Available online on www.ijcpr.com
International Journal of Current Pharmaceutical Review and Research; 8(3); 266-271
doi: 10.25258/ijcprr.v8i03.9216
ISSN: 0976 822X

Review Article

Neurological Effects of Proton Pump Inhibitors- A Review

Patil T R[1*], Patil ST[2], Patil S[3], Patil A[4]

[1]*Department of Pharmacology, Bharati Medical College and Hospital, Sangli, Maharashtra, India*
[2]*MBBS, DGO, Gynecologist*
[3]*Department of Public Health Dentistry, School of Dental Sciences, Karad, Maharashtra, India*
[4]*MDS, Oral pathologist*

Available Online: 17th June, 2017

ABSTRACT

Proton pump inhibitors [PPIs] are extensively used drugs for various indications. They are not approved for long term use by regulatory authorities. PPIs are also available as over the counter drugs which can lead to their inappropriate use. Amongst the adverse drug reactions [ADRs] of PPIs, dementia and Alzheimers disease [AD] are the recent ones. Inappropriate long term use of PPIs can lead to serious ADRs like myocardial infarction, nephropathy along with dementia. The possible mechanisms for PPIs induced dementia and AD are endothelial dysfunction, its aging and senescence. Effect on lysosomal function and proteostasis, shortening of telomere length, and inhibition of vacuolar ATPases [V-ATPases] of microglial lysosomal membrane also contribute for this pathology. Increased generation of beta amyloid [Aβ] peptide by inverse gama secretase modulation and augmentation of beta secretase are responsible for the generation and accumulation of Aβ along with its decreased degradation as a result of inhibition of V-ATPases in the microglia. Vitamin B 12 absorption is decreased due to long term use of PPIs. This also contributes for nerve damage as a result of impaired DNA synthesis, methylation and homocysteine neurotoxicity along with cognition impairment. Seizure like condition can be the result of hypomagnesemia induced by long term PPIs use. Thus long term, inappropriate use of PPIs invite serious and life threatening conditions which need to be kept in mind by the clinician before prescribing them.

Keywords: Alzheimers disease, Proton pump inhibitors, hypomagnesemia.

INTRODUCTION

Proton pump inhibitors [PPIs] are extensively used drugs in gastroesophageal reflux and acid peptic disorders, erosive oesophagitis, non steroidal anti inflammatory drug induced gastritis, Helicobactor pylori infection and Zollinger-Ellison syndrome[1,2]. They inhibit the release of gastric acid from parietal cells by blocking hydrogen potassium adenosine triphosphatase [H^+K^+ATPase] pump-proton pump[3,4]. Along with blocking H^+K^+ATPase they also block vacuolar ATPases at various sites including those in the brain microglial cells. PPIs are observed to cross blood brain barrier[5,6].

In countries like United states PPIs are available as over the counter drugs. They are not approved for long term use by regulatory authorities. Available evidence suggests that there is an inappropriate use of these drugs[7,8,9]. Though PPIs are considered safe drugs and enjoy eighth position in the list of commonly prescribed drugs, studies have shown that about 25-70% of patients taking PPIs have no appropriate and confirmed indications[10-12] .

Along with other adverse drug reactions, PPIs are found to have serious reactions like myocardial infarction, dementia and renal failure[13-16]. Out of these ADRs of PPI dementia is quite a recently observed one. Elderly patients are exposed to PPIs therapy to prevent or counteract gastrointestinal adverse effects of concurrent drugs used. This overuse of PPIs can invite serious adverse drug reactions like dementia and alzheimers disease [AD] [17,18].

Number of PPI prescriptions have shown four-fold increase in last 10 years[19]. Significant inappropriate prescriptions of PPIs were noted in the aged patients having dementia where they were used in maximum therapeutic doses for more than 8 weeks[20].

Dementia is characterized by decline in cognitive function mainly seen old people. Diabetes mellitus, obesity hypertension and smoking are the potential risk factors for dementia[21,22]. Recent studies have suggested that PPIs could be another potential risk factor for dementia and cognitive decline. It was found that there was a small increased risk of dementia in chronic PPI users than nonusers[16,23-25].

