferior to donepezil, but participants had mild AD and NPI scores were low at baseline so the clinical importance of this result is difficult to interpret. In Pan et al. (2014), the addition of SZL to usual AD medications resulted in improvements in some NPI domains and in MMSE. However, the use of multiple medications in both groups and the presence of a baseline imbalance in MMSE scores made the data difficult to interpret. In the small study of FZS versus placebo (Bi et al., 2011) there were no improvements in total NPI or ADAS-cog scores.

Seven of the unblinded studies that were judged mostly ‘unclear’ or ‘high’ risks of bias reported large improvements in BPSD and cognitive measures within the HM groups (Hao et al., 2006; Cheng & Zang, 2013; Guo et al., 2011; Guo et al., 2013; Hu et al., 2015; Chen & Gao, 2013; and Pu et al., 2014), suggesting lack of adequate randomisation and/or no blinding may have led to overestimation of treatment effects, so these data required cautious interpretation. In the two-year study by Kudoh et al. (2015), NYT combined with donepezil showed no change in total NPI scores but it appeared to improve the domain of depression and had a small effect on ADAS-cog. However, this study was small and was not randomised.

Despite these issues, investigation of the frequencies of herbs used in the 12 other HM formulae (excluding Yokukansan and YKCH) may assist with selecting candidates for further investigation. Notably, five of the six frequently used herbs were also frequently cited in the classical Chinese
medical literature as used for age-related dementia and memory impairment: *P. tenuifolia, R. glutinosa, P. cocos, P. ginseng* and *Acorus* spp. (May et al., 2012). Also, the three placebo-controlled studies included five of the six frequently used herbs: *P. tenuifolia, P. cocos, P. ginseng, Acorus* spp. and *L. chuanxiong* (Bi et al., 2011; Pan et al., 2014; Zhang et al., 2015). Of these herbs, *P. cocos, P. tenuifolia* and *R. glutinosa* were traditionally used for insomnia. *P. tenuifolia* was also for anxiety and disorientation while *L. chuanxiong* was used for relieving pain (Bensky et al., 2004). *Yokukansan* was not traditionally used for memory disorders (May et al., 2015) but its main ingredient, *Uncaria rhynchophylla* (Miq.) Miq. ex Havil., was traditionally used for irritability and short temper (Bensky et al., 2004).

4.5.1 How the HMs might work

Helmstadter and Staiger (2014) argued that research based on traditional knowledge may assist with identification of effective new treatments. Of six approved anti-Alzheimer drugs, five were derived from or based on natural products and there remains potential for further discoveries (Newman & Cragg, 2016). Plant compounds continue to provide novel pharmacology for leads towards development of new interventions for management of behavioural, mood and cognitive symptoms (Carhart-Harris et al., 2016; Mattioli et al., 2009).

A number of the HM interventions and their constituents have been tested in experimental models (Apetz et al., 2014; Cheung et al., 2015; Su et al., 2014; Tang et al., 2016). This topic is reviewed in Chapter Six for *G. biloba* and *Yokukansan*.

No benefits were detected for *C. longa* extract in the present meta-analysis. However, a formula containing curcumin, demethoxycurcumin and bismethoxycurcumin, as used by Ringman et al. (2012), enhanced *in-vitro* beta-amyloid uptake by macrophages of people with AD (Zhang et al., 2006). Cox et al. (2015) reported the short-term administration of oral curcumin and curcuminoids in a formulation with improved bioavailability significantly improved mood and cognition compared to placebo in healthy adults. Brondino et al. (2014) concluded that short-term use of *C. longa* appeared safe and that low oral bioavailability was a likely reason for discrepancies between pre-clinical and clinical studies. It appears that regular and long-term consumption is required (Hugel & Jackson, 2015).

In clinical studies, *Yokukansan* has also shown anxiolytic and sedative properties (Arai et al., 2014; Tsubo et al., 2012), plus effects on irritability in paediatric conditions (Wake et al., 2013; Tanaka & Sakiyama, 2013) and schizophrenia (Miyaoaka et al., 2014). It is hypothesised that *Yokukansan* acts via glutaminergic, serotonergic, GABAergic, dopaminergic and cholinergic systems (Takeda et al.,
A pharmacokinetic study in 21 people showed that following single doses in the normal range (2.5, 5.0, 7.5 g), pharmacologically active components were detected in plasma (Kitagawa et al., 2015).

Pain may contribute to manifestation of BPSD and analgesia may be useful for treatment of agitation and other BPSD in people with dementia without overt pain (Ballard et al., 2011). Individualised, daily administration of analgesics resulted in reduced agitation/aggression in nursing home residents with BPSD (Husebo et al., 2011). However, a systematic review and meta-analysis of 18 studies did not find strong associations between pain and BPSD, although weak associations were detected for pain and depression followed by pain and agitation/aggression (van Dalen-Kok et al., 2015). A Cochrane review reported a lack of data to determine whether opioids relieve or exacerbate dementia-related agitation (Brown et al., 2015). Analgesic effects of Yokukansan and YKCH have been reported in small studies (Kishida et al., 2014; Nakamura et al., 2009; Shibahara et al., 1992; Goto et al., 2010). Ikarashi and Mizoguchi (2016) reported that glutamate-related mechanisms of Glycyrrhiza species in Yokukansan had anti-allodynia actions in a rat model of neuropathic pain. This suggested that Yokukansan may relieve dementia-related agitation via analgesic mechanisms, but this requires further investigation.

4.5.2 Limitations to this systematic review
This review only included HMs administered orally. As discussed by Fung et al. (2012) and Press-Sandler et al. (2016) essential oil aromatherapy might be an effective treatment for BPSD. In addition, a number of single compounds of plant origin have been investigated for BPSD including tetrahydrocannabinol (van den Elsen et al., 2015; Shelef et al., 2016) and huperzine A (Rafii et al., 2011).

While the EGb 761® studies were consistently judged ‘low’ risk of bias, the lack of blinding in Yokukansan, P. ginseng and all but four of the other HM studies limits the strength of conclusions about the effects of these HMs on BPSD.

Heterogeneity was substantial in a number of meta-analysis pools, notably for EGb 761® versus placebo. This suggested variability in results of these studies. There were insufficient data to determine the cause of this heterogeneity, but considerable variation was detected in NPI effect sizes within placebo groups. As shown in Figures 4.2 to 4.5, many subgroups contained few pools and few participants, mainly due to differences in the HM interventions tested, trial designs, outcome measures and the small scale of included studies. This limited the ability to draw conclusions regarding effects of these HMs.
One issue with the studies was the potential role of manufacturers in influencing outcomes. It is notable that there have been conflicting results from studies of the effects of *G. biloba* extracts on cognition (Birks & Grimley-Evans, 2009; Weinmann et al., 2010; Jiang et al., 2013; Yang et al., 2016). The searches did not locate any independently funded study of EGb 761® for BPSD. *Yokukansan* was always provided by the same company but it is unclear whether the manufacturer was otherwise involved in the studies.

Another limitation of the studies reviewed is that they did not focus on treating specific BPSD. Of 21 studies which assessed BPSD using NPI or NPI-Q, 13 required BPSD to be present in all participants at baseline (Table 4.7) but no studies required all participants to have any single symptom in common. Only nine of these 21 studies reported NPI domain scores (Table 4.2). There is potential for misleading results of meta-analyses of clinical trials if the number of participants who experienced symptoms of each domain is not clear. It is of clinical and research relevance to report scores of separate symptoms, as they may have different aetiologies and may respond differently to different treatments. It is recommended that future clinical studies limit recruitment to participants with specific symptoms at baseline.

### 4.6 Conclusions from this systematic review

The meta-analysis results suggested EGb 761® is a well-tolerated intervention that can reduce total NPI scores. However, data for specific BPSD were limited and independently funded studies are needed to confirm these findings. There were insufficient data to draw conclusions for *P. ginseng* or *C. longa*. For *Yokukansan*, the results suggested short-term use (four weeks) may alleviate some BPSD including agitation/aggression and irritability/lability but methodological weaknesses were evident and it is possible that changes were due to non-specific effects. Nevertheless, experimental studies suggested sedative and antipsychotic-like effects which may at least partly explain these findings. The evidence for the other multi-ingredient formulae was based on single studies only, although many had ingredients in common. Future studies should address methodological weaknesses and include larger sample sizes, longer durations and longer follow-up periods.
5 CHAPTER FIVE ANALYSIS OF THE CLASSICAL CHINESE MEDICAL LITERATURE OF HERBS USED FOR THE TREATMENT OF SYMPTOMS RELATED TO BPSD

5.1 Introduction
The classical Chinese medical literature can provide an additional source of herbs to be considered candidates for further investigation for management of BPSD, in addition to the candidate herbs selected from the systematic review and meta-analysis of clinical trials detailed in Chapter Four. As outlined in Chapters One and Two, the aim of the present chapter was to apply an ethnobiological approach to drug discovery. The classical Chinese medical literature was searched for citations of substances used for treatment of symptoms analogous to BPSD. In order to identify candidate Chinese herbs for BPSD, search terms were devised according to symptom domains of the NPI.

5.2 Methods
The Zhong Hua Yi Dian (ZHYD) (Encyclopaedia of Chinese medicine) was searched using methods described in Chapter Three. Search terms and strategies were applied to locate citations of disorders which correspond to dementia and memory loss in this CD-ROM, which contains the full text of 1,000 books from the Chinese classical medical literature. The terms chi dai and jian wang were used as they correspond with the modern Chinese medicine terms for dementia and forgetfulness, respectively.

5.3 Results of the analysis
Following exclusions of citations unlikely to have referred to dementia or memory impairment, the full data set included 1,603 citations from 284 different books written from 363 CE to 1945. The most productive search term was jian wang 健忘 (966 citations) followed by xi wang 喜忘 (183 citations) and shan wang 善忘 (161 citations). The numbers of citations for each search term variable are shown in Table 5.1.

<table>
<thead>
<tr>
<th>Search term variable</th>
<th>Terms included</th>
<th>BPSD set citation frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>jian wang</td>
<td>健忘</td>
<td>966</td>
</tr>
<tr>
<td>hao wang</td>
<td>好忘</td>
<td>34</td>
</tr>
<tr>
<td>duo wang</td>
<td>多忘</td>
<td>147</td>
</tr>
<tr>
<td>shan wang</td>
<td>善忘</td>
<td>161</td>
</tr>
<tr>
<td>xi wang</td>
<td>喜忘</td>
<td>183</td>
</tr>
<tr>
<td>other wang</td>
<td>忘忘 狂忘 患忘 谗忘 忘前失后 忘误 失忘 易忘 忘记事 迷忘 错忘 褫忘 遗事则忘 语后便忘 胤忘 忆忘 怒忘 思忘</td>
<td>113</td>
</tr>
<tr>
<td>weak memory</td>
<td>強忘 不記憶, 不能記, 不能記憶, 不記事, 失記, 不善記, 近事不記, 隨說隨忘, 无所記憶, 记忆减弱</td>
<td>32</td>
</tr>
</tbody>
</table>
Of the classical texts searched, citations related to BPSD were identified from texts dated from before the Tang dynasty (618 CE) until the Minguo period (1912-1949). The majority of citations (721) were identified from texts dated during the Ming dynasty (1369-1644) and 529 citations were from the Qing dynasty (1645-1911). Table 5.2 shows the frequency of citations according to each dynasty.

### Table 5.2: Frequency of citation by dynasty

<table>
<thead>
<tr>
<th>Dynasty</th>
<th>Frequency of citations</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Tang (-618)</td>
<td>5</td>
<td>0.3</td>
</tr>
<tr>
<td>Tang &amp; 5 Dyn (618-959)</td>
<td>75</td>
<td>4.7</td>
</tr>
<tr>
<td>Song Jin (960-1271)</td>
<td>148</td>
<td>9.2</td>
</tr>
<tr>
<td>Yuan (1272-1368)</td>
<td>105</td>
<td>6.6</td>
</tr>
<tr>
<td>Ming (1369-1644)</td>
<td>721</td>
<td>45</td>
</tr>
<tr>
<td>Qing (1645-1911)</td>
<td>529</td>
<td>33</td>
</tr>
<tr>
<td>Minguo (1912-1949)</td>
<td>20</td>
<td>1.2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1603</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

Analysis was conducted to identify the frequency of citations from each text. *Pu Ji Fang* (*Prescriptions for Universal Relief*) (c.1406), which is the largest book in ZHYD, provided 198 citations. The next most productive book was the Song dynasty encyclopaedia *Sheng Ji Zong Lu* (*Complete Record of Sacred Benevolence*) (c. 1117 CE) with 60 citations. The sources of citations of herbs for BPSD are shown in Table 5.3, in order of most to least frequent citations.

### Table 5.3: Sources of the citations of herbs for symptoms analogous to dementia with BPSD

<table>
<thead>
<tr>
<th>Book Name</th>
<th>Frequency of citations</th>
<th>Percentage</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pu Ji Fang</em></td>
<td>198</td>
<td>12.4</td>
<td>1</td>
</tr>
<tr>
<td><em>Sheng Ji Zong Lu</em></td>
<td>60</td>
<td>3.7</td>
<td>2</td>
</tr>
<tr>
<td><em>Ji Yang Gang Mu</em></td>
<td>40</td>
<td>2.5</td>
<td>3</td>
</tr>
<tr>
<td><em>Tai Ping Sheng Hui Fang</em></td>
<td>37</td>
<td>2.3</td>
<td>4</td>
</tr>
<tr>
<td><em>Gu Jin Yi Tong Da Quan</em></td>
<td>36</td>
<td>2.2</td>
<td>5</td>
</tr>
<tr>
<td><em>Zheng Zhi Zhu Sheng - Lei Fang</em></td>
<td>32</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td><em>Bei Ji Qian Jin Yao Fang</em></td>
<td>28</td>
<td>1.7</td>
<td>7</td>
</tr>
<tr>
<td><em>Qi Xiao Liang Fang</em></td>
<td>25</td>
<td>1.6</td>
<td>8</td>
</tr>
<tr>
<td><em>Wai Tai Mi Yao</em></td>
<td>24</td>
<td>1.5</td>
<td>9</td>
</tr>
<tr>
<td><em>Za Bing Yuan Liu Xi Zhu</em></td>
<td>23</td>
<td>1.4</td>
<td>10</td>
</tr>
<tr>
<td>Book Name</td>
<td>Frequency of citations</td>
<td>Percentage</td>
<td>Rank</td>
</tr>
<tr>
<td>----------------------------</td>
<td>------------------------</td>
<td>------------</td>
<td>------</td>
</tr>
<tr>
<td>Ming Yi Zhi Zhang</td>
<td>22</td>
<td>1.4</td>
<td>11</td>
</tr>
<tr>
<td>Bian Zheng Lu</td>
<td>22</td>
<td>1.4</td>
<td>11</td>
</tr>
<tr>
<td>Za Bing Guang Yao</td>
<td>22</td>
<td>1.4</td>
<td>11</td>
</tr>
<tr>
<td>Yi Xue Ru Men</td>
<td>21</td>
<td>1.3</td>
<td>12</td>
</tr>
<tr>
<td>Yi Deng Xu Yan</td>
<td>18</td>
<td>1.1</td>
<td>13</td>
</tr>
<tr>
<td>Shou Shi Bao Yuan</td>
<td>18</td>
<td>1.1</td>
<td>13</td>
</tr>
<tr>
<td>Zhang Shi Yi Tong</td>
<td>18</td>
<td>1.1</td>
<td>13</td>
</tr>
<tr>
<td>Chi Shui Xuan Zhu</td>
<td>18</td>
<td>1.1</td>
<td>13</td>
</tr>
<tr>
<td>Qian Jin Yi Fang</td>
<td>18</td>
<td>1.1</td>
<td>13</td>
</tr>
<tr>
<td>Ben Cao Gang Mu</td>
<td>16</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>16</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Shi Yi De Xiao Fang</td>
<td>16</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Ji Shi Quan Shu</td>
<td>16</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Lei Zheng Zhi Cai</td>
<td>15</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>Yi Xue Gang Mu</td>
<td>15</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td>Zheng Zhi Zhun Sheng-Za Bing</td>
<td>15</td>
<td>0.9</td>
<td>15</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1603</strong></td>
<td><strong>100</strong></td>
<td></td>
</tr>
</tbody>
</table>

Analysis was conducted to identify the most frequently cited formulae in the total BPSD dataset of 1603 citations. These were ranked in order of most to least frequently cited. *Gui pi tang* was the most frequently cited formula for symptoms analogous to dementia with BPSD, with 118 citations. *Tian wang bu xin dan* was the second most frequently cited formula with 66 citations. Results of the 11 most frequently cited formulae are shown in Table 5.4.

**Table 5.4: Most common formulas cited for the total BPSD dataset**

<table>
<thead>
<tr>
<th>Formula Name</th>
<th>Frequency of citations</th>
<th>Percentage of total n citations</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gui pi tang</td>
<td>118</td>
<td>7.4</td>
<td>1</td>
</tr>
<tr>
<td>Tian wang bu xin dan</td>
<td>66</td>
<td>4.1</td>
<td>2</td>
</tr>
<tr>
<td>Tao ren cheng qi tang</td>
<td>29</td>
<td>1.8</td>
<td>3</td>
</tr>
<tr>
<td>Ding zhi wan</td>
<td>25</td>
<td>1.6</td>
<td>4</td>
</tr>
<tr>
<td>Xi jiao di huang tang</td>
<td>23</td>
<td>1.4</td>
<td>5</td>
</tr>
<tr>
<td>Di dang tang</td>
<td>21</td>
<td>1.3</td>
<td>6</td>
</tr>
<tr>
<td>Sang piao xiao san</td>
<td>20</td>
<td>1.2</td>
<td>7</td>
</tr>
<tr>
<td>Zhu que wan</td>
<td>20</td>
<td>1.2</td>
<td>7</td>
</tr>
<tr>
<td>Er dan wan</td>
<td>18</td>
<td>1.1</td>
<td>8</td>
</tr>
<tr>
<td>Niu huang qing xin wan</td>
<td>15</td>
<td>0.9</td>
<td>9</td>
</tr>
<tr>
<td>Shou xing wan</td>
<td>15</td>
<td>0.9</td>
<td>9</td>
</tr>
<tr>
<td>Yuan zhi wan</td>
<td>15</td>
<td>0.9</td>
<td>9</td>
</tr>
<tr>
<td>Ren shen yang rong tang</td>
<td>14</td>
<td>0.9</td>
<td>10</td>
</tr>
<tr>
<td>Yang xin tang</td>
<td>13</td>
<td>0.8</td>
<td>11</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1603</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The numbers and frequency of herb ingredients of the formulae citations were investigated. Results of the BPSD classical literature searches resulted in 16,042 citations of herbs used in the formulas for
symptoms analogous to dementia or age-related memory impairment with BPSD. The herbs were ranked in order of frequency of citation and the herbs ranked top 30 are shown in Table 5.5.

Table 5.5: Frequency ranking of all herbs according to total numbers of citations

<table>
<thead>
<tr>
<th>Herb name (pinyin)</th>
<th>Number of citations</th>
<th>Percentage of total citations</th>
<th>Rank according to frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>fu ling or fu shen</td>
<td>1206</td>
<td>7.5</td>
<td>1</td>
</tr>
<tr>
<td>ren shen</td>
<td>917</td>
<td>5.7</td>
<td>2</td>
</tr>
<tr>
<td>yuan zhi</td>
<td>812</td>
<td>5.1</td>
<td>3</td>
</tr>
<tr>
<td>gan cao</td>
<td>717</td>
<td>4.5</td>
<td>4</td>
</tr>
<tr>
<td>di huang (sheng di or shu di)</td>
<td>573</td>
<td>3.6</td>
<td>5</td>
</tr>
<tr>
<td>dang gui</td>
<td>569</td>
<td>3.5</td>
<td>6</td>
</tr>
<tr>
<td>chang pu (or shi chang pu)</td>
<td>429</td>
<td>2.7</td>
<td>7</td>
</tr>
<tr>
<td>suan zao ren</td>
<td>376</td>
<td>2.3</td>
<td>8</td>
</tr>
<tr>
<td>bai zhu</td>
<td>370</td>
<td>2.3</td>
<td>9</td>
</tr>
<tr>
<td>mai men dong</td>
<td>355</td>
<td>2.2</td>
<td>10</td>
</tr>
<tr>
<td>gui r</td>
<td>333</td>
<td>2.1</td>
<td>11</td>
</tr>
<tr>
<td>jiang r (sheng jiang or gan jiang)</td>
<td>332</td>
<td>2.1</td>
<td>12</td>
</tr>
<tr>
<td>huang qi</td>
<td>307</td>
<td>1.9</td>
<td>13</td>
</tr>
<tr>
<td>zhu sha, dan sha</td>
<td>301</td>
<td>1.9</td>
<td>14</td>
</tr>
<tr>
<td>wu wei zi</td>
<td>246</td>
<td>1.5</td>
<td>15</td>
</tr>
<tr>
<td>bai shao</td>
<td>217</td>
<td>1.4</td>
<td>16</td>
</tr>
<tr>
<td>long gu chi (long gu or long chi)</td>
<td>199</td>
<td>1.2</td>
<td>17</td>
</tr>
<tr>
<td>mu xiang</td>
<td>194</td>
<td>1.2</td>
<td>18</td>
</tr>
<tr>
<td>feng mi</td>
<td>193</td>
<td>1.2</td>
<td>19</td>
</tr>
<tr>
<td>bai zi ren</td>
<td>190</td>
<td>1.2</td>
<td>20</td>
</tr>
<tr>
<td>tian men dong</td>
<td>181</td>
<td>1.1</td>
<td>21</td>
</tr>
<tr>
<td>fang feng</td>
<td>169</td>
<td>1.1</td>
<td>22</td>
</tr>
<tr>
<td>chuan xiong</td>
<td>164</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>shan yao</td>
<td>164</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>ban xia (zhi ban xia)</td>
<td>162</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>jie geng</td>
<td>156</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>wu tou, fu zi</td>
<td>147</td>
<td>0.9</td>
<td>26</td>
</tr>
<tr>
<td>da zao</td>
<td>144</td>
<td>0.9</td>
<td>27</td>
</tr>
<tr>
<td>long yan rou</td>
<td>142</td>
<td>0.9</td>
<td>28</td>
</tr>
<tr>
<td>huang lian</td>
<td>131</td>
<td>0.8</td>
<td>29</td>
</tr>
<tr>
<td>da huang</td>
<td>129</td>
<td>0.8</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>16042</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

5.3.1 Subgroup analysis – Numbers of citations according to each symptom of the Neuropsychiatric Inventory (NPI)

Subgroup analysis of this dataset was conducted to identify citations corresponding to BPSD, with the aim to select herbs as leads for further investigation. Results showed the majority of citations were for symptoms analogous to dementia with anxiety (7,787 herb citations and 690 formula citations). This was followed by symptoms analogous to dementia with NPI-D: depression (3,699 herb citations and 331 formula citations). The symptom with fewest citations was NPI-A: Delusions,
with only 14 herb citations and two formula citations. These results of numbers of citations according to each of the 12 NPI symptom domains are shown in Table 5.6.

<table>
<thead>
<tr>
<th>NPI Domain</th>
<th>Modern Chinese terms</th>
<th>Number of herb citations after filter</th>
<th>Percentage of total n citations</th>
<th>Number of formula citations after filter</th>
<th>Percentage of total n citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPI-A: Delusions</td>
<td>妄想</td>
<td>14</td>
<td>0.1</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>NPI-B: Hallucinations</td>
<td>幻覺</td>
<td>199</td>
<td>1.2</td>
<td>24</td>
<td>1.5</td>
</tr>
<tr>
<td>NPI-C: Agitation/Aggression</td>
<td>煩躁/攻擊行為</td>
<td>276</td>
<td>1.7</td>
<td>32</td>
<td>2</td>
</tr>
<tr>
<td>NPI-D: Depression</td>
<td>抑鬱/情緒低落</td>
<td>3699</td>
<td>23.1</td>
<td>331</td>
<td>20.6</td>
</tr>
<tr>
<td>NPI-E: Anxiety</td>
<td>焦慮</td>
<td>7787</td>
<td>48.5</td>
<td>690</td>
<td>43</td>
</tr>
<tr>
<td>NPI-F: Euphoria</td>
<td>情緒高漲/欣快</td>
<td>75</td>
<td>0.5</td>
<td>7</td>
<td>0.4</td>
</tr>
<tr>
<td>NPI-G: Apathy/Indifference</td>
<td>情緒淡漠/冷漠</td>
<td>1113</td>
<td>6.9</td>
<td>122</td>
<td>7.6</td>
</tr>
<tr>
<td>NPI-H: Disinhibition</td>
<td>抑制解除</td>
<td>110</td>
<td>0.7</td>
<td>13</td>
<td>0.8</td>
</tr>
<tr>
<td>NPI-I: Irritability</td>
<td>易怒/情緒波動</td>
<td>1336</td>
<td>8.3</td>
<td>84</td>
<td>5.2</td>
</tr>
<tr>
<td>NPI-J: Aberrant motor activity</td>
<td>異常的動作行為</td>
<td>50</td>
<td>0.3</td>
<td>6</td>
<td>0.4</td>
</tr>
<tr>
<td>NPI-K: Sleeping and night-time behaviour disturbances</td>
<td>睡眠</td>
<td>1607</td>
<td>10</td>
<td>128</td>
<td>8</td>
</tr>
<tr>
<td>NPI-L: Appetite and eating behaviour disturbances</td>
<td>食慾或飲食失調</td>
<td>2374</td>
<td>14.8</td>
<td>197</td>
<td>12.3</td>
</tr>
<tr>
<td>Totals</td>
<td></td>
<td>16042</td>
<td>100</td>
<td>1603</td>
<td>100</td>
</tr>
</tbody>
</table>

### 5.3.2 Comparison of the ranked lists

Webber et al. (2010) devised a measure of the similarity of incomplete ranked lists – ‘the rank-biased overlap’. This measure was designed for incomplete ranks such as a top ten, rather than the entire list, and it was intended for top-weighted ranks, where the top-ranking item on the list is considered more important than the items on the tail end. This measure was also intended for assessment of indefinite ranks, meaning the ranking may be cut off at any arbitrary point, when it is determined that the lower listed items are not of value or importance.

This section aimed to compare the overlap of the rankings for all herb citations for symptoms analogous to dementia (i.e. the total data set), with the rankings of herb citations for symptoms analogous to specific symptoms of the NPI. The key purpose of conducting these comparisons was to identify herbs which showed the greatest changes in rank in comparison to their overall rank in the total dataset. It could be of interest to further investigate any herbs which have increased in rank for a particular symptom as these could be candidates for treatment of that symptom. A method was devised to prioritise herbs for further investigation according to their increase in rank in the specific symptom dataset ranking compared to their rank in the total dataset. This resulted in a modified rank of top herbs for treatment of dementia with the specific NPI symptom.

It is cogent that the symptoms with more frequent citations would show a greater similarity
between the ranked list for that symptom and the overall dataset, since a higher percentage of the total dataset was made up of citations for treatment of this symptom. Therefore, for example, the ranked list for the total data set and the ranked list for dementia with NPI-E: Anxiety (a high frequency symptom) are likely to be more similar than a comparison between the total dataset and herbs cited for NPI-A: Delusions (a low frequency symptom).

5.3.3 Ranking of herbs for symptoms analogous to dementia with agitation/aggression

The symptom of NPI-C: Agitation/Aggression was chosen for further investigation and analysis. As detailed in Chapter One, agitation has been described as a particularly troublesome symptom for people with dementia, their families and caregivers, and it is the symptom which is most likely to lead to the decision to place a person with dementia into institutional living facilities. Agitation or aggression may also be more likely to be treated with antipsychotics or benzodiazepines, which could worsen cognition. Agitation/aggression were symptoms showing moderate frequency in the overall dataset, with 276 herb citations. Hence, this group was suitable for analysis based on the rank-biased overlap.

A total of 32 books contained citations analogous to agitation/aggression, as shown in Table 5.7. Of these, the books Shi Fang Miao Yong and Pu Ji Fang each contained five citations, with lower frequencies in other books. This revealed that the citations were spread over a wide range of books.

<table>
<thead>
<tr>
<th>Book name</th>
<th>Frequency of citations</th>
<th>Percentage of total n citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shi Fang Miao Yong</td>
<td>5</td>
<td>15.6</td>
</tr>
<tr>
<td>Pu Ji Fang</td>
<td>5</td>
<td>15.6</td>
</tr>
<tr>
<td>Shi Shi Mi Lu</td>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>Zu Ji</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Yu Yao Yuan Fang</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Yi Xue Ru Men</td>
<td>2</td>
<td>6.3</td>
</tr>
<tr>
<td>Shen Nong Ben Cao Jing Shu</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Ben Cao Gang Mu</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Tai Ping Hui Min He Ji Ju Fang</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Ding Gan Ren Xian Sheng Jia Chuan Zhen Fang</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Shi Yi De Xiao Fang</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Shi Zhai Bai Yi Xuan Fang</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Shang Han Guang Yao</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Jin Gui Yu Han Yao Lue Ji Yi</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Ding Zheng Zhong Jing Quan Shu Jin Gui Yao Lue Zhu</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Shang Han Lun Ji Yi</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Ji Yang Gang Mu</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Wai Tai Mi Yao</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
Similarly corresponding to the total dataset, the most productive dynasty for citations related to agitation/agression were dated from the Qing and Ming dynasties (1349-1911), with 13 and 12 citations respectively. These results are shown in Table 5.8. This showed that this subgroup of citations was reflective of the total dataset with regard to their origin.

<table>
<thead>
<tr>
<th>Dynasty</th>
<th>Frequency of citations</th>
<th>Percentage of total citations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tang &amp; 5 Dynasties</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Song Jin (960-1271)</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td>Yuan (1272-1368)</td>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>Ming (1369-1644)</td>
<td>12</td>
<td>37.5</td>
</tr>
<tr>
<td>Qing (1645-1911)</td>
<td>13</td>
<td>40.6</td>
</tr>
<tr>
<td>Minguo (1912-1949)</td>
<td>1</td>
<td>3.1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

The most frequently cited formulae for agitation were *Yu zhi zi wan* (4 citations), followed by *Di dang tang* and *Tao ren cheng qi tang*, each with two citations. Results of top three frequently cited formulae for dementia with agitation are shown in Table 5.9. These formulas were not the same as the top three formulas in the total dataset (see Table 5.4).

<table>
<thead>
<tr>
<th>Formula Name</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Yu zhi zi wan</em></td>
<td>4</td>
<td>12.5</td>
<td>1</td>
</tr>
<tr>
<td><em>Di dang tang</em></td>
<td>2</td>
<td>6.3</td>
<td>2</td>
</tr>
<tr>
<td><em>Tao ren cheng qi tang</em></td>
<td>2</td>
<td>6.3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>32</strong></td>
<td><strong>100</strong></td>
<td></td>
</tr>
</tbody>
</table>

Frequencies of the individual herbs cited for treating dementia with agitation/aggression were investigated. Of the 16,042 citations of herbs for symptoms analogous to dementia with any BPSD, a total of 276 citations mentioned symptoms analogous to dementia with agitation. These were also ranked according to the frequency of citations.

Results indicated that the most frequently cited herbs were *fu ling* (16 citations), *ren shen* (15 citations) and *gan cao* (12 citations). Table 5.10 shows the herb ranking for most frequently cited for treating symptoms analogous to dementia with agitation or aggression.

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>fu ling</em></td>
<td>16</td>
<td>5.8</td>
<td>1</td>
</tr>
<tr>
<td><em>ren shen</em></td>
<td>15</td>
<td>5.4</td>
<td>2</td>
</tr>
<tr>
<td><em>gan cao</em></td>
<td>12</td>
<td>4.3</td>
<td>3</td>
</tr>
<tr>
<td><em>zhu sha, dan sha</em></td>
<td>9</td>
<td>3.3</td>
<td>4</td>
</tr>
<tr>
<td><em>da huang</em></td>
<td>9</td>
<td>3.3</td>
<td>4</td>
</tr>
<tr>
<td><em>shan yao</em></td>
<td>8</td>
<td>2.9</td>
<td>5</td>
</tr>
</tbody>
</table>

105
### Modified rank method

A modified ranking system was devised based on Webber et al. (2010). The changes in rank between the total dataset of herbs and the subset of herbs for dementia with agitation/aggression were calculated and expressed as percentages. The herbs with the greatest percentage change were allocated a modified rank, prioritising those herbs which showed the greatest changes in rank. The aim was to identify any herbs which may have been specifically included for treating agitation or aggression in dementia rather than re-identifying the herbs commonly used for treating dementia, which have been reported already by May (2009) and May et al. (2016).

The method of prioritising each herb was as follows:

- **a.** Herbs were listed in descending order according to the greatest percentage increase in rank.
- **b.** The high-ranked herbs were considered more important that the lower-ranked herbs for further investigation of effects on agitation associated with dementia.

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Frequency</th>
<th>Percentage</th>
<th>Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>chang pu</td>
<td>7</td>
<td>2.5</td>
<td>6</td>
</tr>
<tr>
<td>di huang</td>
<td>7</td>
<td>2.5</td>
<td>6</td>
</tr>
<tr>
<td>yuan zhi</td>
<td>7</td>
<td>2.5</td>
<td>6</td>
</tr>
<tr>
<td>huang qin</td>
<td>6</td>
<td>2.2</td>
<td>7</td>
</tr>
<tr>
<td>gou qi zi</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>huang lian</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>dang gui</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>gui r</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>yu zhu or huang jing</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>mai men dong</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>di gu pi</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>bai zi ren</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>yu zhi zi</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>tao ren</td>
<td>5</td>
<td>1.8</td>
<td>8</td>
</tr>
<tr>
<td>bai zhu</td>
<td>4</td>
<td>1.4</td>
<td>9</td>
</tr>
<tr>
<td>ban xia (zhi)</td>
<td>4</td>
<td>1.4</td>
<td>9</td>
</tr>
<tr>
<td>jiang r</td>
<td>4</td>
<td>1.4</td>
<td>9</td>
</tr>
<tr>
<td>bai shao</td>
<td>4</td>
<td>1.4</td>
<td>9</td>
</tr>
<tr>
<td>chuan xiong</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>chai hu</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>shui zhi</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>feng mi</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>xuan shen</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>xi jiao</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>shen qu</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>wu tou, fu zi</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>meng chong</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td>dan dou chi</td>
<td>3</td>
<td>1.1</td>
<td>10</td>
</tr>
<tr>
<td><strong>Total (all citations)</strong></td>
<td><strong>276</strong></td>
<td><strong>100</strong></td>
<td></td>
</tr>
</tbody>
</table>
Table 5.11 shows the calculated change in rank and the corresponding modified rank of herbs for treatment of dementia with agitation. This list of the top 25 herbs only includes herbs which increased in rank and excludes herbs which did not change rank or which decreased in rank.

### Table 5.11: Modified rank of herbs for dementia with agitation

<table>
<thead>
<tr>
<th>Herb name</th>
<th>Percentage increase from total n citations for all NPI symptoms to n citations for agitation/aggression</th>
<th>Calculated change in rank</th>
<th>Modified new rank for agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>da huang</em></td>
<td>from 0.8% to 3.3%</td>
<td>2.5</td>
<td>1</td>
</tr>
<tr>
<td><em>shan yao</em></td>
<td>from 1% to 2.9%</td>
<td>1.9</td>
<td>2</td>
</tr>
<tr>
<td><em>yu zhu or huang jing</em></td>
<td>from 0.1% to 1.8%</td>
<td>1.7</td>
<td>3</td>
</tr>
<tr>
<td><em>yu zhi zi</em></td>
<td>from 0.1% to 1.8%</td>
<td>1.7</td>
<td>3</td>
</tr>
<tr>
<td><em>huang qin</em></td>
<td>from 0.6% to 2.2%</td>
<td>1.6</td>
<td>4</td>
</tr>
<tr>
<td><em>zhu sha, dan sha</em></td>
<td>from 1.3% to 3.3%</td>
<td>1.4</td>
<td>5</td>
</tr>
<tr>
<td><em>gou qi zi</em></td>
<td>from 0.4% to 1.8%</td>
<td>1.4</td>
<td>6</td>
</tr>
<tr>
<td><em>di gu pi</em></td>
<td>from 0.4% to 1.8%</td>
<td>1.4</td>
<td>6</td>
</tr>
<tr>
<td><em>tao ren</em></td>
<td>from 0.6% to 1.8%</td>
<td>1.2</td>
<td>7</td>
</tr>
<tr>
<td><em>dan dou chi</em></td>
<td>from approx. 0% to 1.1%</td>
<td>1.1</td>
<td>8</td>
</tr>
<tr>
<td><em>huang lian</em></td>
<td>from 0.8% to 1.8%</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td><em>shui zhi</em></td>
<td>from 0.2% to 1.1%</td>
<td>0.9</td>
<td>10</td>
</tr>
<tr>
<td><em>meng chong</em></td>
<td>from 0.2% to 1.1%</td>
<td>0.9</td>
<td>10</td>
</tr>
<tr>
<td><em>shen qu</em></td>
<td>from 0.3% to 1.1%</td>
<td>0.8</td>
<td>11</td>
</tr>
<tr>
<td><em>cong bai</em></td>
<td>from approx. 0% to 0.7%</td>
<td>0.7</td>
<td>12</td>
</tr>
<tr>
<td><em>meng shi</em></td>
<td>from 0% to 0.7%</td>
<td>0.7</td>
<td>12</td>
</tr>
<tr>
<td><em>long dan cao</em></td>
<td>from 0% to 0.7%</td>
<td>0.7</td>
<td>12</td>
</tr>
<tr>
<td><em>hua shi</em></td>
<td>from 0% to 0.7%</td>
<td>0.7</td>
<td>12</td>
</tr>
<tr>
<td><em>bai zhi</em></td>
<td>from 1.2% to 1.8%</td>
<td>0.6</td>
<td>13</td>
</tr>
<tr>
<td><em>xi jiao</em></td>
<td>from 0.5% to 1.1%</td>
<td>0.6</td>
<td>14</td>
</tr>
<tr>
<td><em>da qing</em></td>
<td>from 0.1% to 0.7%</td>
<td>0.6</td>
<td>15</td>
</tr>
<tr>
<td><em>chai hu</em></td>
<td>from 0.6% to 1.1%</td>
<td>0.5</td>
<td>16</td>
</tr>
<tr>
<td><em>e jiao</em></td>
<td>from 0.2% to 0.7%</td>
<td>0.5</td>
<td>17</td>
</tr>
<tr>
<td><em>ban xia (zhi)</em></td>
<td>from 1% to 1.4%</td>
<td>0.4</td>
<td>18</td>
</tr>
<tr>
<td><em>xuan shen</em></td>
<td>from 0.7% to 1.1%</td>
<td>0.4</td>
<td>19</td>
</tr>
<tr>
<td><em>shi gao</em></td>
<td>from 0.3% to 0.7%</td>
<td>0.4</td>
<td>20</td>
</tr>
<tr>
<td><em>mu dan pi</em></td>
<td>from 0.4% to 0.7%</td>
<td>0.3</td>
<td>21</td>
</tr>
<tr>
<td><em>mang xiao</em></td>
<td>from 0.4% to 0.7%</td>
<td>0.3</td>
<td>21</td>
</tr>
<tr>
<td><em>wu tou, fu zi</em></td>
<td>from 0.9% to 1.1%</td>
<td>0.2</td>
<td>22</td>
</tr>
<tr>
<td><em>tu si zi</em></td>
<td>from 0.5% to 0.7%</td>
<td>0.2</td>
<td>23</td>
</tr>
<tr>
<td><em>ba ji tian</em></td>
<td>from 0.5% to 0.7%</td>
<td>0.2</td>
<td>23</td>
</tr>
<tr>
<td><em>she xiang</em></td>
<td>from 0.5% to 0.7%</td>
<td>0.2</td>
<td>23</td>
</tr>
<tr>
<td><em>chuan xiong</em></td>
<td>from 1% to 1.1%</td>
<td>0.1</td>
<td>24</td>
</tr>
<tr>
<td><em>nan xing r</em></td>
<td>from 0.6% to 0.7%</td>
<td>0.1</td>
<td>25</td>
</tr>
<tr>
<td><em>shan zhu yu</em></td>
<td>from 0.6% to 0.7%</td>
<td>0.1</td>
<td>25</td>
</tr>
<tr>
<td><em>niu xi</em></td>
<td>from 0.6% to 0.7%</td>
<td>0.1</td>
<td>25</td>
</tr>
<tr>
<td><em>du zhong</em></td>
<td>from 0.6% to 0.7%</td>
<td>0.1</td>
<td>25</td>
</tr>
</tbody>
</table>

The results shown in Table 5.11 indicated that these herbs were more frequently included in formulae described for treatment of agitation or aggression in dementia, compared to the herbs used in formulae described for general dementia symptoms. This suggested that these herbs may have been believed to have anti-agitation or anti-aggression properties. However, they may have
been added to formulae for other reasons. These herbs were considered separately for their potential as candidates for the treatment of dementia with agitation/aggression.

5.3.5 Traditional use in China and scientific research on the top ranked herbs for dementia with agitation

The literature on the top-ranking herbs in the modified agitation/aggression list was reviewed to determine the traditional use and current scientific evidence for each herb. The highest-ranked eleven herbs were selected since some herbs shared the same modified rank.

1. da huang (rhubarb root and rhizome)
Standard species: Rheum palmatum L. or R. tanguticum Maxim. ex Balf. or R. officinale Baill.
Text in which first cited: Shen Nong Ben Cao Jing (circa 200-250 CE).

According to Bensky et al. (2004), da huang was traditionally used for ‘purging clumped heat in the Intestines, cooling the blood, removing blood stasis; and to stop bleeding when in its charred form’. It was cautioned not to be used in those with a ‘weak Stomach’. Similarly, it was contraindicated for people with ‘qi and blood deficiency’ unless there was evidence of significant ‘accumulations or blood stasis.’ Its primary indication was constipation, but was also used for diarrhoea, jaundice, epistaxis, red eyes, swollen throat, ‘heat toxin sores’ and abscesses. According to Shen Nong Ben Cao Jing it ‘expels pathogens to halt their violence, and has a special ability to uproot chaos and restore normality’. These descriptions may be associated with agitated behaviour but this was not stated explicitly.

Aloe-emodin, an active component of Rheum officinale Baill., was reported to attenuate scopolamine-induced cognitive deficits in mice by inhibiting AChEI and modulating oxidative stress, indicating that aloe-emodin could have neuroprotective effects against AD related to anti-inflammatory activities (Tao et al., 2014). However, da huang was not included in any of the clinical trials of herbal medicines for BPSD reviewed in Chapter Four.

2. shan yao (Chinese yam)
Standard species: Dioscorea opposita Thunb.
Text in which first cited: Shen Nong Ben Cao Jing (circa 200-250 CE).

Shan yao was mainly used for ‘tonifying the qi and yin of the Lungs, Spleen and Kidneys’, and ‘securing the essence’. It was therefore recommended for treatment of such symptoms as diarrhoea, fatigue, spontaneous sweating, and lack of appetite. It was believed to have a mildly
annertent property so could ‘stop diarrhoea and inhibit urinary frequency’. It also treated ‘cough and wheezing due to Lung qi and yin deficiency’, and ‘urinary frequency or spermatorrhoea due to Kidney qi and yin deficiency’. It has long been a commonly consumed food, and long-term consumption is emphasised for its health benefits (Bensky et al., 2004). According to Shen Nong Ben Cao Jing, shan yao ‘tonifies the middle and augments the power of qi, and increases the muscle’. Long-term consumption is said to ‘sharpen the hearing, brighten the eyes, and lighten the body.’

Administration of a soluble extract from D. opposita was reported to lead to significant improvements in spatial learning and memory impairments in mice, as well as showing neuroprotective effects on the primary cultured cortical neurons of rats (Yang et al., 2009). In addition, an oestrogenic protein isolated from D. opposita Thunb. was found to improve cognitive functioning in 18-month-old female rats and was proposed as a potential alternative to hormone replacement therapy to treat cognitive symptoms related to menopause (Wong et al., 2015). Zhang et al. (2016) reported substantial anti-inflammatory activities in-vitro from several steroid glycosides isolated from the rhizomes of Dioscorea species.

As reviewed in Chapter Four, shan yao was included in the formula Zhi bai di huang tang which was tested in the clinical study by Guo et al. (2011), and in Ninjin’yoeito, as tested by Kudoh et al. (2015). Both formulae were combined with donepezil and tested on participants with AD.

3. yu zhu or huang jing (Solomon’s seal)

Standard species: Polygonatum kingianum Coll. & Hems. or P. sibiricum Red. or P. cyrtonema Hua or P. odoratum (Mill.) Druce

Text in which first cited: Ming Yi Bie Lu (circa 536 CE).

Yu zhu or huang jing was mainly used for treating ‘Spleen and Stomach deficiency with lassitude, fatigue and loss of appetite’, and for treating dry mouth, loss of appetite, loss of taste, dry stools and a dry, red tongue, or for any kind of dry cough. Huang jing was considered a mild tonic that was typically used in combination with other tonifying herbs which ‘guide its direction’. When combined with gou qi zi, huang jing was described as ‘an excellent gentle tonic for the aged or weak, best taken over a long period of time in small doses that will not be difficult to digest’. Huang jing was described as ‘moist and a strong yin tonic’. Yu zhu was used to ‘tonify yin and moisten dryness’, such as cough, dry throat, irritability and thirst, and for intense hunger and constipation. Yu zhu was also used to ‘extinguish wind and soften and moisten the sinews, for wind generated by insufficient fluids leading to pain and spasms in the sinews, and for dizziness caused by yin deficiency and internal wind’. Yu zhu was recommended for treating dryness after the course of febrile disease. It was also
considered to be a gentle tonic which required frequent consumption or larger doses for effects to become noticeable (Bensky et al., 2004). According to the Materia Medica of Ri Hua-Zi it could ‘eliminate irritable stifling sensations in the chest, stop thirst...and hot type mania from heaven-sent [infectious] diseases.’

A polysaccharide from Polygonatum sibiricum was found to have protective effects against beta-amyloid (25-35) induced apoptosis in rat adrenal medulla derived cells (Zhang et al., 2015). Huang jing was an ingredient in the formula Bu shen tong luo tang, tested by Hu et al. (2015) for its effects on AD participants, as reviewed in Chapter Four.

4. yu zhi zi (akebia fruit)

Standard species: Akebia trifoliata (Thunb.) Koidz. var. australis (Diels) Rehd. or A. trifoliata (Thunb.) Koidz. or A. quinata (Thunb.) Decne.

Text in which first cited: Ben Cao Shi Yi, elaborated by Chen Zang-Qi (circa 720 CE).

Yu zhi zi was used for chest and hypochondriac pain due to ‘Liver qi stagnation’, and for pain due to ‘Liver/Stomach disharmony’ as well as for treatment of conditions involving ‘nodules, masses or distension’, and for promoting urination (Bensky et al., 2004). Ben Cao Shi Yi described that it ‘expels irritable heat; consuming it eases a patient’s heart, stops thirst, and drives qi downward.’ While these descriptions suggest it may have been used for treatment of agitation, no contemporary studies were identified which investigated its effects on agitation or dementia. In addition, yu zhi zi was not an ingredient in any of the clinical studies reviewed in Chapter Four.

5. huang qin (scutellaria root)

Standard species: Scutellaria baicalensis Georgi

Text in which first cited: Shen Nong Ben Cao Jing (circa 200-250 CE).

Huang qin was traditionally used to ‘clear heat, dry dampness, reduce fever’, and to treat a ‘stifling sensation in the chest’ and ‘thirst but with an inability to drink’, or for treatment of ‘painful urinary dribbling’. It was combined with huang lian for treatment of high fever and irritability. Huang qin was used for ‘heat patterns with high fever, irritability, thirst, cough, expectoration of thick, yellow sputum, or hot sores and swellings’. It also was specifically recommended to ‘calm a restless fetus that is kicking excessively due to heat’, especially if combined with bai zhu and dang gui. Huang qin was also believed to ‘sedate ascendant Liver yang’, to treat headache, irritability, red eyes, flushed face and a bitter taste. Huang qin was described as ‘bitter and cold’ so was often used for treatment of persistent irritability with fever in febrile disorders; for ‘benefiting both mother and fetus when
heat disturbs the pregnancy’; and for ‘nosebleeds, sores and swelling and red, swollen sore eyes’. Huang qin combined with Huang lian treated ‘irritable restlessness, bleeding and sores’ (Bensky et al., 2004). Its perceived benefits for the mother and fetus suggest huang qin was perhaps considered to exert strong effects yet was safe for people with a weaker constitution.

