PRIMARY CARE MANUAL ON WELLNESS IN ELDERS

Primary Care Manual on Wellness in Elders
Table of Contents

1. VASCULAR

PROMOTE CEREBROVASCULAR FITNESS

Hypertension is a significant risk factor for dementia. Multiple longitudinal studies of older subjects with untreated or under-treated hypertension demonstrate a relationship with chronic elevation of both systolic or diastolic blood pressure and risk for cognitive decline, e.g., Rotterdam Study, Framingham Study, and Honolulu Study. The possible mechanisms include hypertensive small vessel disease in white matter, accelerated atherosclerosis, hypoperfusion caused by cardiac disease, and others. The primary care physician should encourage a cerebrovascular fitness program for middle-aged and older individuals that includes meticulous, long-term control of both systolic and diastolic pressures and management of dyslipidemia through the appropriation of statins. Although retrospective studies demonstrate significant reduction in the risk of dementia among persons who take long-term statin medications, prophylactic therapy is not indicated in persons with a normal lipid profile. The precise protective mechanism of statin therapy is unknown but the effect seems unrelated to lipid levels or many risk factors for Alzheimer's disease. Individuals with low cardiac ejection fractions and those with untreated or under-treated atrial fibrillation are at greater risk for developing both Alzheimer's disease and vascular dementia. Meticulous cardiac care may reduce the likelihood of cognitive decline. Exercise in older persons, e.g., walking four hours per week, will significantly reduce the risk for cardiovascular complications and newer studies suggest that frequent exercise reduces the likelihood of cognitive decline. Aspirin is not shown to be effective against cognitive loss. Patient non-compliance is the major clinical obstacle to any cerebrovascular fitness program proposed by the primary care physician **(Click here – 2514.1)**.

Recommendation

Available data indicates that meticulous control of blood pressure, lipids, and cardiovascular fitness may decrease the risk for developing dementia in later life. Education about the potential "neuroprotective" effect of blood pressure control may enhance compliance **(CLICK HERE FOR MORE INFORMATION -- 2513.11, 2513.91). (Click here for references – 2513.13).**

The Primary Care Guide of Cerebrovascular Prevention Strategies for Dementia

1. Introduction

The primary care clinician can use clinical and pathological research to recommend cardiovascular and cerebrovascular fitness as part of their cognitive wellness message. The American Heart Association predicts that 25% of the adult population is hypertensive and about one-third are undiagnosed. The clinician can develop recommendations about the role of hypertension in dementia for patients in three broad age groups: midlife (40 to 65 yrs), older (65 to 75 yrs) and very old age groups (over 75). This segment reviews the available biomedical data that defines the role of hypertension in middle-aged and older patients as a risk factor for dementia in late life (1), (2). A lay person's fact sheet (Consumer Guide) is attached to this document for use as patient education. **(Click here for Fact Sheet – 2513.15).**

The human brain is sensitive to diminished perfusion or oxygenation. Ischemic brain injury can result with as little as three minutes of diminished blood flow. Managing cerebrovascular risk factors in mid or later life may provide significant benefit to cognitive function for all individuals, especially those over age 65. The presence of metabolic syndrome in midlife may increase the risk for dementia in later life **(Click Here For More Information – 2513.9)**. Chronic hypertension (3), risk factors for atherosclerosis (4), and cardiovascular disease (5), (6) are manageable risk factors in middle age that may predict cognitive decline in later life (7), (8), (9).

2. The Role of Hypertension in Cognitive Decline

A. Overview. Numerous longitudinal and cross-sectional studies have examined the rate or risk of cognitive decline in persons with untreated or under-treated hypertension. Longitudinal studies, such as those conducted in Sweden (9), England (10), Honolulu (11), (12), (13), Baltimore (14), and others report that older individuals who have a long-term history of untreated or under-treated hypertension have increased risk for dementia later in life, especially with other risk factors such as the presence of one or two APOE4 alleles (11).. Individuals with untreated hypertension may have diminished cognitive function, even in the absence of dementia (13).

Hypertension can damage both large and small caliber cerebral blood vessels in the brain. Sustained hypertension is a risk factor for accelerated atherosclerosis which is common in the large caliber cerebro-vasculature. Hypertension may damage medium and small size penetrating arterioles in hemispheric white matter producing arteriolar sclerosis in brain parenchyma. Damage to the massive plexus of penetrating arterioles that perfuse brain parenchyma is particularly apparent in white matter where the ubiquitous hyperintensities seen on MRI may be produced by hypertensive small vessel damage (15), (16), (17). Hypertension may be a risk factor for mild cognitive impairment (MCI), Alzheimer's disease, and vascular dementia in older persons (17), (18). **(Click here for more information about MCI).**

B. Longitudinal Studies on the Role of Hypertension in Dementia. A representative sample of studies on the relationship between blood pressure during midlife and cognitive

function in later life is demonstrated in **Table 1**. At least nine studies have employed cross-sectional or longitudinal methodologies to examine this issue with durations from 6 years through 30 years. The majority of studies demonstrate that sustained hypertension is associated with diminished cognitive function or increased risk for developing dementia. Each study group contained a variable mixture of individuals with a range of risk factors for atherosclerosis. The general consensus of long-term longitudinal studies supports the role of chronic hypertension in midlife as a risk factor for dementia in later life. Seven studies are cited that examine the rate of cognitive decline for older individuals based on a pre-existing history of hypertension **(See Table 2).** The study durations ranged from 3 years to 20 years. Location of these studies included the United States and Europe. Study groups were large, ranging from 600 to 4,000 older individuals. In general, studies of older individuals demonstrated more variation of cognitive outcomes for blood pressure levels than studies in midlife.

Table 1. The Relationship Between Blood Pressure During Midlife and Cognitive Function in Later Life

	Location	Duration	Study Size	Relationship to HBP	Refs.
1.	NIH	30 yrs.	392	⇩ Cognitive function	3
2.	Sweden	21	1449	↑ Risk for dementia	9
3.	New Mexico	30	717	⇩ Cognitive function	68
4.	Honolulu	26	3605	⇩ Cognitive function	11
5.	England	14	5838	Small but significant ⇩ Cognitive function	10
6.	Finland	21	1449	↑ Risk for MCI but related to other vascular risk factors	69
7.	Japan	25 to 30	1660	Associated with Vascular dementia	70
8.	USA	30+ yrs	8845	Hypertension and multiple other cardiovascular risk factors ↑ risk for dementia	5
9.	Multi-site/USA	6 yrs.	10,963	↑ Risk and ↑ rate of dementia	71

2513.14 cerebrovascular prevention strategies for dementia

Among studies that include older subjects, a single study **(See Table 2, Line 1)** demonstrated no significant association while the remainder of the studies demonstrated diminished cognition of varying severity. Several studies **(See Table 3)** in elderly subjects cited loss of cognitive function with extremes of blood pressure and negative effect from low pressure as well as high pressure **(19)**. In general, the relationship between hypertension in the older individual, i.e., over age 65, seems less clear, especially for individuals with mild hypertension. Five longitudinal studies examine the relationship between cognitive function and blood pressure in very old individuals, i.e., over age 75 **(See Table 3).** The duration of studies ranged from 3 to 6 years and the population sizes ranged from 377 to 4, 937. The role of hypertension in the very old seemed more obscure than in studies in older individuals (20). Lower blood pressure appeared problematic, as well as significant hypertension (21) and some studies suggest that hypertensive individuals with dementia demonstrate normalization of blood pressure over time (5). Sympathetic autonomic regulation is partially mediated by the right insular cortex which often sustains damage in Alzheimer's disease. Hypertensive demented patients have a steeper rate of cognitive decline than normotensive individuals (22).

Table 2. Rate of Cognitive Decline for Older Individuals Based on Blood Pressure

	Age	Location	Duration	Study Size	Relationship to HBP	Refs
1.	Over 65	Chicago	3-6 years	4284	No Association	72
2.	69-74	Sweden	20 yrs.	502	↓ cognitive function	73
3.	Over 65	Medicare Population	7 yrs.	1259	May ↑risk of dementia, especially with other CV diseases	74
4.	Over 65	Duke, NC	3 yrs.	4136	Decline associated with extremes of BP	75
5.	Over 65	East Boston	6 yrs.	3657	Complex relationship between BP and cognition	76
6.	Over 65	East Boston	13 yrs	634	Not associated with AD	77
7.	Over 65	Baltimore	11	847	↓ Cognition	14

2513.14 cerebrovascular prevention strategies for dementia

Table 3. Relationship Between Cognitive Function and Blood Pressure in the Very Old

	Age	Location	Duration (years)	n	Relations to HBP	Refs
1.	Over 75	Australia	6	377	Unclear relations	78
2.	75-101	Sweden	3.5	1736	Lower BP may be problematic Very high BP is problematic	79
3.	> 75	Sweden	3	924	↓ Cognitive Function	80
4.	70-89	*SCOPE	3.7	4937	Elders with HBP and mild impairment have greater risk for dementia	87
5.	70+	Sweden	15	382	↑ risk for dementia	6

n= study size *SCOPE: Study on Cognition and Prognosis in the Elderly

2513.14 cerebrovascular prevention strategies for dementia

Results of studies in individuals with mild cognitive impairment (MCI) appear less consistent for hypertension as a risk factor for persons with MCI progressing to dementia (23), (24), (25). Cardiovascular risk factors may be associated with the risk of developing MCI and the likelihood of transition from MCI into dementia; however, few studies have carefully examined this relationship **(See Table 4).**

Table 4. A Summary on Studies About the Role of Treating Hypertension in Preventing Dementia

#	t	a	n	Treatment Effect on Dementia Risk and Cognition	Ref.
1	39 m	60+	2902	Reduction of 55% by treatment	32
2	6 m	69+	69	Lowering blood pressure did not lower cognition	66
3	6 wks	25-55	98	No adverse effect on cognition	33
4	22 m	65+	7046	Slight ⇩ risk for dementia, probably vascular	34
5	6yrs	55+	1979	Impaired cognition predicts poor compliance	36
6	5 yrs	60+	4736	No adverse effect from treating hypertension, unclear benefit on cognition	67
7	5 yrs	65+	1900	Antihypertensive treatment reduces odds of increased cognitive impairment by 38%	27
8	2 yrs	55-89	1993	Cognitive impairment may ⇩ compliance	54
9	3 yrs	65+	3308	⇩ AD with potassium sparing diuretics	91

t=duration of study a=age of subjects m=months n=number of subjects

2513.14 cerebrovascular prevention strategies for dementia

Meta-analyses are not available that examine the role of hypertension and cognition in longitudinal studies. A meta-analysis would be limited by the size and variability of the study populations as well as the techniques used to examine the relationship between hypertension and cognition. Substantial, longitudinal data suggests that early onset hypertension may be more damaging to cognitive function than late-life onset hypertension and treatment of early onset hypertension may diminish the risk for developing cognitive impairment in later life.

Brain infarction is a major complication that can result from hypertension and cardiovascular disease. Stroke substantially increases the risk for dementia in persons over the age of 65 (29), (30). Twenty percent of all older individuals have silent strokes which are most commonly lacunar infarcts in the basal ganglia (80%). This often unrecognized cerebrovascular disease doubles the risk for developing dementia in later life (31). Stroke risk factors include hypertension, atherosclerotic vascular disease, and elevated homocysteine.

C. Cognitive Effects of Pharmacological Interventions for Hypertension

Antihypertensive therapy may reduce the risk of cognitive decline in persons with chronic hypertension (26), (27) and treatment should not worsen cognitive function. No specific class of antihypertensive medication is consistently identified as more beneficial to cognition **(See Table 4),** (32), (33), (34). The first step in reducing hypertensive risk factors for cognitive decline is adequate, safe control of hypertension. Sustained compliance by the demented patient may become problematic, as dementia increases the likelihood of non-compliance (35), (36). Neurodegenerative changes such as senile plaques and neurofibrillary tangles begin to develop in some persons over age 50 and aggressive cardiovascular preventive interventions could be reviewed at this point in the patient's life. Protection of left ventricular function and reduction of atherosclerotic risk factors would appear prudent for cognitive as well as cardiac health. Appropriate control of homocysteine in all age groups may diminish the risk of cognitive decline. Long-term folic acid and B-Complex vitamin supplementation appear to reduce the homocysteine level in many older individuals. Demented persons receiving appropriate antihypertensive therapy may have enhanced benefit

from cholinesterase therapy (28). (Click here for additional information on the role of folic acid and homocysteine in cognitive function – DETA 2513.41).

Older persons with atrial fibrillation have increased risk of cognitive decline, as well as stroke and white matter damage (37), (38), (39). The cognitive benefit of prophylactic anticoagulants or anti-arrhythmic agents in older persons with atrial fibrillation has not been adequately studied. Conventional wisdom suggests prudent but aggressive therapy of atrial fibrillation as protection of cognitive and neurological function (40). Demented persons treated with antihypertensive medications may have better response to cholinesterase inhibitor therapy (28).

The majority of studies that examine the role of statins in dementia suggest a protective effect in some individuals, although several studies dispute this beneficial effect (41). The beneficial effect of statins on cardiovascular function suggests a possible reduction of vascular burden in the brain (42). Other putative roles for statin therapy include the reduction of amyloid burden. The risk-benefit ratio for statins supports the aggressive use of these medications in persons with hyperlipidemia; however, the prophylactic use of these drugs in at-risk populations for dementia is not recommended (41). The prophylactic use of low dose aspirin therapy for cognition has not been adequately studied. Click here for additional information on the role of statin therapy and cognition – DETA 2513.91.

D. Neuropathological Correlates to Hypertension

The role of hypertension and cerebrovascular disease in the pathogenesis of dementia or age-related cognitive decline remains vague because neuropathologist lacks precise methodologies to quantitate the extent of vascular damage to the brain. Longitudinal studies suggest that brains from decedents with chronic hypertension exhibit increased Alzheimer's pathology. Senile plaque counts in brains of non-demented older subjects correlate to severity of coronary artery stenosis by atherosclerosis (15), (16), (43), but not premortem cholesterol levels (89). Hypertensive individuals have diminished brain volume in comparison to normotensive and increased microscopic pathology, as well as increased numbers of white matter lucencies (21), (44), (45), (46), (47), (48), (49). White matter damage is present in brains of intact and demented elders but this damage may worsen cognition in Alzheimer patients (50).

Microscopic examination of white matter blood vessels in persons with chronic hypertension demonstrate thickening of vascular media and loss of brain parenchyma around the vessel along with evidence of old perivascular microscopic bleeding as detected by hemosiderin laden macrophages around arterioles (45), (46), (47), (17). This non-specific finding can be seen in other disorders that produce neuropsychiatric symptoms including Systemic Lupus Erythematosis. White matter blood vessels are susceptible to hypertensive injury because they have diminished pressure regulating capacity in comparison to arborizing blood vessels in the cerebral cortex. This hypertensive arteriolar damage is associated with lacunar or slit-like infarcts in the white matter as well as in the basal ganglia and thalamus. Small vessel disease in white matter may correlate with cognitive decline (51).

E. Conclusion about the Role of Chronic Hypertension on Cognition

Mild, chronic hypertension in midlife may produce greater cognitive morbidity in later life than similar elevations of blood pressure in the very old. Hypotension in the elderly person

may be as problematic as moderately severe hypertension. Severe hypertension appears problematic in all groups. A further confounding issue is the role of multiple cardiovascular risk factors. The vague, imprecise neuropathological definitions used to diagnose "vascular dementia" incorporate only discrete quantities of infarcted brain parenchyma despite the fact that diffuse white matter hypertensive small vessel disease can produce wide-spread injury (17). In fact, neuroscientists have no accurate method of measuring total vascular damage in the human brain.

3. The Role of Cerebrovascular Disease in Dementia

Most strokes are produced by extracranial cerebrovascular disease originating in the left ventricle of the heart, the carotid system or the Circle of Willis. Older individuals have a significantly increased risk for developing dementia following a stroke and efforts to reduce risk factors for stroke may reduce risk for cognitive decline (17). Individuals with low left ventricular ejection fraction and atrial fibrillation have increased risk for cognitive decline with aging (40), (52).

The role of atherogenic medical conditions, such as hyperlipidemia, in the pathogenesis of cognitive decline remains contradictory, as some studies dispute the relationship between dyslipidemia and dementia. The protective role of statin medications also remains unclear. Elevated homocysteine and decreased folic acid are known risk factors for accelerated atherosclerosis (55). Folic acid supplementation may reduce the serum level of homocysteine and benefit cognition through cerebral vascular benefits or other undetermined mechanisms (56), (57). Click here for more information about risk factors for atherosclerosis – DETA 2513.91).

Data from the Nun Study suggests that vascular pathology is an important benchmark for cognitive decline in aging members of well-characterized populations, such as the clergy (58). Individuals with microscopic features of Alzheimer's disease may retain intellectual function into later life; however, those individuals with both Alzheimer pathology and vascular damage were more likely to demonstrate cognitive deficits before death. Mixed dementias often include both vascular damage and Alzheimer's disease.

The concept of cognitive reserve remains controversial; however, the newest science supports this principle. Cognitive reserve may reflect redundancy of synapses, redundancy of strategic cognitive functions through interconnected neural networks or enhanced neural plasticity. Dementia may occur when the cumulative burden of brain damage exceeds a threshold value required to sustain normal intellectual function. ***Click here for more information about cognitive reserve – 2513.51.*** Vascular damage to the brain may occur through several mechanisms including direct loss of neurons, disruption of vascular permeability, damage to vital white matter pathways carrying ascending fibers, such as cholinergic systems or disruption of cortical to cortical pathways that run through the hemispheric white matter (17). The addition of vascular damage to Alzheimer pathology may accelerate the onset of intellectual loss.

4. The Role of Cardiac Disease and Bypass Surgery in Cognitive Decline

Severe left ventricular dysfunction as measured by low ejection fracture (below 30%) is correlated to poor cognitive function (52). Specific kinds of cardiac or peripheral vascular disease, such as past myocardial infarction (90) or thickened carotid arteries may increase the

likelihood of cognitive decline in later life (51). Increased left ventricular mass is associated with diminished cognitive function over five years (93). The role of coronary artery bypass grafting (CABG) as a precipitant for cognitive decline in older persons is problematic for the primary care physician who may recommend bypass surgery. Multiple studies have suggested the adverse effect of CABG on the brain (59), (60), (61), (62); however, recent studies dispute this observation (53), (63). Post-operative functional brain imaging studies suggest diminished metabolic activity in persons undergoing CABG procedure, although obvious variables such as pump time, clamp time and gender do not seem to impact cognition. Post-operative delirium continues to be a major issue and these symptoms may persist for up to six months. CABG surgery can sustain left ventricular function and theoretically reduce other risk factors associated with dementia. The clinician must weigh risk benefits to each patient comparing the severity of cardiac morbidity to cognitive and functional status. Available data will not provide guidance for which patients might suffer greater cognitive loss following CABG surgery.

5. Future Directions for Crafting Preventive Recommendations on Vascular Risk Factors and Cognition

A prospective study that randomizes hypertensive individuals into treated versus non-treated groups to assess the impact of long-term antihypertensive therapy on cognitive decline will not be done for ethical and legal issues. Available data suggests diminished risk for dementia with treatment by potassium sparing diuretics (91) and others (88). The best available science indicates that midlife choices determine later life cardiovascular, cerebrovascular, and cognitive wellness. Hypertension, heart disease or metabolic syndromes are linked to cognitive decline; providing additional incentives to patients for compliance with medications and lifestyle changes (67). The potential impact of a cerebrovascular fitness program on the cognitive function for individuals over the age of 65 is unclear, although conventional, clinical wisdom would encourage the use of these interventions in persons of all age groups.

The concept of a “brain screen” has been proposed that includes prospective assessment of vascular risk factors in the older patient that may identify a substantial yield of disorders that respond to therapy (65). The role of preventive interventions in older persons remains unclear; however, conventional wisdom suggests that cerebrovascular risk reduction will likely benefit middle age and older individuals (92).

Table 5. The Possible Role Of Cardiovascular Preventive Interventions In Midlife And Later Life For Dementia

	Intervention	40-60 Midlife	>60 Older	Recommendation to Clinician	Refs.
1	Weight Control	Obesity correlated to cognitive decline	Unclear	Weight management in midlife	9
2.	Control HBP	Correlated to later cognitive decline	Unclear, except for severe HBP	1. control all severe HBP 2. ↓ BP in midlife to ↓ risk	78, 26, 82, 88, 91
3.	Statin Therapy	Unclear but probably beneficial	Unclear	Treat dyslipidemia	41
4.	Reduce Plasma Homocysteine	Correlated to ↓ cognitive function in late life	Correlated to dementia	Vitamin supplementation	83, 84, 85
5.	Exercise Program	Correlated to ↓ CV disease and ↓ dementia	Correlated to ↓dementia	Promote regular exercise	86

HBP – hypertension **CV**-cardiovascular

2513.14 cerebrovascular prevention strategies for dementia

Recommendations to the Primary Care Providers

1. Monitor BP and treat hypertension as per published national guidelines.
2. Educate patients that cardiovascular fitness protects the aging brain.
3. Monitor for the metabolic syndrome and treat each component.
4. Maximize ejection fraction to optimize cognitive function.
5. Screen cognitive function for all bypass candidates.
6. Empower patients to control their cognitive aging by managing vascular risk factors.
7. Use dementia risk reduction as another compliance tool for medications, diet, and health behaviors.

References

1. Hazzard WB, Blass JP, Halter JB, et al (Eds.) (2003), *Principles of geriatric medicine and gerontology* (5th Edition). New York: McGraw-Hill.
2. Ravona-Springer R, Davidson M, Noy S. The role of cardiovascular risk factors in Alzheimer's disease. CNS Spectr 2003;8(11):824-831.
3. Swan GE, DeCarli C, Miller BL, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. Neurology 1998;51(4):986-93.
4. Aleman A, Muller M, de Haan EH, van der Schouw YT. Vascular risk factors and cognitive function in a sample of independently living men. Neurobiol Aging 2005;26(4):485-90.
5. Whitmer RA, Sideny S, Selby J, et al. Midlife cardiovascular risk factors and risk for dementia in late life.
6. Skoog I, Lernfelt B, Landahl S, et al. 15-year longitudinal study of blood pressure and dementia. Lancet 1996;347:1141-45.
7. Korczyn AD. The underdiagnosis of the vascular contribution to dementia. J. Neuro Sci 2005;229-230(1): 3-6.
8. Papdemetriou V. Blood pressure regulation and cognitive function: a review of the literature. Geriatrics 2005;60(Jan):20-24.
9. Kivilpelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol. 2005;62(10):1556-60.
10. Singh-Manoux A, Marmot M. High blood pressure was associated with cognitive function in middle-age in the Whitehall II study. J Clin Epidemiol. 2005;58(12):1308-15.
11. Peila R, White LR, Petrovich H, et al. Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu-Asia aging study. Stroke 2001;32(12):2882-9.
12. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia: the Honolulu-Asia aging study. Neurobiology of Aging 2000;21:49-55.
13. Launer LJ, Masaki K, Petrovitch H, et al. The association between midlife blood pressure levels and late-life cognitive function. JAMA 1995;274:1846-1851.
14. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. Hypertension 2005;45(3):374-9.
15. White L, Petrovitch H, Hardman J, et al. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann NY Acad. Sci. 2002;977:9-23.
16. Kararia RN, Ballard C. Overlap between pathology of Alzheimer disease and Vascular dementia. Alzheimer Disease and Associated Disorders 1999;13(suppl 3):S115-S123.
17. Bowler JV. Vascular cognitive impairment. J Neurol Neurosurg Psychiatry 2005;(Suppl V):35-44.
18. Goldstein IB, Bartzokis G, Guthrie D, Shapiro D. Ambulatory blood pressure and brain atrophy in the healthy elderly. Neurology 2002;59:713-719.
19. Zuccala G, Onder G, Pedone C, et al. Hypotension and cognitive impairment. Selective association in patients with heart failure. Neurology 2001;57:1986-1992.
20. Starr JM, Whalley LJ. Senile hypertension and cognitive impairment: an overview. Journal of Hypertension 1992;10(suppl 2):S31-S42.
21. Van Dijk EJ, Breteler MM, Schmidt R, et al. The association between blood pressure, hypertension, and cerebral white matter lesions. Cardiovascular determinants of dementia study. Hypertension 2004;44(5): 625-30.
22. Bellew KM, Pegeon JG, Sang PE, et al. Hypertension and the rate of cognitive decline in patients with dementia of the Alzheimer type. Alzheimer Dis Assoc Disord 2004;18(4):208-13.
23. Solfrizzi V, Panza F, Colacicco AM, et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. Neurology 2004;63(10):1882-91.
24. Tervo S, Kivipelto M, Hanninen T, et al. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement. Geriatr. Cogn. Disor. 2004;17(3):196-203.
25. Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the cardiovascular health study cognition study: part 2. Arch Neurol 2003;60(10):1394-9.
26. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment. Arch Intern Med. 2002;162:2046-2052.
27. Murray MD, Lane KA, Gao S, et al. Preservation of cognitive function with antihypertensive medications. Arch Intern Med 2002;162:2090-2096.
28. Rozzini L, Vicini Chilvovi B, Bellelli G, et al. Effects of cholinesterase inhibitors appear greater in patients on established antihypertensive therapy. Int J Geriatr Psychiatry 2005;20(6):547-51.

29. Vermeer SE, Koudstaal PJ, Oudkerk M, et al. Prevalence and risk factors of silent brain infarcts in the population-based Rotterdam Scan Study. Stroke 2002;33:21-25.
30. Rockwood K, Wentzel C, Hachinski V, et al. Prevalence and outcomes of vascular cognitive impairment. Neurology 2000;54:447-451.
31. Blass JP, Ratan RR. "Silent" strokes and dementia. N Engl J Med. 2003;348(13):1277-1278.
32. Forette F, Seux ML, Staessen JA, et al. The prevention of dementia with antihypertensive treatment. Arch Intern Med. 2002;162:2046-2052.
33. Muldoon MR, Waldstein SR, Ryan CM, et al. Effects of six anti-hypertensive medications on cognitive performance. J. Hypertens. 2002;20(8):1643-52.
34. In't Veld BA, Ruitenberg A,Hofman A, et al. Antihypertensive drugs and incidence of dementia: the Rotterdam Study. Neurobiol Aging 2001;22(3):407-12.
35. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
36. Salas M, In't Veld BA, van der Linden, et al. Impaired cognitive function and compliance with antihypertensive drugs in elderly: the Rotterdam Study. Clin Pharmacol Ther. 2001;70(6):561-6.
37. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham study. Stroke 1991;22:983-988.
38. De Leeuw FE, de Groot JC, Oudkerk M, et al. Atrial fibrillation and the risk of cerebral white matter lesions. Neurology 2000;54:1795-1800.
39. Ott A, Breteler MMB, Bruyne MC, et al. Atrial fribrillation and dementia in a population-based study. Stroke 1997;28:316-321.
40. Sabatini T, Frisoni GB, Barbisoni P, et al. Atrial fibrillation and cognitive disorders in older people. J Am Geriatr Soc. 2000;48:387-390.
41. Xiong GL, Benson A, Doraiswamy PM. Statins and cognition: what can we learn from existing randomized trials? CNS Spectr 2005;10(11):867-874.
42. Bestermann W, Houston MC, Basile J, et al. Addressing the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome in the southeastern United States, Part II: treatment recommendations for management of the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome. Am J Med Sci 2005;329(6):292-305.
43. Sparks DL, Hunsaker JC, Scheff SW, et al. Cortical senile plaques in coronary artery disease, aging and Alzheimer's disease. Neurobiology of Aging 1990;11:601-607.
44. Blasko I, Kemmler G, Drampla W, et al. Plasma amyloid beta protein 42 in non-demented persons aged 75 years: effects of concomitant medication and medial temporal lobe atrophy. Neurobiol Aging 2005;26(8):1135-43.
45. Jellinger KA, Attems J. Prevalence and pathogenic role of cerebrovascular lesions in Alzheimer's disease. J. Neurol Sci. 2005;229-230(1):37-41.
46. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US Naitonal Alzheimer's Coordinating Center. Neurology 2005;64(3):494-500.
47. Bennett DA, Schneider JA, Bienias JL, et al. Mild cognitive impairment is related to Alzheimer's disease pathology and cerebral infarctions. Neurology 2005;64(5):834-41.
48. Sparks DL. Coronary artery disease, hypertension, ApoE, and cholesterol: a link to Alzheimer's disease. Annals New York Academy of Sciences 1997;826:128-145.
49. Petrovitch H, Whie LR, Izmirilian G, et al. Midlife blood pressure and neuritic plaques, neurofibrillary tangels, and brain weight at death: the HAAS. Neurobiology of Aging 2000;21:57-62.
50. Burns JM, Chruch JA, Johnson DK, et al. White matter lesions are prevalent but differentially related with cognition in aging and early Alzheimer disease. Arch Neurol 2005;62(12):1870-6.
51. Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl. J. Med. 2003;348(13):1215-22.
52. Zuccala G, Cattel C, Manes-Gravina E, et al. Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. Journal of Neurology, Neurosurgery, and Psychiatry 1997;63:509-512.
53. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the cardiovascular health study cohort. J Am Geriatr Soc. 2005;53(7):1101-7.
54. Farmer ME, Kittner SJ, Abbott Rd, et al. Longitudinal measured blood pressure, antihypertensive medication use, and cognitive performance: the Framingham Study. J Clin. Epidemiol. 1990;43(5):475-80.
55. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476-483.
56. Bazzano LA, He J, Ogden LG, et al. Dietary intake of folate and risk of stroke in US men and women. Stroke 2002;33:1183-1189.

57. Hankey GJ. Is homocysteine a causal and treatable risk factor for vascular disease of the brain (cognitive impairment and stroke)? Annals of Neurology 2002;51:279-281.
58. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease (The Nun Study). JAMA 1997;277:813-817.
59. Raja PV, Blumenthal JA, Doraiswamy PM. Cognitive deficits following coronary artery bypass grafting: prevalence, prognosis, and therapeutic strategies. CNS Spectr 2004;9(10):763-772.
60. Bendszus M, Reents W, Franke D, et al. Brain damage after coronary artery bypass grafting. Arch Neurol. 2002;59:1090-1095.
61. Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary artery bypass surgery. N Engl J Med 2001;344:395-402.
62. Vanninen R, Aikia M, Kononen M, et al. Subclinical cerebral complications after coronary artery bypass grafting. Arch Neurol 1998;55:618-627.
63. Knopman DS, Petersen RC, Cha RH, et al. Coronary artery bypass grafting is not a risk factor for dementia or Alzheimer's disease. Neurology 2005;65(7):986-90.
64. Barnes DE, Yaffe K, Satariano WA, Tager IB. A longitudinal study of cardiorespiratory fitness and cognitive function in healthy older adults. J. Am Geriatr Soc 2003;51(4):459-65.
65. Giladi N, Mordechovich M, Gruendlinger L, et al. "Brain screen" a self-referral, screening program for strokes, falls, and dementia risk factors. J. Neurol 2005.
66. Starr JM, Whalley LJ, Deary IJ. The effects of antihypertensive treatment on cognitive function: results from the HOPE study. JAGS 1996;44:411-415.
67. Applegate WB, Pressel S, Wittes J, et al. Impact of the treatment of isolated systolic hypertension on behavioral variables. Arch Intern Med. 1994;154:2154-2160.
68. Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. Stroke 1998;29(11):2334-40.
69. Kivipelto M, Helkala EL, Hanninen T, et al. Midlife vascular risk factors and late-life mild cognitive impairment: A population-based study. Neurology 2001;56(12):1683-9.
70. Yamada M, Kasagi F, Sasaki H, et al. Association between dementia and midlife risk factors: the Radiation Effects Research Foundation Adult Health Study. J Am Geriatr Soc. 2003;51(3):410-4.
71. Knopman D, Bolland LL, Mosely T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42-48.
72. Hebert LE, Scherr PA, Bennett DA, et al. Blood pressure and late-life cognitive function change: a biracial longitudinal population study. Neurology 2004;62(11):2021-4.
73. Kilander L, Nyman H, Boberg M, Lithell H. The association between low diastolic blood pressure in middle age and cognitive function in old age. A population-based study. Age and Ageing 2000;29(3): 243-248.
74. Posner HB, Tang MX, Luchsinger J, et al. The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function. Neurology 2002;58(8):1175-81.
75. Bohannon AD, Fillenbaum GG, Peiper CF, et al. Relationship of race/ethnicity and blood pressure to change in cognitive function. J Am Geriatr Soc 2002;50(3):424-9.
76. Glynn RJ, Beckett LA, Hebert LE, et al. Current and remote blood pressure and cognitive decline. JAMA 1999;281(5):438-45.
77. Morris MC, Scherr PA, Hebert LE, et al. Association of incident Alzheimer disease and blood pressure measured from 13 years before to 2 years after diagnosis in a large community study. Arch Neurol. 2001;58:1640-1646.
78. Piguet O, Grayson DA, Creasey H, et al. Vascular risk factors, cognition an dementia incidence over 6 years in the Sydney Older Persons Study. Neuroepidemiology 2003;22(3):165-71.
79. Guo Z, Fratiglioni L, Winblad B, Viitanen M. Blood pressure and performance on the mini-mental state examination in the very old. Cross-sectional and longitudinal data from the Kungsholmen Project. Am J Epidemiol. 1997;145(12):1106-13.
80. Zhu L, Viitanen M, Guo Z, et al. Blood pressure reduction, cardiovascular diseases, and cognitive decline in the mini-mental state examination in a community population of normal very old people: a three-year follow-up. J Clin Epidemiol 1998;51(5):385-391.
81. Elias MF, D'Agostino RB, Elias PK, Wolf PA. Neuropsychological test performance, cognitive functioning, blood pressure, and age: the Framingham Heart Study. Exp Aging Res. 1995;21(4):369-91.
82. Mulrow CD, Cornell JA, Herrera CR, et al. Hypertension in the elderly. Implications and generalizability of randomized trials. JAMA 1994;272:1932-1938.