The global prevalence of dementia is likely to increase to more than 80 million people in 2040 as compared to 35 million in year 2016[26,27]. Dementia creates a huge burden on the health care system and financial status[28]. Hence the reduction in the incidence of dementia in terms of primary prevention is important[29]. Finding out the causative and precipitating factors including the drugs, deserves special attention.

*Author for Correspondence: drpatiltr@gmail.com

PPIs like lansoprazole and omeprazole have been reported to cross blood brain barrier and hence can have action on brain cells[30,31,32].

Haenisch et al observed that patients receiving long term PPIs therapy had significantly increased risk of dementia as well as AD[24]. AD is a progressive neurodegenerative disorder characterized by dementia, impairment of memory, language and general intellectual activity[27]. Accumulation of amyloid beta[Aβ] oligomers form insoluble plaques in the brain cells triggering the formation of cytotoxic inflammatory cytokines and reactive oxygen species. This results in neurodegeneration and hamper the brain function[33].

Possible pathogenesis of dementia and AD induced by PPIs could be as follows.

Effect of PPI on lysosomal function and proteostasis

Studies have shown that PPIs impaired endothelial lysosomal acidification, proteostasis and enzyme activity[34]. Disturbed proteostasis results in to deteriorated cell function and accelerated cell aging[35-37]. To complete the process of autophagy the binding of lysosome to autosome is needed[38]. This helps in degradation and elimination of unwanted cellular products including misfolded proteins[39]. Impaired lysosomal acidification and reduced lysosomal enzyme activity results in to an accumulation of protein aggregate. The accumulation of protein aggregate is associated with endothelial dysfunction, increased oxidative stress and endothelial cell senescence[40-42].

Effect of PPI on endothelial function

Endothelial cell [EC] dysfunction plays a major role in the pathogenesis of disorders like myocardial infarction, renal damage and dementia[40-42]. Decrease in nitric oxide [NO] production by endothelial cells and generation of superoxide anions are the features of endothelial dysfunctions[43-45]. Vascular senescence provides rational explaination for vascular pathologies involved in cardiovascular and renal diseases and also for dementia[13-16].

PPI like esomeprazole [ESO] could produce decreased endothelial NO generation, DDAH 1 and 2, eNOS and iNOS. NO dependent angiogenesis and cell proliferation is impaired by long term use of ESO in dose dependent manner. It also increased the expression of cell cycle inhibition gene p21. Thus, PPIs affect various functions adversely[34].

PPI enhance endothelial ageing and senesence

Hallmark of cellular senescence are reduced cell proliferation and impaired proteostsis[37,46]. When cells were treated chronically with ESO and were observed for senescence, it was found that beta galactosidase [SA-beta-gal] positive cells were increased with decrease in total cell count per microscopic field. Cell morphology was changed to that of fried egg appearance which is a characteristic of EC senescence. Expression of genes related to senescence of EC were increased. These were the increased expression of genes involved in endothelial to mesenchymal transition [EndoMT], inflammation and increased oxidative stress. Genes associated with EndoMT including TWIST 1, COLIA 1 and SMAD 3 were upregulated. After treatment with ESO, plasminogen activator inhibitor 1 [PAI-1], a well known marker of endothelial dysfunction characterized by increased thrombogenecity, immune activation, oxidative stress and cellular senescence, was upregulated. Thus chronic exposure of PPIs induce endothelial dysfunction consistent with EndoMT and senescence[34].

Effect of PPI on telomere length

Attrition of telomere length is suggestive of endothelial senescence[46]. In ESO treated group there was significant decrease in telomere length as compared to the control. This was associated with downregulation of genes like TRF 1, TRF 2, POT 1, RAP 1 and TIN 2 of shelterin complex involved in the maintenance of telomere length and function[34].