Scutellaria baicalensis and its components have been investigated for actions related to cognition and dementia pathologies in numerous studies. In particular, the compounds oroxylin A, baicalein and baicalin, derived from S. baicalensis Georgi, have been studied in animal models. Considering huang qin was traditionally used for relieving febrile disease, possibly related to bacterial infection and inflammation, there has been investigation regarding its effect on such brain diseases which involve infection or inflammation. Hwang et al. (2011) reported that chronic cerebral hypoperfusion or chronic lipopolysaccharide infusion rats treated with huang qin extract from S. baicalensis Georgi roots were protected against spatial memory impairments. These authors suggested that S. baicalensis Georgi reported on neuroprotective effects and low toxicity, as well as anti-convulsive, anxiolytic and mild sedative actions of baicalein (Gasiorowski et al., 2011). The Chinese herbal formula Tong luo xing nao, containing S. baicalensis Georgi with Ligusticum chuanxiong and Angelica sinensis, attenuated cognitive deficits in a transgenic AD mouse model, as well as showed significant protection on mitochondrial function and energy supply (Dai et al., 2016). Cao et al. (2016) examined the effects of S. baicalensis stem-leaf flavonoids on spatial learning and memory in a VaD model of rats. Results indicated the flavonoid treatment significantly improved spatial cognition in VaD rats, possibly by reducing tau-hyperphosphorylation-induced neurotoxicity by coordinating the activity of kinases and phosphatase after stroke. Baicalin, the active component of S. baicalensis Georgi, was reported to exert neuroprotective effects against diabetes-associated cognitive deficits in rats via modulation of mitogen-activated protein kinase cascades, brain-derived neurotrophic factor and apoptosis (Ma et al., 2015). Zhang et al. (2013) found that the flavonoid baicalein, from the roots of S. baicalensis, promoted non-amyloidogenic processing of APP in an AD transgenic mouse model. This led to reduced beta-amyloid production and improvements in cognitive performance. These authors suggested that activation of GABA type A receptors may have been an important mechanism. Wang et al. (2013) reported that S. baicalensis stem-leaf total flavonoid attenuated neuronal apoptosis induced by beta-amyloid (25-35) in the hippocampus of rats, with a high dose of 100mg/kg per day for eight days showing more pronounced effects than a lower dose of 50mg/kg. Shang et al. (2013) found that treatment with S. baicalensis Georgi stem and
leaf flavonoids for 13 days improved memory performance in a rat model of cerebral ischemia. Zhuang et al. (2013) found that baicalin from *S. baicalensis* Georgi could stimulate neurogenesis in adult rats. Oh et al. (2013) found that baicalein protected mouse neural progenitor cells from irradiation-induced necrotic cell death, as well as prevented spatial learning and memory retention deficits in six-week-old mice following whole brain irradiation. *Huang qin* was an ingredient of the formula *Fu zhi san* in the study of its effects on participants with AD by Bi et al. (2011).

6. **zhu sha, dan sha** (obsolete substances with unacceptable toxicity) (cinnabar)

   **Standard name:** Cinnabar

   **Text in which first cited:** *Shen Nong Ben Cao Jing* (circa 200-250 CE).

   *Zhu sha* was said to ‘sedate the Heart and calm the spirit’, so was traditionally used for restlessness, palpitations with anxiety, insomnia or convulsions. It also was believed to ‘expel phlegm’ and ‘sedate jitteriness and convulsions while stopping tremors’. For these reasons it was recommended as treatment for seizures and childhood convulsions. It was a key ingredient for ‘clearing fire, sedating the heart, arresting jitteriness and anxiety, and quietening the spirit’ so was used to ‘restore calm to the Heart’. *Zhu sha* was also considered an important medicinal for ‘irritability, restless insomnia and withdrawal-mania’. According to *Shen Nong Ben Cao Jing* it ‘quiets and settles the consciousness…the strength of qi naturally doubles.’ *Zhu sha* was combined with *huang lian* for treatment of restlessness, irritability and delirium. Its toxicity was observed, as described in *Thoroughly Revised Materia Medica*, that ‘used by itself or to excess, it will make people slow-witted and dejected.’ *Harm and Benefit in the Materia Medica* also advised that *zhu sha* ‘should be used unprepared...if refined with fire it is toxic, and taking it has often been fatal.’

   Xie et al. (1996) reported that cinnabaris did not improve impairment of memory and learning in rats with scopolamine-induced memory impairments. However, topical application of the Chinese herbal formula *An gong niu hang*, containing cinnabaris, was reported to protect hippocampal and cortical neurons in rats with cerebral ischemia (Zhang et al., 2015). Neither *dan sha* nor *zhu sha* were included in any of the clinical studies reviewed in Chapter Four.

7. **gou qi zi** (lycium fruit)

   **Standard species:** *Lycium barbarum* L.

   **Text in which first cited:** *Shen Nong Ben Cao Jing* (circa 200-250 CE).

   *Gou qi zi* was traditionally recommended for treatment of ‘Liver and Kidney deficiency’ with such symptoms as ‘sore back and legs, low-grade abdominal pain, impotence, nocturnal emissions,
wasting and thirsting disorder (diabetes) and consumption’. These symptoms were typically associated with older age but could also apply to people of any age. *Gou qi zi* was combined with *long yan rou* for ‘blood deficiency with a sallow complexion, insomnia and multiple dreams’; and combined with *huang lian* for ‘exhausted essence’. *Gou qi zi* has also been used traditionally to ‘brighten the eyes’ and ‘improve vision’. Another traditional use was to ‘reduce sensations of thirst and heat when awakening from sleep at night-time’ (Bensky et al., 2004).

Cheng et al. (2014) reviewed the evidence of pharmacological activities of *Lycium barbarum* polysaccharides (LBP). These authors reported that LBPs protected against neuronal injury and beta-amyloid induced loss of brain matter, as well as glutamate excitotoxicity, and other neurotoxic insults. A review of neuroprotective mechanisms of *L. barbarum* proposed that LBP showed promise for treatment of key pathological events of neuronal diseases such as stroke, AD and PD, by exerting ameliorative effects on oxidative stress, inflammation and cell death (Xing et al., 2016). Zhou et al. (2016) identified 15 compounds, Lycibrarspermidines A-O, from the fruit of *L. barbarum* (goji berries). These were shown to have varying levels of anti-AD activity in a transgenic AD fly model. These compounds were proposed to be responsible for putative neuroprotective, antioxidant and other anti-ageing effects of goji berries. Ho et al. (2010) proposed that the neuroprotective effects of goji berries were not limited to beta-amyloid inhibition, and found that LBP reduced homocysteine-induced tau phosphorylation in rat cortical neurons, suggesting that LBP may have disease modifying potential against AD. A small placebo-controlled RCT (n=34) showed that 15 days administration of goji juice to healthy adults improved subjective ratings of energy levels, athletic performance, sleep quality, ease of awakening, ability to focus on activities, mental acuity, calmness and contentment compared to placebo (Amagase & Nance, 2008). Another study showed 30 days administration of goji juice increased immune measures, including numbers of lymphocytes, compared to placebo, and resulted in significant improvements in subjective feelings of well-being, fatigue and sleep. No adverse effects were observed in either group (Amagase et al., 2009). Perhaps surprisingly, none of the clinical trials reviewed in Chapter Four included *gou qi zi*.

8. *di gu pi* (lycium bark)

Standard species: *Lycium chinense* Mill. or *L. barbarum* L.

Text in which first cited: *Shen Nong Ben Cao Jing* (circa 200-250 CE).

*Di gu pi* was said to ‘cool the blood’ and treat such symptoms as ‘night sweats, chronic low grade fever, irritability and thirst’; and also was indicated for treatment of ‘coughing or wheezing’. It was specifically recommended for ‘restless irritability’ (Bensky et al., 2004). According to *Essays on Medicine Esteeming the Chinese and Respecting the Western*, *di gu pi* was ‘cool by nature’ and
‘excellent at reducing heat. Because its vigor tends downward, it has the power to restrain and inhibit... It unblocks and facilitates both bowel movements and urination, and treats bleeding due to heat in both the stool and urine.’ While multiple studies have investigated Lycium fruit, no studies were found which specifically focussed on the bark. In addition, none of the clinical trials reviewed in Chapter Four included di gu pi as an ingredient.

9. tao ren (peach kernel)
Standard species: Prunus persica (L.) Batsch or P. davidiana (Carr.) Franch.
Text in which first cited: Shen Nong Ben Cao Jing (circa 200-250 CE).

Tao ren was historically described as useful for ‘breaking up blood stasis’ so was used for ‘abdominal pain, traumatic injury, abscesses and fixed abdominal masses’; and also used for ‘constipation due to dry Intestines’. According to The Detailed Materia Medica, ‘the bitterness of tao ren drains stagnant blood, and its sweetness generates new blood. It has four uses: to treat heat entering the blood chamber, to drain stagnant blood in the abdomen, to expel blood heat, dryness, and itching in the skin, and to promote the movement of congealed blood stasis in the skin.’ Tao ren is toxic due to its amygdalin content and overdose causes toxic side effects (Bensky et al., 2004).

While these prescientific descriptions did not explicitly mention memory impairment or agitation, Mokrani et al. (2016) investigated the phenolic composition and concentration of Prunus persica L. extract from peach fruit, identifying and quantifying 15 different phenolic compounds of relevance to dementia. Inhibition of beta-amyloid and neurofibrillary formation was detected, as well as protection against beta-amyloid induced toxicity, from the phenolic extracts. Pu et al. (2014) also tested effects of the formula Tong qiao huo xue tang, containing tao ren, in their clinical trial involving participants with AD and agitation, as reviewed in Chapter Four. This current research suggests tao ren may be of further interest for its effects on dementia with agitation.

10. dan dou chi (prepared soybean)
Standard species: Glycine max (L.) Merr.
Text in which first cited: Ben Cao Hui Yao (circa 1500).

Described as ‘ascending’, dan dou chi was traditionally used to ‘vent and disperse exterior pathogens’, and ‘disseminate and disperse constrained heat above the diaphragm’. It was considered to be ‘mild’ so suitable for treating ‘yin deficiency with superimposed exterior disorders’. It was also used for ‘irritability’, ‘restlessness’, and ‘stifling sensation in the chest from residual heat’ (Bensky et al., 2004). According to Seeking Accuracy in the Materia Medica: ‘when there is a pathogen in the upper body causing symptoms of irritability, restlessness, headache, stifling
sensation in the chest, vexation, insomnia, expression of rashes, and nausea, when combined with
_{zhi zì_} it can lead the pathogen upward to be vomited out.’

_Glycine max_ (L.) Merr. contains vegetable protein, oligosaccharide, fibre, vitamins and minerals as
as well as isoflavones and saponins. Hong et al. (2013) found that soyasaponin I administered orally to
memory deficient rats led to improvements in the passive avoidance, Y-maze and Morris maze tests,
as well as elevated markers related to cell proliferation and neuronal differentiation in neural
precursor cells of the embryonic hippocampus. These results suggested soyasaponin I may improve
hippocampal learning and memory impairment via promotion of cell proliferation and neural
precursor cells. Hong et al. (2014) reported that soyasaponins _Ab_ and _Bb_ significantly prevented
scopolamine-induced memory impairment in mice without inhibiting AChE. These authors found
that soyasaponins may protect against memory impairment by increasing brain-derived
neurotrophic factor expression and cAMP response element binding (Hong et al., 2014). While these
properties suggest potential for soybean as a treatment for symptoms of dementia, effects of _dan
dou chi_ were not tested in any of the clinical trials reviewed in Chapter Four.

11. _huang lian_ (_coptis rhizome_)

Standard species: _Coptis chinensis_ Franch. or _C. deltoidea_ C.Y. Cheng & Hsiao or _C. teeta_ Wall.
Text in which first cited: _Shen Nong Ben Cao Jing_ (circa 200-250 CE).

_Huang lian_ was said to ‘clear heat and drain dampness’ so was traditionally used for ‘damp-heat in
the Stomach or Intestines’ with ‘diarrhoea or dysenteric disorder’, and for ‘vomiting and/or acid
regurgitation’ (Bensky et al., 2004). _Huang lian_ was indicated for treatment of inflammatory diseases
and diabetes. Berberine, the isoquinoline alkaloid from _Coptis chinensis_, has been a focus of
numerous studies for its range of pharmacological effects. Durairajan et al. (2012) reported that
berberine extracted from _C. chinensis_ Franch. ameliorated beta-amyloid pathology in an AD
transgenic mouse model, by regulation of APP. Berberine has been shown to act via multi-target
pathways involving various neurotransmitters and antioxidant activities, according to a review on
berberine in the multi-target treatment of dementia (Huang et al., 2016). Kaufmann et al. (2016)
reported that extracts of _C. chinensis_ substantially inhibited AChE and showed up to 100 times
greater inhibitory activity than galantamine, while not showing cytotoxic properties. These authors
proposed that synergism of isoquinoline alkaloids was likely to play an important role in these
observations. An updated review (Imenshahidi & Hosseinzadeh, 2016) reported that berberine has
poor intestinal absorption and oral bioavailability, which could limit its clinical use, but has shown
anticonvulsant, antidepressant, neuroprotective, anti-Parkinson, anti-Huntington and analgesic

115
effects in experimental studies. However, *huang lian* was not included in any of the clinical trials reviewed in Chapter Four.

5.4 **Summary of the herbs for agitation/aggression in the classical literature**

Many of the herbs on the modified agitation list were traditionally used for actions related to ‘clearing heat’ and were considered to have purgative or ‘downward directing’ properties. These actions and properties may correspond to treatment of such symptoms as bad temperedness, irritability, aggression and agitation, although this was rarely stated explicitly in the traditional medicine text books.

Of the high-ranked herbs, *huang lian* and *huang qin* have received substantial scientific research attention for their effects on pathological processes related to dementia and NCDs. Berberine, isolated from *huang lian*, and oroxylin A, baicalein and baicalin from *huang qin* have been the focus of many of these studies.

5.5 **Discussion of the classical literature analysis**

A comparison between the herbs in the clinical studies of Chapter Four, and the herbs in the classical literature dataset, indicates that there is a degree of overlap with regard to the total classical literature dataset. The overlap is more prominent at the individual herb level rather than at the formula level. For example, as shown in Figure 5.1, *Gui pi tang* and *Tian wang bu xin dan* typically share some similar ingredients to *Yokukansan*. *Angelica* sp. (*dang gui*), *Glycyrrhiza* sp. (*gan cao*), *Atractylodes* sp. (*bai zhu*) and *Poria cocos* (*fu ling*) are commonly in *Gui pi tang*; while *Angelica* sp. (*dang gui*), *Poria cocos* (*fu ling*) and *Glycyrrhiza* sp. (*gan cao*) are also typically included in *Tian wang bu xin dan*. 

116
Figure 5.1: Overlap of the herb ingredients of *Yokukansan*, *Gui pi tang* and *Tian wang bu xin dan*

Of the two most frequently cited formulae in the total data set, both *Gui pi tang* and *Tian wang bu xin dan* also typically contained *Panax ginseng* (*ren shen*), *Ziziphus jujuba* seed (*suan zao ren*) and *Polygala* sp. (*yuan zhi*).

Table 5.12 shows a summary of the highest-ranking herbs from the total BPSD classical literature dataset, including number of times the herb was tested in a clinical trial and any reported effects in animal models related to BPSD.
Table 5.12: Summary of the highest-ranking herbs in the total classical literature BPSD dataset

<table>
<thead>
<tr>
<th>Herb name (pinyin)</th>
<th>Number of times included in a controlled clinical trial for BPSD</th>
<th>Number of citations in classical Chinese medical literature related to BPSD</th>
<th>Reported effects in animal models related to BPSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panax ginseng (ren shen)</td>
<td>7</td>
<td>917</td>
<td>antidepressant-like, amelioration of sleep deprivation, memory enhancement</td>
</tr>
<tr>
<td>Polygala sp. (yuan zhi)</td>
<td>6</td>
<td>812</td>
<td>antidepressant-like, enhanced sleep behaviour, anti-insomnia, memory enhancement</td>
</tr>
<tr>
<td>Rehmannia glutinosa (di huang: sheng di or shu di)</td>
<td>5</td>
<td>573</td>
<td>antidepressant-like, anxiolytic-like, reduced cognitive impairments</td>
</tr>
<tr>
<td>Acorus sp. (chang pu or shi chang pu)</td>
<td>7</td>
<td>429</td>
<td>antidepressant-like, anxiolytic-like, sleep promoting, reduced locomotor hyperactivity, anticonvulsant and sedative, reduced memory and learning impairments</td>
</tr>
<tr>
<td>Zizyphus jujuba seed (suan zao ren)</td>
<td>1</td>
<td>376</td>
<td>antidepressant-like, anxiolytic-like, hypnotic, reduced cognitive impairment</td>
</tr>
<tr>
<td>Ophiopogon japonicus (mai men dong)</td>
<td>1</td>
<td>355</td>
<td>N</td>
</tr>
<tr>
<td>Cinnamomum cassia (gui zhi)</td>
<td>2</td>
<td>333</td>
<td>antidepressant-like, anxiolytic-like, antistress-like, reduced memory and learning impairments</td>
</tr>
<tr>
<td>Zingiber officinale (sheng jiang or gan jiang)</td>
<td>2</td>
<td>332</td>
<td>antidepressant-like, locomotor-reducing, cognitive enhancing</td>
</tr>
<tr>
<td>Astragalus membranaceus (huang qi)</td>
<td>3</td>
<td>307</td>
<td>antidepressant-like, antistress, reduced learning and memory impairments</td>
</tr>
<tr>
<td>zhu sha, dan sha</td>
<td>0</td>
<td>301</td>
<td>N</td>
</tr>
<tr>
<td>Schisandra chinensis (wu wei zi)</td>
<td>2</td>
<td>246</td>
<td>antidepressant-like, sedative, hypnotic, reduced cognitive impairments</td>
</tr>
<tr>
<td>Paeonia lactiflora (bai shao)</td>
<td>1</td>
<td>217</td>
<td>antidepressant-like, antinociceptive</td>
</tr>
<tr>
<td>Fossilised bone (long gu chi: long gu or long chi)</td>
<td>1</td>
<td>199</td>
<td>N</td>
</tr>
<tr>
<td>Aucklandia lappa (mu xiang)</td>
<td>0</td>
<td>194</td>
<td>N</td>
</tr>
<tr>
<td>Apis sp. (feng mi)</td>
<td>0</td>
<td>193</td>
<td>N</td>
</tr>
<tr>
<td>Platycladus orientalis (bai zi ren)</td>
<td>0</td>
<td>190</td>
<td>N</td>
</tr>
<tr>
<td>Semiaquilegia adoxoides (tian men dong)</td>
<td>0</td>
<td>181</td>
<td>N</td>
</tr>
<tr>
<td>Saposhnikovia divaricata (fang feng)</td>
<td>0</td>
<td>169</td>
<td>N</td>
</tr>
<tr>
<td>Dioscorea opposita (shan yao)</td>
<td>2</td>
<td>164</td>
<td>anorexiant, reduced cognitive impairments including learning and memory</td>
</tr>
<tr>
<td>Pinellia ternata (ban xia or zhi ban xia)</td>
<td>2</td>
<td>162</td>
<td>antiagression-like, antidepressant-like, anxiolytic-like, sedative, hypnotic,</td>
</tr>
<tr>
<td>Herb name (pinyin)</td>
<td>Number of times included in a controlled clinical trial for BPSD</td>
<td>Number of citations in classical Chinese medical literature related to BPSD</td>
<td>Reported effects in animal models related to BPSD</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
</tr>
<tr>
<td>Platycodon grandiflorum (jie geng)</td>
<td>0</td>
<td>156</td>
<td>anticonvulsant, antistress, antidepressant-like, antinociceptive, reduced memory impairments</td>
</tr>
<tr>
<td>Aconitum carmichaelii (wu tou, fu zi)</td>
<td>0</td>
<td>147</td>
<td>antidepressant-like, anxiolytic-like, analgesic/anaesthetic</td>
</tr>
<tr>
<td>Zizyphus jujuba fruit (da zao)</td>
<td>1</td>
<td>144</td>
<td>antidepressant-like, anxiolytic-like, antistress, sedative/ hypnotic/ anti-insomnia, reduced memory impairments</td>
</tr>
<tr>
<td>Dimocarpus longan (long yan rou)</td>
<td>0</td>
<td>142</td>
<td>N</td>
</tr>
<tr>
<td>Coptis sp. (huang lien)</td>
<td>0</td>
<td>131</td>
<td>antidepressant-like, analgesic, central depressive action, reduced cognitive impairments</td>
</tr>
<tr>
<td>Rheum sp. (da huang)</td>
<td>0</td>
<td>129</td>
<td>reduced memory impairments,</td>
</tr>
</tbody>
</table>

With regard to the subgroup analysis of herbs cited in the classical literature for memory impairments and agitation or aggression, none of the top ranked herbs were ingredients in the main formulas tested in clinical studies reviewed in Chapter Four—although shan yao, huang jing, huang qin and tao ren were included in the lesser studied formulae. Interestingly, some of the herbs cited frequently for agitation were traditionally used as purgatives. Management of constipation is recommended resource in the initial management of BPSD according to the Irish National Dementia Strategy (University College Cork, 2018). Also, some of the herbs identified in the classical Chinese medical literature have received research attention for their effects related to cognition, BPSD or AD pathologies (da huang, shan yao, huang jing, huang qin, gou qi zi, tao ren, dan dou chi and huang lian). These results suggest directions for future experimental research.
6 CHAPTER SIX  PUTATIVE MECHANISMS OF THE HERBAL MEDICINES CURRENTLY USED FOR MANAGEMENT OF BPSD

6.1 Introduction

Ginkgo biloba and the seven herb ingredients of Yokukansan were chosen for inclusion in this chapter. Of the herbs identified in Chapters Four and Five, these showed the strongest likelihood of being safe, well-tolerated and worthwhile candidates for further investigation for management of BPSD. This chapter reviews and summarises the literature on experimental studies of these herbs, including effects observed in vitro and in vivo, and the possible mechanisms involved which could be of relevance to effects on cognition and BPSD. It covers the animal model studies for evidence of BPSD-like effects. These include antihallucination, antidepressant-like, anxiolytic-like, anti-aggression/anti-agitation, antistress, effects on locomotor activity, sedative effects and analgesic effects.

This chapter also aims to identify possible activities and mechanisms of action of the HMs in relation to BPSD pathologies. The major activities identified in this chapter are: anti-beta-amyloid; anti-inflammatory; anti-tau; promotion of neurogenesis; antioxidant; anti-ROS-induced apoptosis; antihypoxic; NMDA receptor inhibition; AChE receptor inhibition; targeting of dopaminergic, GABAergic, serotoninergic and glutamatergic receptors; mitochondrial protection; and neuroprotective activities.

6.2 Ginkgo biloba (leaf)

As described in Chapters Two and Four, G. biloba leaf extract has been the focus of numerous clinical studies for its effects on cognitive symptoms and BPSD. Its effects are often thought to be exerted by multiple compounds acting on multiple targets. G. biloba and its extracts and compounds have been tested in well over 1,000 published experimental studies for effects of relevance to BPSD. By far the most frequent test intervention identified was EGb 761®, while other standardised extracts and single compounds have also been investigated. These compounds include the terpene trilactones (TTLs): bilobalide, Ginkgolide A and Ginkgolide B; and the flavonol-glycosides: quercetin and kaempferol. Pharmacokinetic studies in humans and animals have demonstrated oral bioavailability of the terpene lactones and flavonol glycosides from Ginkgo leaf extracts (Unger, 2013).

6.2.1 Overview of the experimental studies of G. biloba from the 1980s to 1990s

Numerous French, Italian and German studies investigated effects of oral G. biloba extract on animal models, in relation to ageing and neurodegenerative diseases. Racagni et al. (1986) found that G. biloba extract exerted specific effects on the noradrenergic system and on beta-receptors, providing the first putative evidence of central effects of a pharmacological intervention acting on cerebral...
ageing, related to reactivation of the noradrenergic system in the cerebral cortex. Taylor (1986) reported that oral *G. biloba* increased the apparent muscarinic receptor population in the hippocampus of the aged Fischer 344 rat, which had been frequently used to study ageing. A review of *G. biloba* electroencephalography (EEG) studies in humans and animals reported activity of a *G. biloba* extract on alertness (Pidoux, 1986). Another review proposed that *G. biloba* acted on a number of major pathologies related to AD and dementia, recommending it for further development against cerebral ageing (Allard, 1986). Porsolt et al. (1990) reported that chronic administration of EGB 761® reduced ‘learned helplessness’ stress behaviours and showed anxiolytic-like effects in rats. EGB 761® was reported to diminish hypoxic damage at mitochondrial cristae and matrix in hypoxia experiments with aged rats (Fitzl et al., 1996). A review of *G. biloba* leaf (Smith et al., 1996) identified that Ginkgolide B showed potent platelet activating factor (PAF) antagonist actions, which could contribute to neuroprotective properties. Chermat et al. (1997) proposed that interactions with certain sites of GABA_A and benzodiazepine/Cl- channel receptor complexes might have been involved in observed effects of EGB 761® on the social interaction test in Wistar rats injected with diazepam. Satyan et al. (1998) tested effects of a combination of ginkgolic acid conjugates from *G. biloba* leaves on anxiety in rats, reporting positive dose-related changes in behaviour in the elevated plus maze, open-field behaviour, and novelty-induced feeding latency tests. Hoyer et al. (1999) reported on improvements in passive-avoidance behaviour and neuronal energy metabolism after administration of EGB 761® in an animal model of intracerebroventricular streptotocin treatment. The deficit in cerebral energy metabolism after streptotocin injection was reportedly significantly slowed down after administration of EGB 761®. Doré et al. (1999) reported that EGB 761® was able to both protect and rescue neurons against beta-amyloid toxicity in an *in vitro* model of hippocampal primary cultures.

6.2.2 Overview of Ginkgo reviews

*G. biloba* has been reviewed extensively. An early review (Yoshikawa et al., 1999) identified important biological actions of *G. biloba* leaf extract as antioxidant, free radical scavenging, exerting a relaxing effect on vascular walls, antagonistic on PAF, exerting an improving effect on blood flow or microcirculation, and exerting a stimulating effect on various neurotransmitters. In particular, *G. biloba* was reported to prevent oxidative damage to mitochondria. It was suggested that *G. biloba* leaf extract could benefit degenerative neuronal diseases by preventing chronic oxidative damage. Another review by Praticò and Delanty (2000) also proposed that free radical/oxidative injury appeared to be a fundamental factor contributing to the neuronal death observed in AD, and recommended further exploration by investigating effects of *G. biloba* and other antioxidant treatments. DeFeudis and Drieu (2000) reviewed the literature on EGB 761® in relation to effects on...
central nervous system functions. Christen (2000) summarised the evidence on the role of oxidative stress and AD, from the context of the hypothesis that free radicals are involved in AD pathogenesis. This paper pointed out that neurons are extremely vulnerable to free radicals, and that since AD was linked to mitochondrial dysfunction affecting cytochrome-c oxidase, it could contribute to an abnormal production of free radicals. It was proposed that EGB 761®, as well as Vitamin E and anti-inflammatory drugs, could benefit AD via antioxidant mechanisms (Christen, 2000). Another review (Diamond et al., 2000) also concluded that mechanisms of G. biloba were likely to include antioxidant, neurotransmitter/receptor modulation, and antiplatelet activating effects.

Doraiswamy (2002) proposed G. biloba as a non-cholinergic strategy for treating and preventing AD. Ponto and Schulz (2003) focussed on potential mechanisms of action in relation to effects on the CNS. Müller and Chatterjee (2003) reviewed the literature on cognitive and behavioural effects of EGB 761® in animal models, reporting on stress protection and antidepressant-like effects in animal models. This review highlighted that effect sizes were generally larger in aged animals and after longer term treatment, and suggested that protection against mitochondrial dysfunction could be a major mechanism associated with effects of EGB 761® on behavioural symptoms. These authors proposed that bilobalide was the most important ingredient of EGB 761® for effects on mitochondrial function, and that bilobalide and the ginkgolides had shown effects on chloride conductance by interfering with the function of membrane proteins related to receptor-gated chloride channels. It was proposed that these mechanisms were likely associated with behavioural effects requiring acute changes of neuronal activity, but might indirectly also improve mitochondrial function (Müller & Chatterjee, 2003). Müller and Chatterjee’s (2003) review described improvements in cognitive domains of learning, short-term memory and working memory in mice and rats, reporting on the greater improvements seen in aged animals compared to young. Hoyer (2004) reviewed the evidence on causes and effects of cerebral glucose metabolism disturbances in relation to familial and age-related AD. Evidence that a disturbance in the insulin signal transduction pathway could be a key event in age-related AD was noted. Hoyer (2004) also reported that both hypercortisolaemia and increased adrenergic activity in AD could weaken the function of the neuronal insulin receptor, resulting in reduced ATP production. This reduced availability of ATP could in turn damage the function of the endoplasmic reticulum/Golgi apparatus/trans Golgi network, leading to formation of misfolded and malformed proteins retained in the cell. As APP is found to accumulate intracellularly in AD, this could represent not the main cause but a driving force in the pathogenesis. In addition, both disturbed insulin signalling and reduced ATP were noted to forward the hyperphosphorylation of tau protein. Abnormalities in oxidative brain metabolism therefore were shown to lead to the formation of both senile plaques and neurofibrillary tangles. These
findings provided a strong case that the therapeutic goal in age-related AD should be the improvement of the neuronal energy state, and that EGB 761® should be further investigated from this position (Hoyer, 2004).

Christen (2004) summarised mechanisms of *G. biloba* for neurodegenerative disorders as mainly involving oxidative stress, or specific mechanisms such as those associated with beta-amyloid in AD and the processes of neuronal death. Luo (2006) summarised research on EGB 761® using the roundworm *Caenorhabditis elegans* model of AD. EGB 761® reportedly inhibited beta-amyloid aggregation *in vitro* and attenuated ROS in the transgenic (Tg) *C. elegans*, as well as reduced toxicity of beta-amyloid in *C. elegans*.

A review on EGB 761® for AD (Ramassamy et al., 2007) noted its free radical scavenging properties and the possibility that reported neuroprotection was likely to also involve other intracellular pathways. Potential targets of EGB 761® in the amyloid cascade were pointed out, including its anti-amyloidogenic properties and the regulation of gene expression. Another review suggested that mitochondrial protection and the subsequent reduction of oxidative stress were likely important components of the neuroprotective activity of *G. biloba* leaf extracts (Leuner et al., 2007).

Smith et al. (2007) summarised the research on the role of oxidative stress in AD. AD brains showed increased levels of lipid peroxidation and specific protein oxidation products. These authors noted that the brain accumulated iron, zinc and copper metal ions with normal ageing, and that these should act as antioxidants to prevent the formation of ROS. It was proposed that the excess accumulation of beta-amyloid could be a result of elevated generation from APP, or due to inefficient clearance of beta-amyloid from the brain. These authors proposed that drugs that target oxidative pathways in AD should be further investigated.

Shi et al. (2010) also reviewed the mechanisms of EGB 761® in relation to AD, arguing that EGB 761® was supported by evidence from numerous preclinical studies which had shown neuroprotective effects, so could be effective for treatment and prevention of AD. However, a review on cognitive ageing (Daffner, 2010) reported that there was presently no clear evidence that *G. biloba* or other antioxidants promoted successful cognitive ageing. Also, Howes and Perry (2011), in their review on therapeutic strategies for dementia in relation to known mechanisms and the role of phytochemicals, stated that although *G. biloba* had shown promising clinical data and relevant mechanistic effects, more reliable and consistent data were needed to confirm efficacy.

Zhao and Zhao (2012) summarised the evidence on natural antioxidants for management and prevention of AD. This paper further described the involvement of oxidative stress in the
pathogenesis of AD and neuroprotective effects of *G. biloba* flavonoids, as well as other plant derived antioxidant compounds, in relation to inhibition of beta-amyloid-induced neurotoxicity. Eckert et al. (2012) reviewed the evidence on mitochondrial dysfunction as a pharmacological target in AD. Mitochondrial dysfunction was suggested to play an important role in the pathogenesis of AD and other neurodegenerative diseases. The changes in mitochondrial function were described as mainly related to changes in mitochondrial content, amount of respiratory enzymes, or changes in enzyme activities which lead to oxidative stress, mitochondrial permeability transition pore opening, or enhanced apoptosis. Structural changes were also deemed important for further research. *G. biloba* was identified as a mitochondria-targeting compound. It was suggested that a possible reason for disappointing results of previous clinical studies could be that the intervention was administered too late, as mitochondrial dysfunction represented an early event in disease progression of AD. It was recommended to study effects of mitochondria-targeting compounds at earlier stages.

The approach of multi-target plant-based interventions acting on AD was reviewed by Russo et al. (2013). These authors recommended further research on plant-based multifunctional drugs with multiple targets of relevance to dementia or AD. Apetz et al. (2014) reviewed the evidence on plant compounds acting against AD via anti-inflammatory actions. Biochemical and histochemical studies had suggested a major role of chronic central and peripheral inflammation in the aetiology and pathogenesis of AD, and epidemiological studies had reported that long-term use of NSAIDs was protective against AD but did not slow disease progression. The role of plant-based compounds focussed on cytokine suppression activity as potential anti-inflammatory mechanisms against AD. The flavone glycosides from *G. biloba* were reported to counteract pathological aspects of AD and to ameliorate multiple pathologies related to onset of AD. This suggested *G. biloba* consumption could delay onset of AD.

Montes et al. (2015) reviewed the experimental literature on the use of EGb 761® for treatment of psychiatric disorders including anxiety, depression, schizophrenia and BPSD. Suggested mechanisms focussed on antioxidant effects, modulation of neurotransmission, neuroendocrine regulation and upregulation of neurotrophic factors. Ong et al. (2015) summarised the evidence on selective and potent inhibitors of phospholipases A2, including those derived from plants, for treatment of oxidative stress and neuroinflammation associated with the pathogenesis of neurological disorders. Phospholipases A2 are enzymes that hydrolyse membrane phospholipids into arachidonic acid and lysophospholipids. Arachidonic acid is metabolised to eicosanoids (prostaglandins, leukotrienes, thromboxanes), and lysophospholipids are converted to PAFs. These lipid mediators play critical roles in the initiation, maintenance, and modulation of neuroinflammation and oxidative stress.
Conditions including AD, PD, cerebral ischaemia and depression are characterised by oxidative stress, inflammatory reactions, alterations in phospholipid metabolism, accumulation of lipid peroxides and increased brain phospholipase A2 isoform activity.

Müller et al. (2017) argued that the pharmacological properties of EGb 761® on neuronal and synaptic function, plasticity, and cognitive impairment related to mitochondrial dysfunction all provided strong support favouring the mitochondrial cascade hypothesis. If mitochondrial dysfunction was a major cause of age-related cognitive decline, then a pharmacological intervention that has benefits on impaired mitochondrial function should show clinical efficacy for symptoms of dementia. Interestingly, there was also evidence of oxidative stress and mitochondrial dysfunction in the pathology of schizophrenia, and on impaired plasticity within vestibular pathways in the pathophysiology of vertigo of peripheral and central origin. Positive effects of EGb 761® on schizophrenia and vertigo had been reported in multiple studies. Müller et al. (2017) pointed out that the presence of BPSD in AD or VaD is the norm rather than the exception. As discussed in Chapter Two, the review of clinical trials by Ihl (2013) identified that improvements over baseline were greatest in the participants showing the fastest decline. According to Müller et al. (2017) people with BPSD appeared to have pronounced mitochondrial dysfunction besides other neurobiological deficits, which could be a key factor in the increased benefits reported in the BPSD studies compared to the studies which did not require BPSD for inclusion. Müller et al. (2017) argued that future clinical studies of pharmacological interventions aimed at improving mitochondrial dysfunction might require long term use (years) in participants with pathology consistent with expected decline in symptoms over the study period. Previous studies may have been too short to detect improvements in pathological markers and may have included participants that were too healthy and not prone to cognitive decline, so did not detect any statistical difference between EGb 761® and placebo (Müller et al., 2017).

Multiple converging lines of evidence have suggested involvement of changes in brain metabolism as a critical component in the pathogenesis of age-related cognitive impairment (Kapogiannis & Mattson, 2011). Current research on G. biloba is directed towards focus on the mitochondrial cascade hypothesis as a promising pharmacological strategy. Müller et al. (2017) reported that EGb 761® improved mitochondrial dysfunction and clinical symptoms across the spectrum of age-related cognitive decline, including AD and VaD. These authors recommended EGb 761® as an important pharmacological intervention for further investigation of the plausibility of the mitochondrial cascade hypothesis. EGb 761® was reported to reduce mitochondrial ROS and enhance the availability of ATP in impairment due to ageing, hypoxia, hypoglycaemia, elevated beta-amyloid or
cerebrovascular disease (Müller et al., 2017). Several antioxidants, polyphenols, other natural products and some drugs had shown evidence of improving mitochondrial dysfunction in preclinical studies (Müller et al., 2017). Of these, only EGb 761® had substantial data from RCTs that could provide a case for further drug development (Müller et al., 2017). As there has been some consensus that EGb 761® provides similar improvement as AChEIs, this extract is a candidate for drug discovery research.

6.2.3 Overview of activites of G. biloba of relevance to BPSD

This section provides an overview of the great number of in vitro and in vivo studies on effects of G. biloba of relevance to BPSD. These main activities, as reported in the experimental literature, are:

- antidepressant-like effects
- Anti-aggression effects
- anxiolytic effects
- Effects on locomotor activity, including aberrant motor behaviour and tardive dyskinesia
- Cognitive effects

6.2.3.1 Antidepressant-like effects, including anti-anhedonia-like and antistress effects

Shah et al. (2003) reported on effects of G. biloba on whole brain catecholamine, serotonin and plasma corticosterone levels in rats subjected to forced immobilisation. G. biloba reportedly restored restraint induced elevation of catecholamines and plasma cortisone to almost normal levels, suggesting a role of G. biloba in managing stress and depression symptoms. Walesiuk et al. (2005) reported that EGb 761® reduced stress-induced memory deficits in rats subjected to chronic restraint stress or exogenous corticosterone. Walesiuk et al. (2006) also reported on normalisation of stress and corticosterone-induced cognitive impairment in rats after administration of EGb 761® for both prevention and treatment of post-stress memory dysfunctions following the chronic restraint test or exogenous corticosterone. Rojas et al. (2011) reported on antidepressant-like effects of EGb 761® in the mouse forced swimming test, and the role of oxidative stress, via free radical production, in depression and depression-like behaviour. The forced swimming test was reportedly the most widely used preclinical model for depression-like behaviour. BALB/c mice were subjected to the forced swimming test and spontaneous locomotor activity. EGb 761® reportedly decreased immobility time in the forced swimming test, which was interpreted as exerting an antidepressant-like effect. There was also a reduction in lipid peroxidation and superoxide radical production, which are both indicators of oxidative stress. The protective effect of EGb 761® was not related to effects in locomotor activity, and was associated with modulation of serotonergic and dopaminergic neurotransmission. These authors suggested that EGb 761® produces an
antidepressant-like effect, and that its antioxidant activity against oxidative stress could at least partly explain this outcome. EGb 761® treatment was reported to reduce anhedonic depressive-like behaviour in male rats which had been subjected to lipopolycaccharide-induced anhedonic behaviour (Yeh et al., 2015). The EGb 761®-treated rats showed more sucrose and food consumption than controls, as well as higher dopamine levels in the nucleus accumbens.

*G. biloba* compounds that have been studied for antidepressant-like effects are the diterpene ginkgolides, bilobalide, the flavonols quercetin and kaempferol, as summarised here. Kalkunte et al. (2007) tested effects of lipophilic extracts of *G. biloba* leaves on rodent models of depression and stress. A dose-dependent, significant antidepressant activity was reported for the behavioural despair test and learned helplessness test of depression. Similar results were observed for EGb 761® and the tricyclic antidepressant imipramine. This study found that intact carboxylic acid groups containing 6-alkyl salicylates were important bioactive compounds of the lipophilic extract in relation to antidepressant and antistress effects. Liang et al. (2016) studied antidepressant-like effects of diterpene ginkgolides in mouse hippocampus, using a GC-MS-based metabolomics approach. Diterpene ginkgolides were observed to significantly increase hedonistic behaviour in the sucrose preference test, and shorten immobility in the tail suspension test, compared to controls, which suggested antidepressant-like effects. The diterpene ginkgolide treated mice also showed significant differences in the metabolic profile compared to controls. Eighteen differential hippocampal metabolites were identified that showed differences between the treatment and control groups. These biochemical changes involved neurotransmitter metabolism, oxidative stress, glutathione metabolism, lipid metabolism, energy metabolism, and kynurenic acid. These findings suggested that diterpene ginkgolides have antidepressant-like effects in mice and that the mechanisms could involve these biochemical changes.

Wu et al. (2016) reported that bilobalide alleviated depression-like behaviour and cognitive deficit induced by chronic unpredictable mild stress in mice. Mice were exposed daily to stressors for five weeks to induce depression-like behaviour and cognitive deficits. Vehicle-treated mice showed a significant increase in immobility in the tail suspension test, a decrease in the discrimination index of the novel object recognition task, and increased latency to perform and decreased number of platform crossings in the Morris water maze, compared to vehicle mice not subjected to the daily stressors. Bilobalide treatment inhibited these changes in a dose dependent manner. The vehicle mice subjected to chronic stressors also showed higher levels of serum corticosterone than the mice not subjected to stressors, while bilobalide treatment also inhibited this effect in a dose-dependent
manner. These results suggested that bilobalide might inhibit depression-like behaviour and cognitive symptoms by acting via the hypothalamic-pituitary-adrenal axis.

Since evidence was accumulating that depression could be both a cause and consequence of AD and other neurological disorders, and that antidepressants could be a useful strategy, Hou et al. (2010) investigated mechanisms of antidepressant effects of EGB 761®. This study reported that the flavonols quercetin and kaempferol stimulated depression-related signalling pathways involving brain-derived neurotrophic factor and phosphorylation of cyclic AMP response element binding protein CREB/post-synaptic density proteins PSD95, and reduced beta-amyloid peptide in neurons isolated from the TgAPPswe/PS1e9 double transgenic AD mice. Flavonol also appeared to enhance BDNF expression and reduce beta-amyloid oligomers in the hippocampus of these models. These results suggested that stimulating BDNF and reducing beta-amyloid using flavonols from EGB 761® could provide benefits for treatment of depression in AD.

6.2.3.2 Anti-aggression effects
Shih et al. (2000) studied effects of an extract of G. biloba (EGb) on an aggression model of mice with deficiency in monoamine oxidase A (MAO A), and increased brain levels of serotonin and norepinephrine. When EGb was administered their aggressive behaviour in resident-intruder confrontations was reduced to levels seen in normal control mice. EGb did not affect the locomotive behaviour, suggesting that its effects on aggression were not due to sedation. A G. biloba extract caused a decrease in [3H] ketanserin binding to serotonin 2A receptors in the frontal cortex of MAO A knockout mice but did not change the receptor affinity for [3H]ketanserin, suggesting that the anti-aggressive effect of the extract could have been mediated by serotonin 2A receptors and that the extract may be developed as a novel anti-aggressive agent. The main actions identified from in vitro and in vivo studies were antioxidant and free radical-scavenging, reversal of age-related losses in brain alpha 1-adrenergic, serotonin 1A and muscarinic receptors, protection against ischaemic neuronal death, preservation of the function of the hippocampal mossy fibre system, increased hippocampal high affinity choline uptake, inhibition of down-regulation of hippocampal glucocorticoid receptors, enhancing neuronal plasticity, and counteracting cognitive deficits after stress or traumatic brain injury. Both flavonoids and ginkgolides were reportedly involved in the free radical-scavenging and antioxidant effects, which decreased levels of ROS and inhibited membrane lipid peroxidation. Importantly, bilobalide was reported to increase the respiratory control ratio of mitochondria by protecting against uncoupling of oxidative phosphorylation, thereby increasing ATP levels. This result could be supported by the finding that bilobalide increased the expression of the mitochondrial DNA-encoded COX III subunit of cytochrome oxidase (DeFeudis & Drieu, 2000).
Anxiolytic-like effects

Ward et al. (2002) found that EGb 761® attenuated the increase in anxiety-like behaviour normally detected in animals after exposure to cold water in a study of 20-month-old senescent male mice administered EGb 761® daily for up to 82 days. Kuribara et al. (2003) assessed anxiolytic-like effects of *G. biloba* extract and the separate components Ginkgolide-A, Ginkgolide-B, Ginkgolide-C, and bilobalide, using the elevated plus-maze test in mice. Results showed that Ginkgolide-A produced dose-dependent anxiolytic effects, while the other three single components did not produce anxiolytic-like effects. The *G. biloba* extract enhanced anxiolytic-like effects of diazepam in the same mice. The authors proposed that *G. biloba* extract produced significant anxiolytic-like effects and that Ginkgolide-A was most likely responsible for this effect.

According to Zamberlam et al. (2016), GABAergic, serotoninergic and glutamatergic receptors are believed to be potential targets of the effects of *G. biloba* on behavioural changes that underlie fear, memory and anxiety. EGb 761® was reported to significantly facilitate short term memory in Wistar rats. It also improved results of the retention test and extinction test, suggesting it exerted anxiolytic effects. These findings suggested that EGb 761® differentially modulated short and long term memory and anxiety-like behaviour (Zamberlam et al., 2016).

Ribeiro et al. (2016) reported on protective effects of *G. biloba* in the prefrontal cortex and dorsal hippocampus of middle-aged male Wistar rats using the comet assay. Effects on short and long-term memory, anxiety-like behaviour and locomotor activity were also tested using the plus-maze discriminative avoidance task. After short-term treatment (30 days) improvements were observed in short-term memory, but not in anxiety-like behaviour or locomotor activity. These rats showed significantly lower levels of DNA damage in the prefrontal cortex compared to the vehicle controls. No significant differences were observed in the level of DNA damage in hippocampal cells, and EGb 761® did not reduce H₂O₂-induced DNA damage in hippocampal cells. This study showed that chronic EGb 761® treatment could improve short-term memory of middle-aged rats, which was associated with a reduction of free radical production in the prefrontal cortex. This finding suggested that *G. biloba* treatment might increase the survival of cortical neurons which could explain therapeutic effects on neurodegenerative diseases. However, the findings did not support short-term administration of EGb 761® for treatment of anxiety-like behaviours.

Ma et al. (2012) studied effects of bilobalide on anxiety, spatial learning, memory and hippocampal glucocorticoid receptor levels in male Kunming mice. The open-field and elevated plus maze tests showed that bilobalide administration decreased levels of anxiety-like behaviour and increased locomotor activity. Bilobalide also reportedly shortened the time taken to find the platform in the
Morris water maze test, and showed higher levels of glucocorticoid receptor expression in the hippocampus, in a dose-dependent manner. These results suggested that anxiolytic and cognitive effects of bilobalide could act via increasing hippocampal glucocorticoid receptor expression.

6.2.3.4 Effects of EGb 761® on locomotion including tardive dyskinesia

An et al. (2016) tested effects of EGb 761® in a rat model of haloperidol-induced tardive dyskinesia. Increased vacuous chewing movements were found to be associated with increased proapoptotic Bax protein expression, decreased antiapoptotic Bcl-2 protein expression, and an increased Bax/Bcl-2 ratio. Treatment with EGb 761® reversed the increase in vacuous chewing movements, decreased Bax expression, increased Bcl-2 expression and decreased the Bax/Bcl-2 ratio. A similar benefit was observed for rats treated with alpha-tocoherol. These results showed that long term haloperidol administration could affect Bcl-2 protein expression and promote neuronal apoptosis in the basal ganglia. Antioxidant treatment including EGb 761® might have played a role in the improvements observed.

