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ORIGINALS

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**Prevalence of the consumption of anticholinergic drugs in HIV patients**

**Prevalencia de prescripción de fármacos anticolinérgicos en pacientes mayores con VIH**

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**Abstract**

**Objective:** To analyse anticholinergic agent consumption in HIV patients 50 years or older; to determine anticholinergic risk using the Anticholinergic Cognitive Burden Scale (ACB) and Anticholinergic Risk Scale (ARS); and to determine if these patients use any type of benzodiazepine.

**Method:** A descriptive observational study of 256 HIV patients 50 years or older.

**Results:** 73.1% were men. Mean age was 56 ± 5.9 years. 55.9% of the patients were coinfectad with HCV. Excluding HIV drugs, mean drug consumption was 2.9 ± 2.9 drugs per patient. The ACB and ARS scales showed that 26.2% and 17.2% of the patients took an anticholinergic agent, and that 43.3% and 36.4% presented high anticholinergic risk, respectively. 30.5% of patients consumed benzodiazepines.

**Conclusions:** The percentage of HIV patients aged 50 years or older who were taking anticholinergic agents was statistically significantly higher on the ACB scale than on the ARS scale. No studies are available on the HIV population with which to compare our results, but there is evidence that this group of drugs can affect older adults.

**Resumen**

**Objetivo:** Analizar el consumo de fármacos con efecto anticolinérgico en pacientes con VIH ≥ 50 años. Determinar el riesgo anticolinérgico mediante las escalas *Anticholinergic Cognitive Burden Scale* (ACB) y *Anticholinergic Risk Scale* (ARS). Determinar si consumen alguna benzodiazepina.

**Método:** Estudio observacional descriptivo de 256 pacientes con VIH cuya edad era ≥ 50 años.

**Resultados:** El 73,1% eran hombres. La media de edad fue de 56 ± 5,9 años. El 55,9% de los pacientes estaban coinfectados por el VHC. El consumo medio de fármacos por paciente, sin incluir los fármacos para el VIH, fue de 2,9 ± 2,9. Según la escala ACB y ARS, el 26,2% y el 17,2% de los pacientes, respectivamente, tomaba un fármaco con efecto anticolinérgico. El 43,3% presentaba alto riesgo anticolinérgico con la escala ACB y el 36,4% alto riesgo según la escala ARS. El 30,5% de los pacientes consumía alguna benzodiazepina.

**Conclusiones:** El porcentaje de pacientes con VIH ≥ 50 años que toma fármacos con efecto anticolinérgico es mayor utilizando la escala ACB que utilizando la escala ARS, obteniendo una diferencia estadísticamente significativa. No hay estudios disponibles en población con VIH con los que comparar nuestros resultados, pero sí una evidencia de que este grupo de fármacos puede afectar a la población anciana.

**KEY WORDS**

HIV; Elderly; *Anticholinergic Cognitive Burden Scale* (ACB); *Anticholinergic Risk Scale* (ARS); Benzodiazepine.

**PALABRAS CLAVE**

VIH; Anciano; *Anticholinergic Cognitive Burden Scale* (ACB); *Anticholinergic Risk Scale* (ARS); Benzodiazepina.



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## Introduction

Several factors underlie the increase in HIV infection rates in individuals 50 years or older: the global increase in the incidence of new cases; the increased and improved communication of HIV cases in older adults compared to that at the beginning of the epidemic; and most importantly, the improved survival rate of these patients due to the effectiveness of highly active antiretroviral therapy (HAART). In the setting of HIV or AIDS infection, 50 years is considered to be the cut-off point to define advanced age<sup>1,2</sup>.

Even in patients in whom HAART is effective, the increase in life expectancy entails a parallel increase in non-AIDS-related comorbidities including cardiovascular, neurocognitive, and neoplastic disease<sup>3</sup> a significant improvement in life expectancy of HIV+ patients has been observed in Western countries. The parallel increase in the mean age of these patients causes a parallel increase in the frequency of non-AIDS related complications (i.e., neurocognitive, cardiovascular, liver and kidney diseases, metabolic syndrome, osteoporosis, non-HIV associated cancers, among others).