83. Prins ND, den Heijer T, Hofman A, et al. Homocysteine and cognitive function in the elderly. Neurology 2002;59:1375-1380.
84. Budge MM, Jager C, Hogervorst E, et al. Total plasma homocysteine, age, systolic blood pressure, and cognitive performance in older people. J Am Geriatr Soc 2002;50:2014-2018.
85. Arrastia RD. Homocysteine and neurologic disease. Arch Neurol 2000;57:1422-1428.
86. Singh-Manoux A, Hillsdon M, Brunner E, Marmot M. Effects of physical activity on cognitive functioning in middle age: evidence from the Whitehall II prospective cohort study. Am J Public Health 2005;95(12): 2252-2258.
87. Skoog I, Lithell H, Hansson L, et al. Effect of baseline cognitive function an antihypertensive treatment on cognitive and cardiovascular outcomes: Study on cognition and prognosis in the elderly (SCOPE). Am J Hypertens. 2005;18(8):1052-9.
88. Skoog I, Gustafson D. Update on hypertension and Alzheimer's disease. Neurol Res 2006;28:605-611.
89. Launer LJ, White LR, Petrovitch H, et al. Cholesterol and neuropathologic markers of AD. A population-based autopsy study. Neurology 2001;57:1447-1452.
90. Bursi F, Rocca WA, Killian JM, et al. Heart disease and dementia: a population-based study. American Journ. of Epidemiology 2006;163:135-141.
91. Khachaturian AS, Zandi PP, Lyketsos CG, et al. Antihypertensive medication use and incident Alzheimer disease. Arch Neurol 2006;63:686-692.
92. Bergmann C, Sano M. Cardiac risk factors and potential treatments in Alzheimer's disease. Neurol Res 2006;28:595-604.
93. Elias MF, Sullivan LM, Elias PK, et al. Left ventricular mass, blood pressure, and lowered cognitive performance in the Framingham offspring. Hypertension 2007;49:439-445.

Physician Fact Sheet About The Potential Role Of Cardiovascular Disease In The Development Of Dementia in Later Life

1. Individuals with untreated or under-treated hypertension during midlife may have increased risk of dementia in later life.

2. Individuals with untreated or under-treated hypertension during midlife may have diminished cognitive function in later life even in the absence of dementia.

3. Midlife obesity may increase the likelihood of late-life dementia.

4. The "metabolic" syndrome includes hypertension, dyslipidemia, obesity, and Type-II diabetes.

5. The metabolic syndrome in midlife is a risk factor for dementia in later life.

6. Midlife diabetes is a risk factor for cognitive decline and depression in later life.

7. Stroke is a significant risk factor for dementia in later life.

8. Elevated serum homocysteine is a risk factor for dementia.

9. Cardiac damage with low ejection fraction and left ventricular hypertrophy are risk factors for cognitive loss in later life.

10. Untreated atrial fibrillation may be a risk factor for dementia in older persons.

11. Available research methodologies cannot accurately quantitate the severity of vascular damage in the aged human brain.

12. Physicians can encourage long-term cardiovascular risk factor reduction and prevention of metabolic syndromes by linking these disorders to risks for dementia in later life.

A CONSUMER'S GUIDE TO PROTECTING MEMORY BY PROTECTING BLOOD VESSELS IN THE BRAIN

How does high blood pressure increase my risk for developing dementia?
Your brain consists of 13 to 19 billion brain cells that require a continuous supply of oxygen and nutrients. Any health problem that disrupts the supply of essential nutrients to the brain may damage or kill brain cells. A rich network of blood vessels exists in the brain to assure a proper flow of blood. A stroke occurs when blockage of a big or small blood vessel stops the flow of essential nutrients and kills brain tissue.

Untreated or unrecognized high blood pressure in middle life (between the ages of 40 and 65) may increase the risk for losing intellectual function in later life. High blood pressure damages the brain by: 1) damaging the heart that pumps blood to the brain, 2) damaging blood vessels in the brain, and 3) producing bleeding in the brain. Measurement of blood pressure produces two numbers -- the systolic or top number and diastolic or bottom number, for example, a normal systolic/diastolic is 120/70. A normal systolic number (top number) should not exceed 140, and the diastolic number (bottom number) should be less than 90, for example 130/85.

Increased blood pressure can increase the work of the heart and causes heart damage. A damaged heart cannot pump properly and provide adequate nutrients to the brain. Untreated high blood pressure damages blood vessels in the brain, causing them to leak or become blocked. Thousands of tiny leaks or blockages can damage a great deal of brain tissue adjacent to the vessels. Blood vessels weakened by high blood pressure in the brain can burst and produce bleeding directly into the brain tissue and a stroke. Most brain damage cannot be seen with the naked eye or with brain scans. This damage can be identified at death by examining the brain with a microscope.

The risk for brain damage produced by chronic or severe high blood pressure can be reduced through medications. Antihypertensive treatment includes medications for high blood pressure that can protect blood vessels in the body and the brain with relatively few side effects to the patient. Diet and exercise also help lower blood pressure.

High blood pressure is a serious and sometimes dangerous threat to your brain function and your intellect. You and your doctor must work hard to keep your blood pressure completely into the normal range for your entire life. Medication can make your blood pressure normal, as well as protect the heart and blood vessels that are essential to proper brain function. **CLICK HERE FOR MORE INFORMATION – 2513.11**

PRACTICAL RECOMMENDATIONS FOR PROTECTING BLOOD VESSELS IN YOUR BRAIN

1. Get your blood pressure checked every 4 to 6 months over age 40.
2. Talk with your doctor about high blood pressure.
3. Control your weight and diet.
4. If you have high blood pressure, take your medicine as prescribed by your doctor.
5. Regular exercise and weight reduction may help lower blood pressure.
6. People of African American heritage have a higher risk for high blood pressure and heart disease.
7. Exercise at least four times per week.
8. Talk with your doctor if your blood pressure medicine causes side effects, like dizziness, fatigue or problems with sex.
9. Follow your doctor's recommendations if you have a heart condition that requires other medicines like blood thinners, or drugs that control heart beats.
10. Always talk with your doctor before you stop or reduce your heart medicine.

2. ALCOHOL

2. PROMOTE MODERATE ALCOHOL CONSUMPTION

Heavy, sustained alcohol consumption is the primary risk factor in the development of alcohol-induced dementia. Many (8%) of older persons are problem drinkers. Heavy alcohol consumption may cause dementia or worsen the symptoms of other dementias such as Alzheimer's disease. Most (2/3) older problem drinkers go unrecognized by primary care doctors. Many will reduce drinking at one year if the primary care physician provides 15-minutes of education about health consequences of excessive alcohol consumption. Alcohol-induced brain disease in older persons is avoidable by screening and counseling.

Selected clinical laboratory abnormalities should trigger further investigation of drinking habits including unexplained falls or injuries, unexplained elevated mean corpuscular volume (MCV) in the results of a routine CBC, unexplained peripheral neuropathies or recent deterioration of health status. Sobriety and proper nutrition may allow some recovery of physical and intellectual function. The degree of end-organ damage such as liver, pancreas, etc., does not predict the severity of alcohol-induced brain damage. Alcohol-related nutritional deficiencies do not fully explain alcohol-induced dementia and a person can develop this syndrome even with normal dietary intake. Persons with dementias of other etiologies should avoid alcohol as this over-the-counter medication can produce confusion **(Click here for references – 2513.23).**

Recommendation

Older individuals should avoid consuming more than 1 oz. of alcohol per day. Vitamin supplementation including B- Complex and Thiamin helps the recovering alcoholic; however, sobriety is the most important intervention for problem-drinkers **(FOR MORE INFORMATION, CLICK HERE). (6110), (6111), (6112)**

Physician's Guide To Talking With Older Persons About Drinking

1. Overview

Primary care physicians often encounter older patients who continue to drink in the latter years of their life. The growing older population will require physicians to focus more on geriatric substance abuse. Aging baby boomers may increase the rate of substance abuse treatment for elders by 70% **(1).** An alcoholic beverage can be part of a pleasurable social event for an older person. Research suggests that drinking small amounts of alcohol may provide certain health benefits; however, the details of these benefits remain unclear. The health problems produced by excessive drinking are clear. Individuals who consume a glass of wine on a regular basis may have some health benefit; however, regular excessive consumption of beer or distilled spirits produces an increased risk for dementia. A consumer fact sheet is attached to this clinical summary for office use by older patients. Alcohol use may contribute to medical problems in 10% of older patients **(2), (3).**

2. Distinguishing Normal Alcohol Consumption from Problem Drinking

Many older persons continue to drink past age 65 and some will drink at age 85. The community prevalence of alcoholism or problem drinking in persons over 60 ranges form 2% to 10%**.** Elderly alcoholics can be divided into two groups: 1) individuals with early onset, life-long drinking, and 2) individuals who begin drinking at a later age **(4)**. ***Click here for more information about alcoholism in the elderly – (Substance Abuse in the Elderly).***

The consumption of 1 oz. of alcohol, such as one bottle of beer, one glass of wine, one shot glass of hard liquor, on a daily basis is probably safe in most older, cognitively intact persons **(See Table 1).** Consumption of more than 35 drinks per week for men and 28 for women meets diagnostic criteria for pathological drinking that may produce alcohol-related dementia. Older persons with any form of dementia or neurological damage should avoid alcohol. Consumption of more than 14 drinks per week is a concern for the primary care clinician in all older individuals **(5).** Individuals consuming sedatives, sleeping pills, or other tranquilizers should avoid the consumption of alcohol. Alcohol can interact with many drugs and patients should discuss alcohol consumption with their pharmacist and physician. Alcohol should not be consumed for "health benefits" but rather as part of a social occasion. Solitary drinking should be discouraged in older persons. Older persons should not consume alcohol to help with sleep as this drug will actually disrupt sleep architecture and increase the risk of obstructive sleep apnea.

Table 1

Guidelines For The Classification of Weekly Alcohol Consumption In Older Persons (7)

Classification	M[1]	F[1]
Healthy Drinking	7-10	7
Moderate Drinking	14	7-14
Problem Drinking[3]	35	28

1=drinks per week 3=sufficient, long-term

consumption to produce dementia

The CAGE Screening Instrument can be used to identify elders at risk for problem drinking using four simple questions **(See Table 2).** The Michigan Alcohol Screening Test may provide greater sensitivity and specificity but this instrument requires more time for computing **(6), (7).** Individuals who smoke are more likely to drink heavily**.** Routine, clinical laboratory values may suggest heavy alcohol consumption including elevated GGT (Gamma glutamyl transferase) and macrocytic indicies on blood count **(8), (9), (10).** Unexplained peripheral neuropathies or frequent falls may also result from alcohol abuse.

Table 2

The CAGE Screening Questionnaire for Possible Alcohol Abuse (6)

1.	Have you ever felt you should **C**ut down on your drinking?	**C**
2.	Have people **A**nnoyed you by criticizing your drinking?	**A**
3.	Have you every felt bad or **G**uilty about your drinking?	**G**
4.	Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye opener)?	**E**
	Scoring: Item responses on the CAGE are scored 0 for "no" and 1 for "yes" answers, with a higher score an indication of alcohol problems. A total score of 2 or greater is considered clinically significant.	

3. Longitudinal Studies on the Impact of Alcohol Consumption and Cognitive Function

Several longitudinal studies have examined the relationship of alcohol consumption and cognitive decline for older individuals **(See Table 3).** No studies support drinking as a preventive intervention for cognitive function. Several studies suggest that individuals with moderate alcohol consumption have better cognitive function than abstinent individuals. All studies confirm the harmful effect of heavy drinking on cognition.

Table 3. Longitudinal and Cross-sectional Studies on Alcohol Consumption and Cognitive Function

#	n	Duration	Age	Outcome and Measure	Ref.
1	6033	11	46-68	Small benefit up to 30 drinks per week	11
2	801	CS	65+	No relationship between alcohol consumption and MMSE scores	12
3	3100	CS	30-69	↑ BP in 7% over 30 drinks/week	13
4	1870	CS	45-59	No correlation in active drinkers, but cognitive function in former drinkers	14
5	383	CS	65+	95% of geropsych patients cognitively impaired with alcohol abuse	15
6	1709	15yrs	65+	Moderate consumption of wine may ↓ risk for dementia	16
7	4461	4.2yrs	65-79	Moderate drinking ↓ risk in females	17

CS=cross-sectional **MMSE**=mini mental status exam **BP**=blood pressure

2513.24 Older Persons and Drinking

Doctors often overlook problem-drinking in older persons, as two-thirds remain undiagnosed in primary care (2). The solitary, elderly male with a serious mental illness and multiple health problems is at greatest risk for alcoholism and suicide. Physicians may detect alcoholism when an elderly patient develops withdrawal during hospitalization for a medical or surgical problem. Heavy consumption of alcohol in later life can produce many health problems by damaging heart, liver, pancreas, muscles, peripheral nerves, and brain (8), (9). Alcohol-induced dementia is one of the five leading causes of intellectual loss in older persons (7).

4. Physician Management of Alcohol Consumption in Older Patients

Individuals who drink more than 1 oz. of alcohol per day should discuss this drinking with their primary care doctor. Individuals who drink more than 2 oz. per day should attempt to reduce alcohol consumption or eliminate alcoholic beverages from their diet. People who drink 3 or more oz. of alcohol per day have a drinking problem that requires medical attention. Binge drinking is usually an indication of an alcohol abuse problem. Individuals with a past history of alcoholism or heavy drinking should be advised to strive for total sobriety.

Older persons are encouraged to drink responsibly and encourage their friends to do the same. Many doctors take a "live and let live" attitude with older problem drinkers. A few doctors will make statements such as "they are old; what does it matter;" however, it does matter greatly to the health and wellbeing of that older person. Some older problem drinkers will significantly reduce alcohol consumption for over one year when encouraged by physicians to cease drinking **(See Table 4)**. Responsible drinking is part of successful aging.

Table 4. Studies of Brief Physician Interventions to Reduce Alcohol Consumption

#	n	t	Outcome and Measure	Ref.
1	774	12m	⇩ Social/health care expenditure - $1,151 per subject	18
2	247	9 yrs	⇩ GGT values at 9 yrs	19
3	530	6m	⇩ Alcohol consumption - 5.8 drinks/wk	20
4	447	12m	⇩ Alcohol consumption - 5.7 drinks/wk	21
5	118	3yrs	⇩ Consumption in 27% to 75% of groups	22
6	665	12m	Significant ⇩ consumption in older drinkers	23
7	146	12m	62% ⇩ older adults exceeding 21 drinks (wk, 74% ⇩ binge drinking)	24
8	674	48 mos	⇩Healthcare cost $10,000 ⇩ Drinks /⇩ binges	25

m=month **yr**=year **n**=study subjects **t**=duration of study

2513.24 Older Persons and Drinking

Older individuals with alcohol addiction may require medical detoxification and long-term support through organizations such as Alcoholics Anonymous. Older patients who develop withdrawal during hospitalization for an unrelated health problem should not be discharged until the alcohol abuse is addressed (3), (4).

Doctors should provide clear encouragement for sobriety to any patient with evidence for end-organ damage such as liver disease, pancreatitis or neurological problems including ataxia or peripheral neuropathy. These types of damage are associated with alcoholic dementia and sobriety may avoid future brain damage (9).

Sobriety can produce clinical and radiographic improvement with alcoholic patients. Some individuals with alcohol-related dementia will regain some cognitive function with prolonged sobriety. Radiographic ventriculomegaly may also improve with cessation of drinking and cortical volume may slightly increase (5).

5. The Value of Brief, Educational Interventions by Physicians

Multiple studies have examined the role of brief physician interventions in reducing acute and long-term alcohol consumption. Most interventions consist of a 15-minute discussion between the doctor and patient about the health problems produced by problem drinking as identified by patient screening. Sobriety is measured by self-reporting, normalization of laboratory indicators, such as serum GGT or reduction of alcohol-related expenses. Many studies describe interventions that occur in outpatient primary care screenings (27). Multiple trials describe the impact of brief primary care screening and interventions (16) for reducing consumption, medical morbidity, hospital care, health care expenditures, and alcohol-related deaths (17). Most studies show a variable reduction in the rate of drinking, improvement of health problems, and reduction of mortality (26) **(See Table 4 above).**

6. Conclusion

Alcohol and substance abuse will increase in older patients with the aging baby boomers (1), (18). Alcohol abuse and alcohol-related dementia may become a growing problem in older

persons. Primary care physicians should screen and treat older persons with alcohol abuse to reduce the risk of cognitive damage, beginning with a 15-minute discussion about long-term health consequences of heavy alcohol consumption (28). Primary care physicians should encourage sobriety of minimal alcohol consumption in most or all older patients using the IMBIBE guidelines **(See Table 5).**

Table 5

I M B I B E

Table 5. Recommendations for Primary Care Physicians About Alcohol Consumption by Older Patients

1. **I**dentify at risk individuals.
2. **M**onitor for specific, abnormal neurological findings or laboratory values.
3. **B**eware of unrecognized withdrawal during hospitalization.
4. **I**nquire about drinking or use the CAGE
5. **B**rief education about alcohol-related diseases may reduce pathological drinking.
6. **E**ncourage limited drinking or sobriety in elders who imbibe.

The role of alcohol consumption in dementia or preventing dementia 19

References:

1. Gfroerer J, Penne M, Pemberton M, Folsom R. Substance abuse treatment need among older adults in 2020: the impact of the aging baby-boom cohort. Drug and Alcohol Dependence 2003;69:127-135.
2. Patterson TL, Jeste DV. The potential impact of the baby-boom generation on substance abuse among elderly persons. Psychiatric Services 1999;50:1184-1188.
3. Wagenaar DB, Mickus MA, Wilson J. Alcoholism in late life: challenges and complexities. Psychiatric Annals 2001;31(11):665-672.
4. Coble YD, Davis RM, Head CA, et al. Alcoholism in the elderly. JAMA 1996;275(10):797-801.
5. Oslin DW, Cary MS. Alcohol-related dementia. Validation of diagnostic criteria. Am J Geriatr Psychiatry 2003;11:441-447.
6. Kaplan HI, Sadock BJ, eds. Comprehensive Textbook of Psychiatry/V, Baltimore: Williams & Wilkins, 1989.
7. Hirata ES, Almeida OP, Funari RR, Klein EL. Validity of the Michigan Alcoholism Screening Test (MAST) for detection of alcohol-related problems among male geriatric outpatients. Am J Geriatr Psychiatry 2001;9(1):30-34.
8. Blazer DG, Steffens DC, Busse EW (Eds.), (2004), Textbook of Geriatric Psychiatry (3rd ed.) American Psychiatric Publishing Inc.
9. Wagenaar DB, Mickus MA, Wilson J. Alcoholism in late life: challenges and complexities. Psychiatric Annals 2001;31(11):665-672.
10. Allen JP, Anthenelli RM. Problem drinking. The case for routine screening. Current Psychiatry 2003;2(6):27-42.
11. Britton A, Singh-Manoux A, Marmot M. Alcohol consumption and cognitive function in the Whitehall II Study. Am J Epidemiol. 2004;160(3):240-7.
12. Reid MC, Macierjewski PK, Hawkins KA, Bogardus ST Jr. Relationship between alcohol consumption and Folstein mini-mental status examination scores among older cognitively impaired adults.
13. Keil U, Chambless L, Remmers A. Alcohol and blood pressure: results from the Luebeck Blood Pressure Study. Prev. Med. 1989;18(1):1-10.
14. Elwood PC, Gallacher JE, Hopkinson CA, et al. Smoking, drinking, and other life style factors and cognitive function in men in the Caerphilly cohort. J Epidemiol Community Health 1999;53(1):9-14.
15. Rains VS, Citzler TF. Alcohol use disorders in cognitively impaired patients referred for geriatric assessment. J Addict. Dis. 1993;12(1):55-64.
16. Truelsen T, Thudium D, Gronbaek M. Amount and type of alcohol and risk of dementia. The Copenhangen City Heart Study. Neurology 2002;59:1313-1319.
17. Espeland MA, Gu L, Masaki KH, et al. Association between reported alcohol intake and cognition: results from the Women's Health Initiative Memory Study. Am J Epidemiol. 2005;161(3):228-38.
18. Fleming MF, Mundt MP, Franch MT, et al. Benefit-cost analysis of brief physician advice with problem drinkers in primary care settings. Med Care 2000;38(1):7-18.
19. Nilssen O. Long-term effect of brief intervention in at-risk alcohol drinkers: a 9-year follow-up study. Alcohol Alcohol. 2004;39(6):548-51.
20. Ockene JK, Adams A, Hurley TG, et al. Brief physician- and nurse practitioner-delivered counseling for high-risk drinkers: does it work? Arch Intern Med 1999;159(18):2198-205.
21. Reiff-Hekking S, Ockene JK, Hurley TG, Reed GW. Brief physician and nurse practitioner-delivered counseling for high-risk drinking. Results at 12-month follow-up. J. Gen Intern Med. 2005;20(1):7-13.
22. Aalto M, Saksanen R, Laine P, et al . Brief intervention for female heavy drinkers in routine general practice: a 3-year randomized, controlled study. Alcohol Clin Exp Res 2000;24(11):1680-6.
23. Fink A, Elliott MN, Tsai M, Beck JC. An evaluation of an intervention to assist primary care physicians in screening and educating older patients who use alcohol. J. Am Geriatr Soc 2005;53(11):1937-43.
24. Fleming MF, Manwell LB, Barry KL, et al. Brief physician advice for alcohol problems in older adults: a randomized community-based trial. J. Fam Pract. 1999;48(5):378-84.
25. Fleming MF, Mundt MP, French MT, et al. Brief physician advice for problem drinkers: long-term efficacy and benefit-cost analysis. Alcohol Clin Exp Res. 2002;26(1):36-43.
26. Kristenson H, Osterling A, Nilsson JA, Lindgarde F. Prevention of alcohol-related deaths in middle-aged heavy drinkers. Alcohol Clin Exp Res 2002;26(4):478-84.
27. Bertholet N, Daeppen JB, Wietlisbach V, et al. Reduction of alcohol consumption by brief alcohol intervention in primary care: systematic review and meta-analysis. Arch Intern Med. 2005;165(9):986-95.
28. Fleming MR, Barry KL, Manwell LB, et al. Brief physician advice for problem alcohol drinkers. JAMA 1997;277:1039-1045.

29. Ngandu T, Helkala EL, Soininen H, et al. Alcohol drinking and cognitive functions: findings from the cardiovascular risk factors aging and Demetnia (CAIDE) study. Dement Geriatr Cogn Disor 2007;23(3):140-9.
30. Stella F, Banzato CE, Gasparetto Se Ev, et al. Risk factors for vascular dementia in elderly psychiatric outpatients with preserved cognitive functions. J Neurol Sci 2007 Feb 19.

PHYSICIAN FACT SHEET ON RESPONSIBLE DRINKING IN ELDERS

1. Physicians can safely accept patient consumption of 1 oz. of alcohol per day in any form with minimal end-organ damage.

2. About 8% of elders have a drinking problem and some will develop withdrawal during hospitalization for unrelated health problems.

3. Patients with excessive alcohol consumption are more likely to develop medical problems, such as hypertension, and complications, such as neuropathy or liver disease.

4. Some problem drinkers will maintain sobriety at one year if you provide basic advice to them about the health consequences of excessive drinking.

5. The CAGE alcoholism screening instrument requires approximately one minute for administration and is valid in older patients.

6. Alcohol can be a serious health hazard when consumed with benzodiazepines.

7. Alcohol is a poor hypnotic and may disrupt sleep.

8. All patients with cognitive impairment should be screened for drinking and encouraged to immediately cease consumption of all alcohol products.

9. Unexplained anemia, macrocytic indices, such as MCV>100, elevated GGT or peripheral neuropathy may be produced by excessive drinking.

10. Alcohol-induced cognitive loss may slowly improve with long-term sobriety.

11. Alcohol damages heart, peripheral nerve, liver, pancreas, skeletal muscle, and brain.

12. Your patients benefit from screening for alcohol abuse in elders and providing basic counseling for problem drinkers.

CONSUMER'S GUIDE TO SAFE DRINKING

Alcohol is a beverage and drug. Alcohol produces many pleasurable experiences including relaxation and a sense of wellbeing. Alcohol is highly addictive when consumed in large quantities over many years. Modest amounts of alcohol, such as one glass of wine, a beer, or one ounce of alcohol in a mixed drink may be slightly beneficial to some older people. Drinking more than two ounces of alcohol per day can produce harmful health effects to the brain, heart, liver, as well as sensation in the feet and legs of older person.

Alcohol is broken down by the body into many chemicals that is similar to a substance similar to formaldehyde, which is used to pickle organs. Large amounts of alcohol can damage your brain. Dementia can result from heavy long-term drinking over a period of years. Alcohol-induced dementia is one of the five most common causes of intellectual loss in the older person.

Older persons should drink in moderation or not at all. One ounce of alcohol per day may be beneficial to persons who are physically healthy. Two ounces of alcohol per day is the maximum that an older person should drink and more than two ounces per day can produce health problems.

Any person with memory difficulty over the age of 65 should stop drinking alcohol. Alcohol worsens confusion in the older person, even those who do not suffer from dementia. Regular consumption of alcohol is not part of a successful aging program and older people should not drink for the "health benefits of alcohol". Older persons with normal intellectual function can continue to drink in moderation but they should alert their doctor that they are drinking alcohol to prevent potential interactions with medications. In general, red wine is probably the least likely to produce health problems when consumed in moderation. Occasional drinking in normal older individuals is most likely safe.

3. DEPRESSION

3. IDENTIFY AND TREAT DEPRESSION

Untreated or under-treated depression may increase the likelihood of medical and cognitive morbidity. Depressed elders are more likely to have cardiovascular disease, fatal outcomes from myocardial infarction, disability from heart disease, cerebrovascular accidents, poor medication compliance, and dementia. Depressed elders often conceal depressive symptoms and screening is necessary to identify at-risk individuals. Depressive anxiety is often treated with benzodiazepines that may worsen confusion. Suicide is common in elders, especially single males who live alone and drink heavily.

Depression produces significant psycho-physiological stress that results in excessive secretion of cortisol. High sustained circulating steroids may be neurotoxic; especially to the hippocampus which is damaged by Alzheimer's disease. Most, i.e., up to 90%, depressed patients are improved with routine antidepressant therapy. Depression is linked to dementia at two levels. First, depressed patients can develop a dementia-like syndrome termed "pseudo-dementia". Although the cognitive deficits are generally corrected with treatment of the depression, about 20% of these individuals will be demented at two years from Alzheimer's or some other dementia. Second, depressed elders have increased life-time risks of developing dementia via molecular mechanisms that are poorly understood. **(Click here for references – 2315.33).**

Recommendation

Routinely screen for depression and treat elders until the patient achieves full symptom remission. Avoid long-term use of benzodiazepines, nightly use of sedative hypnotics for sleep, or the use of chronic, long half-life tranquilizers. **(FOR MORE INFORMATION, CLICK HERE - 8000, 8002)**

A Primary Care Guide To Understanding The Interaction Between Depression And Dementia

1. OVERVIEW

Primary care physicians often diagnose depression in adult patients and this disorder may produce memory dysfunction in some older patients. Depression is a risk factor for patient non-compliance with treatment for other medical problems, including hypertension and diabetes. The primary care physician can assure older patients that treatment of depression may protect physical and cognitive health.

Depression is a common disorder in the elderly and specific groups of individuals have greater risk for developing mood disorders including persons with stroke, Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders **(1), (2), (3), (4)**. Several key issues remain unanswered in the depression puzzle. First, do people with depression experience increased risks for developing dementia? Second, would treatment of depression earlier in life mitigate the risk of depression in later life? Third, is the neuropathological substrate that produces depression in later life similar to that of dementia? Fourth, is depression simply a preclinical manifestation of dementia? Finally, how does the neurobiology of depression enhance our understanding of the relationship between dementia and mood disorders? The complexity of these scientific questions is further complicated by the limited prospective data on depression and dementia **(5).**

2. LONGITUDINAL STUDIES OF DEPRESSION AND COGNITION

Few longitudinal studies define the relationship between midlife depression and later life dementia. Several studies suggest that individuals with a history of depression in midlife may experience greater risks for dementia in later life and the risk of dementia increases with the frequency of hospitalization to treat the mood disorder (42) **(See Table 1).** Numerous methodological problems exist in relating treatments to cognitive outcomes because depression may be caused by multiple neurological mechanisms and patients demonstrate variable adherence to treatment **(3), (6).**

People with mild cognitive impairment and dementia exhibit greater rates of depression than age-matched cognitively intact individuals (7). Depressive symptoms may precede the onset of cognitive decline by several years. Memory dysfunction associated with depression, sometimes termed "pseudodementia", may be a significant red flag for future dementia, as about 20% of these individuals exhibit permanent cognitive loss even with complete remission of depressive symptoms **(8), (9).** Chronic depression may produce hippocampal volume reductions in younger persons with normal cognition (8). Repeated bouts of depression that produce hospitalization may increase the risk for late-life dementia by 13% for each hospitalization **(42).**

Table 1

The Effect of Depression on the Risk for Developing Dementia in Normal Elders or Persons with MCI

#	n (study size)	Age of Subject	Duration of Study	Effect of depression on risk for dementia	Ref.
1	1070	60+	1-5 yrs	↑ risk (2.94)	30
2	1357	LS	40	X2 ↑risk; independent of vascular risks	6
3	1366	65+	10	Minor ↑ risk - (1.28)	31
4	766	65+	5	Depressive symptoms predict AD	32
5	594	78.5	10	Predementia /depressive episode ↑ risk	33
6	3346	65-84	5	↑risk @2yr (1.9) and 5 yrs (1.6)	34
7	114*	65	3	↑ risk (2.6) for MCI	7
8	5781	65+	4	↑ symptoms = ↑ risk	35
9	2812	65+	12 yrs	Depressive symptoms not related to onset of dementia	36
10	4046	50+	1-25 yrs	Depressive symptoms are risk factor for late dementia	37
11	2220	65+	6 yrs	↑ risk for MCI	40

LS= 40 year longitudinal study (odds ratio) *Individuals with isolated amnestic syndromes at baseline

2513.34 The effect of Depression on Developing Dementia

3. THE RELATIONSHIP OF DEPRESSION AND HEALTH STATUS

Depression can be linked to health status and chronic midlife depression increases the risk for hypertension **(10)** and morbidity from cardiac disease in later life **(11).** Depressed elders with cardiovascular disease, stroke, diabetes, or multiple other medical conditions exhibit worse outcomes than those individuals with normal mood. Prospective randomized studies have not been performed to measure the impact of treating depression versus placebo therapy on medical outcomes **(12), (13), (14).**

Depression in the setting of dementia increases the likelihood of psychiatric and behavioral disability. In contrast, treatment of depression in persons with dementia is safe and effective **(1), (15).**

4. NEUROPATHOLOGICAL SUBSTRATES FOR DEPRESSION AND DEMENTIA

Depression often occurs in persons with Alzheimer's disease and diffuse Lewy body disease **(16), (17), (18).** The neuropathological substrate for depression in aging and dementia remains unclear **(19).** Serotonin is produced by neurons located in the midline of the brainstem in the structure referred to as the "Raphe nuclei". Alzheimer's patients with depression have increased densities of tangles in brain stem structures **(20)** and reduced numbers of neurons that produce norepinephrine and serotonin **(46).** A central component to depression in Alzheimer's patients is apathy and anergy **(21).** Individuals with Alzheimer's disease and depression demonstrate increased severity of microscopic damage in the prefrontal cortices that is linked to apathetic symptoms **(22).** Cortical and brain stem Lewy body counts do not appear related to depression **(23).** Many persons with late life onset dementia have Alzheimer's disease neuropathology at death **(24);** however, neither the severity nor the distribution of cortical damage appears related to concurrent depressive symptoms **(25).** However, postmortem examination of hippocampi from individuals with AD and lifetime depression reveals higher densities of senile plaques and neurofibrillary tangles than non-depressed demented individuals **(38).**

The role of vascular brain pathology in the pathogenesis of depression remains unclear. White matter damage in the frontal cortices as manifested by MRI abnormalities appears related to risks for depression and perhaps dementia (10). White matter hyperintensities are most likely produced by hypertensive small vessel disease in regions like the centrum semiovale.

5. LINKING THE NEUROBIOLOGY OF DEPRESSION TO SUCCESSFUL COGNITIVE AGING

The neurobiology of depression in humans has been related to dysfunction of ascending catecholiminergic systems and abnormalities in cerebral cortical regions linked to regulation of mood, including the orbitofrontal cortices, subgenual prefrontal cortex and portions of the cingulate cortex. Memory deficits produced by depression may be attributable to dysregulation of serotonergic and noradrenergic innervation of the human hippocampus. Rodent models of depression are limited by issues of experimental design. Rodent models that use persistent stress to produce symptoms of depression suggest that high circulating endogenous steroids alter dendritic connections and reduce the capacity of rodent neurons to reproduce (neurogenesis) **(27).** Human hippocampal neurons may retain the ability to regenerate; however, this data remains unclear. Antidepressant medications, mood stabilizing agents, such as lithium and electroshock therapy, enhance the ability of rodent neurons to reproduce. This rodent data suggests the possibility that depression may have a substantial impact on human neuronal plasticity and regeneration, while antidepressant therapy may enhance reparative or regenerative capacity in the human brain **(27).**

6. THERAPEUTIC CONSIDERATIONS

Treatment of depression in all adult age groups is usually safe, effective, and affordable **(28), (29).** Compliance remains a major problem in the treatment of depression as well as all other medical comorbidities **(Click here for more information - DETA 2514.12).** Treatment of depression may enhance the likelihood that other risk factors, such as psychosocial stimulation, management of hypertension, regular exercise, and others are optimally managed. Second and third generation antidepressants, such as selective serotonin reuptake inhibitors, are highly effective for older patients. Assessment and management of depression in mid and later life should be part of the primary care strategy for cognitive wellness. Prophylactic treatment of non-depressed individuals with antidepressant medications is not indicated for the prevention of dementia. Exercise training of elders may also reduce the risk of depression and dementia **(43).**

The role of treating depression or heart disease in the prevention of "vascular depression" remains unclear. Randomized controlled studies have not been performed to determine the benefit of blood pressure control in the reduction of risks for either depression or dementia. Such studies are unlikely as the consequence of untreated depression precludes withholding long-term antidepressant therapy. (Click here for additional on information on the role of vascular disease in depression or dementia – 2513.12).