6.2.3.5 Effects of EGb 761® on cognitive symptoms

Nooshinifar et al. (2008) investigated whether NMDA receptors were involved in effects of a G. biloba extract on memory retention, using a model of male Wistar rats suffering from forgetfulness due to MK-801-induced NMDA receptor inhibition. Results indicated that the induced forgetfulness was removed, suggesting that G. biloba might benefit cognitive symptoms due to inhibited NMDA receptors.

Takuma et al. (2007) used a combination of ovariectomy and the chronic restraint test in rats, which had been found to cause cognitive dysfunction and reduce hippocampal CA3 neurons. Effects of EGb 761® on cognitive dysfunction and neuromorphological change were tested in these ovariectomied and stress-subjected female Fischer rats. EGb 761® was reported to improve memory impairment and neuronal loss of hippocampal neurons, without affecting loss of bone mineral density or increased body weight after ovariectomy. These results suggested that EGb 761® could have cognitive enhancing and neuroprotective effects in postmenopausal women, but that the mechanisms appeared different to those of oestrogen, which showed similar effects on memory impairment and neuronal loss of hippocampus, but attenuated loss of bone mineral density and body weight increase.

Walesiuk and Braszko (2009) tested effects of EGb 761® on post-stress cognitive dysfunction in rats exposed to chronic restraint stress or administered a subcutaneous dose of exogenous
corticosterone. EGb 761® was found to prevent stress and corticosterone-induced impairments of spatial memory.

Belviranli and Okudan (2015) investigated effects of a G. biloba extract on cognitive function in young and aged female rats, and in particular, the role of oxidative stress and brain-derived neurotrophic factor. Rats were administered G. biloba or vehicle, and then subjected to a series of behavioural tests. According to results of the Morris water maze probe trial, aged rats treated with G. biloba showed an increased number of platform crossings than untreated aged rats. In addition, malondialdehyde and 8-hydroxy-2'-deoxyguanosine levels were lower in the brain tissue, and brain-derived neurotrophic factor levels were higher in the plasma of the rats treated with G. biloba. Based on these results, the authors suggested that G. biloba treatment improved cognition in aged female rats by decreasing oxidative damage and increasing brain-derived neurotrophic factor levels.

A G. biloba extract significantly improved cognitive performance in rats with cognitive deficits induced by exposure to Bisphenol A. It was proposed that this was due to the increased hippocampal levels of oestogen-dependent biogenic amines. G. biloba may therefore ameliorate Bisphenol A induced hippocampal neuronal damage and subsequent cognitive deficits through mechanisms involving its ability to enhance the release of biogenic amines, as well as via anti-oxidant and adiponectin pro-secretory effects (El Tabaa et al., 2017).

Li et al. (2017) reported on effects of YY-1224, a modified G. biloba extract with strengthened terpene trilactone, on transgenic (APP/PS1 Tg) mice. Repeated treatment with YY-1224 was found to significantly attenuate beta-amyloid(1-42)-induced memory impairment, upregulation of platelet-activating factor (PAF) receptor gene expression, reactive oxygen species, and pro-inflammatory factors. These changes were generally more pronounced in COX-2 (+/+ ) mice than in COX-2 (-/-) mice. Results suggested that the COX-2 gene was a critical mediator of the neuroprotective effects of YY-1224.

Li et al. (2013) reported on effects of bilobalide in a VaD rat model. Bilobalide significantly protected rats against cognitive deficits, according to results of the Morris water maze test. Biochemical investigation showed that bilobalide increased the superoxide dismutase activity and glutathione content, and decreased nitric oxide synthase activity and malondialdehyde content. Bilobalide was also reported to reduce neuronal apoptosis and the expression of tumor necrosis factor-alpha in the brain cortex and the hippocampus. These findings suggested that bilobalide could protect against cognitive impairment by reducing free radical injury and inhibiting neuronal apoptosis in the brain cortex and hippocampus in VaD.
6.2.4 Effects of G. biloba on pathological models related to BPSD

This section overviews the effects on pathological models, which indicate activities related to BPSD or AD. Table 6.1 summarises these activities:

<table>
<thead>
<tr>
<th>Activity</th>
<th>Putative benefit relevant to AD or BPSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-beta-amyloid</td>
<td>Reduce injury due to beta-amyloid production, deposition, accumulation</td>
</tr>
<tr>
<td>Antiplatelet/ anti-ischaemia</td>
<td>Improve blood flow or microcirculation, reduce ischaemia or hypoxia</td>
</tr>
<tr>
<td>Modulation of neurotransmission</td>
<td>Inhibition of MAO A and MAO B</td>
</tr>
<tr>
<td>Anti-inflammation</td>
<td>Reduce neuroinflammation</td>
</tr>
<tr>
<td>Neuroprotection</td>
<td>Antiapoptotic effect; anti-beta-amyloid</td>
</tr>
<tr>
<td>Antioxidant, free radical scavenging</td>
<td>Mitochondrial protection</td>
</tr>
</tbody>
</table>

6.2.4.1 Anti-beta-amyloid activities

Oxidative stress resulting from beta-amyloid plaques could mediate the plaques’ effects on local neuronal processes. Garcia-Alloza et al. (2006) observed the generation of ROS in beta-amyloid plaques, using multiphoton microscopy on the APPswe/PS1d9 transgenic AD mouse model. The same team then assessed effects of orally administered G. biloba extract in the same model, finding reduced oxidative stress resulting from the plaques as monitored by intracranial imaging, and a progressive reversal of the structural changes to the dystrophic neuritis associated with the plaques. These results suggested a causal relationship between beta-amyloid-associated oxidative stress and neuritic alterations, as well as that the neurotoxicity associated with beta-amyloid plaques could be at least partly reversed, using antioxidant-based interventions.

Garcia-Alloza et al. (2010) tested effects of various antioxidants, including EGb 761®, on neuritic abnormalities in the APPswe/PS1dE9 mouse model of AD. EGb 761® did not affect the size of existing senile plaques. However, all antioxidants had a straightening effect on curved neuritis. This finding suggested that amelioration of neuritic distortions associated with senile plaques could be an important effect of antioxidants including EGb 761® for changes to the brain related to AD.

Wan et al. (2016) tested effects of long-term treatment of EGb 761® (six months) on the APP/PS1 transgenic mouse model of AD. The treated mice reportedly showed improved cognitive function and significantly alleviated beta-amyloid plaque deposition. However, the soluble content of beta-amyloid was not changed. The treated mice also showed an increase in activated microglia around beta-amyloid plaque, indicating change in central inflammation. In addition, they showed downregulation of pro-inflammatory cytokines and inducible nitric oxide synthase, and upregulation of anti-inflammatory cytokines and Arginase-1. These findings suggested that EGb 761® regulated the phenotype of activated microglia. The results demonstrated that EGb 761® exerted a protective
effect in APP/PS1 mice, which was correlated with an inhibition of the pro-inflammatory effects of microglia and an induction of anti-inflammatory effects. EGb 761® therefore appeared to provide protective effects via regulation of inflammation in the brain.

Augustin et al. (2008) investigated the efficacy of EGb 761® and its flavonol and terpenelactone fraction to modulate beta-amyloid secretase (BACE-1) enzyme activity and mRNA levels *in vitro* and *in vivo* in transgenic Tg2576 mice. BACE enzymes play a crucial role in the formation of beta-amyloid from APP in the brain. No significant effect of EGb 761® on BACE-1 enzyme activity or mRNA levels was detected, suggesting that BACE-1 does not appear to be a major molecular target of EGb 761® or the selected fractions. Augustin et al. (2009) also studied the impact of short and long-term administration of EGb 761® on APP metabolism in Tg2576 mice. The long-term (16 months) treated mice showed significantly lowered human APP levels compared to controls in the cortex but not in the hippocampus. However, APP levels were not affected by EGb 761® in short-term (one month) treated mice. These findings suggested that APP might be an important molecular target of EGb 761® and neuroprotective properties of EGb 761® could be at least partly due to its APP lowering activity.

Liu et al. (2015) reported on effects of long-term treatment with EGb 761® in the transgenic TgCRND8 AD mouse model, which overexpresses human APP specifically in neurons. Mice treated with EGb 761® for five months showed significantly improved cognitive function, compared to untreated mice, according to results of the Barnes Maze test. EGb 761® also attenuated loss of synaptic structure proteins including PSD-95, Munc18-1, and SNAP25. Mice treated for five months also showed inhibited microglial inflammation in the brain, while mice treated for two months did not show significant changes. EGb 761® was reported to activate autophagy in microglia and decrease beta-amyloid-induced microglial secretion of TNF-α and IL-1β and to activate caspase-1. These changes were reportedly abolished by the inhibition of autophagy. Treatment with EGb 761® also reduced the concentrations of NLRP3 protein that co-localised with LC3-positive autophagosomes or autolysosomes in microglia. It was suggested that five-month treatment with EGb 761® may reduce cerebral beta-amyloid pathology by inhibiting beta-secretase activity and beta-amyloid aggregation. Therefore, long-term EGb 761® treatment could ameliorate AD pathology by anti-inflammatory and beta-amyloid-directed mechanisms.

He et al. (2008) investigated interactions between the TTL compounds of *G. biloba* extract and beta-amyloid peptides. The TTLs Ginkgolide A, Ginkgolide B, Ginkgolide C and bilobalide, and beta-amyloid(25-35) peptide were used. It was reported that the TTLs modulated the aggregation of beta-
amyloid(25-35), although the effect was small. This suggested that the therapeutic effect of *G. biloba* was not caused by the direct interactions between TLLs and beta-amyloid (25-35).

Shi et al. (2012) studied whether bilobalide had an influence on the beta-secretase-mediated APP cleavage via the phosphatidyl inositol 3-kinase (PI3K) pathway. The senescence-accelerated strain of mice SAMP8 and HT22 cells were used. Results indicated that bilobalide reduced generation of two beta-secretase cleavage products of APP, the beta-amyloid peptide and soluble beta-APP. These authors recommended that the effects of bilobalide on decreasing beta-amyloid production in the brain via modulation of APP metabolism are an important research direction for prevention and treatment of AD.

Shi et al. (2010) investigated possible mechanisms of Calcium (Ca2+) dyshomeostasis induced by the oligomeric form of beta-amyloid (1-42), and possible mediators of its toxicity: hydrogen peroxide and platelet activating factor (PAF). Ca2+ dyshomeostasis could play an important role in mediating the neurotoxic action of beta-amyloid. Ginkgolide B was reported to protect neurons against Ca2+ dyshomeostasis induced by beta-amyloid 1-42 or PAF but not by H2O2. This suggested that beta-amyloid1-42 induced Ca2+ dyshomeostasis could be mediated by the formation of H2O2 and PAF, and that increased levels of H2O2 and PAF in the brain could be important in the pathogeneses of AD and other neurodegenerative diseases. H2O2 and PAF could therefore be important therapeutic targets.

Colciaghi et al. (2004) reported on effects of EGB 761® in rat hippocampi in relation to APP metabolism. This study found that alpha-secretase, the enzyme which regulates the non-amyloidogenic processing of APP and the release of alpha APPs, showed increased release through a protein kinase C (PKC)-independent manner. This finding suggested that the benefit of EGB 761® could be related to a specific biological mechanism exerted on APP metabolism, directly affecting the release of the non-amyloidogenic metabolite.

Tchantchou et al. (2007) reported that this group had previously found that EGB 761® inhibited beta-amyloid oligomerisation *in vitro*, showed protective effects on neuronal cells and improved cognitive symptoms in the Tg 2576 mouse model of AD. A follow-up study investigated effects on the TgAPP/PS1 double transgenic mouse model. EGB 761® was reported to significantly increase cell proliferation in the hippocampus in both young and old mice. Beta-amyloid oligomers are known to inhibit phosphorylation of CREB and cell proliferation in the hippocampus of TgAPP/PS1 mice, but EGB 761® administration was found to reduce these beta-amyloid oligomers and restore CREB
phosphorylation in the hippocampus in the test mice. The authors suggested that enhanced neurogenesis of EGB 761® could be mediated by CREB activation.

Wan et al. (2014) reported on protective effects of EGB 761® against beta-amyloid (1-42) oligomer induced cell damage and BBB disruption in an in vitro model cell line with incubation of beta-amyloid (1-42) oligomer, to mimic a monolayer BBB model under conditions found in the AD brain. EGB 761® reportedly attenuated beta-amyloid (1-42) oligomer-induced cell injury, apoptosis, and generation of intracellular reactive oxygen species (ROS). EGB 761® also decreased BBB permeability and increased tight junction scaffold protein levels relevant to AD. EGB 761® also reportedly significantly decreased beta-amyloid (1-42) oligomer-induced upregulation of the receptor for advanced glycation end-products (RAGE), which mediates beta-amyloid cytotoxicity and plays an essential role in AD progression. This study suggested that EGB 761® has effects on brain endothelium exposed to beta-amyloid (1-42) oligomer, the expression of tight junction scaffold proteins and RAGE.

6.2.4.2 Anti-ischaemia activity
Ahlemeyer and Krieglstein (2003) reported that the Ginkgolides A, B, C, J and bilobalide appeared to exert neuroprotective and anti-apoptotic activities in focal cerebral ischaemia models. Paganelli et al. (2006) evaluated effects of orally administered EGB 761® on ischaemia-induced learning/memory impairments and hippocampal damage in rats. EGB 761® was administered before and after ischaemia and was reported to completely reverse acquisition impairment according to latency and number of reference errors. EGB 761® also reportedly significantly reduced the extent of hippocampal CA1 cell loss for up to 40 days after ischemia. It was proposed that observed effects on behavioural recovery could be dissociated from the neuroprotective effect on the hippocampus.

Kim et al. (2016) investigated effects of G. biloba extract on a rat model of chronic cerebral hypoperfusion induced by bilateral common carotid artery occlusion. Rats were treated with G. biloba extract or saline daily for 42 days. Results indicated that bilateral common carotid artery occlusion increased glial proliferation in the hippocampus and white matter, whereas this was attenuated in the G. biloba treated rats. The G. biloba treated rats also showed attenuation of the related increases in the hippocampal expression of proinflammatory cytokines. G. biloba treatment restored the choline acetyltransferase expression in the basal forebrain. These results suggested that G. biloba may be a useful treatment for chronic cerebral hypoperfusion via modulation of inflammatory mediators and the cholinergic system.

Wang et al. (2013) reported that intragastrically administered EGb 761® promoted proliferation of endogenous neural stem cells in a VaD rat model. The number and proliferation of these cells in the
subventricular zone and dentate gyrus was significantly higher in the treated rats compared to untreated. In addition, the escape response in the Morris water maze was significantly shorter in the VaD rats treated with EGB 761® compared to the untreated group.

6.2.4.3 Neurotransmission modulation activities

Numerous studies have found that administration of *G. biloba* leaf extracts or their individual components led to increased brain levels of dopamine, noradrenaline, acetylcholine and other neurotransmitters. For example, Das et al. (2002) reported that a *G. biloba* extract showed a dose-dependent inhibitory effect on AChE activity *in vitro*, which could at least partly explain its effects in the treatment of dementia. Stein et al. (2015) reported that EGB 761® decreased extracellular choline release and moderately elevated choline acetyltransferase activity in aged (24-months-old) rats. These reduced choline levels suggested neuroprotective properties. Suzuki et al. (2011) investigated effects of bilobalide on synaptic transmission and plasticity in rat hippocampus. Bilobalide was reported to facilitate synaptic plasticity at medial perforant path dentate gyrus synapses only, with no effect of other synapses. This finding suggested that bilobalide has differential effects on synaptic efficacy in each hippocampal synapse type.

6.2.4.4 Neuroprotection including anti-apoptosis

Notably, bilobalide was reported to exert neuroprotective effects in multiple animal models. Rossi et al. (2009) investigated pharmacokinetic properties of bilobalide when administered orally to rats. Results confirmed that bilobalide had improved oral bioavailability when administered as a phospholipidic complex, and significant amounts of bilobalide were detected in the brain, which supported the proposal that bilobalide exerts neuroprotective activity.

Zhou and Zhu (2000) reported that the nonflavone compound bilobalide protected neurons against oxidative stress in reactive oxygen species-induced apoptosis in phaeochromocytoma PC12 cells.

Tchantchou et al. (2009) reported that bilobalide and quercetin from EGB 761® significantly increased cell proliferation in the hippocampal neurons of a mouse model of AD, in a dose-dependent manner. Also, bilobalide and quercetin increased phosphorylation of cyclic-AMP Response Element Binding Protein (CREB) in these cells, and elevated the levels of p-CREB and brain-derived neurotrophic factor in the mouse brain. In addition, these compounds restored beta-amyloid oligomers (ADDL)-induced synaptic loss and phosphorylation of CREB. These findings suggested that bilobalide and quercetin could enhance neurogenesis and synaptogenesis, and that they could share a common final signalling pathway mediated by phosphorylation of CREB.
Liu et al. (2014) reported that bilobalide induced neuronal differentiation of P19 embryonic carcinoma cells via activation of the Wnt/β-catenin signaling pathway, in a concentration and time-dependent manner. This finding supported previous evidence of bilobalide promoting neuronal differentiation, which could provide a rationale for its therapeutic effects in neurodegenerative diseases.

The focus of *G. biloba* studies continued to shift towards the roles of apoptosis and ROS in ageing and neurodegenerative diseases. Ahlemeyer et al. (2001) reported that ginkgolic acids exerted neurotoxic effects, causing death of cultured chick embryonic neurons in a concentration-dependent manner. The cell death showed typical hallmark features of apoptosis. Schindowski et al. (2001) reported that EGB 761® reduced apoptosis *in vitro* in lymphocytes from aged mice, and that mice treated with EGB 761® daily for two weeks showed significantly reduced ROS-induced apoptosis. This effect was more pronounced in old mice (Schindowski et al. 2001).

Baliutyte et al. (2014) reported on anti-apoptotic effects and protection of mitochondrial functions of EGB 761® in rat heart and liver mitochondria. Uncoupling of oxidative phosphorylation was observed in the rat heart mitochondria by EGB 761®. This was not observed in the liver mitochondria respiring on pyruvate + malate. Also, oxidation of succinate in the heart mitochondria was inhibited by EGB 761®, in a concentration-dependent manner. The uncoupling effect of EGB 761® was reportedly due to increase in H(+) and K(+) permeability of inner membrane of the mitochondria, which is most likely to be mediated by the ATP/ADP-translocator and uncoupling proteins.

6.2.4.5 **Anti-tau activities**

Chen et al. (2012) investigated the effect of ginkgolide A on tau hyperphosphorylation, cell viability and the PI3K-Akt signalling pathway in N2a cell lines. Results showed that ginkgolide A increased cell viability and suppressed the phosphorylation level of Tau in cell lysates. Ginkgolide A increased phosphorylation of PI3K and Akt, which suggested that the mechanism for ginkgolide A to prevent intracellular accumulation of p-tau could be via the activation of the PI3K-Akt signalling pathway.

Excessive zinc in the brain has been shown to promote deposition of beta-amyloid proteins and the intraneuronal accumulation of neurofibrillary tangles composed of hyperphosphorylated tau proteins (Kwon et al. 2015). These authors investigated whether EGB 761® could counteract zinc-induced tau phosphorylation in rat primary cortical neurons, using Western blot analyses, MTT assay, ROS measurements and immunocytochemistry. EGB 761® was reported to attenuate the zinc-induced tau hyperphosphorylation at Ser262 in a concentration-dependent manner. The antioxidant N-acetylcysteine showed a similar result. Also, EGB 761® prevented zinc-induced activation of p38
MAPK and GSK3beta, and prevented the zinc-induced increase in ROS production and neuronal cell death. Lithium chloride did not affect ROS levels, but also inhibited the zinc-induced tau phosphorylation. These authors suggested that EGb 761® could inhibit zinc-induced tau phosphorylation at Ser262 via antioxidant actions, involving regulation of GSK3beta, so could be considered a candidate anti-tauopathy treatment for conditions including AD.

6.2.4.6 Anti-inflammation effects
Ginkgolide A was found to have anti-inflammatory mechanisms in vitro and in vivo. Ginkgolide A suppressed the expression of pro-inflammatory mediators cyclooxygenase-2 and nitric oxide, and the pro-inflammatory cytokines tumor necrosis factor alpha, interleukin 6 and IL-1beta in an inflammatory model of liposaccharide-stimulated macrophages (Li et al., 2017).

6.2.4.7 Antioxidant activities
Boveris et al. (2007) reported that rats administered EGb 761® did not show significant changes in microsomal enzymes, the rate of generation of superoxide anion or the iron reduction rate according to measurements from rat liver microsomes. However, lipid peroxidation was significantly reduced as was the generation of thiobarbituric acid reactive substances (TBARS). These findings suggested that benefits of EGb 761® could be related to its ability to limit lipid peroxidation and scavenge lipid radicals. EGb 761® was also reported to protect membranes from oxidative damage.

A C. elegans model of human beta-amyloid showed significant attenuation of basal and induced levels of hydrogen peroxide-related ROS after administration of EGb 761®. Of the individual EGb 761® components tested, kaempferol and quercetin provided maximum attenuation in both models (Smith & Luo, 2003). Kamptkötter et al. (2007) reported on reductions in stress sensitivity, ROS accumulation and expression of the stress-inducible glutathione S-transferase and catalase genes in C. elegans which had been administered EGb 761®. These authors found EGb 761® increased resistance to thermal stress and attenuated ROS accumulation in these worms subjected to thermal stress. The lifespan was also reportedly extended in the EGb 761® worms.

Wu et al. (2006) reported that EGb 761® and Ginkgolide A alleviated beta-amyloid-induced behaviours including paralysis, and serotonin hypersensitivity in a transgenic C. elegans. EGb 761® also reportedly inhibited beta-amyloid oligomerisation and beta-amyloid deposits in the model. Importantly, reducing oxidative stress was not thought to be the mechanism by which EGb 761® and Ginkgolide A suppressed beta-amyloid-induced paralysis. The authors suggested that the protection against beta-amyloid toxicity by EGb 761® could be mediated primarily by modulating beta-amyloid oligomeric species.
Effects of EGb 761® on nitric oxide (NO)-induced toxicity in rat hippocampal cell cultures were tested by Bastianetto et al. (2000). Results indicated that EGb 761® was protective and that flavonoids blocked sodium nitroprusside induced neuronal damage, whereas the terpenoid constituents did not display any significant effects. The beneficial effects of EGb 761® were attributed to antioxidant properties of its flavonoids and also to their ability to inhibit NO-stimulated protein kinase C activity (Bastianetto et al., 2000). In a different study, Bastianetto et al. (2000) reported that EGb 761® protected hippocampal neurons against beta-amyloid-induced cell death in hippocampal primary cultured cells, suggesting that the neuroprotective effects of EGb 761® could be associated with its antioxidant properties. The flavonoid fraction of the extract showed less potent protective effects while the terpenes showed no effect. Liu et al. (2008) asserted that the antioxidant activity of *G. biloba* extract is likely to be at least partly through the induction of the catalytic subunit of glutamate cysteine ligase, the rate-limiting enzyme for glutathione synthesis.

Pierre et al. (2008) reported that EGb 761® protected adhesive properties and endothelial lipoperoxide levels of human umbilical-vein endothelial cells exposed to native or oxidised low density lipoprotein (LDL). EGb 761® also limited the decrease in Na, K-ATPase activity induced by oxidised LDL to levels similar to native LDL. These findings suggested that EGb 761® could be protective against endothelial adhesion and therefore help to reduce onset of atherosclerosis. This study proposed that the antioxidant properties of EGb 761® therefore appeared to be an important mechanism for protection of endothelial properties.

Mohamed and Abd El-Moneim (2017) reported that protective effects of *G. biloba* in rat brain and testis tissues might be due to antioxidant properties. Rats administered aluminium chloride plus *G. biloba* showed significant improvements in biochemical and histological changes compared to rats administered aluminium chloride only, as these tissues showed decreases in glutathione, catalase, and superoxide dismutase, as well as noradrenaline, dopamine and serotonin levels in brain tissue, and decrease in serum zinc and copper and increase in serum Iron, and decreased testosterone, as well as degenerative changes in brain and testis tissue.

6.3 *Yokukansan* mechanisms and activities in experimental studies

This section summarises the experimental literature on the proposed mechanisms of the seven herb ingredients of *Yokukansan* of relevance to effects on BPSD. Numerous potential actions and compounds have been identified and previously reported. Of the multiple compounds contained in *Yokukansan*, the predominant focus has been on geissoschizine methyl ether from *Uncaria rhynchophylla* and 18beta-glycyrrhetinic acid from *Glycyrrhiza uralensis*. These have been found to cross the blood brain barrier in rats administered oral *Yokukansan*. According to recent reviews of
the neuropharmacological actions of *Yokukansan* related to AD or BPSD (Mizoguchi & Ikarashi, 2017; Ikarashi & Mizoguchi, 2016), the main effects reported in the experimental literature are similar to those reported for *G. biloba*, i.e.:

- Antistress-like effects
- Antidepressant-like effects
- Anti-aggression-like effects
- Anxiolytic-like effects
- Effects on locomotor activity, including aberrant motor behaviour and tardive dyskinesia
- Cognitive effects

The following section summarises the experimental research literature on the individual herb ingredients of *Yokukansan*.

### 6.3.1 *Uncaria rhynchophylla*

*Uncaria rhynchophylla* has been the focus of numerous experimental studies in relation to effects on mood and behaviour, with aggressive behaviours a main focus. Nishi et al. (2012) tested effects of Gou teng (*U. rhynchophylla* hook) for ameliorating aggression in socially isolated mice. Oral administration of Gou teng ameliorated aggressive behaviour and promoted social behaviours, while these effects were not detected in *Yokukansan* with Gou teng removed (Nishi et al., 2012). The main compounds of interest are listed below:

- Geissoschizine methyl ether
- Hirsuteine
- Hirsutine
- Rhynchophylline
- Isorhynchophylline
- Corynoxeine
- Isocorynoxeine
- Procyanidin B1

Aggression and other behavioural disturbances may be due to serotonin and dopamine receptor activity. Geissoschizine methyl ether has shown actions at these receptors. It is a partial agonist at the serotonin1A receptor and an antagonist at serotonin2A, 2C and 7 receptors, and a partial agonist/antagonist at the dopamine 2L receptor. This action is similar to the second generation antipsychotic aripiprazole. As rats administered oral *Yokukansan* were found to have geissoschizine methyl ether in the blood and brain, the compound is a strong candidate for drug development for
management of BPSD. Whether these effects require the presence of other compounds contained in Yokukansan is yet to be determined. However, the combination of geissoschizine methyl ether with 18beta-glycyrrretinic acid (GA), contained in Glycyrrhiza uralensis, was suggested to lead to amelioration of aggressive behaviour in socially isolated and zinc deficient rats administered Yokukansan.

Dopamine deficits or receptor blockades may also induce extra-pyramidal symptoms. It is suggested that the combination of geissoschizine methyl ether and corynoxeine in U. rhynchophylla is responsible for improvements observed in the age-related dopaminergic transmission in the prefrontal cortex, leading to the improvements observed in extra-pyramidal symptoms including tardive dyskinesia. (-)-Uncarilin B (2a) showed activities on melatonin receptors MT1 and MT2, which may be of relevance to circadian rhythm disturbances and other actions including release of dopamine (Geng et al., 2017).

6.3.1.1 Antidepressant-like activity
Isorhynchophylline was reported to have antidepressant-like effects in mice following forced swimming and tail suspension tests. Isorhynchophylline treatment was reported to significantly improve levels of monoamine neurotransmitters including norepinephrine and 5-HT, and the activity of monoamine oxidase A (MAO0A) in the frontal cortex and hippocampus of mice, suggesting that antidepressant-like effects of isorhynchophylline are related to MAO inhibition (Xian et al., 2017).

6.3.1.2 Anxiolytic activity
Jung et al. (2006) reported on anxiolytic effects of the aqueous extract of U. rhynchophylla stem with hooks, in rats and mice. Results indicated that the animals treated with the U. rhynchophylla extract showed a significant increase in the time spent and entries into the open arms of the elevated plus maze, and these animals also showed a reduction in time spent and entries into the closed arms, compared to animals treated with saline. No differences were seen between extract versus saline treated animals for spontaneous locomotor activity or muscle relaxant effects. According to results of the hole board test, repeated treatment with the U. rhynchophylla extract led to a significant increase in number of head dips. Also, the anxiolytic-like effects of the extract were reportedly abolished by the serotonin 1A antagonist WAY100635. These findings suggested that U. rhynchophylla aqueous extract acts via the serotonergic system to exert anxiolytic effects.

6.3.1.3 Effects on Locomotion
Sakakibara et al. (1999) investigated effects on locomotion of the four indole alkaloids: corynoxine, corynoxine B, isorhynchophylline and geisoschizine methyl ether, as well as aqueous extracts of U.
rhynchophylla, U. sinensis and U. macrophylla on a mouse model of locomotor activity. Results showed that oral administration of all the tested extracts except U. rhynchophylla significantly decreased locomotor activity in the mice. Further investigation suggested that the depressed locomotion appeared to be due to mediation of the central dopaminergic system.

6.3.1.4 Cognitive impairment
Xian et al. (2011) investigated effects of the 70% aqueous ethanol extract of U. rhynchophylla stem with hooks, on cognitive impairment in mice induced by subcutaneous injection of D-galactose. Mice treated with the U. rhynchophylla extract showed significantly increased exploratory behaviour, according to results of an open-field test, as well as improvements in spatial learning and memory function, according to results of the Morris water maze test. Neurochemical analysis found that the U. rhynchophylla treated mice showed increased levels of Ach and glutathione, and decreased activity of AChE, and decreased levels of malondialdehyde in the brains, compared to D-galactose mice who did not receive the herbal extract. The results indicated that the U. rhynchophylla extract can ameliorate cognitive deficits induced by D-galactose in mice, and that inhibition of AChE activity and increased antioxidant activity in the brain tissue appear to be involved in the mechanism.

Xian et al. (2014) investigated effects of isorhynchophylline treatment in a rat model of beta-amyloid-induced cognitive impairment. Beta-amyloid25-35 injection caused spatial memory impairment, neuronal apoptosis and tau hyperphosphorylation. Rats treated with isorhynchophylline for 21 days showed significant amelioration of the cognitive impairment. It also attenuated the induced neuronal apoptosis in the hippocampus by down regulating the protein and mRNA levels of the ratio of Bcl-2/Bax, cleaved caspase-3 and caspase-9, and suppressed tau hyperphosphorylation at the Ser396, Ser404 and Thr205 sites. The results indicated that down-regulation of GSK-3beta activity and activation of PI3K/Akt signalling pathway are involved in neuroprotective mechanisms of isorhynchophylline, which supports further research of this compound as a candidate for treatment of AD and other neurodegenerative diseases which involve tauopathy.

6.3.1.5 Anti-beta-amyloid activity
Guo et al. (2014) reported on the terpene alkaloids rhynchophylline and isorhynchophylline from U. rhynchophylla, in relation to a digital gene expression analysis aiming to predict the biosynthetic pathways. RNA sequencing of pooled U. rhynchophylla capsules RNA samples were used to generate >50 million high-quality reads from a cDNA library, and de novo were assembled. Also, 193 CYP450, 280 methyltransferase, and 144 isomerase genes were identified, that are potential candidates for enzymes involved in the synthesis of rhynchophylline and isorhynchophylline. According to results of
the digital gene expression profile analysis and other analyses, four CYP450s, three methyltransferases and three isomerases were identified as candidates likely to be involved in rhynchophylline and isorhynchophylline synthesis. These findings provided an important resource for better understanding the formation of the major bioactive compounds in *U. rhynchophylla*, which could lead to increased yields of these alkaloids via metabolic engineering.

Shao et al. (2015) also reported on anti beta-amyloid activity. This study found that rhynchophylline, the active tetracyclic oxindole alkaloid isolated from *U. rhynchophylla*, was protective against soluble beta-amyloid(1-42) oligomers-induced hippocampal activity. An *in vivo* rat model was used with spontaneous discharges in the hippocampal CA1 region monitored by electrophysiological measurements. Results indicated that the mean frequency of spontaneous discharge was increased after local application of soluble beta-amyloid(1-42) oligomers, and treatment with rhynchophylline inhibited this induced enhancement of spontaneous discharge, in a dose-dependent manner. This finding provided further evidence to support use of rhynchophylline as a candidate for AD.

6.3.1.6 Anti-inflammatory activity

Song et al. (2012) reported on inhibitory effects of rhynchophylline isolated from *U. rhynchophylla*, on the production of pro-inflammatory mediators in microglia which had been stimulated with lipopolysaccharide to provide a model of neuroinflammation. The results showed that rhynchophylline reduced the production of NO, prostaglandins E(2) (PGE(2)), monocyte chemoattractant protein (MCP-1), TNFalpha and IL-1beta in the model. Also, the mRNA expression levels of iNOS and COX-2 were decreased in a dose-dependent manner. In addition, rhynchophylline was reported to block I(1),Balpha phosphorylation and inhibit the phosphorylation of mitogen-activated protein kinases. Overall, these findings suggested that rhynchophylline effectively suppressed inflammatory responses of microglia, indicating that it could be an important candidate for neurodegenerative diseases which involve neuroinflammation.

6.3.1.7 Vasodilative, vasorelaxing effects

Kuromochi et al. (1994) investigated effects of *gou teng* from *U. rhynchophylla* on endothelium dependent and independent relaxations in the isolated Wistar Kyoto rat aorta, *in vitro*. The *U. rhynchophylla* extract was reported to relax the NE-precontracted aortic ring preparations isolated from rats with and without intact endothelium. The *U. rhynchophylla* extract was suggested to relax the NE-precontracted rat aorta through endothelium-dependent and to a lesser extent, endothelium-independent mechanisms. The endothelium-dependent component appeared to be mediated by the EDRF/NO pathway, and no involvement of the muscarinic cholinoreceptors was
detected. Overall, *U. rhynchophylla* extract was found to be a longlasting and potent vasodilator, and its main mechanism appeared to involve EDRF/NO release.

### 6.3.2 *Poria cocos* (sclerotium) (*fu ling*)

Hügel et al. (2012) identified *P. cocos* as one of four frequently used traditional Chinese herbs for dementia diseases, proposing that as oxidative stress may directly initiate neurodegeneration, neuroprotection from herbal antioxidants such as *fu ling* could be considered as preventative and therapeutic approaches. Further, May et al. (2012) identified *P. cocos* as one of four most frequently used herbs in well-designed RCTs that were associated with improved cognitive outcomes, while Lin et al. (2012) identified *P. cocos* as the most frequently listed herb used for treatment of dementia, based on a literature survey of classical Chinese pharmacopoeias and medical texts. May et al. (2016) also found that *P. cocos* was the most frequently cited herb ingredient of formulae in the classical Chinese medical literature for treatment of dementia and memory disorders consistent with the signs and symptoms of AD. Further, a review of the literature on *P. cocos* by Wang et al. (2013) found that modern pharmacological and phytochemical studies showed numerous pharmacological activities, including antioxidant, anti-inflammatory and anti-hypertonic stress activities. These could mainly be explained by the presence of the various triterpenes and polysaccharides. Wang et al. (2015) reported on nine bioactive triterpene acids in samples of *P. cocos*, with significantly different amounts detected in the epidermis (*fu ling pi*) compared to the inner parts (*bai fu ling*).

#### 6.3.2.1 Enhanced sleep behaviour

Shah et al. (2014) reported that oral administration of the lanostane-type triterpenoid pachymic acid, extracted from *P. cocos*, exerted GABA<sub>x</sub>-ergic mechanisms in mice, leading to enhanced pentobarbital-induced sleeping behaviour and prolonged sleeping time. These authors also suggested a synergistic effect of pachymic acid combined with the psychoactive compound muscimol from various mushroom species.

#### 6.3.2.2 Effects on beta-amyloid

Park et al. (2009) reported that *P. cocos* extract protected PC12 neuronal cells from Abeta-induced cell death, through antiapoptotic and antioxidant actions. The findings suggested that *P. cocos* might protect cells by suppression of oxidative stress and apoptosis induced by beta-amyloid (1-42), suggesting it as a candidate for treatment of AD.

Yu et al. (2017) investigated possible mechanisms to explain the traditional use of *fu ling*. Dehydropachimic acid, a major triterpene of *P. cocos*, was isolated and its effects were tested on the clearance of beta-amyloid accumulation in bafilomycin A1 induced PC12 cells. Results showed no
significant effect of dehydropachimic acid on the cell viability, but a significant decrease in beta-amyloid\textsubscript{1,42} content was detected in culture medium and the intracellular accumulation of APP and beta-amyloid\textsubscript{1,42} in these cells was eliminated. These findings suggested that dehydropachimic acid could effectively clear the accumulation of beta-amyloid\textsubscript{1,42} in this cell model, through restoring the lycosomal acidification and recovering the autophagic flux, which is impaired by bafilomycin A1.

6.3.2.3 Other formulae containing *P. cocos*

In addition to the above studies, effects of various multi-herb formulae containing *P. cocos* have been reported in relation to BPSD or pathologies related to cognitive impairment. These formulae include *Kai Xin San*, *Dang gui shao yao san*, *Xiao yao san*, *Ban xia hou pou tang*, and ‘invigorating qi and warming yang’ formula, *Kyung ok ko*. *Dang gui shao yao san*, containing *P. cocos* and other herbs, has been reported to alleviate cognitive symptoms of AD (Fu et al., 2015). This review reported on multiple effects related to AD. *Kyung Ok Ko*, containing *P. cocos*, was reported to show anti-platelet and anti-thrombotic effects in rat and mouse models, with less adverse bleeding than ASA (Kim et al., 2016). *Kai Xin San*, containing *P. cocos*, was reported to exert memory enhancing effects in rats subjected to weightlessness, and reverse abnormal serum levels of ROS, 8-OHdG and 3-NT (Qiong et al., 2016).

6.3.3 *Glycyrrhiza uralensis*

In Chinese traditional medicine, *G. uralensis* is commonly added to multi-ingredient formulae. Its use is therefore widespread. However, *G. uralensis* is the herbal ingredient of *Yokukansan* that is the cause of the frequent AE, hypokalaemia, due to the effect of glycyrrhizic acid on Potassium excretion. A review of the pharmacology of the phenolic flavonoid isoliquiritigenin, contained in *G. uralensis*, reported on anti-inflammatory, anti-microbial, anti-oxidant, anticancer, immunoregulatory, hepatoprotective and cardioprotective effects, as well as neuroprotective and anti-anorexia activities (Peng et al., 2015).

6.3.3.1 Antidepressant-like activities

The forced swimming test and tail suspension test were used to evaluate antidepressant-like effects of liquiritin and isoliquiritin from *G. uralensis* in mice (Wang et al., 2008). Both liquiritin and isoliquiritin were reported to reduce the immobility time in both tests. According to measurement of locomotor activity, neither liquiritin nor isoliquiritin appeared to exert any stimulating effects on the CNS. Both liquiritin and isoliquiritin were found to increase the concentrations of the neurotransmitters 5-HT and NE in the hippocampus, hypothalamus and cortex, and to reduce the ratio of 5-HIAA to 5-HT in the hippocampus, hypothalamus and cortex, and to slow down metabolism of 5-HT, compared to the vehicle-treated depression-induced mice. These findings
suggested that liquiritin and isoliquiritin both exerted antidepressant-like effects and the mechanism appeared to be related to increased serotonin and NE in the mouse hippocampus, hypothalamus and cortex.

Zhao et al. (2008) also reported on antidepressant-like effects of liquiritin, the flavone compound isolated from *G. uralensis*, in a rat model of depression induced by chronic variable stress. Rats were exposed to the stressor once daily for five consecutive weeks to induce depression-like behaviour. Results showed that the chronic variable stress reduced open-field activity and sucrose consumption significantly, and increased immobility time in the forced swimming test. Rats treated with liquiritin showed reversal of the changes in immobility time and sucrose consumption, but no effect was seen on the open-field activity. Also, liquiritin reportedly increased SOD activity, inhibited lipid peroxidation and lowered the production of the lipid peroxidation marker malondialdehyde, while the antidepressant fluoxetine did not. These findings suggested that liquiritin exerted antidepressant-like effects on rats subjected to chronic variable stress-induced depression, and that the mechanism appeared to be related to antioxidant activity.

Fan et al. (2012) reported on antidepressant activities of a total flavonoids extract of *G. uralensis* in an adult model of rats subjected to chronic unpredictable stress to induce depression-like symptoms. Rats were exposed to nine kinds of unpredictable stressors. Rats treated with the flavonoids extract showed antidepressant-like benefits according to results of the open-field test, forced swimming test and tail suspension test. These rats showed an increase in the sum of line crosses and number of rears, and a decrease in the number of faecal boli produced in the open field test. Also, these rats showed a decrease in immobility time in the forced swimming test and in the tail suspension test. Serum cortisone levels were also tested, revealing that rats treated with the flavonoid extract showed decreased serum cortisone levels as well as an increase in the number of new BrdU positive progenitor cells, at the subgranular zone of the dentate gyrus in the hippocampus. These findings suggested that the total flavonoids extract of *G. uralensis* could produce antidepressant-like effects on rats subjected to chronic unpredictable stress, and that the mechanism appeared to be related to neurogenesis and neuroprotective activities.

6.3.3.2 Effects on cognition

Ahn et al. (2006) investigated effects of a water-soluble extract of *G. uralensis* on cognitive impairment and oxidative stress in a mouse model that had been subjected to intracerebroventricular injection of beta-amyloid (25-35). According to results of the passive avoidance test and Morris water maze test, mice treated with the *G. uralensis* extract showed amelioration of the cognitive deficits induced by the beta-amyloid injections. The beta-amyloid
injected mice showed higher concentrations of thiobarbituric acid reactive substances compared to controls, and the *G. uralensis* treated mice showed attenuation of these high levels. Mice treated with the extract also showed reduced AChE activity compared to the mice which did not receive the *G. uralensis* treatment. Overall, the results suggested that a water-soluble extract of *G. uralensis* exerts protection against cognitive impairment associated with beta-amyloid and that this appeared to be due to antioxidant activity against oxidative stress.

Ma et al. (2015) reported on effects of isoliquiritigenin, the chalcone from *G. uralensis*, on learning and memory impairments induced by a high fat diet in the Institute for Cancer Research (ICR) mouse model. According to results of the Morris water maze, isoliquiritigenin treated mice showed significant alleviation of cognitive impairments. These mice also showed attenuation of peripheral insulin resistance. Further testing showed that IL-1beta and TNF-alpha levels were lowered in mice after treatment with isoliquiritin. The results suggested that isoliquiritin could alleviate cognitive deficits in mice induced by a high fat diet, and the mechanism appeared to be related to inhibition of the TNFalpha/JNK/IRS pathway.

6.3.3.3  Anti-beta-amyloid activity

Link et al. (2015) studied effects of *G. uralensis* and isoliquiritigenin on beta-amyloid toxicity in two models of *C. elegans*, including the transgenic *C. elegans* which expresses human beta-amyloid peptides. A LC-MS/MS analysis revealed that glycyrrhizic acid and glycosated forms of isoliquiritigenin and liquiritigenin were the major constituents of water and methanol extracts. These two extracts and the pure compounds were tested in two *C. elegans* models of beta-amyloid aggregation and beta-amyloid toxicity. The *C. elegans* treated with isoliquiritigenein showed the greatest decrease in number of beta-amyloid aggregates (30%). Both extracts and isoliquiritigenin also showed significant activity against acute beta-amyloid toxicity in the transgenic *C. elegans* which expresses human beta-amyloid peptides. These changes led to delayed paralysis in the model, suggesting that these secondary compounds of *G. uralensis* were candidates for treatment of AD.

6.3.3.4  Neuroprotection

Kim et al. (2012) investigated effects of dehydroglyasperin C, isolated from *G. uralensis*, against glutamate-induced oxidative stress in mouse hippocampal HT22 cells. Results showed a significant reduction in cytotoxicity and ROS generation induced by glutamate. A further investigation also tested whether dehydroglyasperin C showed effects on the expression of haem oxygenase-1, a major cellular system involved with antioxidant defence. Results showed that dehydroglyasperin C increased haem oxygenase-1 expression in a dose-dependent manner. These results showed that
dehydroglyasperin C exerts protective effects on neuronal cells against glutamate-induced oxidative injury via the induction of haem oxygenase-1 expression.

Yang et al. (2012) investigated effects of isoliquiritigenin isolated from G. uralensis in relation to glutamate-induced mitochondrial dysfunction in HT22 hippocampal neuronal cells. Glutamate-mediated excitotoxicity, which is associated with ROS, is hypothesised to be a major contributing factor to pathological cell death and to be involved in many chronic brain diseases. This study found that isoliquiritigenin reversed the glutamate-induced ROS production and mitochondrial depolarisation, as well as reversed glutamate-induced changes in expression of the apoptotic regulators Bcl-2 and Bax. The HT22 cells which had been pre-treated with isoliquiritigenin showed suppression of the release of apoptosis–inducing factor from the mitochondria into the cytosol. Overall, the results indicated that isoliquiritigenin from G. uralensis exerts protective effects against glutamate-induced mitochondrial damage and hippocampal neuronal apoptosis, suggesting it as a candidate for treatment or prevention of neurodegenerative diseases.

6.3.3.5 Anti-inflammatory activity
A review of anti-inflammatory activities of G. uralensis found that three triterpenes and 13 flavonoids exhibited anti-inflammatory properties, largely by decreasing TNF, MMPs, PGE2 and free radicals (Yang et al., 2017).

6.3.3.6 MAO-B inhibiting activities
Zarmouh et al. (2016) utilised high-throughput screening of 155 natural products for the identification of selective MAO-B inhibitors, which are used to treat PD and may play a role in treatment of other neurodegenerative diseases (Foley et al., 2000). G. uralensis was reported to exhibit potent selective relative inhibition of human MAO-B.

6.3.4 Atractylodes lancea (rhizome)
Atractylodes species has been studied for antihallucination-like, sedative and analgesic effects, as reviewed in this section.

6.3.4.1 Antihallucination-like effects
Murayama et al. (2014) reported on effects of A. lancea rhizome in an animal hallucination model. The aim was to clarify which component of Yokukansan and Yokukansan-jia-chimpi-hange might contribute to benefits reported in hallucinations in people with PD and other dementias. Results showed that a water extract of Atractylodes japonica exerted a stronger inhibitory action according to results of the DOI-induced head twitch response, compared to A. lancea. This corresponded to levels of the main compounds atracylenolide III and beta-eudesmol, suggesting that these
compounds contribute to the anti-hallucination-like effects observed. Also, the butenolide part of atracylenolide III was reported to have a similar structure to serotonin, suggesting this B-C ring might play a role as a serotonin receptor antagonist. These authors recommended that butenolide-related compounds should be further investigated in terms of structure-activity relationships.

6.3.4.2 Sedative effects
An in vitro study by Singhuber et al. (2012) investigated effects of atracylenolide II and III, extracted and isolated from Atractylodes macrocephala Koidz., for ability to modulate GABA-induced chloride currents. A two-microelectrode voltage clamp technique was used on recombinant alpha1beta2gamma(2s) GABA(A) receptors expressed in Xenopus laevis oocytes. Results indicated that each of these compounds showed more activity than the similar compound atracylodes I. The team also found that the effect was mediated independently of the benzodiazepine binding site. These results suggested that the two sesquiterpene lactones atracylodes II and III exert in vitro activity on recombinant GABA9A receptors, which may at least partially justify its use as a sedative.

6.3.4.3 Analgesic effects
Kimura et al. (1991) studied effects of beta-eudesmol isolated from A. lancea to investigate a rationale for this herb’s traditional use to alleviate pain in skeletal muscle. A mouse model was used to determine any mechanism of a blocking action of beta-eudesmol on the nicotinic acetylcholine receptor channel. Results indicated that the blocking effect of beta-eudesmol on nerve-evoked skeletal muscle contraction was due to a blockade of nicotinic Ach receptor channels at the neuromuscular junction. This study found that beta-eudesmol acted via a similar mechanism as the hallucinogenic and disassociative anaesthetic drug phencyclidine.

