

BÖLÜM 4

ALZHEİMER HASTALIĞI TEDAVİSİ

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TANIM VE KLİNİK

Alzheimer hastalığı (AH) daha çok yaşlı bireyleri etkileyen ve mekanizması ve sebebi tam olarak açıklanamayan nörodejeneratif bir hastalıktır. 2011 yılındaki verilere göre dünyada 24 milyon kişide demans olduğu düşünülmektedir. İleri yaş grubunda hastada demansın sebebinin multifaktöriyel olduğu ve serebrovasküler hadiselerin demans etyolojisinde önemli bir yeri olduğu gözlenmekle beraber AH günümüzde demansın en sık sebebi olarak kabul edilmektedir (1).

Medial temporal atrofi (MTA), demansın erken görüntüleme bulguları arasında olup, kesitsel çalışmalarda medial temporal atrofinin preklirik AH döneminde ortaya çıktığı gösterilmiştir. Yine preklirik evrede hipokampal volüm kaybının AH'nın progresyonuna işaret edebileceği gösterilmiştir. (Twamley ve ark. 2006) (2). Temporal ve neokortikal yapılar ile ilişkili olduğu düşünülen güncel hafıza AH'da belirgin olarak etkilenirken, karar verme ve motor öğrenme sorunları hastalığın geç dönemlerine kadar ortaya çıkmayabilir. Hafıza bozukluğu, AH'nın en sık ve sıklıkla da en erken bulgusu olmakta beraber hastalar, davranışlarında değişme, kendini toplumdan soyutlama, anksiyete ve irritabilite, günlük yaşam

KAYNAKLAR

- Adolfsson O, Pihlgren M, Toni N, Varisco Y, Buccarello AL, Antonello K, Lohmann S, Piorkowska K, Gafner V, Atwal JK, Maloney J, Chen M, Gogineni A, Weimer RM, Mortensen DL, Friesenhahn M, Ho C, Paul R, Pfeifer A, Muhs A, Watts RJ. (2012) An effector-reduced anti- β -amyloid ($A\beta$) antibody with unique $a\beta$ binding properties promotes neuroprotection and glial engulfment of $A\beta$. *J Neurosci.*, 32(28):9677-89.
- Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF, Bottilieri T, Jin S, Stokes KT, Thomas RG, Thal LJ, Alzheimer Disease Cooperative Study (2008) High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. *JAMA*, 300(15):1774-83.
- Alves L, Correia AS, Miguel R, Alegria P, Bugalho P. (2012) Alzheimer's disease: a clinical practice-oriented review. *Front Neurol.* 3:63.
- Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E (2011) Alzheimer's disease. *Lancet*, 377(9770):1019-31.
- Ballard C, Waite J. (2006) The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. *Cochrane Database Syst. Rev.* (1):CD003476.
- Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues JF, Renaud S. (2002) Fish, meat, and risk of dementia: cohort study. *BMJ.*, 325(7370):932-3.
- Benitez BA, Karch CM, Cai Y, Jin SC, Cooper B, Carrell D, Bertelsen S, Chibnik L, Schneider JA, Bennett DA; Alzheimer's Disease Neuroimaging Initiative; Genetic and Environmental Risk for Alzheimer's Disease Consortium GERAD, Fagan AM, Holtzman D, Morris JC, Goate AM, Cruchaga C. (2013) The PSEN1, p.E318G variant increases the risk of Alzheimer's disease in APOE- ϵ 4 carriers. *PLoS Genet.*, 9(8):e1003685:1-15.
- Birks J, Grimley Evans J. (2009) Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev.*, (1):CD003120.
- Birks J, Grimley Evans J, Iakovidou V, Tsolaki M, Holt FE (2009) Rivastigmine for Alzheimer's disease. *Cochrane Database Syst Rev.* 2009. Apr 15;(2):CD001191.
- Blasko I, Apochal A, Boeck G, Hartmann T, Grubeck-Loebenstien B, Ransmayr G. (2001) Ibuprofen decreases cytokine-induced amyloid beta production in neuronal cells. *Neurobiology of Disease*, 8(6):1094-1101.
- Bohlsón SS, Fraser DA, Tenner AJ. (2007) Complement proteins C1q and MBL are pattern recognition molecules that signal immediate and long-term protective immune functions. *Molecular Immunology*, 44(1-3):33-43.
- Bonin-Guillaume S, Martin G, Zafack J, Gentile G, Allaria-Lapierre V, Sciortino V, Thirion X, Micallef J. (2014) Antipsychotic use in the cohort PACA-Alz in patients with Alzheimer's disease and other dementia in 2010. *Therapie*, 69(3):213-22.

