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Polypharmacy as a risk factor for depressive symptoms in geriatric patients: an observational, cross-sectional study

La polifarmacia como un factor de riesgo para síntomas depresivos en pacientes geriátricos: un estudio observacional transversal

Spandel Leszek[1], Jośko-Ochojska Jadwiga[1], Batko-Szwaczka Agnieszka[2]

1. Chair and Department of Environmental Medicine and Epidemiology, School of Medicine with Division of Dentistry in Zabrze, Medical University of Silesia, Katowice, Poland
2. Department of Geriatrics, School of Health Sciences in Katowice, Medical University of Silesia, Katowice, Poland

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Correspondencia
Correspondence

Leszek Spandel
Clinical Pharmacist
Chair and Department of Environmental Medicine and Epidemiology, School of Medicine with Division of Dentistry in Zabrze, Medical University of Silesia, ul. Jordana 19, 41-808 Zabrze, Poland
+48 608 205 759
leszekspandel@gmail.com

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RESUMEN

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Objetivo: El objetivo de este estudio es investigar la correlación entre la polifarmacia y los síntomas depresivos en adultos hospitalizados mayores de 65 años.

Pacientes y métodos: Se obtuvo la historia clínica y los datos actuales de tratamiento de las historias clínicas. Se utilizó la puntuación de la prueba Mental Abreviado (AMTS) para excluir a los pacientes con demencia. La Escala de Depresión Geriátrica (GDS) se utilizó para evaluar los síntomas depresivos. Se usaron coeficientes Pearson y Spearman para determinar la relación entre las variables.

Resultados: Se incluyó a un total de 206 individuos. El número medio de medicamentos tomados por los individuos fue de 6,9 ± 2,7 y la puntuación media GDS fue de 4,9 ± 3,4 puntos. Los síntomas de depresión (GDS puntuación> 5 puntos) se observaron en 68 (33,0%) individuos. La puntuación GDS de una correlación positiva con el número de medicamentos que se usaron (R = 0,74; P = 0,0001), el número de condiciones crónicas (R = 0,78; P = 0,001), y quejas de dolor (Z = 7,94; P = 0,0001). Se observó una asociación significativa entre la partitura GDS y el uso de los siguientes medicamentos: estatinas, agentes citostáticos, corticoesteroides, benzodiazepinas, glucósidos cardíacos, los fármacos no esteroides antiinflamatorios, relajantes musculares, medicamentos sin psicotrópicas con propiedades anticolinérgicas, y de acción central analgésicos (todos P <0,05).

Conclusiones: Nuestro estudio indica que la polifarmacia se correlaciona positivamente con la presencia de síntomas depresivos en pacientes geriátricos. Se identificó una serie de medicamentos asociados con una mayor prevalencia de síntomas depresivos; Sin embargo, estas relaciones requieren un examen más detenido.

Palabras clave: adulto mayor; efectos adversos de la droga; salud mental; psiquiatría.

ABSTRACT

Aim: The aim of this study was to investigate the correlation between polypharmacy and depressive symptoms in hospitalized adults aged over 65 years.

Patients and methods: We obtained medical history and current treatment data from clinical records. We used the Abbreviated Mental Test Score (AMTS) to exclude patients with dementia. The Geriatric Depression Scale (GDS) was used assess depressive symptoms. Pearson and Spearman coefficients were used to determine the relationship between variables.

Results: A total of 206 individuals were included. The average number of medications taken by the individuals was 6.9 ± 2.7 and the average GDS score was 4.9 ± 3.4 points. Depressive symptoms (GDS score >5 points) were observed in 68 (33.0%) individuals. GDS score positively correlated with the number of medications used (R = 0.74; *P* = 0.0001), the number of chronic conditions (R = 0.78; *P* = 0.001), and pain complaints (Z = 7.94; *P* = 0.0001). A significant association between GDS score and the use of the following medications was observed: statins, cytostatic agents, corticosteroids, benzodiazepines, cardiac glycosides, non-steroidal anti-inflammatory drugs, muscle relaxants, non-psychotropic drugs with anticholinergic properties, and centrally acting analgesics (all *P* < 0.05).