6.3.5 Angelica species including A. acutiloba, A. archangelica, A. sinensis
No relevant experimental studies were identified that investigated effects of the single herb A. acutiloba or compounds isolated from this species, that involved symptoms analogous to BPSD or pathologies related to dementia. However, A. archangelica has been investigated for anxiolytic-like effects and memory improvements in several animal studies, and A. sinensis has been tested in animal models for antidepressant-like activities, improvement in cognitive impairment due to chronic stress, and antioxidant activities.

6.3.5.1 Anxiolytic effects
Kumar et al. (2012) reported on anxiolytic-like effects of A. archangelica extracts on rats subjected to the elevated T-maze and forced swimming tests. The elevated T-maze test is an animal model of generalised anxiety. The results showed that oral diazepam and extracts exerted anxiolytic effects
according to the elevated T-maze test. An increase was detected in the one-way escape and decreased inhibitory avoidance on the first, third and seventh day. In the forced swimming test, imipramine and the *A. archangelica* extract both appeared to exert antidepressant-like and anxiolytic-like effects, as determined by increased climbing time and swimming time and decreased immobility time. These findings suggested that *A. archangelica* extracts possess anxiolytic-like activity. Of the various extracts tested, aqueous and methanol extracts showed the most anxiolytic activity, while ethyl acetate showed the least and the chloroform extract was intermediate.

Further, Kumar and Bhat (2012) tested anxiolytic-like effects of various methanolic extracts of *A. archangelica*, including extracts of the root, stem, leaf, fruit and whole plant. Again, the elevated plus maze test was used in rats. The methanol extracts were reported to show similar anxiolytic-like effects as diazepam according to results showing increased number of entries and time spent in open arms, as well as decreased number of entries and duration of time spent in the closed arm of the test. The whole plant and leaf showed the most anxiolytic-like effects, while the stem showed the least.

Budzynska et al. (2012) investigated effects of the nonpolar coumarin imperatorin, isolated from *A. archangelica* fruits, on anxiety and memory-related behaviour in male Swiss mice. Two different procedures of the elevated plus maze test were used. Mice were administered imperatorin via injection, at various dosages and times, in order to investigate effects on anxiety, memory acquisition and memory consolidation. Acute and repeated doses of imperatorin were reported to exert anxiolytic-like effects on mice tested 30 minutes after injection, but not in mice tested after 15 and 60 minutes. Also, acute and repeated administration of imperatorin was reported to improve both the acquisition and consolidation stages of memory processes in a modified elevated plus maze test. The results suggested that imperatorin might exert benefits for disorders that involve both memory impairment and high anxiety levels.

Kumar et al. (2013) also tested anxiolytic effects of nonpolar coumarins isolated from *A. archangelica*, using the elevated plus maze test. The non-polar coumarins included imperatorin and isoimperatorin. A further multi-compound extract was produced of petroleum ether. All three interventions were found to exert anxiolytic-like effects according to results of the elevated plus maze, light and dark arena and hole board models in rats. However, the petroleum extract reportedly showed the most promising activity, which the authors suggested could have been due to a synergistic action of the multiple compounds, or multiple mechanisms. Overall the results indicated that the mixture of coumarins isolated from *A. archangelica*, and the single compounds imperatorin and isoimperatorin, showed anxiolytic-like activities.
Imperiton has been described as a main compound of *A. archangelica* fruit that has been shown to exert effects on various neurotransmitters. Sigurdsson and Gudbjarnason (2013) tested effects of imperatorin on memory in ten-month-old mice. The passive avoidance test was used to measure step-down latency and step-through latency in mice who had received either pure imperatorin daily, or the same dosage but as part of a herbal extract. Step-down latency was significantly higher in both groups receiving imperatorin compared to the control group, whereas no difference was detected between groups for step-through latency. These results provided further evidence that imperatorin is the main active ingredient of *A. archangelica*.

### 6.3.5.2 Antidepressant-like effects

Shen et al. (2016) reported on antidepressant-like effects of an *A. sinensis* extract in male Sprague Dawley rats subjected to chronic unpredictable mild stress-induced depression. Rats were subjected to the test for five weeks which induced depressive behaviours including reduced sucrose consumption and lessened sucrose preference ratios in the sucrose preference test, prolonged immobility times and decreased struggling times in the forced swim test, as well as decreased locomotor activity in the open field test. Also, the expression of brain derived neurotrophic factor (BDNF) and other related protein molecules were decreased in the hippocampus of depressed rats. Depressed rats which were treated with *A. sinensis* showed normalised behaviours related to depression, and normal molecular profiles. These results indicated that the antidepressant-like effect was mediated via up-regulation of the BDNF signalling pathway.

### 6.3.5.3 Alleviation of cognitive impairment

Deng et al. (2015) studied effects of *A. sinensis* on cognitive impairment induced by chronic restraint stress in rats. The results showed that the treated rats had alleviated cognitive deficits. This was associated with enhanced synaptic efficacy due to improved field excitatory postsynaptic potential amplitudes, alleviation of adverse changes in synapse structure and neurons in the hippocampus, and increased levels of brain derived neurotrophic factor, microtubule associated protein-2 and synaptophysin in the hippocampus. These results appeared to provide evidence to support *A. sinensis* for treatment of chronic stress-induced neuronal deterioration.

Xin et al. (2013) reported on beneficial effects on cognitive impairment from the compound Z-ligustilide, extracted from *A. sinensis* root, and associated promotion of neurogenesis, in a rat model with permanent bilateral common carotid artery occlusion. This model is used to represent chronic cerebral hypoperfusion-related neurodegenerative diseases. An extract of *A. sinensis* root reportedly enhanced adult neurogenesis in the hippocampus following chronic cerebral hypoperfusion, and improved the cognitive symptoms related to the hypoperfusion. These protective effects on
cognition were abolished by cranial irradiation, which ablated the adult hippocampal neurogenesis. Rats treated with the *A. sinensis* root extract showed a restoration of the reduced brain derived neurotrophic factor expression, and phosphorylation of cAMP-responsive element binding protein CRE as well as GAD65 staining intensity in these rats with chronic cerebral hypoperfusion. Overall, these results suggested that adult neurogenesis is required for *A. sinensis* root extract to exert benefits on cognitive impairment induced by chronic cerebral hypoperfusion, and that neurogenic enhancement secondary to the herbal intervention might be related to the increased BDNF and p-CREB levels, and increased GABA expression. These authors suggested *A. sinensis* root as a candidate for treatment of dementia associated with vascular injury.

Further, Feng et al. (2012) reported on protective effects of ligustilide on the parietal cortex and hippocampus of a rat model of chronic cerebral hypoperfusion, induced by permanent, bilateral common carotid artery occlusion. The Morris water maze test was used to assess spatial learning and memory abilities. Rats treated with oral ligustilide for seven days after the induced hypoperfusion showed decreased escape latency and swimming distance in the Morris water maze test, and an increase in time spent in the target quadrant. According to coronal sections of cortex and hippocampus, the ligustilide-treated rats also showed less neuronal loss, dendrite damage and neuronal apoptosis. Ligustilide treated rats also showed inhibited astrocytic activation and inhibited proliferation stimulated by the hypoperfusion. These results suggested that ligustilide exerted neuroprotective activity in rats subjected to chronic cerebral hypoperfusion injury, and this could be due to anti-apoptosis of neurons and anti-proliferation of astrocytes in the cortex and hippocampus. The authors suggested ligustilide as a candidate for prevention of VaD.

6.3.5.4 Analgesic effects
Zhao et al. (2014) reported on analgesic effects (anti-nociceptive and anti-inflammatory effects) of ligustilide, suggesting a new application of ligustilide for the treatment of chronic inflammatory pain. A rodent model underwent unilateral hindpaw injection of complete Freund’s adjuvant to induce persistent pain hypersensitivity. Models which also received repeated daily intravenous injection of ligustilide, either before or after the complete Freund’s adjuvant injection, showed attenuated thermal hyperalgesia and mechanical allodynia. The same treatment was also reported to inhibit the induced keratinocyte-derived chemokine and other protein levels in spinal cord samples of astrocytes. Also, single intravenous injection of ligustilide appeared to attenuate intrathecal injection of lipopolysaccharide-induced mechanical alldynia induced by the lipopolysaccharide, as well as decreased lipopolysaccharide-induced nuclear factor-kappaB activation and keratinocyte-derived chemokine and monocyte chemoattractant protein-1 upregulation in the spinal cord. These results
indicated that ligustilide treatment attenuated chronic inflammatory pain, possibly by inhibition of NF-KB-mediated production in spinal astrocytes.

6.3.5.5 Effects on memory impairments
Duan et al. (2016) found that *A. sinensis* reduced memory impairments in rats that had been induced by beta-amyloid injections. According to results of the Morris water maze, the *A. sinensis* treated rats showed reversal of the induced social behaviour impairments. Also, Western blot analysis showed lower levels of hippocampal beta-amyloid and beta-site APP-cleaving enzyme in the *A. sinensis* treated rats. Further investigation indicated that the treated rats showed inhibited apoptosis via effects on nuclear factor kappa B signalling. The treated rats also showed inhibited inflammation and upregulated expression of glial cell line derived neurotrophic factor and brain derived neurotrophic factor in the hippocampus, according to immunohistochemical staining and other tests. These findings suggested that *A. sinensis* could be a candidate for drug development for AD, and that its effects related to AD were due to inhibition of inflammation, apoptosis and the NF-KB signalling pathway.

6.3.5.6 Antioxidant activities
Wang et al. (2016) reported on the capability of peptides from *A. sinensis* for increasing oxidative survival in a model *C. elegans* intoxicated by the herbicide paraquat. An antioxidant fraction extracted from *A. sinensis* was purified by gel filtration to obtain antioxidant *A. sinensis* peptides. These were generally composed of peptides with less than 20 amino acid residues. Results indicated that these antioxidant peptides were able to reduce the endogenous ROS level, increase activities of the antioxidant enzymes SOD and catalase, and decrease the content of the lipid peroxidation product malondiadehyde in the nematodes treated with paraquat or undergoing senescence. The intervention also reportedly reduced aged pigment accumulation and extended lifespan, although it did not affect food-like behaviour. The authors suggested that these results demonstrated that the antioxidant peptides of *A. sinensis* were able to delay the ageing process in *C. elegans*, via antioxidant activities, independently of dietary restriction.

N-butylidenephthalide, a major phthalide extracted from *A. sinensis*, was reported to reduce secretions of beta-amyloid (40) deposits, reduce total tau levels and reduce hyperphosphorylated status of tau in stem cell derived neurons with induced Down syndrome. As Down syndrome shares neurodegenerative features with AD, these results suggested that N-butylidenephthalide might benefit AD by scavenging beta-amyloid aggregates and neurofibrillary tangles (Chang et al., 2015).
Angelica sp has been studied in various multi-herb formulae including Xiao yao san for effects of relevance to BPSD.

6.3.6  Bupleurum species, including B. falcatum and B. chinense.
No studies were identified which reported on Bupleurum chinense (Apiaceae) in relation to effects on BPSD-like symptoms in experimental models. One study was identified which investigated B. falcatum (chai hu) for antidepressant-like and anxiolytic-like effects in rats.

6.3.6.1 Antidepressant-like and anxiolytic-like effects in rats exposed to repeated restraint test
Antidepressant-like effects of oral administration of the methanolic extract in the tail suspension test. The methanolic B. falcatum extract showed dose-dependent possibility of antidepressant-like activity which could provide a lead for new treatments for depression. The mechanism was reported to involve the serotonergic and noradrenergic systems although the precise means was not elucidated (Kwon et al., 2010).

6.3.7  Cnidium officinale / Cnidium officinale Makino and Ligusticum chuanxiong [Syn. Ligusticum wallichii].
Cnidium species or Ligusticum chuanxiong have been studied for effects on pain and cognition, as well as potassium channel blocking, antioxidant and anti-apoptosis effects, as described in this section.

6.3.7.1 Analgesic effects
Ligustrazine, also known as tetramethylpyrazine, is an anti-inflammatory compound extracted from the roots of L. chuanxiong. Zhang et al. (2015) tested effects of ligustrazine on a rat model of angina. It is known that angina is mediated by cardiac afferent sensory neurons and that these neurons show large acid-evoked depolarising sodium current that can initiate action potentials, in response to the acidification that accompanies myocardial ischaemia. This current is mediated by acid-sensing ion channels. Results of this study showed that ligustrazine attenuated acid-induced acid-sensing ion channel currents and reduced the electrical dysfunction and infarct size induced by cardiac ischaemia, as well as decreased the nociceptive behaviour in the rat model. These results suggested that ligustrazine may act via inhibition of acid-sensing ion channels to exert beneficial effects on angina and ischaemic heart disease.

6.3.7.2 Effects on cognitive impairment
Ni et al. (1995) investigated effects of tetramethylpyrazine, isolated from L. chaunxiong, on spatial cognitive impairment, in a rat model of spatial cognitive impairment induced by permanent occlusion of bilateral common carotid arteries, and in a scopolamine-induced model. The first model
showed a severe learning deficit in non-pretrained rats, but this was improved in rats administered daily tetramethylpyrazine. These rats showed improvements in their learning deficit but did not show changes in the impaired retention task test, and showed improvements in numbers of errors associated with a three-minute delay interposition in these rats. The rats subjected to scopolamine showed a significant decrease in the initial correct response and an increase in number of errors, indicating spatial cognitive impairment. Treatment with tetramethylpyrazine showed a dose-dependent reversal of this scopolamine-induced impairment in the maze performance. These results suggested that tetramethylpyrazine may exert therapeutic effects for treatment of spatial cognitive impairment due to either decreased cerebral blood flow or cholinergic dysfunction.

Ozaki et al. (1989) investigated effects of a chloroform soluble fraction of *C. officinale* rhizome, and its main components, the phthalide compounds ligustilide, cnidilide and senkyunolide. A rat model was used to test for centrally acting muscle relaxant effects of these three compounds separately. Results showed that each of the compounds, and the chloroform soluble fraction, exerted similar effects on depression of reflex response in the rat model. The potencies were reportedly similar to mephenesin, the centrally acting muscle relaxant. These results suggested that the three compounds may exert central origin muscle relaxation activity.

6.3.7.3 K+ channel blocking effects

Shih et al. (2015) investigated effects of butylidenephthalide, a main constituent of *L. chuanxiong*, on systolic pressure in conscious rats with reduced systolic pressure induced by cromakalim, the ATP-dependent potassium + channel opener. Rats treated with butylidenephthalide did not show changes in baseline systolic pressure in the conscious normotensive or spontaneous hypertensive rats. However, a rightward shift was found in the log dose-systolic pressure reduction curve of cromakalim in normotensive rats treated with butylidenephthalide. These results suggested that butylidenephthalide exerted an antagonistic effect against cromakalim, similar to other K+ channel blockers. Therefore butylidenephthalide might be a novel K+ channel blocker, which could be a therapeutic strategy for clinical management of AD.

6.4 Discussion of the experimental literature

For both EGb 761® and Yokukansan, there is evidence from the experimental literature for beneficial effects on animal models of stress, depression, aggression, anxiety, excessive motor activities and cognitive impairments. These effects are of direct relevance to cognitive symptoms and BPSD.

The terpene trilactones (TTLs) and flavonoids appear to be important for the main pharmacological effects of EGb 761® in relation to BPSD and cognitive decline. An important consideration of
Yokukansan is whether it can be modified to improve its putative benefits and reduce risks of adverse effects. As covered in Chapter Four, hypokalaemia is the main adverse event found in clinical studies and is known to be caused by intake of Glycyrrhiza species. Glycyrrhizic acid inhibits 11-beta-hydroxysteroid dehydrogenase, which allows cortisol to exert an aldosterone like effect; i.e. cortisol is not metabolised to cortisone and thus stimulates sodium retention, potassium wastage, and acid excretion. An important consideration for future research is therefore whether Glycyrrhizic acid could and/or should be removed from the formula. Table 6.2 summarises the literature on G. biloba and the seven herb ingredients of Yokukansan, based on Chapters Four, Five and Six:

Table 6.2: Summary of the literature on G. biloba and the ingredients of Yokukansan

<table>
<thead>
<tr>
<th>Herb name (pinyin)</th>
<th>Number of times included in a test intervention in a controlled clinical trial for BPSD</th>
<th>Number of citations in classical Chinese medical literature related to BPSD</th>
<th>Reported effects in animal models related to BPSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginkgo biloba leaf (yin xing ye)</td>
<td>7</td>
<td>0</td>
<td>anti-aggression-like, antidepressant-like, anxiolytic-like, reduced cognitive impairments, mental stress and abnormal motor activities</td>
</tr>
<tr>
<td>Uncaria rhynchophylla or U. sinensis (gou teng)</td>
<td>8</td>
<td>0</td>
<td>anti-aggression-like, antidepressant-like, sedative, anxiolytic-like, reduced cognitive impairments, and abnormal motor activities</td>
</tr>
<tr>
<td>Poria cocos (fu ling or fu shen)</td>
<td>12</td>
<td>1206</td>
<td>enhanced sleep behaviour</td>
</tr>
<tr>
<td>Glycyrrhiza sp. (gan cao)</td>
<td>11</td>
<td>717</td>
<td>antidepressant-like, reduced learning and memory impairments,</td>
</tr>
<tr>
<td>Angelica sp. (dang gui)</td>
<td>10</td>
<td>569</td>
<td>antidepressant-like, anxiolytic-like, reduced cognitive and memory impairments, analgesic</td>
</tr>
<tr>
<td>Atractylodes lancea (bai zhu)</td>
<td>9</td>
<td>370</td>
<td>antihallucination-like, sedative, analgesic</td>
</tr>
<tr>
<td>Ligusticum chuanxiong (chuan xiong)</td>
<td>5</td>
<td>164</td>
<td>analgesic, reduced cognitive impairments</td>
</tr>
<tr>
<td>Bupleurum falcatum (chai hu)</td>
<td>8</td>
<td>0</td>
<td>antidepressant-like, anxiolytic-like</td>
</tr>
</tbody>
</table>

Limitations of this review

Although activities on BPSD-like symptoms were reported in the animal model studies, this does not mean that the same activities were exerted in the clinical studies included in Chapter Four. The dosages of EGB 761® used in the preclinical studies were found to be relatively higher than the dosages typically used in clinical trials (100 mg/kg compared to <2 mg/kg) (Nash, 2015). The concentrations used in the in vitro pharmacological studies and in vivo studies of EGB 761® indicated
that the \textit{in vivo} brain concentrations were lower than the concentrations used for \textit{in vitro} experiments, but within the same approximate range (Ude et al., 2013). The degree of absorption is also not typically reported in clinical or experimental studies. Although \textit{G. biloba} leaf, \textit{Yokukansan} and its ingredients have been studied extensively, the exact mechanisms, activities of the contained compounds and efficacy in treating BPSD have not been determined. In addition, this review did not assess risk of bias, and methodological or reporting issues in the experimental studies. Risk of publication bias and other potential weaknesses limit the ability to draw strong conclusions about effects of the HMs in the experimental models.

6.5  \textbf{Conclusions from this review}

The experimental evidence supporting EGb 761® and \textit{Yokukansan}, or at least its separate herb ingredients, of relevance to BPSD is vast. Based on the abundance of positive findings reported in the literature, EGb 761® and \textit{Yokukansan} are strong candidates for further testing in well-designed clinical studies:
CHAPTER SEVEN VARIATION IN PLACEBO EFFECT SIZE IN CLINICAL TRIALS OF THE BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: A SYSTEMATIC REVIEW AND META-ANALYSIS

7.1 Abstract
Increasing placebo effect sizes over time have been reported in randomised controlled trials (RCTs) for outcomes related to psychiatric symptoms. The Neuropsychiatric Inventory (NPI) is a key outcome measure in clinical trials of the behavioral and psychological symptoms of dementia (BPSD). Accurate placebo effect size estimates for NPI are needed for sample size calculations in order to adequately power future studies. This study investigated variation in placebo effect sizes for NPI in RCTs testing oral interventions for BPSD. A search of PubMed was conducted in April 2016 for two-armed, double-blinded, placebo-controlled RCTs testing any oral intervention for management of BPSD, using the NPI. Meta-analysis was conducted of baseline versus end of treatment placebo group data of included studies. Twenty-five RCTs published from 2000 to 2015 were included. Substantial variation in placebo effect sizes was detected. Participants in placebo groups showed greater improvements in recent studies compared to earlier studies. Subgroup analyses indicated robustness of this finding. From 2000 to 2008 there was no significant change in total NPI scores within placebo groups (12 studies; 1056 participants), while from 2009 to 2015 there was significant improvement (mean difference: -2.68; 95% confidence interval: -4.38, -0.99; z=3.10; p=0.002, random effects; I²=76%; 13 studies; 1170 participants). This increase in NPI effect sizes in placebo groups has important implications for power calculations for future clinical trials of BPSD. Effect size estimates for NPI need to be based on more recent studies.

7.2 Introduction
Randomised controlled trials (RCTs) incorporating a placebo or sham control group are the typical method for testing efficacy of interventions. An intervention that produces a significant improvement in an outcome measure compared to an inert control is generally considered to be efficacious but substantial improvements within the control group can impact upon this comparison (Gotzsche, 1994; Shorter, 2011; McQueen et al., 2013). For example, a meta-analysis of repetitive transcranial magnetic stimulation (rTMS) for treatment of auditory hallucinations in schizophrenia found that studies that showed no improvements in sham groups reported a significant benefit of rTMS, while studies which showed improvements within the sham groups did not find a significant benefit for rTMS (Dollfus et al., 2016).

The current study investigates the variability of effect sizes within the placebo groups of RCTs that assessed the efficacy of oral interventions for management of the behavioral and psychological
symptoms of dementia (BPSD) using the Neuropsychiatric Inventory (NPI) as an outcome measure.

In the present study, the placebo effect size was calculated as the mean difference (MD) and 95% confidence interval (CI) of the total NPI scores in placebo groups at baseline versus end of treatment.

It is generally expected that participants receiving placebo will show the normal progression of their medical condition, since they are not receiving an active treatment. However, certain known factors may cause variation in placebo effect size within a trial setting. These can include regression to the mean (McDonald et al., 1983), spontaneous improvement, fluctuation of symptoms, scaling bias, and polite and conditioned answers (Kienle & Kiene, 1997). Other contributing factors include diagnostic misclassification, issues concerning inclusion/exclusion criteria, lack of sensitivity to change of measurement scales, measurement errors, poor quality of data entry and verification, participants’ and investigators’ expectations, high attrition, and bias due to methodological issues (Fava et al., 2003). Also, the Hawthorne effect (altered behavior of participants due to awareness of being observed), Rogers phenomenon (improved diagnostic methods that falsely increase prevalence of a medical condition, leading to apparent improved prognosis) and the Simpson paradox (a trend that appears in different subgroups of data but disappears or reverses when the groups are combined) can influence placebo effect size (Kleist, 2006). Other possible modifiers include therapeutic effects related to the participant-clinician relationship and encounter (Hrobjartsson, 2002; Kaptchuk & Miller, 2015). This list is not exhaustive and it is likely that other contributing factors exist (Weimer et al., 2015). These factors can produce statistically significant and clinically relevant changes within placebo groups (Miller & Kaptchuk, 2008).

Substantial placebo effect sizes have been documented for at least 50 years for various psychiatric symptoms (Weimer et al., 2015). Previous systematic reviews and meta-analyses have found placebo effect sizes that were inconsistent between studies and that have increased over time. In antidepressant studies, the changes within placebo groups were highly variable and symptom improvements in both placebo and medication groups had increased over the past thirty years (Walsh et al., 2002). A ‘publication year effect’ was detected in a meta-analysis of 96 antidepressant trials, with a strong linear association between publication year and placebo effect size (Rief et al., 2009). Similarly, two studies have reported a trend of increasing placebo effect sizes in clinical trials of antipsychotics for schizophrenia (Kemp et al., 2010; Alphs et al., 2012). Notably, much the same trend has been reported in psychological interventions, including Cognitive-Behavioural Therapy for unipolar depression in adolescents. In a meta-analysis, earlier studies showed greater effectiveness than recent studies (Klein et al., 2007), which is likely due to the poorer methodological quality of earlier studies leading to overestimation of treatment effects (Davey & Chanen, 2016).
In studies of donepezil for Alzheimer’s disease (AD), participants in placebo groups showed significantly greater rates of deterioration in cognitive function in studies initiated between 1990 and 1994, compared to participants in studies initiated from 1996 to 1999 (Jones et al., 2009). This was based on analysis of cognitive assessment scores using individual patient data. In BPSD, an unexpectedly large placebo effect size was reported for NPI in an RCT of memantine versus placebo, resulting in a lack of significance at the end of 24 weeks treatment (Bakchine & Loft, 2008). Recent BPSD trials also have reported unusually large improvements in NPI scores within placebo groups (Herrmann et al., 2013; Nikolova et al., 2013; Rosenberg et al., 2015).

7.2.1 Behavioral and psychological symptoms of dementia (BPSD)

BPSD refer to disturbed perception, thought content, behavior and mood occurring in people with dementia (Finkel et al., 1996). The presence of BPSD is associated with more rapid deterioration, increased risk of institutionalisation and death, and greater level of caregiver distress (Donaldson et al., 1998; Lyketsos et al., 2000; Lopez et al., 2013). Treatment guidelines suggest non-pharmacological approaches to management (Guideline Adaptation Committee, 2016; NICE, 2007). Despite being effective, these may not be available in routine practice (de Oliveira et al., 2015). Pharmacological interventions can be used for specific cases (Guideline Adaptation Committee, 2016; NICE, 2007). However, risk to benefit profiles may be unfavorable, so appropriate prescribing is a challenge (McClam et al., 2015; Antonsdottir et al., 2015; Magierski & Sobow, 2016; Schneider et al., 2006; Maree et al., 2016). Antipsychotics are associated with increased mortality in older people with dementia (Maust et al., 2015) and their overuse is a far-reaching issue (Looi & Macfarlane, 2014). Antidepressants, anticonvulsants and benzodiazepines may also increase risk of falls (Naples et al., 2016; Ensrud et al., 2002).

7.2.2 The Neuropsychiatric Inventory (NPI)

The NPI (Cummings et al., 1994) is widely used in placebo-controlled trials for assessing efficacy of interventions for BPSD management, by questioning the primary caregiver about the frequency and severity of each symptom during a specified period. A minimum score of zero indicates no BPSD with a maximum total score of 120 for NPI-10, which assesses ten symptom domains, including delusions, hallucinations, agitation, depression, anxiety and others. The NPI-12 (Cummings, 1997) has a maximum total score of 144 as it contains two additional symptom domains of sleep and night-time behaviour change and appetite and eating change. A decrease in four points may be regarded as a clinically meaningful change (Mega et al., 1999) but a smaller change in troublesome symptoms such as agitation might be relevant for caregivers.
The NPI is commonly used in placebo-controlled RCTs for testing the efficacy of new interventions for BPSD, so it is important to determine the variation in NPI scores within placebo groups in order to best interpret the results of these studies and design future studies with suitable sample sizes.

The aim of this study was to investigate the placebo effect sizes in RCTs of oral interventions for BPSD to determine:

1. the variation in placebo effect sizes for total NPI scores;
2. whether the placebo effect size in BPSD studies has changed over time;
3. any variables that influence placebo effect sizes; and
4. implications for the design of BPSD studies that use NPI as an outcome measure.

7.3 Methods

PubMed was searched from its inception in 1996 to April 2016 using the query: “neuropsychiatric inventory [all fields] AND placebo [all fields] AND random* [all fields]”. Reviews and reference lists of included publications were searched for additional studies.

7.3.1 Inclusion criteria

Randomised, double-blind, placebo-controlled clinical trials testing the efficacy of oral interventions for BPSD were included. Participants could be diagnosed with any type of age-related dementia or neurocognitive disorder (NCD). Continuation of stable-dose concomitant medications that had been commenced at least two weeks before enrollment and/or use of rescue medications were allowed. Participants were assigned a 1:1 probability of receiving active treatment or placebo. Total NPI-10 or NPI-12 mean (SD) scores were reported numerically.

7.3.2 Exclusion criteria

Comparative effectiveness, double-dummy or add-on effect studies were excluded, as were discontinuation studies. Flexible-dose or incremental-dose studies were excluded unless this was a brief initial phase and the main treatment duration involved a fixed or mostly fixed dose of the test intervention.

Placebo effect sizes for subjective outcomes may be influenced by the number of arms in a study and the resultant participants’ and assessors’ knowledge of the probability of receiving active treatment or placebo (Sinyor et al., 2010). Therefore, studies in which the probability of allocation to treatment or placebo was not equal were excluded to avoid confounding results. Studies reporting NPI-Questionnaire version (NPI-Q), a simplified version of NPI-12 with a maximum total score of 36 (Kaufer et al., 2000) were considered separately.
7.3.3 Risk of bias

Risk of bias was assessed using the Cochrane risk of bias tool by AJ Hyde and BH May independently, with mediation by AL Zhang.

7.3.4 Statistical methods

Analysis of NPI scores was conducted in RevMan 5.3, using MD with random effects (RE) models and meta-regression analysis was conducted using Stata®. If NPI baseline and change scores were reported, change scores were converted to end of treatment (EoT) scores by adding/subtracting the means and using the baseline SD for EoT values.

For the placebo groups, meta-analysis was conducted of total NPI scores at baseline versus EoT to provide assessments of change in NPI scores. To investigate whether placebo effect sizes have increased over time, the pool of studies was divided into two equal groups according to median publication year. Studies published in the earlier period were labelled Group 1 and studies published in the more recent period were labelled Group 2.

To investigate potential differences between Groups 1 and 2, analyses were conducted when data were available, including differences in baseline characteristics of participants between Groups 1 and 2 for total NPI score, age, numbers of males and females enrolled, and differences in numbers of dropouts.

Meta-analyses were conducted for Groups 1 and 2 based on categorical participant characteristics such as dementia diagnosis, and study design characteristics including active treatment tested, and studies funded by the manufacturer of the test intervention.

Meta-regression analysis was conducted to investigate any impacts of continuous variables on placebo effect size including publication year, treatment duration, sample size and baseline mean NPI score.

For the active treatment groups meta-analyses were conducted for Groups 1 and 2 for: 1. baseline versus EoT for total NPI scores in the active treatment groups; and 2. total NPI scores at EoT for active treatment versus placebo groups. Meta-regression was conducted for continuous variables.

7.4 Results:

Searches of Pubmed and reference lists located 203 potentially relevant references. After screening and full-text assessment, 26 studies published from 2000 to 2015 were included in the review (Figure 7.1).
Figure 7.1: Flow diagram of search and selection process for randomised, placebo-controlled oral intervention trials for management of BPSD

The meta-analyses of total NPI scores were based on 25 studies which enrolled 4,798 participants in total, with 2,355 participants in placebo groups at baseline (see Table 7.1).
Table 7.1: Characteristics of the included studies of oral interventions for BPSD

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Study name; location; duration</th>
<th>Diagnosis for inclusion; n participants at baseline; n in placebo group at baseline</th>
<th>Mean (SD) age of participants in placebo group at baseline; mean (SD) total NPI score in placebo group at baseline</th>
<th>Test intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>McKeith 2000; UK, Spain &amp; Italy; 20wks</td>
<td>LBD; 120; 61</td>
<td>73.9 (6.4); 20.2 (14.2)</td>
<td>Rivastigmine 12mg daily (6mg bid)</td>
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<tr>
<td>2</td>
<td>Tariot 2001; US; 24wks</td>
<td>AD or AD with CVD and ≥3 points on ≥1 NPI domain; 208; 105</td>
<td>85.9 (NS); 20.5 (14.7)</td>
<td>Donepezil 10mg daily</td>
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<tr>
<td>3</td>
<td>Tune 2003; US; 24wks</td>
<td>AD; 28; 14</td>
<td>72.2 (NS); 8.79 (9.79)</td>
<td>Donepezil 10mg daily</td>
</tr>
<tr>
<td>4</td>
<td>Peskind 2005; US; 6wks</td>
<td>AD with disruptive behaviors; 31; 14</td>
<td>84 (8); 29.5 (15.5)</td>
<td>Propranolol ≤ 120mg daily</td>
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<tr>
<td>5</td>
<td>Winblad 2006; Sweden; 24wks</td>
<td>Severe AD and living in assisted care; 248; 120</td>
<td>85.3 (5.9); 19.6 (15.8)</td>
<td>Donepezil ≤10mg daily</td>
</tr>
<tr>
<td>6</td>
<td>Peskind 2006; US; 24wks</td>
<td>Mild to moderate AD; 403; 202</td>
<td>77 (8.2); 12.2 (13)</td>
<td>Memantine 20mg daily</td>
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<tr>
<td>7</td>
<td>Chappell 2007; US; 8wks</td>
<td>Mild to moderate AD; 181; 91</td>
<td>74.5 (8.7); 16.1 (18.9)</td>
<td>LY451395® 0.4mg daily</td>
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<td>8</td>
<td>Napryeyenko 2007; Ukraine; 22wks</td>
<td>AD, AD with CVD or VaD, with BPSD; 400; 200</td>
<td>63 (8); 21.6 (9.9)</td>
<td>EGb 761® 240mg daily</td>
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<tr>
<td>9</td>
<td>Mok 2007; Hong Kong; 26wks</td>
<td>Subcortical VaD; 40; 20</td>
<td>74.1 (6.6); 9.5 (6.5)</td>
<td>Rivastigmine 6mg daily</td>
</tr>
<tr>
<td>10</td>
<td>van Dyck 2007; US; 24wks</td>
<td>Moderate to severe AD; 350; 172</td>
<td>78.3 (7.6); 17.5 (16.4)</td>
<td>Memantine 20mg daily</td>
</tr>
<tr>
<td>11</td>
<td>Howard 2007; UK; 12wks</td>
<td>AD with clinically significant agitation; 259; 131</td>
<td>84.4 (8.2); 23.6 (16.7)</td>
<td>Donepezil 10mg daily</td>
</tr>
<tr>
<td>12</td>
<td>De Jong 2008; The Netherlands; 52wks</td>
<td>Mild to moderate AD; 51; 25</td>
<td>72.2 (9); 7.1 (6.7)</td>
<td>Indomethacin (NSAID) 100mg daily + omeprazole 20mg daily</td>
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<td>13</td>
<td>Wang 2009; US; 8wks</td>
<td>AD with agitation and aggression; 22; 11</td>
<td>78.1 (10.8); 43 (18)</td>
<td>Prazosin ≤6mg daily</td>
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<td>14</td>
<td>Emre 2010; Austria, France, Germany, the UK, Greece, Italy, Spain, and Turkey; 24wks</td>
<td>PDD or LBD; 199; 101</td>
<td>72.5 (7); 17.4 (15)</td>
<td>Memantine 20mg daily</td>
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<td>15</td>
<td>Vercelletto 2011; France; 52wks</td>
<td>bvFTD; 52; 26</td>
<td>66.6 (7.4); 31.1 (19.6)</td>
<td>Memantine 20mg daily</td>
</tr>
<tr>
<td>16</td>
<td>Bi 2011; China; 12wks</td>
<td>Mild to moderate AD; 25; 12</td>
<td>68.6 (6.35); 19.8 (6.11)</td>
<td>Fu zhi san® herb granules 10g daily</td>
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<tr>
<td>17</td>
<td>Ihl 2011; Ukraine; 24wks</td>
<td>AD, AD with CVD or VaD, with BPSD; 410; 204</td>
<td>204; 65 (9); 17 (8.2)</td>
<td>EGb 761® 240mg daily</td>
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<tr>
<td>18</td>
<td>Herrschaf 2012; Republics of</td>
<td>AD or VaD, and BPSD; 410; 205</td>
<td>64.9 (9.4); 16.7 (6.4)</td>
<td>EGb 761® 240mg daily</td>
</tr>
<tr>
<td>Study ID</td>
<td>Study name; location; duration</td>
<td>Diagnosis for inclusion; n participants at baseline; n in placebo group at baseline</td>
<td>Mean (SD) age of participants in placebo group at baseline; mean (SD) total NPI score in placebo group at baseline</td>
<td>Test intervention</td>
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<td>19</td>
<td>Belarus, Moldova &amp; Russian Federation; 24wks</td>
<td>AD with clinically significant agitation; 153; 79</td>
<td>84.4 (6.6); 36.1 (19.2)</td>
<td>Memantine 20mg daily</td>
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<td>20</td>
<td>Herrmann 2013; Canada; 24wks</td>
<td>Moderate to severe AD with BPSD, total NPI ≥13 and NPI agitation/aggression ≥1 point; 369; 187</td>
<td>75.1 (6.9); 29.18 (13.3)</td>
<td>Memantine 20mg daily</td>
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<tr>
<td>21</td>
<td>Nikolova 2013; Bulgaria; 22wks</td>
<td>AD, AD with CVD, VaD, with BPSD; 408; 205</td>
<td>NS ; 16.9 (8.7)</td>
<td>Egb 761® 240mg daily</td>
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<tr>
<td>22</td>
<td>Schwam 2014; Chile, US, Canada, Czech Republic; 12wks</td>
<td>Mild to moderate AD; 191; 100</td>
<td>73.5 (7.5); 12.2 (12.9)</td>
<td>PF-04447943® 50mg daily</td>
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<tr>
<td>23</td>
<td>Tsai 2014; Taiwan; 8wks</td>
<td>PDD; 30; 15</td>
<td>77.3 (6.6); 13.4 (11.2)</td>
<td>Sarcosine&lt;sup&gt;d&lt;/sup&gt; 2g daily</td>
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<tr>
<td>24</td>
<td>Gavrilova 2014; Russian Federation; 24wks</td>
<td>MCI and neuropsychiatric symptoms; 160; 79</td>
<td>63 (7); 11.6 (3.7)</td>
<td>Egb 761 240mg daily</td>
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<td>25</td>
<td>Van den Elsen 2015; The Netherlands; 3wks</td>
<td>AD, VaD or mixed with BPSD, total NPI ≥10 with agitation, aggression or aberrant motor behaviour; 50; 26</td>
<td>78 (7); 35.6 (13)</td>
<td>Tetrahydrocannabinol tablets 4.5mg daily and all received 3000mg acetaminophen daily</td>
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<td>26</td>
<td>Furukawa 2015&lt;sup&gt;f&lt;/sup&gt;; Japan; 4wks</td>
<td>Probable AD with BPSD; total NPI-Q &gt;4; with sum total agitation/aggression + irritability/lability ≥2 on NPI-Q; 145; 70</td>
<td>78.5 (5.1); 9.4 (4.4) (NPI-Q)</td>
<td>Yokukansan&lt;sup&gt;f&lt;/sup&gt; herb granules 7.5g daily</td>
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AD: Alzheimer’s disease; BPSD: Behavioral and psychological symptoms of dementia; bvFTD: behavioral variant frontotemporal dementia; CVD: cerebrovascular disease; Egb 761®: Extract of *Ginkgo biloba* leaf 761; EoT: end of treatment; LBD: Lewy body dementia; NPI: Neuropsychiatric Inventory; NS: not specified; NSAID: Non-steroid anti-inflammatory drug; PDD: Parkinson’s disease with dementia; US: United States; VaD: vascular dementia; wks: weeks

<sup>a</sup> α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor modulator.

<sup>b</sup> *Fu zhi san* herbal formula contains *Panax ginseng*, *Scutellaria baicalensis*, *Acorus gramineus* or *A. tatarinowii*, *Glycyrrhiza uralensis*.

<sup>c</sup> inhibits recombinant PDE9A.

<sup>d</sup> N-methylglycine, a metabolite of glycine; used as a cognitive enhancer.

<sup>f</sup> Furukawa 2015 not included in meta-analysis of NPI scores as this study used NPI-Q.

<sup>f</sup> Yokukansan herbal formula contains *Uncaria rhynchophylla*, *Angelica acutiloba*, *Poria cocos*, *Bupleurum falcatum*, *Cnidium officinale*, *Atractylodes lancea* and *Glycyrrhiza uralensis*.
7.4.1 Risk of Bias

All included studies were randomised and double-blinded. Two of 26 studies did not state methods of sequence generation, such as random number generator, coin tossing or throwing dice, so were judged ‘unclear’ risk for this domain. Nine studies did not describe the method of allocation concealment, such as telephone-based central allocation, or sequentially numbered opaque sealed envelopes, so were judged ‘unclear’ risk for this domain. All studies were judged ‘low’ risk of bias for blinding of participants, personnel and outcome assessors. Risk of bias due to incomplete outcome data was judged ‘unclear’ in one study and risk of bias due to selective outcome reporting was judged ‘low’ in all studies. All other judgements were ‘low’ risk of bias. No studies received any ‘high’ risk judgements (see Table 7.2 for assessments). Funding source was reported as the manufacturer of the test intervention in 16 of 25 studies, government or other grants in eight studies and was unclear in one study (see Table 7.2 for summary).

Table 7.2: Risk of bias assessments and summary of funding sources for included studies, in chronological order by publication year

<table>
<thead>
<tr>
<th>Included studies</th>
<th>Risk of Bias Categories</th>
<th>Summary of funding sources</th>
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<tr>
<td>Study ID</td>
<td>SG</td>
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Results of meta-analysis

Figure 7.2 shows a forest plot of effect sizes for total NPI scores in the placebo groups. The 25 studies are presented in chronological order according to publication year. Based on visual inspection of Figure 7.2 there appears to be a curvilinear trend towards greater improvements (i.e. decreases in NPI scores) within placebo groups occurring from 2012 onwards.

Figure 7.2 Total Neuropsychiatric Inventory (NPI) effect sizes of placebo groups, in chronological order according to year of publication

Statistical test: Mean difference using a Random effects model showing 95% Confidence interval (CI); SD: Standard deviation

Note: Studies identified by first author and publication year only.

For the combined pool of 25 studies, there was no significant change in total NPI scores within the placebo groups (2,216 participants at EoT). However, there was considerable variability between individual studies. The greatest increase in total NPI scores (MD: 9.40; 95% CI: 5.61, 13.19; z=4.86; p<0.00001; 23 participants) was in the 52-week study of indomethacin for mild to moderate AD (de Jong et al., 2008), while the greatest decrease (MD: -11.70; 95% CI: -20.08, -3.32; z=2.74; p=0.006;
24 participants) was detected in the three-week study of tetrahydrocannabinol for BPSD with agitation, aggression or aberrant motor activity (van den Elsen et al., 2015).

Based on publication year, we divided the studies into half at 2008/2009 since this produced the most even division for number of studies and spans of years. For the 12 studies published from 2000 to 2008 (Group 1) there was no significant change in BPSD (1,056 participants at EoT), whereas for the 13 studies published from 2009 to 2015 (Group 2) there was significant improvement (MD: -2.68; 95% CI: -4.38, -0.99; z=3.01; p=0.002; I²=76% RE; 1170 participants at EoT) (see Table 7.3).
Table 7.3: Results of meta-analysis and meta-regression of changes from baseline to end of treatment in total NPI scores in placebo groups of studies testing oral interventions for management of BPSD

| Results of meta-analysis of categorical variables | n studies (n participants EoT in placebo groups); range of durations of treatment | Change in total NPI Mean difference [95%Confidence Interval]; z score; p value; I² (Random Effects model) |
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<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N studies (n participants at EoT)</th>
<th>Regression analysis Weighted mean difference Adjusted R-squared value %; P value; 95% Confidence interval; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of publication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>12 (1056) 6-52wks</td>
<td>45.42%; p = 0.059, -0.038, 1.630; 48.17%a,b</td>
</tr>
<tr>
<td>Group 2</td>
<td>13 (1170) 3-52wks</td>
<td>100.00%; p =0; -2.311 -0.964*; 22.27%</td>
</tr>
<tr>
<td>Combined Groups 1 and 2</td>
<td>25 (2226) 3-52wks</td>
<td>21.93%; p = 0.041, -0.821, -0.018*, 72.12%a,b</td>
</tr>
<tr>
<td>Treatment duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>12 (1056) 6-52wks</td>
<td>40.90%; p =0.058; -0.008, 0.381; 50.44%a,b</td>
</tr>
<tr>
<td>Group 2</td>
<td>13 (1170) 3-52wks</td>
<td>-18.20%; p=0.284; -0.135, 0.418; 78.24%</td>
</tr>
<tr>
<td>Combined Groups 1 and 2</td>
<td>25 (2226) 3-52wks</td>
<td>24.25%; p = 0.014; 0.046, 0.370*; 81.88%c</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined Groups 1 and 2</td>
<td>25 (2226) 3-52wks</td>
<td>-4.75%; p=0.553; -0.016, 0.009; 83.33%a,a</td>
</tr>
<tr>
<td>Mean baseline total NPI score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1</td>
<td>12 (1056) 6-52wks</td>
<td>25.29%; p= 0.12; -0.693, 0.093; 59.57%a,a</td>
</tr>
<tr>
<td>Group 2</td>
<td>13 (1170) 3-52wks</td>
<td>-6.87%; p= 0.371; -0.392, 0.159; 78.04%</td>
</tr>
<tr>
<td>Combined Groups 1 and 2</td>
<td>25 (2226) 3-52wks</td>
<td>16.98%; p = 0.047; -0.453, -0.003*, 83.7%a,a</td>
</tr>
</tbody>
</table>

* significant (p<0.05)
a: distribution not linear;
b: result affected by outliers

---

**Notes:**
- Studies of memantine as test intervention
- Studies funded by manufacturer of test intervention
- Studies funded by independent grants
- Combined Groups 1 and 2
AD: Alzheimer’s disease; BPSD: Behavioural and psychological symptoms of dementia; CI: Confidence interval; EGB 761*: Extract of Ginkgo biloba leaf 761; EoT: End of treatment; I²: Index of heterogeneity; LBD: Lewy body dementia; MD: Mean difference; NPI: Neuropsychiatric Inventory; NS: not specified; PDD: Parkinson’s disease with dementia; wks: weeks; WMD: Weighted mean difference.

Meta-analysis test details- Statistical method: Inverse Variance; Analysis model: Random effects; Effect measure: Mean difference; Totals and subtotals; 95% Confidence intervals

Meta-regression test details- Stata * METAREG; Adjusted R-squared = proportion of between study variance explained (by the covariate); with Knapp-Hartung modification; 95% Confidence intervals; I² = % residual variation due to heterogeneity.

See Appendices for Bubble graphs of meta-regression analysis
The single study that used NPI-Q (Furukawa et al., 2015) found a significant improvement in both active treatment and placebo groups at the end of four weeks treatment, resulting in no significant difference between groups. This large placebo effect size appears consistent with the Group 2 studies (see Table 7.4 for meta-analysis results).

Table 7.4: Results of meta-analysis for single study of NPI-Q scores

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean difference; 95% CI;</th>
<th>Z value; (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group: baseline vs EoT; n=65 at EoT</td>
<td>-1.90 [-3.55, -0.25]*</td>
<td>Z = 2.26 (P = 0.02)</td>
</tr>
<tr>
<td>Treatment group: baseline vs EoT; n=72 at EoT</td>
<td>-2.30 [-3.68, -0.92]*</td>
<td>Z = 3.27 (P = 0.001)</td>
</tr>
<tr>
<td>Treatment vs Placebo groups EoT (4 weeks); n at EoT (72,65)</td>
<td>-0.20 [-1.83, 1.43]</td>
<td>Z = 0.24 (P = 0.81)</td>
</tr>
</tbody>
</table>

*significant
Reference for study: Furukawa et al. (2015)
CI: Confidence interval; EoT: End of treatment

7.4.3 Subgroup meta-analysis:

Subgroup meta-analyses were conducted for categorical data. These included dementia type: 1. AD; and 2. Parkinson’s disease dementia (PDD) or Lewy body dementia (LBD); participant characteristics: 1. agitation required for inclusion; 2: agitation not specified; test intervention (the Ginkgo biloba leaf extract EGb 761®, donepezil, memantine); and reported funding source. Results are shown in Table 7.4.

In the subgroup of 13 studies of participants with AD, there was no significant change in placebo groups for Group 1 and significant improvements for Group 2. This was consistent with the total pool. In the three studies of participants with PDD or LBD (McKeith et al., 2000; Emre et al., 2010; Tsai et al., 2014), there were no significant changes in total NPI scores in placebo groups of the single Group 1 study or in the two Group 2 studies.

For the six studies in which agitation was required as an inclusion criterion, Group 1 showed no significant change while Group 2 showed a significant improvement. The 19 studies that did not require agitation at baseline showed no change for Groups 1 or 2.

