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Professional paper

FREQUENCY OF COMORBIDITY THERAPIES IN PARKINSON'S AND ALZHEIMER'S PATIENTS

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Abstract

Introduction: Alzheimer's disease (AD), a leading cause of dementia, is a progressive neurodegenerative disorder. This disease begins slowly, first involving the parts of the brain that control thoughts, memory and language. People with AD may have trouble remembering things that have happened recently or the names of people they know. Aim: The aim of this paper is to analyze and evaluate the frequency of comorbidity therapies in patients with Parkinson's and Alzheimer's disease. Study design: Retrospective study Method: Were involved 945 patients who were hospitalized in the Neurology Department of Skopje Clinical Hospital for the period from January 2014 to January 2024, of whom 772 patients met all the conditions for the study.
The statistical program for social sciences (SPSS) version 25.0 with license was used for data analysis. Results: Approximately 339 or 43.9% of the therapy of acetylsalicylic acid was used, Amitriptyline therapy was used by 202 or 26.2% of patients, followed by atorvastatin therapy used by 112 or 14.5% of patients, while diazepam was used by 167 patients or 21.6%, other therapy that was used by 112 or 14.5% of patients is enalapril. A smaller number of patients have used Lisinopril therapy, 53 or 6.9% of patients. Ranitidine was used by 45 or 5.8% of patients and the last therapy vitamin therapy but not least important, was used by patients who were involved in this study approximately 76 or 6.9% of patients. Conclusion: Furthermore, early diagnosis, early symptomatic treatment, and especially the introduction of neuroprotective therapies will improve the pharmacological management of Parkinson's and Alzheimer's disease.

Keywords: Acetylsalicylic acid, amitriptyline, diazepam and combination of drugs

Introduction

Alzheimer's disease (AD), a leading cause of dementia, is a progressive neurodegenerative disorder. (Khan, S. et al. 2020)
This disease begins slowly, firstly involving the parts of the brain that control thoughts, memory and language. People with AD may have trouble remembering things that have happened recently or the names of people they know. (Moawad, H. 2024)
Parkinson's disease is the second most common neurodegenerative disorder and a significant increase in its prevalence has been documented in the past three decades. (Cabreira,V., Massano, J. 2019)
Parkinson's disease and Alzheimer's disease are both neurological conditions caused by neurodegeneration (gradual damage to brain cells). Like other progressive brain diseases, they are associated with a build-up of certain proteins in the brain. Each of these conditions has its own set of symptoms and a specific type of protein accumulation in certain brain areas. (Tong Q, Chen L 2021)
Parkinson's disease and Alzheimer's disease can cause anxiety, depression and early stage sleep disorders. In later stages, both conditions can lead to delusions, hallucinations and other psychotic symptoms. Dementia of Parkinson's disease has some similarities to Alzheimer's disease dementia. Although, there are some differences, too. Alzheimer's disease causes dementia slowly over time, while Parkinson's disease dementia often develops more quickly

and dramatically. Parkinson's dementia symptoms can come and go from day to day, while Alzheimer's dementia symptoms won't go away. (Tong Q, Chen L 2021)

Aim of the study

We decided to do an analysis on the frequency of comorbidity therapies, bearing in mind that the therapy of comorbidities in Parkinson's and Alzheimer's disease is a complex challenge, due to the use of various therapies that patients can use simultaneously. Therefore the aim of this paper is to analyze and evaluate the frequency of comorbidity therapies in patients with Parkinson's and Alzheimer's disease. The study aims to provide a deeper understanding on the spread and nature of comorbidities, with the aim of improving diagnostics, treatment and healthcare planning for patients affected by these diseases.

Material and methods

In this retrospective study were involved 945 patients in total who were hospitalized in the Neurology Department of Skopje Clinical Hospital for the specific period from January 2014 to January 2024, of whom just 772 patients met all the conditions for the study. The statistical program for social sciences (SPSS) version 25.0 with license was used for data analysis.

Results

Descriptive data for comorbidity therapies

Depending on the diagnoses and diseases that the patients had, they have used different therapies, which in this study were also cleared or identified and comorbidity therapies used by patients and the total number of patients that used the respective therapies. Table 1 discloses these data, showing that by 339 or 43.9% of patients the therapy of acetylsalicylic acid was used. Then amitriptyline therapy was used by 202 or 26.2% of patients, followed by atorvastatin therapy by 112 or 14.5% of patients, while diazepam used by 167 patients or 21.6% of them. Other therapy that was used by 112 or 14.5% of patients is enalapril, then a smaller number of patients have used Lisinopril therapy, 53 or 6.9% of patients. Also another used therapy is ranitidine by 45 or 5.8% of patients and the last but no least important therapy used by 76 or 6.9% of patients who were involved in this study is vitamin therapy. About 9.8% of patients, according to the analysis, showed that the therapies used by more patients are acetylsalicylic acid and amitriptyline, while the therapies used by fewer patients are metformin and ranitidine.