- Braak H, Thal DR, Ghebremedhin E, Del Tredici K. (2011) Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol.*, 70(11):960-9.
- Breitner JC1, Baker LD, Montine TJ, Meinert CL, Lyketsos CG, Ashe KH, Brandt J, Craft S, Evans DE, Green RC, Ismail MS, Martin BK, Mullan MJ, Sabbagh M, Tariot PN; ADAPT Research Group (2011) Extended results of the Alzheimer's disease anti-inflammatory prevention trial. *The Journal of the Alzheimer's Association*, 7(4): 402–411.
- Canevelli M, Adali N, Kelaiditi E, Cantet C, Ousset PJ, Cesari M; ICTUS/DSA Group. (2014) Effects of Gingko biloba supplementation in Alzheimer's disease patients receiving cholinesterase inhibitors: data from the ICTUS study. *Phytomedicine*, 21(6):888-92.
- Cederholm T, Salem N Jr, Palmblad J. (2013) ω -3 fatty acids in the prevention of cognitive decline in humans. *Adv Nutr.*, 4(6):672-6.
- Cerhan JH, Ivnik RJ, Smith GE, Tangalos EC, Petersen RC, Boeve BF (2002) Diagnostic utility of letter fluency, category fluency, and fluency difference scores in Alzheimer's disease. *Clin Neuropsychol*, 16(1):35-42.
- Chen KH, Reese EA, Kim HW, Rapoport SI, Rao JS. (2011) Disturbed Neurotransmitter Transporter Expression in Alzheimer Disease Brain. *J Alzheimers Dis.*, 26(4):755-66.
- Courtney C, Farrell ID, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, Lendon C, Shaw H, Bentham P, AD2000 Collaborative Group (2004) Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet*, 363(9427):2105-15.
- Cutuli D, De Bartolo P, Caporali P, Tartaglione AM, Oddi D, D'Amato FR, Nobili A, D'Amelio M, Petrosini L. (2013) Neuroprotective effects of donepezil against cholinergic depletion. *Alzheimers Res Ther.*, 5(5):50.
- Dangour AD, Allen E, Elbourne D, Fasey N, Fletcher AE, Hardy P, Holder GE, Knight R, Letley L, Richards M, Uauy R. (2010) Effect of 2-y n-3 long-chain polyunsaturated fatty acid supplementation on cognitive function in older people: a randomized, double-blind, controlled trial. *Am J Clin Nutr.*, 91(6):1725–32.
- Davinelli S, Intrieri M, Russo C, Di Costanzo A, Zella D, Bosco P, Scapagnini G. (2011) The "Alzheimer's disease signature": potential perspectives for novel biomarkers. *Immun Ageing.*, 8:7.
- Dehghani L, Meamar R, Askari G, Khorvash F, Shaygannejad V, Pour AF, Javanmard SH. (2013) The effect of pioglitazone on the Alzheimer's disease-induced apoptosis in human umbilical vein endothelial cells. *Int J Prev Med.*, 4(Suppl 2): S205-10.
- DeKosky ST, Ikonomic MD, Styren SD, Beckett L, Wisniewski S, Bennett DA, Cochran EJ, Kordower JH, Mufson EJ (2002) Up-regulation of choline acetyl-