For the five studies of EGB 761®, the placebo group of the single Group 1 study showed no significant change, compared to a significant improvement for the four Group 2 studies. For the donepezil studies, the four studies in Group 1 showed no significant change in placebo groups but no studies were conducted in the time period of Group 2. For the six studies of memantine, there was no significant change in placebo participants in either Groups 1 or 2.

Overall, the subgroup analyses appeared to confirm the robustness of the data, with no significant changes in NPI scores detected in Group 1 and a tendency towards reduced NPI scores in Group 2.
Group 1 studies showed effect sizes consistent with symptoms not changing while symptoms improved in Group 2 studies.

7.4.4 Meta-regression analysis:
Continuous data included publication year, trial duration, sample size and mean baseline NPI scores of participants (see Table 7.4 and Appendices, Bubble Graphs 1-21 for results of meta-regression analyses). Regression analysis was significant for publication year, with NPI scores reducing more in the recent years, but the distribution was not linear. For Group 1 the regression analysis was not significant or linear but for Group 2 the result was significant and appeared linear.

Treatment duration showed a significant association with placebo effect size, with greater reductions in the shorter duration studies and increases in scores in the longer duration studies. The result was not significant in Group 1 but significant and linear in Group 2. However, 14 of the 25 studies were in the range 20 to 26 weeks. When outliers were excluded and only 20 to 26 week studies were assessed, the overall association with duration was not significant.

There were no associations between sample size and placebo effect size. For baseline mean NPI scores, regression analysis was significant but the distribution was not linear overall or in the two groups.

7.4.5 Comparison of baseline versus EoT within active treatment groups
For the pool of 25 studies combined, the active treatment groups showed a significant reduction in total NPI scores.
Figure 7.3: Effect sizes within active treatment groups of all included studies, in chronological order by publication year and in Groups 1 and 2 according to publication year (Mean difference; random effects model; 95% Confidence intervals)

For Group 1 there was no significant change while there was significant improvement for Group 2 (MD: -4.85; 95% CI: -6.50, -3.20; z=5.77; p<0.00001; I²=76%; RE; 13 studies; 1137 participants at EoT) (see Figure 7.3 for the forest plot and Table 7.5 for results).

Table 7.5: Results of meta-analysis of changes from baseline to end of treatment in total NPI scores in active treatment groups of studies testing oral interventions for management of BPSD

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n studies (n participants EoT in placebo groups); range of durations of treatment</th>
<th>Change in total NPI MD, 95%CI, RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Published 2000 - 2008</td>
<td>12 (978) 6-52wks</td>
<td>-1.15 [-3.68, 1.38]; 75%</td>
</tr>
<tr>
<td>Group 2: Published 2009 - 2015</td>
<td>13 (1137) 3-52wks</td>
<td>-4.85 [-6.50, -3.20]; 76%</td>
</tr>
<tr>
<td>Combined: all studies</td>
<td>25 (2115) 3-52wks</td>
<td>-3.30 [-4.72, -1.89]; 78%</td>
</tr>
</tbody>
</table>

BPSD: Behavioural and psychological symptoms of dementia; EoT: end of treatment; I²: Index of heterogeneity; MD: mean difference; NPI: Neuropsychiatric Inventory; RE: Random effects model; wks: weeks

* significant (p<0.05)

7.4.6 Comparison of active treatment groups versus placebo control groups at EoT

There was a significant overall reduction in total NPI scores in the active treatment groups versus placebo at EoT.
Figure 7.4: Results of meta-analysis at end of treatment (EoT) for active treatment vs placebo control for all included studies, in chronological order by publication year

Presented as Groups 1 and 2 according to publication year

Note: excluding Tune et al. (2003) from pool due to significant baseline imbalance in total NPI scores.

In Group 1 studies there was no significant difference between active and placebo groups but there were significant benefits for active treatment compared to placebo in Group 2 (MD: -2.13; 95% CI: -3.57, -0.69; z=2.91; p=0.004; I²=66%; RE; 13 studies; 2,307 participants) (see Figure 7.4 for the forest plot and Table 7.6 for results).

Table 7.6: Results of meta-analysis at End of treatment (EoT) in total NPI scores in active treatment groups vs placebo control groups of studies testing oral interventions for management of BPSD

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n studies (n participants EoT T,C); range of durations of treatment</th>
<th>EoT TvsC total NPI MD, 95%CI, RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Published 2000 - 2008</td>
<td>12 (978,1056) 6-52wks</td>
<td>-0.71 [-4.18, 2.76]; 87%</td>
</tr>
<tr>
<td>Group 1: Published 2000 – 2008*</td>
<td>11 (964,1043) 6-52wks</td>
<td>-1.62 [-4.96, 1.73]; 86%</td>
</tr>
<tr>
<td>Group 2: Published 2009 - 2015</td>
<td>13 [1137,1170] 3-52wks</td>
<td>-2.13 [-3.57, -0.69]*; 66%</td>
</tr>
<tr>
<td>Combined: all studies</td>
<td>25 (2115,2239) 3-52wks</td>
<td>-1.74 [-3.29, -0.20]*; 81%</td>
</tr>
</tbody>
</table>

BPSD: Behavioural and psychological symptoms of dementia; EoT: end of treatment; FE: Fixed effects model; I²: Index of heterogeneity; MD: mean difference; NPI: Neuropsychiatric Inventory; NS: not specified; RE: Random effects model; wks: weeks;

* significant (p<0.05)
7.4.7 Baseline characteristics and dropouts analysis:

No significant differences in baseline characteristics were detected between Groups 1 and 2. Participants in placebo groups in Group 1 were slightly older at baseline, with a mean age of 75.9 (SD 10.7) years, compared to Group 2, who had a mean age of 70.3 (SD 10.1) years. Total NPI scores in Group 1 at baseline were slightly lower (mean 18.2, SD 15) compared to Group 2 (mean 20, SD 13.4) (see Appendices, Tables 1-10 for calculations). Participants in placebo groups of Group 1 were 32% male and 68% female compared to 37% male and 63% female in Group 2. There were significantly more dropouts in the Group 1 placebo groups (15.35%), compared to 8.83% dropouts in the Group 2 studies (see Appendices, Table 11).

Appendix Figure 7.4: Results of risk ratio meta-analysis for numbers of dropouts at end of treatment for active treatment vs placebo for all included studies, in chronological order by publication year

Presented as Groups 1 and 2 according to publication year

(Mean difference; random effects model; 95% Confidence intervals)
7.5 Discussion of this study on placebo effect sizes in BPSD

There was substantial variation in effect sizes for total NPI scores in the placebo group and these effect sizes appear to have increased over time. When studies were considered according to Groups 1 and 2, the tendency for the placebo groups to improve was evident in the recent studies but not in the earlier studies. Similar trends were detected in the subgroup analyses.

The pooled results of NPI scores for participants receiving active treatment also showed a tendency for effect sizes to increase in the more recent studies. In the Group 2 time period effect sizes increased in both the treatment and placebo groups.

Possible reasons for increased placebo effect sizes in total NPI scores

A number of explanations have been offered in the literature for variable effect sizes in placebo groups, including differences in severity at baseline, regression to the mean, changes in quality of clinical care, quality of trial methodology and expectations of clinical effect.

1. Effect of severity at baseline and regression to the mean

A meta-analysis of 35 RCTs of antidepressants for depression found that the placebo effect size decreased as baseline severity worsened, while treatment response was consistent (Kirsch et al., 2008). The authors argued that the efficacy of antidepressants only reached clinical significance, as defined by the United Kingdom’s National Institute of Health and Clinical Excellence (NICE) guidelines of 2004 (NICE, 2004), in trials of the ‘most extremely depressed’ participants. Similarly, the present meta-regression analysis showed larger placebo effect sizes occurring in studies of participants with higher baseline NPI scores, although the distribution was not linear.

McDonald et al. (1983) asserted that ‘most improvements attributed to the placebo effect are actually instances of statistical regression’. Also, McAllister-Williams (2008) argued that inflated baseline scores might have enabled participants to enter into depression studies conducted in the United States, which might have led to early improvements in symptoms in both treatment and control groups. Rosenberg et al. (2015) observed greater improvements in agitation in participants with more severe agitation symptoms at baseline in their secondary analysis of the placebo group of a citalopram for AD with agitation trial (Porsteinsson et al., 2014). These authors noted that improvements in agitation and Mini-Mental State Examination scores were evident at week three and maintained until week nine, and the improvements were most evident in participants with severe agitation at baseline. This rapid improvement in severe symptoms suggested regression to the mean rather than natural progression (Rosenberg et al., 2015).
The present meta-analysis tends to support this interpretation but only in the more recent studies. It is possible that recent studies included more people with acute agitation at baseline but the available data did not allow assessment of the separate contribution of agitation to total NPI scores and the baseline characteristics did not appear to be significantly different between Groups 1 and 2.

2. Improved standards of clinical care and concomitant medications

Nikolova et al. (2013) reported that the placebo effects of their EGb 761® trial had by far exceeded previous placebo effects, while changes in cognitive and NPI scores in EGb 761® groups had remained within a similar range to those observed in the previous trials. These authors could not determine the reason for this large placebo effect size but speculated that the investigational sites may have adopted new standards to improve overall care for people with dementia, leading to increased non-specific effects. Similarly, Herrmann et al. (2013) found improvements in severe BPSD in the placebo group, including reductions in agitation/aggression and total NPI scores. They suggested this may have been due to ‘good clinical care’ including ‘close clinical monitoring, stimulating environments, and psychosocial support for the patient and the caregiver’. Rosenberg et al. (2015) also reported a significant improvement in agitation in the placebo group of Porsteinsson et al. (2014) and proposed that a psychosocial intervention and other aspects of clinical care may have contributed to these improvements. This study did not meet the inclusion criteria for the present meta-analysis as both groups received a specific psychosocial intervention.

The study of individual participants with AD in RCTs from 1990 to 1994 versus 1996 to 1999 found that the post 1995 placebo participants were older, had more severe cognitive impairment and comorbidity compared to the pre-1995 placebo group participants. Nevertheless, the post 1995 participants showed slower rates of cognitive decline (Jones et al., 2009). The older, more severe participants could have been expected to have declined more. One difference between groups was greater use of concomitant medications for coexisting medical conditions including hypertension, atrial fibrillation, depression, diabetes and hypercholesterolaemia in the post 1995 group. The author proposed that improvements in the concomitant medications, which did not include cholinesterase inhibitors, were a likely factor in the relatively better outcomes in the placebo groups in the later studies.

The patient-practitioner relationship was reportedly the most robust component contributing to placebo effect size in a study of irritable bowel syndrome (Kaptchuk et al., 2008). The relationships between the person with dementia and the clinical trial investigators, the person with dementia and their caregiver, and/or the caregiver and the clinical trial investigators, may have contributed to non-
specific therapeutic effects during the trial. Some BPSD have been found to be associated with specific characteristics of the caregiver. For example, angry behavior was associated with caregiver depression, and apathy was associated with a deterioration of the relationship between the person with BPSD and the caregiver (Ornstein & Gaugler, 2012). These suggest that differences in the interactions between participants, caregivers and researchers could have played a role in the observed variation in placebo effect sizes. In the present meta-analysis, updates in clinical practice guidelines may have led to improved management of symptoms and better support for participants and caregivers in the Group 2 studies (2009-2015). Treatment of comorbid conditions such as pain may also have been improved or given more emphasis and there may have been other improvements in concomitant medications in the more recent trials.

In addition to improved supportive care in a clinical trial setting, there may have been recent changes in public awareness of dementia and access to information and advice, which may have led to an increase in support for people with dementia and their caregivers. This could include increased application of behavior management strategies amongst participants and caregivers. An online focus group study of 32 family caregivers of people with dementia living in the Netherlands found that family caregivers used self-management strategies for influencing BPSD in their relative, and for managing their own stress levels (Huis In Het Veld et al., 2016). However, the available data did not allow assessment of changes in medical care, level of support or the relationships between participants, caregivers and clinicians.

3. Changes in methodological quality and study design

Based on the risk of bias assessments, no evidence was found that changes in methodological quality had affected placebo effect sizes in the BPSD studies. Group 1 studies received slightly more ‘unclear’ risk of bias judgements compared to Group 2 studies, but this could be due to changes in reporting rather than changes in methodological quality. Studies reported after 2010 are likely to have followed the CONSORT 2010 statement for reporting parallel group randomised trials (Schulz et al., 2010). This may have resulted in more ‘low’ risk of bias assessments in these studies. We also did not detect any differences in funding sources of the studies between Groups 1 and 2, although reporting of the details of manufacturer involvement was not consistent across studies. Notably, all five EGb 761® studies received identical risk of bias judgements for all domains and appeared to have similar manufacturer funding and involvement, but substantial variation in placebo effect sizes was detected across these studies, suggesting change in methodological quality was not the reason for the substantial variation of placebo effect sizes in these studies.
Hróbjartsson and Gøtzsche (2010) reported that larger placebo effect sizes were associated with certain study characteristics including more elaborate placebo interventions and smaller sample sizes. In the present analysis, the interventions were not elaborate and the sub-group analyses found no association with sample size.

Changes in the approaches to the treatment of missing data might have contributed to the variation in placebo effect sizes. For example, use of last observation carried forward (LOCF) can introduce a bias favoring the group with more dropouts, since dementia tends to worsen over time (van Dyck et al., 2007). There was no apparent difference over time in the methods used or the use of LOCF (see Appendices, Table 9). Overall, the percentage of dropouts was lower in the Group 2 studies, which does not favour greater improvement in Group 2 as a result of LOCF. Nevertheless, our analyses were based on published aggregate data only, so it remains possible that changes in imputation methods affected the results.

4. Changes in expectations of pharmacological response to psychiatric symptoms:

A positive expectation bias has been reported to influence results in antidepressant trials (Sinyor et al., 2010; Khan & Brown, 2015). Expectations of the effectiveness of pharmacological treatments for BPSD may have increased in the community, including people with dementia, caregivers, and clinical trial assessors. This may have caused a positive expectation bias but we could not test this possibility.

7.6 Summary of Chapter Seven

The present study indicated substantial variability in placebo effect sizes and a trend towards increasing placebo effect size over time. Studies published after 2008 (Group 2) were more likely to have significant improvements within placebo groups compared to studies published earlier (Group 1). NPI scores tended to increase in the longer studies (52 weeks) and tended to decrease or not change in the short studies but this relationship was not robust since 14 of 25 studies were of 20 to 26 weeks duration. Subgroup analyses tended to confirm the significant decrease in NPI scores in Group 2 studies (published 2009-2015). The magnitude of change within the Group 2 placebo groups was statistically significant but less than the four points considered clinically meaningful (Mega et al., 1999).

Meta-analysis of active treatment groups found that these have improved over time as well. Differences between treatment and placebo groups tended to be significant in the more recent studies. However, the considerable variation in the treatments used limits the meaningfulness of these findings (see Table 7.5 for results).
7.6.1 Implications of the variation in placebo effect sizes

The variable placebo effect size in NPI scores has important implications for clinical trials of new treatments for management of BPSD, due to potential for under or over-estimation of the specific effects of a test intervention. In the design of future placebo-controlled clinical trials that use NPI as an outcome, power calculations may need to be based on the placebo effect size data from more recent studies rather than the total data. Consequently, studies may require larger sample sizes to reduce the chance of false negative findings. Factors that may contribute to changes in NPI scores in placebo groups require further investigation.

7.6.2 Limitations of this review

These findings are based on a single database search. NPI was the only outcome measure included in the analysis. We did not assess whether the same pattern of results was present for other measures used in BPSD due to the relative paucity of available data. Some EoT scores were calculated from change scores, affecting the data precision. There was substantial heterogeneity in meta-analysis results, indicating considerable variation between studies. Notably, the heterogeneity was reduced in the time-based groups. We did not perform analysis based on baseline severity of cognitive symptoms since the diversity of measures used limited the available data. Other factors, including detection and recall bias (Lai, 2014), could not be assessed due to lack of reported data. It is also possible that there may have been a scale-shift upward in the administration of the NPI over time but this could not be assessed. The tendency towards greater improvement in placebo groups over time may have been due to methodological, measurement, detection or other instrumental factors rather than actual clinical improvements in participants. A Cochrane review of placebo effects found that placebo interventions appear to influence the subjective outcomes of patient reported pain and nausea but they did not find evidence of effects on objective outcomes (Hróbjartsson & Gøtzsche, 2010).

We could not confirm the causes of the variation and increase in placebo effect sizes over time. This was in part due to the relatively small volume of available published data which limited the number of possible subgroups. Although our results indicate increases in NPI effect sizes over time, this does not predict that these increases will continue into the future.

7.7 Conclusions from this systematic review

There is substantial variation in placebo effect sizes in total NPI scores in BPSD studies and the placebo effect size has increased over time. A similar trend has been found for other outcome measures in various disorders. These findings may have implications for interpretation of the results of studies of interventions for the management of BPSD. The variability in placebo effect size should
be taken into account when evaluating studies of pharmacological interventions conducted in different years. Future clinical trials should calculate sample sizes for NPI according to recent placebo effect size data rather than incorporate effect sizes observed before 2009. Future research is needed to investigate factors leading to variability in NPI effect sizes in placebo groups to enable greater precision in measurement.
8 CHAPTER EIGHT A CLINICAL TRIAL PROTOCOL FOR A TESTING HERBAL MEDICINE INTERVENTION FOR MANAGEMENT OF THE COGNITIVE, BEHAVIOURAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA

8.1 Introduction

This chapter describes the process of developing a protocol for a randomised, double-blind, placebo-controlled clinical trial testing efficacy, safety and tolerability of the combined Ginkgo biloba leaf extract EGb 761® (Schwabe pharmaceuticals) and the multi-herb formula Yokukansan TJ-54 (Tsumura Japan), containing Uncaria rhynchophylla, Atractylodes lancea, Poria cocos, Cnidium officinale, Angelica acutiloba, Bupleurum falcatum and Glycyrrhiza uralensis. The choice of intervention was informed by the findings of the systematic review and meta-analysis of the clinical trials detailed in Chapter Four, the classical literature analysis of Chapter Five and the overview of experimental literature detailed in Chapter Six, as well as the broader literature on use of these products for other conditions. Both formulations are commonly used for management of the behavioural and psychological symptoms of dementia (BPSD) and both products have established quality control standards. The present study is the first to test these interventions in an Australian population and is the first to combine the two interventions in a controlled setting.

8.1.1 Rationale for testing the combination of Yokukansan and EGb 761® for BPSD

There is a need for efficacious and safe treatment options for people with BPSD. Combination therapies, notably acetylcholinesterase inhibitors (AChEIs) plus memantine, have previously shown benefits for BPSD management (Tsoi et al., 2016). The clinical trial literature reviewed and analysed in Chapter Four indicated EGb 761® showed benefits on BPSD and cognition. Data were limited for the specific Neuropsychiatric Inventory (NPI) domains but an analysis of the NPI domain data from the four key randomised controlled trials (RCTs) reported moderate benefits for depression/dysphoria, agitation/aggression, aberrant motor behaviour, apathy, sleep/night-time behaviour, anxiety and irritability/lability in more than 50% of participants over the 22 to 24 week treatment durations (Savaskan et al., 2017).

For Yokukansan, there was a lack of clinical evidence for effects on cognition, while benefits were suggested for agitation/aggression, irritability/lability, anxiety, depression/dysphoria and aberrant motor activity, as shown in Table 8.1.
Table 8.1: Clinical trial evidence of effects of EGB 761® and Yokukansan on symptoms of dementia

<table>
<thead>
<tr>
<th>Dementia symptom</th>
<th>EGB 761®</th>
<th>Yokukansan</th>
</tr>
</thead>
<tbody>
<tr>
<td>cognition</td>
<td>√</td>
<td>N</td>
</tr>
<tr>
<td>agitation/aggression</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>depression/dysphoria</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>aberrant motor behaviour</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>apathy</td>
<td>√</td>
<td>N</td>
</tr>
<tr>
<td>sleep/night-time behaviour</td>
<td>√</td>
<td>N</td>
</tr>
<tr>
<td>anxiety</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>irritability/lability</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

N: no significant effect, or no data, as detailed in Chapter Four

The experimental literature reviewed in Chapter Six found that for EGB 761®, in addition to attenuation of cognitive impairments, there was evidence of benefits related to antidepressant-like and anxiolytic-like activities, anti-aggression, reduction in mental stress and tardive dyskinesia (Shi et al., 2010; Yeh et al., 2015; Liang et al., 2016; Mazumder et al., 2017; Zamberlam et al., 2016; An et al., 2016; Hoerr & Weber, 2015, pp1021-1029; Müller et al., 2017). For Yokukansan, there was experimental evidence of benefits for the formula or at least one of its herbal ingredients for effects on reduction of aggression, antidepressant-like activity, anxiolytic-like activity, decreased aberrant locomotor activity and amelioration of cognitive impairments (Nishi et al., 2012; Jung et al., 2006; Sakakibara et al., 1999; Ikarashi & Mizoguchi, 2016; Mizoguchi & Ikarashi, 2017).

Table 8.2: Experimental evidence of effects of EGB 761® and Yokukansan in animal models

<table>
<thead>
<tr>
<th>Symptom(s) reported in animal models</th>
<th>EGB 761®</th>
<th>Yokukansan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attenuation or amelioration of cognitive impairments</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Anti-aggression</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Antidepressant-like</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Anxiolytic-like</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Reduction in mental stress</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Tardive dyskinesia</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Aberrant locomotor activity</td>
<td>N</td>
<td>√</td>
</tr>
</tbody>
</table>

N: no significant effect, or no data, as detailed in Chapter Six

In an analysis of prevalence rates of BPSD in people with dementia in general practices, the most common BPSD were agitation/aggression, depression/dysphoria and irritability/lability, while the most common clinically relevant BPSD were aberrant motor behaviour, agitation/aggression and apathy/indifference (Borsje et al., 2017). Agitation, depression, anxiety, delusions, irritability and...
Apathy are the prominent BPSD seen in AD, and agitation/aggression can be a major issue in mild to moderate AD (Lovheim et al., 2008) while apathy is more prevalent in severe AD (McKeith & Cummings, 2005). The prevalence of agitation in people with AD was 76% according to Mussele et al. (2015). An Australian study considered agitation, aggression and psychosis ‘harder to ignore’ than the other BPSD (Macfarlane & O’Connor, 2016) which suggests that these symptoms could be a motivator to move to residential care and/or try antipsychotics. Although antipsychotics were considered the best short-term pharmacological option for severe and persistent dementia-related agitation/aggression (Azermai, 2015), there has been concern about their overuse in people with dementia in Australia (Looi & MacFarlane, 2014). Further options for efficacious and safe oral interventions would be of value to the community – especially if the implementation of the interventions could be fast-tracked into routine healthcare in clinical, organisational and policy contexts.

*Yokukansan* was ranked the fourth highest selling kampo formula in Japan in 2010 and had the second highest number of papers when searched by PubMed (Uezono et al., 2012). *Yokukansan* may have antipsychotic effects without causing extrapyramidal symptoms and also appears to reduce uncontrolled movement in people with neuroleptic-induced tardive dyskinesia (Horiguchi, 2012; Miyaoka et al., 2008; Sekiguchi, 2012), although data are insufficient to support or refute its use for tardive syndromes (Bhidayasiri et al., 2013). *Yokukansan* may also assist with sleep disturbance and may have anxiolytic properties without causing over-sedation (Arai et al., 2014; Kamei et al., 2009; Mizoguchi et al., 2010; Yamaguchi et al., 2012; Wada et al., 2017). A placebo-controlled RCT of *Yokukansan* for treatment resistant schizophrenia (Miyaoka et al., 2014) reported statistically significant benefits in excitement/hostility scores in the *Yokukansan* group, but not placebo, as assessed by the Positive and Negative Syndrome Scale.

The combination of EGb 761® and *Yokukansan* was chosen due to the Level 1a evidence, according to the Oxford Centre for Evidence-Based Medicine (OCEBM) hierarchy (Howick et al., 2011), that EGb 761® improves cognition and total NPI scores in people with BPSD, while *Yokukansan* has shown Level 2a evidence for improving the clinically important symptoms of agitation, aggression, irritability, aberrant motor activity and sleep disturbances (Miyaoka et al., 2012; Miyaoka et al., 2013; Miyaoka et al., 2014; Saito et al., 2010; Wake et al., 2016). These effects of *Yokukansan* appear likely due, at least in part, to sedative, antidepressant, anxiolytic and antipsychotic-like effects (Mizoguchi & Ikarashi, 2017; Ikarashi et al., 2017; Ikarashi & Mizoguchi, 2016; Okamoto et al., 2014; Uezono et al., 2012; de Caires & Steenkamp, 2010).
Both EGb 761® and Yokukansan are frequently used by people with dementia and BPSD (Chang et al., 2008; Uezono et al., 2012; Duffy et al., 2017). Literature searches did not find any direct clinical assessment of their combined use or any reports of adverse events associated with combined use.

This proposed clinical trial focuses on testing the combination of the two interventions for management of the symptoms of agitation, aggression, irritability, lability, aberrant motor behaviour, night-time disturbances, anxiety, depression, dysphoria, as well as for management of cognitive symptoms. In addition to their effects on BPSD and cognition, the safety, tolerability and acceptability of these interventions will be assessed.

8.1.2 Safety assessment and monitoring of known and potential adverse effects associated with the HMs

Previous clinical studies have indicated that EGb 761® and Yokukansan are safe and well-tolerated at normal doses but there remains potential for AEs (Napryeyenko & Borzenko, 2007; Ihl et al., 2011; Herrschaft et al., 2012; Nikolova et al., 2013; Gavrilova et al., 2014; Furukawa et al., 2015; Shimada et al., 2017). Consequently, safety was an important consideration in the trial design. The key safety considerations were:

1. avoiding and monitoring any known and potential adverse effects reported in the literature on the HMs;

2. monitoring for unknown or unpredicted adverse interactions related to combining the two interventions, or related to concomitant use of other oral interventions which may be used by Australians with BPSD that had not been detected in the previous studies.

Known and potential adverse effects (AEs), including unwanted interactions, are addressed in this protocol by using comprehensive inclusion and exclusion criteria according to previous findings and recommendations (Napryeyenko & Borzenko, 2007; Ihl et al., 2011; Herrschaft et al., 2012; Nikolova et al., 2013; Gavrilova et al., 2014; Furukawa et al., 2015; Shimada et al., 2017) (see 8.4.5), as well as frequent and rigorous monitoring of participants for the trial duration and follow-up (see 8.9.7).

8.1.3 Known and potential adverse effects associated with EGb 761® and Yokukansan

G. biloba leaf exerts inhibitory effects on platelet aggregation and several case studies have reported an increased risk of bleeding associated with the use of G. biloba leaf extracts, as reviewed by Ernst et al. (2005). Ernst et al. (2005) concluded that causality was unlikely but further observation was recommended. An overview of systematic reviews reporting adverse events of HMs from RCTs noted only minor AEs for G. biloba (Posadzki et al., 2013). A systematic review and meta-analysis of risk of bleeding associated with EGb 761® from RCTs found a positive association of G. biloba on blood
perfusion, as shown by a significant reduction in blood viscosity, but no evidence of any significant effect on platelet aggregation, fibrinogen concentration and prothrombin time. There was a statistically significant reduction in activated partial thromboplastin time for participants receiving 240 mg/day or more and for studies testing participants with medical conditions rather than healthy volunteers, but neither of these findings were clinically meaningful (Kellermann & Kloft, 2011).

Excessive liquorice consumption has been associated with hypertension, which resolved after stopping liquorice, according to case reports (Brouwers and van der Meulen, 2001; Ruiz-Granados et al., 2012) and the association between liquorice, hypertension, hypokalaemia and pseudohyperaldosteronism has received considerable research attention. Glycyrrhetinic acid appears to be the major substance involved in the mechanism for liquorice-induced hypokalaemia. Glycyrrhetinic acid inhibits 11β-hydroxysteroid dehydrogenase type 2, which catalyses the conversion of cortisol to cortisone and prevents the binding of cortisol to the mineralocorticoid receptor in the mineralocorticoid target tissues. This inhibition leads to increased cortisol levels in the tissues and excess cortisol binding to the mineralocorticoid receptor with the same affinity as aldosterone. The mineralocorticoid receptor activation increases sodium reuptake and inhibits potassium reabsorption in the kidney, resulting in pseudohyperaldosteronism with hypertension, metabolic alkalosis, and hypokalaemia which may develop into life-threatening events such as congestive heart failure (Shimada et al., 2017).

Liquorice-induced hypokalaemia was detected in four of 72 participants receiving Yokukansan in the only placebo-controlled trial for BPSD (Furukawa et al., 2015). This was typically managed by reducing the dose from 7.5 g/day to 5 g/day. The G. uralensis content of Yokukansan is 1.5 g per day, while 2.5 g per day is normally considered to increase the risk of liquorice-induced pseudohyperaldosteronism according to the Japanese Ministry of Health (1978). The glycyrrhizin content of Yokukansan is approximately 70 mg/daily dosage of 7.5 g (Nose et al., 2017). This is within the upper limit of 100 mg per day of glycyrrhizin proposed by the European Commission Scientific Committee on Food (European Commission Heath and Consumer Protection Directorate General, 2003).

A retrospective analysis of 389 patients aged 68.6±16.1 years, who were treated with Yokukansan for a mean of 231 days (range 6–2788 days), found that 94 patients (24.2%) developed hypokalaemia (potassium levels <3.6 mEq/L). The median time to develop hypokalaemia was 34 days (range 1–1600 days) after administration of Yokukansan. These authors recommended that serum potassium should be tested at least monthly in people taking Yokukansan (Shimada et al., 2017). Abe et al., (2016) advised that people with BPSD are at an increased risk of developing electrolyte
imbalances compared to the healthy population, due to increased incidence of dehydration and irregular eating habits. These authors evaluated serum electrolytes in 52 patients with BPSD admitted to Showa University Karasuyama Hospital in Japan. On admission, 11 patients (22%) had hypokalaemia, and serum potassium was significantly lower in 13 patients taking Yokukansan for three months compared to 37 patients who were not taking Yokukansan. These authors recommended routine serum electrolyte measurements play an important role in the care of people with BPSD (Abe et al., 2016).

As G. uralensis root is frequently used in foods and medicines, its pharmacokinetics have been studied previously (Krahenbuhl et al., 1994; Raggi et al., 1994). However, a more recent pharmacokinetic study in healthy humans showed that the area under the curve of glycyrrhetinic acid after Yokukansan administration tended to be slightly larger than that of glycyrrhetinic acid after other G. uralensis-containing kampo medicines were administered (Kitagawa et al., 2015). These results suggested that the absorption and metabolism were altered due to interactions with other components of Yokukansan, although the exact underlying mechanism was not elucidated (Kitagawa et al., 2015).

Table 8.3: Known and potential adverse effects of the HMs and consequent safety monitoring procedure

<table>
<thead>
<tr>
<th>HM</th>
<th>AE</th>
<th>Safety monitoring at each monthly assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGb 761*</td>
<td>Inhibitory effects on platelet aggregation</td>
<td>Platelet aggregation test; Inspection for haematoma; Question caregiver and person with dementia for incidence of haematoma, haemorrhage, nose bleeds, melena; Check daily diary for records of haematoma, haemorrhage, nose bleeds, melaena.</td>
</tr>
<tr>
<td>Yokukansan</td>
<td>hypokalaemia</td>
<td>Serum potassium test; BP test; Inspection and palpation for oedema; Record body weight; Question caregiver and person with dementia for incidence of myopathies; muscle weakness or spasms, fatigue, constipation, palpitations, tingling or numbness; Question caregiver about diet and water intake; Check daily diary for records of myopathies, muscle weakness or spasms, fatigue, constipation, palpitations, tingling or numbness; and diet and water intake</td>
</tr>
</tbody>
</table>

BP: blood pressure
In addition, the present study includes the provision of an oral potassium chloride supplement aimed to address the issue of liquorice-induced hypokalaemia, as detailed in section 8.8.

8.1.3.1 Known and potential herb-drug interactions

This section summarises the possible unwanted interactions between the test interventions and a number of drugs including warfarin, aspirin and corticosteroids (Fugh-Berman et al., 2000; Izzo et al.,
The Australian Government's Department of Health reported that the ten most frequently used drugs, as defined by daily dose in 2015, were atorvastatin, perindopril, rosuvastatin, amlodipine, paracetamol, irbesartan, candesartan, ramipril, telmisartan and colchicine (Mabbott & Storey, 2016). Therefore, it was important to consider whether there were potential interactions with any of these drugs and drugs used to treat dementia.

The following sections summarise known and potential herb-drug interactions for *G. biloba* extracts and *Yokukansan*. In each case proposals are made regarding inclusion in the proposed study and the safety monitoring required.

The most common herb-drug interactions typically involve the metabolism of drugs catalysed by the cytochrome P450 (CYP) enzymes (Wanwimolruk et al., 2014; Wanwimolruk & Prachayasittikul, 2014). Clinical studies aimed at determining the effects of standardised *G. biloba* extracts on many CYP isoforms and other drug metabolising enzymes have found no significant effects in older participants (Wanwimolruk & Prachayasittikul, 2014). However, there have been concerns about unwanted interactions.

**Interactions with warfarin and aspirin**

One report described an association of *G. biloba* with bleeding in a 78-year-old patient who had also been taking warfarin (Matthews, 1998). However, Bone et al., (2008) asserted that high level safety concerns for interactions between Egb 761® and antiplatelet or anticoagulant drugs were not supported by the available clinical trial or case report evidence. Another study has reported that *G. biloba* at recommended doses did not significantly affect the pharmacokinetics or pharmacodynamics of a single dose of 25 mg warfarin (Chua et al., 2015).

Warfarin undergoes CYP-mediated metabolism by many different CYPs including CYP2C9 and CYP3A4 as the major enzymes (Shaik et al., 2016). An open label study of *Yokukansan* in healthy volunteers concluded that the occurrence of herb-drug interactions is unlikely with concomitantly administered medications that are predominantly metabolised by the CYP1A2, CYP2D6, CYP3A, xanthine oxidase and N-acetyltransferase 2 enzymes (Soraoka et al., 2016). However, warfarin has been reported to interact with *Angelica* species, resulting in over-anticoagulation, in a review of risk of drug interactions (Izzo et al., 2005). Another review of case studies, animal studies and *in-vitro* studies has advised against concomitant use of warfarin with *G. biloba*, *Angelica sinensis* or *Glycyrrhiza* species (Chua et al., 2015). Tsai et al., (2013) also strongly discouraged use of the combinations of antiplatelet or anticoagulant drugs with *Angelica sinensis* or *Glycyrrhiza uralensis*, due to the risk of SAEs, in a review of potential harmful herb-drug interactions.
A RCT testing co-administration of aspirin and EGB 761® concluded that the combination did not constitute a safety risk, including in an elderly population (Wolf, 2006). Two RCTs reported significantly increased benefits on cognition in vascular cognitive impairment with no dementia (VCIND) from the combined treatment (Zhang & Xue, 2012; Wang et al., 2015). Another RCT reported that combined G. biloba and aspirin did not have a clinically or statistically detectable impact on coagulation, and observed no adverse bleeding events (Gardner et al., 2007). An experimental study in human coronary artery endothelial cells found that the combination of G. biloba extract and aspirin exerted a synergistic effect and was correlated with increased suppression of oxidative stress (Zhu et al., 2013). Experimental studies have also reported antiplatelet and anti-aggregation actions of isoliquiritigenin from Glycyrrhiza species (Tawata et al., 1992) and similar actions from Angelica species (Lee et al., 2003).

For the present protocol, caution was taken for people with increased risks of bleeding, especially if taking medications exerting synergistic effects on coagulation. People taking warfarin will be excluded from the study. People taking a stable low dose of aspirin may be included. The procedure for monitoring the risk of bleeding is shown in 8.7.6.

**Interactions with corticosteroids**

A review by Fugh-Berman et al., (2000) reported potentiation of corticosteroids with Glycyrrhiza species. In accordance with this finding, people using oral or topical corticosteroids will be excluded from the present protocol.

**Table 8.4: Important herb-drug interactions documented in the literature**

<table>
<thead>
<tr>
<th>Drug name; drug class or category</th>
<th>Main indications</th>
<th>Potential risk</th>
<th>Safety procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin; anticoagulant</td>
<td>Thrombosis and stroke prevention</td>
<td>bleeding</td>
<td>Exclude from study</td>
</tr>
<tr>
<td>Aspirin; NSAID</td>
<td>Mild to moderate pain, inflammation, thrombosis and stroke prevention</td>
<td>bleeding</td>
<td>May include in study; monthly assessment of risk of bleeding as described above, as recommended for all participants taking EGB 761®, including platelet aggregation test and physical examination for haematoma</td>
</tr>
<tr>
<td>Prednisolone, hydrocortisone; corticosteroids</td>
<td>Dermatological conditions including atopic dermatitis; respiratory conditions including asthma; rheumatologic conditions including rheumatoid arthritis</td>
<td>Potentiation of corticosteroids with Glycyrrhiza species</td>
<td>Exclude from study</td>
</tr>
</tbody>
</table>
8.1.3.1.1 Potential for interaction with drugs commonly used by people with dementia in Australia

This section details the evidence for interaction between EGB 761® or Yokukansan and drugs commonly used by people with dementia, and the consequent safety monitoring procedures.

**Donepezil and memantine**

No evidence was found of increased risk of AEs under the combination of either EGB 761® or Yokukansan with donepezil or memantine. One RCT reported fewer AEs under the combination of EGB 761® and donepezil than under donepezil monotherapy (Yancheva et al., 2009). No AEs were detected under the combination of Yokukansan and donepezil in one RCT (Okahara et al., 2010).

People on a stable dose of donepezil or memantine may be included.

**Table 8.5: Other drugs commonly used by people with dementia, and safety procedure**

<table>
<thead>
<tr>
<th>Drug name; class or category</th>
<th>Main indications</th>
<th>Potential risk</th>
<th>Evidence of interaction</th>
<th>Safety procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil, galantamine, rivastigmine; AChEIs</td>
<td>cognitive impairment, BPSD</td>
<td>Reduction in effect, increased toxicity</td>
<td>EGB 761® appears safe according to RCT by Yancheva et al. (2009); Yokukansan appears safe according to RCT by Okahara et al. (2010)</td>
<td>Include if stable dose. Monitor in accordance with usual care</td>
</tr>
<tr>
<td>Memantine; NMDA receptor blocker</td>
<td>cognitive impairment, BPSD</td>
<td>Reduction in effect, increased toxicity</td>
<td>No evidence of unwanted interaction found</td>
<td>Include if stable dose. Monitor in accordance with usual care</td>
</tr>
</tbody>
</table>

8.1.3.1.2 Potential for interactions with other drugs frequently used by Australians

This section outlines the potential for interactions between the HM interventions and commonly used pharmaceuticals.

**Statins**

*G. biloba* extract did not cause significant differences in simvastatin acid pharmacokinetics or its cholesterol lowering efficacy in 14 healthy volunteers (Dai et al., 2013), and did not cause significant effects on cholesterol-lowering efficacy of atorvastatin in 16 healthy volunteers (Guo et al., 2012).

There have been reports of myopathies associated with use of liquorice products, including one case of rhabdomyolysis in a 73-year-old male after combining a liquorice supplement concomitantly with simvastatin, atenolol and other medications (Lapi et al., 2008). The present protocol includes
participants on a stable dose of statins. Cholesterol levels and incidence of myopathies will be monitored.

ACE inhibitors, calcium channel blockers, angiotensin receptor blockers (and beta blockers)

No evidence was found of interactions between *G. biloba* and angiotensin receptor blockers, ACE inhibitors or beta blockers. One study in rats reported that oral *G. biloba* leaf tablets inhibited the metabolism of the calcium channel blocker amlodipine (Wang et al., 2016). Izzo et al. (2005) reported that liquorice might interact with antihypertensives leading to hypokalaemia due to an additive effect on potassium excretion, but there was inadequate information to draw strong conclusions. Case studies have reported hypertension, hypokalaemia, muscle cramps and weakness, and elevated sodium excretion in people taking atenolol, candesartan, hydrochlorothiazide or calcium channel blockers, who were later discovered to have been consuming large amounts of liquorice products. These included liquorice tea, salted liquorice or liquorice sweets (Brouwers & van der Meulen, 2001; Ruiz-Granados et al., 2012; Machalke et al., 2015). In all cases, blood pressure normalised after stopping consumption of the liquorice. For the present protocol people with hypertension controlled by stable doses of antihypertensives, ACE inhibitors, beta blockers or calcium channel blockers may be included. The dose of *Yokukansan* may be reduced to 5 mg/day. People with congestive heart failure will be excluded.

Paracetamol

*G. biloba* extract was reported to potentiate paracetamol toxicity in cultured rat hepatocytes, and Ginkgolide A was found to contribute to this effect by inducing CYP3A (Rajaraman et al., 2006). Conversely, possible hepatoprotective effects from glycyrrhizin, matrine, glycyrrhetinic acid and *Angelica keiskei* against paracetamol-induced hepatotoxicity have been reported (Choi et al., 2017). People taking paracetamol within the recommended daily doses may be included. Liver function and symptoms of paracetamol toxicity will be assessed monthly.
<table>
<thead>
<tr>
<th>Drug name; drug class or category</th>
<th>Main indications</th>
<th>Potential risk</th>
<th>Safety procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin, rosuvastatin; statins</td>
<td>elevated LDL cholesterol</td>
<td>1. Reduction in cholesterol lowering efficacy with G. biloba; 2. Myopathy with Glycyrrhiza sp.</td>
<td>May include if stable dose; Monthly complete lipid profile; Ask about myopathies; Check diary for incidence of myopathies</td>
</tr>
<tr>
<td>Perindopril; ramipril; ACE inhibitors</td>
<td>hypertension, congestive heart failure (CHF)</td>
<td>Interfere with blood pressure (BP) control</td>
<td>Include if stable dose and monitor BP and heart rhythm, oedema. People with CHF excluded from study</td>
</tr>
<tr>
<td>Amlodipine; Calcium channel blocker</td>
<td>hypertension, CHF</td>
<td>Interfere with BP control</td>
<td>Include if stable dose and monitor BP and heart rhythm, oedema. People with CHF excluded from study</td>
</tr>
<tr>
<td>Irbesartan; candesartan; telmisartan; Angiotensin receptor blockers (ARBs)</td>
<td>hypertension</td>
<td>Interfere with BP control</td>
<td>Include if stable dose and monitor BP</td>
</tr>
<tr>
<td>Colchicine; anti-gout agent</td>
<td>gout</td>
<td>Interfere with anti-gout effect or increased toxicity of colchicine</td>
<td>Include and monitor for exacerbation or changes of gout</td>
</tr>
<tr>
<td>Paracetamol; analgesic</td>
<td>Mild to moderate pain, fever</td>
<td>Interfere with analgesic effect or increased toxicity of paracetamol</td>
<td>May include if stable dose; Monthly LFT; Inspect for jaundice; Question caregiver about incidence of pain and/or fever; Check diary for records of pain and/or fever; tiredness, abdominal pain, nausea; jaundice, blood clotting problems, confusion</td>
</tr>
</tbody>
</table>

In addition, based on reviews of other herb-drug interactions by Izzo and Ernst (2009) and Diamond and Bailey (2013), people taking the proton pump inhibitor omeprazole, the hypoglycaemic tolbutamide, antiepileptics, the antidepressant trazodone, monoamine oxidase inhibitors, haloperidol or the benzodiazepine anxiolytic alprazolam will be excluded.

### 8.1.4 Design of the proposed clinical trial

The study design was informed by the findings of the systematic reviews and meta-analyses in Chapters Four and Eight. These previous chapters revealed two important issues in clinical trials of herbal medicines (HMs) for BPSD which are addressed in this protocol. The first issue, which was identified in Chapter Four, was the broad inclusion criteria of some previous HM clinical trials. These studies did not specify which NPI symptom domains were likely to benefit from the test intervention, included participants with different symptoms and severity levels, or included participants who may...
not have exhibited the symptom(s) likely to be targeted by the intervention. The present trial was
designed to test the effect of the intervention on the symptoms for which it is most likely to be of
benefit, and to therefore include participants who show at least one of these symptoms. This is
detailed further in Chapter Eight, section 8.3 below.

The second issue, as detailed in Chapter Seven, was the variation in placebo effect sizes in previous
BPSD trials and the observation of increasing placebo effect sizes over time in NPI scores.
Consequently, the present study required a larger sample size to reduce the chance of Type II error,
as detailed in section 8.3.8 below.

The present trial design tests the efficacy, safety and tolerability of the combined interventions in
participants with a dementia diagnosis and at least one of the BPSD agitation/aggression,
irritability/lability, anxiety, depression or aberrant motor activity, using a two-armed, head-to-head,
double blind, randomised, placebo-controlled design. Efficacy on caregiver distress related to these
symptoms is also assessed.

8.2 Objectives of this clinical trial
Based on the results of the previous stages, the present clinical trial was designed to rigorously
evaluate the efficacy, safety and tolerability of the combined HM intervention for management of
BPSD, with the aim to add to the body of evidence regarding oral interventions for reducing
symptoms of dementia and provide better-informed options for management of BPSD in the
Australian population.

An important consideration was to address specific issues in trials involving people with dementia,
and common limitations of previous dementia trials. These included: issues of measurement of
meaningful endpoints; obtaining informed consent from participants with cognitive and
neuropsychiatric symptoms; the influence of the caregiver on trial outcomes; ensuring benefit to the
participants with BPSD and their caregivers from the knowledge gained; and avoiding
methodological issues of previous clinical trials on disease-modifying drugs for dementia (Gauthier,
2017, pp. 613-617).

8.3 Trial registration and compliance with relevant Codes
The trial protocol complies with the Declaration of Helsinki and Good Clinical Practice guidelines.
These guidelines include the following:

- CPMP/ICH, Note for Guidance on Good Clinical Practice (Therapeutic Goods Administration
  (TGA), 2000)
Approval will be obtained from RMIT University Human Research Ethics Committee and any other relevant ethics committees. The trial design will be in accordance with:

- Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Chan et al., 2013);
- The Australian Code for the Responsible Conduct of Research (NHMRC, 2007);
- The CONSORT 2010 statement recommendations for reporting participant characteristics in clinical trials (Schulz et al., 2010);
- The requirements for registration with the Australian New Zealand Clinical Trials Registry (ANZCTR); and
- Recommendations for reporting randomised controlled trials of herbal interventions (Gagnier et al., 2006).

### 8.4 Participants

Participants will be community dwelling and living under the supervision of a caregiver. Participants will meet the DSM-5 criteria for Major Neurocognitive Disorder (NCD) due to probable Alzheimer’s disease (AD) (American Psychiatric Association, 2013) with mild to moderate severity of cognitive symptoms, and with at least one BPSD (see below). Participants are required have a reliable caregiver at least three days per week (four hours per day) as per Homma et al. (2008) for the duration of the trial, to ensure consistent reporting of symptoms and oversee compliance.

#### 8.4.1 Minimising trial-related risks to participants

Any potential participant who would be placed at a risk greater than minimal by taking part in the trial will be excluded. Minimal risk is defined as the same as that faced in routine clinical care or daily life (Karlawish & Casarett, 2001). Risks related to the HM interventions have been minimised by the selection of HM interventions with well-established safety records. Consequently, the trial does not require participants to be subjected to an early-phase safety study. Participants will undertake cognitive and other testing more frequently than they would normally experience. Collection of
venous blood samples and other methods to assist with adverse event monitoring will be additional to that required in the participant’s normal clinical evaluations. If not previously tested, the Apolipoprotein E (ApoE) genotype will be determined using the method of Hixson and Vernier (1990) or equivalent. The ApoE genetic test for Alzheimer’s risk, or similar, may be used. This involves the collection of three buccal (cheek) swabs. Participants and caregivers may receive a copy of the results if they wish. If previously tested, results will be requested, with no restrictions on recency of test results. Overall, these tests may cause inconvenience or frustration. These risks are considered no more than minimal.

8.4.2 Determining mild to moderate severity of cognitive symptoms
Dementia severity will be determined according to the judgement of the primary physician and Mini-Mental State Examination (MMSE) score. A score of 20 to 24 suggests mild dementia, 13 to 20 suggests moderate and less than 12 suggests severe dementia. Consequently, scores of 13 to 24 points can be considered to indicate mild-moderate dementia (Alzheimer’s Association, n.d.-b).

