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RESEARCH ARTICLE

Association Between Drug Burden Index and Functional and Cognitive Function in ~~Polypathological Patients DBI and Comorbidity~~

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Abstract: ***Background*:** Anticholinergic and sedative drugs are associated with adverse events such as cognitive and functional impairment in elderly. The Drug Burden Index (DBI) is a measure of an individual's total exposure to anticholinergic and sedative drugs.

***Objetive*:** The study aimed to evaluate the association between the total DBI and cognitive and functional impairment in ~~polypathological patients (PP)~~.

***Setting*:** ~~Polypathological patients~~ enrolled in the IMPACTO project.

***Methods*:** Cross-sectional observational study.

***Main outcome measure*:** The anticholinergic and sedative exposure was calculated using DBI. The Pfeiffer Test (PT) was used for cognitive status and the Barthel Index (BI) for functional status.

***Results*:** 336 patients were included (mean age 77.6 ± 8.7 years, 54.2% men and a mean of 11.5 ± 3.7 prescribed drugs). 180 patients (53.6%) exposed to anticholinergic and/or sedative drugs were identified. The median score obtained in PT was slightly higher in exposed patients (1 (IQR 0-2) and 2 (IQR 0-4), p = 0.082 in "non-exposed" and "exposed", respectively). The bivariate analysis showed an association [0.544 (95% CI 0.044-1.063, p = 0.03)]. The median obtained in the BI analysis was 85.0 (IQR 30.0) and 75.5 (IQR 42.5) p = 0.002, in "non-exposed" and "exposed", respectively. After the adjusted analysis, a relationship was obtained between both the variables [-9,558 (95% CI-15,794; -3,321, p = 0.03)].

***Conclusion*:** Higher DBI is associated with the impairment of functional status and, slightly to the deterioration of cognitive function in ~~PP~~. DBI should be considered in ~~PP~~ to optimize the pharmacological treatment of a group of special interest due to its vulnerability.

Keywords: Anticholinergic burden, anticholinergic drugs, drug burden index, frail elderly, multimorbidity.

1. INTRODUCTION

Continuous growth in the prevalence of chronic diseases [1] leads to an increase in patients with multimorbidity. They are older patients who present two or more chronic diseases associated to severity or disability, suffer from frequent exacerbations of their underlying pathology and generate a constant demand for different care settings [2].

The prevalence of multimorbidity, although low in general population, is high in the hospital environment [3]. 83.6% of patients in Internal Medicine have at least one chronic disease and 48.3% are patients with multimorbidity [4]. These patients tend to suffer from problems such as the increase of polymedication, the presence of comorbidities and continuous care transitions [5].

On the other hand, approximately 50% of elderly uses at least one drug with anticholinergic activity [6]. These drugs are considered potentially inappropriate in older people, however, are often prescribed for the symptomatic treatment of clinical situations as urinary incontinence.

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Anticholinergic drugs may produce peripheral adverse effects such as urinary retention, constipation, decreased secretions, amongst others, and central ones, such as delirium or cognitive and functional impairment [7].

Pharmacokinetic and pharmacodynamics changes (mainly metabolism and excretion) may alter significantly the effect of pharmacological treatment with advancing age [8]. All these changes predispose the older patient to develop adverse reactions and drug interactions more frequently. They are estimated to face seven times more adverse drug reactions that lead to hospital admission than in young adults [9].

When a patient receives one or more drugs with anticholinergic activity, a cumulative effect occurs, which increases the risk of developing anticholinergic adverse effects. This is known as an anticholinergic burden [10]. There are anticholinergic risk scales that estimate the exposure to these drugs and calculate the total burden that a patient receives based on their treatment.

Drug Burden Index (DBI), developed by Hilmer *et al.* in 2007 [11] quantifies exposure to anticholinergic and sedative medications in older patients, based on the hypothesis that the cumulative effect is linear. The total burden is obtained by a simple mathematical formula: Total Burden = $\Sigma D / \delta + D$, where D is the daily dose of the drug that the patient receives and δ is the recommended minimum daily dose of the drug.