7. RECOMMENDATION FOR PRIMARY CARE PHYSICIANS ON THE MANAGEMENT OF DEPRESSION IN OLDER PATIENTS

A randomized controlled longitudinal study will not be performed on the impact of treating depression as a preventive intervention for dementia in middle aged or older patients. Like

hypertension, depression is a serious health problem that physicians are obliged to treat in order to reduce the risk for suicide and associated health problems. A meta analysis of 20 studies in eight nations demonstrated an odds ratio of 2.02 linking midlife depression to late-life dementia**(41).** A reasonable interpretation of this data would suggest that aggressive management of depression in midlife may reduce morbidity and mortality in later life. A consensus opinion from the National Institute of Mental Health states that late life depression may represent an independent risk factor predisposing to dementing disorders, even when depressive symptoms occur more than ten years before the onset of dementia **(5).** Depression screening is now recommended as a component to the annual Medicare evaluation.

The appearance of depression in an older individual who has otherwise normal cognitive function increases the likelihood that that person will develop dementia later in life **(5), (8).** Depressive symptoms may not correlate to the rate of cognitive decline over time **(39).** These individuals should be monitored on a regular basis with cognitive testing. Aggressive management of other health problems, such as hypertension, atrial fibrillation, cardiovascular disease, etc., is warranted in these individuals. There is inadequate research data to advise patients about "increased risks for dementia" with depression and such statements can produce distress in many patients, especially those with a past history of depression. Rather, the clinician is encouraged to advise the patient of the beneficial effect of treating depression on physical health and cognitive fitness. This positive message encourages a sense of self-determination and motivates the patient towards proactive interventions that may enhance their long-term cognitive function.

RECOMMENDATIONS TO PRIMARY CARE PHYSICIANS

1. Screen older patients for depression on an annual basis.
2. Monitor cognitive function in older persons with a past history of depression.
3. Treat depression until the patient returns to baseline and sustain normal mood through antidepressant maintenance therapy.
4. Avoid chronic prescription of benzodiazepines in depressed elders.
5. Monitor compliance for antidepressant therapy.

References

1. Lyketsos CG, Olin J. Depression in Alzheimer's disease: overview and treatment. Biol Psychiatry 2002;52(3):243-52.
2. Bennett DA, Wilson RS, Schneider JA, et al. Cerebral infarctions and the relationship of depression symptoms to level of cognitive functioning in older persons. Am J. Geriatric Psychiatry 2004;12(2):211-9.
3. Cooper B, Holmes C. Previous psychiatric history as a risk factor for late-life dementia: a population-based case-control study. Age Ageing 1998;27(2):181-8.
4. Ginsberg D (Ed.). Depression in the elderly. The unique features related to diagnosis and treatment. CNS Spectrums 2005;10(8):1-14.
5. Steffens DC, Otey E, Alexopoulos GS, et al. Perspectives on depression, mild cognitive impairment, and cognitive decline. Arch Gen Psychiatry 2006;63(2):130-8.
6. Dal Forno G, Palermo MT, Donohue JE, et al. Depressive symptoms, sex, and risk for Alzheimer's disease. Ann. Neurol. 2005;57(3):381-7.
7. Modrego PJ, Ferrandez J. Depression in patients with mild cognitive impairment increases the risk of developing dementia of Alzheimer type: a prospective cohort study. Arch Neurol. 2004;61(8):1290-3.
8. Posener JA, Wang L, Price JL, et al. High-dimensional mapping of the hippocampus in depression. Am J Psychiatry 2003;160:83-89.
9. Verhey FRJ, Visser PJ. Phenomenology of depression in dementia. International Psychogeriatrics 2000;12(Suppl.1):129-134.
10. Jonas BS, Franks P, Ingram DD. Are symptoms of anxiety and depression risk factors for hypertension? Longitudinal evidence from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study. Arch Fam Med 1997;6(1):43-9.
11. Carney RM, Freedland KE. Depression, mortality, and medical morbidity in patients with coronary heart disease. Biol Psychiatry 2003;54:241-247.
12. Katon WJ. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry 2003;54:216-226.
13. Carney RM, Freedland KE. Depression, mortality, and medical morbidity in patients with coronary heart disease. Biol Psychiatry 2003;54:241-247.
14. Seeman TE, Berkman LF, Charpentier PA, et al. Behavioral and psychosocial predictors of physical performance: MacArthur studies of successful aging. Journal of Gerontology: Medical Sciences 1995;50A(4):M177-M183.
15. Tasman A, Kay J, Lieberman JA (Eds.)., (2003). *Psychiatry therapeutics* (2nd Edition). London: Wiley.
16. Zubenko GS, Zubenko WN, McPherson S, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. Am J Psychiatry 2003;160(5):857-66.
17. Zubenko GS, Moossy J. Major depression in primary dementia. Arch. Neurol. 1988;45:1182-1186.
18. Zubenko GS, Zebenko WN, McPherson S, et al. A collaborative study of the emergence and clinical features of the major depressive syndrome of Alzheimer's disease. Am J. Psychiatry 2003;160:857-866.
19. Zubenko GS. Neurobiology of major depression in Alzheimer's disease. International Psychogeriatrics 2000;12(Suppl.1):217-230.
20. Hendricksen M, Thomas AJ, Ferrier In, et al. Neuropathological study of the dorsal raphe nuclei in late-life depression and Alzheimer's disease with and without depression. Am J. Psychiatry 2004;161(6):1096-102.
21. Starkstein SE. Apathy and withdrawal. International Psychogeriatrics 2000;12(Suppl.1):135-137.
22. Hirono N, Mori E, Ishii K, et al. Frontal lobe hypometabolism and depression in Alzheimer's disease. Neurology 1998;50:380-383.
23. Samuels SC, Brickman AM, Burd JA, et al. Depression in autopsy-confirmed dementia with Lewy bodies and Alzheimer's disease. Mt. Sinai J. Med. 2004;71(1);55-62.
24. Sweet RA, Hamilton RL, Butters MA, et al. Neuropathologic correlates of late-onset major depression. Neuropsychopharmacology 2004;29(12):2242-50.
25. Wilson RS, Schneider JA, Bienias JL, et al. Depressive symptoms, clinical AD, and cortical plaques and tangles in older persons. Neurology 2003;61(8):1102-7.
26. Sultzer DL. Selective serotonin reuptake inhibitors and trazodone for treatment of depression, psychosis, and behavioral symptoms in patients with dementia. International Psychogeriatrics 2000;12(Suppl.1):245-251.
27. Bremner JD. Does stress damage the brain? Biol Psychiatry 1999;45:797-805.
28. Lyketsos CG, DelCampo L, Steinberg M, et al. Treating depression in Alzheimer's disease. Arch Gen Psychiatry 2003;60:737-746.

29. Lee HB, Lyketsos CG. Depression in Alzheimer's disease: Heterogeneity and related issues. Biol. Psychiatry 2003;54:353-362.
30. Devanand DP, Sano M, Tang MX, et al. Depressed mood and the incidence of Alzheimer's disease in the elderly living in the community. Arch Gen. Psychiatry 1996;53(2):175-82.
31. Chen P, Ganguli M, Mulsant BH, DeKosky ST. The temporal relationship between depressive symptoms and dementia: a community-based prospective study. Arch Gen. Psychiatry 1999;56(3):261-6.
32. Gatz JL, Tyas SL, St. John P, Montgomery P. Do depressive symptoms predict Alzheimer's disease and dementia? J. Gerontol A. Biol Sci. Med. Sci. 2005;60(6):744-7.
33. Speck CE, Kukull WA, Brenner DE, et al. History of depression as a risk factor for Alzheimer's disease. Epidemiology 1995;6(4):366-9.
34. Andersen K, Lolk A, Kragh-Sorensen P, et al. Depression and the risk of Alzheimer disease. Epidemiology 2005;16(2):233-8.
35. Yaffe K, Blackwell T, Gore R, et al. Depressive symptoms and cognitive decline in nondemented elderly women: a prospective study. Arch Gen Psychiatry 1999;56(5):425-30.
36. Bassuk SS, Berkman LF, Wypij D. Depressive symptomotology and incident cognitive decline in an elderly community sample. Arch Gen Psychiatry 1998;55(12):1073-81.
37. Green RC, Cupples LA, Auerbach S, et al. Depression as a risk factor for Alzheimer's disease: The Mirage Study. Arch Neurol 2003;60:753-759.
38. Rapp MA, Schnaider-Beeri M, Grossman HT, et al. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. Arch Gen Psychiatry 2006;63:161-167.
39. Ganguli M, Du Y, Dodge HH, et al. Depressive symptoms and cognitive decline in late life. Arch Gen Psychiatry 2006;63:153-160.
40. Barnes DE, Alexopoulos GS, Lopez OL, et al. Depressive symptoms, vascular disease, and mild cognitive impairment. Arch Gen Psychiatry 2006;63:273-280.
41. Ownby RL, Crocco E, Acevedo A, et al. Depression and risk for Alzheimer's disease. Arch Gen Psychiatry 2006;63:530-538.
42. Kessing LV, Andersen PK. Does the risk of developing dementia increase with the number of episodes in patients with depressive disorder and in patients with bipolar disorder? J Neurol Neurosurg Psychiatry 2004;75:1662-1666.
43. Barbour KA, Blumenthal JA. Exercise training and depression in older adults. Neurobiology of Aging 2005;Suppl 26:S119-S123.
44. Duman RS. Neurotrophic factors and regulation of mood: role of exercise, diet and metabolism. Neurobiology of Aging 2005;Suppl 26:S88-S93.
45. Lyness SA, Zarow C, Chui HC. Neuron loss in key cholinergic and aminergic nuclei in Alzheimer's disease: a meta-analysis. Neurobiology of Aging 2003;24:1-23.

PHYSICIAN FACT SHEET ON DEPRESSION AS A RISK FACTOR FOR DEMENTIA

1. Depression is a common disorder in mid and later life.

2. Depression occurs more often in patients with neurodegenerative diseases including Alzheimer's disease, stroke, Parkinson's disease and others.

3. Depression may worsen health outcomes in older persons, including cardiovascular disease, cerebrovascular disease, and diabetes.

4. Persons with adult-onset depression demonstrate increased risks for late life dementia.

5. Persons with dementia or mild cognitive impairment have significantly increased risk for depression.

6. Rodent models for depression suggest that stress may reduce the reparative and regenerative capacity of neurons.

7. Treatment for depression in all age groups is simple, safe, and cost-effective.

8. Most antidepressant medications are effective for treating mid or later life depression.

9. Physicians should avoid alarming patients with a past history of depression by focusing on the beneficial effect of antidepressant therapy.

10. Insufficient data is available to advise patients that treating mid or late life depression reduces their risk of developing dementia.

Consumer's Guide to Understanding the Health Consequences of Untreated Depression

How Can Untreated Depression Impact Health and Memory?

Depression is a common health problem in all age groups. Depression is a brain chemical disorder that causes significant stress and suffering for the patient. Chronic depression increases the likelihood of health problems such as heart disease, disability from stroke, and poor control of diabetes. Many older persons with depression also complain of memory problems. Chronic depression that begins in later life may be an early sign of dementia. The physical and mental stress produced by depression may hasten intellectual decline in some older persons. Untreated depression in older persons may produce memory problems that resemble dementia, but these memory problems may improve with medications. **CLICK HERE FOR MORE INFORMATION – 2513.31**

How Can We Treat Depression?

Medication treatment for depression is highly effective in all age groups. The treatment of depression may reduce or eliminate long-term health consequences produced by chronic depression. Medicines for depression are simple, non-addictive and similar to medicines for high blood pressure or other chronic diseases. Depression can cause anxiety (nervousness) in many patients and these individuals often receive tranquilizers called "benzodiazepines" (Valium, Librium, etc.). These tranquilizers are often addictive. Treating the depression with antidepressant medications will often reduce anxiety. Nerve pills or tranquilizers can sometimes worsen memory. Antidepressant medications are not addictive and sometimes help memory.

How Does Stigma Impact Treatment?

Many persons with depression refuse to seek treatment because of fear or embarrassment of being labeled "crazy". Depression often causes patients to lose hope or faith that treatment can correct the problem. People who are depressed are not going crazy. If you suffer from depression, you should seek medical assistance. Depression is not caused by human failure anymore than high blood pressure or diabetes. If your friend is depressed, you should encourage them to seek treatment.

WHAT YOU CAN DO FOR DEPRESSION

1. Treat depression like any other health problem.

2. Tell your doctor when you feel depressed.

3. Take your medicines that your doctor prescribes for depression.

4. Don't stop your medications for depression until you speak with your doctor.

5. Stay physically, emotionally and spiritually active; even when you want to stay home.

6. Avoid nerve pills and alcohol for nervousness.

7. Avoid sleeping pills unless prescribed by the doctor.

8. Don't drink at night to help with your sleep.

9. Encourage your friends with depression to seek medical help.

10. **Remember:** Depression is a disorder of brain chemistries – not a weakness of the soul.

4. NUTRITION

4. ADVISE A HEALTHY DIET AND PRUDENT NUTRITIONAL SUPPLEMENTATION

Calorie restriction is the only dietary intervention that may slow aging. Severe restriction of dietary calories may reduce oxidative damage in humans and diminish the expression of age-related apoptotic genes in rodents. The severity of calorie restrictions necessary to slow aging also lowers the quality of life for most individuals and this method of longevity promotion is unreasonable for most humans. Several diets or nutritional supplements may reduce the risk of cognitive decline. A heart-healthy diet may reduce other risk factors associated with dementia.

Vitamin supplements may help reduce the risk for dementia. Elevated homocysteine levels may be produced by deficiencies of B-Complex vitamins and Folic acid. Minor elevations of homocysteine in older persons increase the risk for heart disease, cerebrovascular disease, and dementia. Folic acid and B-12 deficiencies are common in persons over the age of 65 where many deficient individuals show no evidence of neurological or hematological abnormalities. Folic acid and B-Complex vitamin supplementation is a simple, safe, cost-effective intervention that may lower homocysteine levels in older persons.

Individuals with low levels of Omega-3 Fatty Acids may be related to increased risk for dementia. Omega-3 supplementation has not been shown to prevent dementia; however, patients may benefit from consuming two helpings of fish per week.

Elders with low levels of natural antioxidants such as Beta Carotene and Vitamin E have increased risks for developing dementia. A standard dose of Vitamin E supplementation is reasonable in older persons not receiving potential interactive drugs, e.g., coumadin. Many other vitamins, minerals, and substances have been mentioned as possible neuro-protectants or precipitants for Alzheimer's disease. For instance, aluminum has no proven role in the pathogenesis of Alzheimer's disease despite considerable discussion in the lay press. **(Click here for references – 2513.43).**

Recommendation

Elders need a balanced diet with basic vitamin supplementation for Folic acid and B-Complex vitamins. Encourage a heart-healthy diet to protect cerebro-vasculature and cerebral perfusion. In general, a heart-healthy diet is probably brain-healthy. **For more information, click here – 2513.41, 2513.411, 2513.45.**

A Physician's Guide to the Role of Nutrition and Diet in Successful Cognitive Aging

1. Introduction

Primary care physicians are often queried by older patients about the wisdom of vitamin supplementation and proper nutrition in maintaining normal intellectual function. The precise role of midlife or later-life nutrition in aging and dementia remains unclear, although individuals with reduced levels of natural antioxidants appear to experience increased age-related morbidity. The role of vitamins, minerals, dietary supplements, and herbal remedies also remains unclear (1). Physicians are often queried about the role of nutritional choices in intellectual function and aging. This segment outlines common nutritional issues where sufficient peer-reviewed data exists to make specific recommendations.

A three-step process can be used to determine a recommendation by a primary care clinician: 1) is the nutritional supplement safe at standard doses, 2) is there credible scientific evidence to suggest possible efficacy and, 3) is the supplement reasonably priced. Since nutritional supplements are not regulated by the FDA, patients cannot be sure of the product's content, safety or efficacy.

2. Vitamin Supplementation As A Neuro-Protectant

Homocysteine is a thiol-containing amino acid produced by demethylation of methionine (2). In older persons, elevated serum levels of homocysteine are related to accelerated atherosclerosis, as well as increased risk for heart disease and stroke. The major cause of death in younger individuals with homocysteinuria produced by cystathionine β synthethase deficiency is atherosclerotic vascular disease. Elevation of serum homocysteine above 15 to 20 μmd/l predicts adverse cardiovascular outcomes and increased risk for cognitive decline with aging (3), (4), as well as increased plasma levels of β amyloid (5). Elevated homocysteine can be related to deficiencies of folic acid and B-complex vitamins. Folic acid deficiency and B-complex vitamin deficiencies are common in older individuals, including those without evidence of pernicious anemia. Low folate status as measured by red blood cell folate may be related to risk for dementia in all ethnic groups including Latinos (7). Chronic, low levels of folic acid, Vitamin B12 or B6 can produce symptoms of dementia (8), (9). Most diets that include some green, leafy vegetables, meats, and other "fortified" food staples contain sufficient folic acid and B-complex vitamins to achieve minimum daily requirement. A standard "daily" vitamin supplement for older individuals typically contains adequate folic acid and B-complex vitamins to achieve adequate supplementation. Measurement of serum B12 and folate may be predictive of homocysteine levels. Neither evaluation will predict the onset of dementia; however, elevated homocysteine is associated with increased risk for cognitive loss in elders, cerebrovascular disease and dementia in older persons. Elevated homocysteine in a diabetic patient increases the risk for cognitive decline beyond the risk produced by diabetes (13).

Homocysteine levels (tHcy) may be linked to risk for dementia via vascular disease or other mechanisms. Supplementation of folic acid in the 0.5mgm to 5mgm range reduces tHcy by 25% and the concurrent use of vitamin B12 in the 0.5mgm range reduced tHcy by an additional 7% (10), (11). Typical, clinical supplementation includes both Folic acid and B12

to prevent unrecognized B12 deficiency (12). Supplementation of dietary niacin may also provide some protection against AD (6).

Clinicians are encouraged to discuss routine "senior" vitamin supplementation with midlife or older patients to reduce the potential risk factor associated with elevated homocysteine. Randomized controlled prospective studies have not been performed to confirm the "protective" effect of vitamin supplementation and available data does not show clear protective benefit (11), (12). A single study suggests that individuals who have suffered an acute myocardial infarction may have slightly worse outcome with post infarction supplementation of folic acid and B12. The risk-benefit and cost/potential benefit ratios would support vitamin usage in middle aged and older patients (14), (15). (Click here for additional information about homocysteine and dementia – 2513.411).

3. Antioxidants As Neuro-Protectants

Antioxidant supplementation as a cognitive protectant remains a controversial issue. Several longitudinal studies fail to confirm a relationship between antioxidant consumption and dementia risk (1), (16), (17), (18). Others studies have linked levels of natural antioxidants, such as Vitamin E, C, and beta carotene to risk reduction and reduction of inflammatory markers such as C-reactive protein (19). A wide range of food stuffs, including red wines, contain natural antioxidants which may reduce organ damage produced by excessive production of free radicals. Vitamin E is a potent antioxidant that may slow progression of Alzheimer's disease. Rodent models of Alzheimer's disease demonstrate reduced amyloid load with chronic antioxidant therapy (15). The therapeutic value of Vitamin E supplementation is unclear; however, this vitamin can produce toxicity when taken in large continuous doses. A standard supplementation of 300 units per day is included in many vitamins; however, some clinicians will prescribe 1,000 units of Vitamin E per day in persons at risk for Alzheimer's disease. The beneficial effect of long-term, high-dose Vitamin E supplementation in humans remains controversial. Individuals receiving coumadin should exercise great care and patients are recommended to discuss any Vitamin E supplement with their pharmacist to exclude drug-drug interactions. The use of other potential antioxidants, such as Gingko Biloba, is equally controversial. Insufficient data exists to recommend antioxidant therapy as a dementia prevention measure (32).

4. Weight Control to Reduce Risk Factors for Dementia

Mid-life obesity and Type II diabetes are linked to dementia in later life ***(CLICK HERE FOR MORE INFORMATION-2513.91)*****.** The precise mechanism by which obesity and diabetes contribute to cognitive decline in later life remains unclear; however, obesity appears linked to the metabolic syndrome (20), (21). "Weight reduction" diets do not appear to impact risk of dementia; in fact, individuals who consume large amounts of tofu may have greater risk of cognitive decline (19), (22). Long-term dietary control with maintenance of normal body mass is probably beneficial to later life cognitive function. Prospective randomized studies comparing obese to normal individuals will not be performed and clinicians must advise middle-aged patients based on best available data. Many middle-aged caregivers of persons with dementia can be encouraged to maintain normal weight as a possible protective intervention against metabolic syndrome and increased risk of cognitive decline in their later life.

5. The Role of Metals and Trace Elements in Dementia

A variety of trace elements or heavy metals have been linked to dementia or cognitive decline. Certain metals, such as lead, are neurotoxic and toxic levels in humans can produce cognitive loss. Aluminum is the metal that has received the greatest attention over time. Aluminum is found within neurofibrillary tangles and human aluminum toxicity can produce fibrillary masses within neurons. Dialysis dementia was produced by excessive amounts of aluminum in the dialysate.

There is no conclusive evidence that links aluminum toxicity to Alzheimer's disease. Acute or chronic exposure to many toxic substances, such as lead, can produce intellectual deficits and many metals can be found within neurofibrillary tangles. Amyloid has high affinity for certain metals, such as Fe (Iron), Al (aluminum), and Zn (zinc), which may promote the generation of reactive oxygen species (23). Aluminum is readily absorbed through the gastrointestinal tract; however, there is no evidence that individuals receiving aluminum-based antacids have suffered greater rates of intellectual decline. Anecdotal reports of improved cognitive function with chelation are not corroborated by randomized controlled studies and this potentially dangerous procedure is not recommended for individuals unless specific defined toxic levels of metals are identified. Available evidence does not support cognitive enhancement by nutritional supplementation with vitamins and minerals beyond those routinely included in "senior vitamins".

6. Nutritional Programs or Dietary Supplementation to Protect Cognition

Long-term consumption of typical "Mediterranean" diet that is rich in mono-saturated fatty acids may be protective against cognitive decline. A diet with low animal fat, but high fish and cereal consumption may be protective (33), (46). Features of the Mediterranean diet may reduce complications from the metabolic syndrome including reduction of markers of vascular inflammation such as creactive protein (CRP) (29). Trans-fatty acids are produced by the partial hydrogenation of vegetables oils that helps solidify the fat. These fats account for 2% to 3% of calories consumed in American diets, especially in "fast foods". These artificial food substances increase vascular risk factors (34). Paradoxically, high tofu intake may be associated with increased risk for cognitive decline (22), **(Table 1**). Long-term consumption of diets that are high in fish content may diminish the risk for dementia (30), (31). High intake of unsaturated fatty acids in mid-life may reduce the long-term risk for Alzheimer's disease in later life (49).

Table 1. **Studies on Dietary Supplements to Improve Memory or Prevent Dementia**

Study	Molecule	Outcome	Ref
Meta n=0	Omega 3 Fatty Acid	Inadequate Data	24
Meta n=12	Lecithin	Demonstrated no benefit	25
Meta n=11	AcetyL Carnitine	Not recommended	26
4 Studies	phosphatidylserine	Slight improvement with AAMI/Minimal data	27
1 Study	DHA	⇩Risk	45
Meta – Meta analysis of available data			

2513.44. Nutrition/homocysteine and folic acid

There is incomplete scientific evidence to prove a preventive or therapeutic effect of nutritional supplementation for older persons. Prospective randomized controlled studies have not been performed to examine the protective effect of these dietary supplements over decades. Many other herbal substances and nutritional supplements have been touted as possessing anti-aging, antioxidant or anti-Alzheimer benefits; however, these claims are not substantiated by randomized controlled studies.

Clinicians must distinguish a genuine preventive benefit from a placebo effect. Many psychotropic medication trials produce significant placebo effects in persons not receiving the active molecule. Many patients provide personal attestations that a specific combination of vitamins and dietary measures will substantially improve their intellectual vitality or sense of cognitive ability. Nationally advertised "memory enhancing supplements" are not shown to improve cognition or reverse cognitive loss through large scaled, randomized controlled studies. The active constituents for these products are often available in cheap, generic forms.

As long as the dietary programs do not produce other health problems and the supplements are not excessively expensive, the clinician can encourage the patient to continue those interventions which are perceived as beneficial. The secondary benefits to the patients beyond a possible placebo effect may include enhanced awareness of health maintenance and stress reduction produced by a sense of control and self-mastery.

7. Consumption of Alcohol as a Risk Factor for Dementia

A consumption of alcohol as an antioxidant or cognitive protectant is controversial and contradictory. Frenchmen who consume wine in moderation may have diminished risk of cognitive decline; however, these individuals may have other lifestyle features that are not captured by available research (48). Individuals with excessive alcohol consumption may sustain a wide range of health problems; however, moderate drinking is associated with slightly diminished risk for cognitive decline ***(CLICK HERE FOR MORE INFORMATION – 2513.2)***. Clinicians are not advised to encourage patients to commence drinking in later life as a health intervention. Heavy drinkers in all age groups should be encouraged to abstain or reduce alcohol consumption. Social drinkers can be advised that moderate drinking is acceptable within certain limits. Wine is probably the preferable

beverage for these individuals. For more information on alcohol consumption in the elderly, please see DETA 2513.21.

Conclusion and Recommendation

Primary care doctors should examine three issues in crafting dietary recommendations for older patients: 1) safety, 2) evidence for efficacy, and 3) financial tolerability. A balanced diet with one or two servings of fish per week and basic vitamin supplementation is probably beneficial to all middle-aged and older individuals (32), (33), (34), (46), (47), (50). Normal weight in middle age should be maintained by proper diet and regular exercise. Folic acid and B-complex vitamin supplementation may be helpful to reduce risk factors associated with elevated homocysteine levels (28) although caution may be required in persons who have suffered an acute myocardial infarction (35). Moderate alcohol consumption is acceptable (48). Patient handouts on weight, alcohol, and diet are available (Click here for handouts – 2513.25, 2513.45, 2513.45-1).

Recommendations to Primary Care Clinicians

1. Educate patients that nutritional behaviors in midlife may impact cognitive function in later life.
2. Encourage heart healthy diets with additional servings of fish and less red meat.
3. Advise patients to take a standard, daily vitamin with B-complex and folic acid.
4. Monitor patient's weight, avoid central obesity, and provide nutritional advice.
5. Advise patients who drink alcohol to consume in moderation. Red wine is probably the best form of alcohol.
6. Advise patients to avoid extreme diets and maintain an active life with exercise.

References

1. Pope SK, Shue VM, Beck C. Will a healthy lifestyle help prevent Alzheimer's disease? Annu. Rev. Public Health 2003;24:111-32.
2. Diaz-Arrastia R. Homocysteine and neurologic disease. Arch Neurol 2000;57:1422-1428.
3. Penninx BWJH, Guralnik JM, Ferrucci L, et al. Vitamin B12 deficiency and depression in physically disabled older women: epidemiologic evidence from the women's health and aging study. Am J Psychiatry 2000;157:715-721.
4. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. JAMA 1995;274:1049-1057.
5. Irizarry MC, Gurol ME, Raju S, et al. Association of homocysteine with plasma amyloid beta protein in aging and neurodegenerative disease. Neurology 2005;65(9):1402-8.
6. Morris MC, Evans DA, Beinias JL, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J. Neurol Neurosurg Psychiatry 2004;75(8):1093-9.
7. Ramos MI, Allen LH, Mungas DM, et al. Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging. Am J Clin Nutr 2005;82(6):1346-52.
8. Hassing L, Wahlin A, Winblad B, Backman L. Further evidence on the effects of vitamin B12 and folate levels on episodic memory functioning; A population-based study of healthy very old adults. Biol Psychiatry 1999;45:1472-1480.
9. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476-483.
10. Homocysteine Lowering Trialist's Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. BMJ 1998;316:894-8.
11. Scott DJ, MacIntosh G, Lowe GD, et al. Randomized controlled trial of homocysteine-lowering vitamin treatment in elderly patients with vascular disease. Am J Clin Nutr 2005;82(6):1320-6.
12. Quinlivan EP, McPartlin J, McNulty H, et al. Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. Lancet 2002;359:227-228.
13. Robbins MA, Elias MF, Budge MM, et al. Homocysteine, type 2 diabetes mellitus, and cognitive performance: The Maine-Syracuse Study. Clin Chem Lab Med 2005;43(10):1101-6.
14. Malouf M, Grimley EJ, Areaosa SA. Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Syst Rev 2003;(4):CD004514.
15. Malouf R, Grimley EJ. The effect of vitamin B6 on cognition. Cochrane Database Syst Rev 2003;(4):CD004393.
16. Laurin D, Masaki KH, Foely DJ, et al. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolullu-Asia Aging Study. Am J Epidemiol 2004;159(10):959-67.
17. Morris MC, Evans DA, Bienias JL, et al. Dietary intake of antioxidant nutrients and the risk of incident Alzheimer's disease in a biracial community study. JAMA 2002;287:3230-37.
18. Englehart MJ, Geerlings MI, Ruitenberg A, et al. Dietary intake of antioxidants and risk of Alzheimer's disease. JAMA 2002;287:3223-29.
19. Hu P, Reuben DB, Crimmins EM, et al. The effects of serum beta-carotene concentration and burden of inflammation on all-cause mortality risk in high-functioning older persons: MacArthur studies on successful aging. J. Gerontol A Biol. Sci. Med. Sci. 2004;59(8):849-54.
20. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer's disease. Arch Neurol 2005;62(10):1556-60.
21. Whitmer RAN, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330(7504):1360.
22. White LR, Petrovich H, Ross GW, et al. Brain aging and midlife tofu consumption. J. Am. Coll. Nutr. 2000;19(2): 242-255.
23. Staehelin HB. Micronutrients and Alzheimer's disease. Proc. Nutr. Soc. 2005;64(4):565-70.
24. Lim W, Gammack J, Van Niekerk J, Dangour A. Omega 3 fatty acid for the prevention of dementia. Cochrane Database Syst Rev 2006;25(1):CD005379.
25. Higgins JP, Flicker L. Lecithin for dementia and cognitive impairment. Cochrane Database Syst Rev 2003; (1):CD001015.
26. Hudson S, Tabet N. Acetyl-L-carnitine for dementia. Cochrane Database Syst Rev 2003;(2):CD003158.
27. Crook TH, Tinklenberg J, Yesavage J, et al. Effects of phosphatidylserine in age-associated memory impairment. Neurology 1991;41:644-649.
28. Morris MC, Evans DA, Bienias JL, et al. Dietary fat intake and 6-year cognitive change in an older biracial community population. Neurology 2004;62(9):1573-9.

29. Esposito K, Marfella R, Ciotola M, Di Palo C, et al. Effect of a Mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004;292(12):1440-6.
30. Kalmijn S, Launer LJ, Ott A, et al. Dietary fat intake and the risk of incident dementia in the Rotterdam study. Ann Neurol 1997;42:776-82.
31. Kalmijn S, Feskens EJM, Launer LJ, Kromhout D. Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. Am. J. Epidemiol 1997;145:33-41.
32. Launer LJ, Kalmijn S. Antioxidants and cognitive function: a review of clinical and epidemiologic studies. J Neural Transm Suppl 1998;53:1-8.
33. Del Parigi A, Panza F, Capurso C, Solfrizzi V. Nutritional factors, cognitive decline, and dementia. Brain Res. Bull 2006;69(1):1-19.
34. Mazaffarian D, Katan MB, Ascherio A, et al. Trans fatty acids and cardiovascular disease. N Engl J Med 2006;354:1601-13.
35. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. NEJM 2006;354:1578-1588.
36. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer's disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004;61(1):82-8.
37. Maxwell CJ, Hicks MS, Hogan DB, et al. Supplental use of antioxidant vitamins and subsequent risk of cognitive decline and dementia. Dement Geriatr Cogn Disord. 2005;20(1):45-51.
38. Kontush K, Schekatolina S. Vitamin E in neurodegenerative disorders: Alzheimer's disease. Ann N Y Acad Sci 2004;1031:249-62.
39. Cherubini A, Martin A, Andres-Lacueva C, et al. Vitamin E levels, cognitive impairment and dementia in older persons: the InChianti study. Neurobiol Aging 2005;26(7):987-94.
40. Englehart MJ, Ruitenberg A, Meijer J, et al. Plasma levels of antioxidants are not associated with Alzheimer's disease or cognitive decline. Dement Geriatr Cogn Disord. 2005;19(2-3):134-9.
41. Whalley LJ, Starr JM, Deary IJ. Diet and dementia. J Br Menopause Soc. 2004;10(3):113-7.
42. Luchsinger JA, Mayeux R. Dietary factors and Alzheimer's disease. Lancet Neurol 2004;3(10):579-87.
43. Larrieu S, Letenneur L, Helmer C, et al. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. J Nutr Health Aging 2004;8(3):150-4.
44. Laurin D, Masaki KH, Foley DJ, et al. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol. 2004;159(10):959-67.
45. Schaefer EJ, Bongard V, Beiser AS, et al. Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer's disease. Arch Neurol 2006;63:1545-1550.
46. Scarmeas N, Stern Y, Tang MX, et al. Mediterranean Diet and risk for Alzheimer's disease. Ann Neurol 2006;59:912-921.
47. Kawas CH. Diet and the risk for Alzheimer's disease. Annals of Neurology 2006;59(6):877-879.
48. Orgogozo JM, Dartigues JF, Lafont S, et al. Wine consumption and dementia in the elderly: a prospective community study in the Bordeaux area. Revue Neurologique 1997;153(3):185-192.
49. Solfrizzi V, Colacicco AM, D'Introno A, et al. Dietary intake of unsaturated fatty acids and age-related cognitive decline: a 8.5-year follow-up of the Italian Longitudinal Study on Aging. Neurobiology of Aging 2006;27:1694-1704.
50. Donini LM, De Felice MR, Cannella C. Nutritional status determinants and cognition in the elderly. Arch Gerontol Geriatr 2007;Suppl 1:143-153.
51. Donini LM, De Felice MR, Canella C. Nutritional status determinants and cognition in the elderly. Arch Gerontol Geriatr 2007, Suppl1:143-153.
52. MacLean CH, Issa AM, Newberry SJ, et al. Effects of omega-3 fatty acids on cognitive function with aging, dementia, and neurological diseases. Agency for Health Research and Quality. Evidence Report/Technology Assessment: No. 114, 2005.