Table 1. Number of patients who have used comorbidity therapies

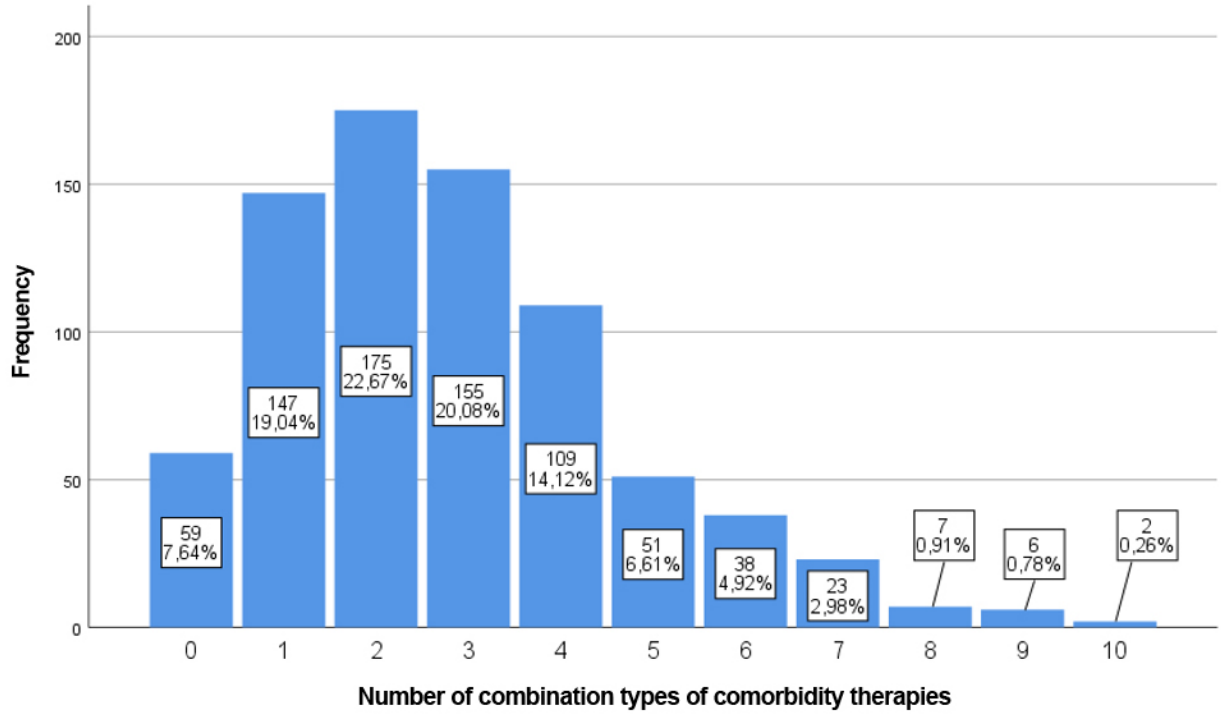
		N	%
Acetylsalicylic acid	No	433	56,1%
	Yes	339	43,9%
Amitriptyline	No	569	73,7%
	Yes	202	26,2%
Atorvastatin	No	660	85,5%
	Yes	112	14,5%
Diazepam	No	604	78,2%
	Yes	167	21,6%
Enalapril	No	660	85,5%
	Yes	112	14,5%

Lisinopril	No	719	93,1%
	Yes	53	6,9%
Metformin	No	730	94,6%
	Yes	42	5,4%
Paroxetine	No	719	93,1%
	Yes	53	6,9%
Pentoxiphylline	No	713	92,4%
	Yes	59	7,6%
Ranitidine	No	727	94,2%
	Yes	45	5,8%
Vitamin therapy	No	696	90,2%
	Yes Po	76	9,8%
	Total	772	100 %