The δ value is estimated with the minimum registered or licensed dose on the national formulary and there are some differences between countries. DBI has been adapted and validated against a range of clinical outcomes in different countries (United States [11], Australia [12], Finland [13] and United Kingdom [14]). For example, diazepam has a minimum registered or licensed dose of 4 mg in the United States and 5 mg in Australia [15]. Until now, there is no version adapted to Spain.

Several studies have shown that increased exposure to anticholinergic and/or sedative drugs is associated with impaired physical function and functional status in community-dwelling older people, who maintain a stable level of health [11, 12, 15]. Patients with comorbidity and, specifically, older adults with multiple chronic conditions require greater attention to their treatment. Because of their old age and frailty, they are especially vulnerable to the prolonged and cumulative administration of anticholinergic and sedative drugs.

The aim of the study is to evaluate the associations between total DBI score and cognitive and functional status measures in patients with multimorbidity, enrolled in the IMPACTO project.

2. MATERIAL AND METHODS

This is a retrospective, observational cross-sectional study of patients with multimorbidity (according to the definition of the Integrated Care Process, Health Ministry [2]) included in the IMPACTO project, a multicenter study developed between October 2010 and April 2012. The objective of this study was to evaluate the clinical impact of a multilevel intervention model based on shared care between Reference Internist and Primary Care in a population of patients with multimorbidity after hospital discharge.

The target population of our study was elderly patients (aged> 60 years) with multimorbidity, i.e. those with two or more chronic diseases included in one of the eight defined clinical categories [2]. Patients with severe dementia and/or Alzheimer's disease were excluded.

Demographic variables (age and sex), clinical (Pfeiffer's test (PT), Barthel's index (BI), Lawton-Brody Instrumental activities of daily living scale (IADL), Charlson's index (CI) and pharmacological profile (drug, posology and route of administration) were collected for each patient from electronic data. Data were collected prior to the development of the disease that leads to hospitalization. Drugs such as antibiotics due to their limited duration, as well as drugs of topical application due to their low systemic effect (not applicable to transdermal patches) were not included. The anticholinergic and sedative burden was calculated with those drugs administered chronically, i.e. drugs prescribed at discharge were excluded. For our study, we calculated the total burden developing DBI adapted to Spain. The list of medications considered to be sedating and/or anticholinergic was generated utilizing the original list by the authors of the DBI study [16] and the contributions of the Dispennette *et al.* study [17]. Drugs not marketed or not available in Spain were not included. On the other hand, a minimum registered dose review was performed by consulting the label of each drug in the Spanish Agency of Medicines [18] (SAM). Total DBI range was set as 0 without risk, <1 low risk and ≥1 high risk [18].

For our study, "exposed" or "at risk" patients were considered those who were prescribed or took at least one anticholinergic and/or sedative drugs, i.e. patients with a higher score than zero.

To determine the cognitive status, PT was used, a questionnaire specifically designed to detect cognitive impairment in elderly patients [2, 20]. Patients are divided into four levels according to the number of errors: normal (0-2 errors), mild impairment (3-4 errors), moderate impairment (5-7 errors), severe impairment (8-10 errors).

For the functional status, we used BI which assesses the autonomy of the person to perform basic and essential activities of daily life [2, 21]. The BI measures the functional independence at personal care, mobility, locomotion and excretion: feeding, bathing, grooming, dressing, bowl and bladder care, toilet use, transfers, ambulation, and stair climbing. Scores are allocated according to their capacity to perform them: total dependency (0-20), severe (21-60), moderate (61-90), low (91-99) and independence (100). Also the IADL, which assesses the capacity to perform instrumental activities of daily living that are necessary to live self-sufficiently in the community [2, 22] was used. IADLs are defined as those activities whose accomplishment is necessary for continued independent residence in the community as they are more sensitive to subtle functional deficiencies than the activities of daily living. The items evaluate the capacity to use the telephone, shopping, food preparation, housekeeping, laundry, mode of transportation, responsibility for own medications and ability to handle finances. The score ranges from 0 (maximum dependence) to 8 (total independence).