Thus, long term use of PPIs impairs acidification of lysosomes and enzyme activity associated with accumulation of protein aggregates, impair endothelial NO release and increase the generation of reactive oxygen species. There is an acceleration of telomere erosion with downregulation of genes of shelterin complex. It also enhances endothelial aging suggested by impaired angiogenesis and cell proliferation along with histological markers of EndoMT and endothelial senescence. EndoMT is a measure of endothelial cell senescence and plays an important role in diseases characterized by fibrosis and loss of vasculature like those of cardiovascular and other disorders. Long term exposure to PPIs upregulate the genes involved in EndoMT.

Role of vacuolar ATPase proton pumps in AD

Abnormal generation of amyloid beta peptide plays an important role in the pathogenesis of AD[47]. Microglia in the brain are the mononuclear phagocytic cells[48]. They have acidic lysosomes and can engulf and digest amyloid beta peptides[48]. For optimal function, lysosomal proteases should have acidic environment. But in patients of AD lysosomes of microglia are less acidic than that of the normal one. Thereby they have less capacity to clear ABP. Lyosomal pH in the microglia is regulated by vacuolar proton pumps [V-ATPase] which pump protons from cytoplasm to the lumen of the vacuoles or in to the extracellular space. The B and E subunits of the V-ATPase present in the microglia and macrophages play an important role in the acidification of lysosomes of these cells.

PPIs have been shown to cross the blood brain barrier and enter CNS[30,31]. It has been demonstrated that PPIs can block V- ATPase of lysosomal membranes and make lysosomal pH less acidic. PPIs given for long term inhibit V-ATPases on the lysosomal membranes of microglia, decrease acidification of lysosomes and hinder the process of degradation of abnormal ABP. Acidic vacuolar pH is essential for degradation and clearance of AB peptide[49,50]. Thus chronic PPI therapy proves to be a potential risk factor for AD.

Increased Aβ generation by PPI

Lansoprazole and other PPIs could increase Aβ levels not only in cell culture but in mice also. PPIs like

lansoprazole have been reported to cross the blood brain barrier and affect brain tissue[32].

Badiole et al showed that PPIs can interact with the brain enzyme and observed the increased Aβ levels in the brains of mice treated with these drugs[51]. It was suggested that inverse gama secretase modulation and augmentation of beta secretase BACE 1 activity can lead to accumulation of Aβ peptide[51].

Alzheimers disease is a neurodegenerative disorder characterized by extracellular deposition of amyloid beta [Aβ] peptide in the brain leading to oxidative stress and inflammatory damage resulting into synaptic dysfunction and energy failure[52,49].

Proteases like beta and gama secretases sequentially cleave amyloid precursor protein [APP] and produce Aβ 42 and Aβ 40.In the pathogenesis of AD, Aβ 42 is the main pathological species[51,53]. Severity of dementia is correlated to the soluble form of Aβ than the fibriller one[54-57]. Brain oligomeric Aβ correlates with the neuronal loss and astrocyte inflammatory response than total amyloid plaque burden[58]. Aβ oiligomers are found to alter dendritic spine density and affect synaptic plasticity of hippocampus[59-63]. Direct association between oligomers and cognitive impairment is strongly observed[64-66].

In the experimental studies conducted, it was observed that production of Aβ 37, Aβ 40 and Aβ 42 were increased by pantaprazole in AD like cell model. It was hypothesized that lansoprazole could inversely modulate the gama secretase activity resulting in to higher Aβ 42 and lower Aβ 38 levels due to shifting of cleavage site[67].

Effect of PPI on vitamin B12 absorption:

Lam et al considered possible association between decreased cognition due to PPIs induced deficiency of vitamin B 12[68]. Chronic use of PPI can lead to suboptimal GI absorption of vitamin B12 resulting in to its deficiency[68]. Vitamin B12 deficiency is known to decrease cognition by impairing DNA synthesis, methylation and homocysteine neurotoxicity[69,70].

Vitamin B12 level in the blood is reduced as result of its decreased absorption due to chronic PPIs therapy. PPIs increase intragastric pH, inhibit intragastric proteolysis and the release of vitamin B 12 from food which is required prior to its binding to R proteins and gastric intrinsic factor for its adequate absorption. Risk of hypovitaminosis of B 12 is more in elderly and malnourished[68,71,72].