Conclusions: Our study indicates that polypharmacy is positively correlated with the presence of depressive symptoms in geriatric patients. We identified a number of medications associated with a higher prevalence of depressive symptoms, however these relationships require further examination.

Key words: elderly; adverse drug effects; mental health; psychiatry.

INTRODUCTION

The process of aging has perplexed mankind since ancient times, but it has never been subject to as extensive consideration as it is now. The aged population continues to rise worldwide as a result of demographic transition (ie, the reduction in mortality resulting from civilizational advancement, and concomitant decline in fertility rates). According to Eurostat, the proportion of individuals aged over 65 years currently exceeds 18% of the European Union population, and is estimated to reach 28% by 2060.[1] As a consequence, clinicians can expect to increasingly face issues inextricably associated with senility, such as coexistence of several chronic conditions in an individual, functional impairment, and the necessity to use multiple medications.

According to literature, depression is the most prevalent mental disorder in the elderly affecting up to 20% of individuals in the community setting,[2] and 5–58% of geriatric patients treated in general hospitals.[3] However, available data on the prevalence of depression in the elderly are inconsistent, and some numbers may be underrated given the diagnostic challenges in this age group. Diagnosis may be hindered by communication difficulties that stem from hearing problems or cognitive impairment, as well as the presence of other disorders with somatic symptoms resembling those of depression. Furthermore, lowered mood and psychomotor retardation in the elderly are often erroneously viewed as part of the aging process, which contributes to underreporting of the disease and, as a consequence, the lack of proper treatment.

A host of predisposing factors for geriatric depression have been identified to date, including: decreased functional capacity associated with chronic physical illnesses, a low degree of social support, widowed or divorced status, and polypharmacy.[4] As the goal of care shifts from further extending the life span to improving the quality of living, we now look more into the means of reducing morbidity and maintaining independence in the elderly population. Due to the high prevalence of multiple medication therapies, as well as altered drug metabolism attributable to the old age, particular attention is being given to the effects of medications on cognition and geriatric syndromes, in addition to their efficacy and safety measures. According to some authors, side effects of pharmacotherapy contribute to up to 30% of hospitalizations in individuals aged over 70 years. In this group of patients, central nervous system (CNS) disorders comprise approximately one third of all adverse drug reactions.[5]

This observational, cross-sectional study was designed to investigate the relationship between polypharmacy and depressive symptoms in adults over 65 years of age in a hospital setting. We also aimed to establish whether a particular therapeutic class of medication was associated with increased prevalence of depressive symptoms in this population.

MATERIAL AND METHODS

Subjects and ethical approval

Inpatients aged over 65, hospitalized for three or more days, normally responsive and verbally coherent, who scored the minimum of seven points on the Abbreviated Mental Test Score (AMTS) were eligible for enrolment. Individuals previously diagnosed with dementia or other psychiatric disorders, receiving antipsychotic or antidepressant medication, and those reporting a traumatic event such as serious accident or bereavement within the preceding year were excluded. Ethics approval was obtained from the Ethics Committee of the Silesian Medical University, Katowice, Poland (reference number KNW/0022/KB/207/14). All patients obtained detailed information regarding the study and signed a written consent form prior to participation.

Information regarding patient's history and current pharmacological treatment were gathered by a clinician based upon medical records. Material status, social contacts, degree of physical dependence, and prevalence of pain were determined according to self-report. Nutritional status was assessed using Nutritional Risk Screening (NRS) 2002 system. Epidemiological methods were used to analyze collected data.

Psychometric assessments

The Abbreviated Mental Test Score (AMTS) is a widely recognized diagnostic instrument used for initial assessment of the mental status in elderly patients, and a valuable dementia-screening tool. It comprises ten questions, each scoring one point if answered correctly. A total score of less than seven or eight is suggestive of cognitive impairment, although further testing is required to establish the diagnosis of dementia.[6] The scale was adopted as part of a questionnaire applied to the general patient population in order to enroll study participants.