The CI is a system of evaluation of life expectancy at ten years depending on the age at which it is evaluated and the subject's comorbidities [23]. In general, it is stratified into three levels: no comorbidity (0-1), low comorbidity (2), high comorbidity (> 3).

The study was approved by the Ethical Committee of the Virgen del Rocío University Hospital from IMPACT project and informed consent was obtained from the patient.

Statistical analysis was performed using the SPSS® program (version 22 for Windows). Student's t or Mann-Whitney U were performed to study the association between total DBI range (0, <1 or ≥1 and the total scores of PT, BI and IADL whether they followed a normal distribution or not. The PT, BI, IADL scores were described and were re-encoded in quartiles. A linear regression by bivariate analysis was performed to detect possible relationships between the variables and, subsequently, a multivariate analysis by adding confounding factors to verify if there were variables that distorted the measure. These confounding factors were age, sex and Charlson's index, adjusting the previous model by these factors.

The means and 95% confidence intervals were obtained and it was assumed that the differences found were statistically significant when $p < 0.05$.

3. RESULTS

A total of 336 patients were included in the analysis. The average age was 77.6 ± 8.7 years and 54.2% were males. The average number of drugs taken per patient was 11.5 ± 3.7 and the average number of different anticholinergic/sedative drugs per patient was 3.2 ± 0.1. Out of the 234 drugs prescribed in total, 38 (16.2%) were drugs with anticholinergic and/or sedative activity, according to DBI (Table **1**).

The most frequently prescribed anticholinergic and/or sedative drugs were benzodiazepines and analogues (30.2%), alpha adrenergic inhibitors (21.7%), antidepressants (18.9%, of which 13.9% were serotonin reuptake inhibitors), antipsychotics (9.3%), opiates (6.9%), antipyretics (5.4%), antispasmodics (2.7%), antidiarrheals and antiemetics (2.3%), antihistamines (1.9%) and others (0.7%).

A total of 180 patients (53.6%) had an anticholinergic and/or sedative burden (DBI score >0) with a average DBI of 0.44 ± 0.53. The patients were distributed according to DBI category: 129 (38.4%) at low risk (DBI<1), with a mean value of 0.59 ± 0.13; and 51 (15.2%) at high risk (DBI≥1), with a mean value of 1.43 ± 0.46.

The statistical analysis is summarized in Tables **2** and **3**.

The PT was available for 286 patients. In descriptive analysis, the average PT score of patients increases as total DBI score does. It was one point higher in patients with total DBI ≥ 1 (2; IQR 0-3.7) than patients not exposed, i.e. total DBI zero (1; IQR 0-2), however, without statistical significance ($p = 0.221$). Results of the linear regression analysis were similar. For every unit increase in DBI, the PT score increased by 0.554 (95 % CI 0.044; 1.063; p= 0.03). When adjusting with confounding factors (age, sex and CI), loses statistical significance (0.420; 95 % CI 0.053; 0.893; p=0.08).

Table 1. Demographical and clinical characteristics.

Characteristics	Not exposed	Exposed
Number of patients N=336, (n,%)	156 (46.4)	180 (53.6)
Age (years, average± SD)	76.3±9.2	77.3±9.1
Women (%)	43.6	48.3
Total number of drugs (average± SD)	11.7±4.3	11.6±3.4
Charlson index (median [IQR])	4(2-5)	4(3-5)
Number of exposed patients according to risk, (n,%):		
No risk (DBI=0)	156 (46.4)	
Low risk (DBI <1)	129 (38.4)	
High risk (DBI≥1)	51 (15.2)	

SD: Standard deviation. IQR: Interquartile range. DBI: Drug Burden Index

Table 2. Descriptive analysis of the association between DBI and functional and cognitive impairment.

