



Vascular Dementia: Advances in Diagnosis and Treatment

CME Home Study Booklet

Sponsored by



Supported through an unrestricted educational grant from
Eisai Inc. and Pfizer Inc



Contents

Poster 1	
Vascular dementia: an emerging healthcare problem	4
Poster 2	
Vascular dementia: risk factors	5
Poster 3	
Vascular dementia: societal burden	6
Poster 4	
Vascular dementia: signs and symptoms	7
Poster 5	
Vascular dementia: diagnosis	8
Poster 6	
Vascular dementia: current management strategies	9
Poster 7	
Vascular dementia: cholinergic mechanisms	10
Poster 8	
Vascular dementia: potential treatments	11
Poster 9	
Vascular dementia: summary	12
CME Posttest	14
Program Posttest and Evaluation	

Who Should Participate

Healthcare professionals responsible for the diagnosis and treatment of dementia.

Needs Assessment

Vascular dementia (VaD) is the second most common cause of dementia after Alzheimer's disease (AD) in some areas of the world and may be more prevalent than AD in certain populations. Early identification of risk factors is crucial in managing VaD. This program will address the diagnosis of VaD, risk factors and prognosis, and treatment outcomes with cholinesterase (ChE) inhibitors.

Learning Objectives

- Recognize the prevalence and impact of vascular dementia
- Describe the risk factors for vascular dementia
- Identify the characteristics and causes of vascular dementia subtypes
- Understand data demonstrating cholinesterase inhibitor efficacy in vascular dementia

Accreditation

The Center for Bio-Medical Communication, Inc. (CBC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. This CME activity was planned and produced in accordance with the ACCME Essentials.

CME Credit

CBC designates this activity for a maximum of 1 hour in Category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

Disclosure Statement

Disclosure is requested when faculty members are confirmed. This educational activity may include discussion of an unlabeled use or an investigative use not yet approved for a commercial product. Therefore, it is incumbent on individuals participating in this activity to be aware of these factors in interpreting its contents and evaluating its recommendations. Every effort has been made to encourage faculty to disclose any commercial relationships or personal benefits that may be associated with their participation in this activity. The following indicates the faculty and the nature of their commercial relationships.

Dr Stephen Salloway has disclosed that he receives research support and honoraria and provides consultation to Eisai Inc., Pfizer Inc, and Janssen. He will discuss unlabeled or investigative use of a commercial product.

Dr David Wilkinson has disclosed that he is a consultant and a member of the speakers bureau for Eisai Inc., Pfizer Inc, and Janssen. He will discuss unlabeled or investigative use of a commercial product.

Release date: February 21, 2004

Expiration date: February 28, 2005

Sponsored by



Overview

Vascular dementia is the second most common form of dementia worldwide, and the care of VaD patients is an increasing problem to society and to healthcare professionals. However, there are currently no approved treatments for the symptoms of VaD.

Patients with cardiovascular and cerebrovascular conditions are at risk of developing VaD. Therapy for vascular conditions helps to prevent or delay VaD onset, and monitoring for signs of impairment enables early detection of this condition.

The clinical presentation of VaD may be quite distinct, and specific tools for screening and identifying VaD are available. However, many VaD cases go unrecognized, as memory loss is not always apparent. Provision of optimal care to the VaD patient, and communication of appropriate treatment expectations to the patient's caregiver and family, may only be possible following accurate diagnosis of this condition.

Using a case study example, this program presents an overview of VaD causes, subtypes, diagnosis, and current management strategies, as well as showing data on ChE inhibitor therapies in VaD.

Faculty

Stephen Salloway, MD, MS, is Director of Neurology and The Memory Disorders Program at Butler Hospital in Providence, Rhode Island, and Associate Professor of Clinical Neurosciences and Psychiatry at Brown Medical School. He received his medical degree from Stanford Medical School and completed residencies in neurology and psychiatry at Yale University. Dr Salloway has published more than 75 scientific articles and book chapters, including 2 books. He is the Past President of the American Neuropsychiatric Association and serves on national

and international committees to help develop criteria for stroke and VaD. He is a scientific reviewer for the National Institutes of Health and for more than 25 journals, universities, and research foundations. Dr Salloway has received numerous grants for his research, which focuses on a) clinical trials for prevention and treatment of VaD, AD, and mild cognitive impairment, b) brain imaging of microvascular changes in the elderly, and c) assessment of frontal behavior and executive function. He is the Director of the Brown Combined Residency in Neurology and Psychiatry and Co-Principal Investigator of the Brown Dementia Research Fellowship Program. He lectures widely on dementia and neuropsychiatric disorders.

