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Concordance Among 10 Different Anticholinergic Burden Scales in At-Risk Older Populations

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Objective: The aim of the study was to evaluate the concordance among 10 anticholinergic scales for the measurement of anticholinergic drug exposure in at-risk elderly complex chronic patients in primary care.

Methods: An 8-month cross-sectional, multicenter study was carried out in a cohort of complex chronic patients older than 65 years in treatment with at least 1 drug with anticholinergic activity. Demographic, pharmacological, and clinical data were collected. Anticholinergic burden and risk were detected using the 10 scales included on the anticholinergic burden calculator (<http://www.anticholinergicscales.es/>). We used κ statistics to evaluate the concordance 2 to 2 (according to risk: high, medium, low or without risk) among the included scales.

Results: Four hundred seventy-three patients were recruited (60.3% female, median age of 84 years [interquartile range = 10]). Eighty was the total number of anticholinergic drugs with any scale (1197 prescriptions), with a median of 2 drugs with anticholinergic activity per patient (interquartile range = 2). The κ statistics comparing all the 10 scales ranged from -0.175 (Drug Burden Index versus Chew Scale) to 0.708 (Anticholinergic Activity Scale [AAS] versus Chew Scale). The best concordance was obtained between AAS and Chew Scale ($\kappa = 0.708$), followed by Clinician-Rated Anticholinergic Scale and Duran Scale ($\kappa = 0.632$) and AAS and Anticholinergic Cognitive Burden Scale ($\kappa = 0.618$), being considered substantial strengths of concordance.

Conclusions: The agreement among the 10 scales in elderly patients with complex chronic conditions was highly variable. Great care should be taken when assessing anticholinergic drug exposure using existing scales because of the wide variability among them. The only scales that showed agreement were the AAS-Chew, Clinician-Rated Anticholinergic Scale–Duran, and AAS–Anticholinergic Cognitive Burden Scale pairs. In the rest of the cases, the scales are not interchangeable.

Key Words: anticholinergic agents, anticholinergic burden scales, comorbidity, concordance, older complex chronic patients

(*J Patient Saf* 2022;18: e816–e821)

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The authors disclose no conflict of interest.

Supported by health research projects from Consejería de Salud, Junta de Andalucía, Spain (exp N° PI-0195-2016).

The study was approved by the ethical committee of the Virgen del Valme University Hospital.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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It is known that anticholinergic drugs can have a series of adverse effects on both the peripheral (decreased secretions [manifested as dry mouth, dry eyes], constipation, blurred vision, and urinary retention) and central nervous systems (loss of memory, dizziness leading to falls, confusion, disorientation and delirium).¹ These effects are more common in older patients because this population has lower baseline cholinergic activity and is more likely to have pharmacokinetic disorders that may favor their occurrence.²

Despite recommendations to avoid the use of these drugs, especially in older patients,^{3,4} their consumption is high in this population⁵; patients with chronic illnesses are especially likely to use these drugs because of polypharmacy.

There are several scales that classify drugs according to their anticholinergic activity. In a systematic review,⁶ our group identified 10 scales that measure the anticholinergic burden of older patients. The difficulty of applying these scales in clinical practice lies in their great variability, first, in identifying and classifying anticholinergic drugs, and second, in terms of the target population. This variability leads to different results for the same patient depending on which scale is applied.

The source of this heterogeneity may lie in the different ways that each scale was developed⁶:

- Anticholinergic Drug Scale (ADS),⁷ Clinician-Rated Anticholinergic Scale (CrAS),⁸ and Duran Scale (Duran)⁹ are based on previously published scales and expert opinions.
- Anticholinergic Cognitive Burden Scale (ACB)¹⁰ and Anticholinergic Risk Scale (ARS)¹¹ are based on systematic reviews of drugs with described anticholinergic activity and expert opinions.
- Anticholinergic Burden Classification (ABC)¹² and Chew Scale (Chew)¹³ are based on the in vitro anticholinergic activity of drugs.
- Anticholinergic Activity Scale (AAS)¹⁴ and Anticholinergic Load Scale (ALS)¹⁵ use a combination of all the previous criteria.
- Drug Burden Index (DBI)¹⁶ shows the greatest differences from the other measurement tools; it measures the anticholinergic effect using a mathematical formula that considers the prescribed dose and the minimum effective dose of the drug.