Clinical Variables	Median	IQR (p25-p75)	P value
Pfeiffer Test[a]			0.221
DBI =0 (n=140)	1.0	0-2.0	
DBI<1 (n=106)	1.5	0-4.0	
DBI≥1 (n=40)	2.0	0-3.7	
Barthel Index[b]			0.008
DBI =0 (n=119)	85	70-100	
DBI<1(n=97)	75	47-95	
DBI≥1 (n=36)	75	55-95	
Lawton and Brody Index[b]			0.139
DBI =0 (n=137)	3	1-6	
DBI<1 (n=105)	3	1-5	
DBI≥1 (n=42)	3	1-7	

DBI: Drug Burden Index IQR: Interquartile range.
[a]Higher scores indicate worse cognition. Pfeiffer Test score range 0-10.
[b]Higher scores indicate less impairment. Barthel Index score range 0-100, Lawton and Brody Index score range 0-8.

Table 3. Adjusted analysis of the association between DBI and functional and cognitive impairment.

	Model 1			*Model 2*		
Clinical Variables	***Beta value***	***CI 95%***	***P value***	***Beta value***	***CI 95%***	***P value***
Pfeiffer Test[a]	0.554	0.044;1.063	0.03	0.420	0.053;0.893	0.08
Barthel Index[b]	-9.558	-15.794; -3.321	0.03	-7.116	-13.093;-1.139	0.02
Lawton and Brody Index[b]	-0.419	-1.007;-1.169	0.16	-0.360	-0.935;-0.215	0.22

DBI: Drug Burden Index Model 1: Bivariate analysis. Model 2: Multivariate analysis adjusted by age, sex and Charlson Index. CI: Confidence interval.
[a]Higher scores indicate worse cognition. Pfeiffer Test score range 0-10.
[b]Higher scores indicate less impairment. Barthel Index score range 0-100, Lawton and Brody Index score range 0-8.

Table 4. DBI list of drugs. DBI δ adapted in Spain.

DRUGS	DBI δ (mg)
alfuzosin	7.5
alprazolam	0.5
amitriptyline	25
aripiprazole	10
asenapine	10
baclofen	15
benztropine	0.5
brompheniramine	9
bromocriptine	1.25
buspirone	10
carbamazepine	200
cetirizine	10
cyclobenzaprine	20
cyproheptadine	4
citalopram	10
clomipramine	10
clonazepam	1.5
clonidine	0.15
clorazepate	5
chlordiazepoxide	5
chlorpheniramine	4
chlorpromazine	25
clozapine	12.5
codeine	28.7
dexchlorpheniramine	6
dextromethorphan	60
diazepam	4
dicyclomine=dicycloverine	5
diphenhydramine	50
dimenhydrinate	50
disopyramide	400
doxazosin	1
doxepin	25
doxylamine	12.5
escitalopram	10
phenelzine	15

(Table 4) Contd....

DRUGS	DBI δ (mg)
phenytoin	300
phenobarbital	50
fentanyl transderman system	0.012
fesoterodine	4
flavoxate	200
fluoxetine	20
flurazepam	30
gabapentin	300
haloperidol	1.5
hydromorphone	4
hydroxyzine	25
imipramine	10
lamotrigine	25
levetiracetam	500
levocetirizine	5
lithium	400
loperamide	2
loratadine	10
lorazepam	1
meclizine	25
methadone	5
methyldopa	250
methocarbamol	500
metoclopramide	10
mirtazapine	15
morphine intravenous	4
morphine oral	10
nabilone	2
nortriptyline	10
olanzapine	5
orphenadrine	100
oxazepam	10
oxcarbazepine	600
oxybutynin	15
oxycodone	20
paliperidone	3
paroxetine	20

(Table 4) Contd....

DRUGS	DBI δ (mg)
perphenazine	8
pimozide	1
pramipexole	0.264
prazosin	1
pregabaline	150
primidone	250
propantheline	22.5
quetiapine	50
risperidone	0.5
ropinerole	0.25
selegiline oral	5
sertraline	50
silodosin	8
solifenacin	5
tamsulosin	0.4
terazosin	1
tiagabine	5
thiothixene	10
tizanidine	6
tolterodine	4
tramadol	150
tranylcypromine	10
trazodone	100
triazolam	0.125
trifluoperazine	4
trihexyphenidyl	1
trimipramine	25
trospium	40
venlafaxine	75
zaleplon	5
ziprasidone	40
zolpidem	5
valproic acid	200

The BI was available for 252 patients. In descriptive analysis, the average BI score of patients not exposed to anticholinergic and/or sedative drugs was 85.0 (IQR 70-100) whereas that patients with total DBI >0 was lower (p = 0.002). In bivariate analyses, for every unit increased in DBI the PT score decreased by 9.558 (95 % CI -15.794; -3.321; p= 0.03). In multivariate analysis, the results were similar (-7.116; 95 % CI -13.093; -1.139; p= 0.02).