PPI induced Hypomagnesemia

PPI induced Hypomagnesemia was noted with long term use of PPIs and warning was also released by FDA in March 2011[73]. The symptoms of hypomagnesemia include seizure, tetany, cardiac arrhythmias and hypotension which can prove fatal sometimes[74]. Decreased absorption of magnesium was observed with all PPIs. Hypomagnesemia was more common with older patients having mean age of 64.4 years and mean time for the onset of hypomagnesemia was 5.5 years after the initiation of PPIs therapy. Hypomagnesemia was found to be associated with hypokalemia and hypocalcemia also[75] Withdrawal of PPIs was found to correct this deficiency[76]. Concurrent use of diuretics can potentiate the risk of hypomagnesemia[74]. Hence it is recommended that patients on chronic PPIs therapy should have regular monitoring of serum magnesium and also that of potassium and calcium.

Now there is a serious need to propogate the knowledge about the rational use of PPI as they are being used by millions of people for indications which are often never confirmed and the duration which were never tested and approved. It is the responsibility of prescriber and manufacturer of PPIs to stress the measures for the safety of the patients on PPIs therapy.

REFERENCES

1. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: what the clinician needs to know. Ther Adv Gastroenterol. 2012;5: 219–32.
2. Chubineh S, Birk J. Proton pump inhibitors: the good, the bad, and the unwanted. South Med J. 2012;105: 613–8.
3. Lew EA. Pharmacokinetic concerns in the selection of anti-ulcer therapy. Aliment Pharmacol Ther. 1999;13:11–6.
4. Norman A, Hawkey CJ. What you need to know when you prescribe a proton pump inhibitor. Frontline Gastroenterol. 2011; 2: 199–205.
5. Fallahzadeh MK, Borhani Haghighi A, Namazi MR. Proton pump inhibitors: predisposers to Alzheimer disease? J Clin Pharm Ther. 2010; 35: 125–6.
6. Majumdar A, Capetillo-Zarate E, Cruz D, Gouras GK, Maxfield FR. Degradation of Alzheimer's amyloid fibrils by microglia requires delivery of ClC-7 to lysosomes. Mol Biol Cell. 2011; 22: 1664–76.
7. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ. 2008; 336: 2–3.
8. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. Am J Gastroenterol. 2013; 108: 308-328.
9. Hollingworth S, Duncan EL, Martin JH. Marked increase in proton pump inhibitors use in Australia. Pharmacoepidemiol Drug Saf. 2010;19: 1019-1024.
10. Ksiądzyna D, Szeląg A, Paradowski L. Overuse of proton pump inhibitors. Pol Arch Med Wewn. 2015; 125: 289–98.
11. Pasina L, Nobili A, Tettamanti M, et al; REPOSI Investigators. Prevalence and appropriateness of drug prescriptions for peptic ulcer and gastro-esophageal reflux disease in a cohort of hospitalized elderly. Eur J Intern Med. 2011; 22: 205-210.
12. Heidelbaugh JJ, Goldberg KL, Inadomi JM. Magnitude and economic effect of overuse of antisecretory therapy in the ambulatory care setting. Am J Manag Care. 2010;16(9):e228-e234.
13. Shah NH, LePendu P, BauerMehren A, Ghebremaria m YT, Iyer SV, Marcus J, et al. Proton pump inhibitor usage and the risk of myocardial infarction in the general population. PLoS One. 2015;**10**:e0124653.
14. Ghebremariam YT, LePendu P, Lee JC, Erlanson DA, Slaviero A, Shah NH, et al. Unexpected effect of proton pump inhibitors: elevation of the