The Geriatric Depression Scale (GDS) was developed specifically to measure depressive symptoms in the elderly. A Short Form GDS consists of 15 yes/no questions concern-

ing individual's mood in the week prior to survey, ten of them suggest the presence of depressive symptoms if answered affirmatively, the rest are indicative of depression if a negative answer is given. The results are interpreted as follows: 0-5 points – no depressive symptoms, 6-10 points – moderate depressive symptoms, 11-15 points – severe depressive symptoms.[7]

Both scales employed in the study are generally available, validated in a Polish population, and did not require investigators' consent before their use. Due to frequent cognitive impairment in elderly patients (the most common problems are with reading and writing), all questions were read to the participants during face-to-face interviews, and the investigator filled out the questionnaires.

Statistical methods

All statistical calculations were performed using STATISTICA version 10.0 (StatSoft Inc., Tulsa, USA) and Microsoft Excel 2010 (Microsoft, Redmond, USA). Quantitative variables were expressed as mean ± standard deviation (SD) when normally distributed and otherwise as median (95% confidence interval, 95% CI). Qualitative variables were expressed as absolute numbers and percentage. Shapiro-Wilk normality test was used to determine distribution of quantitative variables. Differences between two independent groups were examined with Student's t-test or Mann-Whitney U-test. Pearson and Spearman correlation coefficients were used depending on whether the data was normally distributed to determine the strength and the direction of the relationship between variables. Additionally, a multivariable linear regression model was developed to assess the association between GDS score and select response variables. A *P*-value of less than 0.05 was considered significant for all statistical analyses.

RESULTS

The study was conducted between September 2014 and October 2015 in three internal wards of two hospitals in the Silesian region of Poland. A total of 206 subjects were enrolled, with a mean age of 75.8 years (median = 75; 95% CI: 74.9–76.7). A summary of patients' characteristics is shown in Table 1.

Table 1. Sociodemographic and clinical characteristics of the study group (n = 206)

Variable		n	%
Gender	Female Male	121 85	58.7 41.3
Marital status	Widowed In a relationship Single Divorced	105 90 9 2	51.0 43.7 4.3 1.0
Education	Vocational Primary Secondary Tertiary	97 62 41 6	47.1 30.1 19.9 2.9
Living arrangements	Living with family Independent Nursing/residential home	158 47 1	76.7 22.8 0.5
Chronic disorders	Cardiovascular Endocrine and metabolic Musculoskeletal Digestive Genitourinary Respiratory Neurological Neoplastic (malignant & benign) Other	198 98 60 52 46 39 26 25 19	96.1 47.6 29.1 25.2 22.3 18.9 12.6 12.1 9.2
Pain complaints		155	75.2

[a]Mann-Whitney U-test, SD: standard deviation, NSAIDs: non-steroidal anti-inflammatory drugs

The overall mean GDS score was 4.9 (SD=3.4). Of the 68 (33.00%) individuals presenting depressive symptoms (GDS score > 5), 45 (21.8%) were rated as moderate, and 23 (11.2%) as severe. There was no statistically significant difference in the prevalence of depressive symptoms between genders (P = 0.4734). Pain was reported by 155 (75.2%) individuals. The GDS score was significantly higher (Z = 7.94, P = 0.0001, Mann-Whitney U-test) in individuals reporting pain (median = 5.0; 95% CI: 5.3–6.3) compared to those without (median = 2.0; 95% CI: 1.7–2.4).

The average number of medications taken was 6.9 (SD = 2.7). The average number of chronic physical disorders was 3.6 (median = 3.0; 95% CI: 3.3–3.8). We observed a significant association between the GDS score and the use of statins, cytostatic agents, corticosteroids, benzodiazepines, cardiac glycosides, non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, non-psychotropic drugs with anticholinergic properties, and centrally acting analgesics (all P < 0.05; Table 2).

Table 2. Geriatric Depression Scale scores based on the type of medications used

Medication class	Medication use		
	No	Yes	P-value[a]
Statins (mean, SD)	4.8 (3.3)	5.6 (3.5)	0.0437
Cytostatic agents (mean, SD)	4.9 (3.3)	8.3 (3.0)	0.0072
Corticosteroids (mean, SD)	4.9 (3.3)	8.2 (3.4)	0.0021
Benzodiazepines (mean, SD)	4.9 (3.3)	8.1 (3.0)	0.0007
Cardiac glycosides (mean, SD)	4.9 (3.3)	7.1 (3.9)	0.0319
NSAIDs (mean, SD)	4.8 (3.3)	7.1 (3.4)	0.0001
Muscle relaxants (mean, SD)	4.9 (3.3)	9.9 (3.4)	0.0012
Non-psychotropic drugs with anticholinergic properties (mean, SD)	4.8 (3.3)	7.9 (3.3)	0.0001
Centrally acting analgesics (mean, SD)	4.8 (3.3)	7.4 (3.3)	0.0001

