

Rivastigmine in Chinese patients with subcortical vascular dementia

Vincent Mok¹
 Adrian Wong¹
 Simon Ho²
 Thomas Leung¹
 Wynn WM Lam²
 Ka Sing Wong¹

¹Department of Medicine and Therapeutics; ²Department of Radiology and Organ Imaging, The Chinese University of Hong Kong, Shatin, Hong Kong, China

Background: We explored the efficacy and tolerability of rivastigmine among Chinese patients with subcortical vascular dementia.

Methods: Forty subjects were randomized to either placebo (n = 20) or rivastigmine (n = 20) in a double-blind 26-week trial. Outcome measures were cognition (mini-mental state examination, frontal assessment battery), neuropsychiatric inventory (NPI), instrumental activities of daily living, clinical dementia rating scale, and adverse events.

Results: No statistical significant benefit could be observed in the active group in any of the efficacy measures. A trend favoring active group was observed only in the NPI subscore of irritability (p = 0.066) and aberrant motor behavior (p = 0.068). Withdrawal rate was 30% and 15% in the active and placebo group, respectively.

Conclusion: Among Chinese subcortical vascular dementia patients, there was no apparent cognitive benefit associated with use of rivastigmine over the 6 months period. A trend favoring rivastigmine was observed in certain behavioral measures. Rivastigmine was associated with more withdrawals relative to placebo.

Keywords: rivastigmine, subcortical vascular dementia, Chinese

Introduction

Subcortical vascular dementia is the commonest subtype of vascular dementia (Ikeda et al 2001). Its underlying vascular pathology is small vessel disease (Erkinjuntti et al 2000). Apart from memory problems, which may be mild, the dementia syndrome commonly includes prominent executive dysfunction. Behavioral changes are frequent in subcortical vascular dementia and are present regardless of the severity of cognitive impairment (Aharon-Peretz et al 2000). Other clinical features may include gait disturbance, parkinsonism, and urinary incontinence.

Although acetylcholinesterase inhibitor has been shown to be effective in Alzheimer's disease, its effects upon subcortical vascular dementia remain controversial. Donepezil was found to be effective in vascular dementia in terms of cognition and daily functions in 2 randomized controlled studies (Black et al 2003; Wilkinson et al 2003). However, subgroup analyses showed that it was less effective in subcortical type relative to cortical type of vascular dementia (Salloway 2003). Furthermore, its effects on behavioral measures had not been explored. Results from 2 randomized studies on galantamine suggest that it was effective mainly for mixed dementia rather than for probable vascular dementia (Craig and Birks 2006). A third acetylcholinesterase inhibitor, rivastigmine, was shown by open labeled studies to be effective among Caucasians with subcortical vascular dementia in improving cognition, functions, and behavioral symptoms (Moretti et al 2002, 2003).

Currently, China has the highest number of people with dementia (5 million) and the growth in dementia was estimated to be more than 300% over the next 40 years (Ferri et al 2005). Vascular dementia accounts for almost a third of dementia cases

Correspondence: Vincent Mok
 Division of Neurology, Department
 of Medicine and Therapeutics, The
 Chinese University of Hong Kong, Shatin,
 Hong Kong, China
 Tel +852 2632 2195
 Fax +852 2637 3852
 Email vctmok@cuhk.edu.hk

(Chiu et al 1998) and a third of the Chinese dementia patients are illiterate (Zhang et al 2005). Despite its high prevalence, clinical studies for vascular dementia among Chinese are scarce (Jirong et al 2004). Since most international clinical trials included only literate subjects who were able to perform detailed psychometric tests, many demented Chinese patients would not be eligible for participation to such trials due to their illiteracy. To date, effects of acetylcholinesterase inhibitor among Chinese patients with subcortical vascular dementia are largely unknown. We thus performed a pilot randomized double-blind placebo-controlled study exploring the efficacy and tolerability of rivastigmine among Chinese patients with subcortical vascular dementia. We used simple validated Chinese version of psychometric tests and questionnaires that allowed participation of subjects who were illiterate as well.