- ransferase activity in hippocampus and frontal cortex of elderly subjects with mild cognitive impairment. *Ann Neurol*, 51(2): 145-155.
- del Ser T, Steinwachs KC, Gertz HJ, Andrés MV, Gómez-Carrillo B, Medina M, Vericat JA, Redondo P, Fleet D, León T. (2013) Treatment of Alzheimer's disease with the GSK-3 inhibitor tideglusib: a pilot study. *J Alzheimers Dis.* 33(1):205-15.
- DeLaGarza VW (2003). Pharmacologic treatment of Alzheimer's disease: an update. *Am Fam Physician*, 68(7):1365-72.
- Ding Q, Dimayuga E, Keller JN. (2007) Oxidative damage, protein synthesis, and protein degradation in Alzheimer's disease. *Curr Alzheimer Res.*, 4(1):73-9
- Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD (2001) Donepezil Study Group Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol.* 58(3):427-33.
- Douaud G, Refsum H, de Jager CA, Jacoby R, Nichols TE, Smith SM, Smith AD (2013) Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. *Proc Natl Acad Sci USA.*, 110(23):9523-8.
- Dunn NR, Pearce GL, Shakir SA. (2000) Adverse effects associated with the use of donepezil in general practice in England. *J Psychopharmacol.*, 14(4):406-8.
- Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, Love S, Schellenberg GD, McCarten JR, Malphurs J, Prieto S, Chen P, Loreck DJ, Trapp G, Bakshi RS, Mintzer JE, Heidebrink JL, Vidal-Cardona A, Arroyo LM, Cruz AR, Zachariah S, Kowall NW, Chopra MP, Craft S, Thielke S, Turvey CL, Woodman C, Monnell KA, Gordon K, Tomaska J, Segal Y, Peduzzi PN, Guarino PD. (2014) Effect of Vitamin E and Memantine on Functional Decline in Alzheimer Disease The TEAM-AD VA Cooperative Randomized Trial. *JAMA*, 311(1):33-44.
- Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, Witteman JC, Breteler MM. (2002) Diet and risk of dementia. Does fat matter? The Rotterdam Study. *Neurology*, 59(12):1915-21.
- Espeland MA, Rapp SR, Shumaker SA, Brunner R, Manson JE, Sherwin BB, Hsia J, Margolis KL, Hogan PE, Wallace R, Dailey M, Freeman R, Hays J (2004) Conjugated equine estrogens and global cognitive function in postmenopausal women: Women's Health Initiative Memory Study. *JAMA*, 291(24):2959-68.
- Farlow MR, Salloway S, Tariot PN, Yardley J, Moline ML, Wang Q, Brand-Schieber E, Zou H, Hsu T, Satlin A, (2010) Effectiveness and tolerability of high-dose (23 mg/d) versus standard-dose (10 mg/d) donepezil in moderate to severe Alzheimer's disease: A 24-week, randomized, double-blind study. *Clin Ther.*, 32(7):1234-51.
- Feldman HH, Doody RS, Kivipelto M, Sparks DL, Waters DD, Jones RW, Schwam E, Schindler R, Hey-Hadavi J, DeMicco DA, Breazna A, LEADe Investigators