Regarding the target population used, most of these scales have been developed in a general older population (ADS, ARS, Chew, ABC, and DBI); however, the ALS was developed specifically in patients with cognitive impairment and Alzheimer disease, the AAS was designed in patients with Parkinson disease, the CrAS was designed in hypertensive patients, and the Duran and the ACB do not specify population characteristics.⁶

A few studies have compared these scales and described their differences,^{17,18} but none has assessed the agreement among these 10 scales. Moreover, to date, no scale has been specifically developed for patients with complex chronic conditions, defined as that population with special clinical fragility derived from the presence of 2 or more chronic diseases that cause progressive deterioration and gradual loss of autonomy and increase the risk of experiencing different interrelated pathologies. All of these factors result in a frequent need for attention in different areas of health care, which has social and economic repercussions.¹⁹

Therefore, our main aim was to evaluate the concordance among 10 anticholinergic scales for the measurement of anticholinergic drug exposure in at-risk older complex chronic patients.

METHODS

Design and Setting

This was a cross-sectional and multicenter study carried out in a cohort of complex chronic patients older than 65 years with frequent attendance in the primary health care centers of the health areas of 4 hospitals in Andalusia, Spain.

The study inclusion criteria included:

- 1) Age of older than 65 years
- 2) Met the criteria for complex chronic patients of the Integrated Assistance Process from the Ministry of Health of the Junta de Andalucía (2007)¹⁹
- 3) Treated with at least 1 drug considered to have anticholinergic risk based on any of the 10 scales considered for the study. Then, they were considered population at risk.

Exclusion criteria excluded patients with Alzheimer disease and severe senile dementia, active malignant neoplastic disease on treatment with curative intention, on the transplant list for heart, liver, and/or renal transplants, predicted entry into a chronic extrarenal clearance program, or any clinical situation that involved pain.

Patient Inclusion Procedure and Data Collection

Thanks to those responsible for the information systems of each primary care area, records of complex chronic patients older than 65 years who were active from February 2018 to September 2018 were obtained.

Then, the researchers responsible for each center reviewed the treatment of each patient using the electronic prescription program, to include in the study those who met the 3 inclusion criteria.

Patients included were collected in an electronic case report form specially designed for the study.

The variables collected were age, sex, number of chronic drugs per patient, number of drugs with anticholinergic burden in any of the scales per patient, daily dose of anticholinergic drugs (required for DBI), and total number of prescriptions and different drugs with anticholinergic activity prescribed. All of these variables were obtained from the electronic medical records of the patients.

Exposure to anticholinergic medications and anticholinergic burden and risk were detected using the 10 scales included on the Anticholinergic Burden calculator (<http://www.anticholinergicscales.es/>).²⁰

With the results obtained, we evaluated the concordance 2 to 2 (according to risk: high, medium, low or without risk) among the 10 scales included.

To express qualitatively the strength of concordance, we used the scale of Landis and Koch.²¹ Strength of concordance: 0.00 (poor), 0.01–0.20 (slight), 0.21–0.40 (fair), 0.41–0.60 (moderate), 0.61–0.80 (substantial), and 0.81–1.00 (almost perfect).

Statistical Analysis

All qualitative variables are described as frequencies and percentages. Quantitative variables, because they do not follow a normal distribution, are expressed as medians and interquartile ranges (IQRs).

We have evaluated the degree of agreement of the patients evaluated with the different anticholinergic scales using a 2-to-2 comparison matrix. κ statistics was used to quantify concordance.

All statistical analyses were performed using RStudio software v. 1.1.456.

Ethics Approval

The study was approved by the ethical committee of the Virgen del Valme University Hospital.

RESULTS

A total of 473 patients were included, predominantly female (60.3%), with a median age of 84 years (IQR = 10). The most common comorbidities associated with these at-risk older complex chronic patients are shown in Table 1.