HIV and ageing may mutually reinforce their adverse effects on brain structure and function<sup>4</sup>. Cognitive disorders associated with HIV are very common during the ageing process, although since the introduction of HAART there has been a reduction in the incidence of most of the more severe forms of cognitive impairment<sup>5</sup>. The cognitive skills impaired by HIV include several domains, such as learning, memory, information processing speed, executive functions, and motor skills<sup>6</sup>.

Ageing is also associated with a greater susceptibility to the toxic effects of drugs and to drug-drug interactions. This risk is partly aggravated by the polypharmacy characteristic of this age group<sup>4</sup>. Anticholinergic agents are widely used in current clinical practice for the treatment of such disparate entities as urinary incontinence, peptic ulcer, irritable bowel syndrome, depression, and tremor, or for sedation. Despite their widespread use, adverse effects are relatively common<sup>7</sup>. Thus, at the peripheral level, the most common adverse effects include decreased secretions, decreased intestinal motility, blurred vision, increased heart rate, and urinary retention<sup>8</sup>. At the level of the central nervous system, due to the involvement of muscarinic receptors in mediating attention, learning, and short-term memory mechanisms, the use of anticholinergic agents can lead to a deterioration of cognitive function and even precipitate delirium<sup>9</sup>. In addition to causing neurological deterioration, all these aspects can limit adherence to HAART.

The adverse effects of anticholinergic agents on the cognitive functions of these patients depend on total anticholinergic burden, baseline cognitive function, and individual pharmacokinetic and pharmacodynamic variability. The metabolism and excretion of these agents decrease with age. The ageing-associated reduction in brain cholinergic activity is another mechanism that increases the risk of exceeding the symptomatic threshold for the anticholinergic effect. Symptoms related to the anticholinergic effect are lack of concentration and memory loss and, in the case of people with cognitive deficits, the exacerbation of cognitive symptoms and functional deterioration, which leads to false diagnoses of dementia or mild cognitive impairment<sup>10</sup>.

Therefore, the use of anticholinergic agents is considered inappropriate even in healthy older adults. Of the patients with suspected dementia, an estimated 2% to 12% do not have dementia syndrome; in reality they are experiencing the adverse effects of their medication. This situation is even more common in the setting of polypharmacy<sup>7</sup>.

Different scales are available to quantify the burden of the anticholinergic effect. Two of these are the Anticholinergic Cognitive Burden (ACB) scale<sup>11</sup> and the Anticholinergic Risk Scale (ARS)<sup>12</sup>. These scales rank anticholinergic agents into 3 categories: category 1, agents with a moderate effect; category 2, those with a strong effect; and category 3, those with a very strong effect. However, there are differences between the 2 scales in the medications they include and in the way the medications are ranked.

The Drug Burden Index (DBI) includes the dose of active ingredients, and is thus a good scale to measure anticholinergic burden<sup>13</sup>.

The study objectives were: To determine the prevalence of anticholinergic agent consumption in HIV patients 50 years or older; to determine the anticholinergic risk of each patient using the ACB scale and the ARS; and to determine if these patients also use any type of benzodiazepine (BZD).

## Methods

A descriptive observational study reviewing all the treatments administered to HIV patients 50 years or older recorded by the Department of Epidemiological Surveillance and Control of Communicable Diseases of the Autonomous Community of La Rioja. The exclusion criteria were: Patients with a life expectancy of less than 3 months; or patients with no available primary and specialized care history.

The study variables were: age, sex, year of diagnosis, HIV transmission, HCV coinfection, number of agents prescribed as chronic medication, number of anticholinergic agents, ACB scale score, ARS score, and BZD consumption.

Data collection was conducted using the Selene-Siemens<sup>®</sup> electronic medical record software package for primary and specialized care and the Athos Prisma<sup>®</sup> electronic assisted prescribing software package.

This study applied 2 of the most commonly used validated scales: the ACB scale<sup>11</sup> and the ARS<sup>12</sup>. Drugs included in these scales are classified according to their anticholinergic effect. Each drug has a value of 1 to 3 based on its risk of causing anticholinergic effects, such as dry mouth, dry eyes, dizziness, confusion, constipation, or falls. 1 represents a moderate effect, 2 represents a strong effect, and 3 represents a very strong effect. The sum of the scores shows whether there is a decreased or increased risk of experiencing adverse anticholinergic effects. It must be noted that the consumption of several anticholinergic agents increases the risk of adverse events. An overall score of 1 represents a low level of risk, 2 represents a moderate risk, and 3 or more represents a high level of risk.