8.4.3 Age of participants
It was not clear whether a specific age group would be more likely to benefit from the test intervention. Savva et al. (2009) proposed that therapeutic interventions targeting AD might be effective for people aged in their 70s but not aged 80 years or older. However, as this has not been well established the present protocol does not have a maximum age limit. Age will be used in data analysis as a covariate for subgroup analysis. In order to maintain broad inclusion criteria, the minimum age is 55 years, which is consistent with Furukawa et al. (2015).

8.4.4 BPSD symptoms
The clinical trial literature on EGb 761® and Yokukansan reviewed and analysed in Chapter Four suggested benefits on agitation, aggression, irritability, lability, anxiety, depression and aberrant motor activity.

Based on the clinical and experimental literature and the symptoms considered clinically meaningful and difficult to ignore, this study requires participants to have at least one of the NPI symptoms of agitation/aggression, irritability/lability, aberrant motor activity, depression/dysphoria or anxiety.

8.4.5 Inclusion criteria of the participant with BPSD
Participants of the study will be required to meet the following criteria:

- Diagnosed with Major NCD due to probable AD, according to DSM-5 criteria; or
- An MRI scan consistent with a diagnosis of AD, i.e. cortical and overall atrophy; white matter lesions and lacunas are permitted; or
- Probable AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS-ADRDA) criteria (McKhann et al., 1984); or
- possible AD with cerebrovascular disease according to NINDS-AIREN criteria (Román et al., 1993); and
- Have mild to moderate severity of cognitive impairment based on the primary physician’s judgement and MMSE scores of 13 to 24; and
- Have had cognitive complaints for at least six months; and
- A total score of six points or higher on the NPI-12 (Cummings, 1997) with at least one of the domain scores of agitation/aggression, irritability/lability, aberrant motor activity, depression/dysphoria or anxiety being at least four points; and
- Aged at least 55 years old; and
- Agree to undergo testing to determine ApoE genotype and provide results to be used as a covariate in secondary analysis of results, or provide results if this test has been undertaken previously; and
- Agree to abstain from excessive alcohol consumption or use of recreational drugs for the duration of the trial; and
- Not be concurrently involved in other clinical trials; and
- Agree to participate for the study duration, and
- Provide written consent for participation as described below, and approval from the participant’s physician; and
- Pass a swallow test – able to swallow an empty capsule (EGb 761® size), able to swallow a typical dose of herbal granules (not Yokukansan) and able to swallow a dose of potassium electrolyte supplement per manufacturers’ directions; and
- Stable use of AChEIs and/or memantine for at least three months is allowed; and
- Anxiolytics, hypnotics, antidepressants other than those listed in the exclusion criteria, and anticonvulsants are allowed, with approval from the physician; and
- Agree to undergo 3 x 60 minute consultations with a clinical psychologist (enrollment stage, baseline and end of treatment) to assess (1) additional mood and psychological factors which may influence trial outcomes, to be used as a covariate for subgroup analysis, as noted in 8.9.6.2; (2) psychological factors likely to influence trial compliance including suicide risk.
8.4.6 Exclusion criteria of the participant with BPSD

People with one or more of the following criteria at the initial screening will be excluded from the study:

- Diagnosis of Major Depressive Disorder or Bipolar Disorder according to DSM-5 criteria (American Psychiatric Association, 2013); or
- Diagnosis of other current or recurrent major psychiatric disorder apart from BPSD; or
- Diagnosis of Probable or Possible Major Neurocognitive disorder (NCD) primarily due to vascular disease, frontotemporal lobar degeneration, Lewy body disease, traumatic brain injury, substance/medication use, HIV infection, Prion disease, Parkinson’s disease, Huntington’s disease or another medical condition according to DSM-5 criteria (American Psychiatric Association, 2013); or
- MRI scan showing signs of normal pressure hydrocephalus, intracranial haemorrhage/haematoma, brain tumour, cerebral infarction or other structural brain disease likely to be a substantial contributor towards cognitive symptoms; or
- Any type of neurological disorder, including stroke with sequelae, within the last three months or haemorrhagic stroke within the last 12 months before enrollment; or
- Diagnosis of mild cognitive impairment according to Petersen’s diagnostic criteria (Petersen et al., 2001); or
- High suicide risk requiring urgent management; or
- Unable to pass the swallow tests; or
- Have a history of sensitivity towards HMs; or
- Frequent anorexia, nausea, vomiting, diarrhoea or epigastric distress; or
- Have abnormal full blood count, renal or liver function tests; or
- Currently using corticosteroids, as these are contraindicated with Glycyrrhiza uralensis; or
- Hypokalaemia; or
- Significant cardiac arrhythmias or currently receiving a maintenance dose of digoxin, as these people would be at increased risk if hypokalaemia developed; or
- Current respiratory disorder, or unexplained fever, cough, dyspnoea or abnormal pulmonary sound, as interstitial pneumonia has been associated with Yokukansan use; or
- Currently using other complementary medicines or specific psychosocial interventions for management of BPSD and not able to pause for the duration of the study; or
- Currently using AChEIs and/or memantine at irregular or poorly controlled doses for management of BPSD and not able to pause for the duration of the study; or
- Currently using omeprazole, tolbutamide, antiepileptics, trazodone, monoamine oxidase inhibitors, alprazolam or haloperidol and not able to pause for the duration of the study; or
- Unable to understand English adequately to take part in cognitive testing; or
- Pregnant/intention to get pregnant/breastfeeding; or
- Severe or insufficiently controlled cardiovascular disorder or insulin-dependent diabetes mellitus; severe hepatic or renal dysfunction; or vitamin deficiency; or
- Gastrointestinal disorders with uncertain absorption; or
- Alcohol or substance abuse; or
- Active malignant disease; or
- Severe and insufficiently corrected impairment of hearing or vision; or
- Received EGb 761®, Yokukansan or similar HM within the previous four weeks; or
- Prescribed warfarin in the last 2 months; or
- Received typical or atypical antipsychotics, or tricyclic or tetracyclic antidepressants within the previous four weeks

8.4.7 The caregiver as a secondary participant

The NPI involves questioning the caregiver about the frequency and severity of the symptoms of the person with BPSD. In addition, as the NPI-D will be used to assess caregiver distress, the caregiver is considered a secondary participant and is required to provide informed consent and meet inclusion criteria to be enrolled in the trial. The definition of a caregiver for this trial is a knowledgeable informant, task-doer who assists with daily living activities, and decision maker for the person with BPSD. A checklist will be used to determine whether a potential caregiver may be included, in accordance with Karlawish et al. (2001):

- Is the potential participant a knowledgeable informant of the daily activities and symptoms of the person with BPSD?
- Is the potential participant a key task-doer for the person with BPSD, at least three days per week (four hours per day)?
- Is the potential participant a decision maker for the person with BPSD?
- Is the potential participant willing and able to be responsible for administering the interventions to the person with BPSD and report accurately on compliance, concomitant medication use, adverse events and any other important information which could affect the results of the trial?

8.4.7.1 Inclusion criteria of the caregiver

Caregivers will be required to meet the following criteria to be included in the study:
• Meet the definition of caregiver as described in 8.3.7; and
• Expected to have sufficient contact with the person with BPSD in order to provide 
  information about the symptoms, compliance with test interventions and adverse events; 
  and
• Able to understand English; and
• Agree to ensure that the participant with BPSD complies with all aspects of the protocol, 
  including ensuring regular intake of the test interventions and reporting adverse events; and
• Agree to accompany the participant to the clinical assessment visits, and provide 
  information about the participant; and
• Agree to undergo 3 x 60 minute sessions (enrollment stage, baseline and end of treatment) 
  with a clinical psychologist or general physician to assess (1) mood and psychological factors 
  which may influence trial outcomes, to be used as a covariate for subgroup analysis, as 
  detailed in 8.9.6.3; (2) psychological factors likely to influence trial compliance; and
• Agree to record their own daily medication use in the diary provided (Karlawish and 
  Casarett, 2001).

8.4.7.2 Exclusion criteria of the caregiver
Caregivers with one or more of the following conditions will be excluded from the study:

• Unable to understand English; or
• Not expected to be a primary caregiver for the duration of the study; or
• Current alcohol or substance abuse and not able to abstain for the duration of the study, or 
  other condition likely to reduce trial compliance, as judged by the clinical psychologist or 
  primary physician.

8.4.8 Dropout and sample size calculation
This section details sample size calculation based on total NPI scores as the primary outcome.

8.4.8.1 Calculation of dropout rate
The estimated dropout rate was calculated according to results of the Chapter Seven meta-analysis. 
The mean number of dropouts was calculated for the six BPSD studies of 20 to 26 weeks duration, 
published from 2009 to 2015.
Table 8.7: Numbers of dropouts from published RCTs of oral interventions for BPSD

<table>
<thead>
<tr>
<th>Study name; duration</th>
<th>Proportion of dropouts from placebo groups</th>
<th>Proportion of dropouts from active treatment groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emre et al. 2010; 24 wks</td>
<td>20/99</td>
<td>16/96</td>
</tr>
<tr>
<td>Ihl et al. 2011; 24 wks</td>
<td>12/204</td>
<td>16/206</td>
</tr>
<tr>
<td>Herrschaft et al. 2012; 24wks</td>
<td>5/205</td>
<td>7/205</td>
</tr>
<tr>
<td>Herrmann et al. 2013; 24wks</td>
<td>32/187</td>
<td>31/182</td>
</tr>
<tr>
<td>Nikolova et al. 2013; 22wks</td>
<td>4/205</td>
<td>7/203</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td><strong>76/979 = 7.8%</strong></td>
<td><strong>79/972 = 8.1%</strong></td>
</tr>
</tbody>
</table>

Based on these findings, the present protocol estimates a 10% dropout rate.

8.4.8.2 Sample size

The sample size for this trial was based on the mean difference effect size calculations detailed in Chapters Four and Eight. Based on findings from Chapter Eight regarding increasing placebo effect sizes over time, only studies conducted from 2009 onwards were included for NPI effect size estimations, as shown in Table 8.8.

Table 8.8: Mean difference (Confidence Intervals) of total NPI scores from the placebo-controlled oral intervention studies of 22 – 24 week duration, published from 2009 to 2015

<table>
<thead>
<tr>
<th>Study name; duration</th>
<th>MD (CI) NPI change in placebo group</th>
<th>MD (CI) NPI change in active treatment group</th>
<th>MD (CI) difference between groups at EoT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emre et al. 2010; 24 wks</td>
<td>-0.10[-4.52, 4.32]</td>
<td>-4.90[-9.21, -0.59]</td>
<td>-6.00 [-10.60, -1.40]</td>
</tr>
<tr>
<td>Ihl et al. 2011; 24 wks</td>
<td>0.00[-1.60, 1.60]</td>
<td>-3.20[-4.77, -1.63]</td>
<td>-3.80 [-5.39, -2.21]</td>
</tr>
<tr>
<td>Herrschaft et al. 2012; 24wks</td>
<td>-2.10[-3.34, -0.86]</td>
<td>-4.60[-5.94, -3.26]</td>
<td>-2.40 [-3.70, -1.10]</td>
</tr>
<tr>
<td>Herrmann et al. 2013; 24wks</td>
<td>-5.13[-8.00, -2.26]</td>
<td>-3.90[-6.91, -0.89]</td>
<td>2.99 [0.07, 5.91]</td>
</tr>
<tr>
<td>Nikolova et al. 2013; 22wks</td>
<td>-3.06[-4.75, -1.37]</td>
<td>-3.81[-5.67, -1.95]</td>
<td>-0.55 [-2.34, 1.24]</td>
</tr>
<tr>
<td>Gavrilova et al. 2014; 24wks</td>
<td>-5.50[-6.65, -4.35]</td>
<td>-7.00[-8.08, -5.92]</td>
<td>-1.60 [-2.72, -0.48]</td>
</tr>
<tr>
<td><strong>Combined results (n at EoT=909,928)</strong></td>
<td><strong>-2.79 [-4.75, -0.82]</strong> RE; <strong>-3.11 [-3.77, -2.46]</strong> FE; (P = 0.001); 87%</td>
<td><strong>-4.47 [-5.88, -3.06]</strong> MD RE; <strong>-5.04 [-5.69, -4.38]</strong> FE; (P = 0.001); I² = 73%</td>
<td><strong>-1.74 [-3.30, -0.18]</strong> RE; <strong>-1.90 [-2.57, -1.24]</strong> FE; (P = 0.0005); I² = 78%</td>
</tr>
</tbody>
</table>

The primary variable for the assessment of BPSD efficacy is the difference between groups in total NPI scores at EoT. The sample size of 2 x 176 participants was calculated to detect a difference between HM and placebo groups on total NPI with a type I error rate of 0.05 and 80% power for the rejection of the null hypothesis. This was calculated using G*Power with the effect size $d$ value at 0.3 as shown in Table 8.9.
### Table 8.9: G*Power 3.0.10 sample size calculations

<table>
<thead>
<tr>
<th>Test family</th>
<th>t tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Statistical test</strong></td>
<td>Means: Difference between two independent means (two groups)</td>
</tr>
<tr>
<td><strong>Type of power analysis</strong></td>
<td>A priori: Compute required sample size – given alpha, power, and effect size</td>
</tr>
<tr>
<td><strong>Input parameters</strong></td>
<td>Tail(s) 2</td>
</tr>
<tr>
<td><strong>Effect size d</strong></td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Alpha error prob</strong></td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Power (1-beta error prob)</strong></td>
<td>0.80</td>
</tr>
<tr>
<td><strong>Allocation ratio N2/N1</strong></td>
<td>1</td>
</tr>
<tr>
<td><strong>Sample size group 1</strong></td>
<td>176</td>
</tr>
<tr>
<td><strong>Sample size group 2</strong></td>
<td>176</td>
</tr>
<tr>
<td><strong>Total sample size</strong></td>
<td>352</td>
</tr>
<tr>
<td><strong>Actual power</strong></td>
<td>0.801</td>
</tr>
</tbody>
</table>

Attrition rate estimated at 10% raises the sample size to $2 \times 196$ to obtain a statistical power of 80%.

### 8.5 Recruitment procedure

This section describes recruitment procedure including participant requirements and details of advertising that will be utilised.

#### 8.5.1 Setting and participant source

The RCT will be conducted at RMIT University Bundoora and/or a collaborating medical centre or research institute in Australia. Participants with BPSD will be required to visit at least one of these sites on multiple occasions with their caregiver.

#### 8.5.2 Advertising

Participants will be recruited via advertising in the form of posters or flyers on display within RMIT University and the collaborating medical centre or research institute. Assistance in recruitment will be sought from collaborators who are employed by or liaise with these organisations.

The Alzheimer’s Australia Dementia Research Foundation (AADRF) free service to Australian researchers will be utilised to invite people to participate in the study (AADRF, 2017). A similar invitation with study and site details will also be listed on the Alzheimer’s Association TrialMatch® free service provided by alz.org® (Alzheimer’s Association, n.d.-a).

Social media including Facebook, twitter and LinkedIn will be utilised to invite people to participate. In addition, email will be used to inform health and medical practitioners in Melbourne of the study so that they may let their patients know. Flyers will be distributed to these health professionals. Where possible, public lectures or other events related to ageing or BPSD will be attended by one of the study team and permission sought to distribute flyers to other attendees. In addition, permission will be sought to display posters or flyers at the University Hill medical centre, the Mill Park.
Community Centre, local libraries and leisure centres, and the Bundoora Square notice board. The study will be publicised on the RMIT news website and in the RMIT School of Health and Biomedical Sciences newsletter. The study will also be advertised in the Whittlesea U3A newsletter, the Leader news, any other newsletters aimed at older people in the region, and on local radio station Plenty Valley FM 88.6.

8.5.3 Screening
Interested caregivers may make enquiries by email or telephone. Participant information and consent forms (for both the person with BPSD and the caregiver) will be emailed or posted to potential participants prior to the telephone interview and scheduling of the initial face-to-face consultation with a trial investigator and a registered GP, neurologist or other professional with clinical experience relevant to geriatric psychiatry. The potential participants will undergo preliminary screening for eligibility during the initial face-to-face consultation. The consultation will take place at RMIT University, the participating medical centre or research institute.

Participants’ detailed medical history and current condition will be collected (for both people with BPSD and caregivers). A registered physician will be present to assist with evaluation and monitoring. If contraindications towards the intervention or abnormal test results are detected, these participants will be excluded from the trial. The condition of the participant with BPSD will also be closely monitored throughout the trial to ensure their safety and wellbeing.

8.5.3.1 Swallow test
Dysphagia, or swallowing impairment, is a concern in older adults and people with dementia and has been detected in mild AD (Alagiakrishnan et al., 2013; Forster et al., 2011). For the present study, swallowing ability will be assessed. At screening, potential participants will be asked to swallow an EGb 761® tablet or placebo, and 2.5g Yokukansan granules or placebo. Water will be supplied and participants will be allowed to use other drinks if preferred. Potential participants will also be asked to swallow a standard 600g Slow-K® (Novartis Pharmaceuticals Australia P/L), or equivalent potassium chloride (KCl) tablet according to manufacturer’s instructions. If unable to swallow the KCl tablet, another product may be provided at the physician’s discretion. The rationale for this supplementation is detailed below in section 8.8.6.

8.6 Informed consent
A clinical diagnosis of mild to moderate dementia may impair decision-making capacity, suggesting lack of ability to decide whether to enrol in a clinical trial (Karlawish & Casarett, 2001). Many potential participants may therefore not have the capacity to provide informed consent. This section
details strategies for determining decision-making capacity of potential participants with BPSD and methods for ensuring enrollment is based on genuine informed consent.

8.6.1 Compliance with Australian laws
Informed consent will be obtained according to Australian Federal laws and Victorian State laws. In the Australian State of Victoria, a decision-maker for personal and/or health care decisions appointed by the person with BPSD is the Agent Enduring Power of Attorney (Medical Treatment). A decision-maker appointed by the Victorian Civil & Administrative Tribunal (VCAT) for personal and/or health care decisions is the Enduring Guardian (VCAT, n.d.). For the present protocol, the Agent Enduring Power of Attorney (Medical Treatment) or the Enduring Guardian does not need to be the caregiver who is directly involved in the trial.

8.6.2 Assessment of decision making capacity
Where possible, informed consent will be obtained directly from the participant with BPSD. However, there is no current gold standard assessment for determining decision-making capacity. Karlawish and Casarett (2001) proposed that people with mild symptoms and a MMSE score of 18 to 20 may be able to provide informed consent.

For the present protocol, if the MMSE score is less than 18, informed consent may be obtained from the Agent Enduring Power of Attorney (Medical Treatment) or the Enduring Guardian only, at the judgement of the primary physician and in accordance with principles of the NHMRC National Statement on Ethical Conduct in Human Research (2007, updated 2015). If the MMSE is 18 or over, informed consent will be sought from the participant with BPSD and the caregiver, at the judgement of the primary physician. For the participant with BPSD, decision-making capacity may fluctuate over time and depend on context such as time of day, current medication, concurrent illness, location and noise or mood. If informed consent is sought, this will be obtained only after it is established that the participant understood the nature and effect of deciding to enrol, is capable of freely and voluntarily making decisions about their enrollment, and is able to communicate their decisions verbally in English, or in another way deemed suitable by the primary physician and caregiver. In the case of questionable decision-making capacity, supported decision-making will be attempted, based on agreement between the person with BPSD and the caregiver. This will be in accordance with the United Nations Convention on the Rights of People with a Disability (CRPD) (2006).

8.6.3 Advanced consent option
A potential participant with preclinical AD or very mild symptoms may provide advance consent, as proposed by Karlawish and Casarett (2001). These participants can be included in a future trial if
inclusion criteria are met, with approval from their future caregiver, legal decision-maker and primary physician.

8.6.4 Procedure for informed consent
Informed consent will be sought during the initial face to face consultation prior to the randomisation process and run-in period. Written and verbal explanation and information will be provided to the caregiver and person with BPSD. A full explanation will be given to any questions that arise prior to signing information and consent forms. The person providing informed consent must be able to understand spoken and written English with adequate fluency and be able to write in English. The trial investigator will record the date, time and location of the provision of Informed Consent.

8.7 Trial design
This section details aspects of the trial design.

8.7.1 Randomisation
Randomisation will be carried out after the run-in period, using computer generated randomisation. Each participant (and their matched caregiver) will be assigned an ID code. An independent statistician will be responsible for stratification of the randomisation to ensure balance in BPSD severity (total NPI scores). The randomisation list will be produced by a qualified statistician with no direct contact with the trial participants or eligibility assessment.

8.7.2 Allocation concealment
Allocation concealment will be ensured by use of a centralised telephone system administered by the trial co-ordination centre, as recommended by Kennedy et al. (2017). This will involve use of a dedicated telephone line. To allocate a participant, the trial investigator will telephone the trial administration centre giving details of the participant with BPSD and caregiver. Details will be entered directly into a customised database package to generate the allocation. The allocation concealment method of using opaque, sealed, sequentially numbered envelopes will not be used.

8.7.3 Blinding
Participants with BPSD, their caregivers and legal decision-makers, assessors, sponsors and study team members who have direct contact with any of these people will be blinded to treatment allocation. The two placebo interventions have been used in previous trials and each is reported to be indistinguishable from the active intervention in taste, smell and appearance (see Chapter Four for studies). Blinding will be carried out using treatment codes and pre-packaging of the placebo and active interventions. If available from the manufacturers, the approved products used in the
previously published EGb 761® and Yokukansan studies will be used. The codes and labelling will be recorded in a password-protected digital file. Participants, investigators and outcome assessors will remain blinded to the treatment allocation until the end of the follow-up period.

8.7.4 Trial duration

Short trials are arguably less likely to provide clinically relevant results in a long-term condition like AD, while long trials could lead to increased drop-outs, protocol violations and deterioration of comorbidities (Liang et al., 2014). The treatment duration of 24 weeks is consistent with the published EGb 761® RCTs. The only placebo-controlled study of Yokukansan for BPSD was four weeks with eight weeks open label extension (Furukawa et al., 2015), but longer term use of Yokukansan for BPSD is not uncommon in Japan (Shimada et al., 2017) and Tsumura Japan (2016) does not specify any limitations for duration of use. In addition, there will be a one-week run-in period and a four-week follow-up.

8.7.5 Screening and run-in period

After initial screening, eligible participants will undergo assessments for baseline data collection. Baseline measurements will include total NPI-12 including all domains, NPI-D caregiver assessments, MMSE, Cohen-Mansfield Agitation Inventory (CMAI) (Cohen-Mansfield, 1999), Alzheimer’s disease Assessment Scale-cognitive subsection (ADAS-cog) (Mohs et al., 1983), measurement of vital signs (temperature, blood pressure and heart rate), full blood count, kidney function test and liver function test.

During the one-week run-in period the baseline measures will be established. Diaries will be checked at the end of the run-in to assess compliance. If some participants have poor compliance, an effort will be made to improve adherence, as per Liang et al. (2014). If, after the run-in period, a participant is judged to be unlikely to comply for the trial duration, the participant may be excluded. The principal investigator will report any protocol violation or deviation including exclusion or early termination, with reasons, to the coordinating principal investigator, the research governance officer and the reviewing HREC, using a standard report template for protocol deviation or violation report and in accordance with requirements of the NHMRC National Statement on Ethical Conduct in Human Research (NHMRC, 2007).

8.7.6 Procedure for participant dropouts/withdrawals

A participant may be withdrawn from the trial at any time if a serious adverse event (SAE) occurs. Participants, their legal decision-makers and caregivers are permitted to withdraw from the study at any time. All withdrawn participants and their caregivers will be contacted four weeks following
withdrawal, as the follow-up period, to obtain information regarding the participant’s and caregiver’s conditions, using the NPI and NPI-D.

8.7.7  Early trial termination
EGb 761® and Yokukansan have been well-studied and used in clinical practice, as detailed in Chapters Four and Six. However, if it becomes apparent that there are associated SAEs the whole trial will be discontinued. SAEs are defined as ‘any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically-important event or reaction’ (TGA, 2006).

8.7.8  Breaking code and early trial termination for individual participants
This section describes the procedure if codes are broken and early trial termination for individual participants.

8.7.8.1  Procedure if codes are broken
Emergency 24 hour access to the participant ID and treatment codes will be made available to authorised personnel at the study site (University or collaborating centre or institute). The authorised personnel will have access to the treatment code upon request of the trial investigator or member of the investigatory team. Details of AEs and the unmasking of the treatment code will be recorded by the investigator with endorsement from one other member of the investigatory team.

8.7.8.2  Procedure for suspected risk of suicide
If risk of suicide is suspected participants will be referred to their primary physician.

8.7.8.3  Protocol violation due to adverse reactions
Based on findings of a clinical survey of adverse reactions of 3,141 patients treated with Yokukansan between October 2012 and March 2014 (Hisahi et al., 2016), if any of the following adverse reactions are detected during the treatment period, treatment may be discontinued immediately at the judgement of the primary physician. The participant should be monitored, and appropriate measures taken:

- Pseudoaldosteronism: including hypokalaemia, increased blood pressure, retention of sodium/body fluid, oedema, increased body weight. If any abnormality is observed, appropriate measures should be taken such as administration of KCl preparations.
- Heart failure: if fluid retention, rapid weight gain, and signs and symptoms of heart failure (e.g., shortness of breath, increased cardiothoracic ratio, pleural effusion) are observed, the participant should be monitored, and appropriate measures taken.

- Myopathy: myopathy and rhabdomyolysis may occur as a result of hypokalaemia. The participant should be monitored, and appropriate measures taken such as administration of a KCl preparation if sluggishness, muscular weakness, myalgia, limb cramping/paralysis, elevated CK (CPK) levels, and elevated blood and urine myoglobin levels are observed.

- Hepatic dysfunction and jaundice: if hepatic dysfunction and/or jaundice with remarkable elevation of AST (GOT), ALT (GPT), Al-P and γ-GTP etc. occurs, the participant should be carefully monitored for abnormal findings, and appropriate therapeutic measures should be taken.

- Interstitial pneumonia: if unexplained fever, cough, dyspnea or abnormal pulmonary sounds are observed, examinations such as X-ray or chest CT should be performed immediately and appropriate measures such as administration of adrenocortical hormones taken.

8.8 Trial interventions and placebos

This section details the HM and placebo interventions, as well as the KCl supplement which will be provided and may be used on a case-by-case basis, as determined by the primary physician.

Incorporating the findings of the Chapter Four systematic review of clinical trials, and Chapter Six summary of experimental literature, the intervention will be the combination of the two existing products: EGb 761® herbal extract capsules (Schwabe pharmaceuticals) and Yokukansan TJ-54 herbal extract granules (Tsumura Japan), or matching placebo capsules and granules.

8.8.1 EGb 761®

The active EGb 761® herbal extract tablet and its placebo will be produced by Schwabe Pharmaceuticals. Approval for use in Australia will be obtained in accordance with a TGA-approved GMP certificate. Alternatively, the equivalent Australian product, Blackmores Ginkgo 6000 mg (Tebonin® EGb 761®), may be used if a placebo is available. Active treatment consists of tablets containing 240 mg of EGb 761®. EGb 761® is a dry extract from *G. biloba* leaves (35–67:1); extraction solvent: acetone 60% (w/w). The extract is adjusted to 22.0–27.0% ginkgo flavonoids calculated as ginkgo flavone glycosides and 5.0–7.0% terpene lactones consisting of 2.8–3.4% ginkgolides A, B, and C and 2.6–3.2% bilobalide and contains less than 5 ppm ginkgolic acids. Participants with BPSD are to take one capsule of the active HM or placebo every morning, with water or juice, either with or without food. This dosage is consistent with the published RCTs of EGb 761® for BPSD (Napryeyenko & Borzenko, 2007; Ihl et al., 2011; Herrschaft et al., 2012; Nikolova et al., 2013; Gavrilova et al.,
The standard dose in Europe for any condition is 120-360mg. The study of Ginkgo for prevention of dementia by DeKosky et al. (2008) involved a twice daily dose of 120 mg for 1,545 participants in the active treatment group, over a time period of six years, in community-dwelling volunteers aged 75 years or over with normal cognition in the US.

8.8.2 Yokukansan

Tsumura Yokukansan Extract Granules for Ethical Use (TJ-54) and its placebo will be produced by Tsumura Japan. Approval for use in Australia will be obtained in accordance with a TGA-approved GMP certificate. Active treatment consists of a water extract from the following mixture of seven HMs listed in the Japanese Pharmacopoeia: Atractylodes lancea rhizome (4.0 g, rhizome of Atractylodes lancea De Candolle), Poria sclerotium (4.0 g, sclerotium of Poria cocos Wolf), Cnidium rhizome (3.0 g, rhizome of Cnidium officinale Makino), Uncaria hook (3.0 g, thorn of Uncaria rhynchophylla Miquel), Japanese Angelica root (3.0 g, root of Angelica acutiloba Kitagawa), Bupleurum root (2.0 g, root of Bupleurum falcatum Linné), and Glycyrrhiza (1.5 g, root and stolon of Glycyrrhiza uralensis Fisher) (Ikarashi & Mizoguchi, 2016). Each plant material is identified by its external morphology and authenticated by marker compounds of plant specimens according to the methods of the Japanese Pharmacopoeia and Tsumura Japan’s standard. To produce the dried Yokukansan extract powder, the mixture of seven herbs is extracted with purified hot water at 95 °C for one hour. The extract solution is separated from the insoluble waste and spray-dried to produce the dried extract powder. The quality is standardised based on GMP defined by the Ministry of Health, Labour and Welfare of Japan (Ikarashi & Mizoguchi, 2016). At least 25 key compounds related to BPSD have been identified in the methanol extract: glycyroside; isoliquiritin apioside; isoliquiritin; isoliquiritigenin; liquiritin; liquiritin apioside; formononetin; glycoumarin; acetylatractylodinal; atracylodin; Ligustilide; atractylodinol; 14-isovaleroyl-2E,8E,10E-triene-4,6-diyne-1,12-diol; 12-isovaleroyl-2E,8E,10E-triene-4,6-diyne-1,14-diol; saikosaponin b1; saikosaponin b2; hirsutine; xanthotoxin; hirsuteine; geissoschizine methyl ether; glycyrrhizin; liquiritigenin; formononetin-7-O-glucosede; 4E,6E,12E-tetradecatriene-8,10-diyne-1,3,14-triol and ferulic acid (Ikarashi & Mizoguchi, 2016).

For the present trial, the dosages for people with BPSD are in accordance with the usual adult dose (Tsumura Japan, 2016) and are consistent with the published Yokukansan for BPSD clinical trials (Furukawa et al., 2015; Iwasaki et al., 2005; Okahara et al., 2010; Teranishi et al., 2013; Mizukami et al., 2009). Participants with BPSD are to take one sachet of the active granules or placebo three times a day (2.5 g each, 7.5 g per day) before or between meals. At any time during the 24-week trial
duration, depending on the participant’s condition or adverse reactions, the dosage may be
decreased to two doses of 2.5 g each (5.0 g/day).

8.8.3 Placebo interventions
The placebo tablets and granules contain no active compounds. These placebos are well established
and have been approved previously and used in the published RCTs reviewed in Chapter Four
(Napryeyenko & Borzenko, 2007; Ihl et al., 2011; Herrschaft et al., 2012; Nikolova et al., 2013;
Gavrilo et al., 2014; Furukawa et al., 2015), as well as in other participant types including the
Yokukansan for treatment-resistant schizophrenia trial by Miyaoka et al. (2015). As used in the
previous trials, the HM and placebo interventions will be indistinguishable in appearance, taste,
smell, packaging and labelling.

8.8.4 Quality control measures
Quality control checks on the packaging and contents of the interventions will be undertaken by the
manufacturers to ensure their stability and quality. EGb 761® by Schwabe Pharmaceuticals is
currently manufactured to the quality standards required in Europe, and Yokukansan is
manufactured in accordance with the requirements for approval in Japan. In order to be used in
Australia, both products will need TGA approval. The products are not currently entered onto the
Australian Register of Therapeutic Goods (ARTG). Approval will be sought by the manufacturer in
accordance with standards of Good Manufacturing Practice as outlined in Annex 13 of the Australian
GMP code (TGA, n.d.).

8.8.5 Concurrent interventions
Throughout the treatment duration, the use of other oral interventions for management of BPSD,
including rescue medications, will be allowed according to the inclusion and exclusion criteria.
Caregivers will be requested to record use of other interventions in addition to trial medication
compliance, occurrence of AEs and use of any other pharmacological or non-pharmacological
interventions for any medical condition, including analgesics, during the treatment period.

8.8.5.1 Use of medication by caregivers
Use of medications by caregivers that might affect reporting of caregiver distress or severity of BPSD,
including antidepressants, opioids or benzodiazepines, will be monitored. Caregivers will be asked to
record their own medication use in their diaries on a daily basis.
8.8.6 Provision of an oral potassium supplement and guidance regarding liquorice-induced hypokalaemia

Previous studies have indicated a risk of hypokalaemia in people taking Yokukansan. This section details the risk to participants of hypokalaemia and the provision of an oral KCl supplement with the aim to reduce this risk.

G. uralensis root (a component of Yokukansan) is one of the most commonly used herbs in Chinese herbal medicine (Wang et al., 2013). It has been suggested that 18β-glycyrrhetinic acid, a metabolite of the compound glycyrrhizin, exerts a neuroprotective effect via reduction of extracellular glutamic acid levels through the activation of a glutamate transporter located on astrocytes. However, glycyrrhetinic acid also appears to be the major substance involved in the mechanism for liquorice-induced hypokalaemia (Shimada et al., 2017).

For the present trial, caregivers will be provided with detailed guidance and instructions regarding risk of hypokalaemia in people taking Yokukansan and strategies for maintaining normal serum potassium levels for the person with BPSD. For people over 50 years old, the NHMRC recommended dietary intake (NHMRC, 2006, updated March 2017) is 3,800 mg per day for men, and 2,800 mg per day for women. Caregivers will be asked to include food items with naturally occurring potassium each day to the participant with BPSD. According to the NHMRC Nutrient Reference Values (NHMRC, 2006, updated March 2017) particularly good sources include leafy green vegetables, vine fruit such as tomatoes, cucumbers, zucchini, eggplant and pumpkin, and root vegetables; while moderate sources include beans and peas, tree fruits such as apples, oranges and bananas, milks and yoghurts and meats. Participants will also be advised not to consume additional liquorice products including sweets, salted liquorice or liquorice tea during the course of the trial.

Currently, little formal guidance exists for management of liquorice-induced hypokalaemia (Gallacher et al., 2017) although case studies indicate that full recovery of signs and symptoms generally occurs quickly if liquorice intake is discontinued (de Klerk et al., 1997; Dai et al., 2016; Schröder et al., 2015). For the present trial, based on personal correspondence from Dr Andrew Walby, Director of Emergency Medicine, St Vincent’s Hospital Melbourne, 5 August 2017, all caregivers will be provided with one bottle of 100 x 600 mg oral potassium chloride (KCl) tablets (Slow-K®, Novartis Pharmaceuticals Australia P/L, or equivalent) together with the trial interventions.

At the physician and caregivers’ judgement, one tablet may be provided to the participant with BPSD if there is poor daily dietary intake on particular days. The potassium chloride supplement will not be
administered every day during the trial. It will only be used when required. The tablet will be taken with water or juice and according to the manufacturer’s directions. Caregivers will also be advised about risks of hyperkalaemia due to excessive intake of KCl and will be asked to record dates and reasons for the KCl tablet use in their diaries. If the poor dietary intake persists for more than five days, caregivers are required to consult the primary care physician. Importantly, it is not confirmed that taking a potassium supplement will reduce the risk of liquorice-induced hypokalaemia. Participants will also be questioned about consumption of any other liquorice products during the course of the trial and asked to note these in their diaries.

8.8.7 Assessment of caregiver compliance with diary keeping requirements
The one-week run-in period will be used to determine whether the caregiver complies with the data-collection requirement for keeping a daily diary. At the week 0 interview the importance of the daily diary and the procedures for completing the diary will be explained to the caregiver. At the end of the run-in week compliance will be checked. If 80% of entries have been completed this will be considered acceptable for inclusion and randomisation. The caregiver will again receive instruction on how to achieve 100% compliance. If compliance is not satisfactory, randomisation will not be undertaken. In such cases, when the caregivers and participants with BPSD are determined to improve their compliance, another one-week run-in will be offered.

8.9 Assessments and Outcome Measures
This section provides details of primary and secondary outcome measures and safety monitoring. Between baseline and end of treatment, assessments will be made at four-week intervals, as shown in Table 10. These will be conducted at RMIT University or the collaborating centre or institute. At each monthly assessment, caregivers will be asked to return their diaries and intervention packaging to enable counting of leftover tablets, granule sachets and KCl tablets for monitoring of participant adherence and AEs. After the treatment period of 24 weeks, comprehensive assessments will be conducted at RMIT University or the collaborating centre or institute.

8.9.1 Biological techniques and measurement of biomarkers
Conclusive fluid biomarker evidence for measurement of disease modification in BPSD is yet to be determined. Sharma et al. (2016) did not find strong evidence of the utility of the biomarkers interleukin 2, -6 and -10 (general systemic inflammation), pentraxin 3, or serum amyloid P (vascular inflammation), plasminogen activator inhibitor-1, adiponectin, and resistin (metabolic function), receptor for advanced glycation end product (oxidative stress); and endothelin-1 (endothelial function), for identifying people at risk of cognitive decline. These authors recommended further studies on any association between PTX3, SAP and adiponectin and cognitive assessment scores.
Also, Webster et al., (2017) agreed not to recommend a fluid biomarker as currently no changes in putative CSF biomarkers had shown correlations with MMSE, so this did not appear useful for detecting disease modification. In addition, collection of CSF involves lumbar puncture which would be expensive and require increased medical care afterwards, as well as being a potential cause of discomfort, distress and/or inconvenience for the participant and caregiver. The present protocol therefore does not include fluid biomarker measurements.

8.9.2 Measurement of clinically meaningful endpoints

The present trial design aimed to measure clinically relevant changes in participants’ symptoms and milestone changes in disease progression. Successful outcomes include improvements in neuropsychiatric symptoms for the person with BPSD, improvements in caregiver distress, improvements or slower decline of cognitive symptoms and delay in clinical milestones in AD as an indication of possible disease modification.

The present trial uses validated clinical outcome measures. Primary outcomes will include total NPI, NPI-D, ADAS-cog, MMSE, CMAI (Cummings et al., 1994; Rosen et al., 1984; Folstein et al., 1975; Cohen-Mansfield et al., 1989). Formal permission to use these measures will be purchased as required or obtained from the authors via email.

Secondary outcomes will include wrist actigraphy, milestone changes related to disease progression, serum potassium, AEs, vital signs, full blood count, and liver and kidney function tests. Details of these assessments are provided in this section.

8.9.3 Assessment of BPSD

The present protocol uses NPI-12 as primary measure 1. This measure is most consistent with other trials of Yokukansan and EGb 761®, allowing for better comparison and pooling of results on an international level. Jeon et al., (2011) reviewed the published instruments for BPSD and recommended the NPI and BEHAVE-AD as most appropriate for both clinical practice and research. In a systematic review of core outcome measures for dementia intervention trials, Webster et al., (2017) found that of 58 trials that measured at least one neuropsychiatric outcome, 38 used NPI followed by 7 which used ADAS-noncog. Webster et al. (2017) also conducted consensus conference discussions with expert researchers and clinicians in order to propose recommendations for assessing disease modification in dementia trials. These authors recommended that the NPI was the best of the available BPSD measures which their panel had considered. However, the Cohen-Mansfield Agitation Inventory (CMAI) has been reported to be a more reliable measurement of
agitation compared to NPI-C (Agitation/Aggression) (Zuidema et al., 2011). Therefore, this protocol uses the CMAI as primary measure 2.

### 8.9.4 Assessment of cognitive symptoms

There has been recent concern that the major clinical scales used to assess cognitive function are not suitable for clinical studies of participants with dementia, and that they do not adequately reflect the level of cognitive ability of the participants, leading to significant problems in the current research into pharmacological interventions for NCDs (Wesnes & Edgar, 2014). As described in Chapters One and Four, the MMSE may be less sensitive to change than the ADAS-cog, although the MMSE is by far the most commonly used measure to report cognitive outcomes in dementia trials. Webster et al. (2017) found that of 117 intervention trials for dementia that measured at least one cognitive outcome, 92 used ADAS-cog and 83 used MMSE, indicating that these measures are commonly used together. The consensus group agreed that either the MMSE or ADAS-cog be used, with MCID for MMSE of 1.4 points and MCID for ADAS-cog at 3 or 4 for early AD. Therefore, this protocol uses both MMSE and ADAS-cog to measure cognition at baseline, end of treatment and end of follow-up.

### 8.9.5 Assessment of caregiver distress

Previous studies reviewed in Chapter Four suggest that the NPI-D (caregiver distress scale) is a useful measure (Napryeyenko & Borzenko, 2007; Ihl et al., 2011; Herrschaft et al., 2012; Nikolova et al., 2013; Gavrilova et al., 2014). The Zarit Burden Interview and Zung Self-Rated Depression Scales have been used elsewhere in small studies (Hayashi et al., 2010; Okahara et al., 2010) but these do not separately assess the caregivers’ attitudes to the individual NPI symptoms. In addition, the Zung scale is not caregiver specific.

### 8.9.6 Sleep and night-time behaviour measures

Night-time motor activity disturbances will be measured using the Philips Respironics Actiwatch 2 Activity monitor actigraphy device (Philips, 2017). It is preferred that the participant with BPSD shall wear this waterproof device on the wrist for the entire run-in period and trial duration. The Actiwatch model uses actigraphy principles to assess activity patterns including sleep schedule variability, sleep quantity and sleep quality statistics. This device is the gold standard and well validated. Alternatively, the ActiGraph Corporation ActiGraph accelerometry monitor (http://actigraphcorp.com/) may be used, provided by RMIT SHBS Sleep medicine research group. If RMIT cannot provide these devices, they will be purchased directly from the United States. If the participant with BPSD cannot tolerate wearing the wristband for the full trial duration, it may be worn for five consecutive days per month. These data will be analysed separately.
Measurement of milestones of disease progression as a possible indicator of disease modification

For the issue of measurement of disease modification in AD, Mani (2004) believed that disease modification required the intervention to address the neurobiological processes that lead to cell death. However, Sampiao (2006) suggested that delaying a clinically meaningful milestone should also be included. Cummings (2007) agreed that there needed to be an impact on a clinically relevant milestone in addition to evidence of disease modification. Wesnes and Edgar (2014) also argued that biochemical, neuroimaging, electrophysiological and/or neuropsychological markers should be tracked if relevance to symptom and disease progression can be determined. Otherwise, the most accepted and validated question-based clinical scales should be used.

The present protocol includes measurement of impact on the milestones of: (1) decision to place the participant into residential care; and (2) conversion from mild severity to moderate severity dementia, or moderate to severe according to MMSE or ADAS-cog score and physician’s judgement. Decision to place the participant in residential care will be followed up by email and phone six months and one year after the treatment duration is completed, and analysed separately. Conversion from mild to moderate severity, or moderate to severe, will be assessed by numbers of participants who convert between baseline and end of treatment; and will be followed up by email and phone six months and one year after the treatment duration is completed. These data will be analysed separately.

Webster et al. (2017) recommended that optical serial structural MRI in a voluntary subgroup of participants was the best biological technique for assessing disease modification. As earlier trials had indicated that fewer participants were needed to fully power MRI studies compared to cognitive assessments, it was agreed that a subgroup of willing and able participants would be acceptable. As a separate analysis, participants will be invited to volunteer to participate in structural MRI assessments at baseline and end of treatment.

Safety assessments and AE monitoring

The monthly safety assessments will include blood tests, physical examination and assessments, questioning the caregiver about AEs and review of the daily diary, as follows:

Blood tests will include full blood count, kidney and liver function tests, lipid profile, platelet aggregation and serum K tests, to be carried out by a pathology laboratory. The physical examination will include blood pressure, body weight, body temperature, hand grip strength, oedema, jaundice and haematoma. These will be assessed by the trial investigators. Questioning will initially be open
in order to identify any unknown or unpredicted AEs, but followed by a series of questions on whether there has been any unusual bleeding, jaundice, myopathy or weakness, constipation or diarrhoea, changes in appetite or medication use, or changes in food and water intake.

Caregivers will be asked to use the daily diary (either hard copy or emailed version) to record the occurrence and details of any uncharacteristic behavioural events, changes in habits, physical events, AEs, and medication use. At the monthly assessments, caregivers will be asked to hand in their diaries to the trial investigators and these will be reviewed and discussed with the caregivers and participants, and analysed as AE data. The contact details of the investigators will be given to participants and caregivers in case of emergency or AE, and investigators will be made available to contact 24 hours a day.

The trial investigators will keep a record of all adverse effects and events, including type of event, dates started and resolved, severity and whether it should be considered a serious adverse event (SAE). Depending on the nature of the AE, a group decision will be made to determine the best course of action (no action; adjust treatment; discontinue treatment). A medically qualified trial investigator will attempt to assign causality of the AE or SAE as either unrelated, possibly, probably, definitely, or not assessable.

In the case of abnormal test results, the investigators will inform the caregiver/power of attorney and the primary physician, for discussion on appropriate measures to be taken. Changes that may indicate health risk will be brought to the attention of the person’s primary physician.

In the case of any SAE, these will be immediately reported to the RMIT University HREC Human Research Ethics Committee, followed by submission of a detailed report to the HREC and the TGA according to their guidelines. Participants will be identified by their ID codes to maintain confidentiality. All AEs will be followed up until the date the AE is determined to be resolved by the physician and caregiver. The participant and caregiver will be followed up via telephone and in person one week later to ensure that there are no further issues.

In the case of a fatality, the investigator will provide RMIT HREC and any other related ethics committee with details on the cause of death and a statement on its likelihood of being related to the intervention or other aspect of the trial, and any other information which might be relevant to the case, such as autopsy reports, post-mortem findings or medical history, if available.

If a participant has measurable improvements at the end of the treatment period, withdrawing from the intervention may pose a risk. Participants will be monitored for a follow-up period of four weeks by weekly phone calls or email to the caregiver to identify any post-study AEs.
8.9.8 Assessment of blinding credibility

The success of blinding will be tested at the end of the week 5 and week 24 assessments. The participant with BPSD will be asked to answer the question: “Which group do you think you are in? A. herbal medicine, B. placebo or C. don’t know”. The caregiver will be asked the same question. The responses will be recorded and analysed based on the method proposed by Bang et al. (2004).
<table>
<thead>
<tr>
<th>Assessment No.</th>
<th>Week No.</th>
<th>MMSE</th>
<th>NPI -12</th>
<th>NPI-D</th>
<th>CMAI</th>
<th>ADAS-cog</th>
<th>Clinical psych.</th>
<th>Actigraphy</th>
<th>Physical tests</th>
<th>AES</th>
<th>Blood tests</th>
<th>Review of diary</th>
<th>Blinding Credibility</th>
<th>Follow up AE questions by telephone</th>
<th>Milestone changes</th>
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<tbody>
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<td>Week 0 (screening)</td>
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<td>√</td>
<td>x</td>
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<td>Week 26 (1wk follow-up)</td>
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<td>9</td>
<td>Week 29 (1 month follow-up)</td>
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</table>
8.10 **Data collection and analyses**

Data will be entered into case record forms (CRFs) by the investigator or authorised personnel. Training sessions for data entry will be provided to all personnel prior to the screening and study commencement. All entries will be dated and initialled by the person who entered the data. Assessors and data collectors will be blinded to treatment allocation until after data analysis.

8.10.1 **Case report forms (CRFs)**

These will be developed according to the NHMRC Clinical Trials Centre Design principles for CRFs. The CRF includes details on participant demographics, eligibility checklist, general medical history, informed consent and authorisation documentation, concomitant medication tracking log, physical examination, vital sign measurements, device accountability log (per protocol), HM intervention accountability log (per protocol), HM intervention accountability log (per participant), research sample tracking, adverse event (AE) tracking log, severe adverse event (SAE) log (per participant), SAE log (per protocol), participant deviation/violation form, telephone and email contact documentation, subject off study form (completed, withdrawn, ineligible) and a note to file template. Standard templates from the University of Wisconsin-Madison were adapted for this purpose (UW Institute for Clinical and Translational Research, 2016).