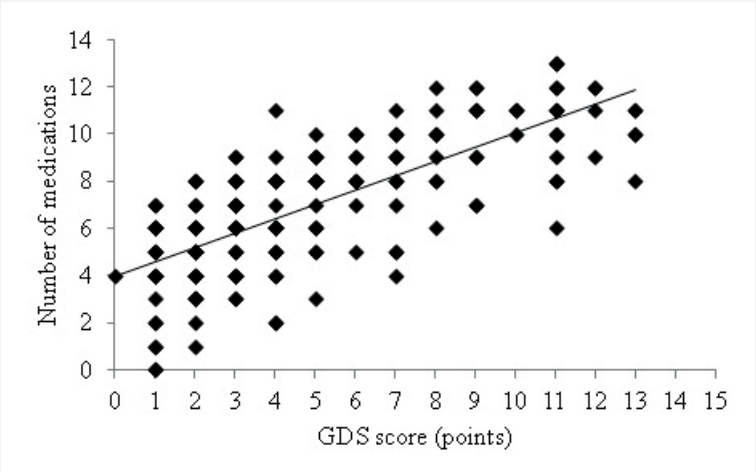

Figure 1. Correlation between the number of medications and Geriatric Depression Scale (GDS) (Spearman coefficient, R = 0.74, P = 0.0001)

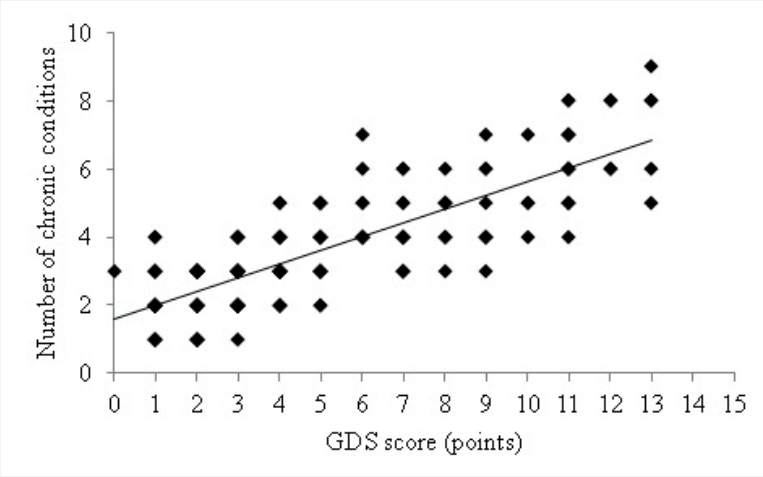

Figure 2. Correlation between the number of chronic conditions and Geriatric Depression Scale (GDS) (Spearman coefficient, R = 0.78, *P* = 0.0001)

Table 3. Relationship between GDS score and select response variables, multivariate analysis

	B	P-value
Gender	-0,18	0,4963
Age	-0,01	0,8738
Marital status	-0,19	0,1656
Education	0,08	0,6654
Place of living (urban/rural area)	-0,12	0,6446
Material status	0,61	0,0127
Social contacts	0,64	0,0047
Degree of physical independence	-0,99	0,0001
Chronic pain complaints	0,62	0,0384
Nutritional status	0,01	0,6616
Number of chronic conditions	0,57	0,0001
Number of medications taken	0,18	0,0487

GDS: Geriatric Depression Scale; B: Unstandardized Coefficients

GDS score was positively correlated with the number of medications used (R = 0.74, *P* = 0.0001; Figure 1) and the number of chronic conditions (R = 0.78, *P* = 0.0001; Figure 2). No correlation was found between depressive symptoms and age (R = 0.05, *P* = 0.1149). A multivariable linear regression model showed positive relationship between GDS score and the number of medication taken, number of chronic conditions, material impoverishment, social deprivation, and chronic pain complaints. The relationship was negative for degree of physical independence (Table 3).

