

PROLONGED USE OF PROTON PUMP INHIBITORS AND COGNITIVE FUNCTION IN OLDER ADULTS

ANNA MARIE HERGHELEGIU, GABRIEL IOAN PRADA*, RALUCA NACU

“Ana Aslan” National Institute of Geriatrics and Gerontology, 9 Căldărușani Str., Sector 1, Bucharest, Romania

**corresponding author: giprada@gmail.com*

Manuscript received: September 2015

Abstract

Dementia is an irreversible severe impairment of cognitive function associated with age, which ultimately leads to loss of independence and disability. Recent interest has been placed on potential pathological links between proton pump inhibitors (PPI) and the neuropathology of dementia. This study evaluates the relationship between long term use of PPIs (more than > 6 months/year and more than > 3 consecutive years) and cognitive function in a sample of 74 subjects, 65 years of age and older. The control group included an equal number of age-matched subjects. Patients in the study group had significantly lower Mini Mental State Examination (MMSE) ($p = 0.004$) and Clock Drawing Test (CDT) ($p = 0.02$) scores compared to age matched controls. Prolonged utilization of PPIs resulted in a significant increase of dementia risk after controlling for diabetes and hypertension in midlife (OR = 3.67; 95% CI; $p = 0.002$).

Rezumat

Demența reprezintă un deficit sever și ireversibil al funcției cognitive ce este asociat cu înaintarea în vârstă și are drept consecințe dizabilitatea și pierderea independenței în desfășurarea activităților zilnice. Există un interes crescut în ultimii ani privind potențiala implicare a inhibitorilor pompei de protoni (IPP) în mecanismele neuropatologice din demență. Acest studiu evaluează corelația dintre administrarea IPP pe termen lung (peste 6 luni/an timp de peste 3 ani consecutivi) și funcția cognitivă într-un grup de 74 de pacienți cu vârste de peste 65 de ani. Lotul martor a inclus un număr de 74 de subiecți cu vârste similare celor din grupul de studiu. Pacienții din grupul de studiu, care urmau tratament de lungă durată cu IPP, au avut scoruri semnificativ mai mici ale *Mini Mental State Evaluation* (MMSE) ($p = 0,004$) și *Clock Drawing Test* (TDC) ($p = 0,02$) comparativ cu grupul martor cu vârste similare, care nu au urmat astfel de terapie. Utilizarea pe termen lung a IPP a crescut semnificativ riscul de demență (OR = 3,67; 95% CI; $p = 0,002$).

Keywords: proton pump inhibitors, dementia, geriatric care, Mini Mental State Examination (MMSE), Clock Drawing Test (CDT)

Introduction

Dementia is one of the main determinants of disability in older age [1]. It mainly affects people of advanced age, and after the age of 65 years, its prevalence doubles with every five years age increment [1]. The prevalence of dementia in people aged 60 years and over is 5% - 8% and the number of people suffering from dementia across the world is expected to increase three times by 2050 [1, 2]. Neuropathological events start to develop decades before the clinical onset that could be seen as a critical point in brain damage accumulation over time. Gradual memory impairment, deficiencies in reasoning, logic and decision making, difficulties with language, behaviour and mood changes along with other cognitive function alterations are progressive and at present irreversible eventually leading to complete loss of independence in activities of daily living [2, 3].

Dementia syndrome is linked to a variety of conditions, the most frequent forms being Alzheimer's

disease (50% - 75%) and vascular dementia, recent opinions highlighting the mixed pathologic processes within the brain [4-6]. Structural cellular changes are present in most cases of dementia and consist of accumulation of amyloid β (A β) peptides organized into intercellular plaques and hyper phosphorylation of *tau* proteins resulting in microscopic appearance of intracellular tangles, which eventually lead to loss of synapses and ultimately cell death [7-9]. Recent interest has been placed on the potential involvement of proton pump inhibitors (PPIs) in dementia neuropathology. PPIs effectively suppress gastric acid secretion by inhibition of the H^+/K^+ ATPase present on the plasma membrane of the gastric parietal cells [10]. These drugs are widely used for the treatment of most acid-related conditions. Animal studies have demonstrated that PPIs can cross the blood-brain barrier [11] and block the vacuolar proton pumps on the lysosomal membrane of inflammatory cells including macrophages and potentially microglia, the mononuclear phagocytic system of the brain,

thus impeding degradation of fibrillary A β [12]. Recent *in vivo* and *in vitro* research has shown that PPIs use increased the levels of A β pathological species likely, by modulating secretase activity, although the underlying mechanisms are still unknown [13]. Another possible link between PPIs and dementia might be cobalamin deficiency. It has been shown that reduced levels of vitamin B12 and folic acid are associated with vascular disease and cognitive impairment [14-17]. Several studies have reported that vitamin B12 status is negatively affected by the prolonged use of PPIs [18-20].