The median number of chronic drugs per patient was 11 (IQR = 6). After pharmacological evaluation, median of drugs with anticholinergic risk with any scale per patient was of 2 (IQR = 2), which presented a median of anticholinergic burden between 1 (IQR = 1)—3 (IQR = 2) according to each scale, except DBI. The DBI data were of 0.8 (IQR = 0.7).

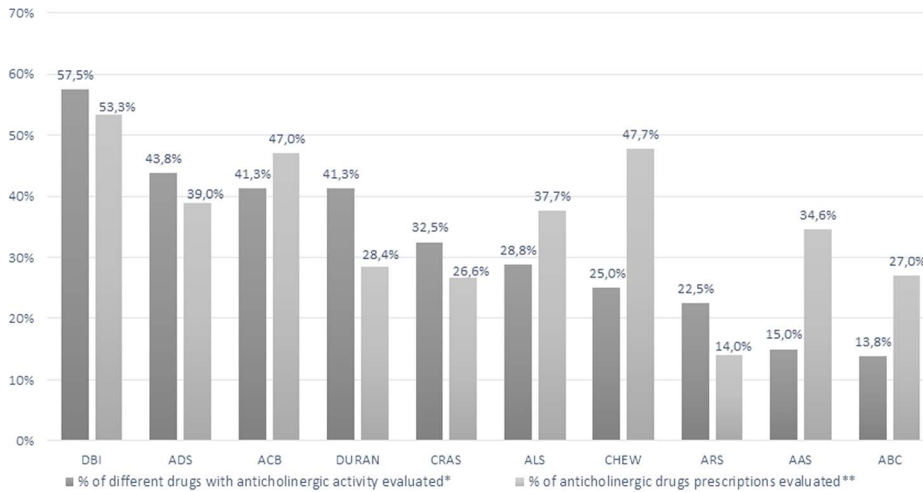
A total of 1197 prescriptions of drugs with anticholinergic activity were registered, which corresponded to 80 different drugs. Figure 1 show the number of different drugs with anticholinergic activity and prescriptions evaluated by each scale. Of the 80 drugs with anticholinergic activity evaluated by all scales, more than 50% (n = 46) were catalogued by DBI, followed by the other scales (Fig. 1).

Figure 2 shows the differences observed between the scales in the proportions of individuals that take drugs with anticholinergic activity. Prevalence of any anticholinergic use was highest with the Chew (374 patients, 79.1%), followed by DBI (368 patients, 77.8%), ACB (359 patients, 75.9%), AAS (319 patients, 67.4%), ALS (318 patients, 67.2%), ADS (306 patients, 64.7%), ABC (262 patients, 55.4%), Duran (250 patients, 52.9%), CrAS

TABLE 1. Demographic and Clinical Characteristics of Included Patients

Characteristics	
No. patients	473
Sex female, n (%)	285 (60.3)
Median (IQR) age, y	84 (10)
Chronic diseases,* n (%)	
A1. Chronic heart failure	192 (40.6)
A2. Coronary heart disease	181 (38.3)
B1. Vasculitis and/or systemic autoimmune diseases	16 (3.4)
B2. Chronic renal disease	95 (20.1)
C1. Chronic lung disease	218 (46.1)
D1. Chronic inflammatory bowel disease	6 (1.3)
D2. Chronic liver disease	44 (9.3)
E1. Stroke	124 (26.2)
E2. Neurological disease with permanent motor impairment	31 (6.6)
E3. Neurological disease with permanent moderate-severe cognitive impairment	60 (12.7)
F1. Symptomatic peripheral artery disease	42 (8.9)
F2. Diabetes mellitus with proliferate retinopathy or symptomatic neuropathy	57 (12.1)
G1. Chronic anemia	21 (4.4)
G2. Solid-organ or hematological active neoplasia not tributary of treatment with curative intention	116 (24.5)
H1. Chronic osteoarticular disease	51 (10.8)

*Classification of pathologies according to Ollero Baturone et al.¹⁹



* Percentage is based in total different anticholinergic drugs evaluated N=80
 ** Percentage is based in total of anticholinergic drugs prescriptions evaluated N=1197
 Abbreviations: AAS = Anticholinergic Activity Scale; ABC = Anticholinergic Burden Classification; ACB = Anticholinergic Cognitive Burden Scale; ADS = Anticholinergic Drug Scale; ALS = Anticholinergic Load Scale; ARS = Anticholinergic Risk Scale; Chew = Chew's scale; CrAS = Clinician-Rated Anticholinergic Scale; DBI = Drug Burden Index; Duran = Duran scale.

