

LONG-TERM USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND DEPRESSION IN ELDERLY PATIENTS

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Abstract

Medication is a recognized factor that increases the risk of depression and is more important in the elderly patients due to polytherapy and secondary changes in pharmacokinetics and pharmacodynamics. Of all long-term use drug classes administered in elderly, we have found out significant differences in the mean scores of the Geriatric Depression Scale (GDS) only for the following drug classes old persons use: sedatives, anxiolytics and hypnotics, and non-steroidal anti-inflammatory drugs, respectively (NSAIDs). There have been no significant differences among the GDS mean scores when the main NSAIDs were used. For the sedatives' group after excluding patients who received simultaneously NSAIDs, the GDS mean score was not significantly different from that in the whole group. These data suggest that NSAIDs could have a direct effect on mood when they are long-term used by the elderly patients.

Rezumat

Medicația este un factor recunoscut de creștere a riscului pentru depresie și este cu atât mai importantă la pacienții vârstnici din cauza polimedicației și a modificărilor secundare de farmacocinetică și farmacodinamică. Dintre toate clasele de medicamente utilizate cronic la pacienții vârstnici am identificat diferențe semnificative statistic ale mediei scorului obținut la scala de depresie geriatrică (GDS) doar pentru următoarele clase de medicamente: sedative, anxiolitice și hipnotice, respectiv antiinflamatorii nesteroidiene (AINS). Nu s-au obținut diferențe semnificative ale mediei GDS la principalele substanțe AINS folosite. La grupul de pacienți ce au utilizat sedative după excluderea subiecților care au utilizat concomitent și AINS, valoarea medie a GDS nu a mai fost semnificativ diferită de cea a întregului lot de studiu. Aceste date sugerează că AINS ar putea avea un efect direct asupra dispoziției atunci când sunt utilizate cronic, la pacienții vârstnici.

Keywords: NSAIDs, chronic use, Geriatric Depression Scale, elderly patient

Introduction

The psychiatric disorders are an important public health issue in elderly patients. In accordance to the American Association for Geriatric Psychiatry, 20% of the people aged 55 years and older have mental

disorders that are not part of a normal aging process [Medical News Today, 2009]. The most common are mood, anxiety and cognitive impairment. Depression in elderly has a variable prevalence depending on diagnosis criteria, specific features of the analysed population sample (community residents, hospitalized or institutionalised people) or cultural differences between groups and can reach 45% of the hospitalized patients or even higher percentages in people with Alzheimer's disease [1,4,5,8,9]. The epidemiological data show that 35 million US citizens were aged 65 years or older in 2000; if in 1970 statistics reported 4 million elderly people with mental disorders, it is estimated that this number will increase to 15 million in 2030 [7]. There are many known risk factors for elderly depression: genetic susceptibility and family history, age related hormonal change, personality, multiple chronic health conditions, disabilities, economical conditions, life events and, also, the medication. Certain substances and drug classes are recognised for inducing depression; cited systematically are the alcohol abuse, benzodiazepines, beta-blockers, central antihypertensive drugs and corticosteroids [3,4,9,10]. Sometimes analgesics or digoxin are mentioned. Considering the fact that elderly people use approximately 50% of the commercialized drugs on the pharmaceutical market [11], the present paper aims to analyse the relationship between medication long term medication and depression in elderly people.

Materials and Methods

The patients group included 199 subjects randomly selected (ensuring the representativeness for elderly patients who have access to geriatric health care), by using as algorithm the elderly's admission at the "Ana Aslan" National Institute of Gerontology and Geriatrics (NIGG) IIIrd Clinical Department Admission Office from 12 January 2009 till 14 January 2010. The inclusion criteria were: patients aged 65 years or older, females or males who had been using at least a drug in the last six month, whatever its pharmaceutical delivery form. The exclusion criteria were: individuals without any form of scholar education, with impairment of consciousness at admission at the NIGG, with major sensorial impairments, bone or joint and motor disorders (that caused severe disabilities, or even the immobilization syndrome) or those who declined to participate to this research study. We obtained the informed written consent from each subject who was included in our study.

We collected anamnesis information, especially about the drug use history in the last six months and carried out the depression screening using the GDS scale (scores between 0-15).

The statistical analysis was performed using parametric (t test) and non-parametric (Mann Whitney U test) tests.

Results and Discussion

The study group enrolled 199 patients aged 65 to 89 years old; the mean age was 74.4 years and the mean GDS score was 6.4. There was a normal distribution of the study group depending on patient age (Kolmogorov-Smirnov test; $Z=1.024$; $p=0.245$) but not regarding the GDS scores ($Z=1.782$; $p=0.003$). The main features analysed for the study group are presented in table I. The females from urban areas with primary school (69.3%) and without spouse (59.3%) represented the majority in our study group. The study group was homogenous concerning the stress events patients declared (binominal test, $p=0.156$).