Materials and methods

Patients

Chinese patients with subcortical vascular dementia of age between 40 to 90 years old and had mini-mental state examination (MMSE) score between 3 and 24 were potentially eligible for the study. Patients were recruited from our neurology clinic. We used standardized diagnostic criteria to define subcortical vascular dementia (Erkinjuntti et al 2000). In brief, these criteria include all of the following: (1) cognitive syndrome including both dysexecutive syndrome and memory deficit that indicate deterioration from a previous higher level of functioning, and are interfering with complex (executive) occupational and social activities not due to physical effects of cerebrovascular disease alone; and (2) cerebrovascular disease including both evidence of relevant cerebrovascular disease by brain imaging and presence or a history of neurological signs such as hemiparesis, sensory deficit, gait disorder, or extrapyramidal signs consistent with subcortical brain lesions. We also used the brain imaging criteria as described by Erkinjuntti et al (2000). for computerized tomography (CT) or magnetic resonance imaging (MRI). In brief, patients with extensive white matter lesion and at least 1 lacune on CT and extensive white matter lesion with at least 1 lacune, or multiple lacunes with at least moderate white matter lesion on MRI were eligible for the study. All the subjects had either cerebral CT (65%) or MRI (35%). A radiologist (SH) reviewed the neuroimaging films of all potential subjects. Patients were excluded from the study if they had known other concurrent dementing diseases (eg, B12 deficiency), unstable medical conditions, stroke within 3 months of study, concurrent use of cholinergic

drugs, frequent change in dose of centrally acting drugs (eg, benzodiazepines) 3 months prior to entry of study, severe dementia or language problems making participation in cognitive testing impossible, and no closed caregivers as defined by less than 3 visits per week. The Clinical Research Ethics Committee of the Chinese University of Hong Kong approved the study protocol. All patients and their carers gave their written consents for the study.

Study design

The study was a 26-week, double-blind, placebo-controlled, single-center study in which treatment with 6 mg daily of rivastigmine or placebo was evaluated. It was conducted at an university affiliated hospital, Prince of Wales Hospital, Hong Kong. The recruitment commenced in November 2002 and completed in December 2004. Forty eligible patients were assigned randomly to either placebo ($n = 20$) or rivastigmine ($n = 20$) via a computer program generated code. Treatment was started at 1.5 mg bid. The dose was escalated to 3 mg bid after 4 weeks and to be maintained at this dose. Patients having any intolerable adverse effects at a dose of 3 mg bid or lower that did not abate after a maximum of 1 week were discontinued from the study. Since, based on previous experience, doses higher than 6 mg daily may be associated with more side-effects among Chinese subcortical vascular dementia patients, we used the minimal effective dose of 6 mg daily in this study. Patients who experienced significant deterioration in behavioral problems and required increase or addition of psychiatric medications would also be discontinued from the study. All the study medications were produced by Novartis Pharmaceuticals (Geneva, Switzerland).

Outcome measures

Efficacy measures were cognition (Chinese version of MMSE [Chiu et al 1994] and frontal assessment battery [FAB] [Dubois et al 2000; Mok et al 2004]), behavioral symptoms (Chinese version of NPI [Leung et al 2001]), Chinese version of instrumental activities of daily living (IADL) (Tong and Man 2002), and sum of boxes in clinical dementia rating scale (CDR) (Morris 1993). The FAB evaluates executive function and it consists of 6 items, with each item evaluates one executive domain (conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy). The NPI evaluates 12 different neuropsychiatric disturbances including delusion, hallucination, dysphoria, anxiety, euphoria, aggression, apathy, irritability, disinhibition, troublesome behavior,