DISCUSSION

The results of this study indicate that the use of multiple medications in geriatric patients is associated with an increased rate of depressive symptoms. Although information regarding the correlation between polypharmacy and depression in older populations is scarce, the results presented here are consistent with previous findings.[8] For example, an Italian study of 2,568 elderly patients previously showed that a GDS score of > 6 correlated positively with

the number of medication taken, which, together with previous assumptions, indicates that the relationship between depression and polypharmacy is bidirectional.[9]

The definition of polypharmacy varies across researchers, who arbitrarily set various cut-off points to characterize this phenomenon. Most simply, polypharmacy can be described as the use of multiple medications or, to denote its pejorative connotation, the use of more medications than is clinically justified. Epidemiological data show that the average number of medications taken by community-dwelling older adults ranges from 4 to 8.[10] According to a population-based survey by Qato *et al.*, 29% of patients aged 57 to 85 living in the community took >5 prescription medications.[11] The prevalence of polypharmacy in hospital setting is also high: the mean number of medications received in our study population was seven, which is similar to findings by other researchers. For example, a REPOSI study conducted in Italy showed that 51.9% of patients admitted to internal wards took more than 5 medications (4.9 on average) and the numbers increased further at discharge.[12] Similarly, in a multicenter European study, the median number of medications taken by elderly hospitalized patients was 6 (IQR = 4.0–9.0).[13]

The use of extensive drug regimens reflects the need to treat multiple conditions that often coexist in the elderly. According to a systematic review by Marengoni *et al.*, multimorbidity (defined as the co-occurrence of two or more chronic disorders) affects from 55 to 98% of the elderly.[14] Major physical illnesses also constitute a risk factor for geriatric depression, and evidence exists that the prevalence of depressive syndromes is significantly higher in multimorbid individuals.[15] Due to the overlap of depressive and somatic symptoms, assessing depression in older adults with multiple chronic conditions may be difficult and subject to confounding variables.

Patients reporting pain complaints are also more prone to misdiagnosis. Indeed, data regarding the correlation between pain and depressive symptoms are conflicting, and the attempts to measure pain perception threshold in depressed and non-depressed individuals has led to controversial results.[16] In our study, individuals reporting pain complaints more often had depressive symptoms, which is consistent with some of the previous findings, especially those regarding chronic pain.[17] This observation, however, raises a question regarding the correlation between depressive symptoms and the use of analgesics (both non-steroidal and centrally acting), as the experience of physical suffering may lead to an increased consumption of pain medications and therefore act as a confounder.

Polypharmacy is associated with a higher potential for pharmacological interactions and a greater possibility of prescribing cascade, that is, adding an extra medication to treat side effects wrongly interpreted as a new ailment.[18] The likelihood of adverse drug events (ADEs) rises along with the number of medications taken by the patient.[19, 20] According to an 11-year population-based observation by Bourgeois *et al.*, individuals taking 5 or more medications were 88% more likely to experience an ADE compared to those taking less.[21] Similar data were provided by other authors: a literature review by Fulton and Allen indicated the risk of ADEs correlated positively with the number of medications, and amounted to 82% when seven or more drugs were used.[22] The particular vulnerability of geriatric patients to ADEs results from biological changes in organ functioning and diminished drug clearance.[23] Therefore, due to age-related differences in pharmacokinetics and pharmacodynamics, therapeutic effects and pharmacological interactions in the elderly are more difficult to predict.

When investigating relationships between medications and depression, we must consider a drug's capacity to cause or exacerbate psychiatric disorders. This can be attributed to their specific action on neurotransmitters and receptors in the CNS, as well as their indirect impact on brain metabolism via peripheral regulation. In addition to drugs that act primarily on the CNS, psychotropic properties are also observed in other pharmaceuticals, including cardiovascular therapeutics, antiepileptics, antihistamines, analgesics, antimicrobial and chemotherapeutic agents, and cytostatics.[24] In our study, we found that many of the medications were associated with depressive symptoms in the elderly, as discussed below.