Table I

The socio-cultural characteristics and the GDS score for the study group

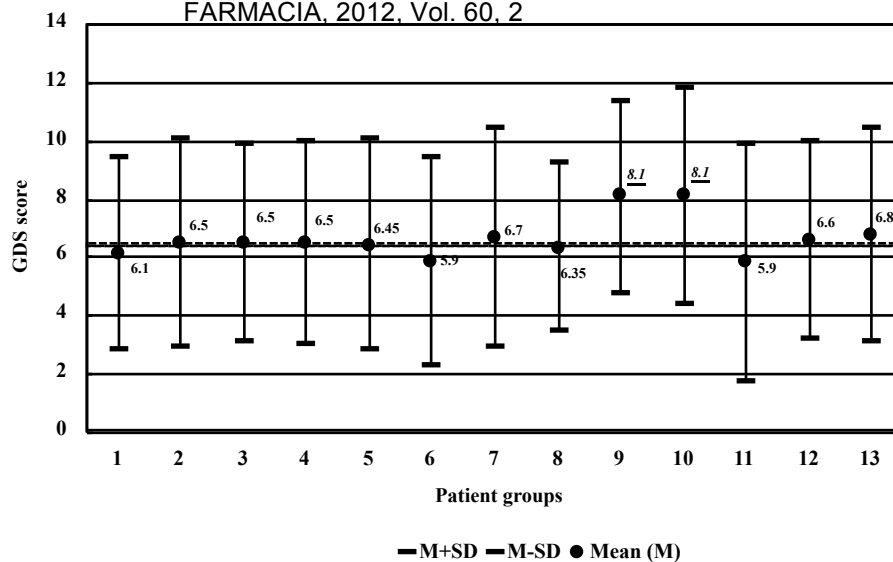
Variable	Results
Age, years mean $\pm$ SD interval of values	74.4 $\pm$ 5.7 65-89
Sex, % Women/Men	82.5/17.5
Environment living conditions % Urban/Rural	70.9/29.1
Educational level, % Primary(2-8 classes)/Secondary(high school)/Upper(faculty)	69.3/22.1/8.5
Declared stress events, % Yes/No	55.3/44.7
Living – alone or with someone else, % Yes/No	40.7/59.3
Marriage status, % Married/Widowed/Divorced/Unmarried	40.7/55.8/3.0/0.5
GDS, score mean $\pm$ SD interval of values	6.4 $\pm$ 3.5 0-15
Number of drugs mean $\pm$ SD interval of values	5.8 $\pm$ 2.4 1-12

We noted that elderly patients used many medications (the mean is 5-6 drugs) when we analysed the drug use history in the last six months. The main drug classes used were: angiotensin-converting enzyme inhibitors, cardiac metabolic drugs, vasodilators; diuretics, β -blockers, antiplatelet drugs, statins, calcium channel blockers, sedatives, anxiolytics, hypnotics, NSAIDs, antidiabetic drugs (without insulin medication), cholinergic drugs and analgesics.

First, the study group was divided successively in two subgroups, with and without drug use, for each of the above drug classes and we compared the results using non-parametric (Mann Whitney U test) and parametric (t test) tests. A patient could be included only one time in one of the two subgroups formed according to the medication use criterion. We obtained significant differences regarding GDS scores only for sedatives, anxiolytics and hypnotics [$Z=-3.124$; $p=0.002$, $t(197)=-3.171$; $p=0.002$, respectively] and NSAIDs [$Z=-2.386$; $p=0.017$, $t(197)=-2.475$; $p=0.014$, respectively].

The next step of the statistical analysis was to extract from the study group all patient subgroups, selected according to medication use criterion. This time a patient could be included in more than one group, depending on the number of chronic therapeutic agents they used on long-term. By comparing the GDS scores, we found out significant differences ($p<0.05$) between subgroups for the same two drug classes, for all combinations of two subgroups, by using both non-parametric and parametric tests. So, there are significant differences among groups, NSAIDs and angiotensin-converting enzyme inhibitors [$Z=-2.432$; $p=0.015$, $t(131)=-2.575$; $p=0.011$, respectively], vasodilators [$Z=-1.969$; $p=0.049$, $t(127)=-2.021$; $p=0.045$, respectively], β -blockers ($Z=-1.961$; $p=0.05$), antiplatelet drugs [$Z=-2.529$; $p=0.011$, $t(102)=-2.602$; $p=0.011$, respectively] and calcium channel blockers [$t(64)=-2.125$; $p=0.037$].