Many studies conducted during the last decade have highlighted the over prescription and overutilization of PPIs, while people aged over 50 years old are the main chronic consumers of anti-secretory medication. This use does not commensurate with prevalence of gastro-oesophageal reflux disease or with prescribing guidelines for PPIs [21-24]. Self-medication, consumption of various drugs that do not require a medical prescription when purchased and without medical advice, is a wide spread phenomenon. In developing countries like Romania, the risk for this practice is even higher and closely related to the level of education and pharmaceutical products advertising, while governmental policies for health care play a key role in controlling the occurrence of self-medication [25, 26].

In this study we evaluated the effects of long-term use of PPIs on the cognitive function in a group of older subjects. This is one of the very few available clinical studies conducted on the potential risk of cognitive decline associated with prolonged use of PPIs in adults over 65 years old.

Materials and Methods

Prior to initiation, the study received approval from the Ethics Committee of the "Ana Aslan" National Institute of Gerontology and Geriatrics.

For this study, we recruited community dwelling patients over 65 years old, referred by general practitioners to the Geriatrics Outpatient Clinic of the "Ana Aslan" National Institute of Gerontology and Geriatrics, Bucharest, over a period of 8 months between 2014 and 2015. Out of a total number of 432 evaluated subjects, 89 were long-term users of PPIs defined as more than 6 months of continuous or nearly continuous administration of any PPI per year for the previous 3 years or more. After being checked against exclusion criteria, a total number of 74 participants were eligible for inclusion in the study group. Exclusion criteria were: prior diagnosis of dementia, hypothyroidism, chronic excessive alcohol consumption, Parkinson's disease, multiple sclerosis, clinical depression and terminal illness. As age is the most important risk factor for dementia [27], subjects in

the control group were age matched with the participants in the study group. The control group comprised an equal number of patients (74) without usage of PPIs during the previous 3 years and checked against the same exclusion criteria. The presence of diabetes mellitus (DM) and arterial hypertension (HT) in midlife were also recorded because these risk factors are the most consistently evidenced to be associated with dementia syndrome [27]. All exclusion criteria and the presence of DM and arterial HT in midlife (age 45 to 64) were identified from patients' medical records or from anamnesis. Patients who refused to sign the informed consent were also excluded.

Long-term use of PPIs was evaluated by directly interviewing the patients and was based on their reports. To identify the profile of PPIs utilisation we used a short questionnaire that included questions about the type of medication used by the patient, the manner in which the patient obtained the medication, the reason for using PPIs and also a question regarding the existence of a gastro-enterological examination prior to treatment initiation. The cognitive function was assessed with the modified short version of Mini Mental State Examination (MMSE) instrument and the Clock Drawing Test (CDT). The MMSE appraises time and space orientation, immediate and short-term recall, attention and calculation, the ability to follow verbal and written commands, language and visual construction [28]. The maximum score is 30 points, a score over 26 is considered normal and a score ≤ 25 indicates dementia [28, 29]. The CDT is a brief test that accounts for comprehension, planning, abstraction, visual memory and image reconstruction, motor programming, execution and concentration [30]. We have used the 10 points scoring system described by Sunderland *et al.* [31]. A score of at least 6 points is considered normal [31].

Descriptive statistics was used to present frequency distribution, means with standard deviation (SD) and median values with interquartile range (IQR) for MMSE and CDT scores. As the controls were age matched to the long-term PPI users, the data were analysed as paired data. Firstly, group differences in continuous variables were analysed with the Wilcoxon signed ranks test with 95% confidence interval (CI), as these variables were not normally distributed. The odds of developing dementia syndrome if exposed to prolonged use of PPIs were then evaluated in *conditional logistic regression models* according to the effects of DM and arterial HT in midlife. A multiple imputation technique was employed if $> 5\%$ of the outcome data were missing. All p-values are two-tailed and a $p < 0.05$ was considered statistically significant. The statistical analysis was performed using DATAPLOT.