A Clinician's Guide To The Role Of Vitamin Supplementation In The Prevention Of Dementia

1. Overview

Vitamin supplementation can be an important issue to the patient and medical professionals. Middle-aged individuals often query primary care doctors about the role of nutritional supplements in the prevention of common disorders, such as vascular disease or dementia. Older individuals are often concerned about maintaining cognitive vitality. Primary care physicians may be queried about the role of homocysteine in the pathogenesis of vascular brain damage and Alzheimer's disease. Specific vitamin supplementations can be recommended for folic acid and B-Complex vitamins.

2. Linking Vitamins to Neurobiology

Vitamin supplementation for the prevention of dementia can be conceptualized in two-part categories: those vitamins that provide a neuroprotectant effect and those that reduce vascular risk factors. Vitamin supplementation has not been demonstrated to promote neuronal synaptogenasis or neuronal plasticity. The neuroprotectant vitamins often use antioxidant pathways, while many vascular protectants are mediated through reduction of homocysteine levels.

Studies show that 1 to 2% of all respired oxygen may be converted into free radicals which can produce neurotoxic effects. Mitochondrial damage is implicated as a contributory factor in senescent brain dysfunction. Both Vitamin E and Vitamin C may have antioxidant effects. Beta Carotene may also reduce overall oxidative stress. Large doses of Vitamin E have been reported to slow the progress of Alzheimer's disease; however, the value of long-term, high dose Vitamin E supplementation as a neuroprotectant is unproven.

4. Homocysteine and Brain Function

Numerous publications document the relationship of homocysteine to neurological disease (1). Homocysteine is a sulfur-containing amino acid that plays a major role in the metabolic processing of thiol compounds. High levels of homocysteine in children will accelerate atherosclerotic deposits in arteries. Homocystenuria is a genetic metabolic abnormality produced by a cystathionine β-synthethase deficiency (CSD). Cystathionine β synthethase deficiency can raise homocysteine levels above 200 micromoles per liter. The heterozygote state for CSD is estimated to occur in 1 to 2% of the population and produces mild elevation of homocysteine in the 20 to 30 micromolar per liter range (1). Homocysteine may also play an important role in other disorders, such as Parkinson's disease (2).

In adults, moderate elevations of plasma homocysteine in the 15-20 micro-molar per liter range significantly enhance risk factors for vascular disease. Other additional risk factors, such as diabetes and hypertension, enhance the overall impact of the elevated homocysteine. Vitamin B12 is an integral part of the metabolic pathway that converts methionine into homocysteine. Excessive quantities of homocysteine contribute to the production of increased quantities of excessive reactive oxygen species and lipid peroxidation that result in vascular damage (1). Vitamin supplementation with folic acid, B12 and B6 is recommended

for the reduction of serum levels of homocysteine. Depressed levels of vitamin B12 and folic acid are associated with cognitive loss and depression (3), (4).

Some estimates suggest that up to 10% of vascular disease risk in the general population is due to elevated homocysteine (1). A single study of B-complex and folic acid supplementation following acute myocardial infarction demonstrated worse cardiovascular outcomes (23). Homocysteine levels appear to remain stable through the first four decades of life; however, after age 70, they appear to rise sharply.

The role of elevated homocysteine and B-Complex vitamin or folic acid deficiencies may be linked or may be separate factors. The connection between cognitive function and vitamin deficiencies or elevated homocysteine may be related to vascular damage in the brain or other unknown CNS effects.

5. The Role Of Folic Acid And B12 In Vascular Disease

Numerous studies have examined the role of homocysteine to atherosclerotic vascular disease. In a meta analysis of 27 studies on homocysteine and 11 studies on folic acid, the authors concluded that elevations of five micromoles per liter increments of serum homocysteine increase the risk for coronary artery disease and high intake of folic acid reduces the risk for atherosclerotic vascular disease (5). Multiple studies demonstrate an inverse relationship between dietary intake of folate and consequent risk of stroke and cerebrovascular disease (6). Elevated levels of homocysteine are also related to the severity of white matter pathology in older persons (7). Overall, available data suggests that either elevated homocysteine or diminished folic acid will increase the risk for peripheral and cerebral vascular disease **(See Table 1).**

Table 1. The Association of Homocysteine and Folic Acid to Vascular Disease and Dementia

Study	t	n	age	Results	Refs.
1	CS	5918 (M) 6348 (F)	65-67	↑ tHcy = ↑ cardiovascular risk factor	14
2	CS	1077	60-90	↑ tHcy = ↑ cardiovascular for ↑ silent CVA and ↑ Wm disease	3,7
3	19 yrs	9764	25-74	⇩ Dietary folic acid = ↑ risk of CVA	6
4	6.1	965	65+	↑ Folic acid = ⇩ risk for AD, B6=NC, B12=NC	36

tHcy = total homocysteine **ND**=non-demented **CS**=cross sectional

2513.44. Nutrition/homocysteine and folic acid

6. The Relationship of Homocysteine Levels and Cognitive Function

Multiple studies have examined the relationship between total homocysteine levels and the risk for cognitive loss or dementia with aging **(See Table 2).** Most studies support an inverse relationship between late life cognition and elevated homocysteine levels. The

studies suggest that levels above 14μm/l increase the risk of cognitive decline in a dose-dependent manner. The severity of elevation and duration of elevation may be related to the relative risk for producing dementia in an older individual (8).

Table 2. Effect of tHcy Levels on Cognitive Function

Study	t	n	age	Results	Refs.
1	CS	1077	60-90	↑ tHcy = ↓ cognitive testing in ND	22
2	7 yrs	499	70-79	↑ tHcy = and ↓ folic acid = ↓ cognitive testing in ND	15
3	CS	2096	Over 60	↑ tHcy = ↓ cognitive testing in ND	16
4	CS	817	60+	↑ tHcy = ↓ cognitive performance with ↑ effect for Type II diabetics in ND	9
5	4 yrs	599	85+	↑ tHcy = and ↓ folic acid = ↓ cognitive function in ND	17
6	8 yrs	1092	76	↑ tHcy = ↑ risk for dementia /Alzheimer's disease	8
7	CS	248	55+	↑ tHcy = ↓ cognitive function in African Caribbeans	18

tHcy = total homocysteine **ND**=non-demented **CS**=cross sectional

2513.44. Nutrition/homocysteine and folic acid

The precise mechanism that produces increased risk for cognitive decline is unclear. Elevated homocysteine may increase synaptic damage in the aging brain by accelerating the rate of vascular damage through infarctions and microvascular pathology. Elevated homocysteine may relate to elevated levels of β amyloid in aging humans (2).

A likely explanation involves accelerated vascular damage to the brain with consequent reduction of synaptic reserve as the primary event. Other vascular risk factors, such as diabetes, may enhance risk factors for cognitive decline produced by homocysteine (9).

7. Therapeutic Approaches to Lowering Homocysteine in Middle-aged and Older Individuals

A meta analysis of 12 clinical trials that include over 1,000 research subjects demonstrated that folic acid supplementation in the range of 0.5 to 5mgm would reduce plasma homocysteine levels by approximately 25% (10). Additional supplementation with doses of vitamin B12 in the dose range of 0.5mgm per day produced an additional 7% reduction of serum homocysteine; however, additional vitamin B6 did not appear to have significant impact on these serum levels (10), (37), (38), (39). In older individuals with vascular risk factors, supplementation with both folic acid and vitamin B12 appears to lower homocysteine by approximately 5 micromoles per liter (11). Combined supplementation with folic acid and B12 appears to be recommended by many clinical researchers (12). The long-term beneficial effect of folic acid and B12 supplementation in the maintenance of cognitive function or slowing of decline in demented patients has not been confirmed because long-term prospective studies have not been performed. The relative risk of B12-folic acid supplementation to middle-aged and older individuals is low. Folic acid supplementation is

routinely provided during pregnancy because of the impact of folate on neural systems. Dietary supplementation should exceed 500micrograms of folic acid to achieve the desired effect.

Routine screening for homocysteine levels has not been endorsed by national organizations; however, clinicians may choose to assess this potential blood marker in at-risk populations. The risk-benefit ratio for mid-life supplementation with folic acid and B-complex vitamins appears to be low for long-term vitamin supplementation in the general population with recommended doses of folic acid (0.5 to 1mg) and vitamin B12 (5mg daily). Vitamin B6 supplementation is usually provided in standard dietary supplements; however, insufficient data is available to support any neuroprotective effect of this dietary supplementation with this vitamin (13), (19). Deficiency of folic acid and B-complex vitamins adversely impacts cognition in Black and Latino elders suggesting little ethnic difference in this relationship (18), (20). Sufficient indirect evidence is available to recommend vitamin supplementation during middle years when homocysteine levels begin to rise.

Vitamin	ID	Dose	ND*
Thiamin	B1	1.5 mgm	Y
Pyridoxine	B6	2 mgm	Y
Cyanocobolamin	B12	0.5 mgm	Y
Riboflavin	B2	1.5 mgm	?
Folic Acid	---	0.5 mgm	Y
Alpha tochopheryl	E	300 IU	N
Niacin	---	20 mgm	Y

***Neurological Disease Associated with Deficiency**

2513.44. Nutrition/homocysteine and folic acid

Recommendations to the Primary Care Physician

1. Encourage middle-aged patients to take a standard "senior" vitamin that contains B-Complex vitamins and folic acid.
2. Recommend routine daily doses of Vitamin E, i.e., 300 IU per day contained in standard OTC vitamins.
3. Mega doses of vitamins are not shown to reduce the risk of dementia and may produce drug-drug interactions, as well as increased morbidity.
4. Encourage healthy diets that provide a balanced nutritional intake.

References

1. Diaz-Arrastia R. Homocysteine and neurologic disease. Arch Neurol 2000;57:1422-1428.
2. Irizarry MC, Gurol ME, Raju S, et al. Association of homocysteine with plasma amyloid beta protein in aging and neurodegenerative disease. Neurology 2005;65(9):1402-8.
3. Penninx BWJH, Guralnik JM, Ferrucci L, et al. Vitamin B12 deficiency and depression in physically disabled older women: epidemiologic evidence from the women's health and aging study. Am J Psychiatry 2000;157:715-721.
4. Hassing L, Wahlin A, Winblad B, Backman L. Further evidence on the effects of vitamin B12 and folate levels on episodic memory functioning; A population-based study of healthy very old adults. Biol Psychiatry 1999;45:1472-1480.
5. Boushey CJ, Beresford SAA, Omenn GS, Motulsky AG. A quantitative assessment of plasma homocysteine as a risk factor for vascular disease. JAMA 1995;274:1049-1057.
6. Bazzano LA, He J, Ogden LG, et al. Dietary intake of folate and risk of stroke in U.S. men and women: NHANES I epidemiologic follow-up study. Stroke 2002;33:1183-1189.
7. Vermeer SE, van Dijk EJ, Koudstaal PJ, et al. Homocysteine, silent brain infarcts, and white matter lesions: The Rotterdam Scan Study. Ann Neurol 2002;51:285-289.
8. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476-483.
9. Robbins MA, Elias MF, Budge MM, et al. Homocysteine, type 2 diabetes mellitus, and cognitive performance: The Maine-Syracuse Study. Clin Chem Lab Med 2005;43(10):1101-6.
10. Homocysteine Lowering Trialist's Collaboration. Lowering blood homocysteine with folic acid based supplements: meta-analysis of randomized trials. BMJ 1998;316:894-8.
11. Scott DJ, MacIntosh G, Lowe GD, et al. Randomized controlled trial of homocysteine-lowering vitamin treatment in elderly patients with vascular disease. Am J Clin Nutr 2005;82(6):1320-6.
12. Quinlivan EP, McPartlin J, McNulty H, et al. Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. Lancet 2002;359:227-228.
13. Morris MC, Evans DA, Beinias JL, et al. Dietary niacin and the risk of incident Alzheimer's disease and of cognitive decline. J. Neurol Neurosurg Psychiatry 2004;75(8):1093-9.
14. Nygard O, et al. Total plasma homocysteine and cardiovascular risk profile. JAMA 1995;274:1526-33.
15. Kado DM, Karlamangla AS, Huang MH, et al. Homocysteine versus the vitamin folate, B6, and B12 as predictors of cognitive function and decline in older high-functioning adults: MacArthur Studies of Successful Aging. Am J Med 2005;118(2):161-7.
16. Elias MF, Sullivan LM, D'Agostino RB, et al. Homocysteine and cognitive performance in the Framingham offspring study: age is important. Am J Epidemiol 2005;162(7):644-53.
17. Mooijaart SP, Gussekloo J, Frolich M, et al. Homocysteine, vitamin B12, and folic acid and the risk of cognitve decline in old age: the Leiden 85-Plus study. Am J. Clin Nutr 2005;82(4):866-71.
18. Stewart R, Asonganyi B, Sherwood R. Plasma homocysteine and cognitive impairment in an older British-African-Caribbean population. J Am Geriatr Soc 2002;50:1227-1232.
19. Malouf R, Grimley EJ. The effect of vitamin B6 on cognition. Cochrane Database Syst Rev 2003;(4):CD004393.
20. Ramos MI, Allen LH, Mungas DM, et al. Low folate status is associated with impaired cognitive function and dementia in the Sacramento Area Latino Study on Aging. Am J Clin Nutr 2005;82(6):1346-52.
21. Malouf M, Grimley EJ, Areaosa SA. Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Syst Rev 2003;(4):CD004514.
22. Prins ND, Den Heijer T, Hofman A, et al. Homocysteine and cognitive function in the elderly. The Rotterdam Scan Study. Neurology 2002;59:1375-1380.
23. Bonaa KH, Njolstad I, Ueland PM, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. NEJM 2006;354:1578-1588.
24. Tucker JM, Townsend DM. Alpha-tocopheral: roles in prevention and therapy of human disease. Biomed

Pharmacother 2005;59(7):380-7.
25. Boothby LA, Doering PL. Vitamin C and Vitamin E for Alzheimer's disease. Ann Pharmacother 2005;39(12): 2073-80.
26. Pham DQ, Plakogiannis R. Vitamin E supplementation in Alzheimer's disease, Parkinson's disease, tardive dyskinesia, and cataract: Part 2. Ann Pharmacother 2005;39(12):2065-72.
27. Zandi PP, Anthony JC, Khachaturian AS, et al. Reduced risk of Alzheimer's disease in users of antioxidant vitamin supplements: the Cache County Study. Arch Neurol 2004;61(1):82-8.
28. Maxwell CJ, Hicks MS, Hogan DB, et al. Supplental use of antioxidant vitamins and subsequent risk of cognitive decline and dementia. Dement Geriatr Cogn Disord. 2005;20(1):45-51.
29. Kontush K, Schekatolina S. Vitamin E in neurodegenerative disorders: Alzheimer's disease. Ann N Y Acad Sci 2004;1031:249-62.
30. Cherubini A, Martin A, Andres-Lacueva C, et al. Vitamin E levels, cognitive impairment and dementia in older persons: the InChianti study. Neurobiol Aging 2005;26(7):987-94.
31. Englehart MJ, Ruitenberg A, Meijer J, et al. Plasma levels of antioxidants are not associated with Alzheimer's disease or cognitive decline. Dement Geriatr Cogn Disord. 2005;19(2-3):134-9.
32. Whalley LJ, Starr JM, Deary IJ. Diet and dementia. J Br Menopause Soc. 2004;10(3):113-7.
33. Luchsinger JA, Mayeux R. Dietary factors and Alzheimer's disease. Lancet Neurol 2004;3(10):579-87.
34. Larrieu S, Letenneur L, Helmer C, et al. Nutritional factors and risk of incident dementia in the PAQUID longitudinal cohort. J Nutr Health Aging 2004;8(3):150-4.
35. Laurin D, Masaki KH, Foley DJ, et al. Midlife dietary intake of antioxidants and risk of late-life incident dementia: the Honolulu-Asia Aging Study. Am J Epidemiol. 2004;159(10):959-67.
36. Luchsinger JA, Tang MX, Miller J, et al. Relation of higher folate intake to lower risk for Alzheimer disease in the elderly. Arch Neurol 2007;64:86-92.
37. Malouf M, Grimley EJ, Areosa SA. Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Syst Rev 2003;(4):CD004514.
38. Malouf R, Grimley EJ. The effect of vitamin B6 on cognition. Cochrane Database Syst Rev 2003;(4):CD004393.
39. Lonn E, Yusuf S, Arnold MJO, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. New England Journal of Medicine 2006;354(15):1567-1577.

A Consumer's Guide to Understanding the Role of Middle Life Obesity on Intellectual Function in Later Life

How does my weight at age 45 impact my brain at age 65?

Over 60% of Americans are overweight or obese in their middle-aged years. Our modern lifestyles provide lots of food and little time for regular exercise. Overweight, older people have five times the risk of people with normal weight for developing diabetes (sugar) and very overweight people have 28 times the risk (CLICK HERE FOR MORE INFORMATION – 2513.97). New studies show that a "spare tire" or obesity around the belt in mid life can increase the risk of many health problems in later life, including memory trouble. Significant obesity around the beltline is produced by fatty deposits under the skin and inside the body cavity that holds your organs, like the stomach, liver and bowel. These fatty deposits alter the manner in which our body produces and destroys insulin. Insulin in the blood stream can alter the activity and health of brain cells. The disruption of proper insulin balance may trigger signals for a body response of inflammation that may attack the brain. (CLICK HERE FOR MORE INFORMATION – 2513.95, 2513.96, 2514.15)

A spare tire may increase the risk for problems with cholesterol, triglycerides, high blood pressure, and other health problems that are bad for your brain. Persons with a strong family history for Alzheimer's disease or dementia should work hard in their 30's, 40's, and 50's to reduce health risks that may worsen memory function in their 60's, 70's, and 80's.

Your brain is only as healthy as the body that carries it around. All age groups benefit from maintaining normal healthy weight and deflating the spare tire.

How can I reduce risk factors for dementia associated with body weight?

1. Monitor your weight.
2. Eat healthy.
3. Exercise daily for at least 30 minutes.
4. Talk to your doctor about weight control.
5. Remember: Your brain is as healthy as the body that holds it. **(CLICK HERE FOR MORE INFORMATION – 2513.41, 2513.411)**

Consumer's Guide to Dietary Issues for the Prevention of Dementia

How does diet impact brain function?
A proper diet is essential to good health. Many different kinds of diets are promoted to the public; however, no specific diet is proven to reduce the risk for developing dementia. A heart-healthy diet is recommended for all individuals to reduce risk factors for obesity, hypertension, and to avoid membership in the metabolic club **(Click here for more information – 2513.95)**. Diets that provide sensible amounts of fish, fresh vegetables, and fruits are preferred over diets that include multiple servings of meats and fried foods. Moderate alcohol consumption that is limited to one or two drinks per night is strongly recommended if a person chooses to drink alcohol.

How does vitamin supplementation benefit the adult brain?
Vitamin supplementation may have two beneficial effects for the brain: first, vitamins may protect brain cells against harmful molecules that are normally produced in the brain called "free radicals". Second, vitamin supplements may reduce damage to blood vessels that are essential proper brain function.

The body produces large quantities of toxic molecules that damage brain cells, called "free radicals'. Free radicals are super-charged molecules that often involve oxygen. Some substances such as Vitamin E or C may reduce the damage produced by free radicals. Nutritional supplements often advertise their ability to "scavenge free radicals" meaning that the supplement will clean out these toxic substances. The scientific evidence does not support the protective role of scavenger molecules such as Vitamin E or C in protecting the brain or reducing the risk of developing dementia. Modest doses of these vitamins are present in most supplements and persons who take a daily vitamin should be assured that they are receiving adequate amounts to meet nutritional guidelines.

Does aluminum or other metals cause Alzheimer's disease?
Aluminum cookware or aluminum content in drinking water has not been shown to cause Alzheimer's disease. There is no clear scientific link between aluminum and dementia. Herbal supplements have not been shown to reduce the risk for dementia based on available science.

How do antioxidants impact my risk for dementia?
Food substances that are rich in molecules called "antioxidants" may be beneficial to persons as they grow older. Free radicals are super-charged molecules that can damage brain tissue. Antioxidants can reduce the toxicity of free radicals. Consumers should consider taking a vitamin that contains the recommended daily allowances of Vitamin E and other nutrients called antioxidants which are food stuffs that reduce the level of toxic molecules.

Which vitamins are best at protecting my brain?
The B-Complex vitamins including B6 and B12 may help protect your brain. Folic acid may be beneficial to brain and blood vessels. A standard daily senior vitamin contains the recommended dose of these essential substances. Individuals should discuss vitamin usage with their doctor if they have recently had a heart attack. **(Click here for more information-2513.411)**

How can I pick a healthy diet for my brain?
1. Eat a balanced diet with fruits and green vegetables.
2. Include at least two servings of baked or broiled fish in your weekly diet.
3. If you drink alcohol, consume moderate amounts (1 drink per day).
4. Take a standard daily senior vitamin.
5. Maintain a normal body weight throughout life.
6. Avoid large doses of vitamins or expensive, exotic diets.

5. EXERCISE

5. Encourage Exercise and Psychosocial Stimulation

Life-long, physical exercise and psychosocial stimulation promote successful aging. Midlife obesity and development of the metabolic syndrome may increase the risk for dementia in later life**.** Life-time learning, late-life intellectual stimulation, and enhanced leisure activity may reduce the risk of dementia. Novel intellectual tasks are probably better than over-learned tasks because novel stimuli may activate under-utilized neural networks. Rodent studies demonstrate that synaptogenasis is promoted by environmental stimulation. Regular exercise or environmental stimulation will reduce amyloid load in the brains of transgenic mice that serve as a model for Alzheimer's disease. Lifetime intellectual achievement may enhance cerebral blood flow and promote synaptic reserve that enhances intellectual resilience.

Human synaptic plasticity persists into the eighth decade based on human hippocampal studies. Psychosocial and intellectual vitality may promote synaptogenasis in the aging brain. Although exercise produces numerous benefits to the person over 65, less than half of elders exercise on a regular basis and over half of elders are physically inactive. Many diseases of the elderly are actually produced by disuse or preventable diseases **(Click here for references – 2513.53).**

Recommendation

Physical exercise is beneficial to elders of all ages and improves cardiovascular fitness, mood, bone density, muscle strength, and sustained exercise may diminish the risk for developing dementia. Intellectual and spiritual activity may enhance cognitive reserve and reduce the risk for dementia **(FOR MORE INFORMATION, CLICK HERE - 2513.51, 2513.55)**

A Clinician's Guide to the Impact of Lifetime Education, Physical Exercise and Psychosocial Stimulation on Intellectual Function

1. Clinical Overview

Primary care physicians are often asked to recommend behavioral changes that might improve an older person's chance for successful aging. The primary care physician can use insights from clinical, basic science, and pathological research to recommend intellectual, physical, and psychosocial stimulation as part of their cognitive wellness program for middle aged and older patients. The definition of successful aging can be divided into three domains including physical, social, and psychocognitive (1). In one study, 20% of older individuals reported poor physical functioning, 40% reported problems with social function, and 36% were identified as having psychiatric or severe cognitive disability. Only 13% achieved optimal scores for high overall functioning and 10% met all criteria for successful aging. Although elders experience many types of physical, mental, and social stressors, the majority continue to endorse a sense of wellbeing. This sense of accomplishment can become a major support for the successful aging of an older person (1).

2. Defining Intellectual Reserve in Humans

The interplay between lifetime intellectual achievement and late life cognitive function has been scrutinized by numerous scientists. Recently, the concept of "brain reserve" has achieved greater validity in the scientific community (2), (3). Brain reserve implies that a patient has sufficient functional capacity or redundancy to compensate for brain injury of subclinical functional loss. Some scientist would argue that there are three types of human brain reserve: 1) the number of neurons and synapses or the sophistication of synaptic connectivity, as well as the resilience of neurotransmitters or trophic factors, 2) the number of backup cognitive strategies to solve specific types of neuropsychological tasks presented to elders, and 3) the quantity or speed of brain tissue loss with advancing age.

Several studies support the role of early life intellectual achievement on later life intellectual function (4), (5), (6), (7), (8). Early and mid life intellectual achievement may predict enhanced metabolic activity on brain imaging in later life (9), (10). The Nun Study was first to suggest that individuals with greater, early life intellectual achievement experienced a diminished risk for developing dementia, even when the brain demonstrated significant Alzheimer-type pathology (11), (12). Subsequent studies have examined the role of early life intellectual function and late life cognitive function. Childhood mental ability appears related to the risk of late-onset dementia (13), as well as enhanced late-life function (14). Other studies suggest that the rate of cognitive decline in later life may be dose-dependent upon the intensity of academic achievement in early life (15). Other variables related to late life cognitive function include the number of siblings and rural location of childhood that predicts socioeconomic strata (16). A similar phenomenon is seen in other types of diseases or conditions that may produce intellectual decline, including cognitive loss following coronary artery bypass surgery and risk for HIV-related dementia (17). About 10% of postmortem brains from intellectually normal individuals will demonstrate Alzheimer pathology at death. Individuals with higher academic achievements are less likely to demonstrate cognitive decline, even with Alzheimer's pathology in the brain (39).

3. Animal Models for Intellectual Reserve

Animal models of early life intellectual achievement are difficult to interpret. Environmental or physical enrichment paradigms involve more complex activities than simple learning. Rodent environmental enhancement includes intellectual stimulation as well as opportunities for exercise. Animal models of environmental enrichment suggest enhanced neural production, glial proliferation, trophic factor production and enhancement of neurotransmitters (18). The brains of animals raised in enhanced environments demonstrate enhanced production of neurons in the hippocampus and accelerated production of dendrites and synapses in both the hippocampus and the occipital lobe. The production of glia and blood vessels also appear to be enhanced in these animal models. Environmental enrichment also appears to increase the levels of certain trophic factors such as nerve growth factors or brain derived neurotrophic factors as well as specific neurotransmitters such as serotonin or acetylcholine. Transgenic models of amyloid-producing mice appear to exhibit diminished quantities of brain amyloid and enhanced cognitive function when those animals are raised in enhanced environments.

4. Leisure Activities as Promoters of Cognitive Reserve in Older Persons

A surrogate activity for intellectual stimulation in elders is leisure activities. Passive intellectual activities, such as watching television, demonstrate no significant benefit on cognitive loss. Other stimulating late-life activities, such as writing letters or social interactions, appear to diminish the risk for cognitive decline in elders. One activity during any particular day of the week reduces this risk by 7%. A 63% diminished risk of cognitive decline is detected in those elders in the top third of late life intellectual activity (19). Numerous other studies suggest a similar positive impact of leisure activities on cognitive abilities inferring that other types of intellectual or emotional stimulation may preserve intellect with aging (19), (20), (21), (22). For instance, loneliness will almost double the risk of developing dementia in older persons (40).

Rodent models of environmental enrichment appear to benefit rodents subjected to a variety of other brain disorders to include stroke, trauma, and epilepsy. The mechanisms of environmental enhancement for rodent models of brain damage are similar to those seen with rodent aging brain, i.e., improving neural plasticity or neurogenasis (23), (24).

5. Physical Exercise as a Promoter of Cognitive Reserve in Older Persons

Long-term physical exercise appears to exert a protective effect against clinical symptoms of dementia in humans (41). Older individuals who exercise on a regular basis, such as three or more times per week, appear to have an enhanced sense of wellbeing and a diminished risk for developing cognitive decline in later life or a delay in onset of symptoms (35). Walking and bicycling appears to have many beneficial effects to these individuals when done on a daily basis for 30 minutes or more (26), (27), (33). Physical exercise reduces the impact of age-related neuronal reproduction (36).

Rodent models of high exercise environments suggest that physical stimulation promotes neurological resilience and enhancement of vascular networks in rat brain (23), (24). Transgenic rodent models with high levels of exercise demonstrate diminished amyloid load in the neocortex. The cerebral brain mechanism that diminishes brain amyloid content is unclear but appears linked to overall brain function within the affected mouse (25), (27), 28).

Late-life, human cognitive decline appears related to mid-life obesity (29) and perhaps the metabolic syndrome that includes obesity, insulin resistance, diabetes, and elevated lipids (30). Central obesity appears to be a risk factor for hypertension and excessive insulin secretion which may be harmful to long-term neurological function. Obesity is related to life-time exercise which may correlate with relative risks for developing dementia. **CLICK HERE FOR ADDITIONAL INFORMATION ON THE METABOLIC SYNDROME – 2513.91**

The newest scientific data suggests that the brain is a use-it or lose-it organ with regards to physical and intellectual stimulation (16). Newer data suggests that exercise and cognitive stimulation exert benefits beyond maintaining synaptic resilience. Long-term effects from stimulation may actually diminish disease-specific changes based in rodent models. This second benefit remains unsubstantiated in human models; however, this scientific assumption appears reasonable based on other information. Mechanisms of synaptic plasticity detected in rodent brain appear present in human brain based on human surgical specimens (31).

6. Impact of Cognitive Training on Age-Related Changes in Function or Brain Imaging

Cognitive training may slow age-related cognitive decline for over five years for individuals using computer-based, training systems that included ten sessions with four booster sessions (37). Functional imaging shows enhancement in markers of neuronal plasticity in the brains of aged individuals who engage in "cognitive conditioning" (38).

A variety of commercial and free cognitive activity programs are available to promote "mental gymnastics". Programs conducted by the individual, in groups, and on-line show significant promise for improving cognition and promoting cognitive longevity.

Each person has individualized tastes for intellectual or social activity. The clinician should encourage selection of an appropriate intervention and continued participation. Novel intellectual activities are preferred to repetition of already over-learned tasks; for example, learning a new language or discovering the computer.

7. Possible Conclusions Based on Available Science about the Role of Education, Exercise and Psychosocial Factors on the Risk of Developing Late-life Dementia in Humans

Comprehensive, prospective studies have not been performed on the role of physical, intellectual or environmental stimulation in preventing dementia. These studies will not likely be performed because of technical obstacles. No intervention provides an insurance policy against the development of dementia, especially in those individuals with a high genetic risk for Alzheimer's disease. The available studies in humans indicate that lifetime exercise enhances overall physical wellbeing, cardiovascular fitness and cognitive wellness. Three mechanisms might explain this benefit including: 1) enhanced angiogenesis in the brain, 2) enhanced synaptic reserve, and 3) diminished amyloid load. A second issue is the role of midlife obesity and hypertension that may reflect diminished exercise and the increased risk for dementia in those individuals who may suffer from metabolic syndrome.

The second "protective" issue is the role of lifetime intellectual achievement on risks for cognitive decline. Synaptic reserve, neuroplasticity, and perhaps other factors such as neurotransmission, trophic factor, and neurogenasis may be impacted by lifetime intellectual achievement. The role of late-life intellectual stimulation is less compelling than early and midlife intellectual achievement (42), (43), (44). The relationship of leisure activities or other forms of intellectual stimulation such as social interactions to diminished risk for dementia suggests several mechanisms including stress reduction and overall cognitive stimulation. These interventions are difficult to quantitate and therefore, the beneficial consequence of these activities are more difficult to define than other variables such as blood pressure or homocysteine levels.

The combined package of intellectual, physical, and social stimulation appears to be the optimal recommendation by primary care clinicians for patients in mid to later life.

Recommendations to Primary Care Clinicians

1. Encourage middle aged patients to develop a regular physical exercise schedule.
2. Encourage all age groups to maintain normal body weight to reduce risk of dementia in later life.
3. Encourage life-long learning.
4. Promote social and intellectual activity in older patients.
5. Encourage participation in "mental gymnastic" programs that appeal to the individual.
6. Identify lonely elders and encourage social reconnection.
7. Screen for depression in lonely or isolated elders.