The last step of the statistical analysis was using the one sample t test to compare the GDS means for each subgroup formed depending on the medication taken with the GDS mean for the whole study group which was 6.4 (figure 1). We observed significant differences in the cases of the subgroup that used sedatives, anxiolytics and hypnotics [$t(33)=2.905$; $p=0.007$] and the subgroup which used NSAIDs [$t(22)=2.199$; $p=0.039$]. We obtained the same results whatever the statistical approach performed and hence, we considered that the results were consistent.

**Figure 1**

The GDS score mean for patient groups depending on their chronic therapy

- 1= Angiotensin-converting enzyme inhibitors; 2= Cardiac metabolic drugs;
 3=Vasodilators; 4=Diuretics; 5=β-blockers; 6= Antiplatelet drugs; 7=Statins;
 8= Calcium channel blockers; 9=Sedatives, anxiolytics, hypnotics; 10=NSAIDs;
 11=Antidiabetic drugs; 12=Cholinergic drugs; 13= Analgesics;

The NSAIDs subgroup had 23 subjects. The substances most used on long-term, were: diclofenac (7 subjects), meloxicam (7 subjects) and ketoprofen (4 subjects). Comparing the subgroups: diclofenac with ketoprofen [$Z=-0.666$; $p=0.527$, $t(9)=-0.344$; $p=0.739$, respectively], diclofenac with meloxicam [$Z=-0.518$; $p=0.620$, $t(12)=0.587$; $p=0.568$, respectively] and meloxicam with ketoprofen [$Z=-0.761$; $p=0.527$, $t(9)=-0.657$; $p=0.528$, respectively], we did not point out significant differences among GDS scores depending on the NSAID substances taken. The patients were asked about the frequency by which they used NSAIDs. They generally answered that they used NSAIDs for short a period of time, 7-10 days per month, although there were patients that were taking this medication every day and others who used them occasionally, for 2-3 days, depending on their symptoms.

We did not find out significant differences regarding the GDS scores ($Z=-1.136$; $p=0.256$) when the NSAIDs group was compared with the analgesics group (tramadol or acetaminophen). The GDS mean score for the NSAIDs group was 8.1, for analgesics group 6.8 and for the whole study group was 6.4. The 1.3 difference in GDS mean scores between the groups (NSAIDs - analgesic drugs), even it was high, was not statistically significant even after using the t test [$t(39)=1.086$; $p=0.284$]. As well, the mean GDS score for the analgesics group was not significantly different from that for the study group [$t(17)=0.504$; $p=0.621$]. There were no significant differences in GDS scores between the above mentioned groups [$Z=-1.492$; $p=0.140$, $t(27)=1.403$; $p=0.172$, respectively] even after excluding common cases from both of them.

The sedative-anxiolytic-hypnotic group included 34 patients and the GDS mean score was 8.1, significantly higher than the study group mean score [$t(33)=2.905$; $p=0.007$]. The most used substances in elderly were bromazepam and alprazolam. We found out that 8 subjects received sedatives and also NSAIDs. By excluding them, the subgroup remained only of 26 subjects; their GDS mean score was 7.5 and this time once more, not significantly different from the whole study group GDS mean score [$t(25)=1.709$; $p=0.100$]. So, for the sedative-anxiolytic-hypnotic group the higher GDS mean score was due to GDS scores of subjects who use NSAIDs as well.

Conclusions

The statistical analysis carried out has shown some drug classes that when chronically used lead to higher GDS mean scores: sedatives, anxiolytics and hypnotics and NSAIDs, respectively. For the first drug class mentioned, the results are in line with the literature data, but for the NSAIDs, the results were less expected. Taking into account that the osteoarthritis and disabilities are frequent complications of advanced osteoarthritis that may trigger depression, we considered two explaining hypothesis in this case. First, the inflammatory processes that trigger the pain and low mobility (that impose NSAIDs prescription) might cause depression in elderly. In this case, it is not a direct causal relationship between NSAIDs and depression. The second possible hypothesis is that this drug class has effects on mood, which would imply a direct relationship between NSAIDs and depression.

Our results do not imply the support of the first hypothesis. The results for the analgesics' group have shown no differences in GDS mean

scores compared with those for the whole study group, although analgesics are used as well for joint pain. Regarding the second hypothesis, we have several arguments: the GDS mean score in the NSAIDs group was significantly different (higher) than the GDS mean score in the whole study group. Comparing results for the most used NSAID substances, we did not find out significant differences between them and, in addition, in the case of the sedatives' group, the significant difference has been made by subjects who used simultaneously, the NSAIDs. So, our results suggest that NSAIDs when administered on long term could have a depressive effect, as a drug class adverse event. By reviewing the cited data on this topic, we found reported cases of patients with psychiatric disorders who received NSAIDs and their symptoms (depression or paranoia) were exacerbated being more severe and more frequent than expected; these symptoms have improved when the NSAIDs use was stopped [2,6]. Our results associated with information from clinical practice might open up a new research area for further experimental studies to confirm and explain the aforementioned hypothesis.

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