The IADL was available for 284 patients. No differences were observed in IADL averages. Results of linear regression analysis shows that, for every unit increase in DBI the IADL score decreased, but were not statistically significant.

Finally, Table **4** shows the list of anticholinergic and/or sedative drugs used in study calculations with their respective δ values, i.e.

Spanish version of DBI. A total of 106 drugs were included in the list.

4. DISCUSSION

The results of this study suggest fail to demonstrate that the cumulative effect of anticholinergic and/or sedative drugs on patients with multimorbidity worse cognitive status, because it didn´t reach statistical significance. The results of the relationship with the functional impairment are more consistent.

This was the first study to investigate the total DBI in older patients with multimorbidity. Most studies have focused in community-dwelling elders [12, 15, 16, 17]. Although the studies in institutionalized old people could be similar to this study in patients with multimorbidity [13, 24]. Also, it is the first study that used adapted DBI in our country, i.e. Spanish version. Therefore, the results obtained are interesting both by the population studied and by the testing of the tool in these patients.

Wilson *et al*.'s work performed on institutionalized older patients shows slightly higher percentages of exposed patients (69.9%) as well as patients at high risk (26.2%) than our study [24].

In this same work, the most commonly prescribed drugs are similar to those submitted herein. The most important difference lies in the alpha-adrenergic inhibitors, since they are not reflected in Wilson *et al*.'s article while they represent a 21.7% in our analysis, and in antidepressants (except SSRIs), whose percentage in the cited article is 17.4% [24], while our results show only 5.0%.

Our research group developed a systematic review to identify anticholinergic scales applicable to patients with multimorbidity (or with similar characteristics) [25]. The association results between cognitive status and total DBI were few and contradictory. For example, the DBI validation study developed by Hilmer *et a*l., is highlighted in which 3075 patients older than 70 years were analyzed. The Digit Symbol Substitution Test was used as an instrument to measure cognitive status and an association was obtained with the total DBI [15] (34.5 vs 35.5 p = 0.045). In contrast, the study by Bostock *et al.* found no association when using the Short Mental Test, a questionnaire similar to PT (correlation coefficient: -0.106 (p = 0.084) [26].

In other studies no results of association with cognitive impairment were found either. Gnjidic *et al.* studied patients older than 70 years and found no association between increasing DBI scores and lower performance in any of the results [27]. A recent prospective cohort study with a 5-year follow-up performed in the same population yielded little significant data about the influence of anticholinergic and sedative exposure on the cognitive status, referring to a small impairment of cognitive performance [28].

These results are consistent with our results. Exposure to medications with anticholinergic and sedative effects measured with the DBI was associated with poorer cognitive performance measures, however, after adjusting for confounders factors was not statistically significant. The instruments used in each study to measure cognitive status are different and can affect the results.

On the other hand, increasing DBI exposure was associated with poorer functional status in patients with multimorbidity. These findings are consistent with previous analysis in patients with similar characteristics to multimorbidity, i.e. institutionalized older people [13, 24]. Many studies of the systematic review previously cited, found an association between anticholinergic burden and functional impairment measured with different instruments [25]. Two studies included in this systematic review used the same test that our study (BI). Bostock *et al*. [26] in old hospitalized patients and Lowry *et al.* [14] in old frail patients with comorbidities admitted to geriatric wards. In both, their results showed a relationship between the DBI and functional impairment: RR 2.96 (1.21-7.27, p = 0.02) and OR 0.71 (95% CI 0.55-0.91; p = 0.007), respectively. The validation study of DBI also showed a positive association [11], using the Health, Aging, and Body Composition Study tool, 2.08 vs 2.21 p <0.001. Conversely, Wilson *et al*. studied 602 institutionalized elderly patients and showed no association after multivariate analysis in one of the *items*, gait speed [24] (-0.01 m / s (p = 0.3).

