Original Article

# Investigation of the Effects of Polypharmacy on Cognitive Functions: Cohort Study

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## ABSTRACT

**Background:** Alzheimer's Disease (AD) is a major concern in growing chronic diseases in the geriatric society and its connection with polypharmacy has not been sufficiently understood. **Aim:** This Study investigate the association between Alzheimer's disease and polypharmacy. **Methods:** A prospective cohort study. Patients with diagnosis of the AD and being older than 55 included in study between March 2017 and September 2017 who applied at the Bezmialem Vakif University Hospital, Istanbul. According to number of used medicine participant divided 3 groups. Age, sex, weight, height were recorded as Socio-demographic variables, a physical and cognitive examination was also performed to determine Mini-Mental State Exam (MMSE) and Katz-Activities of Daily Living (KATZ-ADL) scores. Deterioration of cognitive functions has been associated with alteration of MMSE between 6 months among the groups. **Results:** We included 79 AD patients and >55 years old into study. Reduction of MMSE scores between six month period were, 1.0 point decrease ($p=0.034$), 1.29 points decrease ($p=0.003$) and 2.05 points decrease ($p=0.001$) respectively. There is statistically significant difference between group I to III, KATZ- ADL ($p=0.07$). **Conclusion:** In our study the largest decline in cognitive function seen in group with the highest number of medicine used. Cognitive functions has declined in three groups after 6 months but this cannot be directly linked with polypharmacy. Cognitive and functional status has affected from multiple drug use. There is a need for more detailed and bigger clinical studies about the relationship between polypharmacy and AD.

**Key words:** Alzheimer's disease, Dementia, Polypharmacy, Elderly, KATZ-ADL, MMSE.

## INTRODUCTION

Dementia is a syndrome characterized by the impairment of cognitive functions including memory, executive and visuospatial functions, language and gnostic functions.[1] The most prevalent form of dementia is Alzheimer's disease (AD), as it occurs in 60-70 % of cases.[2] Neurodegeneration is an important feature of the disease and neurodegeneration is due to astrogliosis, microglial cell proliferation, amyloid plaques and neurofibrillary tangles.[3] While certain drugs are available for AD care options but there is no innovative medication that prevents or delays the disease progression.[4,5] Polypharmacy, referred to as the use of multiple medicines and/or the use of more drugs than strictly prescribed, reflecting a wasteful usage of medications,[6] is one of the biggest issues in the management of AD. In cases where AD can be found with many diseases due to old age, choosing the right drug regimen is one of the primary goals of the physician to increase the life quality of elderly patients. Improper prescription including polypharmacy is selected as a

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leading drug safety issue in 'Healthy people 2020' report.[7] Gnjidic *et al.* stated that polymedicated patients with dementia had 4 times more risk of presenting at least one adverse drug reactions (ADR).[8] It is important to detect interactions between these drugs, to minimize side effects (depression, confusion, restlessness, falling, memory loss, constipation and incontinence) and to alleviate the course of other existing diseases, particularly AD.[9,10] Proposed risk factors such as vascular and metabolic diseases, lifestyle, diet and genetic have an impact on the risk of the AD[11] and it is estimated that up to one in three of the world's AD cases is caused by modifiable risk factors such as diabetes, middle-aged hypertension and physical inactivity.[12]

A few studies have investigated the association between polypharmacy and AD. It is shown in a study that 46.8% of community-dwelling patients diagnosed with mild to moderate AD use potentially inappropriate medications (PIM). It was also suggested that doctors in the prescribing process did not properly take into account the symptoms of the illness and the pharmacological profile of the approved drugs.[13] Lau *et al.* showed the association between polypharmacy and PIM use in AD patients using a 4-year dataset from the National Alzheimer's Coordinating Center in the United States. Results indicate that as the total number of drugs used increased, the odds of having PIM also increased, controlling for AD diagnosis and other subject characteristics.[14] However, because of the cross-sectional study design, Lau *et al.* were unable to determine the causal relation between AD and polypharmacy. And we used a 6-month prospective analysis to determine the relationship between polypharmacy and worsening of AD.