The patients who were included in this study did not use just one therapy of comorbidities for the treatment of their diseases, but also received different combinations depending on the diagnosis, so table 2 discloses the amount of possible combinations of comorbidities therapies used as well as the number of patients who did not use any therapy, of whom 59 or 7.6% were included in this category. While only 1 therapy was used by 147 patients or 19% of them, 2 combinations of therapies used by 175 or 22.1% of patients, while the following shows also that 3 combinations have used 155 patients or 20.1% of them, 109 patients used 4 combinations of therapies and 51 or 6.6% of patients used 5 combinations of therapies. The number of combinations of comorbidities therapies increases, while the number of patients who use these combinations decreases, where 6 combinations are used by 38 or 4.9% of patients, 7 combinations use 23 patients, and 8 combinations use only 7 or 0.9% of patients. Also, 9 combinations of therapy are used only by 6 or 0.8% of patients and fewer have used 10 combinations of comorbidity therapies 2 or 0.3% of patients. This analysis shows that the more the combinations of therapy are used by fewer patients, versus the smaller amount of comorbidity therapy combinations used by more patients. The analysis of these results is also presented graphically in the following graph.

Table 2. Number of combinations of comorbidity therapies used

	Number of therapies	Frequency	%	% valuable	% cumulative
Valuable	0	59	7,6	7,6	7,6
	1	147	19	19	26,7
	2	175	22,7	22,7	49,4
	3	155	20,1	20,1	69,4
	4	109	14,1	14,1	83,5
	5	51	6,6	6,6	90,2
	6	38	4,9	4,9	95,1
	7	23	3	3	98,1
	8	7	,9	,9	99
	9	6	,8	,8	99,7
	10	2	,3	,3	100
	Total	772	100	100	



Discussion

Moderate depression always requires antidepressants. The choice of an antidepressant should be based primarily on the unique comorbidities and characteristics of the patient. Evidence for the greater effectiveness of antidepressant drugs is primarily seen with amitriptyline, but we should be cautious in elderly patients (Costa, F. H et al 2012). Our results show a number of 202, respectively, 26.2% of the patients use Amitriptyline, values that respond to the other studies above.

Paroxetine can quickly increase 5-HT concentration in the synaptic cleft of neurons, and actually alleviate patients' negative emotions like depression, anxiety, cognitive impairing and sleep disorder (**Ceravolo, R et al. 2000**). At the same time, motor function in the PD patient is also significantly improved along with improved 5-HT activity.

Paroxetine therapy reduced the number of each adverse event markedly in patients with PD, the number of patients using Paroxetine was 64.9%, (**Jiang, L.-L et al**. 2023 ;Barker MJ et al. 2004) percentage this is very high compared to our results, in our study we have a total of 6.9%.

Benzodiazepines are drugs that are widely prescribed for anxiety and sleep disorders in the general population, and not just in Parkinson's patients. (Picton JD et al. 2023) In patients we analyzed found that Diazepam was used by 167 patients or 21.6% of the total 772 patients in our study.

Given the high prevalence of self-reported anxiety mood disorders and sleep dysfunction in Patients with Parkinson's, benzodiazepines (including Diazepam) are often described as the first line of treatment for these patients. (Chen JJ, Marsh L. 2014; Chuang C, Fahn S. 2001)

The study (Wu, C.-C et al. 2022) also found that statin use was associated with 19% reduced risk of Parkinson's disease patients. Our study showed a value of 112 or 14.5% of patients who used atorvastatin as therapy. Moreover, using statins for over 5 years significantly lowers the risk for Parkinson's disease. In general, statin use and specifically atorvastatin use was associated with a decreased risk of developing Parkinson's disease.

Recent epidemiological studies have found that the risk of developing Parkinson's disease is reduced in people who use nonsteroidal analgesic therapy including acetylsalicylic acid.

Consequently, it has been hypothesized that they may delay or prevent the onset of Parkinson's disease. (**Esposito, E et al. 2007**) Perhaps we are on the cusp of a promising new career for NSAIDs especially in the prevention of neurodegenerative diseases and not for treating them. Indeed, it is very possible that NSAIDs will be ineffective once the pathological process has begun, pharmacological intervention should begin very early in the pre-symptomatic period, according to some experimental epidemiological evidence. (Chen, H, et al. 2003 Chen C.,Bazan N.G. 2005; Hernán, M.A et al. 2006) Through our analysis that we have done, we encountered these data from which it is shown that 339 or 43.9% of acetylsalicylic acid was used in patients who were already in different stages of development of the disease.