FIGURE 1. Proportion of different drugs and prescriptions with anticholinergic activity evaluated by each scale.

(243 patients, 51.4%), and finally ARS (140 patients, 29.6%; Fig. 2).

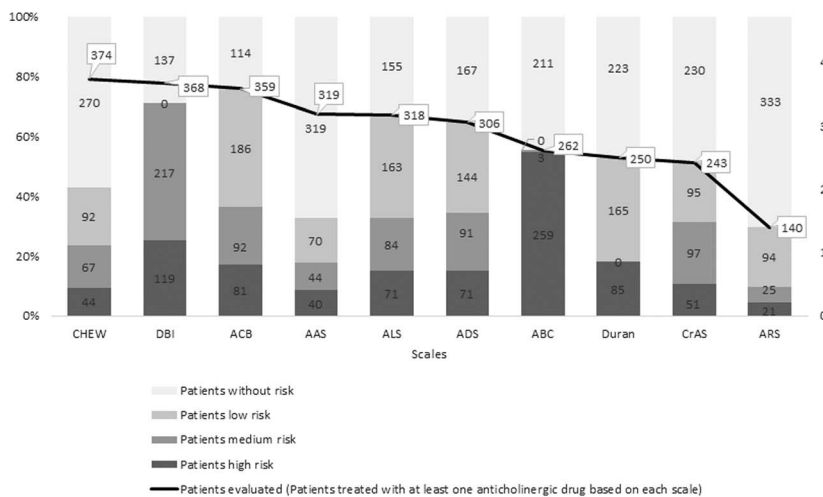
Table 2 shows the κ statistics comparing all the 10 scales, which ranged from -0.175 (DBI versus Chew) to 0.708 (AAS versus Chew). Therefore, the best concordance was obtained between AAS and Chew ($\kappa = 0.708$), followed by CrAS and Duran ($\kappa = 0.632$) and AAS and ACB ($\kappa = 0.618$). According to the scale of Landis and Koch,²¹ strength of concordance is substantial.

For further analysis, we evaluated the agreement between pairs of scales only across high score categories. Weighted κ statistics were between -0.023 for the ABC versus ADS and 0.687 for the AAS versus Chew (Table 3), which also obtain a substantial degree of agreement.

DISCUSSION

The objective of our study was to analyze the degree of agreement among the 10 scales for measuring the anticholinergic burden of at-risk older patients with complex chronic conditions in primary care. To date, no study has compared such a large number of scales in this population.

First, it is worth noting that large differences were found in the prevalence of anticholinergic consumption when different scales were used; these differences ranged from 29.6% of patients according to the ARS scale to 79.1% according to the Chew. These discrepancies could be related to differences in how each scale was developed and therefore to the differences in the drugs that each scale considers anticholinergic. This situation is also evident in



Abbreviations: AAS = Anticholinergic Activity Scale; ABC = Anticholinergic Burden Classification; ACB = Anticholinergic Cognitive Burden Scale; ADS = Anticholinergic Drug Scale; ALS = Anticholinergic Load Scale; ARS = Anticholinergic Risk Scale; Chew = Chew's scale; CrAS = Clinician-Rated Anticholinergic Scale; DBI = Drug Burden Index; Duran = Duran scale.

FIGURE 2. Number and percentage of patients evaluated based on characteristics related to drugs with anticholinergic activity according to each scale.