## MATERIALS AND METHODS

### Study Setting

Prospective, randomized cohort research conducted at Bezmialem Vakif University Hospital in a dementia unit specializing in the treatment of patients with Alzheimer's disease. Data collected between March 1, 2017 and September 1, 2017. Inclusion criteria were a diagnosis of the AD and being older than 55. Dementia diagnosis was developed by a senior physician (neurologist or psychiatrist) based on the requirements of the Mental Disorders Diagnostic and Statistical Manual, Fifth Edition (DSM-V).[15] Dementia diagnosis by a senior physician (neurologist or psychiatrist) based on the requirements of the Mental Disorders Diagnostic and Statistical Manual, Fifth Edition (DSM-V) and the National Institute of Neurological and Communicative Disorders and Stroke and AD and Related Disorders Association (NINCDS-ADRDA) and patients were listed as 'Definite AD.[16]

### Ethical Aspect

Ethical approval granted on 24 January 2017 by the Committee on Clinical Research Ethics at Bezmialem Vakif University Istanbul, Turkey with decision number 2/4. Written consents were taken from patients, in case of severe dementia (Clinical Dementia Rating[17] (CDR=3) caregivers signed the written consents.

### Study Design

For all 79 patients there were reported the following socio-demographic variables: age, sex, weight, height. Dependency level was assessed using Katz 's Daily Living Scale (ADL) tasks, which included six items (bathing, dressing, toilet, move, continence and feeding).[18] Such subjects were considered to be reliant on ADLs if they had missed at least one ADL.

Seventy-nine patients have been evaluated according to the number of medicines used and have been divided into three groups. Group I included patients who have been taking 1-4 medicine (minor polypharmacy)[19] while Group II included patients who have been taking 5-9 medicines (major polypharmacy).[19] The rest of the patients who have been taking 10 or more drugs were classified as Group III (hyper polypharmacy).[8] Medications data have been obtained with medical reports and pharmacy-dispensing records. Herbals, vitamins, OTCs and supplements are excluded from data. Drugs are classified according to ATC/DDD Index 2019 proposed by WHO.[20] The participants were followed for six months. During these six months there was no change in participants treatments (i.e. dosage, usage).

Mini-Mental State Examination (MMSE) is one of the significant factors for the AD prognosis and is a brief indicator of cognitive status in dementia patients. It is used to determine severity of cognitive impairment, to follow the course of cognitive changes among two different times and to screen a patient's response to treatment.[21] It is a scale of 0-30 points. 9 or fewer points represent for severe impairment, 10-18 points: moderate impairment, 19-23 points: mild impairment, 24 and above represents for no cognitive impairment.[22] Changes in MMSE scores of each group (groups I, II and III) over the course of six months were correlated with worsening in cognitive functions and changes in MMSE score were compared between groups.

### Data Analysis

IBM SPSS Statistics 22.0 (Statistical System for Social Sciences) was used for statistical research. The distribution status of variables was evaluated with the Kolmogorov-Smirnov test and the result showed that variables are not normally distributed. Wilcoxon Signed Ranks Tests compared the baseline and final (after 6 months of follow-up) MMSE scores and KATZ-ADL (just baseline) in each group. Mann-Whitney U used measures for double-group discrepancies (Groups I, II; II, III; I, III) (median, standard deviation) as well as quantitative results when analyzing the study data. The findings were tested at a 95 % confidence interval and a $p<0.05$ considered as statistically difference.

## RESULTS

In total there were 79 patients aged 76 ± 8 years (range: 55–90 years); the majority were women (62.0 %) (Table 1). Average MMSE score of 17 ± 4 was found on cognitive assessment. In terms of dementia severity, 24 patients (30 %) had mild disability (19 random MMSE score < 24), 41 (51 %) had moderate disability (10 random MMSE score < 18) and 7 (8 %) had serious impairment (MMSE < 8).