David Wilkinson, MB, ChB, MRCP, FRCPsych, is a Consultant in Old Age Psychiatry at the Western and Moorgreen Hospitals, Southampton, UK, and Honorary Clinical Senior Lecturer at the University of Southampton. He is also Director of the University's Memory Assessment and Research Centre and established the Centre's Psycho-Pharmacology Research Unit in 1990 to investigate treatments for AD. The Unit has been involved in many clinical studies of ChE inhibitors in the treatment of AD. Dr Wilkinson has published numerous peer-reviewed journal articles and book chapters in the fields of dementia and geriatric psychiatry. Dr Wilkinson's research interests include the mode of action of ChE inhibitors in AD, the efficacy and tolerability of excitatory amino acids and ChE inhibitors in VaD, and novel antipsychotics in late paraphrenia.

1

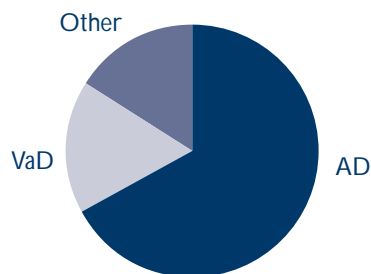
Vascular dementia: an emerging healthcare problem



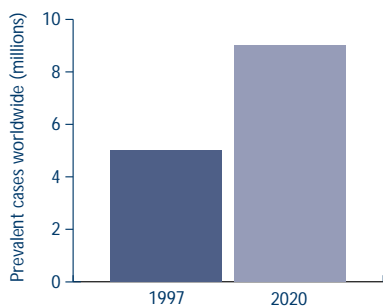
Vascular dementia (VaD) is a common condition that is

- ◆ Underrecognized
- ◆ Increasing in prevalence
- ◆ In need of treatment

Vascular dementia is the second most common form of dementia worldwide¹



Dementia types (% incident cases)



Estimated number of prevalent vascular dementia cases worldwide

The number of vascular dementia patients is expected to increase as the world population ages²

Some numbers relating to vascular dementia

0	approved treatments available
3	times greater mortality risk than those with no dementia ³
>10 000	US dollars annual care cost per patient ⁴
~600 000	prevalent cases of vascular dementia in Europe in 2000 ⁵
>1 000 000	prevalent cases of vascular dementia in the USA in 2002 ⁶



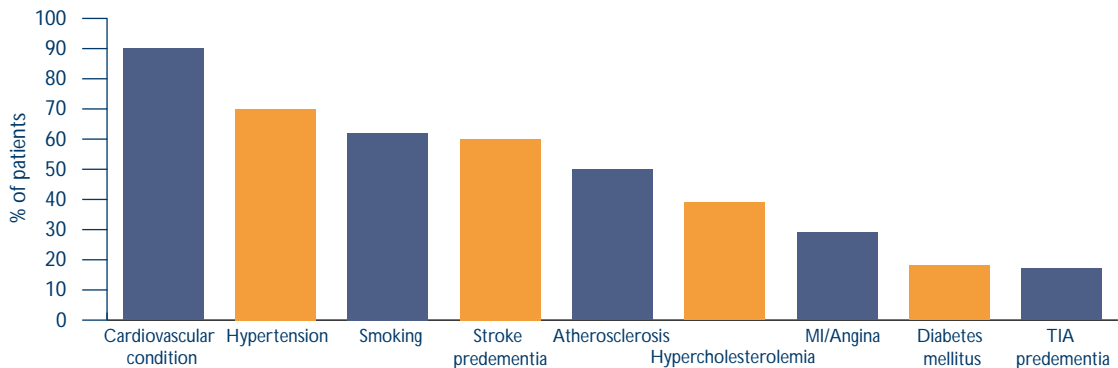
Mrs D's story

"Hello, I'm Mrs D. I'm 85 years old and my doctor says I have vascular dementia. Look for my face on each panel and you can follow my story."