sleep, and appetite. The Lawton IADL was used to assess performance of daily activities (use of telephone, transportation, shopping, meal preparation, housework, handyman work, laundry, medication management, and money management). The score for each item ranges from 0 to 3, with a lower score representing better function. As some items in the IADL were not scored because these items might not be applicable to all patients owing to personal habits or motor impairment, we took the average of all scored items as the final IADL score. The CDR evaluates global functioning in the following domains: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. The sum of boxes of CDR was used as the score for CDR. The above efficacy measures were rated at baseline, week 12, and week 26 or early termination by a single trained psychologist. Periodic physical examination including blood pressure, pulse, and reports of adverse events were done at each visit. Electrocardiogram, laboratory tests including complete blood count, renal/liver function test, glucose, bone profile, vitamin B12, folate, and thyroid function test were done at screening only.

Statistical analysis

Since at the planning stage of this study in 2001, no study has been published using acetylcholinesterase inhibitor in subcortical vascular dementia, we thus defined the sample size as 40 patients based on feasibility consideration. Patients who had at least one dose of study medication and had at least one safety evaluation were included for safety analysis. 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. In the baseline comparisons, independent *t* tests were used for comparison for continuous variables and χ^2 tests for categorical variables. For categorical variables with less than an expected count of 5 in any of the 2×2 table the Fisher's Exact Test was used. Since age and education did not differ between the two groups these variables were not controlled in the comparisons of psychometric test performances. Post-hoc analysis showed that results were not altered with or without these variables co-varied. For analysis of change of efficacy measures, the outcome measure $\times$ group interaction model was created using a 2×2 repeated measure analysis of variance with group as between-subject factors and outcome measures at baseline and termination as within-subject variables. This analysis involved 20 patients in active arm and 19 patients in placebo arm, as 1 patient in the placebo arm died before second assessment and thus no follow up data was available. All

comparisons to placebo were two-tailed, with *p* values ≤ 0.05 being considered statistically significant.

Results

The baseline characteristics of the patients were shown in Table 1. There was no significant difference in clinical characteristics between the 2 groups at baseline.

There was no statistical significant difference in change from baseline between the 2 treatment groups in any of the efficacy measures (Table 2). We observed that the mean total score of NPI changed from 15 to 11.4 ($p = 0.28$) in the active group, whereas score in the placebo group increased slightly. A favorable trend in 2 behavioral measures (irritability, $p = 0.066$; aberrant motor behavior, $p = 0.068$) was noted in the active group.

More patients in the active group experienced adverse effects and had withdrawn ($n = 6$; 30%) compared with those in the placebo group ($n = 3$; 15%) (Table 3). However, only 3 out of the 6 patients in the active group who withdrawn had side effects that were probably related to the study drug and all these 3 patients had severe dementia with MMSE ≤ 11 . One patient in the placebo group died of hemorrhagic stroke during the study. Types of common adverse effects (eg, nausea, vomiting, loss of appetite, leg cramp) were typical to that seen with use of acetylcholinesterase inhibitors (Table 4). None of the patients necessitated change of psychiatric medications during the study period.

Discussion

The present small randomized double-blind placebo-controlled study explored the efficacy and tolerability of rivastigmine among a relatively unselected group of Chinese subcortical vascular dementia patients. Mean education level was only around 3 years, which was similar to that of our local elderly stroke patients (Tang et al 2004) and 40% of our patients were illiterate. We also allowed participation of patients with more severe dementia (MMSE < 10) as its effects and tolerability among more severe subcortical vascular dementia have not been explored before. The mean MMSE of our cohort was 13, which was 7 points lower than that of the cohort of another open labeled study using rivastigmine in subcortical vascular dementia (Moretti et al 2003). Note also that using an upper MMSE cutoff score of 24 as inclusion criteria, we might have excluded certain subcortical vascular dementia patients who may have predominant severe executive dysfunction despite having a MMSE score of greater than 24. Frequency of traditional vascular risk factors was high and was similar to that among patients of other vascular dementia studies (Black et al 2003; Wilkinson et al 2003).