Two studies performed on community-dwelling old patients validate DBI in other countries, such as the United Kingdom [14] and Finland [13]. Although these populations are not similar to ours, , it is interesting to know that the BI was significantly lower with higher DBI in both studies.

Regarding IADL, there was no association in any of the analyses performed. When the DBI value increases no change in IADL was observed. Therefore, a relationship between exposure to total DBI and a worsening in complex activities that provide autonomy within the community in patients with multimorbidity cannot be established.

There are some limitations to this study. The inferences about the cause and the effect of the study findings are limited by the cross-sectional design. The medication use was based on medical records and electronic data. It would be convenient more accurate information on exposure, i.e. interviews or visual inspection during a clinic visit.

Further interventional studies and longitudinal designs are required to evaluate whether the association between increasing total DBI and impaired cognitive and functional status is causative, and to test if the reduction in DBI scores might improve multimorbidity patients' health status.

Despite these limitations, there are interesting results. Multimorbidity in older adults leads to polypharmacy with all its drug related problems [29]. It is necessary to understand the impact of these drugs and tend to reduce the polypharmacy. This is still not a common procedure because there are many barriers to stop the medications. However, this type of study provides evidences to perform an assessment of patient treatment, taking into account the situation of the patient, the prognosis and life expectancy. Therefore, to make decisions about the treatment, it is important performance an individualized assessment of the patient.

CONCLUSION

The use of medications with anticholinergic and sedative properties is common among patients with multimorbidity. Higher DBI scores are strongly associated with reduced functional status in this group. Our study provided that this correlation is also found with DBI adapted to the Spanish specifications.

DBI should be considered to optimize the pharmacological treatment of a group of special interest due to its vulnerability.

The prescriber can assess the potential effects of the disease and different treatment options on the patient's cognitive and functional status. Further research is required with longitudinal designs to examine and reinforce these results. It is important to determine whether the strategies aimed at decreasing the total DBI scores, either by decreasing doses, replacing or suspending drugs that are considered anticholinergic and/or sedative, may benefit this group of patients.

LIST OF ABBREVIATIONS

PT = Pfeiffer's test

BI = Barthel's index

IADL = Lawton-Brody Instrumental activities of daily living scale

CI = Charlson's index

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

~~Not applicable.~~

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Ward S, Parikh S, Workman B. Health perspectives: international epidemiology of ageing. Best Pract Res Clin Anaesthesiol 2011; 25: 305-17.

[2] Ollero M, Alvarez T, Barón F, *et al*. Proceso Asistencial Integrado. Atención al Paciente Pluripatológico. Consejería de Salud. Junta de Andalucía 2nd ed. Sevilla; 2007.

[3] García-Morillo JS, Bernabeu-Wittel M, Ollero-Baturone M, *et al*. Incidence and clinical features of patients with comorbidity attended in internal medicine areas. Med Clin (Barc) 2005; 125: 5-9.

[4] Plan Andaluz de Atención Integrada a Pacientes con Enfermedades Crónicas (PAAIPEC). Sevilla: Consejería de Salud y Bienestar Social. [Online].; 2012. Available from: http://juntadeandalucia.es/export/drupaljda/PlanAtencEECC.pdf.

[5] Galvan M, Santos B, Vega M, *et al*. Adecuación del tratamiento farmacológico en pacientes pluripatológicos. Aten Primaria 2013; 45(1): 6-20.

[6] Fox C, Richardson K, Maidment I, *et al*. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. J Am Geriatr Soc 2011; 59: 1477-83.

[7] López J, Zea M, Agüera L, Fernández M, Valentí M. Efecto de los fármacos anticolinérgicos en el rendimiento cognitivo de las personas mayores. Rev Psiquiatr Salud Ment (Barc) 2015; 8: 35-43.

[8] Shi S, Klotz U. Age-related changes in pharmacokinetics. Curr Drug Metab 2011; 12: 601-10.