Analyses of the difference of MMSE score in before and after results in each group, Wilcoxon Signed Ranks test has been used. According to subgroup analysis; for the group I, before and after results of mean MMSE scores were 16.9±5.4 and 15.9±5.7 respectively. 1.0 point decrease observed in group I (Wilcoxon Signed Ranks Test; Z= -2.118c; $p=0.034$; $p<0.05$), for group II results were 17.3±4.8 and 16.0±4.7 respectively with a decrease of 1.2 points (Wilcoxon Signed Ranks Test; Z= -2.967c; $p=0.003$; $p<0.05$) and for group III results were 18.5±6.0 and 16.2±5.6 respectively with a decrease of 2.05 points (Wilcoxon Signed Ranks Test; Z= -3,480c; $p=0.001$, $p<0.05$) (Table 2). KATZ-ADL comparison between groups is given in Table 3. (Wilcoxon Signed Ranks Test; $p=0.182$; $p>0.05$)

Our results show that there is an association between polypharmacy and KATZ-ADL scores (Table 4). Especially in double comparison with the group I and group III, KATZ-ADL levels show a downward trend. Also, by the means of the AD, MMSE score drop was expected in 6 months. Indeed, the drop was seen from group I to group III, but results showed that there is not significance between double group analyses according to Mann-Whitney U test (Table 4).

**Table 1: Socio-Demographic Features of Participants.**

| | Total (*n*=79) | Group I (*n*=23) | Group II (*n*=31) | Group III (*n*=25) |
|---|---|---|---|---|
| **Age, mean mean (years±SD)** | 75.7±4.9 | 74.1±1.0 | 75.4±0.9 | 77.6±0.7 |
| **Female gender, (%)** | 62.00 | 53.8 | 54.8 | 73.9 |
| **Weight (kg)** | 71.6±1.4 | 70.3±1.4 | 72.7±1.7 | 71.3±1.1 |
| **Height (cm)** | 158.5±1.1 | 160.4±1.0 | 158.3±1.3 | 157.1±0.7 |
| **Body Mass Index(kg/m²)** | 28.8±0.6 | 27.3±0.5 | 29.5±0.6 | 29.3±0.5 |
| **Medications per patient, mean (±SD)** | 6.6±0.8 | 3.1±0.8 | 5.6±0.7 | 11.0±0.9 |

## DISCUSSION

The findings of this research showed that more medications may be associated with memory loss. Lai

**Table 2: Alteration of MMSE Scores of Groups in 6 Months.**

| | | MMSE (before[b]) | MMSE (after[c]) | P | Z |
|---|---|---|---|---|---|
| **Group I** | **Median** | 17.0 | 16.0 | 0.034[a] | -2.118 |
| | **Minimum** | 6.0 | 4.0 | | |
| | **Maximum** | 25.0 | 26.0 | | |
| | **Percentile 25** | 13.0 | 13.0 | | |
| | **Percentile 75** | 21.0 | 21.0 | | |
| | **Interquartile range** | 8.0 | 8.0 | | |
| **Group II** | **Median** | 15.5 | 15.0 | 0.005[a] | -2.834 |
| | **Minimum** | 8.0 | 8.0 | | |
| | **Maximum** | 29.0 | 25.0 | | |
| | **Percentile 25** | 14.0 | 13.0 | | |
| | **Percentile 75** | 21.0 | 20.0 | | |
| | **Interquartile range** | 7.0 | 7.0 | | |
| **Group III** | **Median** | 18.0 | 16.5 | 0.002[a] | -3.051 |
| | **Minimum** | 6.0 | 3.0 | | |
| | **Maximum** | 29.0 | 27.0 | | |
| | **Percentile 25** | 15.0 | 12.0 | | |
| | **Percentile 75** | 24.0 | 19.0 | | |
| | **Interquartile range** | 9.0 | 7.0 | | |

**Table 3: Comparison of KATZ-ADL scores between groups in baseline[b].**

| | Median | Minimum | Maximum | Percentile 25 | Percentile 75 | P |
|---|---|---|---|---|---|---|
| **Group I** | 6.0 | 3.0 | 6.0 | 4.0 | 6.0 | 0.18[a] |
| **Group II** | 5.0 | 2.0 | 6.0 | 4.0 | 6.0 | |
| **Group III** | 5.0 | 2.0 | 6.0 | 4.0 | 6.0 | |

Notes: [a]Relationship is not statistically significant in Wilcoxon Signed Ranks test ($P$>0.05).
[b]Represents for baseline of 6 months.
Abbreviations: KATZ-ADL, Katz Activites of Daily Living.