Enalapril was associated with significantly reduced risk of MCI (Mild Cognitive Impairment) compared to other users of antihypertensive drugs, where out of 68 participants in the study 37 patients, respectively 54% have used enalapril, and on the basis of the results we have concluded that out of 772 patients only 112, respectively 14.2% have used enalapril. This is a decrease compared to the study. (**Solfrizzi, V** et al.2013)

In the study (**Ping, F** et al. 2020) we see that it remains inconclusive whether metformin plays a beneficial or harmful role in various neurodegenerative diseases, despite some compelling evidence suggesting its positive effect against age-related neurodegenerative diseases. The use of metformin therapy in our study was in 42 or 5.4% of patients, which is worth analyzing in depth in the future so that it can be more accurate whether it is a high or low use value. Metformin, as one of the first-line pharmacological agents for the treatment of type 2 diabetes, has increasing evidence for delaying aging in model organisms and reducing diseases associated with aging. (**Soukas, A. A** et al. 2019)

Recent clinical studies have shown that low levels of vitamin B12 in serum and cerebrospinal fluid predict greater worsening of clinical progression of Parkinson's disease. (**Christine, C. W et al.**2018; **Christine, C. W et al.**)

Findings from (**Costantini, A et al.2013**) suggest that vitamin B1 deficiency promotes neuronal death, leading to increased risk for PD, and supplementing with the same may improve pathological changes associated with PD. A clinical study on patients with Parkinson's disease found that high doses of vitamin B1 improve motor symptoms from 31.3% to 77.3% of the Unified Parkinson's Disease Assessment Scale (UPDRS) in patients with Parkinson's disease.

The lack of various vitamins, including vitamins A, B, C, D, E and K, has been shown to be a vital risk factor for the onset of Parkinson's disease. Thus, proper intake of these vitamins can be considered a critical preventive measure against Parkinson's disease. Previous pre-clinical and clinical studies have shown that dietary supplementation of various vitamins can reduce the prevalence of Parkinson's disease and improve motor deficits and clinical changes associated with Parkinson's disease in the general population. (**Sandeep, M et al. 2023**)

The last therapy used by patients involved in this study is vitamin therapy from 76 or 9.8% of patients. Even from the prior knowledge we know that vitamins are used to a large extent with or without the consultation of the doctor or pharmacist, because we always rely on vitamins help in general health. Some studies suggest that vitamin use may slow the development of neurodegenerative diseases, but we should always bear in mind that vitamin therapy plays an important role as therapeutic support, but are not a substitute for pharmacological treatments.

Conclusion

Furthermore, early diagnosis, early symptomatic treatment, and especially the introduction of neuroprotective therapies will improve the pharmacological management of Parkinson's and Alzheimer's disease. Like any retrospective study, this one has some limitations. It may be subject to measurement errors, including guesswork, classification or erroneous coding, as well as selection biases. Furthermore, our assessments were based primarily on data of existing

epidemiological studies, which limited the possibility to apply new or different diagnostic criteria.

References

[1] Barker MJ, Barker M, Greenwood K: Cognitive effects of long-term benzodiazepine use. CNS Drugs. 2004, 18:37-48.

[2] Cabreira, V., & Massano, J. (2019). Parkinson's disease: Clinical review and update [Article in Portuguese]. *Acta Médica Portuguesa, 32*(10), 661–669. https://doi.org/10.20344/amp.11978

[3] **Ceravolo, R., Nuti, A., Piccinni, A., Dell' Agnello, G., Bellini, G., Gambaccini, G., Dell' Osso, L., Murri, L., & Bonuccelli, U.** (2000). Paroxetine in Parkinson's disease: Effects on motor and depressive symptoms. *Neurology, 55*(8), 1216–1218. https://doi.org/10.1212/WNL.55.8.1216

[4] Chen JJ, Marsh L: Anxiety in Parkinson's disease: identification and management. Ther Adv Neurol Disord. 2014, 7:52-59. 10.1177/1756285613495723

[5] Chen, C., Bazan, N.G., 2005. Lipid signaling: sleep, synaptic plasticity, andneuroprotection. Prostaglandins Other Lipid Mediat. 77, 65–76.

[6] Chen, H., Zhang, S.M., Hernan, M.A., Schwarzschild, M.A., Willett, W.C.,Colditz, G.A., Speizer, F.E., Ascherio, A., 2003. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch. Neurol. 60,1059–1064.

[7] **Christine, C. W., Auinger, P., Joslin, A., et al.;** Parkinson Study Group-DATATOP Investigators. (2018). Vitamin B12 and homocysteine levels predict different outcomes in early Parkinson's disease. *Movement Disorders, 33*(5), 762–770. https://doi.org/10.1002/mds.27334

[8] **Christine, C. W., Auinger, P., Saleh, N., et al.** (2020). Relationship of cerebrospinal fluid vitamin B12 status markers with Parkinson's disease progression. *Movement Disorders, 35*(6), 907–915. https://doi.org/10.1002/mds.28037

[9] Chuang C, Fahn S: Dramatic benefit with clonazepam treatment of intractable anxiety and panic attacks in Parkinson's disease. Mov Disord. 2001, 16:35.