2

Vascular dementia: risk factors

Vascular dementia is associated with cardiovascular and cerebrovascular risk factors and events⁷



Prevalence of vascular risk factors and conditions in a sample of vascular dementia patients⁷

Poststroke vascular dementia⁶

- ◆ 25%-41% of stroke survivors develop vascular dementia within 3 months

Cardiogenic vascular dementia⁶

- ◆ >40% of patients undergoing coronary artery bypass graft (CABG) surgery have cognitive impairment 5 years later
- ◆ 26% of patients hospitalized and treated for congestive heart failure (CHF) have vascular cognitive impairment

Different cerebrovascular and circulatory events can result in specific subtypes of vascular dementia⁸



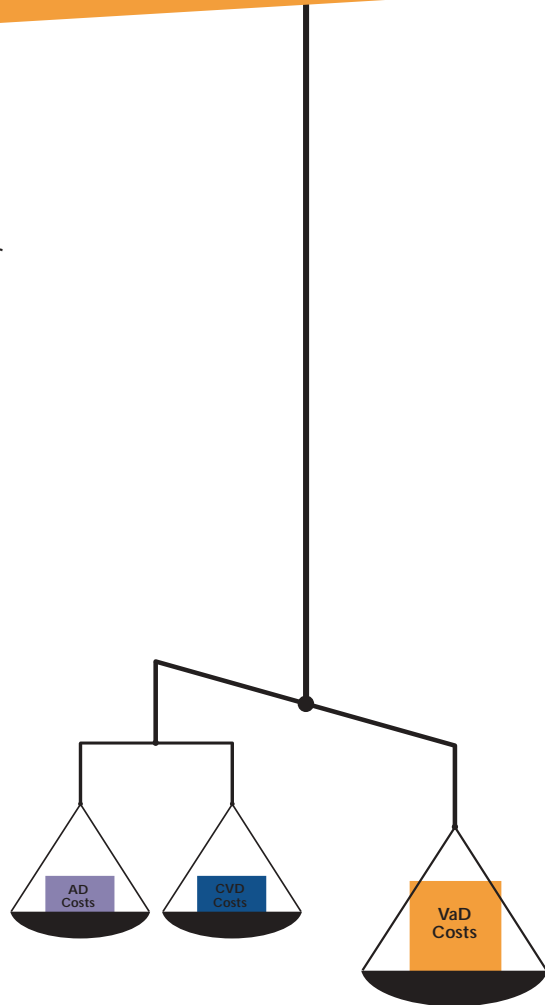
Mrs D's story

Mrs D suffers from hypercholesterolemia. At the age of 82, she had a stroke and was treated in intensive care until she recovered sufficiently to return home.

3

Vascular dementia: societal burden

- ◆ Societal costs of caring for vascular dementia patients are significantly greater than the costs of caring for patients with Alzheimer's disease or cerebrovascular disease alone^{4,9,10}
- ◆ The high healthcare costs of vascular dementia are due mostly to hospital utilization¹⁰
- ◆ The healthcare⁹ and caregiver¹¹ burdens of vascular dementia may be explained by
 - ❖ Existence of many comorbid conditions
 - ❖ The increased complexity of managing dementia and cerebrovascular disease in the same patient



Relative annual healthcare costs for vascular dementia (VaD), Alzheimer's disease (AD), and cerebrovascular disease (CVD).¹⁰



Mrs D's story

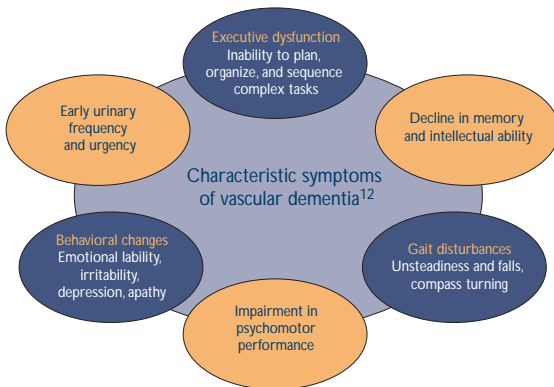
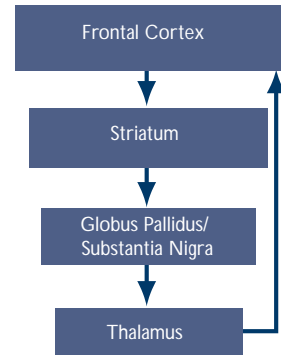
After her stroke, Mrs D moved in with her daughter. The time and care devoted by her daughter as the caregiver is an important factor in the total costs for the management of Mrs D's condition.