TABLE 2. κ Statistics Comparing the Risk of the Patients Evaluated by the Different Scales (Comparison 2 to 2)

Duran	AAS	ALS	DBI	ACB	ARS	CHEW	CrAS	ADS	ABC
Duran	1	0.245 (0.19 to 0.30)	0.482 (0.42 to 0.54)	0.354 (0.32 to 0.39)	0.185 (0.13 to 0.24)	0.521 (0.46 to 0.58)	0.152 (0.09 to 0.21)	0.632 (0.58 to 0.69)	0.407 (0.35 to 0.47)
AAS	1	0.169 (0.12 to 0.26)	-0.075 (0.02 to 0.10)	0.618 (0.57 to 0.67)	0.101 (0.03 to 0.17)	0.708 (0.65 to 0.77)	0.146 (0.09 to 0.20)	0.015 (-0.04 to 0.07)	0.565 (0.52 to 0.61)
ALS	1	1	0.121 (0.07 to 0.17)	0.048 (-0.01 to 0.11)	0.236 (0.19 to 0.29)	0.344 (0.29 to 0.34)	0.330 (0.27 to 0.39)	0.228 (0.23 to 0.35)	-0.054 (-0.09 to -0.01)
DBI	1	1	1	-0.075 (-0.12 to -0.03)	0.125 (0.09 to 0.16)	-0.175 (-0.022 to -0.13)	0.291 (0.24 to 0.34)	0.404 (0.36 to 0.45)	-0.107 (-0.15 to -0.06)
ACB	1	1	1	1	0.173 (0.13 to 0.22)	0.401 (0.35 to 0.46)	0.236 (0.18 to 0.29)	-0.002 (-0.06 to 0.06)	0.566 (0.53 to 0.60)
ARS	1	1	1	1	1	0.050 (-0.01 to 0.11)	0.436 (0.38 to 0.49)	0.215 (0.17 to 0.26)	-0.029 (-0.07 to 0.01)
CHEW	1	1	1	1	1	1	0.050 (-0.01 to 0.11)	-0.010 (-0.07 to 0.05)	0.350 (0.310 to 0.39)
CrAS	1	1	1	1	1	1	1	0.322 (0.26 to 0.38)	-0.039 (-0.08 to 0.00)
ADS	1	1	1	1	1	1	1	1	-0.109 (-0.015 to 0.07)
ABC	1	1	1	1	1	1	1	1	1

TABLE 3. κ Statistics Comparing the High-Risk Patients Evaluated by the Different Scales (Comparison 2 to 2)

Duran	AAS	ALS	DBI	ACB	ARS	CHEW	CrAS	ADS	ABC
Duran	1	0.449 (0.34 to 0.56)	0.417 (0.32 to 0.51)	0.459 (0.36 to 0.56)	0.350 (0.24 to 0.46)	0.373 (0.26 to 0.49)	0.507 (0.40 to 0.61)	0.510 (0.41 to 0.61)	0.036 (-0.03 to 0.10)
AAS	1	0.343 (0.22 to 0.46)	0.172 (0.08 to 0.26)	0.432 (0.32 to 0.55)	0.426 (0.27 to 0.58)	0.687 (0.57 to 0.80)	0.332 (0.20 to 0.47)	0.424 (0.30 to 0.55)	0.071 (0.03 to 0.12)
ALS	1	1	0.274 (0.18 to 0.37)	0.358 (0.25 to 0.47)	0.253 (0.13 to 0.37)	0.420 (0.30 to 0.54)	0.531 (0.42 to 0.64)	0.370 (0.26 to 0.48)	0.056 (0.00 to 0.11)
DBI	1	1	1	0.347 (0.25 to 0.45)	0.088 (0.01 to 0.16)	0.198 (0.10 to 0.29)	0.238 (0.14 to 0.33)	0.326 (0.23 to 0.42)	0.055 (-0.02 to 0.13)
ACB	1	1	1	1	0.325 (0.21 to 0.44)	0.500 (0.39 to 0.61)	0.406 (0.29 to 0.52)	0.499 (0.39 to 0.60)	0.109 (0.05 to 0.17)
ARS	1	1	1	1	1	0.362 (0.21 to 0.52)	0.348 (0.20 to 0.49)	0.347 (0.22 to 0.47)	0.035 (0.00 to 0.07)
CHEW	1	1	1	1	1	1	0.427 (0.29 to 0.56)	0.460 (0.34 to 0.58)	0.078 (0.03 to 0.13)
CrAS	1	1	1	1	1	1	1	0.419 (0.30 to 0.54)	0.024 (-0.03 to 0.07)
ADS	1	1	1	1	1	1	1	1	-0.023 (-0.08 to 0.04)
ABC	1	1	1	1	1	1	1	1	1

the literature, where various studies have reported this problem.^{22–24} However, in our study, the overall prevalence of anticholinergic exposure was higher than that reported in other publications. This could be mainly because we included complex chronic patients who were being treated with at least 1 drug considered anticholinergic by any of the scales. The inclusion of this very specific group of patients would logically inflate these prevalence rates in our study.