References

1. Von Faber M, van der Wiel AB, van Exel E, et al. Successful aging in the oldest old. Who can be characterized as successfully aged? Arch Intern Med. 2001;161:2694-2700.
2. Whalley LJ, Deary IJ, Appleton CL, Starr JM. Cognitive reserve and the neurobiology of cognitive aging. Ageing Res. Rev. 2004;3(4):369-82.
3. Mortimer JA. Brain reserve and the clinical expression of Alzheimer's disease. Geriatrics 1997;52(supp2):S50-S53.
4. Rodgers B, Henderson AS, Korten A, et al. Occupation type as a predictor of cognitive decline and dementia in old age. Age and Ageing 1998;27(4):476-484.
5. Albert MS. How does education affect cognitive function? Ann. Epidemiol. 1995;76-78.
6. Schmand B, Smit JH, Geerlings MI, Lindeboom J. The effects of intelligence and education on the development of dementia. A test of the brain reserve hypothesis. Psychological Medicine 1997;27:1337-1344.
7. Le Carret N, Auriacombe S, Letenneur L, et al. Influence of education on the pattern of cognitive deterioration in AD patients: the cognitive reserve hypothesis. Brain Cogn 2005;57(2):120-6.
8. Fritsch T, Smyth KA, McClendon MJ, et al. Associations between dementia/mild cognitive impairment and cognitive performance and activity levels in youth. J Am Geriatr Soc. 2005;53(7):1191-6.
9. Goekoop R, Rombouts SA, Jonker C, et al. Challenging the cholinergic system in mild cognitive impairment: a pharmacological fMRI study. Neuroimage 2004;23(4):1450-9.
10. Eisenberg DP, London ED, Matochik JA, et al. Education-associated cortical glucose metabolism during sustained attention. Neuroreport 2005;16(13):1473-1476.
11. Snowdon DA. Aging and Alzheimer's disease: lessons from the Nun study. The Gerontologist, 1997;37(2):150-156.
12. Snowdon DA, Kemper SJ, Mortimer JA, et al. Linguistic ability in early life and cognitive function and Alzheimer's disease in late life (Findings from the Nun Study). JAMA 1996;275:528-532.
13. Whalley LJ, Starr JM, Athawes R, et al. Childhood mental ability and dementia. Neurology 2000;55:1455-1459.
14. Starr JM, Deary IJ, Lemmon H, Whalley LJ. Mental ability age 11 years and health status age 77 years. Age and Aging 2000;29:523-528.
15. Schmand B, Smit J, Lindeboom J, et al. Low education is a genuine risk factor for accelerated memory decline and dementia. J Clin Epidemiol 1997;50(9):1025-1033.
16. Moceri VM, Kukull WA, Emanuel I, et al. Early-life risk factors and the development of Alzheimer's disease. Neurology 2000;54:415-420.
17. Potter GG, Plassman BL, Helms MJ, et al. Age effects of coronary artery bypass graft on cognitive status change among elderly male twins. Neurology 2004;63(12):2245-9.
18. Van Praag H, Kemperman G, Gage FH. Neural consequences of environmental enrichment. Nature Neuroscience 2000;1:191-198.
19. Verghese J, Lipton RB, Katz MJ, et al. Leisure activities and the risk of dementia in the elderly. N Engl J Med. 2003;348:2508-16.
20. Fratiglioni L, Wang HX, Ericsson K, et al. Influence of social network on occurrence of dementia: a community-based longitudinal study. Lancet 2000;355:1315-19.
21. Fabrigoule C, Letenneur L, Dartigues JF, et al. Social and leisure activities and risk of dementia: a prospective longitudinal study. Journal of the American Geriatric Society 1995;43(5):1-10.
22. Friedland RP, Fritsch T, Smyth KA, et al. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. PNAS 2001;98(6):3440-3445.

23. Rosenzweig MR, Bennet EL. Psychobiology of plasticity: effects of training and experience on brain and behavior. Behavioral Brain Research 1996;78:57-65.

24. Van Praag H, Kempermann G, Gage FH. Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. Nature Neuroscience 1999;2(3):266-270.

25. Van Pragg H, Christie BR, Sejnowski TJ, Gage FH. Running enhances neurogenasis, learning, and long-term potentiation in mice. PNAS 1999;96(3):13427-13431.

26. Singh-Manoux A, Hillsdon M, Brunner E, Marmot M. Effects of physical activity on cognitive functioning in middle age: evidence from the Whitehall II prospective cohort study. Am J Public Health 2005;95(12):2252-2258.

27. Karsten SL, Geschwind DH. Exercise your amyloid. Cell 2005;120(5):572-4.

28. Marx J. Play and exercise protect mouse brain from amyloid buildup. Science 2005:307:1547.

29. Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330(7504):1360.

30. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer's disease. Arch Neurol 2005;62(10):1556-60.

31. Beck H, Goussakov IV, Lie A, et al. Synpatic plasticity in the human dentate gyrus. The Journal of Neuroscience 2000;20(18):7080-7086.

32. U.S. Department of Health and Human Services, Center for Disease Control and Prevention. Promoting active lifestyles among older adults. U.S. Surgeon General 1996.

33. Marx J. Preventing Alzheimer's: a lifelong commitment? Science 2005;309:864-866.

34. Scarmeas N, Levy G, Tang MX. Influence of leisure activity on the incidence of Alzheimer's disease. Neurology 2001;57:2236-2242.

35. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern 2006;144:73-81.

36. Kronenberg G, Bick-Sander A, Bunk E, et al. Physical exercise prevents age-related decline in precursor cell activity in the mouse dentate gyrus. Neurobiology of Aging 2006;27:1505-1513.

37. Willis SL, Tennstedt SL, Marsiske M, et al. Long-term effects of cognitive training on everyday functional outcomes in older adults. JAMA 2006;296:2805-2814.

38. Erickson KI, Colcombe SJ, Wadhwa R, et al. Training-induced plasticity in older adults: effects of training on hemispheric asymmetry. Neurobiology of Aging 2007;28:272-283.

39. Roe CM, Xiong C, Miller JP, Morris JC. Education and Alzheimer disease without dementia. Neurology 2007;68:223-228.

40. Wilson RS, Krueger KR, Arnold SE, et al. Loneliness and risk of Alzheimer disease. Arch Gen Psychiatry 2007;64:234-240.

41. Larson EB, Wang L, Bowen JD, et al. Exercise is associated with reduced risk for incident dementia among persons 65 years of age and older. Ann Intern Med 2006;144:73-81.

42. Gatz M, Prescott CA, Pedersen NL. Lifestyle risk and delaying factors. Alzheimer's Disease & Associated Disorders 2006;20(Suppl 2):S84-S88.

43. Karp A, Paillard-Borg S, Wang HX, et al. Mental, physical and social components in leisure activities equally contribute to decrease dementia risk. Dement Geriatr Cogn Disord 2006;21:65-73.

44. Wang HX, Karp A, Winblad B, Fratiglioni L. Late-life engagement in social and leisure activities is associated with a decreased risk of dementia: a longitudinal study from the Kungsholmen project. Am J Epidemiol 2002;155(12):1081-7.

Primary Care Fact Sheet on the Impact of Lifetime Education, Physical Exercise and Psychosocial Stimulation on Intellectual Function

1. Most elders describe themselves as "well" despite physical, social or neuropsychiatric deficits.

2. Higher, early lifetime educational achievement is associated with a diminished risk for late life dementia.

3. Each older human may have individual cognitive reserves that might protect against cognitive decline.

4. Animals raised with environmental enrichment will show enhanced markers for neuronal vitality.

5. Animal models for amyloid production show that environmental enrichment will reduce amyloid load in the rodent brain.

6. Regular exercise may diminish the risk of cognitive decline in human elders.

7. Midlife obesity is a risk factor for late life dementia.

8. Passive intellectual activities, such as watching television, may have minimal protective benefits for the aging brain.

9. Social and leisure activities may be highly beneficial for cognitive protection in the older individual.

10. Available scientific data suggests that lifetime intellectual and physical activity may reduce the risk for dementia in later life or delay the onset of symptoms.

The Consumer's Guide to Understanding the Role of Physical and Mental Exercise in Preventing Dementia

New studies show that people who exercise on a regular basis throughout life may reduce their risk of developing intellectual problems with aging. Walking, bicycling, and swimming all seem to provide physical and intellectual health benefits for persons in all groups. Regular exercise also improves the health of your heart and blood vessels in the brain. Regular exercise is part of your plan to deflate that spare tire of excess weight around your beltline. Research on humans and rats suggest that exercise may increase your brain's ability to keep functioning in the face of damage caused by aging or dementia.

Your brain is like your body – you can "use it" or "lose it". Regular brain exercise may strengthen your brain against memory disorders like Alzheimer's disease. Life-long learning and new mental challenges are good for your brain. Begin by shutting off the television. Older persons should accept new intellectual challenges, such as learning to use a computer or studying a new language. Avoid the same routine day-in and day-out. Shake-up those brain connections by writing letters to old friends and meeting new people.

People of all age groups should exercise their brain and body on a daily basis. Everyone should exercise 30 to 60 minutes per day in midlife. Older persons with health problems may need to consult with their doctor about safe, appropriate exercise. Your brain is only as healthy as the body that carries it around. **CLICK HERE FOR MORE INFORMATION – 2513.55-1).**

The Consumer's Guide to Memory Exercises

Getting The Big Picture

Your brain is a "use it" or "lose it" organ. You can increase the reserve of your brain by exercising your brain cells on a regular basis. Intellectual challenges, new learning and social interactions provide the best form of exercise.

Mental Exercise Is Like Physical Exercise

A person who simply lifts dumbbells as exercise will not have total body strength. Muscular strength training includes balanced exercises that work all your muscle groups. The same principles probably apply for your brain. Watching television is no better exercise for your brain than lying on the couch helps condition your body. Each person has different interest and mental skills. People should continue to learn new information and accept new mental challenges as they grow older. Cross-word puzzles, learning the computer, joining clubs for new social or intellectual activities, expanding your circle of friends, learning a new skill such as choir or gardening, and many other new intellectual challenges exercise more parts of your brain.

How Can I Increase My Brain Strength?

1. Maintain intellectual activities through life, such as reading, spiritual studies, politics or other subjects that interest you.

2. Learn something new every day.

3. Change the little things in your life on a daily basis, like going to a new store, walking a different route and others.

4. Develop new mental skills like using a computer, taking classes, developing new friends or social contacts.

6. SPIRITUALITY

6. Understanding the Role of Spiritual Vitality in Aging

Spirituality is an inherent human feature that is often manifested through religious activity. The measurement of religious activities can be quantitated; however, spirituality lacks an accurate metric. This potential inaccuracy of spirituality measurement limits the availability of scientific data; however, the consensus of researchers supports the finding that individuals with increased religious activities or self-described spirituality have reduced age-related morbidity.

Physicians must carefully weight their words when discussing matters of faith and religion with the patient. The relationship between cognition, spirituality, and religious activity remains unclear; however, the social and intellectual stimulation produced by faith-based activities probably provides a protective effect for human cognitive function.

Physicians are encouraged to define the benefit associated with active spiritual lives in the older individual. Such discussions must avoid judgmental statements or suggestions that the physician is proselytizing to a specific faith **(Click here for references – 2513.63).**

Recommendation

Active, spiritual lives are beneficial to middle-aged and older individuals. Physicians can encourage older individuals to engage in faith-based activities and encourage faith communities to maintain active contacts with older persons. The healthcare system should respect all spiritual attitudes including those that deny the need for spiritual activities. **(For more information, click here – 2513.61)**

A Primary Care Guide to Addressing Spirituality in Midlife or Older Persons as a Component to Successful Cognitive Aging

1. **Issues of Incorporating Faith Issues into Medical Practice**
   Physicians are often hesitant to discuss spiritual matters or religion with patients for ethical and personal reasons (1). Some physicians may perceive questions about religion or spirituality as intrusive or a violation of physician-patient relationship; however, recent trends in medical education have caused 70% of medical schools to include course work on spirituality in clinical practice (2). Physicians are trained to treat patients regardless of the patient's ethnic or religious background. The lack of quantitative methodologies to measure spiritual or religious activity limits the value of correlative studies that compare health outcomes to "spirituality". This lack of clinical data reduces certainty among physicians about any demonstrated beneficial effect from personal faith as professed by the patient. Some physicians may doubt the existence of a higher power and some may harbor negative feelings towards religious or spiritual beliefs, as well as organized worship (3).

2. **Defining The Measurement of Spirituality and Religion**
   Spirituality can be defined based on the HOPE paradigm. The HOPE spiritual assessment follows the acronym with "H" representing sources of hope or strength; "O" represents the role of organized religion; "P" represents personal spirituality and practices; and "E" depicts the effect on medical care and end of life decisions. Some longitudinal studies with specific diseases, such as HIV infection suggest that patient survival is related to frequency of prayer and inversely proportional to the patient's judgmental attitudes (4). The intensity and quality of a patient's spiritual life is difficult to measure (18).

   The measurement of religion and spirituality may not provide equal prediction for outcomes. Several studies indicate that greater spirituality but not greater religiosity are more likely to predict good health in an older individual (5), (6).

3. **The Link Between Spiritual and Physical Vitality in Older Persons**
   Spirituality appears correlated to health outcomes and quality of life in older individuals. For hospitalized older individuals, increased spirituality predicts fewer depressive episodes and better cognitive function (7), (8). Longitudinal studies suggest that increased lifetime organized religious activity may predict decreased likelihood for prolonged, utilization of long-term care services by the older patient. Likewise, the magnitude of intrinsic, self-described spirituality appears correlated to outcomes of health and pain management (9).

   Individuals with active, spiritual and religious lives demonstrate a diminished risk of developing depression in later life, as well as severe functional impairment produced by the psychiatric disability (10), (11), (19), (20). The relationship between spirituality, religion, and health outcomes may be related to stress coping and maintenance of mood. Individuals with active spiritual lives appear to enjoy diminished levels of stress and less evidence for depression producing better outcomes for chronic health problems or hospital care. The role

of formalized religious activity is less clear; however, some studies do support the relationship between organized activity and reduced long-term medical morbidity (12), (13).

4. Conclusion About the Role of Spiritual Vitality in Maintaining Cognitive Vitality

Older individuals can become marginalized in spiritual communities. Pastors may not recognize the positive impact of spiritual activity on the quality of an elder's life and longevity. No data exists to compare spiritual activity with risks for developing cognitive decline. Spirituality may enhance psychosocial function (22). Depression, chronic stress, and diminished activity are potential risk factors for cognitive decline in later life that may be mitigated by active, personal spirituality **(CLICK HERE FOR MORE INFORMATION – 2513.31, 2513.51)**. A growing body of medical literature defines the role of spirituality in clinical practice (14), (15), (16). Physicians are encouraged to promote spiritual and religious activity in those patients who have selected to achieve these internal goals. Each physician must determine their level of comfort in discussing this matter with mid-aged and older individuals. Physicians should avoid proselytizing or attempts at convincing patients who hold contrary beliefs (13). Older persons often serve as caregivers and spirituality improves their overall outcome (20) (21).

Recommendations to Primary Care Physicians

1. Recognize that any active spiritual life may promote successful aging.
2. Consider the individual spiritual needs of each patient.
3. Encourage an active spiritual life in appropriate patients.
4. Respect those patients who do not maintain or value an internal spiritual life.
5. Empower patients to expect that their spiritual community will include them in all aspects of a faith life.

References:

1. Post SG, Puchalski CM, Larson DB. Physicians and patient spirituality: professional boundaries, competency, and ethics. Ann. Intern. Med. 2000;132(7):578-83.
2. Puchalski C. Spiritual assessment in clinical practice. Psych Annals 2006;36(3):150-156.
3. Powell LH, Shahabi L, Thoresen CE. Religion and spirituality. Linkages to physical health. Am. Psychol 2003;58(1):36-52.
4. Anandarajah G, Hight E. Spirituality and medical practice: using the HOPE questions as a practical tool for spiritual assessment. Am. Fam. Physician 2001;63(1):81-9.
5. Daaleman TP, Perera S, Studenski SA. Religion, spirituality, and health status in geriatric outpatients. Ann. Fam. Med. 2004;2(1):49-53.
6. Curlin FA, Roach CJ, Gorawara-Bhat R, et al. How are religion and spirituality related to health? A study of physicians' perspectives. South Med. J. 2005;98(8):761-6.
7. Ironson G, Solomon GF, Balbin EG, et al. The Ironson-Woods spirituality/religiousness index is associated with long survival, health behaviors, less distress, and low cortisol in people with HIV/AIDS. Ann Behav Med. 2002;24(1):34-48.
8. Koenig HG, George LK, Titus P. Religion, spirituality, and health in medically ill hospitalized older patients. J. Am. Geriatr Soc. 2004;52(4):554-62.
9. McBride JL, Arthur G, Brooks R, Pilkington L. The relationship between a patient's spirituality and health experiences. Fam. Med. 1998;30(2):122-6.
10. Baetz M, Griffin R, Bowen R, et al. The association between spiritual and religious involvement and depressive symptoms in a Canadian population. J. Nerv. Ment. Dis. 2004;192(12):818-22.
11. Bosworth HB, Park KS, McQuoid DR, et al. The impact of religious practice and religious coping on geriatric depression. Int J. Geriatr Psychiatry 2003;18(10):905-14.
12. Koenig HG, Pargament KI, Neilsen J. Religious coping and health status in medically ill hospitalized older adults. J. Nerv. Ment. Dis. 1998;186(9):513-21.
13. Koenig HG, George LK, Titus P, Meador KG. Religion, spirituality, and acute care hospitalization and long-term care use by older patients. Arch Intern Med. 2004;164(14):1579-85.
14. Yang CP, Lukoff D. Working with spiritual issues. Psychiatric Annals 2006;36:3.
15. Sperry L. Working with spiritual issues of the elderly and their caregivers. Psychiatric Annals 2006;36:3.
16. Cloninger CR. Fostering spirituality and well-being in clinical practice. Psychiatric Annals 2006;36:3.
17. McKee DD, Chappel JN. Spirituality and medical practice. J. Fam. Pract. 1992;35(6):617-8.
18. Nelson-Becker H, Nakashima M, Canda ER. Spiritual assessment in aging: a framework for clinicians. J Gerontol Soc Work 2007;48(3-4):331-47.
19. Yoon DP, Lee EK. The impact of religiousness, spirituality, and social support on psychological well-being among older adults in rural areas. J. Gerontol Soc Work 2007;48(3-4):281-98.
20. Hebert RS, Dang Q, Schulz R. Religious beliefs and practices are associated with better mental health in family caregivers of patients with dementia: findings from the REACH study. Am J Geriatr Psychiatry 2006 Dec 8.

21. Haley WE, Gitlin LN, Wisniewski SR, et al. Well-being, appraisal, and coping in African-American and Caucasian dementia caregivers: findings from the REACH study. Aging Ment. Health 2004;8(4): 316-29.

22. King DE, Cummings D, Whetstone L. Attendance at religious services and subsequent mental health in midlife women. Int. J. Psychiatry Med 2005;35(3):287-97.

Physician Fact Sheet on
Addressing Spirituality in Middle Age or Older Persons as a Component to Successful Cognitive Aging

1. Spirituality is an important component of psychosocial wellbeing for some elders.

2. Physicians can discuss the value of spirituality with patients who express an interest in this subject.

3. A patient's active spirituality may improve their hospital outcomes.

4. Active spirituality may reduce the risk for depression during hospitalization.

5. An active spiritual life may improve quality of life at the end of life for some elders.

6. Physicians should avoid proselytizing with patients.

7. Most patients are receptive to a respectful discussion about their spiritual life.

8. Lonely elders have an increased risk for dementia.

9. Spiritual communities offer intellectual and social stimulation.

10. Doctors can encourage continued participation in spiritual activities as part of the "wellness program".

The Consumer's Guide for Spirituality

The human spirit and soul are powerful forces in all people. Every human has a unique spiritual life despite the fact that scientists cannot measure or define this human feature. Human spiritual activity is often channeled through religious activity. People are capable of active spiritual lives even when they do not practice an organized religion.

Spiritual activity is important for the physical and mental wellbeing of a person. Spirituality does not go down in aging and often increases as the person gathers more knowledge and wisdom. Science shows that persons with active spiritual lives have better results from hospital care. Spirituality produces a powerful stimulation to the brain and body.

Scientists cannot measure spiritual energy and therefore no science proves that active spiritual lives protect the brain. Despite the scientific limitation, many scientists believe that an active spiritual life is part of an active intellectual life that promotes brain health in older age. Middle aged and older persons are encouraged to maintain an active mental and spiritual life throughout their entire life to promote wellness.

7. HORMONE REPLACEMENT THERAPY

7. The Value of Hormonal Replacement

Hormone Replacement Therapy in Women. Hormone replacement therapy (HRT) is a controversial intervention for post-menopausal women. Estrogen and progesterone are powerful, psychoactive substances with receptors located in the hippocampus and the basal forebrain. Women who undergo oophorectomy for other medical purposes during midlife demonstrate specific neuropsychological deficits that improve over time. Rodent models of transgenic mice indicate that estrogen levels may play some role in the deposition of amyloid within the brain.

The Agency for Health Care Quality and Research concluded that hormone replacement therapy was not proven to be beneficial for long-term cognitive function. The possibility remains for subgroups of aging women who benefit from HRT.

HRT has not been evaluated in other forms of dementia, especially vascular dementia and diffuse Lewy body disease. The slight female predilection for developing Alzheimer's disease beyond age-adjusted rates of survival has not been linked to differences in hormonal content **(Click here for references – 2315.73).**

Hormone Replacement Therapy in Men. Multiple studies have examined the role of testosterone in the risk and pathogenesis of Alzheimer's disease. Diminished levels of testosterone in men have been associated with increased risk for developing dementia in later life.

Testosterone supplementation may have potentially adverse effects, especially on the prostate gland. The risk-benefit ratio for long-term supplementation of testosterone in aging men has not been determined. Testosterone supplementation has not been proven to be protective or beneficial in patients with Alzheimer's disease. Individuals undergoing testosterone supplementation for other medical or physiological reasons could theoretically experience some preventive benefit from this medication; however, supplementation is not recommended as a preventive intervention for older individuals, even with a family history of Alzheimer's disease. The role of testosterone in other forms of dementia, such as vascular dementia or diffuse Lewy body disease is undetermined **(Click here for references – 2315.73).**

Recommendation

Post-menopausal women should be encouraged to have a thoughtful discussion with a women's health specialist to discuss the beneficial effects and the potential risks of HRT. Testosterone supplementation for men is not recommended as a preventive intervention for dementia. HRT is not recommended as a routine preventive intervention for dementia in men or women. **For more information click here – 2513.71, 2513.75.**

Basic Facts for the Primary Care Physician on Hormone Replacement Therapy (HRT) as a Preventive Strategy for Dementia in Women and Men

1. Overview for Hormone Replacement Therapy in Women

Estrogen and progesterone are powerful, psychoactive substances with receptors located in the hippocampus and the basal forebrain. Some women who undergo oophorectomy for other medical purposes during midlife demonstrate transient neuropsychological deficits after surgical removal of the gonads. The relationship between endogenous estrogen levels and risk for cognitive decline in older women remains controversial (1), (2), (27). Transgenic rodent models of Alzheimer's disease demonstrate that estrogen levels may play some role in the deposition of amyloid within the brain (2).

Hormone replacement therapy (HRT) to prevent senescent memory loss or functional decline is controversial. Many studies have identified cognitive benefits from these medications in postmenopausal women while others demonstrate no improvement **(See Table 1).** Serious health consequences are reported with HRT, such as increased risk for deep venous thrombosis, hemorrhagic stroke and others (3), (4). Potential beneficial effects from hormone replacement therapy include suppression of menopausal symptoms, e.g., hot flashes, as well as slowing of osteoporosis (5).

The interpretation of scientific studies on hormone replacement treatment is complicated by several issues. First, which kind of hormone preparation is best suited for cognitive protection and does that preparation produce excessive morbidity or mortality in at-risk individuals? Second, at what age does initiation of HRT provide optimal protection for dementia? Some studies suggest that early treatment is beneficial while others cannot draw specific conclusions on this matter. Third, how long should treatment continue? Some studies suggest that treatment limited to the perimenopausal period may provide the best benefit. Other studies cannot substantiate that observation. Fourth, are there subgroups of individuals who would benefit from hormone replacement treatment? For instance, does the presence of a strong family history of Alzheimer's disease, APOE 4 alleles, hypertension, metabolic syndrome or other potential risk factors increase the likelihood that estrogen will provide beneficial results in women? Fifth, are some women at excessive risk for complications from HRT as a "dementia prevention"?

Table 1. A Summary of Recent Studies on the Role of Hormone Replacement Therapy on Cognitive Function

No.	t	a	n	Hormone	Outcome from Replacement Therapy	Refs.
1	CS	65+	2816	Mixed	⇩ Dementia risk	9
2	4.2 yr.	65+	4894	Mixed	NC - dementia, few side effects	10
3	4 yr.	65+	13807	Mixed	No benefit for cognition	11
4	5yr.	50+	103*	Mixed	Possible benefit in verbal memory for non-demented women	12
5	CS	75+	3924	Mixed	No cognitive benefit	13
6	1 yrs	65+	4532	Mixed	↑ Risk of dementia, NC-MCI	14
7	16	50+	472	ERT	⇩ Risk for AD	15
8	1-5	65+	1124	ERT	ERT delayed onset of dementia and decreased risk	16

t= study of duration *Matched Study, mixed variable - mixture of estrogen and progestin
NC- no change **CS**-cross-sectional a=age of entry
Mixed - estrogen and progestin of variable doses and mixture
ERT- estrogen replacement therapy

2513.71 Hormone Replacement Therapy (HRT)

2. Longitudinal Studies

Over 30 studies have examined the role of estrogen levels, perimenopausal events, and hormone replacement therapy on the risk for developing dementia (6), (26). Multiple, longitudinal studies have failed to conclusively determine the role of HRT in the prevention of Alzheimer's disease **(See Table 1).** The preponderance of recent data suggests that hormone replacement therapy does not provide a significant protective benefit to women. The Agency for Health Care Research and Quality examined this issue and concluded that hormone replacement therapy was not proven to be beneficial for long-term cognitive function (29). The possibility remains that responsive subgroups exist within populations of aging women who may benefit from HRT.

3. Potential Toxicity of HRT Therapy in Women

Potential toxicity of HRT includes cardiovascular, biliary disease and stroke. The effect of HRT on coronary artery disease (CAD) remains controversial; however, there may be a "protective" effect on heart function (3). Risk for breast cancer remains controversial (5). Increased rates of mortality are reported with some forms of HRT and some variable benefit on bone density **(See Table 2), (3).**

Table 2. Major Complication of HRT in Post-Menopausal Women (3), (5), (8)

Potential Complication	Conventional Wisdom	Study Results
Breast Cancer	NC or SL⇩	10 observation studies
Stroke	↑ Risk	Over 4 studies
Coronary Artery Disease	Undetermined	Multiple conflicting studies
Deep Venous Thrombosis	↑ Risk	Multiple conflicting studies

NC – no change

2513.71 Hormone Replacement Therapy (HRT)

4. Clinical Recommendations

Although lower estradiol levels in older women may be related to decreased cognitive function in later life (27), physicians should not recommend HRT as a preventive intervention for Alzheimer's disease or other types of dementia. The risk-benefit ratio for HRT exceeds the uncertain benefit from this intervention; however, women receiving HRT to suppress perimenopausal symptoms or prevent osteoporosis may enjoy a small cognitive benefit from the medication (5), (6), (7), (16).

The effect of HRT on the risk of developing other forms of dementia, especially vascular dementia and diffuse Lewy body disease has not been evaluated. The slightly increased risk among older females for developing Alzheimer's disease beyond age-adjusted rate of survival has not been proven to depend on differences in hormonal content.

The identification of groups with specific sensitivity to hormone replacement therapy might enhance the therapeutic selection process and reduce the risk to patients. This type of selective targeting awaits further research on the dementias. Other variables such as exercise, or genetic features, such as APOE typing, may play some role in predicting outcomes from therapy.

Hormone Replacement Therapy in Men

1. Overview of HRT for Men

The use of testosterone in aging males has increased 500% since 1994 and 30% in the year from 2003 to 2004 (17). The probable risk to older patients for prescription of endogenous testosterone is low; however, the cognitive benefit has not been conclusively proven (17), (18).

Several studies have examined the role of testosterone on the risk and pathogenesis of Alzheimer's disease **(See Table 3).** Male andropause is described as a potential cause of some age-related brain pathology. Diminished levels of testosterone in men have been associated with increased risk for developing dementia in later life. Dietary supplementation of testosterone in mice that are genetically altered to produce amyloid demonstrate diminished amyloid load in medicated rodents. Rodent studies suggest that testosterone may alter the production and metabolism of amyloid in the brains of transgenic mice (19), (23). Post mortem studies on older human subjects demonstrate higher densities of neurofibrillary tangles and micro-infarcts in persons with lower levels of free testosterone (28).

Testosterone supplementation has potentially adverse effects on the prostate gland, although this effect remains controversial. The risk-benefit ratio for long-term supplementation of testosterone in aging men has not been determined. Testosterone supplementation has not been proven to be protective or beneficial in patients with Alzheimer's disease (24). Individuals undergoing testosterone supplementation for other medical or physiological reasons could theoretically experience some preventive benefit from this medication; however, supplementation is not recommended as a preventive intervention for older individuals, even with a family history of Alzheimer's disease. The role of testosterone in

other forms of dementia, such as vascular dementia or diffuse Lewy body disease is undetermined (24).

2. The Use of Testosterone as a Neuroprotectant

The interpretation of available scientific data on the role of testosterone and cognition is complicated by several scientific obstacles. First, what dose and preparation of testosterone or combinations of male gonodal hormones are best suited to enhance cognitive function? Second, do all males respond to hormonal replacement or do specific hormone-sensitive subgroups exist that would benefit from targeted therapy? Third, what is the optimal age for initiation of therapy? Fourth, do specific disease markers, such as APOE 4 alleles or metabolic syndrome, exist that can predict at-risk group of males who benefit from testosterone therapy? Fifth, what are the long-term, i.e., 20 years, complications of testosterone supplementation on hormone-sensitive tissue such as the prostate gland? Clarification of specific groups of older individuals who are at risk for developing dementia and exhibit certain markers for hormonal sensitivity may provide targeted therapeutic interventions that enhance benefit and substantially reduce any long-term risk form hormone treatment.

Table 3

The Relationship of Testosterone Levels in Older Males and the Risk for Developing Dementia

#	a	t	n	Outcome of Study	Ref.
1	65+	CS	310	↑ Serum testosterone predicts ↑ cognitive function	20
2	32+	19 yr	574	⇩ Serum testosterone predicts ↑ risk of dementia	21
3	65+	CS	210	Low free testosterone is a predictive of AD	22
4	65+	PM	232	⇩Testosterone related to ↑ NFT's and ↑ micro-infarcts	28

t- duration of study CS - cross-sectional study a-age of entry n-study size
NFT-neurofibrillary tangles

2513.74 Hormone Replacement Therapy (HRT)

Recommendations for Primary Care Physicians

1. HRT for both men and women is an unproven intervention to slow aging or prevent dementia.
2. HRT is not recommended as a "dementia prevention" strategy for women but this treatment may benefit women who receive hormones for other specific clinical indications.
3. HRT is not recommended for older males as a form of dementia prevention therapy.
4. Future clinical research may produce specific guidelines for selection of patients and HRT preparation as well as treatment duration to reduce the risk of dementia.

References – Hormone Therapy

1. Tang MX, Jacobs D, Stern Y, et al. Effect of estrogen during menopause on risk and age at onset of Alzheimer's disease. Lancet 1996;348(9025):429-32.
2. Pinkerton JV, Henderson VW. Estrogen and cognition, with a focus on Alzheimer's disease. Semin. Reprod Med. 2005;23(2):172-9.
3. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. JAMA 2002;288:58-66.
4. Wasserheil-Smoller S, Hendrix SL, Limacher M, et al. Effect of estrogen plus progestin on stroke in postmenopausal women. JAMA 2003;289:2673-2684.
5. Peterson HB, Thacker SB, Corso PS, et al. Hormone therapy. Making decisions in the face of uncertainty. Arch Intern Med 2004;164:2308-2312.
6. LeBlanc ES, Janowsky J, Chan BK, Nelson HD. Hormone replacement therapy and cognition: systematic review and meta-analysis. JAMA 2001;285(11):1489-99.
7. Baum LW. Sex, hormones, and Alzheimer's disease. J. Gerontol A. Biol. Sci. Med. Sci. 2005;60(6):736-43.
8. Stevenson JC. Hormone replacement therapy: review, update, and remaining questions after the Women's Health Initiative Study. Curr. Osteoporos Rep. 2004;2(1):12-6.
9. Baldereschi M, Di Carlo A, Lepore V, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian longitudinal study on aging. Neurology 1998;50(4):996-1002.
10. Rapp SR, Espeland MA, Shumaker SA, et al. Effect of estrogen plus progestin on global cognitive function in postmenopausal women. JAMA 2003;289:2663-2672.
11. Kang JH, Weuve J, Grodstein F. Postmenopausal hormone therapy and risk of cognitive decline in community-dwelling aging women. Neurology 2004;63:101-107.
12. Maki PM, Zonderman AB, Resnick SM. Enhanced verbal memory in nondemented elderly women receiving hormone-replacement therapy. Am J Psychiatry 2001;158:227-233.
13. Buckwalter JG, Crooks VC, Robins SB, Petitti DB. Hormone use and cognitive performance in women of advanced age. J Am Geriatr Soc. 2004;52:182-186.
14. Shumaker SA, Legault C, Rapp SR, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. JAMA 2003;289:2651-2662.
15. Kawas C, Resnick S, Morrison A, et al. A prospective study of estrogen replacement therapy and the risk of developing Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 1997;48(6):1517-21.
16. Yaffe K, Grady D, Pressman A, Cummings S. Serum estrogen levels, cognitive performance, and risk of cognitive decline in older community women. J. Am Geriatr Soc 1998;46(7):816-21.
17. Tan RS, Salazar JA. Risks of testosterone replacement therapy in aging men. Expert Opin Drug Saf. 2004;3(6): 599-606.
18. Hogervorst E, Bandelow S, Moffat SD. Increasing testosterone levels and effects on cognitive functions in elderly men and women: a review. Curr Drug Targets CNS Neurol Disord. 2005;4(5):531-40.
19. Gouras GK, Xu H, Gross RS, et al. Testosterone reduces neuronal secretion of Alzheimer's β-amyloid peptides. PNAS 2000;97(3):1202-1205.
20. Yaffe K, Lui LY, Zmuda J, Cauley J. Sex hormones and cognitive function in older men. J Am Geriatr Soc 2002;50:707-712.
21. Moffat SD, Zonderman AB, Metter EJ, et al. Free testosterone and risk for Alzheimer disease in older men. Neurology 2004;62:188-193.
22. Hogervorst E, Bandelow S, Combrinck M, Smith AD. Low free testosterone is an independent risk factor for Alzheimer's disease. Exp Gerontol 2004;39(11-12):1633-9.
23. Moffat SD. Effects of testosterone on cognitive and brain aging in elderly men. Ann NY Acad Sci 2005;1055:80-92.
24. Henderson VW, Hogervorst E. Testosterone and Alzheimer disease. Neurology 2004;62:170-171.
25. Erickson KI, Colcombe SJ, Elavsky S, et al. Interactive effects of fitness and hormone treatment on brain health in postmenopausal women. Neurobiology of Aging 2007;28:179-185.
26. Roberts RO, Cha RH, Knopman DS, et al. Postmenopausal estrogen therapy and Alzheimer's disease: overall negative findings. Alzheimer Dis Assoc Disord. 2006;20(3):141-6.
27. Yaffe K, Barnes D, Lindquist K, et al. Endogenous sex hormone levels and risk of cognitive decline in an older biracial cohort. Neurobiology of Aging 2007;28:171-178.
28. Strozyk D, White LR, Petrovitch H, et al. Sex hormones and neuropathology in elderly men: The HAAS.