Results and Discussion

The mean age in the study group was 76.3 years and 74.2 years in the control group, while women were predominant in both groups. The number of people with high levels of education (high-school, college or university) was somewhat higher in the control group. The presence of DM and arterial HT in midlife was comparable in both groups (Table I). The most frequently used PPI was omeprazole (58.1%) and the least frequently used was

lansoprazole (12.16%) (Table II). In most cases a prescription renewal was not present and most patients directly asked for a familiar PPI at the local pharmacy (Table II). Among reported reasons for PPIs consumption were "Frequent heartburns or stomach aches" and "It was prescribed by the doctor and I continued taking the medication" while in the majority of cases a gastroenterological check-up by a specialist prior to treatment initiation was absent (Table II).

Table I
Socio demographic characteristics in study and control groups

	Control group (n = 74) n (%) / Mean (SD)	Study group (n = 74) n (%) / Mean (SD)
Age	74.2 (10.3)	76.3 (8.7)
Women	49 (66.21)	57 (77.02)
Level of education: high-school or more	48 (64.86)	39 (52.70)
Diabetes Mellitus	11 (14.86)	15 (20.27)
Hypertension in midlife	12 (16.21)	9 (12.16)

Table II
Profile of PPIs consumption in the study group

	Type of PPI:	n/%
	omeprazole	43/58.10
	pantoprazole	12/16.21
	esomeprazole	10/13.51
	lansoprazole	9/12.16
	prescription	7/9.45
Acquired by:	direct purchase	67/90.55
Reasons for chronic consumption:	frequent gastric acid related symptoms	37/50
	continued treatment without medical re-evaluation	18/24.32
	gastric protection for other medication	15/20.27
	other reasons	4/5.41
Gastroenterological specialist check-up:	absent	56/75.67

The MMSE scores were significantly lower in the study group compared to control ($p = 0.004$) (Table III, Figure 1). Scores on CDT were also significantly lower in patients with chronic use of PPIs compared to controls ($p = 0.02$) (Table III). Dementia prevalence among long-term PPIs users was 24.32% whereas in controls was 10.81%. To investigate the potential relationship between prevalent dementia syndrome and long term use of PPIs, we used *conditional logistic regression models* where the effects of DM and arterial HT in midlife, independent risk factors for dementia, were controlled for. Prolonged utilization of gastric acid reducing agents increased the odds of developing dementia syndrome almost 4 folds after adjusting for DM and arterial HT in midlife ($OR = 3.67$; $p = 0.002$; 95% CI) (Table IV). Converting OR to adjusted relative risk (RR) by formula shown below

we had a 185% increase of dementia risk with long term PPIs utilization ($RR = 2.85$).

$$RR = \frac{OR}{(1 - P_o) + (P_o \times OR)}$$

where: OR = odds ratio from logistic regression and P_o = prevalence of the outcome in the unexposed group.

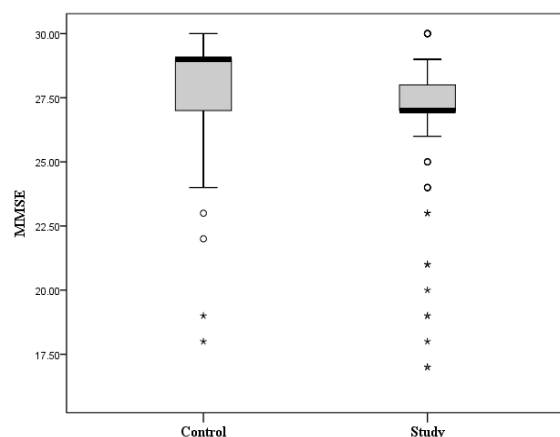
Table III
MMSE and CDT scores in study and control groups

	Control group (n = 74) Median (IQR)	Study group (n = 74) Median (IQR)	p - value
MMSE	29 (2)	27 (1.25)	$p = 0.004$
CDT	8 (1)	7 (0.92)	$p = 0.02$

Table IV

The relationship between the long term use of PPIs, DM, HT in midlife and dementia syndrome

Model	Variable	OR	95% CI	p - value
Dementia syndrome	Long term PPIs	3.67	2.23 - 19.15	p = 0.002
	Diabetes	6.35	4.57 - 52.46	p = 0.001
	HT midlife	3.18	1.73 - 23.62	p = 0.005

**Figure 1.****MMSE scores in study and control groups**

Median values depicted with boxplots; top and bottom of box represent the first and third quartiles, and the band represents the median; the end of the whiskers represent the minimum and maximum of all of the data; the points are outliers defined as values that do not fall in the inner fences and asterisks represent extreme outliers defined as values more than three times the height of the boxes.