[10] Costa, F. H. de R., Rosso, A. L. Z., Maultasch, H., Nicaretta, D. H., & Vincent, M. B. (2012). Depression in Parkinson's disease: Diagnosis and treatment. *Arquivos de Neuro-Psiquiatria, 70*(8), 617–620. https://doi.org/10.1590/s0004-282x2012000800011

[11] **Costantini, A., Pala, M. I., Compagnoni, L., & Colangeli, M.** (2013). High-dose thiamine as initial treatment for Parkinson's disease. *BMJ Case Reports, 2013*, bcr2013009289. https://doi.org/10.1136/bcr-2013-009289

[12] **Esposito, E., Di Matteo, V., Benigno, A., Pierucci, M., Crescimanno, G., & Di Giovanni, G.** (2007). Non-steroidal anti-inflammatory drugs in Parkinson's disease. *Experimental Neurology, 205*(2), 295–312. https://doi.org/10.1016/j.expneurol.2007.02.008

[13] Hernán, M.A., Logroscino, G., García Rodríguez, L.A., 2006. Nonsteroidal anti-inflammatory drugs and the incidence of Parkinson disease. Neurology 66,1097–1099.

[14] **Jiang, L.-L., Wu, Y.-L., Mo, Y., Gou, L., Chen, M.-L., Wang, Y., Zang, Q.-M., & Jiang, D.-Q.** (2023). The effects of paroxetine therapy on depressive symptom and motor function in the treatment of depression with Parkinson's disease: A meta-analysis. *Medicine, 102*(34), e34687. https://doi.org/10.1097/MD.0000000000034687

[15] Khan, S., Barve, K. H., & Kumar, M. S. (2020). Recent advancements in pathogenesis, diagnostics and treatment of Alzheimer's disease. *CNS & Neurological Disorders - Drug Targets, 18*(11), 1106–1125. https://doi.org/10.2174/1570159X18666200528142429

[16] Moawad, H. (2024). *Alzheimer's and Parkinson's disease: What's the connection?* They can have similar symptoms and they may occur together.

[17] Picton JD, Marino AB, Nealy KL: Benzodiazepine use and cognitive decline in the elderly. Am J Health-Sys Pharm. 2018, 75:6. 10.2146/ajhp160381

[18] **Ping, F., Jiang, N., & Li, Y.** (2020) Association between metformin and neurodegenerative diseases of observational studies: systematic review and meta-analysis. *BMJ Diabetes Research & Care, 8*(1), e001370. https://doi.org/10.1136/bmjdrc-2020-001370

[19] **Sandeep, M., Sahu, M. R., Rani, L., Kharat, A. S., & Mondal, A. C.** (2023). Could vitamins have a positive impact on the treatment of Parkinson's disease? *Brain Sciences, 13*(2), 272. https://doi.org/10.3390/brainsci13020272

[20] **Solfrizzi, V., Scafato, E., Frisardi, V., Seripa, D., Logroscino, G., Kehoe, P. G., Imbimbo, B. P., Baldereschi, M., Crepaldi, G., Di Carlo, A., Galluzzo, L., Gandin, C., Inzitari, D., Maggi, S., Pilotto, A., & Panza, F.;** for the Italian Longitudinal Study on Aging Working Group. (2013).

Angiotensin-converting enzyme inhibitors and incidence of mild cognitive impairment: The Italian Longitudinal Study on Aging. *Age*, *35*(2), 441–453. https://doi.org/10.1007/s11357-011-9360-z

[21] **Soukas, A. A., Hao, H., Wu, L., et al.** (2019). Metformin as anti-aging therapy: Is it for everyone? *Trends in Endocrinology and Metabolism*, *30*(10), 745–755. https://doi.org/10.1016/j.tem.2019.07.017

[22] Tong Q, Chen L. Associations of Alzheimer's disease neuropathologic changes with clinical presentations of Parkinson's disease. J Alzheimers Dis. 2021;81(1):201-207. doi:10.3233/JAD-210114

[23] Wu, C.-C., Islam, M. M., Lee, A.-J., Su, C.-H., Weng, Y.-C., Yeh, C.-Y., Lee, H.-H., & Lin, M.-C. (2022). Association between statin use and risk of Parkinson's disease: Evidence from 18 observational studies comprising 3.7 million individuals. *Journal of Personalized Medicine*, *12*(5), 825. https://doi.org/10.3390/jpm12050825