**Table 4: The Difference of MMSE Scores and KATZ-ADL scores of the Participants in double Groups comparisons.**

| | Mean MMSE (before[b]) | Mean MMSE (after[c]) | P(before[b]) | P(after[c]) | Mean KATZ-ADL[e] | Z | P |
|---|---|---|---|---|---|---|---|
| **Group I**<br>**Group II** | 16.9p II<br>17.3p II | 15.9p II<br>16.0p II | 0,97[a] | 0,93[a] | 5.23p I<br>4.83p I | -1,35 | 0,17[a] |
| **Group I**<br>**Group III** | 16.9p II<br>18.5p II | 15.9p II<br>16.2p II | 0,43[a] | 0,49[a] | 5.29p I<br>4.59p I | -1,76 | 0,07[d] |
| **Group II**<br>**Group III** | 17.3p II<br>18.5p II | 16.0p II<br>16.2p II | 0,23[a] | 0,64[a] | 4.84p I<br>4.54p I | -,64 | 0,52[a] |

**Notes:** [a]Relationship is not statistically significant in Wilcoxon Signed Ranks test ($P$<0.05). [b]Represents for baseline of 6 months. [c]Represents for end of the 6 months. [d]Relationship is nearly statistically significant in Wilcoxon Signed Ranks test ($P$>0.05). [e]KATZ-ADL scores are obtained in only the baseline of the 6 months.

*et al.* emphasized that in the AD cases polypharmacy was found at a substantially higher level than in the controls and noted that the increased number of drugs and age were also associated with the incidence of AD.[23] Suffering from a chronic disease is a huge problem all by itself, when considering having a new onset of the AD with it or worsening of the possessed AD could count as an enormous problem for individual's life. According to Clague *et al.* AD patients have a higher burden of comorbid diseases and polypharmacy than those without dementia, even after accounting for age and sex differences.[24] It is indicated that alongside AD, chronic diseases such as hypertension, heart diseases and diabetes can necessitate polypharmacy and taking measures to reduce unwarranted use of medication, optimizing the benefits from important drugs are crucial for improving drug therapy for elderly.[25] Gomm *et al.* accepted diabetes, stroke, ischemic heart diseases and polypharmacy as factors contributing worsening of the AD in their multicentered prospective cohort study in which 76,679 patients took place. Hazard Ratio (HR) of polypharmacy on AD-type dementia were calculated as 1.16 (HR %95 Cl $p$<0.01). Results have shown that HR does not differ in gender-specific sub-analyses.[26] Polypharmacy can also lead to an increased risk of use of dementia-related PIMs. Because of their adverse effects on the central nervous system, the Beers criteria classify anticholinergic medications, benzodiazepines and H2-receptor antagonists as proven PIMs for dementia. Therefore, these PIMs should be used only when necessary and excessive usage is to be avoided among the elderly.[27] Melis *et al.* mentioned that comorbidity brings out multiple medication use. Presence chronic comorbid conditions at baseline were cross-sectionally related to lower baseline functional status and also longitudinally to faster decline in functioning.[28]

## CONCLUSION

Using multiple medications may be a necessity for the elderly. But non-rational drug use is common especially while patients are visiting different physicians for different health problems. In this case, medicine reconciliation has a crucial role to prevent this oversight. In many cases, polypharmacy is a necessity but there is a big proportion of individuals who are on medication without any diagnosis. Some are using before it was prescribed years ago and never stopped until now, some did recommend by a friend who is not a physician, some just taste good and feel good and so on. The therapeutic plan should be prepared according to Beers criteria[29] and STOPP/START criteria,[30] which are among the gold standards in treatment for the approach in the elderly.