Neurobiology of Aging 2007;28:62-68.
29. Agency for Healthcare Research and Quality; pharmacological treatment of dementia 2004;(97): www.AHRQ.gov/clinic.

Physician Fact Sheet on Hormone Replacement Therapy (HRT) as a Protective Intervention for Dementia

1. Data on protective effect of HRT for dementia in men and women is conflicting.

2. HRT may increase risk of stroke and DVT in women.

3. Estrogen supplementation may diminish amyloid deposition in rodent models for Alzheimer's disease.

4. Long-term HRT for women is not currently recommended as a preventive strategy for dementia.

5. Women who receive HRT for other reasons, such as menopausal symptoms, may enjoy a mild cognitive benefit.

6. Testosterone deficiency in aging may contribute to age-related physical senescent changes.

7. Many males presently receive exogenous testosterone for multiple reasons, including andropause.

8. Low testosterone in males may predict increased risk for memory loss.

9. Testosterone therapy is presently considered safe in older males.

10. Testosterone supplementation should not be provided as prevention for dementia in males.

The Consumer's Guide To The Role Of Hormone Replacement Therapy In Growing Older With A Healthy Mind

1. **Can hormone therapy help an older woman reduce her risk for developing Alzheimer's disease?**
   Young women make adult amounts of sex hormones such as estrogen and progesterone. During menopause, several hormone levels change in a woman's body and estrogen levels drop after age 50. The loss of estrogen produces many symptoms of menopause. Replacement of estrogen and progesterone is referred to as HRT or hormone replacement therapy.

   The brains of all humans are sensitive to estrogen. These sex hormones work by sending signals and altering brain function in both men and women. These hormonal sensitivities explain some psychological alterations that occur during pregnancy and menopause.

   Beginning in 1990, scientists recognized that some women who take hormone replacement therapy during menopause seem to have less risk for developing dementia in later life. This observation caused more scientists to examine whether hormones can protect intellectual function and numerous additional studies examined different groups, different types of hormone replacement, and different kinds of side effects or complications from these medicines. Studies suggest that hormone treatment after menopause may increase the risk for stroke, blood clot, and several other complications in women who take hormones as compared to women who take no hormones. Scientist could not agree on whether women with hormone replacement therapy enjoy some protection from intellectual loss in later life. Hormone replacement therapy may protect older women against symptoms of menopause and may protect against osteoporosis (bone softening). Scientists cannot predict which women will benefit from the medication, at what age, in what strength, and for what length of time.

2. **What is the best recommendation for hormone replacement therapy in women?**
   The best recommendation for hormone treatment is that older women should have a careful, thoughtful discussion with a doctor who understands older women's health. Hormone replacement treatment should not be prescribed as a prevention strategy for dementia; however, hormone treatment may be highly beneficial to some patients for other health problems, such as menopausal symptoms or osteoporosis. Any woman who receives hormone therapy should be monitored by their doctor and fully informed about potential complications, such as blood clots in the leg or the lung. Hormone replacement therapy in older women is safe and beneficial to many older women. Some women who receive hormone replacement treatment may also experience some protective effect against intellectual decline or dementia. For details of the scientific evidence that support this fact sheet, please see DETA 2513.71, entitled "*Basic Facts For The Primary Care Physician On Hormone Replacement Therapy as a Preventive Strategy for Dementia in Women and Men*". Future research may help doctors identify women who should use hormone therapy to protect intellectual function over age 65.

Recommendations:

1. Women should discuss hormone replacement therapy (HRT) with a doctor who is an expert on this subject.
2. Hormone replacement therapy (HRT) is not recommended as a preventive intervention for dementia.
3. "Natural" hormones or herbs that are sold as food supplements do not prevent dementia.

Does Male Hormone Replacement Therapy Help Protect the Brain of Older Men from Alzheimer's Disease?

While most persons know about menopause for women, men also undergo hormonal changes with aging referred to as "andropause". Older men begin to experience diminished production of the male hormone called "testosterone". Reduction of testosterone does not eliminate the male's ability to reproduce; however, this change may cause other alterations, such as muscle loss or erectile difficulties.

Men can take testosterone pills to replace hormones lost through aging. Some studies suggest that the loss of testosterone in males may increase the risk for intellectual loss in later life. Scientific studies do not show that hormone replacement will protect an older man from developing Alzheimer's disease or losing intellectual function. These studies will be performed over the next decade and should provide valuable information for the aging male population.

Hormone replacement therapy with testosterone appears to be relatively safe; however, more studies will be required to examine the long-term effect of testosterone on tissue that is sensitive to male hormones such as the prostate gland. Male hormone replacement therapy is not indicated for older individuals because its beneficial effect on intellect is unclear and the medications may have the potential for producing side effects.

Future research will clarify the role of testosterone in the aging process of males and possible clinical markers for men who might benefit from long-term hormone replacement therapy.

Suggested Actions:

1. Testosterone therapy for older men is not presently used to slow aging or prevent dementia.
2. Over-the-counter "male hormone supplements" are not shown to improve memory.

8. Anti-Inflammatory Medications

8. Anti-Inflammatory Medications as Dementia Retardants

Long-term use of non-steroidal anti-inflammatory drugs (NSAID's) may protect against Alzheimer's disease by diminishing inflammatory response to amyloid deposits. The brain's intrinsic inflammatory response may contribute to damage produced by Alzheimer's disease and other degenerative disorders. Inflammatory damage may be mediated through two mechanisms: 1) the immune response provoked by deposition of amyloid within brain parenchyma and 2) immune response to damaged blood vessels within the human cerebral cortex. Human senile plaques often contain microglial cells and other evidence of inflammatory responses. Alpha 1 chymotripsin may be contributory to the neurodegenerative process and this inflammatory protein is over-expressed in the brains of some patients with Alzheimer's disease. Longitudinal studies demonstrate that elevated levels of C-reactive proteins are associated with cognitive decline and cerebrovascular or cardiovascular disease. These non-specific inflammatory molecules may contribute to some microvascular damage that occurs in the brains of patients with Alzheimer's disease.

Several longitudinal studies suggest that older individuals who take non-steroidal inflammatory medication may have a diminished risk for cognitive decline. The impact of non-steroidal anti-inflammatories on individuals with mild cognitive impairment is largely unknown.

Non-steroidal anti-inflammatory medication can produce significant acute and long-term complications including gastrointestinal hemorrhage. Definitive randomized studies to determine the long-term cognitive benefits of NSAIDS in middle life have not been performed and these studies are unlikely to be undertaken. **(Click here for references – 2315.83)**.

Recommendation

Available clinical evidence indicates that NSAIDS should not be used as a preventive intervention for the treatment of Alzheimer's disease or mild cognitive impairment. Individuals receiving these medications for other reasons, such as arthritis, can be informed that a small beneficial effect may be provided from these drugs. **For more information, click here – 2513.81, 2513.85**

Physician Guide to Understanding the Role of Inflammation in the Loss of Cognitive Function or the Development of Dementia in Older Persons

1. Overview on Neuro-inflammation

Primary care physicians may be queried by older patients about the wisdom of taking anti-inflammatory medications to reduce the risk of dementia (1). Several lines of evidence suggest that abnormal inflammatory processes may contribute to cognitive decline and the pathogenesis of dementia (1). Some epidemiological studies suggest that individuals with long-term consumption of anti-inflammatory medications were less likely to develop dementia; however, meta analytic review does not support this linkage (2), (3). A second line of evidence suggests a relationship between elevated serum levels of inflammatory markers such as C-reactive protein or interleukin 6 and increased risk for cognitive decline. Subsequent evidence demonstrates neurochemical and microscopic brain abnormalities that support inflammatory damage in Alzheimer's disease.

2. The relationship of inflammatory markers and cognitive decline

Multiple longitudinal studies have examined the relationship between circulating immunological markers and the risk for cognitive decline in elders. C-reactive protein is a nonspecific inflammatory marker associated with a variety of cardiovascular risk factors. Individuals with metabolic syndrome demonstrate elevated levels of C-reactive protein that correlate to severity of cardiovascular disease. Isolated elevation of C-reactive protein is associated with increased risk for cognitive decline **(See Table 1).** Likewise, elevated markers for interleukin 6 and alpha 1 chymotrypsin are also associated with cognitive decline in later life. Data is not consistent in all studies; however, the general trend indicates that elevated markers for systemic inflammation predict elevated risk for cognitive decline (8).

Table 1

The Relationship of Inflammatory Markers to Cognitive Decline in Humans

#	n	a	t	Finding	Ref.
1	540	>65	CS	Chronic low grade inflammation may ↑ age-related cognitive decline	4
2	3031	>65	CS	Markers for IL6 and CRP may predict ↓ cognitive function	5
3	1284	>62	3yrs	Alpha 1 – antichymotrypsin is associated with cognitive decline but not IL6 or CRP	6
4	799	>70	7 yrs	↑ IL6 may predict ↓ cognitive function	7
5	290	55+	3 yrs	↑ IL6 = ↑ risk in African-Caribbeans	28

n = study size **a =** age **IL6** = interleukin -6 **CRP** = C-reactive protein
CS = cross-sectional

2513.84 NSAIDs

3. Animal models for brain inflammation

Rodents that are genetically altered to produce excessive amounts of Aβeta 42 amyloid in their brain may exhibit a diminished amyloid load after pretreatment with anti-inflammatory medications, as well as diminished inflammatory markers such as IL6 (9), (10). Conversely, excessive amounts of glucocorticoids in aged macaque monkeys are related to increased levels of βeta 42 amyloid in comparison to levels of βeta 40 and this over-production of toxic amyloid may be mediated through alterations of the insulin degrading enzyme (11). Chronic administration of Ibuprofen reduces the density of amyloid plaque pathology in the mouse model of Alzheimer's disease (10). Molecular biological studies from rodent models suggest that NSAIDs directly alter the amyloid pathway by reducing Aβeta 42 peptide levels; however, this effect does not appear dependent on cyclooxygenase (COX) activity (12).

4. Neuropathology and Inflammation

Inflammatory cells may be an integral part of the damage associated with senile plaques and amyloid deposits. The role of inflammation in neurofibrillary pathology is less well understood. Microglial cells are intrinsic brain inflammatory cells that may be activated by glycation of the APOE protein (7), (13). The limited pathological data on the density of senile plaque and tangles counts suggest no difference between brains of persons who took NSAIDs and those who took no anti-inflammatory medication; even in medicated persons with better cognitive function (14).

5. Potential Pharmacological Interventions to reduce Inflammatory Processes

Damage produced by inflammation in the brain might be reduced by multiple methods including: 1) reduction of the severity of metabolic syndrome, and 2) use of non-steroidal anti-inflammatories. Long-term, low dose use of NSAIDs may protect against cognitive decline (15), (16), (17). The overall efficacy of these medications is undetermined. Long-term use of NSAIDs carries significant risks for gastrointestinal bleeding (18), especially during acute initiation of the medication. Long-term use of COX 2 inhibitors may produce significant risk for cardiovascular complications (19). The long-term use of these medications as an anti-Alzheimer protectant is not proven (20); in fact, there is no proven method to reduce possible brain damage produced by pathological immune responses in the older human.

Understanding the efficacy of anti-inflammatory medication is limited by the absence of double-blind placebo controlled trials (21). The suggestion that NSAIDs may act independently of cyclooxygenase (COX) inhibition may explain poor results produced by clinical trials for naproxen, celecoxib and rofecoxib in clinical trials (1). The conventional wisdom suggests that Ibuprophen may provide the safest, most cost-effective intervention for individuals required to take anti-inflammatories (3).

6. The Role of the Metabolic Syndrome in Producing Inflammation

The metabolic syndrome will increase levels of inflammatory markers such as CRP in older persons. The metabolic syndrome and increased inflammatory markers are independent risk factors for cognitive loss. Management of the metabolic syndrome may reduce some component of the inflammatory response (24), (25), (26). **CLICK HERE FOR MORE INFORMATION – 2513.91**

Genes that control proteins involved with inflammatory response may be altered in AD. Other future pharmacologic interventions may target the production of these inflammatory proteins (29), (30).

7. Clinical Recommendations to Reduce Inflammatory-Mediated Brain Damage

The risk-benefit ratio weighs against recommending non-steroidal anti-inflammatory medication to reduce the risk for dementia in older persons. Clinicians can advise patients about two possible methods of reducing the risk for dementia produced by an abnormal systemic inflammatory response. First, passive measures such as reduction of risk factors for metabolic syndrome may provide secondary effects through reduction of risk for excessive production of inflammatory responses. A second direct anti-inflammatory effect may be mediated through the use of Ibuprophen or aspirin. Low dose aspirin may also be protective for declining memory in individuals 75 years in age and older -- a mechanism that maybe mediated by its anti-platelet effect (15), (16), (17). The chronic use of non-steroidal anti-inflammatories may also delay the onset of other neurodegenerative diseases such as Parkinson's disease (23). Patients who use NSAIDs for other medical problems, such as arthritis, may enjoy a slight cognitive benefit from this medication (27) if used chronically (22).

Other immunological interventions to reduce amyloid burden have produced inconsistent results. Active immunization against Aβ amyloid has not been shown to be effective in persons with Alzheimer's disease. Prophylactic vaccination in at-risk individuals may be attempted when safe, effective vaccines are developed.

Recommendations to Primary Care Physicians

1. Encourage treatment of the metabolic syndrome to reduce the risk of abnormal systemic inflammatory responses.
2. Chronic use of NSAIDs for other indications may slightly reduce the risk for dementia.
3. Chronic NSAID use carries significant risk for toxicity.
4. Discourage the use of anti-inflammatory medications to reduce the risk for dementia.

References-Anti-inflammatory Medications

1. Firuzi O, Pratico D. Coxbids and Alzheimer's disease: should they stay or should they go? Ann Neurol. 2006;59(2): 219-28.
2. Klegeris A, McGeer PL. Non-steroidal anti-inflammatory drugs (NSAIDs) and other anti-inflammatory agents in the treatment of neurodegenerative disease. Curr Alzheimer Res. 2005;2(3):355-65.
3. Tabet N, Feldmand H. Ibuprofen for Alzheimer's disease. Cochrane Database Syst Rev. 2003;(2):CD004031.
4. Ravaglia G, Forti P, Maioli F, et al. Serum C-reactive protein and cognitive function in healthy elderly Italian community dwellers. J. Gerontol A. Biol Sci. Med. Sci. 2005;60(8):1017-21.
5. Yaffe K, Lindquist K, Pennix BW, et al. Inflammatory markers and cognition in well-functioning African-American and White elders. Neurology 2003;61(1):76-80.
6. Dik MG, Jonker C, Hack CE, et al. Serum inflammatory proteins and cognitive decline in older persons. Neurology 2005;64(8):1371-7.
7. Weaver JD, Huang MH, Albert M, et al. Interleukin-6 and risk of cognitive decline. McArthur Studies of Successful Aging. Neurology 2002;59:371-378.
8. Tuppo EE, Arias HR. The role of inflammation in Alzheimer's disease. Int. J. Biochem Cell Biol 2005;37(2):289-305.
9. Lim GP, Yang F, Chu T, et al. Ibuprofen suppresses plaque pathology and inflammation in a mouse model for Alzheimer's disease. J. Neurosci 2000;20(15):5709-14.
10. van Groen T, Kadish I. Transgenic AD model mice, effects of potential anti-AD treatments on inflammation and pathology.
11. Kulstad JJ, McMillan PJ, Leverenz JB, et al. Effects of chronic glucocorticoid administration on insulin-degrading enzyme and amyloid-beta peptide in the aged macaque. J. Neuropathol. Exp. Neurol. 2005;64(2):139-46.
12. Weggen S, Eriksen JL, Das P, et al. A subject of NSAIDs lower amyloidogenic Aβ42 independently of cyclooxygenase activity. Nature 2001;414(8):212-216.
13. Dickson DW, Sinicropi S, Yen Shu-Hui, et al. Glycation and microglial reaction in lesions of Alzheimer's disease. Neurobiology of Aging 1996;17(5):733-743.
14. Halliday GM, Shepherd CE, McCann H, et al. Effect of anti-inflammatory medication son neuropathological findings in Alzheimer's disease. Arch Neurol 2000;57:831-836.
15. Jonker C, Comijs HC, Smit JH. Does aspirin or other NSAIDs reduce the risk of cognitive decline in elderly persons? Results from a population-based study. Neurobiol Aging 2003;24(4):583-8.
16. Broe GA, Grayson DA, Creasey HM, et al. Anti-inflammatory drugs protect against Alzheimer disease at low doses. Arch Neurol. 2000;57(11):1586-91.
17. Andersen K, Launer LJ, Ott A, et al. Do non-steroidal anti-inflammatory drugs decrease the risk for Alzheimer's disease? The Rotterdam Study. Neurology 1995;45(8):1441-5.
18. Pilotto A, Francheschi M, Leandro G, et al. The risk of upper gastrointestinal bleeding in elderly users of aspirin and other non-steroidal anti-inflammatory drugs: the role of gastroprotective drugs. Aging Clin. Exp. Res. 2003;p15(6):494-9.
19. Fosslien E. Cardiovascular complications of non-steroidal anti-inflammatory drugs. Ann Clin Lab Sci 2005;35(4):347-85.
20. Gasparini L, Ongini E, Wenk G. Non-steroidal anti-inflammatory drugs (NSAIDs) in Alzheimer's disease: old and new mechanisms of action. J. Neurochem. 2004;91(3):521-36.
21. Szekely CA, Thorne JE, Zandi PP, et al. Nonsteroidal anti-inflammatory drugs for the prevention of Alzheimer's disease: a systematic review. Neuroepidemiology 2004;23(4):159-69.
22. Zandi PP, Anthong JC, Hayden KM, et al. Reduced incidence of AD with NSAID but not H2 receptor antagonists. Neurology 2002;59:880-886.
23. Chen H, Zhang SM, Hernan M, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol 2003;60:1059-1064.
24. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. Am J. Cardiol. 2006;97(2A):3-11.
25. Kuo HK, Yen CJ, Chang CH, et al. Relation of C-reactive protein to stroke, cognitive disorders, and depression in the general population: systematic review and meta-analysis. Lancet Neurol. 2005;4(6):371-80.
26. Ford ES. The metabolic syndrome and C-reactive protein, fibrinogen, and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. Atherosclerosis 2003;168(2):351-8.
27. Landi F, Cesari M, Onder G, et al. Non-steroidal anti-inflammatory drug (NSAID) use and Alzheimer disease in community-dwelling elderly patients. Am J Geriatr Psychiatry 2003;11:179-185.
28. Jordanova V, Stewart R, Davies E, et al. Markers of inflammation and cognitive decline in African Caribbean population. Int J Geriatr Psychiatry 2007; March 8.
29. Weeraratna AT, Kalehua A, Deleon I, et al. Alterations in immunological and neurological gene expression patterns in Alzheimer's disease tissues. Exp Cell Res 2007;313(3):450-61.
30. Candore G, Bal;istreri CR, Grimaldi MR, et al. Polymorphisms of pro-inflammatory genes and Alzheimer's disease risk: a pharmacogenomic approach. Mech Ageing Dev. 2007;128(1):67-75.

Physician Fact Sheet On The Prescription Of Anti-Inflammatories As A Preventive Intervention For Intellectual Loss Or Dementia

1. Individuals who consume non-steroidal anti-inflammatories may have a slightly diminished, long-term risk of developing cognitive decline.

2. Ibuprofen may be beneficial while other medications, such as COX 2 inhibitors, may have less beneficial effect.

3. Individuals with metabolic syndrome may have enhanced, systemic markers for systemic inflammation.

4. Inflammatory responses may play a role in the production of age and disease-related brain changes.

5. Amyloid and senile plaque provoke inflammatory responses in the brain.

6. Anti-inflammatory medications may alter the production of A-beta amyloid 42 in the brain.

7. Steroids may increase A-beta 42 amyloid production or alter levels of insulin degrading enzyme.

8. Long-term use of anti-inflammatory medications can produce significant gastrointestinal and cardiovascular morbidity in selected older patients.

9. Anti-inflammatory medications, such as aspirin, may be beneficial in other degenerative diseases, such as Parkinson's disease.

10. The weak, potential benefit of anti-inflammatory medications does not counter-balance the risk of long-term medication use as a preventive intervention for dementia.

Consumer Guide To The Role Of Anti-Inflammatory Medications In The Prevention Of Dementia

How does your immune system work in the brain?
Inflammation is a protective mechanism in the body to eliminate dangerous bacteria, viruses, tumor cells, and other potential threats to the health and wellbeing of our system. The body is designed to recognize itself through special markers that distinguish "self" from foreign organisms. Specialized cells in the blood stream and the tissue serve as the defense weapons in protecting the body. When the defense cells no longer recognize the body marker as friendly tissue, certain body parts may begin to self-destruct. Auto-immune disorders ("automatic" and "immune"), means that "defense" cells attack the body. Certain auto-immune disorders, such as Lupus Erythematosis, damage the brain. Abnormal immune responses can target brain cells, blood vessels, and outer coverings of nerve processes termed "myelin". Multiple sclerosis is caused by the body attacking its own nerve coating or myelin.

The role of the immune system in Alzheimer disease and dementia
Scientists are studying the role of the body's immune system in changes that occur with Alzheimer's disease and other types of dementia. Medications that suppress some types of immune response may provide a very limited protective benefit against intellectual loss in later life.

People with Alzheimer's disease and other types of dementia have evidence of abnormal inflammatory response in the brain. Abnormal blood factor and immune cells are present in damaged areas of the brain of persons with Alzheimer's disease. This response may worsen damage produced by Alzheimer's disease. Numerous studies examine the benefit of treating patients with Alzheimer's disease with medicines that suppress the body's response to the disease.

The role of anti-inflammatory medications in protecting against dementia
Certain drugs, called non-steroidal anti-inflammatory medications (NSAIDs) can block molecules associated with inflammatory response. All NSAIDs have side effects. Most of these drugs can irritate or damage the stomach, kidneys, and the heart.

The protection provided by chronic use of NSAIDs against dementia is small; however, the risk for side effects is substantial. Current treatment recommendations do not include long-term use of NSAIDs as prevention against dementia. Persons who take NSAIDs for other conditions, such as arthritis, may enjoy a secondary benefit by a slight reduction in the risk of developing dementia.

The role of inflammation in producing brain damage associated with Alzheimer's disease and other dementias remain unclear to scientists. Active research is underway to improve our knowledge and develop treatment strategies as prevention and early intervention. **CLICK HERE FOR MORE INFORMATION – 2513.81**

9. The Metabolic Syndrome

9. Managing the Metabolic Syndrome

The metabolic syndrome is a clinical condition that affects 45% of older persons and includes central obesity, hypertension, dyslipidemia and elevated insulin resistance with Type II diabetes. Several components of the metabolic syndrome have been associated with increased risk of cognitive decline in later life. The relationship with hypertension, cardiovascular disease, and dementia is discussed in the cerebrovascular wellness segment.

Recent studies discuss lack of exercise and midlife obesity as risk factors for the development of dementia in later life. Newer data suggests that Type II diabetes may double the risk for dementia, although the precise mechanism for this connection is unclear. Increased peripheral resistance to insulin may expose the brain to elevated levels of insulin which can alter insulin sensitive receptors in the brain. Diabetes is a demonstrated risk factor for atherosclerotic cardiovascular and cerebrovascular disease. The role of dyslipidemia in the pathogenesis of Alzheimer's disease is unclear despite the role of APO lipoprotein-E Type 4 as a risk factor for dementia.

The metabolic syndrome may alter amyloid metabolism, vascular pathology, systemic inflammatory responses or a combination of all the above. Although scientists cannot precisely explain the interaction of metabolic syndromes and dementia, clinicians are justified in linking long-term intellectual function to management of risk factors for metabolic syndrome including obesity, hypertension, and hyperlipidemia **(Click here for references – 2315.93)**.

Recommendation

Physicians can advise midlife patients that the metabolic syndrome increases risk of cognitive decline in later life. Prophylactic statin use is not recommended for dementia prevention in persons with normal lipid levels. Advice about the potential "neuroprotective" effect may enhance compliance for weight management, blood pressure control and statin therapy for appropriate persons.
For more information, click here – 2513.91, 2513.95.

The Primary Care Guide To Understanding The Role Of The Metabolic Syndrome In Cognitive Decline Of Older Persons

1. Defining the Metabolic Syndrome

A Primary care practice often includes numerous patients who belong to "Club Metabolique"! Patients often want to achieve the health benefits of quitting a very non-exclusive, unhealthy club. The metabolic syndrome, previously termed "Syndrome X" or "insulin resistance syndrome" exists in 25% of the adult population (1). The metabolic syndrome includes central obesity, hypertension, dyslipidemia, and elevated insulin resistance with Type II diabetes and occurs in 40% of older persons. Several components of the metabolic syndrome are associated with increased risk of cognitive decline in later life (2). The relationship with hypertension, cardiovascular disease, and dementia is discussed in the cerebrovascular wellness segment **(CLICK HERE FOR MORE INFORMATION - DETA 2513.11)**. New second and third generation antipsychotic medications may also produce metabolic syndrome in adults with no previous evidence for this condition. Routine monitoring is recommended for these patients **(See Table 2).** ***A patient handout on the price of the Metabolique Club membership is included in this packet- 2513.95, 2513.96.***

Table 1. CLUB METABOLIQUE
NCEP III Definition of Metabolic Syndrome

(includes 3 of 5 features)

1.	Abdominal obesity	M>40 in. F>35 in.
2.	Low HDL-C levels	M<40 mg/dl F<50 mg/dl
3.	High triglyceride level	>150mg/dl
4.	Hypertension	Systolic >130 Diastolic > 85
5.	↑ Fasting BS	>110 mg/dl

Arch Int. Med 2002;162:2033-36

2513.94. Metabolic Syndrome

Table 2
Basic Monitoring of Metabolic Effects In Persons Receiving Antipsychotic Medications

	Priority to therapy	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

2513.94. Metabolic Syndrome

The National Cholesterol Education Program III (NCEP) guidelines define metabolic syndrome as the existence of three of five risk factors identified in **Table 1**. These risk factors include obesity, low HDL-C levels, elevated triglycerides, systolic or diastolic hypertension and elevated fasting blood sugar levels. Some values are adjusted for male versus female. Ancillary features not included in the definition include evidence of chronic mild inflammation as seen with elevated serum levels of C-reactive protein, as well as enhanced oxidative stress, thrombophilia, and endothelial dysfunction ***(Click here for more information about inflammation and dementia – 2513.81).*** Each of these diagnostic features has specific available, safe, therapeutic interventions. Many of the ancillary features of the metabolic syndrome are identified as risk factors for the development of dementia and metabolic syndrome in later life is associated with Alzheimer's disease (7).

2. Risk Factors for Metabolic Syndrome

The risk for metabolic syndrome increases with age and is enhanced in African American citizens, as well as those with less than a high school education (3). Menopause increases the risk for metabolic syndrome by 60%, as well as psychological stress that may increase

plasma cortisol levels (1). The risk for metabolic syndrome increases 23% per 10 pounds of weight gained in older persons; however, the overall risk is reduced with regular exercise. Elders with metabolic syndrome were more likely to have cognitive impairment, especially those with evidence of a systemic inflammatory marker such as creactive protein (4), (7). Metabolic syndrome is also identified as a significant risk factor for silent brain infarction in otherwise healthy persons (5).

Recent studies discuss lack of exercise and midlife obesity as risk factors for the development of dementia in later life (6), (8) ***(Click here for more information – 2513.45-1)***. Central obesity in midlife is a significant risk factor for metabolic syndrome **(See Table 3).** Obesity increases the likelihood of dementia, reduces life expectancy **(See Table 4)** and increases the risk for Type II diabetes, as well as cerebrovascular disease; however, the definition of obesity may be less stringent in the elderly than younger adults (26). Obesity and other risk factors for metabolic syndrome are common health problems in many nations and cultures **(See Table 5).**

Table 3. Definitions of Weight / BMI

Category	BMI
Underweight	<18.5
Normal	18 to 25
Overweight	25 to 30
Obesity	>30

Table 4. Excess Deaths in the U.S. Caused by Obesity (19)

BMI	Excessive Deaths Per Year
< 18.5	+33,746
18 to 25	Baseline comparison
25-30	-86,094
>30	+111,909

JAMA 2005 Apr 20;293(15):1861-7

Table 5. Prevalence of Cardiovascular Risk Factors that may Impact Cerebrovascular Health in Adults

Nation	n	Impact on Population in each Country	Ref
Canada	2237	57% one or more metabolic risk factors 29% BMI >25, 51% sedentary life style	20
Canada	1844	33% altered metabolic profile and only one-third normal	21
Spain	704	42% of HBP not detected 21% of HBP adequately controlled	22
Ireland	1018	One-half overweight and ¼ obese, and 40% sedentary	23
Sey Chelles	1255	25% obese and 22% demonstrate metabolic syndrome	24

Newer data suggests that Type II diabetes in older persons may be a risk factor for the development of dementia (9), although the precise mechanism for this connection is unclear ***(Click here for more information – 2514.31)***. Increased peripheral resistance to insulin may expose the brain to excessive levels of circulatoring insulin which can alter insulin sensitive receptors in the brain (10), (11), (12). Diabetes is a demonstrated risk factor for

atherosclerotic cardiovascular and cerebrovascular disease, as well as dementia. The role of dyslipidemia in the pathogenesis of Alzheimer's disease is unclear despite the fact that the presence of APO- lipoprotein Type 4 alleles is a risk factor for dementia. Neither the levels of total cholesterol nor high density lipoprotein in late life are consistently correlated to risk of subsequent cognitive decline (13).

3. Understanding the Impact of Metabolic Syndrome on Cognitive Function in Later Life

The metabolic syndrome may alter risks for dementia based on a direct impact caused by specific pathologies including: 1) deposition of amyloid, 2) acceleration of vascular pathology, 3) accelerated production of neurofibrillary tangles, 4) enhanced inflammatory response, or 5) a combination of all the above. Although scientists cannot precisely explain the interaction of metabolic syndromes and dementia, clinicians are justified in linking long-term intellectual function to management of risk factors for metabolic syndrome including obesity, hypertension, and hyperlipidemia.

The protective effect of statin therapy remains controversial with multiple studies showing protection (14), (15) and a few studies disputing this beneficial effect (16). Statins may reduce cardiovascular morbidity and this benefit may protect cognition (17), (18), **(Click here for more information about statin use and dementia – 2514.21).** Prophylactic use of statins in persons with normal lipid profiles is not recommended as a preventive intervention **(See Table 5).**

Table 5. **Conclusions About Metabolic Syndrome**

Symptom	Independent Risk Factor for Dementia	Recommended Intervention	Exercise Improves
↑ Blood Sugar	Yes	↓ BS, ↓ weight, meds	✓
↑Triglycerides	?	Diet, meds	✓
Low LDL Cholesterol	?	Diet, meds	✓
Hypertension	Yes	Meds	✓
Obesity	Yes	Diet	✓
Meds-appropriate medications **Diet**-dietary management			

Understanding the role of the metabolic syndrome in dementia 17

4. Treating Metabolic Syndrome in Adults

The metabolic syndrome is a collection of disorders that often produce disease that is greater than the sum of the individual pathogenesis (27). Weight control, exercise and blood sugar management are central features of management (18) **(See Table 5).** ***(Click here for more information about on the role of diabetes in dementia – 2514.31).***

Recommendations For Primary Care Physicians

1. Screen for metabolic syndrome in adults.
2. Promote exercise on a daily basis for all adults.
3. Encourage weight control as a component of cognitive wellness.
4. Treat each component of the syndrome to achieve maximum management.
5. Explain the potential impact of metabolic syndrome on cognitive function to the older patient.