Our results depicted a high rate of chronic utilization of PPIs of one in five people aged 65 years or more. Data on prevalence of chronic use of PPIs varies greatly across studies as there is no consensus definition of “long term use” and available information for older populations is scarce [32]. One study reported a 0.82% rate of more than 6 months per year for 5 years and more usage of gastric acid reducing agents in general population where 65% of long term PPIs users were people aged 65 and over [33]. Continuous or intermittent usage of PPIs over a period of 6 years was identified in 21.43% of an elderly population sample [35]. In a recent study highlighting the association between the use of PPIs and the functional decline in older people, 31.12% received a PPI prescription at the time of discharge from various medical units [36]. It has been consistently showed that PPIs are over prescribed across the world, in 25% - 70% of cases with no appropriate indication while 0.5% to 5% use anti-secretory medication on a long-term basis [23]. In our study the vast majority of long term PPIs users (90.55%) did not have a current prescription and were either self-administering the drugs to alleviate symptoms or were continuing consumption based on a previous medical recommendation while in more than half of the cases, an adequate gastroenterological assessment was missing. Availability of PPIs as over the counter

drugs, prompt symptoms alleviation and lack of any short term side effects may lead to long-term use of PPIs as self-medication, while certain failures in medical practices across different levels of health care systems contribute to overuse of PPIs.

In our population sample, long-term administration of PPIs increased dementia risk for about 4 times in people aged 65 and over. This effect remained significant after controlling for diabetes mellitus and arterial hypertension in midlife. Similar findings were reported by a recent large cohort study on the association between the risk of dementia and the use of any PPI, conducted in primary care settings on subjects 75 years of age and over [35]. Patients receiving PPI medication had a significantly increased risk of dementia after controlling for age, gender, education, Apolipoprotein E4 (ApoE4) allele status, polypharmacy, and comorbidities like depression, diabetes mellitus, ischemic heart disease, and stroke [35]. Another study has reported potential inappropriate prescriptions in aged people with dementia, since PPIs were prescribed at maximum therapeutic doses for more than 8 weeks [37].

In the present study, the drug of choice as reported by patients was omeprazole (58.1%) while other PPIs had a comparable preference distribution. Due to the small sample size, it was not possible to conduct a subgroup analysis on the association between different PPIs and the risk of dementia, thus we report the effects of PPIs as a drug class. To our knowledge, data on the effects of long term use of specific PPIs on cognitive function is missing; therefore future extended trials are needed to elucidate such effects. Other potential limitations of our study are: the subjective nature of data, results being based on patients' reports and recollection of usage of PPIs, while other latent dementia risk factors were not controlled for.

Conclusions

Routine geriatric care practices should include active screening for long-term use of PPIs and re-evaluation of medication after appropriate investigations and diagnosis. Prolonged administration of PPIs should be avoided as it appears to be associated with a significant increased risk of dementia.