4

Vascular dementia: signs and symptoms

Frontal-subcortical-thalamic circuits

- ◆ Parallel circuits that connect the prefrontal cortex, striatum, and thalamus regulate:
 - ❖ executive control function
 - ❖ organization
 - ❖ mood and motivation
- ◆ Subcortical or cortical lesions within these circuits can result in the symptoms seen in vascular dementia⁸



- ◆ Memory loss is not always a prominent feature
- ◆ Cognitive deficits are patchy

Executive dysfunction

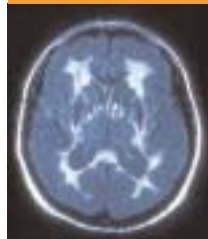
- ◆ Prominent and characteristic feature of vascular dementia¹³
- ◆ Linked to reduced ability to perform activities of daily living,¹⁴ such as handling finances, using the phone, playing chess

Cortical vascular dementia¹²



- ◆ Abrupt onset of symptoms, associated with clinically apparent events
- ◆ Stepwise progression
- ◆ Easier to detect deficits

Subcortical vascular dementia¹²



- ◆ Insidious onset, linked to clinically silent events
- ◆ Gradual progression
- ◆ May appear to resemble Alzheimer's disease



Mrs D's story

Mrs D's daughter takes up the story: "My mom was getting better after her stroke and went back home, but she wasn't acting like herself. She was having trouble managing her finances, and she couldn't find words for simple objects like a paper clip."

5

Vascular dementia: diagnosis

Accurate diagnosis of vascular dementia allows:

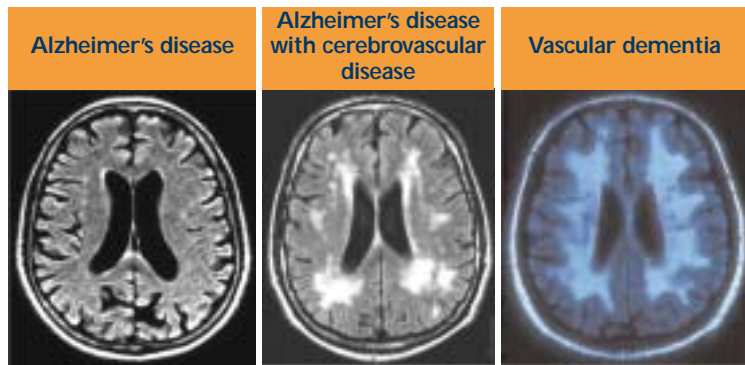
- ◆ Provision of optimal care (ie, risk factor management)
- ◆ Education of the caregiver and family about prognosis and appropriate treatment expectations

Screening for vascular dementia

- ◆ Useful tools include:
 - ❖ Tests of executive function, eg, clock drawing¹⁵
 - ❖ Tests that measure cognitive speed, eg, Trails B
 - ❖ Questioning patients and caregivers on daily activities, eg, a patient may remember telephone messages but forget to deliver them

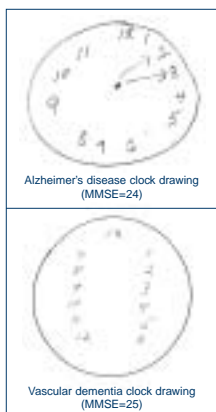
Diagnosing vascular dementia

- ◆ Diagnosis is often challenging, as vascular dementia:
 - ❖ Shares some clinical features with Alzheimer's disease
 - ❖ Coexists with Alzheimer's disease in ~30% of cases
 - ❖ May promote the expression of Alzheimer's disease¹⁶



The clinical presentation of vascular dementia may, however, be quite distinct, and specific diagnostic criteria have been developed¹⁷

	Alzheimer's disease	Alzheimer's disease with concomitant cerebrovascular disease	Vascular dementia
Presence of vascular conditions and risk factors	✓	✓	✓✓
Onset and progression	Insidious and gradual	Insidious and gradual	Abrupt and stepwise
Neuroimaging positive for cerebrovascular disease	✗	✓	✓
Psychiatric comorbidity	May be present	May be present	Frequent
Executive dysfunction	None or mild	✓	✓
Focal neurologic signs and symptoms	✗	May be present	✓
Memory impairment	✓✓	✓✓	May not be prominent
Gait disturbances	✗	May be present	✓
Emotional lability	✗	May be present	✓
Increased urinary frequency	✗	May be present	✓
Diagnostic criteria	DSM-IV, NINCDS	No current criteria	DSM-IV, NINDS-AIREN



Mrs D's story

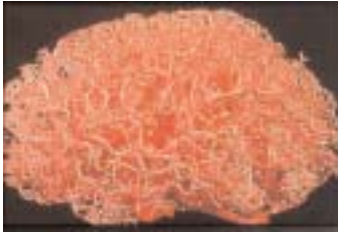
Mrs D's MRI scan and a strong temporal relationship between her stroke and onset of cognitive symptoms strongly suggested a diagnosis of vascular dementia. Her MMSE score was 25, and her clock drawing was mildly impaired (see figure: the clock should be set at 10 past 3).