- (2010) Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology*, 74(12):956-64.
- Freund-Levi Y, Vedin I, Hjorth E, Basun H, Faxén Irving G, Schultzberg M, Eriksson M, Palmblad J, Vessby B, Wahlund LO, Cederholm T, Basu S. (2014) Effects of Supplementation with Omega-3 Fatty Acids on Oxidative Stress and Inflammation in Patients with Alzheimer's Disease: The OmegAD Study. *J Alzheimers Dis.*, 42(3):823-31.
- Gauthier S, Molinuevo JL (2013) Benefits of combined cholinesterase inhibitor and memantine treatment in moderate-severe Alzheimer's disease. *Alzheimers Dement*, 9(3):326-31.
- Gauthier S, Schlaefke S. (2014) Efficacy and tolerability of Ginkgo biloba extract EGb 761® in dementia: a systematic review and meta-analysis of randomized placebo-controlled trials. *Clin Interv Aging.*, (9):2065-77.
- Gorno-Tempini ML, Dronkers NF, Rankin KP, Ogar JM, Phengrasamy L, Rosen HJ, Johnson JK, Weiner MW, Miller BL. (2004) Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*, 55(3):335-46.
- Grantham C, Geerts H (2002) The rationale behind cholinergic drug treatment for dementia related to cerebrovascular disease. *J Neurol Sci*, 203-204: 131-136.
- Gröber U, Kisters K, Schmidt J. (2013) Neuroenhancement with vitamin B12-underestimated neurological significance. *Nutrients*, 5(12):5031-45.
- Harwood DG, Sultzer DL, Wheatley MV (2000) Impaired insight in Alzheimer disease: association with cognitive deficits, psychiatric symptoms, and behavioral disturbances. *Neuropsychiatry Neuropsychol Behav Neurol*, 13(2):83-8.
- Higgins GC, Beart PM, Shin YS, Chen MJ, Cheung NS, Nagley P. (2010) Oxidative stress: emerging mitochondrial and cellular themes and variations in neuronal injury. *J Alzheimers Dis.*, 20 (Suppl 2):S453-73.
- Hogervorst E, Yaffe K, Richards M, Huppert FA. (2009) Hormone replacement therapy to maintain cognitive function in women with dementia. *Cochrane Database Syst Rev.*, 2009;(1):CD003799.
- Holmes C, Boche D, Wilkinson D, Yadegarfar G, Hopkins V, Bayer A, Jones RW, Bullock R, Love S, Neal JW, Zotova E, Nicoll JA. (2008) Long-term effects of A β_{42} immunisation in Alzheimer's disease: follow-up of a randomised, placebo-controlled phase I trial. *The Lancet*, 372(9634):216-23.
- Holtzman DM (2011) CSF biomarkers for Alzheimer's disease: current utility and potential future use. *Neurobiol Aging*, 32 (Suppl. 1): S4-9.
- Hölscher C. (2014) The incretin hormones glucagonlike peptide 1 and glucose-dependent insulintropic polypeptide are neuroprotective in mouse models of Alzheimer's disease. *Alzheimers Dement.*, 10(1 Suppl):S47-54.
- Hundae A, Afzal A, Assar MD, Schussler JM. (2014) Syncope secondary to second-degree atrioventricular block with donepezil use. *Proc (Bayl Univ Med Cent)*, 27(4):325-6.

- Jamshed N, Ozair FF, Aggarwal P, Ekka M. (2014) Alzheimer disease in post-menopausal women: Intervene in the critical window period. *J Midlife Health*, 5(1):38-40.
- Kennelly S, Abdullah L, Kenny RA, Mathura V, Luis CA, Mouzon B, Crawford F, Mullan M, Lawlor B. (2012) Apolipoprotein E genotype-specific short-term cognitive benefits of treatment with the antihypertensive nilvadipine in Alzheimer's patients-an open-label trial. *Int J Geriatr Psychiatry*, 27(4):415-22.
- Lannfelt L, Möller C, Basun H, Osswald G, Sehlin D, Satlin A, Logovinsky V, Gellerfors P. (2014) Perspectives on future Alzheimer therapies: amyloid- β protofibrils - a new target for immunotherapy with BAN2401 in Alzheimer's disease. *Alzheimers Res Ther.*, 6(2):16.
- Liu YH, Wang YR, Xiang Y, Zhou HD, Giunta B, Mañucat-Tan NB, Tan J, Zhou XF, Wang YJ. (2014) Clearance of Amyloid-Beta in Alzheimer's Disease: Shifting the Action Site from Center to Periphery. *Mol Neurobiol.*, Epub: 2014 Apr 15.
- Marczinski CA, Kertesz A. (2006) Category and letter fluency in semantic dementia, primary progressive aphasia, and Alzheimer's disease. *Brain Lang*, 97(3):258-65.
- Mazereeuw G, Lanctôt K, Chau SA, Swardfager W, Hermann N (2012) Effects of omega-3 fatty acids on cognitive performance: a meta-analysis. *Neurobiol Aging*, 33(7):1482.e17-29.
- McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.*, 7(3):263-9.
- Mendez MF, M.D.Shapira JS (2011) Loss of emotional insight in behavioral variant frontotemporal dementia or "frontal anosodiaphoria". *Conscious Cogn.*, 20(4):1690-6.
- Menting KW, Claassen JA. (2014) β -secretase inhibitor; a promising novel therapeutic drug in Alzheimer's disease. *Front Aging Neurosci.* 6:165.
- Miyoshi I, Fujimoto Y, Yamada M, Abe S, Zhao Q, Cronenberger C, Togo K, Ishibashi T, Bednar MM, Kupiec JW, Binneman B. (2013) Safety and pharmacokinetics of PF-04360365 following a single-dose intravenous infusion in Japanese subjects with mild-to-moderate Alzheimer's disease: a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study. *Int J Clin Pharmacol Ther.*, 51(12):911-23.
- Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. (2005) Fish consumption and cognitive decline with age in a large community study. *Arch Neurol.*, 62(12):1849-53.