[9] Budnitz D, Lovegrove M, Shehab N, Richards C. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 2011; 365: 2002-12.

[10] Tune L. Anticholinergic effects of medication in elderly patients. J Clin Psychiatry 2001; 62: 11-4.

[11] Hilmer SN, Mager DE, Simonsick EM, *et al*. A Drug Burden Index to define the functional burden of medications in older people. Arch Intern Med 2007; 167: 781-7.

[12] Gnjidic D, Cumming RG, Le Couteur DG, *et al*. Drug Burden Index and physical function in older Australian men. Br J Clin Pharmacol 2009; 68: 97-105.

[13] Gnjidic D, Le Couteur DG, Naganathan V, *et al*. Effects of Drug Burden Index on cognitive function in older men. J Clin Psychopharmacol 2012; 32: 273-7.

[14] Lowry E, Woodman RJ, Soiza RL, Hilmer SN, Mangoni AA. Drug Burden Index, physical function and adverse outcomes in older hospitalized patients. J Clin Pharmacol. 2012; 52: 1584-91.

[15] Hilmer SN, Gnjidic D, Abernethy DR. Drug Burden Index for international assessment of the functional burden of medications in older people. J Am Geriatr Soc 2014; 62:791-2.

[16] Hilmer SN, Mager DE, Simonsick EM, *et al*. Drug Burden Index Score and Functional Decline in Older People. Am J Med 2009; 122: 1142-9.

[17] Dispennette R, Elliott D, Nguyen L, Richmond R. Drug Burden Index score and anticholinergic risk scale as predictors of readmission to the hospital. Consult Pharm. 2014; 29(3): 158-68.

[18] Spanish Agency of Medicines and Health Products [internet]. Madrid: Spanish Agency of Medicines and Health Products; 2015 [acceso 18 de mayo 2017]. Available in: http://www.aemps.gob.es

[19] Kouladjian L, Gnjidic D, Chen TF, Mangoni AA, Hilmer SN. Drug Burden Index in older adults: theoretical and practical issues. Clin Interv Aging 2014; 9: 1503-15.

[20] Martínez J, Dueñas R, Onís MC, Aguado C, Albert C, Luque R. Adaptación y validación al castellano del cuestionario de Pfeiffer (SPMSQ) para detectar la existencia de deterioro cognitivo en personas mayores de 65 años. Med Clin (Barc) 2001; 117: 129-34.

[21] Mahoney FI, Barthel DW. Functional evaluation: The Barthel Index. Md State Med J 1965; 71: 61-5.

[22] Lawton MP, Brody EM. Assessment of older people: self-maintaining, and instrumental activities of daily living. Gerontologist 1969; 9: 179-86.

[23] Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373-83.

[24] Wilson NM, Hilmer SN, March LM, *et al*. Associations between Drug Burden Index and falls in older people in residential aged care. J Am Geriatr Soc 2011; 59: 875-80.

[25] Villalba-Moreno AM, Alfaro-Lara ER, Pérez-Guerrero MC, Nieto-Martín MD, Santos-Ramos B. Systematic review on the use of anticholinergic scales in polypathological patients. Arch Gerontol Geriatr 2016; 62: 1-8.

[26] Bostock CV, Soiza RL, Mangoni AA. Associations between different measures of anticholinergic drug exposure and Barthel Index in older hospitalized patients. Ther Adv Drug Saf 2013; 4: 235-45.

[27] Jamsen KM, Gnjidic D, Hilmer SN, Ilomäki J, Le Couteur DG, Blyth FM, et al. Drug Burden Index and change in cognition over time in community-dwelling older men: the CHAMP study. Ann Med 2017; 49: 157-64.

[28] Gnjidic D, Bell JS, Hilmer SN, Lönnroos E, Sulkava R, Hartikainen S. Drug Burden Index associated with function in community-dwelling older people in Finland: a cross-sectional study. Ann Med 2012; 44: 458-67.

[29] Halvorsen KH, Selbaek G, Ruths S. Trends in potentially inappropriate medication prescribing to nursing home patients: comparison of three cross-sectional studies. Pharmacoepidemiol Drug Saf 2017; 26: 192-200.