Mrs D's clock drawing (MMSE=25)

Vascular dementia: current management strategies

6

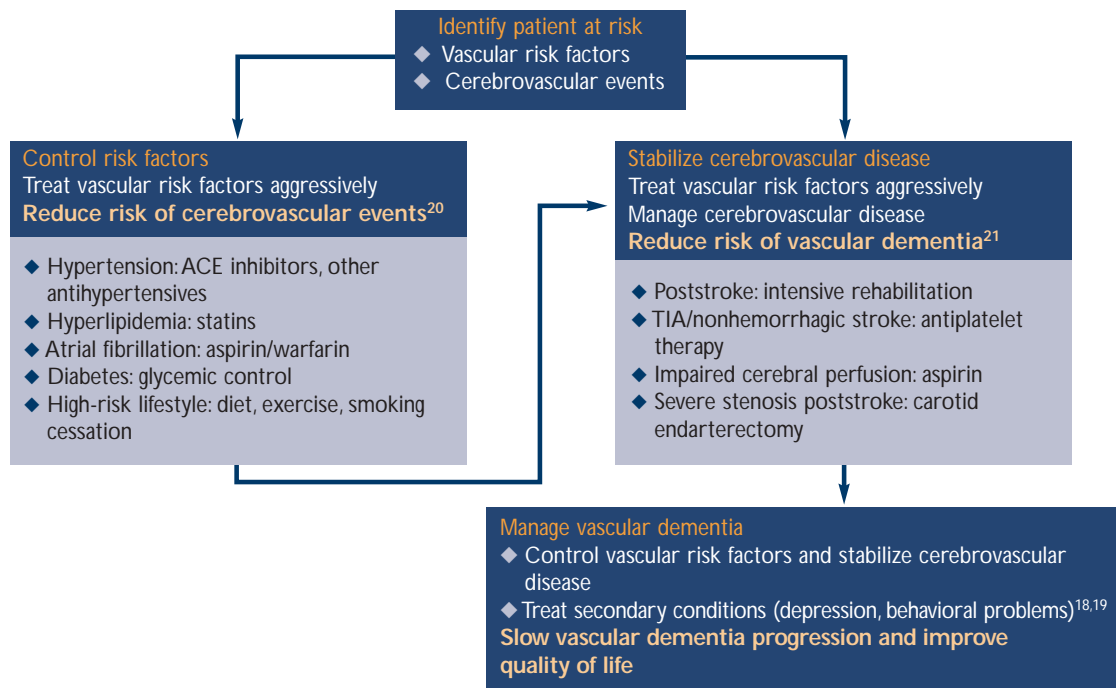


Cerebral vasculature

How is vascular dementia currently managed?^{18,19}

- ◆ Control risk factors for stroke
- ◆ Stabilize underlying cerebrovascular disease
- ◆ Treat secondary conditions (eg, depression)

There are presently no licensed treatments for the symptoms of vascular dementia; risk reduction is important for vascular dementia prevention



Mrs D's story

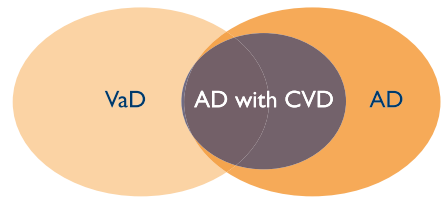
Mrs D's doctor reads her clinical notes: "Mrs D is taking atorvastatin for her hypercholesterolemia and has reached a target cholesterol level of 200 mg/dL. To prevent a recurrent cerebral hemorrhage, controlling Mrs D's blood pressure is extremely important."

Vascular dementia: cholinergic mechanisms

7

There is evidence of a cholinergic deficit in vascular dementia, similar to that in Alzheimer's disease:

- ↓ acetylcholine synthesis^{22,23}
- ↓ acetylcholine levels in cerebrospinal fluid²⁴



There is also evidence of cerebrovascular lesion damage to central cholinergic neurons^{25,26}

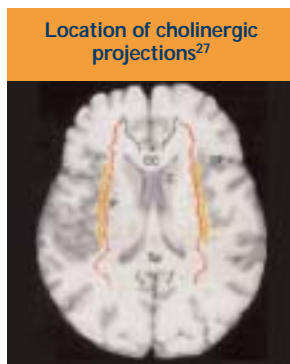
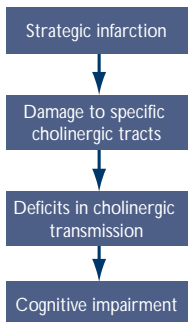
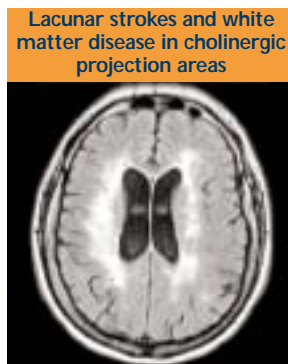


Figure reproduced with kind permission from Oxford University Press



How can the cholinergic deficit in vascular dementia be treated?