cardiovascular risk factor asymmetric dimethylarginine. Circulation. 2013;**128**:845–853.
15. Lazarus B, Chen Y, Wilson FP, Sang Y, Chang AR, C oresh J, Grams ME. Proton pumps inhibitor use and the risk of chronic kidney disease. JAMA Intern Med. 2016; 176: 238–246.
16. Gomm W, vonHolt K, Thomé F, Broich K, Maier W, Fink A, et al. Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA Neurol. 2016; 73: 410–416.
17. Laine L, Ahnen D, McClain C, Solcia E, Walsh JH. potential gastrointestinal effects of long-term acid suppression with proton pump inhibitors. Aliment Pharmacol Ther. 2000;14:651–68.
18. Thomson AB, Sauve MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. World J Gastroenterol. 2010;16: 2323–30.
19. Schwabe U, Paffrath D, eds. Arzneiverordnungs: Aktuelle Daten, Kosten, Trends und Kommentare. Berlin, Germany: Springer; 2014.
20. Parsons C, Johnston S, Mathie E, Baron N, Machen I, Amador S, et al. Potentially Inappropriate Prescribing in Older People with Dementia in Care Homes: A Retrospective Analysis. Drugs & Aging 2012; 29: 143–155.
21. Kawas CH. Clinical practice. Early Alzheimer's disease. N Engl J Med 2003; 349: 1056-63.
22. Barnes DE, Yaffe K. The projected effect of risk factor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10: 819-28.
23. Haenisch B, von Holt K, Wiese B, et al. Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci 2015;265:419-28.
24. Wise J. Proton pump inhibitors may be linked to dementia risk. BMJ 2016;352:i972.
25. Corsonello A, Maggio M, Fusco S, et al. Proton pump inhibitors and functional decline in older adults discharged from acute care hospitals. J Am Geriatr Soc 2014;62:1110-5.
26. Ferri CP, Prince M, Brayne C, et al; Alzheimer's Disease International. Global prevalence of dementia: a Delphi consensus study. Lancet. 2005; 366: 2112-2117.
27. Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol. 2011;7: 137-152.
28. Wimo A, Jönsson L, Bond J, Prince M, Winblad B; Alzheimer Disease International. The worldwide economic impact of dementia 2010. Alzheimers Dement. 2013;9:1-11.
29. Wu YT, Fratiglioni L, Matthews FE, et al. Dementia in western Europe: epidemiological evidence and implications for policy making. Lancet Neurol. 2016;15:116-124.
30. Cheng FC, Ho YF, Hung LC, Chen CF, Tsai TH. Determination and pharmacokinetic profile of omeprazole in rat blood, brain and bile by microdialysis and high-performance liquid chromatography. Journal of Chromatography A. 2002; 949, 35–42.
31. Shamburek RD, Schubert ML. Pharmacology of gastric acid inhibition. Bailliere's Clinical Gastroenterology. 1993; 7, 23–54.
32. Rojo LE, Alzate-Morales J, Saavedra IN, Davies P, Maccioni RB. Selective interaction of lansoprazole and astemizole with tau polymers: potential new clinical use in diagnosis of Alzheimer's disease. J Alzheimers Dis. 2010;19: 573-589.
33. Chiarini A, Dal Pra I, Whitfield JF, Armato U. The killing of neurons by β-amyloid peptides, prions, and pro-inflammatory cytokines. Ital J Anat Embryol. 2006;111: 221–46.
34. Yepuri G, Sukhovershin R, Nazari-Shafti T, Petrascheck M, Ghebre Y, John P. Proton Pump Inhibitors Accelerate Endothelial Senescence Cooke Circulation Research. 2016; 118: e36-e42.
35. Balch WE, Morimoto RI, Dillin A, Kelly JW. Adaptin g proteostasis for disease intervention.Science. 2008; 319: 916–919.
36. Ben-Zvi A, Miller EA, Morimoto RI. Collapse of proteostasis represents an early molecular event in *Caenorhabditis elegans* aging. Proc Natl Acad Sci U S A. 2009; 106:14914–14919.
37. Chondrogianni N, Fragoulis EG, Gonos ES. Protein degradation during aging: the lysosome-, the calpain- and the proteasome-dependent cellular proteolytic systems. Biogerontology.2002; 3: 121–123.
38. Gatica D, Chiong M, Lavandero S, Klionsky DJ. Mole cular mechanisms of autophagy in the cardiovascular system. Circ Res. 2015; 116: 456–467.
39. Liu W, Baker SS, Trinidad J, Burlingame AL, Baker RD, Forte JG, Virtuoso LP, Egilmez NK, ZhuL. Inhibi tion of lysosomal enzyme activities by proton pump inhibitors. J Gastroenterol.2013;48:1343–1352.
40. Goligorsky MS,. Pathogenesis of endothelial cell dysfunction in chronic kidney disease: a retrospective and what the future may hold. Kidney Res Clin Pract. 2015;34:76–82.
41. Di Marco LY, Venneri A, Farkas E, Evans PC, Marzo A, Frangi AF. Vascular dysfunction in the pathogenesis of Alzheimer's disease–a review of endothelium-mediated mechanisms and ensuing vicious circles. Neurobiol Dis. 2015;82:593–606.
42. Flammer AJ, Anderson T, Celermajer DS, Creager M A, Deanfield J, Ganz P, Hamburg NM,Lüscher TF, Sh echter M, Taddei S, Vita JA, Lerman A. The assessment of endothelial function: from research into clinical practice. Circulation. 2012;126:753–767.
43. Harrison DG. Cellular and molecular mechanisms of endothelial cell dysfunction. J Clin Invest.1997;100:2153–2157.
44. Rajapakse AG, Yepuri G, Carvas JM, Stein S, Matter CM, Scerri I, Ruffieux J, Montani JP, MingXF,Yang Z.. Hyperactive S6K1 mediates oxidative stress and endothelial dysfunction in aging: inhibition by resveratrol. PLoS One. 2011;6:e19237.