Table 1 Baseline characteristics

	Active (n = 20)	Placebo (n = 20)	p
Age	75.7 (5.1)	74.1 (6.6)	0.39
Education (years)	3.5 (4.4)	3.1 (4.5)	0.76
Illiterate	7 (35%)	9 (45%)	0.90
Sex (% female)	13 (65%)	11 (55%)	0.52
Vascular risk factors			
Hypertension	19 (95%)	16 (80%)	0.34
Diabetes mellitus	5 (25%)	3 (15%)	0.70
Hyperlipidemia	5 (25%)	9 (45%)	0.19
History of myocardial infarction	0 (0%)	1 (5%)	1.00
History of stroke	14 (70%)	14 (70%)	1.00
Psychiatric medications			
Anti-psychotic	2 (10%)	1 (5%)	
Anti-depressant	1 (5%)	1 (5%)	
Benzodiazepam	1 (5%)	0 (0%)	
Cognition, behavior, daily activities, and global function			
MMSE	13.0 (4.2)	13.4 (5.9)	0.83
MMSE 19–24	3 (15%)	5 (25%)	
MMSE 11–18	12 (60%)	9 (45%)	
MMSE 3–10	5 (25%)	6 (30%)	
FAB (total score)	6.0 (2.6)	5.9 (2.4)	0.90
NPI total score	15.0 (40.4)	10.6 (14.5)	0.14
IADL	2.3 (0.7)	2.4 (0.6)	0.70
CDR (sum of boxes)	8.7 (5.1)	9.5 (4.8)	0.61

Notes: Values in () are standard deviation when not indicated otherwise.

Abbreviations: AVF, animal verbal fluency; CDR, clinical dementia rating; FAB, frontal assessment battery; IADL, instrumental activities of daily living; MMSE, mini-mental state examination; no., number; NPI, neuropsychiatric inventory.

Although an earlier open labeled study showed a significant cognitive benefit with rivastigmine even with a small sample size of 8 subjects per treatment arm (Moretti et al 2002), our present study failed to demonstrate any favorable trend in cognitive response even with a slightly larger sample size. Although it is possible that positive effects in open labeled studies may be due to bias favoring active groups, the 6 months duration of our study may also be too short to yield a significant benefit. Previous positive studies spanned 22 months and continuous cognitive improvement was observed beyond 6 months (Moretti et al 2002). Furthermore, since our patients probably had more severe dementia than those in the previous studies (Moretti et al 2002, 2003), rivastigmine may be less effective among those with more severe subcortical vascular dementia. It is also uncertain whether ethnicity and literacy level affect treatment responses. However, further subgroup analysis stratified by cognitive severity or educational level was not feasible due to the small sample size of this study. The lack of any apparent cognitive benefit in the active group may also be explained by the fact that our brief cognitive measures (MMSE and FAB) were not sensitive for detection of cognitive changes among patients with subcortical vascular dementia. Yet, since there was also no apparent improvement

in IADL or CDR in the active group, any cognitive benefit related to rivastigmine, even if present, may only be subtle and not clinically relevant. Furthermore, the dosage of 6 mg daily may not be able to yield a positive benefit as study among Alzheimer's disease used dose as high as 12 mg daily (Rosler et al 1999). Note that prior positive open labeled studies in subcortical vascular dementia also used a maximum dose of 6 mg daily (Moretti et al 2002, 2003). Last, the lack of cognitive benefit may simply be explained by the small sample size, which lacks the power to detect any significant benefit. Yet, as mentioned earlier, a favorable trend in cognition was already observed in the previous open labeled study involving only 8 subjects per group at 6 months time point (Moretti et al 2002). However, such robustness of drug effects in cognition could not be observed in our present study even though we used a larger sample size. Overall, our findings are consistent with that of other larger randomized double-blind placebo-controlled studies in vascular dementia, which showed that cognitive benefits of other acetylcholinesterase inhibitors among subcortical (Salloway 2003) or probable vascular dementia (Erkinjuntti et al 2002) was small or negligible.