8.10.2 **Data safety monitoring board**

CRFs will be checked by an independent blinded data safety monitoring board after each monthly assessment for safety information according to numbers and severity of AEs, and for quality, completeness and consistency of data entry. Members will include at least one statistician and at least one independent researcher and at least one clinician with knowledge of common AEs seen in people with BPSD. (NHMRC, n.d.).

8.10.3 **Access to source data and documents**

Only trial investigators will have access to the source data and outcomes of analysis of the data. The principal investigator will make available direct access to the source data and/or any other trial-related records upon request from the RMIT HREC or other regulatory authority, at any time during or after the trial.

8.10.4 **Data Quality Control and Quality Assurance**

Quality control will be applied to each stage of data collecting and handling to ensure accuracy and reliability. Any corrections made will be noted as amendments with details documented. The database will be updated and backups saved regularly throughout the study. Double-checking will be
carried out to ensure accuracy. Standard operating procedures will be developed to ensure consistent and accurate data entry into the database. Any changes made to previously entered data will be noted as amendments. Double-checking will be carried out to ensure accuracy. Descriptive statistics will be carried out to detect doubtful data, on each significant variable in the database, without unmasking the codes. Treatment codes may be broken if the data validation and editing processes are completed for each individual, using a code in the database.

The investigator will be available if requested by RMIT HREC or another regulatory authority, for quality assurance.

8.10.5 Data Handling and Record Keeping

All hard copy information of the participants (with BPSD and caregivers), including treatment allocation, assessments and other relevant information, will be recorded in or attached to the CRF, signed and dated by the investigator/personnel and stored in a secure place. All changes made to the CRF will be signed and dated by the personnel. The CRFs will identify participants only by their ID code. If the participant’s identity needs to be unmasked, for example if a SAE occurs, the investigator will obtain access to the treatment codes, with approval from the caregiver and/or physician. Details of the unmasking, and reasons will be documented by the investigator with endorsement from the caregiver and/or the physician.

8.10.6 Data analysis

Data analysis will be carried out by an independent statistician, who will also be blinded to participant allocation. Data analysis will be carried out by, or in collaboration with, RMIT University School of Mathematical and Geospatial Sciences.

Equivalence of baseline characteristics will be assessed using independent samples t-test or chi squared tests as appropriate. Outcome measures with continuous data will be analysed using the General Linear Model as appropriate for baseline, at each assessment point and follow-up. The intention-to-treat (ITT) analysis will be applied to all randomised participants, and per-protocol analysis of completers will be conducted. Outcomes with categorical data, i.e. numbers of dropouts and AEs, will be analysed using chi-square or Fisher exact tests as appropriate. Data analysis will be conducted using SPSS or other statistical software.

Between-group differences in baseline NPI, NPI-D and MMSE data will be examined by ANOVA and further by ANCOVA, with adjustments for sex, age, years of education, ApoE ε4 carriers versus non-carriers, smoking, BMI, and daily energy intake approximated from a description provided by the caregiver. The General Linear Model will be utilised.
The ITT population will be comprised of randomised participants who complete at least one post-baseline NPI-12 and NPI-D assessment. Efficacy analysis will be based on the ITT population. As discussed in Chapter Seven, use of the last observation carried forward (LOCF) method can introduce a bias favouring the group with more dropouts, as symptoms typically worsen over time in dementia. The present protocol uses a similar approach to the memantine study by Van Dyck et al. (2007). A mixed-effects model repeated measures (MMRM) approach was chosen as it is theoretically more robust than LOCF as a method of imputing missing data. This approach was reported to provide superior control of type I and type II errors (Van Dyck et al., 2007). Primary efficacy analysis will also be conducted using the LOCF approach for missing data, with post-baseline data carried forward. Additional supportive analysis will be conducted using the observed cases (OC) approach. These results will be reported alongside the MMRM results for comparison.

8.10.7 Secondary and subgroup analysis

This section details further statistical analysis that will be undertaken secondarily to the primary aims of the RCT.

8.10.7.1 APOE genetic testing

APOE genetic testing results will be used as a covariate for subgroup analysis. Data for participants who tested positive for the APOE-ε4 genotype will be compared with data for the APOE-ε2 and APOE-ε3 participants.

8.10.7.2 Psychological factors of the person with BPSD

Based on the results of the initial psychological assessments, these data will be used as a covariate for subgroup analysis of additional mood and psychological factors which could influence trial outcomes.

8.10.7.3 Psychological factors of the caregiver

Psychological factors of the caregiver, including incidence and severity of depression, stress and anxiety will be used as a covariate for subgroup analysis, including any associations with incidence and severity of the NPI domain symptoms in the person with BPSD.

8.10.7.4 Medication use by the caregiver

Based on the diaries of daily medication use by the caregivers, secondary analysis will investigate any associations in medication use and responses to the NPI questions. Also, any association between caregiver medication use and participant with BPSD concomitant medication use will be investigated.
8.10.7.5 Influence of caregiving factors on decision to enrol the participant and caregiver influence on trial outcomes

As a result of the caregiving role, a caregiver may experience distress leading to anxiety and depression that may require treatment (Karlawish et al., 2001). Caregiver distress and depression may also affect caregiver decision-making (Karlawish et al., 2001). Karlawish et al. (2001) reported that the greater the level of caregiver stress, the less likely the caregiver would allow the patient to enrol in a clinical trial. The potential influence of caregiving factors was addressed in the present trial design. As a separate investigation of recruitment records, differences between caregivers who enrol compared to those who decide not to enrol or decide to drop out before the end of treatment will be analysed. This is aimed to provide useful information regarding generalisability of results and considerations for future trial designs involving caregivers.

8.10.8 Data storage and security

All CRFs and other paper and electronic documents will be stored for 15 years after completion, at RMIT Bundoora, in accordance with the TGA Note for Guidance on Good Clinical Practice (TGA, 2000). At the end of this period, paper documents will be shredded and electronic documents will be permanently deleted, in accordance with RMIT procedures. Storage will involve locked filing cabinets in secure spaces and password-protected files. Access will only be available to authorised personnel involved in the research. Data will not be reused in other projects. Any confidential or participant identifying information will remain undisclosed, unless permission is given by the participant or their legal representative, in accordance with the Privacy Act 1988 (Federal Register of Legislation, updated 2017) and the Victorian Information Privacy Principles (Office of the Victorian Privacy Commissioner, 2011).

8.10.9 Anticipated Outcomes of the study

This section justifies the conduct of the trial according to the present protocol.

8.10.9.1 Benefit to participants from the knowledge gained

The results of the trial and any associated analyses will be published in peer reviewed journals. The findings will benefit people with BPSD and their caregivers by assisting with decision-making regarding treatment options. In addition, detailed feedback of the overall results of the study, as well as each individual’s results, will be provided to the caregiver, the person with BPSD and their primary health care provider.
8.10.9.2  Avoiding limitations of previous dementia trials

Clinical trials testing disease-modifying drugs for NCDs have not yet produced satisfactory results. Knopman (2008) summarised clinical trial design issues in mild to moderate AD. These issues involved choice of diagnostic criteria, choice of outcome measures, treatment duration and analytic strategies. According to Liang et al. (2014) the main limitations of previous trials of Chinese herbal medicines for vascular dementia were insufficient follow-up duration, small sample sizes, lack of randomisation and stringent inclusion criteria, inadequate concealment of allocation and inappropriate cognitive measures. In addition, a systematic review of nine trials involving people with dementia (Smith et al., 2014) found that medical co-morbidities and concomitant medications were poorly reported. Also, as described in Chapter Four, previous reporting of NPI scores in Yokukansan clinical studies has been inconsistent, resulting in ambiguous data. Some studies only reported total NPI scores. Some reported all domain scores, while other studies reported a selection of domains but not all.

Of the trials summarised by Knopman (2008), the accepted diagnostic criteria for the inclusion was NINCDS-ADRDA, used together with the modified Hachinski Ischemic Index (Hachinski et al., 1974) to reduce the chance of including participants with significant cerebrovascular disease. Severity of dementia was generally determined according to a range of scores on the MMSE. The preferred trial design was a randomised, double-blind, placebo-controlled, parallel group for anti-AD drugs for mild to moderate AD. A Cochrane review (Birks, 2006) indicated that the pivotal AChEI trials were five to six months in duration (Winblad et al., 2006; Tariot et al., 2000; Raskind et al., 2000; Gauthier et al., 2002). Table 8.11 shows limitations of previous clinical trials and proposed strategies to overcome these limitations in the present protocol.
Table 8.11: Limitations of previous AD intervention trials and strategies to overcome these

<table>
<thead>
<tr>
<th>No</th>
<th>Limitation of previous trials</th>
<th>Strategy to overcome limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Inappropriate choice of diagnostic criteria</td>
<td>Participants required to have specific NPI domain symptoms at baseline</td>
</tr>
<tr>
<td>2</td>
<td>Inappropriate choice of outcome measures</td>
<td>Selection of measures that are sensitive to change and specific to the putative effects of the test intervention; including clinically meaningful milestones; choice of appropriate cognitive measure (ADAS-cog)</td>
</tr>
<tr>
<td>3</td>
<td>Inappropriate treatment duration</td>
<td>Treatment duration will be 24 weeks based on findings from systematic reviews</td>
</tr>
<tr>
<td>4</td>
<td>Inappropriate analytic strategies</td>
<td>ITT with MMRM</td>
</tr>
<tr>
<td>5</td>
<td>Insufficient follow-up duration</td>
<td>Include 1 month, 6 month and 12 month follow-up assessments</td>
</tr>
<tr>
<td>6</td>
<td>Small sample sizes</td>
<td>Sample sizes and power calculations to be based on findings from systematic reviews</td>
</tr>
<tr>
<td>7</td>
<td>Risks of bias</td>
<td>Trial designed for low risk of bias, including blinding credibility assessment</td>
</tr>
<tr>
<td>8</td>
<td>Poor reporting of comorbidities and concomitant medications</td>
<td>Detailed collection and reporting of these</td>
</tr>
<tr>
<td>9</td>
<td>Inconsistent reporting of NPI scores</td>
<td>Total NPI-12 scores and all domain scores will be reported at baseline and end of treatment</td>
</tr>
</tbody>
</table>

8.11 Discussion of this clinical trial protocol

Research into complementary medicines has received criticism for conduct of trials designed to test biologically implausible interventions with low prior probability. Other criticisms have focussed on conduct of trials with troublesome methodologies, such as lack of adequate controls or unsuccessful blinding (Colquhoun & Novella, 2013; Su et al., 2015; Ernst & Singh, 2008; Chen et al., 2014; Shang et al., 2007). This protocol aims to produce a high quality clinical trial evaluating the efficacy, safety and tolerability of the combined G. biloba extract EGb 761® and multi-herb formula Yokukansan, for management of BPSD in an Australian setting. The protocol also aims to address limitations of previous trials of BPSD. The study will be a randomised, participant, caregiver and assessor blinded, placebo-controlled clinical trial with 24 weeks treatment period.

8.11.1 Strengths of this study

This trial was designed to suit people with mild to moderate dementia. It requires consent from the participants’ legal decision maker and includes participation of the caregiver. The trial intervention is a combination of two well-studied interventions. The results of the trial will provide high quality evidence of the efficacy, safety and tolerability of the combination of Yokukansan and EGb 761® for the management of BPSD. The findings will contribute to a body of evidence which could translate into public health guidelines and evidence-based recommendations to health professionals regarding treatment options for BPSD. This is the first study to test the effect of the combined interventions. It is also the first study to test the effects of these interventions in an Australian setting.
population, and importantly, it is the first study specifically designed to take into account the increase in placebo effect sizes over time in NPI scores, as detailed in Chapter Seven. The study will be conducted in accordance with the guidelines of the Declaration of Helsinki and will be approved by the institutional review boards of the participating centre. Written informed consent will be provided from all participants and/or their legal guardian.

8.11.2 Limitations of this study

One limitation of the present trial is that it is possible that the standard dosages of EGB 761® or Yokukansan will not be suitable for an Australian context due to differences in the test populations in different countries. The dosages of EGB 761® are well established and have been well-tolerated long-term in US participants (DeKosky et al., 2008). Therefore, it is likely that this dose is applicable in the Australian setting.

Dosages of Yokukansan are well established in Japanese populations but not in European or US populations. There may be differences between the Japanese and Australian populations with regard to acceptability and tolerability of this component of the intervention. The present protocol uses the dosages recommended by the manufacturers. An issue of Yokukansan is that there have been no other studies to determine an optimal dose in non-Japanese populations. The dose for Yokukansan in the present protocol is based on dosages typical for a Japanese population. The present trial allows for the dose to be reduced from 7.5g per day to 5g per day, at the discretion of the caregiver and physician, to reduce the risk of liquorice-induced hypokalaemia. This is consistent with the clinical studies conducted in Japan and the manufacturer’s instructions. However, it is possible that the dosages commonly used in Japan will be below a therapeutic level for many Australian participants with BPSD, considering differences in mean body mass between the two populations. A review of weight-based dosing strategy found that the type of medication, clinical indications and physiological factors may determine applicability of weight-based dosing (Pan et al., 2016). However, it is unclear whether weight-based dosing or fixed dosing would be better for determining dosages of EGB 761® and Yokukansan for management of BPSD. It is possible that differences in pharmacokinetics, diet, concurrent medications and co-existing medical conditions in the Australian participants could impact on the therapeutic dose of Yokukansan. The present protocol describes the first study to test Yokukansan in a non-Japanese population, and is designed in accordance with the existing literature and with the major consideration of liquorice-induced hypokalaemia risk reduction.

To further reduce the chance of hypokalaemia, all caregivers will be provided with instructions on including foods naturally containing potassium in the diet, as well as considering the optional KCl
supplement. A confounding factor is that the caregivers and participants with BPSD could pay closer attention than usual to the preparation of meals and the eating habits of participants with BPSD, and make improvements to their diet. This new focus on a healthy diet could affect the mood and behaviour of the person with BPSD and the caregiver.

In addition, the protocol includes an oral potassium supplement. The dosage of the potassium supplement is below the recommended daily intake but it has not been established that taking a potassium supplement could affect the incidence of liquorice-induced hypokalaemia. It is expected that the comprehensive monitoring of AEs during this trial will provide new information on the safety of the combination of EGB 761® and Yokukansan, and will also contribute to determining the effect of potassium supplementation on liquorice-induced hypokalaemia associated with Yokukansan.

Another option could have been to create a modified Yokukansan with reduced 18β-glycyrrhetinic acid, in order to reduce the risk of liquorice-induced hypokalaemia. However, since 18β-glycyrrhetinic acid is considered to be a valuable ingredient for its specific effects on treating BPSD it was decided to retain this ingredient for the present protocol. Alternatively, a novel formula could be designed and tested based on the herbs frequently cited in the systematic review and the classical literature analysis, which also have shown convincing evidence of effects on BPSD in the experimental literature.

8.11.3 Transferability and generalisability of the study results
The transferability and generalisability of findings from the proposed RCT were important considerations. The protocol aimed to address the need for research that directly impacts on public health. The study includes a sample of Australians with BPSD in close to a real-world context, as people with common comorbidities and concomitant medication use may be included, unless there is specific reason to exclude from the study due to likelihood of safety risks.

It is likely that the combination of EGB 761® and Yokukansan will be safe and acceptable, as these products are popular and commonly used already. It is also likely that the study findings will be of international interest. If a benefit is detected, this combination therapy may become a treatment option for BPSD.

However, ethnic and genetic variability in drug metabolism could mean that the Australian participants respond differently to the interventions than participants from the previous trials. Pharmacogenomic studies with AChEIs or memantine, or with a combination therapy using non-cholinergic drugs, revealed that the therapeutic response in AD is genotype-specific. Generally,
participants with the APOE-4/4 genotype, alone or in combination with other deleterious polymorphic variants, were the worst responders (Cacabelos, 2005). The frequency of the ApoE ε4 allele differs internationally and genetic variations might also affect inflammatory, excitotoxic, and oxidative components of AD (Cummings et al., 2011). It is possible that the proposed Australian participants will have different responses to the interventions compared to the participants of the previous studies, due to different prevalence of genetic polymorphisms, or other differences between the populations. In addition, differences in language, cultural factors, education, general health and standard of care, as well as nutrition and diet might impact on responses to the interventions in the present trial. The biology of AD may also differ among the world’s populations (Cummings et al., 2011).

The findings of the present study would therefore be more generalisable to populations similar to the Australian sample, which could include US, European and UK populations. Since BPSD are very common, difficult to treat and are a substantial cause of distress, the results of the present study are likely to impact on treatment options for Australians as well as globally.

Effects of the intervention on maintenance and stability of cognition will provide important information. If there is a benefit on BPSD, the effects of combining the intervention with potassium could also lead to important safety information on whether this could reduce the incidence or severity of liquorice-induced hypokalaemia.

The results of the study will contribute to the body of evidence on the efficacy, tolerability and safety of herbal medicines for management of BPSD. The knowledge gained will translate to better informed decision-making by health professionals, people with dementia and their caregivers when choosing treatment options.

8.12 Implications and conclusions from this clinical trial protocol
Findings from the previous chapters of this thesis have highlighted the need to determine better treatment options for BPSD, and have suggested that the combination of EGb 761® and Yokukansan, with an optional potassium supplement, is likely to be efficacious, safe, acceptable and well-tolerated. This study uses a conservative dose of EGb 761® and Yokukansan, indicating that conduct of the trial would produce useful safety data for the standard dosages of these products in Australian participants. In addition, the provision of an oral potassium supplement will provide data on whether this could prevent or reduce the incidence and severity of liquorice-induced hypokalaemia for people who regularly consume standard doses of Yokukansan.
The study will contribute to research on the development of novel combination therapies, as results could be used to compare whether the proposed combination showed advantages over the monotherapies. Future research on natural products could aim to determine which component or components of the HMs are responsible for any clinical effects, and determine optimal therapeutic doses.
CHAPTER NINE SUMMARY OF ALL EVIDENCE, GENERAL DISCUSSION AND FUTURE DIRECTIONS

9.1 Summary
This project aimed to provide a comprehensive understanding of the use of HMs for management of BPSD, based on the contemporary clinical trial literature on HMs, the classical Chinese medical literature, and the in vitro and in vivo experimental literature. The project also aimed to identify issues, gaps and limitations in the existing research, propose recommendations to address these, and to develop a protocol for a high quality RCT which could test the efficacy of an HM intervention for the treatment of BPSD.

9.2 Synthesis of findings
The original descriptions of AD included behavioural symptoms as prominent manifestations of the disease (Alzheimer, 1906) although the contemporary definition and concept of BPSD were not published until 1999. These symptoms included ‘disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia’ (Finkel & Burns, 1999). The understanding of the complex and multifactorial aetiologies and pathologies related to BPSD has progressed since these publications, while the clinical symptoms have remained broadly consistent.

As reviewed in Chapter One, BPSD can have a profound impact on people with NCDs and their communities, and are associated with increased institutionalisation and decline in independence. For most NCDs, there is no conclusive evidence of a cure or of any intervention showing disease modifying benefits. Previous disease modifying drug trials for AD have largely shown negative results and have also been limited by methodological issues (Wesnes et al., 2014; Cummings, 2011). Currently, for management of BPSD, non-pharmacological interventions are preferred, but these may be less convenient than oral interventions or require resources that are not available (de Oliveira et al., 2015). The oral interventions AChEIs and memantine offer modest benefits for management of cognitive symptoms and BPSD. Benefits on cognition appear to be most pronounced after approximately six months of treatment and significant benefits on cognition have been found to remain at one year (May et al., 2017). It is likely that effects of these interventions would follow a similar trajectory for BPSD. More recently, combination therapies, including AChEIs combined with memantine, have received research attention as possible options for improved management of cognitive symptoms and BPSD, and this combination has shown some benefits over monotherapy (Matsunaga et al., 2015).

As described in Chapter Two, Chinese medicine has a long history of considering mood and behavioural disturbances to be manifestations of physical disease that may be treated with oral
natural product interventions (Willmont, 1998). Since 1958, efforts to promote Chinese medicine, including the use of HMs, have increased in China (Unschuld, 1985, p. 251) and more recently the popularity of Chinese medicine and HM has increased around the world, including in Australia (Zhang et al., 2008). Research on the effects of HMs on BPSD has been published since at least the 1980s (Hara, 1984; Chatterjee & Nolder, 1989; DeFeudis, 2003). A substantial number of clinical and experimental studies has been conducted (Ikarashi & Mizoguchi, 2016; Savaskan et al., 2017). The Chinese herbal medical literature contains recommendations of multiple herbs to treat multiple symptoms. Investigation of the contemporary Chinese medicine clinical guidelines, described in Chapter Two, indicated that BPSD is a new concept in Chinese medicine. These guidelines typically have specified HMs for AD or other dementias based on traditional use, consensus expert opinion or on Chinese medicine syndrome differentiation conjecture rather than on the clinical trial evidence. Contemporary scientific understanding is that symptoms of dementia are primarily due to pathological changes. Some of these pathologies can be modified with plant-based interventions.

Chapter Four detailed a systematic review and meta-analysis of clinical trials. Thirty-one controlled trials were identified which evaluated effects of the HMs, alone or in combination with pharmacological interventions, compared to placebo, usual care, a specific pharmacological intervention or a combination of placebo and the pharmacological intervention. Findings from the meta-analysis indicated that EGb 761® is efficacious and well-tolerated at 24 weeks, at the 1a level of evidence according to the Oxford Centre for Evidence-Based Medicine (OCEBM) hierarchy (Howick et al., 2011). The Yokukansan studies were generally of shorter duration, used smaller sample sizes and were more clinically heterogeneous. Results were mixed but improvements were suggested for the clinically important symptoms of agitation, aggression, irritability, aberrant motor activity and sleep disturbances. The level of evidence was judged as 2a according to the OCEBM hierarchy. The results for the other HMs were inconsistent and mainly based on single studies. Substantial differences were detected between these studies in participant characteristics, interventions tested and trial design. In addition, methodological and reporting issues precluded the ability to draw strong conclusions for these other HMs. Overall, of the various clinical trial design issues identified in Chapter Four, the variability in placebo effect sizes in NPI scores was an important consideration for the design of future RCTs.

Chapter Five described analyses of the classical Chinese medical literature. No specific term in the literature directly corresponded to BPSD. However, the terms for memory impairment and other related terms, combined with the terms for specific neuropsychiatric symptoms, showed that the terms for fear (jingji, jikong and others), worry and anxiety (youlu, yousi and others), sadness
(youchou, silu, beichou and others) and depression (yiyu and others) were frequently mentioned in
the literature together with memory impairment jian wang (健忘) and other related terms. The
earliest citations identified for plant-based medicines and other natural substances for treating
symptoms consistent with memory impairment with concurrent mood and behavioural symptoms
were from before the Tang dynasty (618CE), while the highest number of citations was identified
from the Ming and Qing dynasties (1369-1911CE).

The herbs most frequently cited in the classical literature were generally not the same as the
frequently tested HMs in the contemporary clinical trials reviewed in Chapter Four. Two key herbs
for BPSD identified in Chapter Four, Ginkgo biloba leaf and Uncaria rhynchophylla stem with hooks,
were not found in the dementia dataset analysed in Chapter Five. This indicated that G. biloba and
U. rhynchophylla were not traditionally used in China for the treatment of memory impairment.
However, G. uralensis, Poria cocos and Angelica species, which are ingredients of Yokukansan, were
ranked in the top ten frequently cited herbs in the classical literature dementia dataset for memory
impairment with behavioural or psychological symptoms. Notably, Yokukansan was originally a
paediatric formula. The original citations of Yi gan san from Xue Kai’s Bao Ying Cuo Yao (1555)
included descriptions of childhood irritability, restless sleep, shouting, excessive thirst, fear or
tendency to be easily startled, poor appetite or low food intake due to shock, fright or worry,
irregular daily routine of meals and day and night activity, slow reactions, excessive yawning and
tiredness, as well as childhood spasms, convulsions, contracture, paroxysm, grinding teeth, and
seizure in children with descriptions consistent with opisthotonus (Xue, 1555). Interestingly, these
descriptions showed similarities to BPSD or motor function disorders associated with the
extrapyramidal system.

Chapter Six overviewed the experimental in vitro and in vivo literature on G. biloba and Yokukansan
or its herb ingredients. This showed evidence of multiple compounds present in EGb 761® and
Yokukansan or relevance for treatment of BPSD. EGb 761® was the most extensively studied G.
biloba leaf extract. It contains three main groups of active compounds of relevance to BPSD:
flavonoids, terpenoids and organic acids. The flavonoids and the terpenic lactones Ginkgolides A and
B and bilobalide have been shown to reach the central nervous system and brain after oral
administration in animal models (Ude et al., 2013). The main activities of relevance to BPSD were
antioxidant, neurotransmission modulation, neuroendocrine regulation and upregulation of
neurotrophic factors. Of the herbs contained in Yokukansan, U. rhynchophylla and G. uralensis have
received substantial research attention and showed important mechanisms related to BPSD. Of the
numerous active components of Yokukansan of relevance to BPSD, geissoshizine methyl ether and
18β-glycyrrhetinic acid have received substantial attention and have shown blood-brain barrier permeability after oral administration (Imamura et al., 2011; Tabuchi et al., 2012). There is evidence that Yokukansan acts on neurons and various glial cells that surround them, which might assist to maintain neuronal function. For both EGb 761® and Yokukansan, the main effects reported in animal models were anti-aggression-like, antidepressant-like, anxiolytic-like as well as reducing cognitive impairments, mental stress and abnormal motor activities. Overall, both EGb 761® and Yokukansan are thought to exert their effects via the multiple compounds acting on multiple targets.

Chapters One to Six identified that there has been considerable international interest in the investigation of natural products for management of AD and BPSD. A substantial part of this interest is focussed on whether the traditional medicines from China and East Asia could provide leads for effective treatments. The contemporary Chinese guidelines and text books include recommendations for herbal formulae for treatment of AD, although these recommendations appear to be based on traditional clinical reasoning processes rather than the contemporary clinical trial evidence. The World Federation of Societies of Biological Psychiatry guidelines include EGb 761® for symptomatic treatment of AD dementia (Ihl et al., 2015) and the Japan Geriatrics Society Working Group recommends Yokukansan for treatment of BPSD in AD (Kojima et al., 2016; Takayama & Iwasaki, 2017). Yokukansan has been approved by the Japanese Ministry of Health, Labour and Welfare, and prescriptions are subsidised by the Japanese National Health Insurance Plan (Takayama & Iwasaki, 2017). Overall, these HMs have been frequently studied in the clinical trial and experimental literature and have shown plausibility for being effective. It was difficult to determine the plausibility of the clinical effectiveness of the herbs cited in the classical Chinese literature or the Chinese medicine guidelines.

Based on the findings of Chapters One to Six, a strong case was made for the conduct of a placebo-controlled trial to test the efficacy, tolerability and safety of an HM intervention for BPSD. As the number of people with BPSD is expected to rise globally including in Australia, it is of great importance to propose new treatment options, to then test these using rigorous design methodologies and report the results comprehensively and accurately. Stronger conclusions may then be drawn.

Chapter Seven further explored the issue of variable placebo effect sizes in BPSD, through a systematic review and meta-analysis of placebo group data from published RCTs. The meta-analysis showed that the placebo effect sizes for total NPI scores have increased over time, which could lead to increased chance of Type II error if studies are not adequately powered. Extensive subgroup and meta-regression analysis could not determine the reason for the increase in placebo effect sizes, but
these findings were consistent with reported increases in placebo effect sizes over time in other psychiatric conditions including schizophrenia and depression (Walsh et al., 2002; Rief et al., 2009; Kemp et al., 2010; Alphs et al., 2012; Klein et al., 2007; Jones et al., 2009). Chapter Seven recommended that future placebo-controlled studies which use NPI should calculate sample sizes based on data from the more recent studies published from 2009 onward.

Chapter Eight detailed the design of a clinical trial protocol for testing a HM intervention for treatment of BPSD. The herbs selected for testing were chosen based primarily on the clinical trial and experimental evidence. The classical literature analysis of herbs for memory impairment and BPSD did not result in as strong a rationale for further investigation of the herbs identified. Based on the available data, the clinical and experimental studies suggested that either Egb 761® or Yokukansan would be likely to produce clinically meaningful results in a well-designed RCT. Since combination therapies have shown advantages for management of BPSD and other chronic conditions including diabetes, HIV, cancer and cardiovascular disease, and it appears likely that the combination of Egb 761® with Yokukansan would be safe and acceptable, and act via different mechanisms, the protocol was designed to test the combination of these two popular existing products. Safety as an important consideration for the clinical trial and informed the inclusion and exclusion criteria and specific instructions for comprehensive and regular adverse events (AE) monitoring. It also included an optional potassium chloride supplement. This has not been used in previous studies and would provide useful safety data to test whether this provision could reduce the incidence or severity of liquorice-induced hypokalaemia in people with dementia taking Yokukansan.

The protocol was the first to test the combination of the two well-known interventions Egb 761® and Yokukansan. However, it is likely that these products have been combined in daily use, as Egb 761® is easily available over the counter including at supermarkets in many countries, while Yokukansan was reported to be the fourth most frequently used kampo product in Japan (Uezono et al., 2012) and is also easily available. It is possible that there may be a risk of unwanted interactions when combining these formulations together, although the protocol used a conservative dose of both products. AEs will be closely monitored and reported. It is also possible that the quantities are below a therapeutic dose for an Australian setting, due to differences in the test populations. If so, this study would nonetheless provide important safety data which would contribute towards calculating therapeutic doses of HMs, including kampo products for non-Japanese populations.

9.3 Research questions and main results

The principal research questions and main results of this project were as follows:
9.3.1  What is the current clinical trial evidence for the use of HMs for management of BPSD?

The HM with the strongest evidence from meta-analysis of placebo-controlled RCTs was EGb 761®. Based on the results of the systematic review of clinical trials in Chapter Four, there is evidence of efficacy for EGb 761® for NPI score reduction after 22 to 24 weeks treatment, with clinically meaningful effect sizes. These studies and others detailed in Chapter Two indicated that EGb 761® is well-tolerated and safe. The evidence for Yokukansan was primarily based on other types of clinical studies, as well as experimental studies and widespread use. Yokukansan was not superior to placebo after four weeks in the only placebo-controlled study. However, this trial used NPI-Q which is not as sensitive as the NPI, and also reported a larger than expected improvement in the placebo group, which could have increased the chance of a false negative result. In addition, the treatment duration might have been too short to allow for the intervention to exert any meaningful effects on BPSD. Previous randomised comparative studies have suggested that Yokukansan is equally effective as the pharmacotherapies commonly used in Japan for managing BPSD, at four to 12 week treatment durations. Importantly, the evidence of the risk of liquorice-induced hypokalaemia in people with BPSD means that monitoring of serum potassium levels is required. In a systematic review of East Asian traditional medicine for geriatric conditions, Takayama et al. (2017) reported that hypokalaemia could occur in 6% of cases. The clinical trial evidence for the other HM interventions was based on single studies. The strength of the evidence for these was limited by the lack of replication as well as small sample sizes, short treatment durations, inconsistent reporting between studies of dropouts and adverse effects, and methodological issues including lack of blinding. These limitations meant it was difficult to draw conclusions regarding the efficacy, tolerability and safety of these other HMs.

9.3.2  Which herbs and herbal formulae were used for memory impairment and symptoms consistent with BPSD in the classical Chinese medical literature?

As described in Chapter Five, the analysis of the classical Chinese medical literature indicated the most frequently used herbs for BPSD were similar to the most frequently used herbs for age-related memory disorders consistent with contemporary descriptions of AD. There were occasional modifications to formulae but these were generally secondary to the main focus of treating the memory impairments. The most frequently cited formulae in the BPSD dataset were Gui pi tang (118 of 1603 citations) followed by Tian wang bu xin dan (66 citations). The most frequently cited herbs were fu ling or fu shen (1206 of 16042 citations), ren shen (917 citations), yuan zhi (812 citations) followed by gan cao (717 citations). When the results were grouped according to the citation corresponding to specific symptoms of the NPI, the most frequently...
cited symptoms were NPI-E: Anxiety (7787 of 16042 citations) and NPI-D: Depression (3699 citations). There were 276 herb citations for NPI-C: Agitation/Aggression, allowing for interesting comparison against the total BPSD dataset. The frequency rankings of the Agitation/Aggression herbs were modified according to the change in rank for the frequency of citations for treatment of agitation compared to the frequency of citations for the whole BPSD dataset. This new modified rank of herbs for agitation suggested *da huang*, *shan yao*, *yu zhu* or *huang jing* and *yu zhi zi* as the highest-ranking herbs for agitation. Many of the herbs on this modified list were traditionally considered to have purging actions and were used to ‘clear heat’ and ‘remove masses’. Although rarely stated explicitly in the Chinese literature for treatment of dementia, these pathologies could correspond with symptoms of bad-temperedness, irritability, agitation and aggression. These high-ranking herbs would be of interest for future research for effects on agitation or aggression associated with BPSD. Overall, the classical Chinese medical literature showed numerous citations of herbs for improving memory and cognition with concurrent behavioural or psychological symptoms. However, the current Chinese medicine clinical guidelines mainly focussed on memory, with few recommendations for BPSD. There was a lack of data for herbs believed to treat BPSD specifically.

One limitation was that it was difficult to determine the most suitable terminology for BPSD and the 12 NPI symptoms in the traditional Chinese language. Even in English, it is difficult to accurately define symptoms such as anxiety and depression, and these terms can have different subjective meanings. Overall, the classical literature analysis did not influence the final choice of HMs for further testing, as detailed in the clinical trial protocol. However, as shown in Figure 5.1, the formulae *Gui pi tang* and *Tian wang bu xin dan* typically share similar ingredients to *Yokukansan*. *Angelica* sp. (*dang gui*), *Glycyrrhiza* sp. (*gan cao*), *Poria cocos* (*fu ling*) and *Atractylodes lancea* (*bai zhu*) are commonly contained in *Gui pi tang*; while *Angelica* sp. (*dang gui*), *Glycyrrhiza* sp. (*gan cao*) and *P. cocos* (*fu ling*) are also typical ingredients of *Tian wang bu xin dan*.

**9.3.3 What is the experimental evidence for mechanisms of action of HMs for management of BPSD?**

Based on the results of the overview of experimental studies (Chapter Six), there is considerable evidence of multiple compounds contained in Egb 761® and *Yokukansan* exerting various activities associated with reductions in AD and other dementia pathologies, and evidence of effects on cognitive impairments and BPSD-like symptoms in animal models. Both HMs have been reported to contain compounds that cross the blood-brain barrier after oral administration. The strength of conclusions was limited by certain methodological
considerations of applying experimental results to effects in humans with BPSD. The risk of biases, including publication bias, was also not assessed. In addition, although these studies indicated that at least some of the ingredients of the HMs have shown activities of relevance to BPSD, this does not necessarily mean that the same effects would be exerted after oral administration in humans. In clinical studies of HMs, the concentrations of various compounds are likely to have been variable and the degree of absorption is not typically reported. Overall, the experimental evidence indicated plausibility of the HMs being effective for management of BPSD due to the numerous reported mechanisms. However, further rigorously designed and well-reported studies are required to determine the extent of meaningful transferability into clinical effects.

9.3.4 Which herbs and combinations of herbs showed the greatest promise of efficacy, tolerability and safety for BPSD?

Findings from the three main sources of evidence (clinical trial literature, classical Chinese medical literature and experimental literature) indicated Ginkgo biloba leaf and Yokukansan showed the greatest promise for management of BPSD. Further investigation of these HMs is recommended.

9.3.5 Which of these herbs show potential for use in clinical trials, and what is a suitable HM intervention for management of cognitive symptoms and BPSD?

Results of the previous studies identified that Ginkgo biloba leaf and the multi-herb formula Yokukansan showed potential for use in clinical trials. Based on these findings, the combination of the existing products Egb 761® and Yokukansan was chosen. This decision was based on the results of the previous studies. The clinical trial and experimental literature indicated plausibility of these interventions. Analysis of the classical Chinese medical literature did not lead to any specific herb or combination of herbs with as strong a case for further research attention. However, future studies could follow up on the investigation the frequently cited herbs in the classical literature.

9.3.6 How is this formula likely to work?

The formula of Egb 761® and Yokukansan is likely to work via multiple mechanisms acting on multiple targets. However, the amount of absorption in people with BPSD, the importance of the individual components and the extent of beneficial and adverse interactions remain largely unknown. These aspects require further research. The extent to which the effects of the HM interventions act via mechanisms related to the individual key compounds including geissoschizine methyl ether in Yokukansan, compared to the interaction between the various
compounds has not been determined. It is not known whether a modified or purified intervention would exert similar effects or reduce the incidence of adverse effects. Clinically, we expect that EGB 761® could have a beneficial effect on cognitive symptoms while Yokukansan could act on reducing agitation, aggression, anxiety and other BPSD. The observation of any negative interactions is not expected during the trial. The optimal dose of Glycyrrhiza uralensis is a known issue.

9.3.7 How could the effects of these herbs be measured?
A well-designed randomised, placebo-controlled clinical trial is the preferred method to test the effects of the herbal intervention in BPSD. In clinical trials, the NPI is a suitable measure of the 12 BPSD domains, while the Cohen-Mansfield Agitation Inventory is a suitable addition for specific assessment of agitation. Wrist actigraphy is a suitable objective measure for night-time and motor activity disturbances. MMSE and ADAS-cog could provide useful data on cognitive outcomes. In order to obtain clinically meaningful measurements a clinical trial is preferred to experimental models, due to the complexities of BPSD and the putative mechanisms of the HMs.

9.3.8 What are the issues in clinical trial design of HMs for BPSD?
As explored and detailed in Chapter Seven, variation in placebo effect size was identified as an important issue which could limit the strength of conclusions of clinical trials, unless the sample size was increased in order to reduce the risk of Type II error. Other issues include availability and blinding credibility of placebo controls of herbal medicine interventions, the influence of the caregiver on the results of the trial, obtaining informed consent in people with dementia, the risk of unwanted interactions between the herbal intervention and concurrent medications commonly prescribed to older Australians, and the issue of the relatively high incidence of potassium-induced hypokalaemia in older patients who take Glycyrrhiza uralensis.

9.3.9 What is an appropriate and ethical design of a clinical trial of the HM to assess its effects on BPSD and cognitive symptoms?
This question was addressed in Chapter Eight. A randomised, placebo-controlled clinical trial was designed to test efficacy, safety and tolerability of a HM intervention. The protocol combined the two well-known and well-studied HMs and used a conservative approach to determine dosages. For a clinical trial, the combination is novel. Each intervention has been well-tested and has shown an acceptable safety profile, with no major unwanted drug interactions reported, indicating that the combination is likely to be safe. The protocol involved the caregivers as a separate type of participant. Other important features of the trial were the focus on ethical conduct when involving people with dementia in scientific research, the aim to produce
meaningful outcomes and to address the problem of variable placebo effect sizes. The RCT was
designed to produce valuable safety data. Hypokalaemia data would be useful for the Australian
population and internationally.

9.4 **Strengths and innovative aspects of the project**

This project included the first comprehensive systematic review and meta-analysis of clinical trials
which tested HMs for management of BPSD. It also included the first research to identify and
investigate the substantial variability in placebo effect sizes in BPSD outcomes and the trend of
increasing placebo effect sizes over time in BPSD. This project included evidence from three main
sources: clinical trials, classical literature and experimental studies. This meant a strong rationale
could be formed to support the candidate HM intervention for further investigation in a clinical trial.

The main strengths of the project were as follows:

- Comprehensive systematic review and meta-analysis of clinical trials
- Comprehensive search of classical literature for evidence of historical use
- Search and review of experimental literature for triangulation
- Addressed issues and limitations of previous studies
- Addressed issues with commonly used outcome measures
- Rigorous clinical trial design suitable for conducting in Australia

9.5 **Limitations of the project**

The systematic review and meta-analysis of clinical trials were limited by the weaknesses of included
studies, including methodological issues, inadequate reporting, and diversity of the interventions
tested. In the case of EGB 761®, there is a lack of independently-funded studies. For the other HMs,
there has also been a lack of large-scale, high quality studies with adequate replication to allow for
meaningful meta-analysis.

The investigation and overview of experimental studies aimed to determine putative mechanisms of
the HMs for effects relevant to BPSD. Predictions of effects were limited by possible risks of bias of
the included studies including risk of publication bias. Risk of data fabrication and fake peer review
were considerations that limited the ability to draw strong conclusions. The extent to which these
factors might have played a role in the results of published experimental studies of HMs for BPSD is
yet to be determined.
9.6 Implications for clinical practice

Global emphasis on evidence-based practice means that the clinical relevance of HMs for BPSD will depend on further results of well-designed and internationally recognised clinical trials. EGb 761® appears to be efficacious and well-tolerated but further independently funded research is needed before adding this HM to major international clinical guidelines. There is a need for better clinical guidelines in medicine and health care in general and not only limited to management of BPSD. An important problem identified by Colquhoun (2017) is that in many cases no good treatment exists yet recommendations are still made. While effective treatments for BPSD are limited, new interventions, including HMs, should only be added to guidelines for BPSD management if the evidence clearly shows specific benefit.

Chinese medicine guidelines need to allow for reform of recommendations as new evidence arises. Interventions that do not have a long history of traditional use, but show evidence of benefit, could be added to the guidelines. In addition, when a HM is included in a CM guideline but does not have a strong history of use in the classical literature, there needs to be an explicit reason for its inclusion such as clinical trial research. Importantly, as Chinese medicine aims to move towards evidence-based practice, there is a need to test the clinical relevance of prescribing treatments according to the traditional clinical reasoning processes, such as syndrome differentiation. Contemporary Chinese medicine clinical guidelines typically recommend partially individualised treatments according to these classifications, although these are not well-supported by evidence of benefit. Syndrome differentiation could be incorporated into clinical trial study designs through inclusion and exclusion criteria, subgroup analyses and/or flexibility in determining the test interventions. If there is no evidence of benefit for determining treatment prescriptions according to these categories, guidelines should be modified to reflect this. Emphasis should be placed on differences in patient constitution, presenting signs and symptoms, and any other factors which might be important in predicting response to different treatments, with the long-term aim of development of individualised treatment guidelines which are evidence-based.

In Australia, difficulties in assessing the efficacy of complex complementary medicine products have led to recommendations for more stringent regulations for the Therapeutic Goods Administration (Harvey, 2017). These could allow Australians to better understand the evidence to support the various commercially available HM products, and to therefore make better informed decisions about the purchase of HMs for management of BPSD.
9.7 Future research directions

This project revealed a number of important knowledge gaps regarding the efficacy, tolerability and safety of HMs for BPSD, which should be the focus of future research. A number of issues and limitations were also identified, which need to be addressed in order to improve the quality and reliability of future studies.

This thesis proposes that the focus for future research should be to conduct the clinical trial as detailed in Chapter Eight. Concurrently, more research into hypokalaemia would assist with determining the safety of liquorice use in people with BPSD. Findings from the clinical study could assist to determine any potential risk factors or safety precautions which could reduce the risk of liquorice-induced hypokalaemia in people taking HMs for BPSD. Research is needed into whether body mass makes a difference, whether Potassium chloride supplementation makes a difference, and whether the formula should be modified to reduce the glycyrrhetic acid component. This aspect should include a comprehensive systematic review of Glycyrrhiza case reports and clinical trials reporting adverse events, with the aim to develop informed guidelines on treatment and prevention of liquorice-induced hypokalaemia.

When selecting HM interventions for use in clinical trials, the selection should be informed primarily by the clinical research and experimental literature, but in the case of Chinese HM, the frequency of use in the classical medical literature and contemporary Chinese medicine clinical guidelines should also be taken into account. Importantly, there is a need for consistency between clinical research and clinical guidelines. Further research is needed on HM interventions that appear in contemporary CM guidelines but have not been subject to scientific research investigations.

9.8 General conclusions in relation to the research questions

The majority of people with dementia will experience BPSD. Management of BPSD is currently a particularly challenging aspect of caring for people with dementia. Herbal interventions could play a role in the development of new treatment options. The contemporary clinical trial and experimental literature largely focussed on the newly devised G. biloba leaf extract EGb 761® and the newly appropriated paediatric formula Yokukansan for the management of BPSD. These were the most frequently used HM interventions in clinical studies of HMs for BPSD. Excluding these, the most frequently tested herbs were Acorus gramineus Soland. or A. tatarinowii Schott. (shi chang pu) and P. ginseng C.A. Mey. (ren shen); Polygala tenuifolia Willd., or P. sibirica L. (yuan zhí); Rehmannia glutinosa Libosch. (shu di, sheng di); Ligusticum chuanxiong Hort. (chuan xiong); and Poria cocos (Schw.) Wolf (fu ling). Some of these herbs have also been described in the classical and contemporary Chinese medical literature for treatment of symptoms related to BPSD. Findings from
meta-analysis of well-designed RCTs indicated that EGB 761® improves clinically important outcomes in BPSD at 24 weeks. Lack of replication and methodological issues of the studies testing the other HMs limited the possibility to draw conclusions for these HMs. Variability in placebo effect sizes in BPSD is an important consideration for the design of future RCTs. The combination of EGB 761® and Yokukansan is likely to be safe, well-tolerated and acceptable for use by people with BPSD with agreement from their caregivers. It is recommended to test the efficacy of this combined intervention in a well-designed clinical trial.
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248


265


267


270


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277


278


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282


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Appendix Forest plot 1: Effect sizes within treatment groups of all included studies, in chronological order by publication year and in Groups 1 and 2 according to publication year
(Mean difference; fixed effect model; 95% Confidence intervals)
Appendix Forest plot 2: Effect sizes within treatment groups of all included studies, in chronological order by publication year and in Groups 1 and 2 according to publication year (Mean difference; random effects model; 95% Confidence intervals)
Appendix Forest plot 3: Results of meta-analysis at end of treatment (EoT) for active treatment versus placebo for all included studies, in chronological order by publication year and Groups 1 and 2 according to publication year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean Difference</th>
<th>IV, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3.1.1 Group 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean difference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-12.00 [-26.23, 2.23]</td>
<td></td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>-0.00 [-18.60, 14.40]</td>
<td></td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>-3.80 [-5.30, -2.31]</td>
<td></td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>-0.80 [-3.83, 2.23]</td>
<td></td>
<td>2012</td>
</tr>
<tr>
<td></td>
<td>0.50 [-0.37, 1.37]</td>
<td></td>
<td>2013</td>
</tr>
<tr>
<td></td>
<td>0.50 [-0.37, 1.37]</td>
<td></td>
<td>2014</td>
</tr>
<tr>
<td></td>
<td>0.50 [-0.37, 1.37]</td>
<td></td>
<td>2015</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1137</td>
<td>78.4%</td>
<td>2.98 [-2.54, 4.26]</td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 9.29, df = 10 (P = 0.08901), I² = 98%

Test for overall effect: Z = -2.98 (P = 0.00301)

<table>
<thead>
<tr>
<th><strong>3.1.2 Group 2</strong></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean difference</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2213 100.00%</td>
<td>2.45 [-3.01, 1.99]</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity:** Chi² = 35.25, df = 12 (P = 0.00004), I² = 65%

Test for overall effect: Z = 2.98 (P = 0.00301)

Test for subgroup differences: Chi² = 9.13, df = 1 (P = 0.004), I² = 87.7%

Note: excluding Tune et al. (2003) from pool due to significant baseline imbalance in total NPI scores.
### Appendix Forest plot 4: Results of meta-analysis at end of treatment (EoT) for active treatment versus placebo for all included studies, in chronological order by publication year

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment</th>
<th>Placebo</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
<th>IV, Random, 95% CI, Year</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.1.1 Group 1 (published 2000-2008)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McKie et al. 2000</td>
<td>28.2</td>
<td>15</td>
<td>41</td>
<td>21.4</td>
<td>14.2</td>
</tr>
<tr>
<td>Tariol 2003</td>
<td>18.7</td>
<td>14.5</td>
<td>76</td>
<td>15.6</td>
<td>14.7</td>
</tr>
<tr>
<td>Tune 2003</td>
<td>23.76</td>
<td>12.4</td>
<td>14</td>
<td>11.44</td>
<td>9.79</td>
</tr>
<tr>
<td>Peskind 2005</td>
<td>17.5</td>
<td>14.1</td>
<td>17</td>
<td>29.1</td>
<td>16</td>
</tr>
<tr>
<td>Peskind 2006</td>
<td>10.1</td>
<td>13.2</td>
<td>167</td>
<td>14.3</td>
<td>13</td>
</tr>
<tr>
<td>Winblad 2006</td>
<td>14.9</td>
<td>15.2</td>
<td>95</td>
<td>17.9</td>
<td>15.8</td>
</tr>
<tr>
<td>Mok 2007</td>
<td>11.4</td>
<td>9.4</td>
<td>20</td>
<td>10.4</td>
<td>11.3</td>
</tr>
<tr>
<td>Van Dyck 2007</td>
<td>20.8</td>
<td>17</td>
<td>134</td>
<td>18.8</td>
<td>16.4</td>
</tr>
<tr>
<td>Chappell 2007</td>
<td>13.36</td>
<td>16.4</td>
<td>81</td>
<td>16.09</td>
<td>18.9</td>
</tr>
<tr>
<td>Howard 2007</td>
<td>27.48</td>
<td>15.9</td>
<td>115</td>
<td>27.38</td>
<td>16.7</td>
</tr>
<tr>
<td>de Jong 2008</td>
<td>14.4</td>
<td>12</td>
<td>20</td>
<td>16.5</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>964</td>
<td>1643</td>
<td>45.0%</td>
<td>-1.62 [-4.96, 1.73]</td>
<td></td>
</tr>
</tbody>
</table>

Note: excluding Tune et al. (2003) from pool due to significant baseline imbalance in total NPI scores.