45. Cooke JP, Dzau VJ. Derangements of the nitric oxide synthase pathway, L-arginine, and cardiovascular diseases. Circulation. 1997;96:379–382
46. Lähteenvuo J, Rosenzweig A. Effects of aging on angiogenesis. Circ Res. 2012;110:1252–1264.
47. Archer HA, Edison P, Brooks DJ Barnes J, Frost C, Yeatman T et al. Amyloid load and cerebral atrophy in Alzheimer's disease: an 11C-PIB positron emission tomography study. Annals of Neurology, 2006; 60, 145–147.
48. Majumdar A, Cruz D, Asamoah N, Buxbaum A, Sohar I, Lobel P, et al. Activation of microglia acidifies lysosomes and leads to degradation of Alzheimer amyloid fibrils. Molecular Biology of the Cell, 2007; 18: 1490–1496.
49. Querfurth HW, LaFerla FM. Alzheimer's disease. N Engl J Med 2010;362:329-44.
50. Mattsson JP, Väänänen K, Wallmark B, et al. Omeprazole and bafilomycin, two proton pump inhibitors: differentiation of their effects on gastric, kidney and bone H(+)-translocating ATPases. Biochim Biophys Acta 1991;1065:261-8.
51. Badiola N, Alcalde V, Pujol A, Münter L-M, Multhaup G, Lleó A, et al. The proton-pump inhibitor lansoprazole enhances amyloid beta production. PLoS One. 2013; 8: e58837.
52. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002; 297: 353–356.
53. Younkin SG. The role of Aβ42 in Alzheimer's disease. Journal of Physiology-Paris 1998; 92: 289–292.
54. Wiltfang J, Esselmann H, Bibl M, Smirnov A, Otto M, et al. Highly conserved and disease-specific patterns of carboxyterminally truncated Aβ peptides 1–37/38/39 in addition to 1–40/42 in Alzheimer's disease and in patients with chronic neuroinflammation. Journal of Neurochemistry 2002; 81: 481–496
55. Pitschke M, Prior R, Haupt M, Riesner D. Detection of single amyloid beta-protein aggregates in the cerebrospinal fluid of Alzheimer's patients by fluorescence correlation spectroscopy. Nat Med 1998; 4: 832–834.
56. Lue L-F, Kuo Y-M, Roher AE, Brachova L, Shen Y, et al. Soluble Amyloid β Peptide Concentration as a Predictor of Synaptic Change in Alzheimer's Disease. The American Journal of Pathology. 1999; 155: 853–862.
57. McLean CA, Cherny RA, Fraser FW, Fuller SJ, Smith MJ, et al. Soluble pool of Abeta amyloid as a determinant of severity of neurodegeneration in Alzheimer's disease. Ann Neurol. 1999; 46: 860–866.
58. Gong Y, Chang L, Viola KL, Lacor PN, Lambert MP, et al. Alzheimer's disease-affected brain: Presence of oligomeric β ligands (ADDLs) suggests a molecular basis for reversible memory loss. Proceedings of the National Academy of Sciences 2003; 100: 10417–10422.
59. DaRocha-Souto B, Scotton TC, Coma M, Serrano-Pozo A, Hashimoto T, et al. Brain oligomeric beta-amyloid but not total amyloid plaque burden correlates with neuronal loss and astrocyte inflammatory response in amyloid precursor protein/tau transgenic mice. J Neuropathol Exp Neurol. 2011; 70: 360–376.
60. Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, et al. Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. Nat Neurosci 2005; 8: 79–84.
61. Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, et al. Diffusible, nonfibrillar ligands derived from Abeta1–42 are potent central nervous system neurotoxins. Proc Natl Acad Sci USA. 1998; 95: 6448–6453.
62. Walsh DM, Selkoe DJ. Aβ Oligomers– a decade of discovery. Journal of Neurochemistry. 2007; 101: 1172–1184.
63. Shrestha BR, Vitolo OV, Joshi P, Lordkipanidze T, Shelanski M, et al. Amyloid beta peptide adversely affects spine number and motility in hippocampal neurons. Mol Cell Neurosci. 2006; 33: 274–282.
64. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid [beta]-peptide. Nat Rev Mol Cell Biol 2007; 8: 101–112.
65. Fukumoto H, Tokuda T, Kasai T, Ishigami N, Hidaka H, et al. High-molecular-weight β-amyloid oligomers are elevated in cerebrospinal fluid of Alzheimer patients. The FASEB Journal 2010; 24: 2716–2726.
66. Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, et al. Amyloid-[beta] protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. Nat Med 2008; 14: 837–842.
67. Wang-Dietrich L, Funke SA, Kühbach K, Wang K, Besmehn A, et al. The Amyloid-β Oligomer Count in Cerebrospinal Fluid is a Biomarker for Alzheimer's Disease. Journal of Alzheimer's Disease 2013; 34:985-94.
68. Lam JR, Schneider JL, Zhao W, Corley DA. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA. 2013; 310: 2435-2442.
69. O'Leary F, Allman-Farinelli M, Samman S. Vitamin B12 status, cognitive decline and dementia: a systematic review of prospective cohort studies. Br J Nutr. 2012; 108: 1948-1961.
70. Reynolds E. Vitamin B12, folic acid, and the nervous system. Lancet Neurol. 2006; 5: 949-960
71. McColl KE. Effect of proton pump inhibitors on vitamins and iron**.** Am J Gastroenterol. 2009;104: S5-9.
72. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. *Therapeutic Advances in Drug Safety*. 2013;4:125-133.
73. FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton

Pump Inhibitor drugs (PPIs). https://www.fda.gov/Drugs/DrugSafety/ucm245011.htm accessed on 5th april 2017.

74. Danziger J, William JH, Scott DJ, Lee J, Lehman LW, Mark RG, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. Kidney Int. 2013; 83: 692-9.
75. Luk CP, Parsons R, Lee YP, Hughes JD. Proton pump inhibitor-associated hypomagnesemia: what do FDA data tell us? Ann Pharmacother. 2013; 47: 773-80.
76. Hess MW, Hoenderop JGJ, Bindels RJM, Drenth JPH. Systematic review: hypomagnesaemia induced by proton pump inhibition. Aliment Pharmacol Ther, 2012; 36: 405–413.