Muscle relaxants and other non-psychotropic drugs with anticholinergic properties were associated with a higher GDS score in this study. There is vast clinical evidence of the negative impact of anticholinergic drugs on cognition and functional performance in the elderly patients.[25] Several groups of non-psychotropic medications have been identified to worsen the existing cognitive dysfunction, cause alterations in the mental status, and induce psychotic symptoms. These include: first-generation antihistamines (promethazine, clemastine), alkaloid-containing antispasmodics (scopolamine, hyoscyamine), skeletal muscle relaxants (baclofen, tolperisone), antimuscarinic agents for overactive bladder (oxybutynin, tolterodine), opioids (codeine, morphine, fentanyl), and some cardiovascular drugs (digoxin, captopril). On the other hand, the impact of the anticholinergic medications on the affective status is more complex. In light of physiological evidence suggesting that hyperactivity of the cholinergic system contributes

to the pathogenesis of mood disorders, muscarinic receptor antagonists have been investigated as antidepressants. For example, evidence that scopolamine administered intravenously exerts a rapid antidepressant effect and has a good safety profile was provided by a recent review of randomized controlled trials.[26] However, more research is needed to confirm these findings, and unravel the impact of anticholinergic medications on depression in the elderly.

Cardiac glycosides (eg, digoxin) can also exert strong anticholinergic effects.[27] Due to diminished elimination rates, the risk of side effects with cardiac glycosides is increased in the elderly, although adverse reactions have also been observed at therapeutic concentrations. A number of case reports and small clinical trials support the notion that cardiac glycosides may be associated with depression, but this was not confirmed in prospective studies.[28] We recorded increased prevalence of depressive symptoms in patients treated with digoxin, yet this may partly result from generally high rates of depression in patients with heart failure.[29]

In our study, the GDS score was also increased with the use of corticosteroids, which is consistent with previous findings. Psychiatric side effects associated with systemic corticosteroid use are frequent, affecting approximately 6% of patients.[30] Most often they include agitation, anxiety, insomnia, depressive disorders, delusion, mania, and confusional state, although delirium, aggressive behavior, cognitive impairment, and depersonalization have also been observed. Older age does not seem to be a predictor of a psychiatric risk; however, hypoalbuminemia, or the concurrent use of medications in geriatric patients that increase serum levels of corticosteroids, may heighten the probability of psychiatric adverse reactions.[31]

Neurotoxicity of cytostatic and immunomodulating drugs used in the treatment of various types of cancer is well described in medical literature (in both *in vitro* and *in vivo* studies), yet the underlying mechanisms have not been fully explained. The potential harmful effect of antineoplastic agents on the nervous system can manifest as vascular complications, peripheral neuropathies, cognitive impairment, and psychological distress, including depression.[32] According to literature, a decline in cognitive function and affective status is a frequent observation in a number of cancer survivors. The results of our study are in line with these findings, although the type and intensity of neurological side effects can be influenced by a range of other variables, such as the effect of concomitant conditions or individual patient's characteristics.

Depressive symptoms may also be associated with a prolonged use of benzodiazepines or their withdrawal. Benzodiazepine use in the elderly can precipitate the onset of depression;[33] however, owing to rapid anxiolytic effects and good tolerance, they often constitute the first-line treatment of mood and anxiety disorders. Despite numerous adverse consequences and high addictive potential, benzodiazepines are readily prescribed in geriatric populations to address depressive symptoms and sleeping disturbances. According to a meta-analysis by Sithamparanathan *et al.*, chronic use of benzodiazepines in the elderly is associated with a significant risk of ADEs, including depression, drowsiness, insomnia, and tremor.[34] Additionally, pharmacological interactions with opioids, antihistamines, anticonvulsants, or atypical neuroleptics may result in prolonged or excessive sedation and confusional states, whereas CYP3A4 and CYP2C19 inhibitors (eg, clarithromycin, ciprofloxacin, ketoconazole, dilitiazem, and omeprazole) increase benzodiazepines plasma concentrations and potentiate their depressive effect on the CNS. We observed an association between benzodiazepine use and depressive symptoms in our patients. This, however, may not be attributable solely to the direct effect of medication and should be viewed against other factors, such as the duration of use, or affective status prior to the initiation of treatment.