Clinicians do not have a chance to quit or reduce the use of medications that are mandated by comorbid

conditions. In contrast, the prevention of unnecessary drug use constitutes the basis of pharmaceutical care principles due to the rules of rational use of medicines. In addition to Neurologist, specialists of the related comorbid diseases, geriatric experts, psychologists and especially clinical pharmacists are required to be included in the health team. Socio-demographic characteristics of the patients should be taken into account when medication is reconciled. Pharmacist either work as community pharmacist or clinical pharmacist, should take over responsibility and become an essential part of the healthcare team, through performing medicine reconciliation, assessing and evaluating patients' situation and having a consultation with a physician about patient pharmaceutical care. There is a need for more detailed and bigger clinical studies about the relationship between polypharmacy and AD.

Our study has some limitations that deserve to be underlined. This is a single-center study and results cannot be generalized to the whole population. Second, cause of being small number of participants, Homogeneity of patients was not totally provided so insignificance can be understandable. Conversely, one of the strengths of this study is that only few studies have been performed on MMSE in elderly subjects in Turkey with AD as a longitudinal study, rather than cross-sectional.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Bezmialem Vakif University Istanbul, Turkey with decision number of 2/4 on 24th of January 2017) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

## ABBREVIATIONS

**AD:** Alzheimer's Disease; **ADR:** Adverse Drug Reactions; **ATC/DDD:** Anatomic Therapeutic Chemical/ Defined Daily Dose; **CDR:** Clinical Dementia Rating; **DSM-V:** Mental Disorders Diagnostic and Statistical Manual, 5th Edition; **HR:** Hazard Ratio; **KATZ-ADL:** Katz Activities of Daily Living; **WHO:** World Health Organization; **MMSE:** Mini Mental Score Exam; **NINCDS-ADRDA:** National Institute of Neurological and Communicative Disorders and Stroke and AD and Related Disorders Association; **PIM:** Potentially Inappropriate Medications; **STOPP/STRAT:** Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment.

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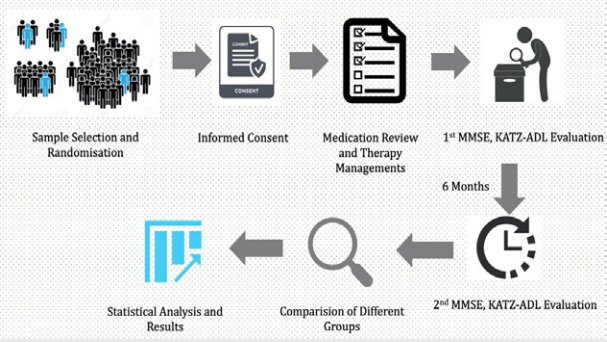
## PICTORIAL ABSTRACT

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## SUMMARY


Alzheimer's disease (AD) is one of the most common type of dementia as it occurs in 60-70% of cases. Although there are some medications for AD treatments options but unfortunately there is no radical treatment that cures or slows the progression of the disease. Most of the AD patients are elderly and have comorbidities which force them to use multiple medication. Polypharmacy, referred as the use of multiple medicines and/ or the administration of more medicines than is clinically prescribed, representing redundant medication use, is one of the biggest issues in the management of AD. In literature polypharmacy has been associated with poor prognosis of AD. In our study we simply try to investigate the effects of polypharmacy on cognitive function. According to our findings a decline is associated with polypharmacy. Clinicians do not have a chance to quit or reduce the use of medications that are mandated by comorbid conditions. In contrast, the prevention of unnecessary drug use constitutes the basis of pharmaceutical care principles due to the rules of rational use of medicines. Pharmacist either work as community pharmacist or clinical pharmacist, should take over responsibility and become an essential part of the healthcare team, through performing medicine reconciliation, assessing and evaluating patients' situation and having a consultation with a physician about patient pharmaceutical care. However our studies have some limitations which could be low number of sample size and short follow up.


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