- Novakovic D, Feligioni M, Scaccianoce S, Caruso A, Piccinin S, Schepisi C, Errico F, Mercuri NB, Nicoletti F, Nisticò R. (2013) Profile of gantenerumab and its potential in the treatment of Alzheimer's disease. *Drug Des Devel Ther.*, 7: 1359–1364.
- Parsons CG, Danyysz W, Dekundy A and Pulte I. (2013) Memantine and Cholinesterase Inhibitors: Complementary Mechanisms in the Treatment of Alzheimer's Disease. *Neurotox Res.* 24(3): 358–369.
- Portet F, Scarmeas N, Cosentino S, Helzner EP, Stern Y (2009) Extrapiramidal signs before and after diagnosis of incident Alzheimer disease in a prospective population study. *Arch Neurol.*, 66(9):1120-6.
- Quental NB, Brucki SM, Bueno OF. (2013) Visuospatial Function in Early Alzheimer's Disease - The Use of the Visual Object and Space Perception (VOSP) Battery. *PLoS One*, 8(7):e68398.
- Rockwood K, Fay S, Song X, MacKnight C, Gorman M. Video-Imaging Synthesis of Treating Alzheimer's Disease (VISTA) Investigators (2006) Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. *CMAJ.*, 174(8):1099-105.
- Rowland JP, Rigby J, Harper AC, Rowland R. (2007) Cardiovascular monitoring with acetylcholinesterase inhibitors: a clinical protocol. *Advances Psych Treatment*, 13:178–184
- Rubio-Perez JM, Morillas-Ruiz JM (2012) A Review: Inflammatory Process in Alzheimer's Disease, Role of Cytokines. *ScientificWorldJournal*, 2012: 756357.
- Rubio-Perez JM, Morillas-Ruiz JM. (2012) A review: inflammatory process in Alzheimer's disease, role of cytokines. *ScientificWorldJournal*, 756357.
- Sano M, Bell KL, Galasko D, Galvin JE, Thomas RG, van Dyck CH, Aisen PS (2011) A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology*, 77(6):556-63.
- Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. (2006) Plasma phosphatidylcholine docosahexaenoic acid content and risk of dementia and Alzheimer disease: the Framingham Heart Study. *Arch Neurol.*, 63(11):1545–50.
- Seltzer B. (2010) Galantamine-ER for the treatment of mild-to-moderate Alzheimer's disease. *Clin Interv Aging*, 5:1-6
- Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. (2011) Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med.*, 1(1):a006189:1-23.
- Seshadri S. Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. (2002) Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N. Engl. J. Med.*, 346(7):476–483.
- Shao H, Breitner JC, Whitmer RA, Wang J, Hayden K, Wengreen H, Corcoran C, Tschanz J, Norton M, Munger R, Welsh-Bohmer K, Zandi PP; Cache County