- ◆ Cholinergic (cholinesterase inhibitor) therapies have proven benefits in Alzheimer's disease patients²⁸
- ◆ Enhancement of cholinergic function in vascular dementia patients may result in similar benefits



Mrs D's story

Mrs D's cognitive symptoms relate to the location of her stroke. Damage to the right caudate may have led to reduced cholinergic transmission within a frontal-subcortical-thalamic circuit. Would you treat her with a cholinesterase inhibitor?

Vascular dementia: potential treatments

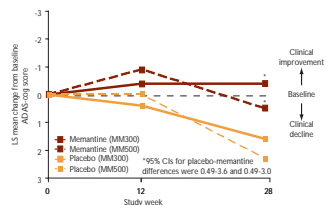
8

There are currently no approved treatments for the symptoms of vascular dementia. Effective, well-tolerated therapies are therefore needed, which address all symptoms across all subtypes.

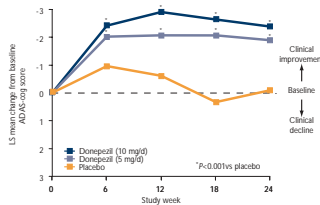
- ◆ Randomized, placebo-controlled trials of ChE inhibitors and other agents in vascular dementia patients have now been completed²⁹⁻³³
- ◆ Vascular dementia patients were selected according to the NINDS-AIREN criteria²⁹⁻³³
- ◆ The resulting populations were distinct from Alzheimer's disease populations⁷

Population studied	Domains exhibiting significant benefits versus control group
Galantamine ²⁹ (n=592)	Probable VaD (all subtypes)+Alzheimer's disease patients with cerebrovascular disease
Memantine ^{30,31} (n=900)	Probable VaD (all subtypes)
Donepezil ^{32,33} (n=1219)	Vascular dementia only (all subtypes) Alzheimer's disease patients excluded

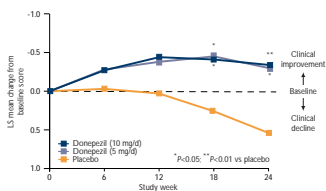
Population studied	Domains exhibiting significant benefits versus control group
Galantamine ²⁹ (n=592)	Vascular dementia subgroup (n=252): no significant benefits (possibly due to sample size)
Memantine ^{30,31} (n=900)	Cognition
Donepezil ^{32,33} (n=1219)	Overall group: cognition, global function, ADL Cortical subgroup (n=129): cognition ³⁴ Subcortical subgroup (n=607): cognition ³⁴



Significant benefits in cognition in memantine-treated VaD patients



Significant benefits in cognition in donepezil-treated VaD patients



Significant benefits in instrumental ADL in donepezil-treated VaD patients

Instrumental activities of daily living (ADL)

- ◆ Surrogate for executive function¹⁴
- ◆ Examples: managing finances, handling mail, housework

- ◆ Other studies have shown that, as expected, ChE inhibitors are also beneficial in patients with Alzheimer's disease plus cerebrovascular disease^{29,35,36}



Mrs D's story

Mrs D has now been taking donepezil HCl 10 mg/d for 4 years. Mrs D's daughter now has greater peace of mind, knowing that her mother is more independent, and that she can help with the grandchildren.

Vascular dementia: summary

Vascular dementia is common and is increasing in prevalence

Caring for vascular dementia patients is more costly and burdensome than caring for Alzheimer's disease patients

Patients with vascular risk factors and cerebrovascular conditions are at risk of vascular dementia

Vascular dementia can be prevented and controlled by effective management of vascular conditions

Characteristic symptoms of vascular dementia can be detected using specific tools

Accurate diagnosis of vascular dementia is necessary for the provision of optimal care