Data regarding the possible role of statins in inducing depression are contradictory.[35] Nevertheless, a large body of evidence indicate that low lipid concentrations may predispose to depressive symptoms, mainly by affecting serotonin activity of the brain and inhibiting neuronal growth.[36] While statins effectively lower blood cholesterol levels and limit the risk of cardiovascular complications, the possible negative impact of long-term statin use on the patient's psychological wellbeing should also be considered.[37] In our study, significantly higher GDS scores were recorded in patients treated with statins (P = 0.0437). Interestingly, this was not observed for fibrates (P = 0.3785), which reduce blood triglyceride levels. Therefore, further research is necessary to investigate the lipid-lowering drugs and various psychiatric outcomes.

In summary, understanding the complexity of geriatric care, as well as recognizing the possible negative effects of medications on the affective status, should help physicians to optimize drug regimens in the future. Other factors, such as socio-economic situation and accessibility of medicines, should also be encompassed in order to derive the desired benefit from pharmacotherapy. Although polypharmacy indisputably carries an increased risk of adverse events and affects adherence, this should not deter the physician from introducing a therapy that is beneficial for the patient. This is especially true when the potential advantages of the therapy outweigh the perils – as Albert Einstein once put it, «*Everything should be made as simple as possible, but not simpler.*»

Our study is subject to several limitations. First, the observation was conducted in a hospital setting and therefore its results should only be extrapolated to other elderly populations (community and nursing home dwellers) with caution. Second, the time of administration of the GDS, in regard to the patient's admission and discharge, varied among individuals, which could have influenced the recorded score. Third, GDS was developed as a screening tool for depression, and its definitive diagnosis can only be established following a thorough psychiatric assessment. Thus, given the exploratory character of this study and its relatively small patient sample, more research is needed to validate the results.

CONCLUSIONS

Maintaining independence and good quality of life is an important health outcome in the elderly and should be the goal of medical interventions. Our study indicates that the use of multiple medications, which has become a necessity in the face of the demographic changes and the growing proportion of seniors, is associated with depressive symptoms in geriatric patients. However, further research is required in order to confirm these associations and provide new guidelines to optimize drug regimens in the elderly.

REFERENCES

1. European Commission; Directorate General for Economic and Financial Affairs. *The 2015 Ageing Report: Underlying Assumptions and Projection Methodologies. European Economy*. 2014.
2. Barua A, Ghosh MK, Kar N, Basilio MA. Prevalence of depressive disorders in the elderly. *Ann Saudi Med*. 2011;31(6):620-624.
3. Royal College of Psychiatrists; Faculty of Old Age. *Who Cares Wins. Improving the outcome for older people admitted to the general hospital: guidelines for the development of liaison mental health services for older people*. London. 2005.
4. Wiese BS. Geriatric depression: The use of antidepressants in the elderly. *BCMJ*. 2011;53:341-347.
5. Parker C. Psychiatric effects of drugs for other disorders. *Medicine*. 2012;40(12):691-695.
6. Hodkinson HM. Evaluation of a mental test score for assessment of mental impairment in the elderly. 1972. *Age Ageing*. 2012;41 Suppl 3:iii35-40.
7. Sheikh J, Yesavage J. Geriatric Depression Scale: recent evidence and development of a shorter version. *Clin Gerontol*. 1986;5:165-173.
8. Liu CP, Leung DS, Chi I. Social functioning, polypharmacy and depression in older Chinese primary care patients. *Aging Ment Health*. 2011;15(6):732-741.
9. Antonelli Incalzi R, Corsonello A, Pedone C, Corica F, Carbonin P. Depression and drug utilization in an elderly population. *Ther Clin Risk Manag*. 2005;1:55-60.
10. Maher RL, Hanlon J, Hajjar ER. Clinical consequences of polypharmacy in elderly. *Expert Opin Drug Saf*. 2014;13(1):57-65.
11. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA*. 2008;300(24):2867-2878.
12. Nobili A, Licata G, Salerno F, *et al*.. Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. *Eur J Clin Pharmacol*. 2011;67(5):507-519.
13. Gallagher P, Lang PO, Cherubini A, *et al*.. Prevalence of potentially inappropriate prescribing in an acutely ill population of older patients admitted to six European hospitals. *Eur J Clin Pharmacol*. 2011;67(11):1175-1188.
14. Marengoni A, Angleman S, Melis R, *et al*.. Aging with multimorbidity: a systematic review of the literature. *Ageing Res Rev*. 2011;10(4):430-439.
15. Spangenberg L, Forkmann T, Brahler E, Glaesmer H. The association of depression and multimorbidity in the elderly: implications for the assessment of depression. *Psychogeriatrics*. 2011;11(4):227-234.
16. Marazziti D, Mungai F, Vivarelli L, Presta S, Dell'Osso B. Pain and psychiatry: a critical analysis and pharmacological review. *Clin Pract Epidemiol Ment Health*. 2006;2:31.
17. Banks SM, Kerns RD. Explaining high rates of depression in chronic pain: A diathesis-stress framework. *Psychol Bull* 1996;119:95-110.
18. Abdulraheem IS. Polypharmacy: A Risk Factor for Geriatric Syndrome, Morbidity & Mortality. *Aging Sci*. 2013;1.
19. Nobili A, Pasina L, Tettamanti M, *et al*.. Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. *J Clin Pharm Ther*. 2009;34(4):377-386.
20. Pirmohamed M, James S, Meakin S, *et al*.. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329(7456):15-19.
21. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: an 11-year national analysis. *Pharmacoepidemiol Drug Saf*. 2010;19(9):901-910.
22. Fulton MM, Allen ER. Polypharmacy in the elderly: a literature review. *J Am Acad Nurse Pract*. 2005;17(4):123-132.
23. Nobili A, Garattini S, Mannucci PM. Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium. *J Comorbidity*. 2011;1:28-44.
24. Turjansk N, Lloyd GG. Psychiatric side-effects of medications: recent developments. . *Adv Psychiatr Treat*. 2011;11:58-70.