Test for overall effect: Z = 0.95 (P = 0.34)

| **3.1.2 Group 2 (published 2009-2015)** | | | | | |
| Enne 2010 | 11.3 | 14.6 | 50 | 17.3 | 15 | 50 | 4.2% | -6.00 [-10.60, -1.40] | 2010 |
| Bf FZS 2011 | 16.83 | 4.82 | 12 | 20.5 | 6.5 | 10 | 4.0% | -3.67 [-4.53, 1.19] | 2011 |
| Vercellotti 2011 | 29.6 | 11.4 | 26 | 38.5 | 19.6 | 17 | 1.6% | -8.99 [-19.20, 1.40] | 2011 |
| INI 2011 | 13.2 | 8.1 | 202 | 17 | 8.2 | 202 | 6.5% | -3.80 [-5.39, -2.21] | 2011 |
| Fox 2012 | 18.4 | 17.4 | 53 | 27.8 | 19.2 | 65 | 3.0% | -9.40 [-16.01, -2.79] | 2012 |
| Herrschaft 2012 | 12.2 | 6.9 | 200 | 14.6 | 6.4 | 202 | 6.7% | -2.40 [-3.70, -1.10] | 2012 |
| Hermann 2013 | 27.04 | 13.2 | 151 | 24.05 | 13.3 | 165 | 5.5% | 2.99 [0.07, 5.91] | 2013 |
| Niklova 2013 | 13.29 | 9.5 | 160 | 13.84 | 8.7 | 201 | 6.4% | -0.50 [-2.34, 1.24] | 2013 |
| Schwam 2014 | 7.84 | 11.3 | 89 | 10.2 | 12.9 | 100 | 5.1% | -2.36 [-5.61, 1.09] | 2014 |
| Tsai 2014 | 10.1 | 13.3 | 14 | 13.6 | 10.4 | 15 | 2.1% | 4.59 [-4.23, 13.23] | 2014 |
| Gardiol 2014 | 4.5 | 3.5 | 80 | 6.1 | 3.7 | 79 | 6.7% | -1.60 [-2.72, -0.48] | 2014 |
| van den Elsen 2015 | 27.8 | 13.1 | 23 | 23.9 | 16.8 | 24 | 2.1% | 3.99 [-4.69, 12.49] | 2015 |
| **Subtotal (95% CI)** | 1137 | 1170 | 55.0% | -2.13 [-3.57, -0.69] | |

Heterogeneity: Tau² = 3.13; CH² = 35.25, df = 12 (P = 0.0004); I² = 66%

Test for overall effect: Z = 2.91 (P = 0.004)

Total (95% CI) | 2101 | 2213 | 100.0% | -2.07 [-3.57, -0.57] |

Heterogeneity: Tau² = 8.41; CH² = 112.71, df = 23 (P < 0.00001), I² = 80%

Test for overall effect: Z = 2.70 (P = 0.007)

Test for subgroup differences: CH² = 0.98, df = 1 (P = 0.78), I² = 0%

Note: excluding Tune et al. (2003) from pool due to significant baseline imbalance in total NPI scores.
Appendix Forest plot 5: Results of risk ratio meta-analysis for numbers of dropouts at end of treatment (EoT) for active treatment versus placebo for all included studies, in chronological order by publication year (Mean difference; random effects model; 95% Confidence intervals)
Appendix Forest plot 6: Effect size of placebo groups at baseline versus end of treatment - subgroup analysis: Studies funded by manufacturer only.

(Mean difference; random effects; 95% Confidence intervals)

Interpretation: The phenomenon of larger placebo effect sizes in recent years remains when studies with independent grant and government funding are excluded from the pool.
Appendix Table 1: Results of meta-analysis for single study of NPI-Q scores

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean difference; 95% CI; Z value; (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo group: baseline vs EoT; n=65 at EoT</td>
<td>-1.90 [-3.55, -0.25]*, Z = 2.26 (P = 0.02)</td>
</tr>
<tr>
<td>Treatment group: baseline vs EoT; n=72 at EoT</td>
<td>-2.30 [-3.68, -0.92]*, Z = 3.27 (P = 0.001)</td>
</tr>
<tr>
<td>Treatment vs Placebo groups EoT (4 weeks); n at EoT (72,65)</td>
<td>-0.20 [-1.83, 1.43] Z = 0.24 (P = 0.81)</td>
</tr>
</tbody>
</table>

*significant

Reference for study: Furukawa et al. (2015)
CI: Confidence interval; EoT: End of treatment

Appendix Table 2: Results of meta-analysis of changes from baseline to end of treatment in total NPI scores in active treatment groups of studies testing oral interventions for management of BPSD

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n studies (n participants EoT in placebo groups); range of durations of treatment</th>
<th>Change in total NPI MD, 95%CI, RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Published 2000 - 2008</td>
<td>12 (978) 6-52wks</td>
<td>-1.15 [-3.68, 1.38]; 75%</td>
</tr>
<tr>
<td>Group 2: Published 2009 - 2015</td>
<td>13 (1137) 3-52wks</td>
<td>-4.85 [-6.50, -3.20]*; 76%</td>
</tr>
<tr>
<td>Combined: all studies</td>
<td>25 (2115) 3-52wks</td>
<td>-3.30 [-4.72, -1.89]*; 78%</td>
</tr>
</tbody>
</table>

BPSD: Behavioural and psychological symptoms of dementia; EoT: end of treatment; I²: Index of heterogeneity; MD: mean difference; NPI: Neuropsychiatric Inventory; RE: Random effects model; wks: weeks
* significant (p<0.05)

Appendix Table 3: Results of meta-analysis at End of treatment (EoT) in total NPI scores in active treatment groups vs placebo control groups of studies testing oral interventions for management of BPSD

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n studies (n participants EoT T,C); range of durations of treatment</th>
<th>EoT TvsC total NPI MD, 95%CI, RE; I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1: Published 2000 - 2008</td>
<td>12 (978,1056) 6-52wks</td>
<td>-0.71 [-4.18, 2.76]; 87%</td>
</tr>
<tr>
<td>Group 1: Published 2000 – 2008*</td>
<td>11 (964,1043) 6-52wks</td>
<td>-1.62 [-4.96, 1.73]; 86%</td>
</tr>
<tr>
<td>Group 2: Published 2009 - 2015</td>
<td>13 (1137,1170) 3-52wks</td>
<td>-2.13 [-3.57, -0.69]*; 66%</td>
</tr>
<tr>
<td>Combined: all studies</td>
<td>25 (2115,2239) 3-52wks</td>
<td>-1.74 [-3.29, -0.20]*; 81%</td>
</tr>
</tbody>
</table>

BPSD: Behavioural and psychological symptoms of dementia; EoT: end of treatment; FE: Fixed effects model; I²: Index of heterogeneity; MD: mean difference; NPI: Neuropsychiatric Inventory; NS: not specified; RE: Random effects model; wks: weeks
* excluding Tune 2003 from pool due to significant baseline imbalance in NPI scores
* significant (p<0.05)
Appendix Table 4: Combined n participants, mean, and SD baseline NPI scores from multiple groups for all 25 included studies, in groups according to year of publication

<table>
<thead>
<tr>
<th>Study ID</th>
<th>N participants at baseline in placebo group</th>
<th>Mean total NPI at baseline</th>
<th>SD total NPI at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>20.2</td>
<td>14.2</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
<td>20.5</td>
<td>14.7</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>8.79</td>
<td>9.79</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>29.5</td>
<td>15.5</td>
</tr>
<tr>
<td>5</td>
<td>107</td>
<td>19.6</td>
<td>15.8</td>
</tr>
<tr>
<td>6</td>
<td>198</td>
<td>12.2</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>91</td>
<td>16.1</td>
<td>18.9</td>
</tr>
<tr>
<td>8</td>
<td>200</td>
<td>21.6</td>
<td>9.9</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>9.5</td>
<td>6.5</td>
</tr>
<tr>
<td>10</td>
<td>165</td>
<td>17.5</td>
<td>16.4</td>
</tr>
<tr>
<td>11</td>
<td>131</td>
<td>23.6</td>
<td>16.7</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>7.1</td>
<td>6.7</td>
</tr>
<tr>
<td>13</td>
<td>12</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>14</td>
<td>101</td>
<td>17.4</td>
<td>15</td>
</tr>
<tr>
<td>15</td>
<td>22</td>
<td>31.1</td>
<td>19.6</td>
</tr>
<tr>
<td>16</td>
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<td>19</td>
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<tr>
<td>20</td>
<td>165</td>
<td>29.18</td>
<td>13.3</td>
</tr>
<tr>
<td>21</td>
<td>205</td>
<td>16.9</td>
<td>8.7</td>
</tr>
<tr>
<td>22</td>
<td>100</td>
<td>12.2</td>
<td>12.9</td>
</tr>
<tr>
<td>23</td>
<td>15</td>
<td>13.4</td>
<td>11.2</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
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<td>3.7</td>
</tr>
<tr>
<td>25</td>
<td>26</td>
<td>35.6</td>
<td>13</td>
</tr>
<tr>
<td>Combined</td>
<td>2355</td>
<td>19.1021</td>
<td>14.2455</td>
</tr>
</tbody>
</table>

NPI: Neuropsychiatric Inventory; SD: Standard deviation
(calculations were made using the online application at: https://www.statstodo.com/ComMeans_Pgm.php)
### Appendix Table 5: Combined n participants, mean, and SD baseline NPI scores from multiple placebo groups for included Group 1 studies, published from 2000 - 2008

<table>
<thead>
<tr>
<th>Study ID</th>
<th>n participants at baseline in placebo group</th>
<th>Mean total NPI at baseline</th>
<th>SD total NPI at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>20.2</td>
<td>14.2</td>
</tr>
<tr>
<td>2</td>
<td>105</td>
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<tr>
<td>3</td>
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<td>9.79</td>
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<tr>
<td>4</td>
<td>14</td>
<td>29.5</td>
<td>15.5</td>
</tr>
<tr>
<td>5</td>
<td>107</td>
<td>19.6</td>
<td>15.8</td>
</tr>
<tr>
<td>6</td>
<td>198</td>
<td>12.2</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>91</td>
<td>16.1</td>
<td>18.9</td>
</tr>
<tr>
<td>8</td>
<td>200</td>
<td>21.6</td>
<td>9.9</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>9.5</td>
<td>6.5</td>
</tr>
<tr>
<td>10</td>
<td>165</td>
<td>17.5</td>
<td>16.4</td>
</tr>
<tr>
<td>11</td>
<td>131</td>
<td>23.6</td>
<td>16.7</td>
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<tr>
<td>12</td>
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<td>6.7</td>
</tr>
<tr>
<td>Combined</td>
<td>1131</td>
<td>18.1833</td>
<td>15.0211</td>
</tr>
</tbody>
</table>

NPI: Neuropsychiatric Inventory; SD: Standard deviation

### Appendix Table 6: Combined n participants, mean, and SD baseline NPI scores from multiple placebo groups for included Group 2 studies, published from 2009 - 2015

<table>
<thead>
<tr>
<th>Study ID</th>
<th>n participants at baseline in placebo group</th>
<th>Mean total NPI at baseline</th>
<th>SD total NPI at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>12</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>14</td>
<td>101</td>
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<td>15</td>
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<td>31.1</td>
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<td>16</td>
<td>12</td>
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<td>204</td>
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</tr>
<tr>
<td>18</td>
<td>205</td>
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</tr>
<tr>
<td>19</td>
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<tr>
<td>21</td>
<td>205</td>
<td>16.9</td>
<td>8.7</td>
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<tr>
<td>22</td>
<td>100</td>
<td>12.2</td>
<td>12.9</td>
</tr>
<tr>
<td>23</td>
<td>15</td>
<td>13.4</td>
<td>11.2</td>
</tr>
<tr>
<td>24</td>
<td>80</td>
<td>11.6</td>
<td>3.7</td>
</tr>
<tr>
<td>25</td>
<td>26</td>
<td>35.6</td>
<td>13</td>
</tr>
<tr>
<td>Combined</td>
<td>1224</td>
<td>19.9511</td>
<td>13.4396</td>
</tr>
</tbody>
</table>

NPI: Neuropsychiatric Inventory; SD: Standard deviation
Appendix Table 7: Combined n participants, mean, and SD baseline ages of participants from multiple placebo groups for all 25 included studies, published from 2000 - 2015

<table>
<thead>
<tr>
<th>Study ID</th>
<th>n participants at baseline in placebo group</th>
<th>Mean age at baseline</th>
<th>SD age at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>73.9</td>
<td>6.4</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>84</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>202</td>
<td>77</td>
<td>8.2</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
<td>85.3</td>
<td>5.9</td>
</tr>
<tr>
<td>7</td>
<td>91</td>
<td>74.5</td>
<td>8.7</td>
</tr>
<tr>
<td>8</td>
<td>131</td>
<td>84.4</td>
<td>8.2</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>74.1</td>
<td>6.6</td>
</tr>
<tr>
<td>10</td>
<td>200</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>172</td>
<td>78.3</td>
<td>7.6</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>72.2</td>
<td>9</td>
</tr>
<tr>
<td>13</td>
<td>11</td>
<td>78.1</td>
<td>10.8</td>
</tr>
<tr>
<td>14</td>
<td>101</td>
<td>72.5</td>
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</tr>
<tr>
<td>15</td>
<td>12</td>
<td>68.6</td>
<td>6.35</td>
</tr>
<tr>
<td>16</td>
<td>26</td>
<td>66.6</td>
<td>7.4</td>
</tr>
<tr>
<td>17</td>
<td>204</td>
<td>65</td>
<td>9</td>
</tr>
<tr>
<td>18</td>
<td>77</td>
<td>84.4</td>
<td>6.6</td>
</tr>
<tr>
<td>19</td>
<td>205</td>
<td>64.9</td>
<td>9.4</td>
</tr>
<tr>
<td>20</td>
<td>187</td>
<td>75.1</td>
<td>6.9</td>
</tr>
<tr>
<td>22</td>
<td>79</td>
<td>63</td>
<td>7</td>
</tr>
<tr>
<td>23</td>
<td>100</td>
<td>73.5</td>
<td>7.5</td>
</tr>
<tr>
<td>24</td>
<td>15</td>
<td>77.3</td>
<td>6.6</td>
</tr>
<tr>
<td>25</td>
<td>26</td>
<td>78</td>
<td>7</td>
</tr>
<tr>
<td>Combined</td>
<td>2079</td>
<td>73.1228</td>
<td>10.7608</td>
</tr>
</tbody>
</table>

SD: Standard deviation
Note: Studies No 2, 3 and 21 excluded as mean (SD) age data were not reported for these studies (Tariot et al. 2001, Tune et al. 2003, Nikolova et al. 2013).
### Appendix Table 8: Combined n participants, mean, and SD baseline ages of participants from multiple placebo groups for included Group 1 studies, published from 2000 - 2008

<table>
<thead>
<tr>
<th>Study ID</th>
<th>n participants at baseline in placebo group</th>
<th>Mean age at baseline</th>
<th>SD age at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61</td>
<td>73.9</td>
<td>6.4</td>
</tr>
<tr>
<td>4</td>
<td>14</td>
<td>84</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>202</td>
<td>77</td>
<td>8.2</td>
</tr>
<tr>
<td>6</td>
<td>120</td>
<td>85.3</td>
<td>5.9</td>
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<td>7</td>
<td>91</td>
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<td>8</td>
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<td>84.4</td>
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<td>10</td>
<td>200</td>
<td>63</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>172</td>
<td>78.3</td>
<td>7.6</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>72.2</td>
<td>9</td>
</tr>
<tr>
<td>Combined</td>
<td>1036</td>
<td>75.9309</td>
<td>10.6874</td>
</tr>
</tbody>
</table>

SD: Standard deviation  
Note: Studies 2 and 3 excluded as did not report age data (Tariot et al. 2001, Tune et al. 2003)

### Appendix Table 9: Combined n participants, mean, and SD baseline ages of participants from multiple placebo groups for included Group 2 studies, published from 2009 - 2015

<table>
<thead>
<tr>
<th>Study ID</th>
<th>n participants at baseline in placebo group</th>
<th>Mean age at baseline</th>
<th>SD age at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>11</td>
<td>78.1</td>
<td>10.8</td>
</tr>
<tr>
<td>14</td>
<td>101</td>
<td>72.5</td>
<td>7</td>
</tr>
<tr>
<td>15</td>
<td>12</td>
<td>68.6</td>
<td>6.35</td>
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<tr>
<td>16</td>
<td>26</td>
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<td>7.4</td>
</tr>
<tr>
<td>17</td>
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<td>9</td>
</tr>
<tr>
<td>18</td>
<td>77</td>
<td>84.4</td>
<td>6.6</td>
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<tr>
<td>19</td>
<td>205</td>
<td>64.9</td>
<td>9.4</td>
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<td>20</td>
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</tr>
<tr>
<td>23</td>
<td>100</td>
<td>73.5</td>
<td>7.5</td>
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<td>77.3</td>
<td>6.6</td>
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<tr>
<td>25</td>
<td>26</td>
<td>78</td>
<td>7</td>
</tr>
<tr>
<td>Combined</td>
<td>1043</td>
<td>70.3336</td>
<td>10.0918</td>
</tr>
</tbody>
</table>

SD: Standard deviation  
Note: Study 21 excluded as did not report age data (Nikolova et al. 2013)  
Means calculated using the online application at statstodo web site:  
Appendix  Table 10: Numbers and proportions of dropouts in placebo groups of studies testing oral interventions for management of BPSD

<table>
<thead>
<tr>
<th>Study ID</th>
<th>First author, publication year</th>
<th>n dropouts (Placebo groups)</th>
<th>n participants at baseline (Placebo groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>McKeith 2000</td>
<td>10</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>Tariot 2001</td>
<td>19</td>
<td>105</td>
</tr>
<tr>
<td>3</td>
<td>Tune 2003</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>Peskind 2005</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>Winblad 2006</td>
<td>21</td>
<td>120</td>
</tr>
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<td>6</td>
<td>Peskind 2006</td>
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<td>202</td>
</tr>
<tr>
<td>7</td>
<td>Chappell 2007</td>
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<td>91</td>
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<tr>
<td>8</td>
<td>Napryeyenko et al, 2007</td>
<td>5</td>
<td>200</td>
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<tr>
<td>9</td>
<td>Mok 2007</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>van Dyck 2007</td>
<td>46</td>
<td>172</td>
</tr>
<tr>
<td>11</td>
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<tr>
<td>13</td>
<td>Wang 2009</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td><strong>Total Group 1</strong></td>
<td><strong>179 dropouts</strong></td>
<td><strong>1166; (15.35% of placebo participants dropped out)</strong></td>
</tr>
<tr>
<td>14</td>
<td>Emre 2010</td>
<td>20</td>
<td>99</td>
</tr>
<tr>
<td>15</td>
<td>Vercelletto 2011</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>16</td>
<td>Bi, MT et al, 2011</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>17</td>
<td>Ihl et al, 2011</td>
<td>12</td>
<td>204</td>
</tr>
<tr>
<td>18</td>
<td>Herrschaft et al, 2012</td>
<td>5</td>
<td>205</td>
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<tr>
<td>19</td>
<td>Fox 2012</td>
<td>15</td>
<td>77</td>
</tr>
<tr>
<td>20</td>
<td>Herrmann 2013</td>
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<td>187</td>
</tr>
<tr>
<td>21</td>
<td>Nikolova 2013</td>
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<td>205</td>
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<tr>
<td>22</td>
<td>Schram 2014</td>
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<td>23</td>
<td>Tsai 2014</td>
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<td>15</td>
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<td>24</td>
<td>Gavriloa et al, 2014</td>
<td>3</td>
<td>79</td>
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<tr>
<td>25</td>
<td>van den Elsen 2015</td>
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<td><strong>Total Group 2</strong></td>
<td><strong>109 dropouts</strong></td>
<td><strong>1235; (8.83% of placebo participants dropped out)</strong></td>
</tr>
</tbody>
</table>

The chi-square statistic is 18.9964. The p-value is .000013. This result is significant at p < 0.05.
Chi squared statistic was calculated using the online application at:
### Appendix Table 11: Methods of treatment of missing data; and reporting of NPI scores for the included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>First author, publication year</th>
<th>Statistical methods for treatment of missing data</th>
<th>Summary of treatment of missing data</th>
<th>Reported change scores (change); or reported EoT scores (EoT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>McKeith 2000</td>
<td>Patients were classed for efficacy analyses as: classic intent to treat, traditional last observation carried forward (randomised patients with at least one assessment while being treated), and observed cases (randomised patients with review done while taking rivastigmine at designated assessment times).</td>
<td>ITT with LOCF (baseline values not carried forward)</td>
<td>change</td>
</tr>
<tr>
<td>2</td>
<td>Tariot 2001</td>
<td>The efficacy analyses were performed on the intent-to-treat population, which consisted of all randomized patients with at least one postbaseline efficacy evaluation.</td>
<td>ITT with LOCF (baseline values not carried forward)</td>
<td>change</td>
</tr>
<tr>
<td>3</td>
<td>Tune 2003</td>
<td>NS but 'NPI results are presented as the adjusted least squares (LS) mean change from baseline.'</td>
<td>NS (must be LOCF)</td>
<td>change</td>
</tr>
<tr>
<td>4</td>
<td>Peskind 2005</td>
<td>If a patient could not complete 6 weeks of treatment following titration, NPI and CGIC were completed at the day of termination and carried forward for statistical analysis. Significance of differences between baseline and 6-week achieved dose end point (or last observation carried forward) for total NPI and individual NPI item scores were compared between treatment groups by unpaired t tests and within treatment groups by paired t tests.</td>
<td>LOCF</td>
<td>EoT</td>
</tr>
<tr>
<td>5</td>
<td>Winblad 2006</td>
<td>We did analyses of the secondary outcome measures of the change from screening (MMSE) and baseline (NPI) to month 6 (total scores) on the modified intention-to-treat population, the intention-to-treat population, and the completer population.</td>
<td>modified ITT (used modified ITT in meta-analysis)</td>
<td>change</td>
</tr>
<tr>
<td>6</td>
<td>Peskind 2006</td>
<td>Efficacy analyses were based on the protocol-specified ITT sample. The protocol's statistical analysis plan specified that the primary efficacy analyses use a last observation carried forward (LOCF) approach for missing data imputation, requiring that only postbaseline data be carried forward. Observed case (OC) analyses were also run by visit. Change from baseline was compared between memantine and placebo groups...To better impute missing data, mixed-model repeated measures (MMRM) analyses were performed on the continuous measures with treatment group, week, centre, treatment by week as factors and baseline score as covariates.</td>
<td>reported LOCF, OC and MMRM; meta-analysis used LOCF (to be consistent with other studies in meta-analysis); meta-analysis used n at EoT with subtracted dropouts, so smaller n than that</td>
<td>change</td>
</tr>
<tr>
<td>Page</td>
<td>Author and Year</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>----------------</td>
<td>-------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Chappell 2007</td>
<td>The primary population was intent-to-treat (ITT). A patient was included in the ITT population if s/he had a baseline and at least one postbaseline efficacy measurement. For the analysis on the ITT population using the mixed effects model, repeated measures approach, this sample size provided approximately 70% power based on a one-sided 0.05 level test. This calculation assumed that the correlation between change from baseline at weeks 5 and 9 was 0.65, the dropout rate would be 10%, and the risk of dropout would not vary over time. Efficacy analyses were also performed on the evaluable population. A patient was included in the evaluable population if s/he completed the designated week double-blind treatment and had been taking between 80 and 120% of the study medication prescribed for each corresponding visit interval in period II. For the analysis on the evaluable population, the sample size provided approximately 69% power based on a one-sided 0.05 level test, assuming a 10% reduction in the analyzable sample size due to dropout rate and noncompliance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Napryeyenko 2007</td>
<td>Missing values were substituted for by carrying forward the last observed value (LOCF) as recommended by the Division of Neuropharmacological Drug Products (DNDP). A per-protocol analysis was performed in addition.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Mok 2007</td>
<td>Efficacy analysis was performed on classical intent to treat for all randomized patients who had received at least 1 dose of treatment and were followed up for at least once.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>van Dyck 2007</td>
<td>The safety population (n=350) consisted of randomized participants who received at least one dose of double-blind study medication. The intention-to-treat (ITT) population (n=336) comprised randomized subjects who completed at least one postbaseline SIB or ADCS-ADL19 assessment. Efficacy analyses were based on the ITT population. Primary efficacy analyses were conducted using the last observation carried forward (LOCF) approach for missing data imputation, with postbaseline data carried forward. Additional supportive analyses used the observed cases (OC) approach...post hoc analyses ...After the protocol-specified analyses were completed, post hoc analyses were performed (1) to assess the impact of other confounding variables, (2) to test normality assumptions, and (3) to examine the data using mixed-effects model repeated measures (MMRM), a theoretically more robust alternative to LOCF as a means of imputing missing data...Although LOCF was the protocol-specified method of imputing missing data, it may introduce biases, including favoring the treatment group with the higher dropout rate in a deteriorating illness. Several alternative statistical methods have emerged for dealing with missing data in clinical trials. The MMRM approach has been found to be more robust to biases from missing data than LOCF ANCOVA, thereby providing superior control of type I and type II errors.20 In the present study, the SIB and ADCSADL19 data were therefore reanalyzed using MMRM, on the basis of change from baseline with treatment group, time from baseline, center, and interaction of treatment group by time as fixed effects, and baseline score as covariate, with an unstructured covariance matrix to model the correlations of residuals over time.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Howard 2007</td>
<td>Primary analysis was performed for patients with complete data at both baseline and week 12, including those who did not adhere to the protocol (e.g., those who never started treatment but for whom we had complete data).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Note:** The table contains data related to clinical trial methodologies and analyses, including ITT (intent-to-treat), LOCF (last observation carried forward), and EoT (end of treatment). The text describes the methods used for handling missing data, including LOCF, and the rationale behind choosing different methodologies for different analyses.
<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>De Jong 2008</td>
<td>The primary efficacy analysis was conducted on the observed values. In addition, the last observation carried forward (LOCF) approach was used.</td>
</tr>
<tr>
<td>13</td>
<td>Wang 2009</td>
<td>We used a modified intent-to-treat approach, where we included all participants with at least one follow-up outcome measure in our statistical analyses.</td>
</tr>
<tr>
<td>14</td>
<td>Emre 2010</td>
<td>Some patients in the all-patients-treated set (APTS) had only a baseline efficacy assessment and were not included in the full-analysis set... Efficacy analyses were done on the full-analysis set (FAS), consisting of all patients in the APTS who had at least one valid postbaseline assessment on any of the efficacy scales. Efficacy and safety analyses were done for the total patient population and for patients with PDD and DLB separately. Efficacy was analysed for the FAS population for both the last observation carried forward (LOCF) data (baseline values not carried forward) and observed cases data (patients with a valid efficacy assessment on the efficacy scale).</td>
</tr>
<tr>
<td>15</td>
<td>Vercelletto 2011</td>
<td>The main analysis for primary and secondary endpoints compared change from baseline for the memantine group versus the placebo group and was based on the intention-to-treat (ITT) population. The ITT population was defined as all randomized patients who received at least one dose of study medication, at least one clinical assessment... There was no imputation of missing data for the secondary endpoints (including NPI).</td>
</tr>
<tr>
<td>16</td>
<td>Bi 2011</td>
<td>The analysis was primarily based on the full analysis data set according to the intention to treat (ITT) principle including all patients who received randomized study treatment at least once and having at least one measurement of the primary efficacy parameters during the randomized treatment period. For sensitivity analysis, a per-protocol (PP) analysis was performed including all patients of the full analysis set without major protocol violations.</td>
</tr>
<tr>
<td>17</td>
<td>Ihl 2011</td>
<td>The analysis was primarily based on the full analysis data set according to the intention to treat (ITT) principle including all patients who received randomized study treatment at least once and having at least one measurement of the primary efficacy parameters during the randomized treatment period. For sensitivity analysis, a per-protocol (PP) analysis was performed including all patients of the full analysis set without major protocol violations.</td>
</tr>
<tr>
<td>18</td>
<td>Herrschaf t 2012</td>
<td>The confirmatory analysis was primarily based on the full analysis set (FAS) including all patients who received randomised clinical trial medication at least once and having at least one measurement of the primary efficacy parameters during the randomised treatment period. Missing Data were handled by the last observation carried forward method (LOCF-method).</td>
</tr>
<tr>
<td>19</td>
<td>Fox 2012</td>
<td>The primary analysis was an intention to treat (ITT) analysis; participants were analysed as part of their allocated group irrespective of medication protocol adherence. Linear mixed effects (lme) modeling was used to handle the repeated measurements data. The dependent variables were score at weeks 2, 4, 6 and 12. Group and week were factors and baseline score was used as adjusting covariate. A first order autoregressive model was used for the correlation structure. Model fit was judged by standard residual analyses. In addition bootstrap analyses were performed that confirmed the parametric results. An 'observed case' is defined as a person who remained in the trial until the assessment date and took medicine according to protocol i.e. did not miss 3 days. A similar approach was taken in the analysis of secondary outcomes (e.g. NPI).</td>
</tr>
<tr>
<td>20</td>
<td>Herrmann 2013</td>
<td>the full-analysis set (FAS) – all randomized patients on current treatment with a ChEI who took at least one dose of study drug and had at least one post-baseline assessment on both co-primary efficacy variables (n = 324). The primary efficacy analyses were performed on the FAS, using the last observation carried forward approach.</td>
</tr>
</tbody>
</table>
primary efficacy analyses were analyses of covariance (ANCOVA) of the changes from baseline to Week 24 in NPI and SIB total scores (considered as co-primary endpoints), with treatment and center as factors and the baseline score as a covariate. In addition, efficacy was analyzed using a mixed-effect model repeated measure and an ANCOVA based on the observed cases approach.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>Nikolova</td>
<td>408 met all inclusion criteria and none of the exclusion criteria and were therefore randomized to EGb 761® (n = 203) or placebo (n = 205). For seven patients of the active treatment group and four patients of the placebo group no post-baseline efficacy data were available. Hence, the full analysis set for efficacy analysis consisted of 397 patients (EGb 761®: 196; placebo: 201)</td>
</tr>
<tr>
<td>2014</td>
<td>Schwam</td>
<td>the full analysis set, consistent with the intention-to-treat principles, was defined as all randomized subjects who consumed at least 1 dose of randomized study medication. This analysis set was used for all analyses presented here.</td>
</tr>
<tr>
<td>2014</td>
<td>Tsai</td>
<td>All data were analyzed according to the intention-to-treat principle and the missing value of observation was imputed using the last observation carried forward procedure.</td>
</tr>
<tr>
<td>2014</td>
<td>Gavrilova</td>
<td>Efficacy analysis was primarily based on the full analysis data set including all patients who received randomized study treatment at least once and having at least one measurement of any efficacy parameter during the randomized treatment period. Missing values were replaced by the last observation carried forward method on an item-for-item basis. Analysed ITT (Full Analysis Set) n=80,79</td>
</tr>
<tr>
<td>2015</td>
<td>van den Elsen</td>
<td>Efficacy and safety analyses were based on the intention-to-treat principle and performed in accordance with a prespecified statistical analysis plan, finalized before unmasking of treatment assignment</td>
</tr>
</tbody>
</table>

FAS; Full analysis set; ITT: Intention-to-treat; LOCF: Last observation carried forward; NS: Not specified
Appendix Table 12: Summary of results for changes in placebo and active groups (baseline versus end of treatment)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n studies (n participants EoT in placebo groups); range of durations of treatment</th>
<th>Change in total NPI MD, 95%CI, Fixed Effect model; $I^2$</th>
<th>Change in total NPI MD, 95%CI, Random Effects model; $I^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo Group 1: Published 2000 - 2008</td>
<td>12 (1056) 6-52wks</td>
<td>1.86 [0.78, 2.94]*; 65%</td>
<td>1.57 [-0.46, 3.59]; 65%</td>
</tr>
<tr>
<td>Placebo Group 2: Published 2009 - 2015</td>
<td>13 (1170) 3-52wks</td>
<td>-3.06 [-3.69, -2.43]*; 76%</td>
<td>-2.68 [-4.38, -0.99]*; 76%</td>
</tr>
<tr>
<td>Placebo Total all studies</td>
<td>25 (2226) 3-52wks</td>
<td>-1.80 [-2.35, -1.26]*; 83%</td>
<td>-0.63 [-2.21, 0.95]; 83%</td>
</tr>
<tr>
<td>Treatment Group 1: Published 2000 - 2008</td>
<td>12 (978) 6-52wks</td>
<td>-2.71 [-3.82, -1.59]*; 75%</td>
<td>-1.15 [-3.68, 1.38]; 75%</td>
</tr>
<tr>
<td>Treatment Group 2: Published 2009 - 2015</td>
<td>13 (1137) 3-52wks</td>
<td>-5.07 [-5.71, -4.44]*; 76%</td>
<td>-4.85 [-6.50, -3.20]*; 76%</td>
</tr>
<tr>
<td>Treatment Total all studies</td>
<td>25 (2115) 3-52wks</td>
<td>-4.50 [-5.05, -3.95]*; 78%</td>
<td>-3.30 [-4.72, -1.89]*; 78%</td>
</tr>
</tbody>
</table>
Meta-regression analysis results

Using Stata metareg command with Knapp-Hartung modification and bubble graphs

Meta-regression analysis results for Placebo groups

Analyses of publication year

Analysis 1: Publication year by change in NPI score (all 25 studies; Group 1; Group 2)

Publication year by NPI score (all 25 studies)

Appendix Meta-regression 1: WMD within placebo groups by year of publication; all 25 studies
% residual variation due to heterogeneity: I-squared_res = 72.12%
Proportion of between-study variance explained (by the covariate): Adj R-squared = 21.93%, P>|t| = 0.041, 95% Conf. Interval -0.8212017, -0.0179248.

Interpretation: Regression analysis was significant, NPI scores tended to reduce more in recent years, but the distribution was not linear and result is affected by outliers.

Publication year by NPI score (Group 1: 12 studies)

Appendix Meta-regression 2: WMD within placebo groups by year of publication; Group 1 studies
% residual variation due to heterogeneity: I-squared_res = 48.17%
Proportion of between-study variance explained: Adj R-squared = 45.42%, P>|t| = 0.059, 95% Conf. Interval [−.0375458, 1.630436].

Interpretation: Regression analysis was not significant. Presence of outliers limits confidence in the result.

Publication year by NPI score (Group 2: 13 studies)

310
Appendix Meta-regression 3: WMD within placebo groups by year of publication; Group 2 studies

% residual variation due to heterogeneity: I-squared_res = 22.27%
Proportion of between-study variance explained: Adj R-squared = 100.00%, P>|t| = 0, 95% CI: -2.310971 - .9637508.

Interpretation: Regression analysis was significant, NPI scores tended to decrease in years 2009-2015, indicating improvement of BPSD within placebo groups. Outliers do not have a major effect on result.

Publication year by NPI score (only 20 to 26 weeks duration studies: 14 studies) all years

Appendix Meta-regression 4: WMD within placebo groups by year of publication; 20 to 26 weeks duration studies

% residual variation due to heterogeneity: I-squared_res = 72.88%
Proportion of between-study variance explained: Adj R-squared = 30.12%, P>|t| =0.071, 95% CI: -0.7186738, 0.0346745

Interpretation: Regression analysis was not significant. Distribution appears not linear. When excluding the very short and very long duration studies, there was no significant association between publication year and change in NPI scores within placebo groups.

Publication year by NPI score (only 20 to 26 weeks duration studies; Group 1)
Appendix Meta-regression 5: WMD within placebo groups by year of publication; 20 to 26 weeks duration studies; Group 1 studies

% residual variation due to heterogeneity: I-squared_res = 22.18%
Proportion of between-study variance explained: Adj R-squared = 94.45%, P>|t| =0.099, 95% CI: -0.1570317, 1.400408

Interpretation: Regression analysis was not significant. Distribution appears not linear. When excluding the very short and very long duration studies, there was no significant association between publication year and change in NPI scores within placebo groups for the studies published from 2000 to 2008. Only 8 studies are included which reduces the validity.

Publication year by NPI score (only 20 to 26 weeks duration studies; Group 2)

Appendix, Meta-regression 6: WMD within placebo groups by year of publication; 20 to 26 weeks duration studies; Group 2 studies

% residual variation due to heterogeneity: I-squared_res = 0%
Proportion of between-study variance explained: Adj R-squared = 100%, P>|t| =0.004, 95% CI: -2.510386, -0.9110586

Interpretation: Regression analysis was significant. Distribution appears linear. When excluding the very short and very long duration studies, there was a significant association between publication year and change in NPI scores within placebo groups for the studies published from 2009 to 2015. Only 6 studies are included which reduces the validity.

Analyses of treatment duration

Analysis 2: Study duration by change in NPI score (all 25 studies; Group 1; Group 2)

Treatment duration (weeks) by NPI score (all 25 studies)
Appendix, Meta-regression 7: WMD within placebo groups by treatment duration (weeks); all 25 studies

% residual variation due to heterogeneity: \( I^2_{\text{res}} = 81.88\% \)
Proportion of between-study variance explained: \( \text{Adj R-squared} = 24.25\% \), \( P>|t| = 0.014 \); 95% CI: 0.0456541, 0.3696421

Interpretation: Regression analysis was significant. There is more reduction in NPI scores in studies of shorter duration than in studies of longer duration. This suggests that NPI score tend to be worse in longer studies since dementia tends to get worse over time. However, most of the studies are in the range 20-26 weeks and the regression result is affected by the short and long duration outliers. This limits the validity of this analysis.

Treatment duration (weeks) by NPI score (Group 1 studies)

Appendix, Meta-regression 8: WMD within placebo groups by treatment duration (weeks); Group 1 studies

% residual variation due to heterogeneity: \( I^2_{\text{res}} = 50.44\% \)
Proportion of between-study variance explained: \( \text{Adj R-squared} = 40.90\% \), \( P>|t| = 0.058 \); 95% CI: -0.0081025, 0.3808327,

Interpretation: Regression analysis was not significant. There was not a significant association between treatment duration and change in NPI scores within placebo groups in the studies published from 2000 to 2008. However, the presence of outliers limits the validity of this regression analysis.

Treatment duration (weeks) by NPI score (Group 2 studies)
Appendix Meta-regression 9: WMD within placebo groups by treatment duration (weeks); Group 2 studies

% residual variation due to heterogeneity: I-squared_res = 78.24%
Proportion of between-study variance explained: Adj R-squared =-18.20%; P>|t| =0.284; 95% CI: -0.1351228, 0.4177287.

Interpretation: Regression analysis was not significant. There was not a significant association between treatment duration and change in NPI scores within placebo groups in the studies published from 2009 to 2015. However, the presence of outliers limits the validity of this regression analysis.

Analyses of Sample size

Analysis 3: Sample size by change in NPI score (all 25 studies; Group 1; Group 2)

Sample size (N participants in both groups at baseline) by NPI score (all 25 studies)

Appendix, Meta-regression 10: WMD within placebo groups by total sample size at baseline in both treatment and control groups; all 25 studies

% residual variation due to heterogeneity: I-squared_res = 83.33%
Proportion of between-study variance explained: Adj R-squared =-4.75%; P>|t| =0.553; 95% CI: -0.016312, 0.0089569.

Interpretation: Regression analysis was not significant and not linear. There was not a significant association between sample size and change in NPI scores within placebo groups in the 25 included studies. No further subgroup analysis on sample size is shown. Results are not significant for sample size and changes in NPI scores and result is affected by outliers.

Analyses of Mean baseline total NPI score

Analysis 4: Mean baseline total NPI score by change in NPI score (all 25 studies; Group 1; Group 2)
Mean baseline total NPI score (all 25 studies)

Appendix Meta-regression 11: WMD within placebo groups by mean total baseline NPI score; all 25 studies

% residual variation due to heterogeneity: I-squared_res = 83.70%
Proportion of between-study variance explained (by the covariate): Adj R-squared = 16.98%; P>|t| = 0.047, 95% CI: -0.4530687, -0.0027982.

Interpretation: Regression analysis is significant. Larger placebo effect sizes were detected in studies with higher mean baseline NPI scores in placebo participants (more severe BPSD), but the distribution was not linear and affected by outliers.

Mean baseline total NPI score (Group 1 studies)

Appendix, Meta-regression 12: WMD within placebo groups by mean total baseline NPI score; Group 1 studies

% residual variation due to heterogeneity: I-squared_res = 59.57%
Proportion of between-study variance explained (by the covariate): Adj R-squared = 25.29%; P>|t| = 0.12, 95% CI: -0.6932756, 0.0932181.

Interpretation: Regression analysis was not significant. There is no association between placebo effect sizes mean baseline NPI scores in placebo participants in the Group 1 studies, but the distribution was not linear and affected by outliers.
Appendix, Meta-regression 13: WMD within placebo groups by mean total baseline NPI score; Group 2 studies

% residual variation due to heterogeneity: I-squared_res = 78.04%
Proportion of between-study variance explained (by the covariate): Adj R-squared = -6.87%; P>|t| = 0.371; 95% CI: -0.3916099, 0.1585951.

Interpretation: Regression analysis was not significant. There is no association between placebo effect sizes mean baseline NPI scores in placebo participants in the Group 2 studies, but the distribution was not linear and affected by outliers.
Meta-regression analysis results for active Treatment groups

Using Stata metareg command with Knapp-Hartung modification and bubble graphs

**Analyses of Publication year**

**Analysis 1:** Publication year by change in NPI score (all 25 studies; Group 1; Group 2)

**Publication year by NPI score (all 25 studies)**

Appendix, Meta-regression 14: WMD within active treatment groups by year of publication; all 25 studies

% residual variation due to heterogeneity: I-squared_res = 71.98%
Proportion of between-study variance explained (by the covariate): Adj R-squared = 29.03%, P>|t| = 0.029, 95% CI: -0.9573651, -0.0560032.

Interpretation: Regression analysis was significant, NPI scores tended to reduce more in recent years (larger effect sizes in active treatment groups), but the distribution was not linear.

**Publication year by NPI score (20 to 26 weeks duration studies)**

Appendix, Meta-regression 15: WMD within active treatment groups by year of publication; 20 to 26 weeks duration studies; of all 25 studies

% residual variation due to heterogeneity: I-squared_res = 77.30%
Proportion of between-study variance explained (by the covariate): Adj R-squared = 31.15%; p= 0.051, 95% CI: -1.258632, 0.0028218.

Interpretation: Regression analysis was not significant (borderline). There was no significant association (borderline) between publication year and effect size within the active treatment groups when treatment duration was limited to 20 to 26 weeks.
Analyses of Treatment duration

Analysis 2: Treatment duration (weeks) by change in NPI score (all 25 studies)
Treatment duration (weeks) by NPI score (all 25 studies)

Appendix, Meta-regression 16: WMD within active Treatment groups by treatment duration (weeks); all 25 studies
% residual variation due to heterogeneity: I-squared_res = 78.45%
Proportion of between-study variance explained (by the covariate): Adj R-squared = -8.23%, P>|t| = 0.43, 95% CI: -0.1115444, 0.2533477.

Interpretation: Regression analysis was not significant. There was no significant association between treatment duration and effect size within the active treatment groups. But analysis is affected by outlier and may not be valid.
Note: subgroup analysis for Groups 1 and 2 not shown – no significant results.

Analyses of Sample size

Analysis 3: Sample size (N participants in both groups) by change in NPI score (all 25 studies)
Sample size (N participants in both groups) by NPI score (all 25 studies)

Appendix, Meta-regression 17: WMD within active treatment groups by total sample size at baseline in both treatment and control groups; all 25 studies
% residual variation due to heterogeneity: I-squared_res = 78.14%
Proportion of between-study variance explained (by the covariate): Adj R-squared = 2.33%, P>|t| = 0.288, 95% CI: -0.0226502, 0.0070381.
Interpretation: Regression analysis was not significant and appears not to be linear. There was no significant association between sample size and effect size within the active treatment groups. However, the analysis is not valid.

Note: subgroup analysis for Groups 1 and 2 not shown – no significant results.
Analyses of Publication year

Analysis 1: Publication year by change in NPI score (all 25 studies; Group 1; Group 2)

Publication year by NPI score (all 25 studies excluding Tune 2003)

Appendix, Meta-regression 18: WMD for TvsC at end of treatment by year of publication; all 25 studies excluding Tune 2003 due to baseline imbalance
% residual variation due to heterogeneity: I-squared_res = 79.55%
Proportion of between-study variance explained (by the covariate): Adj R-squared = -6.31%, P>|t| = 0.612, 95% CI: -0.6046257, 0.3642004.

Interpretation: Regression analysis was not significant and not linear. There was no significant association between publication year and the difference between treatment and placebo groups in effect size.

Publication year by NPI score (Group 1 studies excluding Tune 2003)

Appendix, Meta-regression 19: WMD for TvsC at end of treatment by year of publication; Group 1 studies excluding Tune 2003 due to baseline imbalance.
% residual variation due to heterogeneity: I-squared_res = 80.63%
Proportion of between-study variance explained (by the covariate): Adj R-squared = 29.50%, P>|t| = 0.087, 95% CI: -2.272981, 0.1839488.

Interpretation: Regression analysis was not significant. There was no significant association between publication year and difference between treatment and placebo groups in effect size, for the Group 1 studies. However, the result is affected by outliers.
Publication year by NPI score (Group 2 studies)

Appendix, Meta-regression 20: WMD for TvsC at end of treatment by year of publication; Group 2 studies

% residual variation due to heterogeneity: I-squared_res = 52.21%
Proportion of between-study variance explained (by the covariate): Adj R-squared = 43.58%; P>|t| = 0.017, 95% CI: 0.3328832, 2.680979.

Interpretation: Regression analysis was significant. There was a significant association between publication year and difference between treatment and placebo groups in effect size. This suggests that the difference between groups has increased in recent years.

Publication year by NPI score (20 to 26 week duration studies)

Appendix, Meta-regression 21: WMD for TvsC at end of treatment by year of publication; 20 to 26 weeks duration studies (published 2000-2015)

% residual variation due to heterogeneity: I-squared_res = 87.99%
Proportion of between-study variance explained (by the covariate): Adj R-squared = -7.74%; P>|t| = 0.378, 95% CI: -0.8826715, 0.3629093.

Interpretation: Regression analysis was not significant and not linear. There was no significant association between publication year and difference between treatment and placebo groups in effect size. However, the regression analysis was not valid.

Note: results for other TvsC subgroup analysis not shown – no significant results.