Although no apparent cognitive benefit was observed with use of rivastigmine, we observed that the mean total score of

Table 2 Efficacy measures

	Active (n = 20)		Placebo (n = 19)		p
	Baseline	Termination	Baseline	Termination	
Cognition					
MMSE	13.0 (4.2)	13.6 (5.8)	13.6 (6.0)	13.5 (6.8)	0.563
FAB total	6.0 (2.6)	6.2 (2.7)	6.0 (2.4)	6.6 (2.8)	0.48
FAB sub-items:					
1. Conceptualization	0.1 (0.3)	0.1 (0.3)	0.3 (0.5)	0.5 (0.6)	0.119
2. Mental flexibility	0.7 (0.8)	0.7 (0.8)	0.8 (0.8)	0.8 (0.8)	1
3. Programming	1.4 (0.8)	1.3 (1.1)	0.8 (0.8)	1.3 (1.0)	0.092
4. Sensitivity to interference	0.6 (1.0)	0.6 (1.2)	0.6 (0.8)	0.7 (0.8)	0.876
5. Inhibitory control	0.6 (0.6)	0.6 (0.8)	0.8 (0.5)	0.9 (0.8)	0.648
6. Environmental autonomy	2.7 (0.9)	3.0 (0.2)	2.9 (0.5)	2.8 (0.7)	0.265
Behavioral symptoms					
NPI total	15.0 (14.6)	11.4 (9.4)	9.5 (6.5)	10.4 (11.3)	0.282
NPI sub-items:					
1. Delusions	0.8 (2.4)	0.2 (0.9)	0.5 (1.0)	0.2 (0.9)	0.617
2. Hallucinations	0.0 (0.0)	0.1 (0.2)	0.0 (0.0)	0.1 (0.2)	0.971
3. Aggression	1.2 (2.1)	1.7 (2.8)	1.0 (2.1)	0.9 (1.8)	0.529
4. Dysphoria	0.4 (0.9)	0.5 (1.1)	1.0 (1.9)	1.5 (3.0)	0.493
5. Anxiety	0.8 (1.9)	0.3 (0.7)	0.2 (0.5)	0.2 (0.7)	0.346
6. Euphoria	0.0 (0.0)	0.1 (0.2)	0.0 (0.0)	0.0 (0.0)	0.336
7. Apathy	3.6 (4.4)	3.7 (4.4)	3.3 (3.6)	2.5 (3.8)	0.593
8. Disinhibition	0.3 (0.9)	0.0 (0.0)	0.3 (0.8)	0.1 (0.3)	0.738
9. Irritability/lability	2.4 (3.2)	0.6 (1.6)	1.0 (1.5)	1.2 (2.1)	0.066
10. Aberrant motor behavior	2.4 (4.2)	1.1 (2.9)	0.4 (1.1)	1.3 (2.3)	0.068
11. Sleep disturbance	2.3 (3.0)	1.6 (1.8)	1.1 (1.8)	1.4 (2.4)	0.319
12. Appetite/eating disturbance	1.0 (2.6)	1.9 (3.8)	0.8 (2.9)	1.1 (2.6)	0.583
Daily functions					
IADL	2.3 (0.7)	2.3 (0.5)	2.3 (0.6)	2.2 (0.8)	0.299
Global function					
CDR (sum of boxes)	8.7 (5.1)	9.4 (5.5)	9.1 (4.6)	9.5 (5.4)	0.787

Notes: Values in () are standard deviation when not indicated otherwise.

Abbreviations: AVF, animal verbal fluency; CDR, clinical dementia rating; FAB, frontal assessment battery; IADL, instrumental activities of daily living; MMSE, mini-mental state examination; no., number; NPI, neuropsychiatric inventory.