- Investigators (2012) Hormone therapy and Alzheimer disease dementia: new findings from the Cache County Study. *Neurology*, 79(18):1846-52.
- Shinohara M , Sato N , Shimamura M , Kurinami H , Hamasaki T , Chatterjee A , Rakugi H , Morishita R (2014) Possible modification of Alzheimer's disease by statins in midlife: interactions with genetic and non-genetic risk factors *Front Aging Neurosci.*, 6: 71.
- Shulman KI. (2000) Clock-drawing: is it the ideal cognitive screening test? *Int J Geriatr Psychiatry* 15(6):548-61.
- Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, Hendrix SL, Jones BN 3rd, Assaf AR, Jackson RD, Kotchen JM, Wassertheil-Smoller S, Wactawski-Wende J, WHIMS Investigators (2003) Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized controlled trial. *JAMA*, 289(20):2651-62.
- Steenland K, Zhao L, Goldstein FC, Levey AI. (2013) Statins and cognitive decline in older adults with normal cognition or mild cognitive impairment. *J Am Geriatr Soc.* 61(9):1449-55.
- Sultzer DL, Davis SM, Tariot PN Dagerman KS, Lebowitz BD, Lyketsos CG, Rosenheck RA, Hsiao JK, Lieberman JA, Schneider LS, CATIE-AD Study Group (2008) Clinical symptom responses to atypical antipsychotic medications in Alzheimer's Disease : phase 1 outcomes from the CATIE-AD effectiveness trial . *Am J Psychiatry*, 165 (7) : 844-85.
- Tan ZS, Harris WS, Beiser AS, Au R, Himali JJ, Debette A, Pikula A, DeCarli C, Wolf PA, Vasan RS. Robins SJ, Seshadri S, (2012) Red blood cell omega-3 fatty acid levels and markers of accelerated brain aging. *Neurology*, 78(9):658-64.
- Teipel SJ, Flatz WH, Heinsen H, Bokde AL, Schoenberg SO, Stockel S, Dietrich O, Reiser MF, Moller HJ, Hampel H. (2005) Measurement of basal forebrain atrophy in Alzheimer's disease using MRI. *Brain*, 128(11): 2626-44.
- Terry AV Jr, Buccafusco JJ. (2003) The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. *J Pharmacol Exp Ther.*, 306(3):821-7.
- Twamley EW, Ropacki SA, Bondi MW (2006) Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society*, 12(5):707-35.
- Van de Rest O, Geleijnse JM, Kok FJ, van Staveren A, Hoefnagels WH, Beekman AT, de Groot CP. (2008) Effect of fish oil on cognitive performance in older subjects. A randomized, controlled trial. *Neurology*, 71(6):430-8.
- Vogiatzoglou A. Refsum H, Johnston C, Smith SM, Bradley KM, de Jager C, Budge MM, Smith AD. (2008) Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. *Neurology*, 71:826-832.

- Wharton W, Baker LD, Gleason CE, Dowling M, Jodi H. Barnet JH, Carlsson C, Craft S, and Asthana S (2011) Short-term Hormone Therapy with Transdermal Estradiol Improves Cognition for Postmenopausal Women with Alzheimer's Disease: Results of a Randomized Controlled Trial *J Alzheimers Dis.*, 26(3): 495–505.
- Winblad B, Cummings J, Andreasen N, Grossberg G, Onofrij M, Sadowsky C, Zechner S, Nagel J, Lane R (2007) A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease-rivastigmine patch versus capsule. *Int J Geriatr Psychiatry*, 22(5):456-67.
- Winblad B, Grossberg G, Frölich L, Farlow M, Zechner S, Nagel J, Lane R. (2007) IDEAL: a 6-month, double-blind, placebo-controlled study of the first skin patch for Alzheimer disease. *Neurology*, 69(4 Suppl 1):S14-22.
- Winslow BT, Onysko MK, Stob CM, Hazlewood KA. (2011) Treatment of Alzheimer disease. *Am Fam Physician*, 83(12):1403-12.