References

1. Prince M.J., Wu F., Guo Y., Gutierrez Robledo L.M., O'Donnell M., Sullivan R., Yusuf S., The burden of

- disease in older people and implications for health policy and practice. *Lancet*, 2015; 385: 549-562.
2. World Alzheimer Report, The Benefits of Early Diagnosis and Intervention. London, UK: Alzheimer's disease International. 2011.
 3. Gandy S., The role of cerebral amyloid accumulation in common forms of Alzheimer disease. *J. Clin. Invest.*, 2005; 115: 1121-1129.
 4. Alzheimer's Association, 2013 Alzheimer's disease facts and figures. *Alzheimers Dement.*, 2013; 9(2): 208-245.
 5. Schneider J.A., Arvanitakis Z., Bang W., Bennett D.A., Mixed brain pathologies account for most dementia cases in community dwelling older persons. *Neurology*, 2007; 69: 2197-2204.
 6. Jellinger K.A., Attems J., Neuropathological evaluation of mixed dementia. *J. Neurol. Sci.*, 2007; 257(1-2): 80-87.
 7. Ferreira S.T., Lourenco M.V., Oliveira M.M., De Felice F.G., Soluble amyloid- β oligomers as synaptotoxins leading to cognitive impairment in Alzheimer's disease. *Front. Cell. Neurosci.*, 2015; 9: 191.
 8. Bloom G.S., Amyloid and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurol.*, 2014; 71: 505-508.
 9. Canobbio I., Abubaker A.A., Visconte C., Torti M., Pula G., Role of amyloid peptides in vascular dysfunction and platelet dysregulation in Alzheimer's disease. *Front. Cell. Neurosci.*, 2015; 9: 65.
 10. Shin J.M., Kim N., Pharmacokinetics and pharmacodynamics of the proton pump inhibitors. *Journal Neurogastroenterol. Motil.*, 2013; 19: 25-35.
 11. Cheng F.C., Ho Y.F., Hung L.C., Chen C.F., Tsai T.H., Determination and pharmacokinetic profile of omeprazole in rat blood, brain and bile by microdialysis and high-performance liquid chromatography. *J. Chromatogr. A*, 2002; 949(1-2): 35-42.
 12. Fallahzadeh M.K., Borhani Haghighi A., Namazi M.R., Proton pump inhibitors: predisposers to Alzheimer disease? *J. Clin. Pharm. Ther.*, 2010; 35(2): 125-126.
 13. Badiola N., Alcalde V., Pujol A., Münter L.M., Multhaup G., Lleó A., Coma M., Soler-López M., Aloy P., The proton-pump inhibitor lansoprazole enhances amyloid beta production. *PLoS ONE*, 2013; 8(3): e58837.
 14. Vogiatzoglou A., Smith A.D., Nurk E., Drevon C.A., Ueland P.M., Vollset S.E., Nygaard H.A., Engedal K., Tell G.S., Refsum H., Cognitive function in an elderly population: interaction between vitamin B12 status, depression, and apolipoprotein E ϵ 4: the Hordaland Homocysteine Study. *Psychosom. Med.*, 2013; 75(1): 20-29.
 15. Faux N.G., Ellis K.A., Porter L., Fowler C.J., Laws S.M., Martins R.N., Pertile K.K., Rembach A., Rowe C.C., Rumble R.L., Szoek C., Taddei K., Taddei T., Trounson B.O., Villemagne V.L., Ward V., Ames D., Masters C.L., Bush A.I., Homocysteine, vitamin B12, and folic acid levels in Alzheimer's disease, mild cognitive impairment, and healthy elderly: baseline characteristics in subjects of the Australian Imaging Biomarker Lifestyle study. *J. Alzheimers Dis.*, 2011; 27(4): 909-922.
 16. Kim G., Kim H., Kim K.N., Son J.I., Kim S.Y., Tamura T., Chang N., Relationship of cognitive function with B vitamin status, homocysteine, and tissue factor pathway inhibitor in cognitively impaired elderly: a cross-sectional survey. *J. Alzheimers Dis.*, 2013; 33(3): 853-862.
 17. Eastley R., Wilcock G.K., Bucks R.S., Vitamin B12 deficiency in dementia and cognitive impairment: the effects of treatment on neuro-psychological function. *Int. J. Geriatr. Psychiatry*, 2000; 15(3): 226-233.
 18. Valuck R.J., Ruscin J.M., A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. *J. Clin. Epidemiol.*, 2004; 57(4): 422-428.
 19. Dharmarajan T.S., Kanagala M.R., Murakonda P., Lebelt A.S., Norkus E.P., Do acid-lowering agents affect vitamin B12 status in older adults? *J. Am. Med. Dir. Assoc.*, 2008; 9(3): 162-167.
 20. Lam J.R., Schneider J.L., Zhao W., Corley D.A., Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. *JAMA*, 2013; 310(22): 2435-2442.
 21. Jacobson B.C., Ferris T.G., Shea T.L., Mahlis E.M., Lee T.H., Wang T.C., Who is using chronic acid suppression therapy and why? *Am. J. Gastroenterol.*, 2003; 98(1): 51-58.
 22. Hollingworth S., Duncan E.L., Martin J.H., Marked increase in proton pump inhibitors use in Australia. *Pharmacoepidemiol. Drug Saf.*, 2010; 19: 1019-1024.
 23. Lassen A., Hallas J., Schaffalitzky De Muckadell O.B., Use of anti-secretory medication: a population-based cohort study. *Aliment. Pharmacol. Ther.*, 2004; 20(5): 577-583.
 24. Heidelbaugh J.J., Kim A.H., Chang R., Walker P.C., Over utilization of proton-pump inhibitors: what the clinician needs to know. *Therap. Adv. Gastroenterol.*, 2012; 5(4): 219-232.
 25. Alexa I.D., Pancu A.G., Moroşanu A.I., Ghiciuc C.M., Lupuşoru C., Prada I.G., Cepoi V., The impact of self-medication with NSAIDs/Analgesics in a North-Eastern region of Romania. *Farmacia*, 2014; 62(6): 1164-1170.
 26. Iancu M., Bucsa C., Farcas A., Leucuta D., Dincu A., Mogoşan C., Dumitraşcu D.L., Bojita M., Patient's counselling and management of adverse drug reactions and drug interactions in the community pharmacy. *Farmacia*, 2015; 63(1): 80-85.
 27. Prince M., Albanese E., Guerchet M., Prina M., World Alzheimer Report 2014: Dementia and risk reduction: an analysis of protective and modifiable risk factors. London: Alzheimer's Disease International, 2014.
 28. Folstein M.F., Folstein S.E., McHugh P.R., "Mini-Mental State" - a practical method for grading the cognitive state of patients for the clinician. *J. Psychiat. Res.*, 1975; 12: 189-198.
 29. Woodford H.J., George J., Cognitive assessment in the elderly: a review of clinical methods. *QJM*, 2007; 100: 469-484.
 30. Samton J.B., Ferrando S.J., Sanelli P., Karimi S., Raiteri V., Barnhill J.W., The Clock Drawing Test: diagnostic, functional, and neuroimaging correlates in older medically ill adults. *J. Neuropsychiatry. Clin. Neurosci.*, 2005; 17(4): 533-540.
 31. Sunderland T., Hill J.L., Mellow A.M., Lawlor B.A., Gundersheimer J., Newhouse P.A., Grafman J.H., Clock drawing in Alzheimer's disease: a