NPI changed from 15 to 11.4 in the active group, whereas patients' behavioral symptoms in the placebo group remained similar. This positive treatment effect of about 4 points in NPI score was of similar magnitude as observed in the previous open labeled study (Moretti et al 2002). A trend favoring active group with p values approaching statistical significance was particularly noted in irritability and aberrant motor behavior. A study with a larger sample size may possibly yield a significant treatment benefit. If such study is to be carried out, the sample size can be estimated based on data from this pilot study. The standard deviation of NPI score of our 40 Chinese subjects was 11.5, which was similar to that of another cohort of vascular dementia patients (Erkinjuntti et al 2002). Assuming a treatment effect of 4 points is clinically relevant (Mega et al 1999) and that it can be achieved by rivastigmine as had been suggested in this pilot study, 125 subjects per group are needed to have 80% power at a significance level of 5% to detect such effect. Assuming an expected drop out rate of

30%, then 180 subjects per group will be needed. Such study is warranted given the high prevalence and disabling nature of behavioral symptoms in subcortical vascular dementia and use of traditional antipsychotics is discouraged in patients with multiple vascular risk factors due to its association with stroke and other vascular events (Bullock 2005). Availability of another agent that proves safe and effective in controlling behavioral symptoms in subcortical vascular dementia will thus be extremely helpful.

The use of rivastigmine among our local elderly patients with multiple concurrent medical conditions was generally safe. The types of adverse effects were similar to that seen in studies using acetylcholinesterase inhibitors in dementia patients (Table 4). Mortality was noted only in the placebo group. The withdrawal rate of 30% in the active group was slightly higher than that (20%) observed in other clinical studies using acetylcholinesterase inhibitor among vascular dementia (Black et al 2003; Wilkinson et al 2003). This may be related

Table 3 Overview of adverse effects

	Active (n = 20)	Placebo (n = 20)
Any side effects	12 (60%)	10 (50%)
Withdrawals	6 (30%)	3 (15%)
Recurrent stroke	1 (5%)	4 (20%)
Death	0	1 (hemorrhagic stroke)

to the fact that our patients were more demented than those in other studies. Note however that among the 6 withdrawn patients in the active group, only half of the withdrawal reasons were probably drug-related and that all these 3 withdrawn patients had MMSE less than 11. This may suggest that drug intolerance among those with more severe dementia may be high. Whether a slower and more flexible titration regime may lead to lesser side effects requires further study.

To conclude, although we could not find a positive treatment effect of rivastigmine, findings from this pilot randomized double-blind placebo-controlled study among Chinese patients with subcortical vascular dementia provides useful insights for future study. We propose that future study should particularly investigate the behavioral effects of rivastigmine in subcortical vascular dementia given that behavioral symptoms are often the most distressing problems to both patients and carers and that vascular risk of existing antipsychotic drugs may be particularly high in patients with subcortical vascular dementia. Furthermore, a study longer than 6 months may be needed to demonstrate a cognitive benefit of rivastigmine.

Disclosure

This study was supported by a research grant from Novartis Pharmaceuticals (Hong Kong), Ltd. Apart from this grant, Novartis Pharmaceuticals had no participation in the collection, analysis, and interpretation of data, nor in the preparation of the manuscript.

Table 4 Adverse effects of the rivastigmine group

	N
Nausea and/or vomiting*	2 ^(#) , 1 withdrawn
Confusion*	1
Urinary tract infection	2
Dizziness*	1
Leg cramp*	1
Restroke	1 [#]
Gouty attack	1 [#]
Renal failure	1 [#]
Increased insomnia and loss of appetite*	1 [#]
Loss of appetite*	1 [#]
Total	12

Notes: *probably related to study drug; [#]adverse effects leading to withdrawal.