REFERENCES FOR METABOLIC SYNDROME

1. Hazzard WB, Blass JP, Halter JB, et al (Eds.) (2003), *Principles of geriatric medicine and gerontology* (5th Edition). New York: McGraw-Hill.
2. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer's disease. Arch Neurol 2005;62(10):1556-60.
3. Carnethon MR, Loria CM, Hill JO, et al. Risk factors for the metabolic syndrome: the Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985-2001. Diabetes Care 2004;27(11):2707-15.
4. Yaffe K, Kanaya A, Lindquist K, et al. The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 2004;292(18):2237-42.
5. Kwon HM, Kim BJ, Lee SH, et al. Metabolic syndrome as an independent risk factor of silent brain infarction in healthy people. Stroke 2006;37(2):466-70.
6. Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330(7504):1360.
7. Razay G, Vreugdenhil A, Wilcock G. The metabolic syndrome and Alzheimer disease. Arch Neurol 2007;64:93-96.
8. Whitmer RA, Gunderson EP, Barrett-Connor E, et al. Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study. BMJ 2005;330(7504):1360.
9. Biessels GJ, Kappelle LJ, Utrecht Diabetic Encephalopathy Study Group. Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? Biochem Soc Trans 2005;33(Pt 5):1041-4.
10. Frolich L, Blum-Degen D, Bernstein HG, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm 1998;105:423-438.
11. Fishel MA, Watson GS, Montine TJ, et al. Hyperinsulinemia provides synchronous increases in central inflammation and beta-amyloid in normal adults. Arch Neurol 2005;62(10):1539-44.
12. Vanhanen M, Koivisto K, Kuusisto J, et al. Cognitive function in an elderly population with persistent impaired glucose tolerance. Diabetes Care 1998;21(3):398-403.
13. Li G, Shofer JB, Kukull WA, et al. Serum cholesterol and risk of Alzheimer's disease: a community-based cohort study. Neurology 2005;65(7):1045-50.
14. Jick H, Zornberg GL, Jick SS, et al. Statins and the risk of dementia. Lancet 2000;356:1627-31.
15. Rockwood K, Kirkland S, Hogan D, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol 2002;59:223-227.
16. Zandi P, et al. Do statins reduce the risk of incident dementia and Alzheimer's disease? The Cache County Study. Arch Gen Psych 2005;62:217-224.
17. Bonora E. The metabolic syndrome and cardiovascular disease. Ann Med 2006;38(1):64-80.
18. Bestermann W, Houston MC, Basile J, et al. Addressing the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome in the southeastern United States, Part II: treatment recommendations for management of the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome. Am J Med Sci 2005;329(6):292-305.
19. Flegal KM, Graubard BI, Williamson DF, Gail MH. Excess deaths associated with underweight, overweight, and obesity. JAMA 2005;293(15):1861-7.
20. Joffres MR, Titanich KL, Hessel PA. The Alberta Heart Health Survey: methods and results. Can J Cardiol 1993;9(4):300-8.
21. Scarsella C, Almeras N, Mauriege P, et al. Prevalence of metabolic alterations predictive of cardiovascular disease risk in the Quebec population. Can J Cardiol 2003;19(1):51-7.
22. Plans P, Pardell H, Salleras L. Epidemiology of cardiovascular disease risk factors in Catalonia (Spain). Eur J Epidemiol. 1993;9(4):381-9.
23. Creagh D, Neilson S, Collins A, et al. Established cardiovascular disease and CVD risk factors in a primary care population of middle-aged Irish men and women. Ir Med J 2002;95(10):298-301.
24. Bovet P, Shamlaye C, Gabriel A, et al. Prevalence of cardiovascular risk factors in a middle-income country and estimated cost of a treatment strategy. BMC Public Health 2006;6:9.
25. Leiter LA, Abbott D, Campbell NR, et al. Lifestyle modifications to prevent and control hypertension. Recommendations on obesity and weight loss. CMAJ 1999;160(9 Suppl):S7-12.
26. Heiat A, Vaccarino V, Krumholz HM. An evidence-based assessment of federal guidelines for overweight and obesity as they apply to elderly persons. Arch Intern Med 2001;161(9):1194-203.
27. Firdaus M, Mathew MK, Wright J. Health promotion in older adults: The role of lifestyle in the metabolic syndrome. Geriatrics 2006;61(2):18-25.

Primary Care Fact Sheet on the Role of Metabolic Syndrome in Cognitive Decline in Older Persons

1. Older patients with metabolic syndrome are more likely to have cognitive impairment, especially with elevated systemic indicators for inflammation.
2. Metabolic syndrome includes at least three of the following: 1) central obesity, 2) hypertension, 3) elevated triglycerides, 4) low HDL cholesterol, and 5) increased fasting BS.
3. About 40% of older individuals meet criteria for metabolic syndrome.
4. Central obesity in midlife is a risk factor for dementia in later life.
5. Metabolic syndrome increases the likelihood of coronary artery disease.
6. The risk of metabolic syndrome increases 23% for each additional ten pounds of excess body weight.
7. Menopause produces a 60% increased risk for metabolic syndrome.
8. Metabolic syndrome is associated with silent brain infarctions in otherwise healthy individuals.
9. Treating metabolic syndrome in midlife produces multiple health benefits for later life.
10. Controlling metabolic syndrome requires long-term compliance with medications, diet, exercise, and lifestyle.
11. Hypertension is a consistent risk factor for dementia.
12. Statins and antihypertensive medications may reduce risk for cognitive decline through multiple molecular mechanisms.

The Consumer's Guide for Quitting the "Metabolic Club" or How I Beat the Metabolic Syndrome

Membership Benefits For The Metabolic Club

The metabolic syndrome is a medical term for a condition that is familiar to many middle-aged individuals. Persons with high blood pressure, high blood sugar, high triglyceride or cholesterol and central obesity, termed "a spare tire", have what doctors called the "metabolic syndrome". Persons who have three of these health problems qualify for membership in the metabolic club. Membership privileges include increased risks for heart attack, stroke, and dementia. The fatty tissue that produces the spare tire disturbs the body's response to insulin causing other changes that may be harmful to your brain. These health problems each produce long-term effects in the brain; however, their combination together is more damaging than each alone. These health problems trigger immune responses that may further damage blood vessels, the heart, and the brain.

Quitting The Metabolic Club

Older individuals do not want to be the members in the metabolic club. The reduction of these risk factors is simple and provides multiple health benefits. Losing weight and reducing fatty tissue will improve the body's response to insulin. Weight reduction helps with blood pressure. Regular exercise helps reduce weight and reduce blood pressure, as well as improving intellectual fitness **(For additional information, See DETA 2513.51 on Exercise and Intellectual Stimulation)**. People who take medicine to control high blood pressure must be careful to follow the doctor's directions and take the medications as prescribed. Medicines that lower cholesterol and triglycerides may provide protection against the harmful effects of these health problems. The reduction of symptoms for the metabolic club may also reduce harmful immune responses in the body triggered by these health problems.

Recommendations For Middle-Aged Persons About Avoiding The Metabolic Syndrome

Exercise, proper diet, vitamin supplementation, and sensible weight are key parts of successful aging and maintaining your intellect for as long as possible. These efforts are simple and cheap. The benefits can be dramatic to individuals.

1. Exercise at least four times per week.
2. Check your blood pressure every three to six months.
3. Watch your weight.
4. Ask your doctor about your blood sugar, cholesterol, and triglycerides.
5. Eat a proper, balanced diet.

CLICK HERE FOR MORE INFORMATION – 2513.96

A Consumer's Guide to Understanding the Metabolic Syndrome or How to Quit Club Metabolique

What is the metabolic syndrome?
The metabolic syndrome has many names, including dysmetabolic syndrome, syndrome X, insulin resistance syndrome, and several others. The term, "metabolic syndrome" is applied to persons who suffer from obesity around the waist line, elevated cholesterol or triglycerides, and high blood pressure. These individuals usually suffer from Type II diabetes, which is common in older persons.

Why is the metabolic syndrome important?
The metabolic syndrome is important for three reasons: 1) people with the metabolic syndrome may have increased risks for heart attacks, stroke, and intellectual decline with aging, 2) the metabolic syndrome is often preventable, and 3) the metabolic syndrome can be treated in all persons and eliminated in many people.

What are the consequences of having metabolic syndrome?
People with chronic metabolic syndrome have increased risks of heart attack, stroke, and intellectual loss overtime. The heart attack and stroke may be a direct consequence of high blood pressure and elevated lipids. The intellectual loss may result from blood vessel damage in the brain, poor pump function of the heart, or other consequences of the syndrome. People with metabolic syndrome may have high, increased levels of insulin because their body does not respond to this hormone properly. These high levels of insulin can be harmful to the brain. People with metabolic syndrome may also suffer from increased inflammation directed against the body's organs, including the brain. The cause of the enhanced inflammation is unknown, but this response may worsen brain damage produced by Alzheimer's disease or other brain injury.

What can I do to reduce the risk to my health and intellect produced by metabolic syndrome?
Exercise, weight control, and good primary health care are highly effective in reducing the risk for metabolic syndrome. Middle-aged persons should monitor their health status and reduce health risks.

Why is that spare tire so dangerous to my health?
Beltline obesity is frequently referred to as your "spare tire". This mass of fatty tissue is mostly located inside the abdominal cavity in a shroud of fatty tissue that hangs like an apron from your rib cage. This sheet of tissue expands as a person becomes obese and contains cells that produce a wide range of hormones. This fatty tissue is extremely active in altering levels of blood sugar, fats, and other molecules involved with energy and obesity. Obesity changes many body functions that can damage blood vessels and the brain. Exercise and calorie restriction are the best ways to deflate that spare tire and protect your brain.

What can I do to prevent the metabolic syndrome?
There are many steps a person can take in middle life that may reduce the risk for metabolic syndrome in later life: 1) control your weight and deflate your spare tire, 2) check your blood pressure on a regular basis and take medications prescribed by your doctor to manage your blood pressure, 3) have your doctor check your cholesterol and triglycerides on a regular basis, 4) eat a sensible diet that is low in red meat and include two portions of fish per week, 5) if you have high cholesterol, take your medicine as prescribed by your doctor, and 6) exercise on a regular basis.

10. Medication Management

10. Managing Medication Management

Patient non-compliance is the major obstacle to a dementia prevention program in the primary care setting. Polypharmacy, adverse drug reactions, and patient non-compliance are common problems in patients over the age of 65 that contribute to many hospital admissions. Studies show that between 10-20% of medications consumed by elders are used in error, producing 10% of hospitalizations. Duplicate therapy, incorrect prescriptions, inaccurate dosing, and drug-drug interactions are common problems. Psychotropic medications are often mis-prescribed, especially benzodiazepines or narcotics such as Darvon. Many older persons intentionally use excessive medications or those prescribed for others; especially psychotropic or analgesic drugs. The adverse health effects of inappropriate medications are significant. Inappropriate consumption of psychotropic medications can produce delirium that results in disability or nursing home admission.

Therapeutic non-compliance produces serious medical complications in elders. Depressed elders, elders treated by multiple doctors or those who use multiple medications have greater risk for non-compliance. Elders with unrecognized dementia may forget symptoms, instructions, or dosage changes. Elders may fail to comply with diet, medication, and lifestyle changes for many reasons. About 1/3 of elders admit to medication non-compliance and 3/4 are non-compliant during direct monitoring. Many elders fail to use written instructions for medications and rely on their memory for compliance. Physicians must communicate directly with the older patient to enhance their sense of self-determination and responsibility for their health **(Click here for references – 2514.13).**

Recommendation

Elders should be encouraged to bring all consumed medications to every office visit and seek consultations from their local pharmacist. Discuss compliance and prevention in explicit concrete terms with the older patient. Provide written instructions and frequent reminders about medication. Include family caregiver in the discussion about medication. Advise elders to cross-check all medications with their pharmacist, including over-the-counter medications. **For more information, click here – 2514.11, 2514.15.**

A Primary Care Guide To The Role Of Patient Compliance And Prescriptive Safety In Maintaining Cognitive Function

1. Overview

The successful management of chronic diseases usually requires a combination of pharmacological and health behavior interventions. A successful program requires accurate prescription by the physician and compliance by the patient. Prescriptive safety and compliance are essential in the prevention or treatment of dementia or management of diseases that worsens cognitive function. Medication non-compliance may account for up to one-third of hospital admissions among the elderly. Adverse drug reactions produced by appropriately consumed medications account for about 10% of hospitalizations. Even in monitored clinical trials, medication adherence ranges from 43% to 78% (19). Dispensing errors occur in community, pharmacies, and healthcare institutions **(See Table 1).**

Table 1. Medication Dispensing Errors by Location

Location	n	Outcome	Ref.
Hospitals/SNF	36 institutions	19% doses in error and 7% potentially harmful	2
Community Pharmacies	50 pharmacies 6 cities	1.7% error rate / 6.5% clinically important	3

2514.14 Medication Management

The DETA Dementia Prevention Program focuses on health conditions with defined effective treatments that may reduce risk factors for dementia. For example, the long-term health problems produced by metabolic syndrome may be reduced by managing each of the disorders' component including hypertension, dyslipidemia, diabetes and obesity. Reduction of severity of metabolic syndrome may reduce the risk for cognitive loss. CLICK HERE FOR MORE INFORMATION – 2513.91. The success of any dementia prevention program will depend on long-term medication and health behavior adherence by the patients.

2. Compliance with Pharmacological Interventions for Chronic Health Problems in Adults

Medication compliance is affected by a complex mixture of clinical factors including the patient's functional ability, as well as prescribing and dispensing details. Studies demonstrate that depressed individuals and those with impaired cognitive function, as well as those with low health literacy, are more likely to struggle with following complex pharmacological instructions. For instance, cardiac patients with depression have a threefold increased risk for medication non-adherence (13), (21), (22). Physicians that utilize polypharmacy without adequate patient education increase the likelihood of non-adherence by patients. Pharmacies can assist with problems through patient/customer education. The net cost to the healthcare system for medication non-compliance for older individuals is estimated at one-hundred billion dollars per year. A recent review of non-compliance among community residing elders receiving an average of nine medications indicated that in a sample of 100 individuals, only 35% had adequate health literacy to master medication compliance (20). Follow-up studies have demonstrated that 53% of individuals were non-adherent and about one-third of patients were administered medications which were ineffective or contraindicated for older patients (1). Low health literacy increases health expenditures by Medicare recipients (34). For instance, cardiac patients with depression have a threefold increased risk for medication non-adherence (13), (21), (22). Compliance with medical therapy for disorders such as hypertension, diabetes, and hyperlipdemia may reduce the risk for cognitive loss in later life; however, studies show that adherence ranges from one-third to two-thirds among patients with each disease. Patient non-compliance complicates effective medical management of many common disorders including hypertension, diabetes, dyslipidemia, osteoporosis, and glaucoma **(See Table 2).** As an example, hypertension is a significant risk factor for cognitive loss in later life. Compliance studies that span 10 years in large populations indicate that only 39% of hypertensive patients engage in continuous use, while 22% will start and stop medications and 39% are simply non-compliant with medications. A review of 33 compliance studies showed that about 49% of interventions improved adherence and about one-third produced symptom improvement (23).

Table 2. A sample of medication compliance studies for common chronic diseases in older persons

Disease	n	t	Outcome for Medication Compliance	Ref.
HBP (USA)	2,325	10 yrs.	39% full compliance, 22% partial compliance, 39% full non-compliant	13
HBP (Italy)	13,303	1 yr.	42% discontinue, ↑ medical expenses	14
Diabetes	6,090	1yr.	46% non-adherent	15
Dyslipidemia	4,776	3 yrs.	42 to 47% non adherence	16
Osteoporosis	38,120	1.7 yrs.	3/4 non-compliant	17
Glaucoma	5,300	6 mos.	1/2 non-compliant	18

n=number of study subjects **t**=duration of study

2514.14 Medication Management

3. Assessing Medication Compliance

Specific, clinical conditions increase the likelihood of non-compliance, including depression, cognitive impairment, polypharmacy and poly-physicians, i.e., use of multiple doctors (24) **(See Table 2).** The shopping bag sign, i.e., a shopping bag full of medications, can be disquieting to a physician; however, the provision of a comprehensive list of medications is greatly appreciated by most doctors. Patients may consume four broad classes of medications: 1) prescription drugs, 2) over-the- counter preparations, 3) medications prescribed for other individuals such as a spouse, and 4) medications that don't seem like drugs, such as alcohol, nicotine, and caffeine. Physicians often focus on prescribed and over-the-counter preparations; however, groups 3 and 4 are important. For example, individuals may use sleeping or pain pills prescribed for a spouse because "they seem to work pretty well for the other individual". The consumption of alcohol can produce drug-drug interactions and cigarette smoking can induce hepatic enzymes within the cytochrome P450 system. Individuals who cease drinking or smoking may produce alterations of medications that were previously stable and effective at the present dose.

4. **Understanding The Effect Of Adverse Drug Reactions On Healthcare And Cognitive Function**

The risk for adverse drug reactions is displayed in **Table 3** based on the location of the individual. Hospitalization of elders may involve adverse drug reactions in up to one-fourth of individuals with 16.8% developing an adverse drug reaction and 11.4% demonstrating non-compliance causing hospitalization (25), (26). The Beers Criteria for appropriate versus inappropriate drugs were created in response to the frequency of elderly individuals receiving inappropriate medications, especially psychoactive drugs (1). Data based on the Beers reviews indicates that psychotropic medications are often mis-prescribed for older individuals producing avoidable hospitalization or death (23), (27), 28), **(See Table 4)**. Persons with dementia are quite susceptible to complications of commonly prescribed medications and multiple medications may accelerate functional deterioration (36). Psychotropic medications top the list of harmful drugs in the elderly (1). Polypharmacy predicts poor health outcome (37).

Table 3. Adverse Drug Reaction Rates In Older Persons in Hospitals and Nursing Homes

Location	n	t	Results	Ref.
Nursing Home (n=2)	332	4yrs	67% at least one ADR, cardiovascular most common	4
Nursing Home (n=18)	28,839	1yr	1.89 per 100 resident-months, 6% life-threatening, 38% serious	5
Hospital meta analysis	39 studies	META	2.1% serious ADR and 0.19% fatal	6
Community to Hospital (n=81)*	28,411	10 yrs	3.4% all admits caused by ADR	7

*Patients received medications in community and required hospital admission
n=number of study subjects t=study duration CS-cross-sectional

2514.14 Medication Management

Table 4. Inappropriate Medications in Elders Based on Location of Residence

Location	n	Method	Results	Ref.
Homebound	2,193	26 groups Beers	9.9% drugs are inappropriate 39.7% subject at least one IPD	8
Community	6,171	20 meds+/ consensus	23% received at least one IPD*	9
Community	414	Consensus	14% subjects at least one IPD	10
Nursing Home (n=252)	21,884	Beers*	12% residents at least one IPD	11
ALF (n=193)	2,078	Beers	16% residents at least one IPD	12

*Beers - utilization of Beers criteria *IPD= inappropriately prescribed drug
n=number of study subjects +examined 20 specific meds

2514.14 Medication Management

5. Compliance with Health Behaviors

Cognitive wellness interventions for middle-aged and older individuals involve long-term personal commitment to healthy life choices including exercise, intellectual stimulation, sobriety, weight control, and adherence to medications which are commonly under-utilized by patients. Insufficient data is available to determine the best possible means to maximize appropriate health behaviors that reduce conditions, such as metabolic syndrome. Patient education about the beneficial effects of medication compliance and behavioral adherence would seem a reasonable prudent step in promoting management strategies that might maximize cognitive function in later life (29), (30), (31), (38).

Office schedules and financial pressures will often limit the time available to the primary care physician or pharmacist; however, non-compliance or adverse drug reactions will significantly reduce the benefit of the visit.

Medication compliance is a problem in both standard healthcare paradigm and in the managed care system. For example, non-adherence for anti-diabetic medication in a managed care setting significantly increases associated healthcare expenses such as emergency room visits, etc. (32).

6. Recommendation

Primary care physicians orchestrate the proper pharmacological management of older persons. In a recent caregiver survey, 51% of respondents reported that their physicians do not speak to each other (33). Treatment compliance can improve cognitive function by: 1) avoiding adverse drug reactions, 2) encouraging adherence with medications for chronic diseases that increase risk for dementia, and 3) promotion of lifestyle changes that promote cognitive function. Available studies do not define a "gold standard" method to maximize compliance. Several steps may improve adherence to medication programs:

1. Ask the patient to bring all pill bottles to visit, including OTC's.
2. Check for depression or mild dementia as risk factors for non-compliance.
3. Discuss benefit and side effects for each drug.
4. Encourage the patient to discuss their medications with pharmacists or home health nurses.
5. Insist on the use of a pill box or medication calendar to facilitate compliance.
6. Simplify dosing schedules as much as possible.
7. Identify and praise good compliance.
8. Check blood levels, when possible, if the patient is non-responsive to appropriate dosing.
9. When appropriate, include spouses or caregivers in discussions about medication compliance and health behaviors.

References

1. Fick DM, Cooper JW, Wade WE, et al. Updating the Beers criteria for potentially inappropriate medication use in older adults. Arch Intern Med. 2003;163:2716-2724.
2. Barker KN, Flynn EA, Pepper GA, et al. Medication errors observed in 36 healthcare facilities. Arch Intern Med. 2002;162:1897-1903.
3. Flynn EA, Barker KN, Carnahan BJ. National observational study of prescription dispensing accuracy and safety in 50 pharmacies. J Am Pharm Assoc. 2003;43:191-200.
4. Cooper JW. Probable adverse drug reactions in a rural geriatric nursing home population: a four-year study. J Am Geriatr Soc 1996;44:194-197.
5. Gurwitz JH, Field TS, Avorn J, et al. Incidence and preventability of adverse drug events in nursing homes. Am J Med. 2000;109:87-94.
6. Brennan TA, Leape LL, Laird NM, et al. Incidence of adverse events and negligence in hospitalized patients. N Engl J Med 19913324:370-6.
7. Onder G, Pedone C, Landi F, et al. Adverse drug reactions as cause of hospital admissions: results from the Italian group of pharmacoepidemiology in the elderly (GIFA). Geriatr Soc 2002;50:1962-1968.
8. Golden AG, Preston RA, Barnett SD, et al. Inappropriate medication prescribing in homebound older adults. JAGS 1999;47:948-953.
9. Willcox SM, Himmelstein DU, Woolhandler S. Inappropriate drug prescribing for the community-dwelling elderly. JAMA 1994;272-292-296.
10. Stuck AE, Beers MH, Steiner A, et al. Inappropriate medication use in community-residing older persons. Arch Intern Med. 1994;154:2195-2200.
11. Williams B, Betley C. Inappropriate use of nonpsychotropic medications in nursing homes. J Am Geriatr Soc 1995;43:513-519.
12. Sloane PD, Zimmerman S, Brown LC, et al. Inappropriate medication prescribing in residential care/assisted living facilities. J Am Geriatr Soc 2002;50:1001-1011.
13. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. J Hypertens 2005;23(11):2101-7.
14. Mazzaglia G, Mantovani LG, Sturkenboom MC, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. J. Hypertens 2005;23(11):2093-100.
15. Hertz RP, Unger AN, Lustik MB. Adherence with pharmacotherapy for type 2 diabetes: a retrospective cohort study of adults with employer-sponsored health insurance. Clin Ther 2005;27(7):1064-73.
16. Caspard H, Chan AK, Walker AM. Compliance with a statin treatment in a usual-care setting: retrospective database analysis over 3 years after treatment initiation in health maintenance organization enrollees with dyslipidemia. Clin Ther 2005;27(10):1639-46.
17. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 2005 Dec 1.
18. Nordstrom BL, Friedman DS, Mozaffari E, et al. Persistence and adherence with topical glaucoma therapy. Am J. Ophtalmol 2005;140(4):598-606.
19. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353:487-97.
20. Roth MT, Ivey JL. Self-reported medication use in community-residing older adults: a pilot study. Am J Geriatr Pharmacother 2005;3(3):196-204.
21. Gehi A, Haas D, Pipkin S, Whooley MA. Depression and medication adherence in outpatients with coronary heart disease: findings from the Heart and Soul Study. Arch Intern Med 2005;165(21): 2508-13.
22. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment. Arch Intern Med 2000;160:2101-2107.
23. McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions. JAMA 2002;288(22):2868-2879.

24. Ryan AA. Medication compliance and older people: a review of the literature. International Journal of Nursing Studies 1999;36:153-162.

25. Vik SA, Maxwell CJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. Ann Pharmacother 2004;38(2):303-12.

26. Col N, Fanale JE, Kronholm P. The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly. Arch Intern Med. 1990;150:841-845.

27. Johnson JA, Bootman JL. Drug-related morbidity and mortality. Arch Intern Med 1995;155:1949-1956.

28. Phillips DP, Christenfeld N, Glynn LM. Increase in US medication-error deaths between 1983-1993.

29. Krueger KP, Felkey BG, Berger BA. Improving adherence and persistence: a review and assessment of interventions and description of steps toward a national adherence initiative. J Am Pharm Assoc 2003;43(6):668-78.

30. Young SD, Oppenheimer DM. Different methods of presenting risk information and their influence on medication compliance intentions: results of three studies. Clin Ther 2006;28(1):129-39.

31. Haynes RB, McKibbon KA, Kanai R. Systematic review of randomized trials of interventions to assist patients to follow prescriptions for medications. Lancet 1996;348(9024):383-6.

32. Balkrishnan R, Rajagopalan R, Camacho FT, et al. Predictors of medication adherence and associated healthcare costs in an older population with type 2 diabetes mellitus: a longitudinal cohort study. Clin Ther 2003;25(11):2958-71.

33. Powers RE, et al. (unpublished data)

34. Howard DH, Gazmararian J, Parker RM. The impact of low health literacy on the medical costs of Medicare managed care enrollees. Am J Med. 2005;118(8):933.

35. Schmidt KS, Lieto JM. Validity of the medication administration test among older adults with and without dementia. Am J Geriatr Pharmacother 2005;3(4):255-61.

36. Ellul J, Archer N, Foy CML, et al. The effects of commonly prescribed drugs in patients with Alzheimer's disease on the rate of deterioration. J. Neurol Neurosurg. Psychiatry 2007;78:233-239.

37. Sorensen L, Stokes JA, Purdie DM, et al. Medication management at home: medication-related risk factors associated with poor health outcomes. Age and Ageing 2005;34:626-632.

38. Siegel D, Lopez J, Meier J. Antihypertensive medication adherence in the Department of Veterans Affairs. Am J Med 2007;120(1):26-32.

Physician Fact Sheet
For Statin Therapy As A Protection Against Cognitive Loss In Elders

1. Elevated triglycerides and low HDL cholesterol levels are components of the metabolic syndrome.

2. Most statins reduce LDL-C by at least 30 to 35%.

3. Statin therapy significantly lowers coronary events by as much as 20% to 40%, but long-term medication compliance is low (about 50%).

4. Cardiovascular health is integral component to cerebrovascular fitness.

5. Statins may directly alter the metabolism of A-beta 42 amyloid protein.

6. Some studies suggest that chronic statin therapy may reduce the risk for cognitive decline.

7. Some studies suggest that statin therapy may alter the natural history of persons with mild to moderate Alzheimer's disease.

8. Statin therapy can be a component of dementia prevention in persons with dyslipidemias.

9. Insufficient data exists to warrant the prophylactic use of statins in the prevention of dementia or the treatment of Alzheimer's disease.

10. The potential cognitive protection of statin therapy can be used to encourage compliance in middle-aged and older patients.

A Consumer's Guide To Understanding Medications That Control Cholesterol And Triglycerides

The Role Of Cholesterol And Triglycerides In The Human Body
Cholesterol and triglycerides are molecules in the human body that play essential roles in energy as well as cell structure and these substances are often called lipids. People with excessive amounts of cholesterol and triglycerides have increased risks for certain health problems. Excessive amounts of these fatty substances can increase the risk for heart disease, stroke, and damage to blood vessels. Scientists have not proven a relationship between the risk for dementia and the severity of abnormalities for cholesterol and triglycerides. Scientists have shown that persons who take lipid lowering medications will reduce their risk for developing dementia in later life.

Treating Abnormal Lipids
People can lower cholesterol and triglycerides through diet, weight control, exercise, and medications. Heart-healthy diets that replace red meat with fish are good life choices.

Several forms of cholesterol are present in the body including low density (LDL) or bad cholesterol and high density (HDL) or good cholesterol. People need the proper ratio of the low and high density molecules or they may have increased risk for heart or blood vessel disease. Doctors focus on enhancing good cholesterol while reducing bad cholesterol to the minimum amount. Cholesterol medication will lower bad values or enhance good cholesterol. All such agents seem to have a beneficial effect for reducing the risk of dementia.

Protecting the Brain by Treating Lipids
People with elevated cholesterol and triglycerides can help their brain by protecting blood vessels and heart that sustain brain function. Persons with abnormal cholesterol and triglycerides can help protect their brain against dementia by controlling weight, exercising properly, and taking medications to reduce the level of bad cholesterol, increase good cholesterol, and reduce triglycerides.

Scientists have not performed research to confirm the precise value of managing cholesterol and triglycerides as a method of protecting your brain against Alzheimer's disease. This research may never be performed; however, available information suggests the protective value of treating disorders of cholesterol and triglycerides. Common sense tells people that these steps will benefit some persons' long-term mental function.

We recommend that you take every possible step to control cholesterol and triglycerides in order to reduce your risk for dementia.

Recommended Steps:
1. Control your weight.
2. Eat a healthy, balanced, heart-healthy diet.
3. Ask your doctor about your cholesterol and triglyceride levels.
4. Take medications prescribed to control your cholesterol and triglycerides.

11. STATINS

The Primary Care Guide To The Use Of Statins As A Preventive Intervention For Dementia

1. Overview:

The primary care physician may be queried about the role of dyslipidemia and statin therapy in the pathogenesis or prevention of dementia. Elevated cholesterol and triglyceride levels are significant health problems in middle-aged and older individuals. Reduction of low density lipoprotein cholesterol by 25% to 40% will diminish the frequency of coronary events by 20 to 40%. Longitudinal studies demonstrate as much as 24% reductions in cardiovascular events after long-term treatment over 5 to 6 years. Elevated cholesterol and triglyceride levels are integral parts of the metabolic syndrome which afflicts approximately 25% of older Americans (5).

2. Mechanisms of Action

The potential protective mechanisms of statin use for cognition include: 1) reduction of damage to large caliber and small caliber vasculature, 2) reduction of inflammation in the brain, and 3) retardation of amyloid deposits. Despite these proposed mechanisms, the overall data on protective effect of statin usage remains unclear (11). A review of nine recent studies on the impact of statin therapy in cognition and dementia provided mixed results (11). A meta-analysis of 7 studies with 13,920 subjects demonstrated reduction of dementia (-30%) and Alzheimer's disease (-20%) with treatment; however, this effect "signal" was lost in the study's "noise". A variety of studies using multiple research techniques including longitudinal studies, nested case matching, and other statistical methods provide conflicting data. The CSF beta amyloid levels in older individuals do not appear affected by statin usage; however, plasma beta amyloid 42 levels in non-demented persons over age 75 appear slightly diminished in subjects receiving long-term statin therapy (12). The clinical significance of these scientific observations remains unclear. Treatment with Atorvastin may enhance cognitive function in persons with mild or moderate dementia (17).

Cell culture and rodent studies indicate that statin therapy may reduce the deposition of amyloid or impede aggregation of amyloid fibrils. No benefit is presently identified against the hyper-phosphorylation of tau or other markers for the production of neurofibrillary tangles. Neuropathological studies in humans who receive statin therapy prior to death indicate a strong linear association between increased LDL cholesterol levels and increased numbers of senile plaque or neurofibrillary tangles (13).

3. Clinical Recommendations

The global vascular benefit of statin therapy is supported by most research. Treatment of individuals with abnormal lipid levels is recommended, regardless of the patient's age. The prophylactic use of statins to prevent dementia in persons with normal lipids is not recommended because the risk-benefit ratio does not support the use of these expensive agents (15). The treatment of dyslipidemia in the setting of metabolic syndrome may provide greater benefit, as this intervention may assist with the reduction of intrinsic, brain inflammatory responses. No specific type of medication or diet has been demonstrated as potentially more beneficial for possible cognitive protection. The beneficial effect of statin therapy in mild to moderate dementia also remains controversial (11), (14), (15).

Statin therapy may produce numerous risks and side effects including mylagias and hepatotoxicity with some agents (16). Long-term compliance with diet and medication is a therapeutic challenge in the primary care setting. Longitudinal studies suggest that about 50% of patients comply with long-term statin therapy. Sufficient data exists about brain protection to provide the additional encouragement that long-term lipid management may significantly reduce the risk for cerebrovascular events and cognitive decline in later life. Strict adherence to lipid management may provide a significant beneficial, cognitive effect to those individuals with dyslipidemias (18) ***(For more information on compliance, See 2514.1).*** Dietary restriction of trans-fat may further reduce the risk for dementia.

Recommendations

1. Check lipid profiles in older persons.
2. Promote diet and weight control as lipid lowering interventions.
3. Treat dyslipidemia when identified in patients.
4. Use the concept of brain protection to encourage compliance with statin medications.
5. Do not use statins as a "preventive" measure against dementia in persons with normal lipid profiles.
6. Use "brain protection" as another argument to promote medication and dietary compliance in patients with hyperlipidemia.