25. Pasina L, Djade CD, Lucca U, *et al*.. Association of anticholinergic burden with cognitive and functional status in a cohort of hospitalized elderly: comparison of the anticholinergic cognitive burden scale and anticholinergic risk scale: results from the REPOSI study. *Drugs Aging*. 2013;30(2):103-112.

26. Drevets WC, Zarate CA, Jr., Furey ML. Antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine: a review. *Biol Psychiatry*. 2013;73(12):1156-1163.

27. Cheng JW, Rybak I. Use of digoxin for heart failure and atrial fibrillation in elderly patients. *Am J Geriatr Pharmacother*. 2010;8(5):419-427.

28. Celano CM, Freudenreich O, Fernandez-Robles C, Stern TA, Caro MA, Huffman JC. Depressogenic effects of medications: a review. *Dialogues Clin Neurosci*. 2011;13(1):109-125.

29. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ. Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. *J Am Coll Cardiol*. 2006;48(8):1527-1537.

30. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clin Proc*. 2006;81(10):1361-1367.

31. Kenna HA, Poon AW, de los Angeles CP, Koran LM. Psychiatric complications of treatment with corticosteroids: review with case report. *Psychiatry Clin Neurosci*. 2011;65(6):549-560.

32. Yang M, Moon C. Neurotoxicity of cancer chemotherapy. *Neural Regen Res*. 2013;8(17):1606-1614.

33. van Vliet P, van der Mast RC, van den Broek M, Westendorp RG, de Craen AJ. Use of benzodiazepines, depressive symptoms and cognitive function in old age. *Int J Geriatr Psychiatry*. 2009;24(5):500-508.

34. Sithamparanathan K, Sadera A, Leung L. Adverse effects of benzodiazepine use in elderly people: a meta-analysis. *Int J Geriatr Psychiatry*. 2012;7:107-111.

35. Swiger KJ, Manalac RJ, Blaha MJ, Blumenthal RS, Martin SS. Statins, mood, sleep, and physical function: a systematic review. *Eur J Clin Pharmacol*. 2014;70(12):1413-1422.

36. Ainiyet B, Rybakowski JK. Suicidal behaviour and lipid levels in unipolar and bipolar depression. *Acta Neuropsychiatr*. 2014;26(5):315-320.

37. Tatley M, Savage R. Psychiatric adverse reactions with statins, fibrates and ezetimibe: implications for the use of lipid-lowering agents. *Drug Saf*. 2007;30:195-201.