There is evidence of a cholinergic deficit in vascular dementia

Vascular dementia patients improve when treated with cholinesterase inhibitors

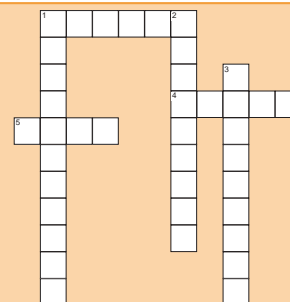
Mrs D's crossword

Across

- One of the main risks for vascular dementia (6)
- Drawing this is a tool useful in vascular dementia diagnosis (5)
- The number of licensed treatments for vascular dementia currently available (4)

Down

- A lesion location commonly seen in vascular dementia (11)
- _____ dysfunction, a characteristic feature of vascular dementia (9)
- An acetylcholinesterase inhibitor that benefits patients with vascular dementia (9)



Internet resources

American Stroke Association: www.strokeassociation.org
 National Family Caregivers Association: www.nfcares.org
 American Association for Geriatric Psychiatry: www.aagoga.org/fp_c/dementia.asp
 American Psychiatric Association: www.psych.org/clin_res/pg_dementia_3.cfm
 American Family Physician Monograph - Diagnosis and Management of Dementia: www.aafp.org/afp/monograph

References

- Fratiglioni L, et al. *Neurology* 2000;54:S10-S15.
- The World Health Report 1997. Available at <http://www.who.int/whr2001/2001/archives/1997/factse.htm>. Accessed April 2003.
- Knopman DS, et al. *Arch Neurol* 2003;60:85-90.
- Rockwood K, et al. *Stroke* 2002;33:1605-1609.
- Launer LJ, Hoffman A. *Neurology* 2000;54:S1-S8.
- Roman GC. *J Neurosci* 2002;20:204-7-10.

- Pratt RD. *J Neurol Sci* 2002;203:204-57-65.
- Kurz AF. *Int J Clin Pract* 2001;(suppl 120):5-8.
- Fillit H, Hill J. *J Neurol Sci* 2002;203:204-35-39.
- Hill J, et al. Presentation at the 17th Annual Meeting of the American Association for Geriatric Psychiatry (AAGP). Baltimore, Md; 2004.
- Vetter PH, et al. *J Gerontol Soc Sci* 1999;54B:593-598.
- Erkinjuntti T. *CNS Drugs* 1999;12:35-48.
- Roman GC, et al. *Alzheimer Dis Assoc Disord* 1999;13(suppl 3):S69-S80.
- Boyle PA, et al. *Int J Geriatr Psychiatry* 2002;17:164-169.
- Royall DR, et al. *J Neurol Neurosurg Psychiatry* 1998;64:588-594.
- Kalaria RN, et al. *Alzheimer Dis Assoc Disord* 1999;13(suppl 3):S115-S123.
- Roman GC, et al. *Neurology* 1993;43:250-260.
- Sachdev PS, et al. *Med J Aust* 1999;170:81-85.
- Nyenhuys DL, et al. *J Am Geriatr Soc* 1998;46:1437-1448.
- Yusuf S. *Lancet* 2002;360:2-3.
- Hajjar J, et al. *J Gerontol A Biol Sci Med Sci* 2002;57:M414-M418.
- Wallin A, et al. *Acta Neurol Scand* 1989;79:397-406.

- Waller SB, et al. *Can J Neurol Sci* 1986;13:528-532.
- Tohji H, et al. *J Neural Transm* 1996;103:1211-1220.
- Swarz RH, et al. *J Stroke Cerebrovasc Dis* 2003;12:29-36.
- Mesulam M, et al. *Neurology* 2003;60:1183-1185.
- Selden NR, et al. *Brain* 1998;121:2249-2257.
- Knopman DS. *Geriatrics* 1998;53(suppl 1):S31-S34.
- Erkinjuntti T, et al. *Lancet* 2002;359:1283-1290.
- Wilcock G, et al. *Int Clin Psychopharmacol* 2002;17:297-305.
- Orgogozo JM, et al. *Stroke* 2002;33:1834-1839.
- Black S, et al. *Stroke* 2003;34:2323-2330.
- Wilkinson D, et al. *Neurology* 2003;61:479-486.
- Salloway S, et al. *Neurology* 2003;60(suppl 1):A14.
- Frollich L, et al. Presentation at the 17th Annual Meeting of the American Association for Geriatric Psychiatry (AAGP). Baltimore, Md; 2004.
- Riepe MW, et al. Presentation at the 17th Annual Meeting of the American Association for Geriatric Psychiatry (AAGP). Baltimore, Md; 2004.

Instructions for Receiving CME Credit

The following examination provides the opportunity to assess your knowledge and understanding of the material presented on the CD-ROM and in the booklet.