References

- Aharon-peretz J, Kliot D, Tomer R. 2000. Behavioral differences between white matter lacunar dementia and Alzheimer's disease: a comparison on the neuropsychiatric inventory. *Dement Geriatr Cogn Disord*, 11:294–8.
- Black S, Roman GC, Geldmacher DS, et al. 2003. Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. *Stroke*, 34:2323–30.
- Bullock R. 2005. Treatment of behavioural and psychiatric symptoms in dementia: implications of recent safety warnings. *Curr Med Res Opin*, 21:1–10.
- Chiu HF, Lam LC, Chi I, et al. 1998. Prevalence of dementia in Chinese elderly in Hong Kong. *Neurology*, 50:1002–9.
- Chiu HFK, Kee HC, Chung WS, et al. 1994. Reliability and validity of the Cantonese version of Mini-mental state examination – a preliminary study. *Hong Kong Coll Psychiatry*, 4(S2):25–8.
- Craig D, Birks J. 2006. Galantamine for vascular cognitive impairment. *Cochrane Database Syst Rev*, CD004746.
- Dubois B, Slachevsky A, Litvan I, et al. 2000. The FAB: a Frontal Assessment Battery at bedside. *Neurology*, 55:1621–6.
- Erkinjuntti T, Inzitari D, Pantoni L, et al. 2000. Research criteria for subcortical vascular dementia in clinical trials. *J Neural Transm Suppl*, 59:23–30.
- Erkinjuntti T, Kurz A, Gauthier S, et al. 2002. Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. *Lancet*, 359:1283–90.
- Ferri CP, Prince M, Brayne C, et al. 2005. Global prevalence of dementia: a Delphi consensus study. *Lancet*, 366:2112–7.
- Ikeda M, Hokoishi K, Maki N, et al. 2001. Increased prevalence of vascular dementia in Japan: a community-based epidemiological study. *Neurology*, 57:839–44.
- Jirong Y, Xiaoyan Y, Taixiang W, et al. 2004. Zhiling decoction for vascular dementia. *Cochrane Database Syst Rev*, CD004670.
- Leung VP, Lam LC, Chiu HF, et al. 2001. Validation study of the Chinese version of the neuropsychiatric inventory (CNPI). *Int J Geriatr Psychiatry*, 16:789–93.
- Mega MS, Masterman DM, O'Connor SM, et al. 1999. The spectrum of behavioral responses to cholinesterase inhibitor therapy in Alzheimer disease. *Arch Neurol*, 56:1388–93.
- Mok VC, Wong A, Yim P, et al. 2004. The validity and reliability of chinese frontal assessment battery in evaluating executive dysfunction among Chinese patients with small subcortical infarct. *Alzheimer Dis Assoc Disord*, 18:68–74.
- Moretti R, Torre P, Antonello RM, et al. 2002. Rivastigmine in subcortical vascular dementia: an open 22-month study. *J Neurol Sci*, 203–204:141–6.
- Moretti R, Torre P, Antonello RM, et al. 2003. Rivastigmine in subcortical vascular dementia: a randomized, controlled, open 12-month study in 208 patients. *Am J Alzheimers Dis Other Dement*, 18:265–72.
- Morris JC. 1993. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*, 43:2412–4.
- Rosler M, Anand R, Cicin-Sain A, et al. 1999. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. *BMJ*, 318:633–8.
- Salloway SCS, Malloy P, Pratt RD. 2003. A comparison of the cognitive benefits of donepezil in patients with cortical and subcortical vascular dementia. 1st Congress of the International Society for Vascular Behavioural and Cognitive Disorders (VAS-COG). Goteburg, Sweden.
- Tang WK, Chan SS, Chiu HF, et al. 2004. Frequency and determinants of poststroke dementia in Chinese. *Stroke*, 35:930–5.
- Tong A, Man D. 2002. The validation of the Hong Kong Chinese Version of the Lawton Instrumental Activities of Daily Living Scale for Institutionalized Elderly Persons. *Occupation, Participation and Health*, 22:132–41.
- Wilkinson D, Doody R, Helme R, et al. 2003. Donepezil in vascular dementia: a randomized, placebo-controlled study. *Neurology*, 61:479–86.
- Zhang ZX, Zahner GE, Roman GC, et al. 2005. Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. *Arch Neurol*, 62:447–53.