Statistical analysis was performed with the SPSS(R) software package version 21.0. Qualitative data are expressed as absolute frequencies and percentages. Quantitative data are expressed as mean  $\pm$  standard deviation.

The study was conducted according to the recommendations of the Helsinki Declaration. All information was treated as confidential and exclusively used in a professional setting. Any personal data that allowed identification of the patient was managed according to data protection legislation. The study participants were identified only by a code in all reports and data analyses.

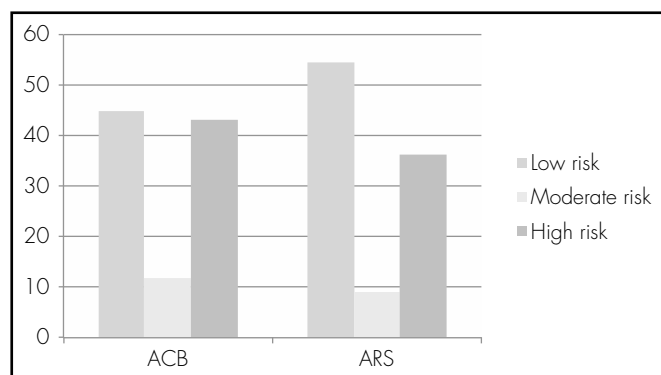
The study protocol was approved by the Research Ethics Committee of La Rioja (CEICLAR) on January 2, 2017 with the identifier P.I 235.

## Results

We reviewed the pharmacotherapeutic records of 296 patients. 40 patients were excluded because of a lack of data in the electronic medical record. Of the 256 patients, 73.1% were men. The mean age was  $56 \pm 5.9$  years (50-81). 55.9% of the patients were coinfecting with HCV.

In descending order, the HIV transmission route was: intravenous drug use (58.9% of patients), high-risk sexual practices (31.6%), and other causes (9.8%, of which 1.2% were documented as blood transfusion).

Of the 256 patients, 73.8% had been prescribed chronic medication. Mean drug consumption for conditions other than HIV was  $2.9 \pm 2.9$  drugs per patient.



**Figure 1.** Anticholinergic risk in the study patients according to the ACB scale and the ARS.

**Table 1.** Percentage of patients taking anticholinergic agents according to the ACB scale and the ARS.

| ACB                           | ARS                     |
|-------------------------------|-------------------------|
| Antidepressants (18.6%)       | Antidepressants (38.4%) |
| Amitriptyline 6.2%            | Amitriptyline 10%       |
| Paroxetine 7.2%               | Mirtazapine 16.7%       |
| Venlafaxine 5.2%              | Paroxetine 11.7%        |
| Antipsychotics (11.4%)        | Antipsychotics (35%)    |
| Olanzapine 5.2%               | Olanzapine 8.3%         |
| Quetiapine 3.1%               | Perphenazine 15%        |
| Risperidone 3.1%              | Quetiapine 6.7%         |
|                               | Risperidone 5%          |
| Benzodiazepines (26.8%)       | Antihistamines (8.3%)   |
| Alprazolam 14.4%              | Cetirizine 3.3%         |
| Chlorazepate dipotassium 8.3% | Hydroxyzine 5%          |
| Diazepam 4.1%                 |                         |

According to the ACB scale, 26.2% of the patients took at least 1 anticholinergic agent. 70.1% of the agents were classified as having a moderate anticholinergic effect and the remainder were classified as having a very strong effect.

Anticholinergic risk was low (44.8% of patients), moderate (11.8%), and high (43.3%) (Figure 1).

According to the ARS, 17.2% of the patients took at least 1 anticholinergic agent ( $P = 0.014$ ) vs 26.2% on the ACB scale. 53.3% of the agents were classified as having moderate anticholinergic effect, 35% a very strong effect, and the remainder a strong effect.

Anticholinergic risk was low (54.6% of patients), moderate (9.1%), and high (36.4%) (Figure 1).

Table 1 shows the percentage of patients taking an anticholinergic effect according to the ACB scale and the ARS.

It was found that 30.5% of the patients consumed some type of BZD. The most commonly used BZDs were lorazepam and lormetazepam.