To obtain 1 hour of Category 1 CME credit, you must:

- Complete the following CME Posttest by circling the correct responses on the answer sheet
- Answer the program evaluation questions
- Provide the requested personal information
- Keep a copy and mail or fax the Answer Sheet/Evaluation to the program sponsor



Center for Bio-Medical Communication, Inc.

433 Hackensack Avenue, 9th Floor

Hackensack, NJ 07601

Attn: VaD Posttest

Fax: 201-342-7555

Tests will be graded and, in approximately 6 weeks, a CME certificate will be mailed to each participant who achieved a score of 70% or greater.

Expiration date: February 28, 2005

Vascular Dementia: Advances in Diagnosis and Treatment

A CME Home Study Program

CME Posttest

- 1. Vascular dementia is the second most common form of dementia worldwide.**
 - a. True
 - b. False
- 2. How many prevalent cases of vascular dementia were there in the United States in 2002?**
 - a. >10 000
 - b. ~600 000
 - c. >1 000 000
- 3. Which of the following are risk factors for vascular dementia?**
 - a. Smoking, hypertension
 - b. TIA, stroke
 - c. Atherosclerosis, MI/angina
 - d. All of the above
- 4. What percentage of stroke survivors develop vascular dementia within 3 months?**
 - a. 4%-12%
 - b. 10%-23%
 - c. 25%-41%

5. Healthcare costs of vascular dementia have been shown to be:

- a. Higher than AD alone
- b. Higher than CVD alone
- c. Both of the above

6. Memory loss is always a prominent feature in vascular dementia patients.

- a. True
- b. False

7. Which of the following features is characteristic of the cortical vascular dementia subtype?

- a. Gradual progression
- b. Abrupt onset and stepwise progression
- c. Insidious onset
- d. May resemble Alzheimer's disease

8. Executive dysfunction is prominent in vascular dementia but not in Alzheimer's disease.

- a. True
- b. False

9. Diagnosis of vascular dementia is often challenging because this condition:

- a. Shares some clinical features with Alzheimer's disease
- b. Coexists with Alzheimer's disease in ~30% of cases
- c. May promote the expression of Alzheimer's disease
- d. All of the above

10. Current management of vascular dementia includes:

- a. Control risk factors for cardiovascular disease
- b. Stabilize underlying cerebrovascular disease
- c. Treat secondary conditions, eg, depression
- d. All of the above

11. There is evidence for a cholinergic deficit in vascular dementia.

- a. True
- b. False

12. Currently, there are no licensed treatments for the symptoms of vascular dementia.

- a. True
- b. False

Vascular Dementia: Advances in Diagnosis and Treatment

CME Home Study Program

PROGRAM POSTTEST AND EVALUATION

Expiration Date: February 28, 2005

The Center for Bio-Medical Communication, Inc. (CBC) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CBC designates this educational activity for a maximum of 1 hour in Category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours that he/she actually spent in the educational activity.

CME Posttest – Answer Sheet

- 1. a b 6. a b 11. a b
2. a b c 7. a b c d 12. a b
3. a b c d 8. a b
4. a b c 9. a b c d
5. a b c 10. a b c d

Please evaluate this CME Home Study Program using the following scale:

1 = poor 2 = fair 3 = average 4 = good 5 = excellent

To what extent were the stated objectives of the activity achieved?

- Recognize the prevalence and impact of vascular dementia 1 2 3 4 5
— Describe the risk factors for vascular dementia 1 2 3 4 5
— Identify the characteristics and causes of vascular dementia subtypes 1 2 3 4 5
— Understand data demonstrating cholinesterase inhibitor efficacy in vascular dementia 1 2 3 4 5
Did the activity meet your expectations? 1 2 3 4 5
Was the activity free of commercial bias? 1 2 3 4 5
Was the activity well organized? 1 2 3 4 5
Did this activity provide you with practical information that could improve the effectiveness of your day-to-day practice? 1 2 3 4 5

If so, how? _____

Please comment on the strengths and weaknesses of this activity, future topics, improvements, etc.

Thank you. This information will assist us in future topic development.

I have participated in the activity indicated above and am eligible for the CME hour claimed.

Signature: _____

Please Print

Name: _____

Mailing Address: _____

City/State/Zip: _____

Phone: _____ Fax: _____ E-Mail: _____



Mail or fax to: 433 Hackensack Avenue, 9th Floor Hackensack, NJ 07601 Phone: 201-342-5300 Fax: 201-342-7555 E-mail: cmeinfo@cbcbiomed.com Website: www.cbcbiomed.com