-
- novel measure of dementia severity. *J. Am. Geriatr. Soc.*, 1989; 37: 725-729.
32. Raghunath A.S., O'Morain C., McLoughlin R.C., Review article: the long-term use of proton-pump inhibitors. *Aliment. Pharmacol. Ther.*, 2005; 22(1): 55-63.
 33. Ryder S.D., O'Reilly S., Miller R.J., Ross J., Jacyna M.R., Levi A.J., Long term acid suppressing treatment in general practice. *BMJ*, 1992; 308(6932): 827-830.
 34. Boutet R., Wilcock M., MacKenzie I., Survey on repeat prescribing for acid suppression drugs in primary care in Cornwall and the Isles of Scilly. *Aliment. Pharmacol. Ther.*, 1999; v13: 813-817.
 35. Haenisch B., von Holt K., Wiese B., Prokein J., Lange C., Ernst A., Brettschneider C., König H.H., Werle J., Weyerer S., Luppä M., Riedel-Heller S.G., Fuchs A., Pentzek M., Weeg D., Bickel H., Broich K., Jessen F., Maier W., Scherer M., Risk of dementia in elderly patients with the use of proton pump inhibitors. *Eur. Arch. Psychiatry Clin. Neurosci.*, 2015; 265(5): 419-428.
 36. Corsonello A., Maggio M., Fusco S., Adamo B., Amantea D., Pedone C., Garasto S., Ceda G.P., Corica F., Lattanzio F., Antonelli Incalzi R., Proton pump inhibitors and functional decline in older adults discharged from acute care hospitals. *J. Am. Geriatr. Soc.*, 2014; 62(6): 1110-1115.
 37. Parsons C., Johnston S., Mathie E., Baron N., Machen I., Amador S., Goodman C., Potentially inappropriate prescribing in older people with dementia in care homes: a retrospective analysis. *Drugs Aging*, 2012; 29: 143-155.