## Discussion

The results show that the percentage of HIV patients 50 years or older taking anticholinergic agents was statistically significantly higher ( $P = 0.014$ ) on the ACB scale (26.2%) than on the ARS (17.2%). The difference between scales was similar to that obtained in an Italian study that used the ARB scale and ARS in elderly inpatients<sup>14</sup>.

These scales differ in the number of drugs they include and in the "anticholinergic burden" attributed to each drug. The ACB scale includes 70 drugs, whereas the ARS only includes 38. Mirtazapine is an example of a drug included in the ARS but not in the ACB scale.

One of the limitations of this study may be the lack of interviews with the patients. Information on the prescribed medications was obtained from the medical record database used and may not correspond to what the patient actually takes each day. A further limitation is that no data on health outcomes were collected.

No studies are available on HIV patients 50 years or older with which to compare the results on the use of anticholinergic agents. Published studies simply refer to risk in older adults<sup>13,15</sup>. A published review established alternatives to the most commonly used anticholinergic agents to avoid their use<sup>16</sup>, and the Beers List recommended avoiding the use of a new drug with anticholinergic risk in older adults<sup>17</sup>. The 2015 Consensus Do-

cument on HIV and Aging recommended avoiding the use of potentially dangerous drugs such as anticholinergics, BZDs, and antidepressants in older patients<sup>18</sup>.

According to the ACB scale and the ARS, 43.3% and 36.4% of the patients had a high anticholinergic risk, respectively. The consumption of agents with higher anticholinergic risk and greater anticholinergic burden was greater on the ACB scale than on the ARS. Given these differences, the choice of using 1 scale over the other may present a challenge.

On the ACB scale, the most commonly used agents with an anticholinergic effect were BZDs, antidepressants, and antipsychotics, whereas on the ARS, they were antidepressants followed by antipsychotics and, to a lesser extent, antihistamines. Unlike the ACB scale, the ARS does not include anxiolytic-type BZDs such as alprazolam, dipotassium chlorazepate, or diazepam.

It is known that patients without cognitive impairment at the start of treatment with anticholinergic agents may develop cognitive impairment associated with long-term consumption<sup>19</sup>. Psychiatric complications in HIV patients may require pharmacological treatment. The neuroleptics and tricyclic antidepressants used to treat these complications have anticholinergic effects which may cause neuropsychological problems, such as memory deficit or confusion<sup>20</sup>. Benzodiazepines, which are used to treat anxiety symptoms, are among other medications which may also cause concentration problems, confusion, or depressive symptoms<sup>21</sup>.

The results showed that 30.5% of patients consumed BZDs. A German study<sup>22</sup> and a French prospective study<sup>23</sup> have referred to the risk of cognitive impairment and falls with the use of these agents in older adults. In Spain, BZDs are used by more than 40% of older adults admitted to hospital emergency units due to a fall. Many patients, especially men, use higher doses than those recommended. As far as possible, the prescription of BZDs for older patients should be avoided<sup>24</sup>.

The main BZDs consumed by the participants in the study were lorazepam and lormetazepam; these BZDs are recommended for use in HIV patients to avoid interactions<sup>25</sup>.

Although no studies are available on the prescription of agents with anticholinergic risk in HIV patients 50 years or older, a systematic review and meta-analysis performed in 2015 in older patients<sup>26</sup> found that anticholinergic agents were associated with cognitive deterioration, falls, and death. The most recent review was conducted in 2017<sup>27</sup>, and concluded that a large number of studies, most of which included older adults, found an association between high values on the DBI and adverse changes in daily life activities.

Given the evidence, clinicians should take into account the risk of cognitive deterioration and falls that this group of drugs causes in an ageing population, such as HIV patients. The prescription of these agents with hypnotic drugs, such as BZDs, could further increase cognitive impairment and falls.

## Conflicts of interest

The authors of this study declare no conflicts of interest.

## Contribution to scientific literature

The increased life expectancy of patients with HIV entails an increase in AIDS-related comorbidities. Polypharmacy is one of the problems associated with chronicity. The prescription of drugs with adverse effects, such as anticholinergic agents, could pose a risk in these types of patients whose neurological status may also be affected by the infection itself.

This study is the first to use the Anticholinergic Cognitive Burden (ACB) scale and the Anticholinergic Risk Scale (ARS) to investigate the prevalence of use of anticholinergic agents in this group of patients.

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