References:

1. Li G, Shofer JB, Kukull WA, et al. Serum cholesterol and risk of Alzheimer disease: a community-based cohort study. Neurology 2005;65(7):1045-50.
2. Rea TD, Brietner JC, Psaty BM, et al. Statin use and the risk of incident dementia: the Cardiovascular Health Study. Arch Neurol 2005;62(7):1047-51.
3. Bernick C, Katz R, Smith NL, et al. Statins and cognitive function in the elderly: the Cardiovascular Health Study. Neurology 2005;65(9):1388-94.
4. Zamrini E, McGwin G, Roseman JM. Association between statin use and Alzheimer's disease. Neuroepidemiology 2004;23(1-2):94-8.
5. Eidelman RS, Lamas GA. The new national cholesterol education program guidelines. Clinical challenges for more widespread therapy of lipids to treat and prevent coronary heart disease. Arch Intern Med 2002;162:2033-2036.
6. Rockwood K, Kirkland S, Hogan D, et al. Use of lipid-lowering agents, indication bias, and the risk of dementia in community-dwelling elderly people. Arch Neurol 2002;59:223-227.
7. Zandi PP, Sparks L, Khachaturian AS, et al. Do statins reduce risk of incident dementia and Alzheimer's disease? The Cache County Study. Arch Gen Psychiatry 2005;62:217-224.
8. Jick H, Zornberg GL, Jick SS, Seshadri S, et al. Statins and the risk of dementia. Lancet 2000;356:1627-1631.
9. Evans RM, Emsley CL, Gao S, et al. Serum cholesterol APOE genotype, and the risk of Alzheimer's disease: a population-based study of African Americans. Neurology 2000;54:240-242.
10. Nass C, Blumenthal RS. Lipid management with HMG CoA reductase inhibitors in the elderly. Annals of Long-term Care: Clinical Care and Aging 2003;11(6):20-25.
11. Xiong GL, Benson A, Doraiswamy PM. Statins and cognition: what can we learn from existing randomized trials? CNS Spectr 2005;10(11):867-874.
12. Blasko I, Kemmler G, Krampla W, et al. Plasma amyloid beta protein 42 in non-demented persons aged 75 years: effects of concomitant medication and medial temporal lobe atrophy. Neurobiol Aging 2005;26(8): 1135-43.
13. Launer LJ, White LR, Petrovitch H, et al. Cholesterol and neuropathologic markers of AD. A population-based autopsy study. Neurology 2001;57:1447-1452.
14. Sparks DL, Sabbagh MN, Connor DJ, et al. Atorvastatin for the treatment of mild to moderate Alzheimer's disease. Arch Neurol 2005;62:753-757.
15. Zhou B, Teramukai S, Fukushima M. Prevention and treatment of dementia or Alzheimer's disease by statins: a meta analysis. Dementr Geriatr Cogn Disorder 2007;23:194-201.
16. Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. Clin Ther 2006;28(1):26-35.
17. Sparks DL, Sabbagh M, Connor D, et al. Statin therapy in Alzheimer's disease. Acta Neurol Scand Suppl 2006;185:78-86.
18. Panza F, D'Introno A, Colacicco AM, et al. Lipid metabolism in cognitive decline and dementia. Brain Res Rev 2006;51(2):275-92.

Physician Fact Sheet For Statin Therapy As A Protection Against Cognitive Loss In Elders

1. Elevated triglycerides and low HDL cholesterol levels are components of the metabolic syndrome.

2. Most statins reduce LDL-C by at least 30 to 35%.

3. Statin therapy significantly lowers coronary events by as much as 20% to 40%, but long-term medication compliance is low (about 50%).

4. Cardiovascular health is integral component to cerebrovascular fitness.

5. Statins may directly alter the metabolism of A-beta 42 amyloid protein.

6. Some studies suggest that chronic statin therapy may reduce the risk for cognitive decline.

7. Some studies suggest that statin therapy may alter the natural history of persons with mild to moderate Alzheimer's disease.

8. Statin therapy can be a component of dementia prevention in persons with dyslipidemias.

9. Insufficient data exists to warrant the prophylactic use of statins in the prevention of dementia or the treatment of Alzheimer's disease.

10. The potential cognitive protection of statin therapy can be used to encourage compliance in middle-aged and older patients.

Physician Fact Sheet On The Role Of Statins And Dementia

1. Hyperlipidemia plays a role in cardiovascular disease and cerebrovascular disease.

2. Hyperlipidemia is a component to the metabolic syndrome.

3. The data on the relationship between lipid level and the risk for dementia is unclear.

4. Statin medications are highly effective at normalizing lipids.

5. Dietary and weight control continue to be a mainstay for lipid management.

6. Animal models suggest statins may alter the inflammatory response to amyloid or retard amyloid deposition in the brain.

7. The "brain-protecting" effect of chronic statin therapy is controversial because many studies support the effect and others fail to document a CNS benefit.

8. Prophylactic statin therapy in people with normal lipids is not recommended to prevent dementia.

9. Aggressive management of lipids in older persons may have a secondary benefit of protecting the brain.

10. Physicians can use the potential "brain-protective" impact of statins to promote compliance which is about 40% in the general public.

The Consumer's Guide to Understanding the Role of Elevated Cholesterol or Triglycerides in Dementia

How does lowering bad cholesterol and triglycerides protect me against developing dementia?

Abnormal levels of cholesterol and triglycerides are common health problems in the older population. Long-term abnormal levels of these two substances called "lipids" are associated with increased risk for heart and blood vessel disease. Most lipid lowering medications are called "statins", and these drugs may reduce your risk of developing dementia in later life. Regular exercise, weight control, and a healthy diet may reduce lipid levels of at all ages.

Medications that reduce cholesterol or triglycerides may help to protect intellectual function by several ways. First, the large and small vessels in the brain may be damaged by fatty deposits in arteries resulting from long-term elevation of lipids. Lowering the levels of bad cholesterol and triglycerides may lower the risk of heart and blood vessel damage. Second, lipids may play a role in the accumulation of toxic proteins in the brain called "amyloid" and the anti-lipid medication may reduce these toxic deposits.

The best available science shows that high levels of bad cholesterol and triglycerides are bad for your brain. Persons with unhealthy lipids should exercise, eat a healthy diet, and take medications to lower the lipids. There is strong evidence that lowering your lipids will reduce damage to the heart and blood vessels that injures the brain. People with normal triglycerides and normal cholesterol should not take statin medications to protect against dementia because the risk of these medications is not worth an unproven benefit in persons with normal lipids.

Suggestions:

1. Eat healthy.
2. Exercise and control your weight.
3. Talk to your doctor about cholesterol and triglycerides.
4. Take your statins when you have unhealthy lipids.

A Consumer's Guide to Understanding Medications That Control Cholesterol and Triglycerides

The Role Of Cholesterol And Triglycerides In The Human Body
Cholesterol and triglycerides are molecules in the human body that play essential roles in energy as well as cell structure and these substances are often called lipids. People with excessive amounts of cholesterol and triglycerides have increased risks for certain health problems. Excessive amounts of these fatty substances can increase the risk for heart disease, stroke, and damage to blood vessels. Scientists have not proven a relationship between the risk for dementia and the severity of abnormalities for cholesterol and triglycerides. Scientists have shown that persons who take lipid lowering medications will reduce their risk for developing dementia in later life.

Treating Abnormal Lipids
People can lower cholesterol and triglycerides through diet, weight control, exercise, and medications. Heart-healthy diets that replace red meat with fish are good life choices.

Several forms of cholesterol are present in the body including low density (LDL) or bad cholesterol and high density (HDL) or good cholesterol. People need the proper ratio of the low and high density molecules or they may have increased risk for heart or blood vessel disease. Doctors focus on enhancing good cholesterol while reducing bad cholesterol to the minimum amount. Cholesterol medication will lower bad values or enhance good cholesterol. All such agents seem to have a beneficial effect for reducing the risk of dementia.

Protecting the Brain by Treating Lipids
People with elevated cholesterol and triglycerides can help their brain by protecting blood vessels and heart that sustain brain function. Persons with abnormal cholesterol and triglycerides can help protect their brain against dementia by controlling weight, exercising properly, and taking medications to reduce the level of bad cholesterol, increase good cholesterol, and reduce triglycerides.

Scientists have not performed research to confirm the precise value of managing cholesterol and triglycerides as a method of protecting your brain against Alzheimer's disease. This research may never be performed; however, available information suggests the protective value of treating disorders of cholesterol and triglycerides. Common sense tells people that these steps will benefit some persons' long-term mental function.

We recommend that you take every possible step to control cholesterol and triglycerides in order to reduce your risk for dementia.

Recommended Steps:
5. Control your weight.
6. Eat a healthy, balanced, heart-healthy diet.
7. Ask your doctor about your cholesterol and triglyceride levels.
8. Take medications prescribed to control your cholesterol and triglycerides.

12. DIABETES

The Primary Care Guide To Understanding The Role Of Diabetes As A Risk Factor For Cognitive Loss Or Dementia In Adults

1. Introduction

Glucose intolerance is common in older individuals and this metabolic symptom can progress to Type II diabetes in older individuals. Type II diabetes is an integral part of the metabolic syndrome in midlife that increases the risk of cognitive loss in later life. Glucose intolerance and diabetes in midlife produce a two-fold increased risk of cognitive loss in later life (8). Older diabetic individuals are more likely to have hypertension, cardiovascular disease, and atherosclerosis that produce diseases associated with dementia, including heart disease and renal failure.

Primary care physicians can encourage middle aged individuals to comply with weight loss, exercise, and dietary discretion by discussing the potential benefit for late life cognitive function, especially those individuals with strong family histories for Alzheimer's disease (8), (9).

2. The Molecular Function Of Insulin In The Brain

Studies show substantial numbers of insulin receptors in the cerebral cortex and hippocampus of the human brain (10). Insulin receptors are linked to second messenger systems within neurons that may control the production of neurofibrillary tangles through the regulation of phosphorylation of the microtubule-associated protein "tau".

Insulin serves many functions in the human brain, including: 1) the regulation of glucose metabolism, 2) mediation of a neurotrophic effect, 3) signal transduction, and 4) modulation of neuroendocrine function. The role of insulin far exceeds simple regulation of glucose that is available to the cerebral cortex via the blood supply.

Brain insulin receptors are diminished in the cerebral cortex during normal aging; however, their density appears greater in persons with Alzheimer's disease versus aged-matched controls. This finding may suggest a compensatory upregulation of insulin receptors to compensate for insulin resistance (19).

The activity of insulin degrading enzyme (IDE) is diminished in brain tissue from Alzheimer's patients as compared to controls. This enzyme also metabolizes intracellular and extracellular Aβ amyloid. Individuals with APOE 4 genes have diminished mRNA expression for IDE in the human hippocampus. Rodent models for Alzheimer's disease demonstrate that elimination of the IDE gene through knockout models increases relative concentration of Aβ in the brain. Hyperinsulinemia can provoke increased markers for inflammation and beta amyloid protein in older humans (18).

3. Clinical studies of diabetes and dementia

Multiple studies have examined the relationship between glucose intolerance or diabetes and cognitive loss or Alzheimer's disease. The majority of studies demonstrate a modest relationship of impaired glucose tolerance to either diminished cognitive function or risk for

Alzheimer's disease. Although a few studies have questioned this result, the majority support the observation that diabetes is a risk factor developing dementia in later life **(See Table 1).**

Table 1. The Relationship of Glucose Dysregulation on Diabetes Mellitus to Cognitive Function

Study	n	Duration	Outcome	Refs
1	1811	30	History and duration ↑ risk	1
2	915	CS	Only minor ↓ cognitive function	2
3	999	4 yrs	↓ Cognitive function in white women	3
4	10963	6 yrs	↓ Cognitive function	4
5	6330	CS	+ relationship (1.3 / 1.0 to 1.9)	5
6	5647	15yrs	Associated with selective poor cognitive function	6
7	1455	15yrs	↑ Risk for dementia	7
8	5510	CS	↑ Insulin = ↓ cognitive function	11
CS – cross-sectional				

2513.94. Metabolic Syndrome

A comparison of cerebral spinal fluid findings from individuals with Alzheimer's disease versus age-matched controlled individuals demonstrates that Alzheimer's patients have diminished CSF insulin in contrast to increased serum insulin, suggesting increased insulin resistance in the brain.

Overall, cross-sectional and longitudinal studies suggest a relative, two-fold increased risk for developing cognitive loss in persons with glucose intolerance or diabetes. Individuals with metabolic syndrome, or diminished physical activity in midlife experience increased risk for developing dementia in later life (8). **CLICK HERE FOR MORE INFORMATION ON THE METABOLIC SYNDROME 2513.91.**

4. Brain Pathology in Persons with Diabetes

The brains of elders with diabetes demonstrate a range of pathological findings to include increased risks for cerebral infarcts and small vessel disease, especially in those individuals with hypertension. Postmortem brain specimens form aging individuals with diabetes do not have greater densities of senile plaques than non-diabetic elders but they demonstrate increased rates of micro and macro infarcts. Demented individuals with both diabetes and APOE 4 genotype have the highest densities of neurofibrillary tangles and senile plaques at autopsy (12), (13). Elevated glycated hemoglobin A1 (HbA1c) may be correlated to accelerated atrophy in elders as demonstrated by brain imaging (17).

5. Conclusion About the Relationship of Cognition and Diabetes

Systemic insulin dysregulation may accelerate damage in the aging human brain through several mechanism, including: 1) increased glucose utilization, 2) increased oxidative stress, 3) accelerated tau phosphorylation, and 4) reduced insulin degrading enzyme that increases amyloid load in the brain (20). Randomized controlled studies to examine the relative benefit of glucose control versus untreated diabetes will not be performed for obvious ethical and legal reasons. The best available information suggests that reduction of health risk

factors for glucose intolerance in midlife through weight control, exercise, and dietary discretion may reduce the risk for late life diabetes. Aggressive management of hyperglycemia in later life may further reduce risk factors for dementia associated with glucose intolerance. Severe episodes of hypoglycemia also correlate to diminished cognitive function (14), (15). Careful management of blood sugars may slightly improve cognition in some elders. (16).

Primary care physicians are justified in advising middle-aged individuals and older patients that risk reduction for diabetes is one of many steps that may reduce risk of late life cognitive loss. Compliance data suggest that about half of diabetic patients are compliant with hypoglycemic agents and the promise of the brain benefit can be added to other potential protections for organs such as heart, eye, kidney, and others. This advice may particularly impact individuals with family histories for Alzheimer's disease or other types of dementia. **FOR MORE INFORMATION, CLICK HERE 2514.11.**

Recommendations to Primary Care Physician

1. Weight control and regular exercise may reduce the risk for diabetes and dementia.
2. Inform patients that risk reduction of glucose intolerance is a component of dementia prevention.
3. Meticulous control of blood sugars in diabetic patients may enhance cognition.
4. Severe or sustained hypoglycemia may be a risk factor for dementia.

REFERENCES:

1. Elias PK, Elias MF, D'Agostino RB, et al. NIDDM and blood pressure as risk factors for poor cognitive performance. Diabetes Care 1997;20(9):1388-1395.
2. Vanhanen M, Juusisto J, Koivisto K, et al. Type-2 diabetes and cognitive function in a non-demented population. Acta Neurol Scan 1999;100:97-101.
3. Kanaya AM, Barrett-Connor E, Gildengorin G, Yaffe K. Change in cognitive function by glucose tolerance status in older adults. Arch Intern Med. 2004;164:1327-1333.
4. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42-48.
5. Ott A, Stolk RP, Hofman A, et al. Association of diabetes mellitus and dementia: The Rotterdam Study. Diabetologia 1996;39:1392-1397.
6. Kumari M, Marmot M. Diabetes and cognitive function in a middle-aged cohort: findings from the Whitehall II Study. Neurology 2005;65(10):1597-603.
7. Leibson CL, Rocca WA, Hanson VA, et al. Risk of dementia among persons with diabetes mellitus: a population-based cohort study. Am J Epidemiol 1997;145:301-8.
8. Grossman H. Does diabetes protect or provoke Alzheimer's disease? Insights into the pathobiology and future treatment of Alzheimer's disease. CNS Spectr 2003;8(11):815-822.
9. Biessels GJ, Staekenborg S, Brunner E, et al. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol. 2006;5(1):64-74.
10. Hopkins DFC, Williams G. Insulin receptors are widely distributed in human brain and bind human and porcine insulin with equal affinity. Diabet Med. 1997;14:1044-1050.
11. Stolk RP, Breteler MMB, Ott A, et al. Insulin and cognitive function in an elderly population. Diabetes Care 1997;20(5):792-795.
12. Ukkola O, Kervinen K, Salmela PI, et al. Apolipoprotein E phenotype is related to macro- and microangiopathy in patients with non-insulin-dependent diabetes mellitus. Atherosclerosis 1993;101:9-15.
13. Heitner J, Dickson D. Diabetics do not have increased Alzheimer-type pathology campared with age-matched control subjects. Neurology 1997;49:1306-1311.
14. Langan SJ, Deary IJ, Hepburn DA, Frier BM. Cumulative cognitive impairment following recurrent severe hypoglycaemia in adult patients with insulin-treated diabetes mellitus. Diabetologia 1991;34:337-344.
15. Deary IJ, Crawford JR, Hepburn DA, et al. Severe hypoglycemia and intelligence in adult patients with insulin-treataed diabetes. Diabetes 1993;42:341-44.
16. Meneilly GS, Cheung E, Tessier D, et al. The effect of improved glycemic control on cognitive functions in the elderly patient with diabetes. Journal of Gerontology: Medical Sciences 1993;48(4):M117-M121.
17. Enzinger C, Fazekas F, Matthews PM, et al. Risk factors for progression of brain atrophy in aging: six-year follow-up of normal subjects. Neurology 2005;64(10):1704-11.
18. Fishel MA, Watson GS, Montine TJ, et al. Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults. Arch Neurol 2005;62(10):1539-44.
19. Frolich L, Blum-Degen D, Bernstein HG, et al. Brain insulin and insulin receptors in aging and sporadic Alzheimer's disease. J Neural Transm 1998;105:423-438.
20. Biessels GJ, Kappelle LJ, Utrech Diabetic Encephalopathy Study Group. Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? Biochem Soc Trans 2005;33(Pt 5):1041-4.

Physician Fact Sheet On The Relationship Between Diabetes And Dementia

1. Persons with diabetes in midlife have about a two-fold increased risk for cognitive loss in later life.
2. Risk factors for diabetes such as midlife obesity and physical inactivity are also risk factors for Alzheimer's disease or vascular dementia in later life.
3. The human brain has substantial numbers of insulin receptors in the neocortex and hippocampus.
4. Insulin degrading enzyme activity may also affect the amount of cerebral amyloid.
5. A combination of diabetes and APOE 4 typing increases the risk for senile plaques and neurofibrillary tangles at time of death.
6. Long-term patient compliance for oral hypoglycemic medications is about 50%.
7. Diabetes is a risk factor for other health problems that increase the risk for dementia, including cardiac dysfunction and renal failure.
8. Randomized controlled studies will not be done to confirm the preventive benefit for cognition of lifetime glucose management.
9. Physicians can advise individuals at risk for dementia that weight control and proper diet may reduce the risk for later life intellectual loss.
10. Aggressive management of blood sugars in later life may provide a small enhancement for cognitive function.

A Consumer's Guide To Understanding The Role Of Diabetes And Dementia

Diabetes is a disease, which is diagnosed by blood tests for high blood sugars. Glucose is a sugar, which is the source of energy in our brain, and the body regulates glucose by production of the hormone, insulin. Insulin acts through a communication system which includes special areas on the outside of cells that collect the insulin and command the cell to use the sugar. These specialized zones are called "receptors" and stimulation of the insulin receptor can produce many changes in the cell. Different types of tissue use insulin in different ways, including the brain.

High blood sugars occur when the body does not produce or use enough insulin. Most children with diabetes do not make enough insulin. The adult body may not respond to normal amounts of insulin, such as in older diabetics with obesity. The failure to respond to insulin is referred to as "insulin resistance" and this condition is common in many older persons, especially those with obesity and lack of exercise.

Insulin is important to the brain because the brain uses a lot of energy. Too much insulin in the blood stream can be harmful to the brain. This form of insulin toxicity may contribute to some of the intellectual loss that is seen in persons with diabetes.

Untreated or under-treated diabetes is bad for blood vessels. People with chronic diabetes can develop more hardening of the arteries and increased risks for heart damage.

Middle-aged people with diabetes can help to protect their brain by controlling their weight and using their medication to control their blood sugar. Poor control of diabetes may increase damage to heart blood vessels in brain. The fatty tissue that accumulates with obesity reduces the efficiency of insulin in your body. Regular exercise and weight control may help reduce the impact of diabetes in the brain.

Scientists have not performed the research to confirm the benefit of exercise, weight control, and strict control of blood sugar on the long-term risk of developing dementia for persons with diabetes. Common sense suggests that these actions will reduce risks associated with this common disease.

A Consumer Guide To Understanding The Role Of Diabetes In Dementia

What is diabetes?

Diabetes is diagnosed when a person has high blood sugars. Diabetes is divided into Type I, which often occurs in younger persons and Type II, which is common in older persons. Many persons with Type I diabetes need insulin while persons with Type II can use medicines that increase the body's ability to produce and release insulin. Chronic high blood sugars are bad for your brain and bad for your body. Many years of elevated blood sugar may increase the risk of heart disease and blood vessel damage. Persons with chronic, poorly controlled diabetes may develop kidney disease, nerve disease, and blindness after 20 or 30 years. Diabetes will double your risk for developing dementia in later life.

What causes diabetes?

Your risk for developing diabetes is a mixture of genes, diet, exercise, and weight. Good nutrition along with regular exercise and normal body weight may dramatically reduce your risk of developing diabetes or suffering complications from this disorder.

What can you do about diabetes?

People with diabetes must control their blood sugar to reduce the risk for complications. Proper diet, checking blood sugars, and taking medication are the best ways to control the symptoms of diabetes. People with poor diabetic control have increased risk for developing intellectual loss in later life.

People with a strong family history of dementia should reduce their risk for developing diabetes by controlling weight, diet, and exercise. People who develop diabetes must follow the doctor's instructions in using medications to reduce risks produced by the disease.

How is diabetes related to dementia?

Chronic diabetes can damage the brain through many pathways including: 1) damage to the heart that sustains the brain, 2) damage to blood vessels in the brain, and 3) production or release of chemicals that can harm the brain. Good control of blood sugar may reduce the risk of damage and protect the brain.

Consumer Fact Sheet on the Role of Diabetes as a Risk Factor for Dementia

1. Persons with diabetes may lose control of their blood sugar, causing high blood sugars.

2. Obesity is a risk factor for diabetes.

3. Physical inactivity is often a risk factor for obesity and diabetes.

4. Diabetes, obesity, and physical inactivity in midlife are possible risk factors for dementia in later life.

5. Diabetes is a serious risk factor for hardening of the arteries, heart malfunction, and other conditions that increase the risk for intellectual loss in older persons.

6. Diabetes is probably a risk factor for dementia caused by hardening of the arteries.

7. Persons with diabetes have increased risks for major strokes and mini strokes.

8. Older persons with high blood sugars have increased risks for memory problems and other forms of intellectual loss.

9. The combination of high blood pressure, high cholesterol, and high blood sugar is very hard on the human brain.

10. Lifestyle changes in midlife, such as diet control, weight reduction, and regular physical exercise will probably help reduce the risk of dementia in later life.

13. GENETICS

Explaining The Role Of Genetics As A Risk Factor For Dementia To Patients In The Primary Care Setting

Overview

Families are often concerned about the possibility that genetics may play some role in the pathogenesis of Alzheimer's disease (AD). A positive, family history for dementia may increase the patient's relative risk for developing dementia. Individuals who have a parent or sibling with AD may have 3.5x increased risk of developing the disease; however, the autosomal dominant variant of Alzheimer's disease is present in only 1-2% of all Alzheimer's disease cases. Many other forms of dementia, such as vascular and diffuse Lewy body disease have a substantially reduced genetic load in comparison to AD. A variety of genes are associated with familial/early onset AD that include chromosomes 1, 2, 14, and 21, as well as late onset or sporadic disease that includes chromosomes 6, 19, and 21 (1), (2), (3) (See Table 1).

Table 1

EMBED PowerPoint.Slide.8

Table 1

Important Genes for Dementia

Chromosome	Disease	Function
1	FAD	PSEN 2
14	FAD	PSEN 1
17	FTD	
19	LOAD	APO E
21	Down's LOAD	APP

FAD – familial AD **PSEN** – Presenilin **FTD**-Frontotemporal Dementia
LOAD – Late onset AD **APP**-Amyloid Precursor Protein

Interpretation of the Family History

A family history of Alzheimer's disease requires a post-mortem confirmation of the reported premortem diagnosis, as studies report a 10% discrepancy between clinical and pathological diagnosis. Many clinical conditions can produce confusion in the older patient and the family history is only as accurate as either the premortem diagnosis or postmortem confirmation.

Assessing the Risk Factors

The relative risk for developing Alzheimer's disease can be crudely assessed by determining how many family members were affected by the disease and what age these individuals developed symptoms. Individuals who develop dementia early in life, i.e., below age 60, are more likely to have a genetic variant of the disease. Proximity in the family tree may be helpful. An individual with a father and uncle who both develop dementia before age 60 might have a significantly increased risk for developing dementia in comparison to a woman who had a maternal aunt develop the disease after age 80 producing the same risk factors as the general population. A family history of dementia may not confirm the presence of Alzheimer's disease,

as a post-mortem examination is required to absolutely diagnose the cause of dementia. The presence of one or two alleles will also increase the risk of developing dementia.

Genetic Testing

Genetic testing is not presently available for Alzheimer's disease or any other form of dementia except for Huntington's chorea. APO lipoprotein E genes are often discussed because the presence of two E4 alleles will increase the risk while homozygote E2 seems protective. APOE typing is now offered as a routine clinical laboratory test. The APOE 4 gene is important but not necessary for dementia (1), (9) and certain ethnic groups, such as pygmies and others, have high rates of APOE 4 without identified increased risk (5), (6), (7), (8). It is unlikely that a single specific gene will be identified for late onset Alzheimer's disease or most other types of dementia, as the genetic risk may be predicted by a variable mixture of independent and inter-related genetic factors. Assessment of multiple genetics risk factors will probably be required to predict the risk in the future.

Understanding the Interaction of Genes, Environment, and Health Behaviors

A variety of health behaviors, e.g., exercise, weight control, or intellectual vitality may interact with medical conditions, e.g., diabetes or hypertension, to amplify the role of genetic predispositions, such as the presence of the APOE 4 allele. This complex equation will require years of further research to clarify and quantitate as a "genetic risk assessment".

The early onset familial AD accounts for less than 2% of dementia and involves genes that impact the amyloid precursor protein gene. About half of the late-onset cases may be related to the APOE gene which is located on chromosome 19. Unlike the amyloid gene on chromosome 21, the APOE gene is a susceptibility gene that may accelerate the age of onset for symptoms (11). Based on studies in elderly twins, genetic liability in late onset disease accounts for 48% of variation in the risk of developing dementia (3).

International studies comparing African Americans from Indianapolis to genetically similar individuals from their homeland in Nigeria show that APOE typing is less predictive of dementia in native Africans. The reduced risk if dementia in the Nigerian group may result from better health behaviors, such as a better diet and increased exercise.

Recommendations

Mixed dementia, such as AD and vascular dementia or AD and diffuse Lewy body disease, has a higher clinico-pathological discrepancy. Individuals, who are concerned about having Alzheimer's disease in the family, should be encouraged to engage in health practices that protect the brain. Although the value of cognitive fitness programs for persons with strong genetic loads for Alzheimer's disease is unproven, conventional wisdom suggests that reducing other associated brain injury would prolong the duration of cognitive fitness. Much or most dementia may result from a complex interaction between susceptibility genes, environment and life choices. Future genetic therapy will be complex and require therapeutic techniques not presently available to clinicians (2), (10), (11). **CLICK HERE FOR A FAMILY HANDOUT ON GENES AND DEMENTIA.**

References

1. Sillen A, Forsell C, Lilius L, et al. Genome scans on Swedish Alzheimer's disease families. Mol Psychiatry 2006;11(2):182-6.
2. Marteau TM, Roberts S, LaRusse S, Green RC. Predictive genetic testing for Alzheimer's disease: impact upon risk perception. Risk Anal 2005;25(2):397-404.
3. Pedersen NL, Gatz M, Berg S, Johansson B. How heritable is Alzheimer's disease late in life? Findings from Swedish twins. Ann Neurol 2004;55(2):180-5.
4. Van der Cammen TJ, Croes EA, Dermaut B, et al. Genetic testing has no place as a routine diagnostic test in sporadic and familial cases of Alzheimer's disease. J Am Geriatr Soc 2004;52(12):2110-3.
5. Benkmann HG, Agarwal DP, Vasisht S, et al. Distribution of apolipoprotein E genotypes in Asian Indians, Hungarians, and Papua New Guineans. Anthropol Anz. 1996;54(1):31-34.
6. Sandholzer C, Delport R, Vermaak H, Utermann G. High frequency of the apo epsilon 4 allele in Khoi San from South Africa. Hum Genet. 1995;95(1):46-8.
7. Gerdes LU, Gerdes C, Hansen PS, et al. The apolipoprotein E polymorphism in Greenland Inuit in its global perspective. Hum Genet 1996;98(5):546-50.
8. Zekraoui L, Lagarde JP, Raisonnier A, et al. High frequency of the apolipoprotein E *4 allele in African pygmies and most of the African populations in sub-Saharan Africa. Hum Biol 1997;69(4):575-81.
9. Kamboh MI. Molecular genetics of late-onset Alzheimer's disease. Ann Hum Genet 2004;68(pt4):381-404.
10. Bertram L, Tanzi RE. The current status of Alzheimer's disease genetics: what do we tell the patients? Pharmacol Res 2004;50(4):385-96.
11. Saunders AM. Gene identification in Alzheimer's disease. Pharmacogenomics 2001;2(3):239-49.

PHYSICIAN FACT SHEET ON THE ROLE OF GENETICS AND DEMENTIA

1. A positive family history for Alzheimer's disease increases the individual's risk for developing dementia.
2. A family history of Alzheimer's disease does not confirm the presence of this disease unless a post-mortem examination is performed.
3. Individuals who have siblings with Alzheimer's disease have up to a 3.5-fold increased risk for developing dementia.
4. The autosomal dominant variant of Alzheimer's disease produces about 2% of all dementias.
5. Multiple "suspect" genes are linked with late onset dementia; most associated with the APOE 4 gene on chromosome 19.
6. APOE typing is not predictive for dementia as some ethnic groups have high rates of APOE 4 and normal rates of dementia.
7. In elderly twins, genetic factors accounts for 48% of variation in risk for dementia.
8. Vascular dementia and diffuse Lewy body disease probably have limited genetic risk factors.
9. Frontotemporal dementia is associated with chromosome 17 that programs tau.
10. A simple genetic test is unlikely for Alzheimer's disease; however, a genetic screen that assesses risk factors is likely within the next five years.
11. Genetic risk can be crudely assessed by determining the number of family members with proven Alzheimer's disease, age of onset, and proximity in the family tree.
12. Genetic risk factors, basic healthcare compliance, and lifestyle decisions may alter the risk for dementia.

The Consumer's Guide to Understanding the Role of Genetics in Dementia

Genetics refers to the study of how traits are passed on from parents to children. These traits are the functions that control all aspects of our body and life. Most traits are controlled by genes and environmental factors. Genes are pieces of a complex molecule that code for proteins and other factors that control how cells of your body functions. Each human being has a set of about 30,000 genes located on 46 chromosomes. Changes in these genes can occur due to many factors, for example, radiation, chemicals, and exposure to supercharged forms of oxygen called free radicals.

Errors in the code contained in genes can cause your body to malfunction by producing defective proteins, which can accumulate and reduce proper function in the brain. Some rare genetic causes of dementia, like Huntington's chorea, cause these defective proteins and these individuals will almost always have this disease. Similar to Huntington's chorea, a small number of persons with familial Alzheimer's disease (4% or less) have genes that predestine them to develop dementia. These genes cause intellectual loss early in life, usually before the age of 65.

Some common forms of dementia are more complex and may result from when an accumulation of genetic changes and certain other health problems in middle or later life. Dementia is most likely to occur in later life. Late onset dementia has certain genes that may be only risk factors for developing intellectual loss; however, some people may not get the disease even if they have some of these "risk" genes. Risk factors or risk genes increase the chance that a person will get the disease, but unlike the genes for early onset dementia, having the risk gene does not predestine them to getting the disease. The gene for the protein APOE is considered a risk gene for dementia and the presence of the "high risk" form of APOE (APOE 4) may increase a person's chance of developing intellectual loss. The "toxic" APOE may increase the rate of intellectual loss by causing symptoms 10 years earlier than others without this high risk gene. Fifty percent or less of those with this high risk marker may develop Alzheimer's disease.

DO MY GENES DETERMINE MY FATE AS I GROW OLDER?

Your genes determine some aspects of how you grow old and your risk for developing dementia. Genes may play a big role in determining how long and how well you live. Genes also determine your risk for developing health problems that may increase your risk factors for dementia. Heart disease, high blood pressure, and elevated triglycerides or cholesterol can be influenced by your genes. Life choices and healthy behaviors play the biggest role in determining how well you age and how many diseases occur that damage your brain. Genes are important but a healthy lifestyle is equally important. You can't change your genes, but you can change your lifestyle.

Click here for ways to help your brain age well - 2513.55

THE TEN COMMANDMENTS FOR Preventing dementia

I. **Thou shalt use thy brain for thy whole life.** Your brain is a "use it" or "lose it" organ.

II. **Thou shalt not become a couch potato.** Obesity, inactivity, and poor health are bad for your brain.

III. **Thou shalt exercise until the day thy die.**
People who exercise on a regular basis have better physical and intellectual life.

IV. **Thou shalt not keep a spare tire.** Obesity around the belt line in middle life is bad for your brain in later life.

V. **Thou shalt protect thy heart and blood vessels.** Your brain needs adequate oxygen and nutrients to stay well.

VI. **Thou shalt treat thy hypertension as a young person to keep thy memories as an old person.** Untreated hypertension damages blood vessels in the brain.

VII. **Thou shalt take a STANDARD vitamin on a daily basis.**
B-Complex vitamins and Folic acid are helpful.

VIII. **Thou shalt fix thy depression and encourage thy neighbor to fix their depression.**
Treating depression may improve your physical and intellectual health. Pass the good news to a friend.

IX. **Thou shalt avoid gluttony with food and alcohol.**
Excessive alcohol and elevated cholesterol or triglycerides are bad for the brain.

X. **Thou shalt find a good doctor and follow their advice.**
Smart doctors and wonder drugs are not beneficial when the advice and the medication sit in the medicine cabinet.