Regarding the data shown on the number of different drugs with anticholinergic activity categorized by each scale, the highest results were observed with DBI, Chew, and ACB, probably because these scales include drugs that are more commonly prescribed for our population and region compared with the other scales.

The agreement among the 10 scales when measuring the anticholinergic risk in older patients with complex chronic conditions in primary care was highly variable, ranging from zero agreement to substantial agreement. This finding generally supports the results of previous studies, although other studies compared fewer scales. In our study, the only scales that showed agreement were the AAS-Chew, CrAS-Duran, and AAS-ACB pairs. In the rest of the cases, the κ index was moderate to null. The agreement between AAS and Chew was confirmed in high-risk categorization.

Among the different factors that can be analyzed to examine the higher degree of agreement found between these 3 pairs of scales, one is the development process. The AAS scale was based on the Chew combined with expert opinion, and the Duran was based on 7 previously published scales,⁹ including the CrAS. However, the agreement observed between AAS and ACB cannot be assessed using this approach because those 2 scales are not related to each other.

On the other hand, trying to explain the reason for the agreement observed between these 3 pairs of scales, we analyzed the anticholinergic drugs considered by each scale and the risk category assigned to each of them. On this way, we found that the AAS and the Chew agree on the classification in the same risk levels almost 90% of the drugs included in the analysis, whereas the other 2 pairs agree on 59% (AAS-ACB) and 70% (CrAS-Duran).

Finally, if we separately analyze the most frequently prescribed drugs, the AAS and the Chew agree on the risk category of the 10 most-prescribed drugs, which represent 61% of the total prescriptions. The CrAS and the Duran coincide on 7 of the 10 most-prescribed drugs, which is equivalent to 50% of the total prescriptions, whereas the AAS and ACB coincide on 5 (32%).

Considering our results with respect to other studies, we found that Pont et al,¹⁸ in 2015, analyzed the agreement of the ACB, ADS, ARS, and DBI in a cohort of community-dwelling Australian men 70 years and older. The researchers obtained κ values similar to ours (although slightly higher), except for the ACB-ADS and DBI-ADS pairs (0.628 and 0.119 in the study by Pont et al¹⁸ versus -0.002 and 0.404 in our study).

Differences between our study and the literature regarding the κ index for the ACB-ADS pair are also present (although to a lesser degree) in an article published by Lertxundi et al¹⁷ in 2013. This was a Spanish study comparing the results of the ADS, ARS, and ACB in a small sample of 83 psychiatric inpatients 65 years and older. In this study, which had results similar to ours, we again noted differences in the ACB-ADS pair (0.21 in the study by Lertxundi et al¹⁷ versus -0.002 in ours).

In the case of the DBI-ADS pair, our κ value coincides with that obtained in the study by Naples et al,²² in 2015, which was carried out in community-dwelling older adults 70 to 79 years. Naples et al²² analyzed the agreement among the ACB, ADS, ARS, DBI, and Summated Anticholinergic Medications Scale. The DBI-ADS pair obtained a κ index of 0.42, almost equal to the 0.404 found in our study. However, for the rest of the pairs, κ indices that were much higher than ours were obtained.

For the subgroup of patients with high anticholinergic risk, the agreement among the scales was slightly lower than for the overall group. This leads us to think that the greater the anticholinergic risk and therefore the more important preventive action is, the results are even more contradictory when using the different scales. In this case, the combination with the highest κ index was still AAS-Chew, which was the only pair that also maintained a substantial degree of agreement.

In contrast, the agreement of the ABC with the other scales in the high-risk patient group was generally the poorest. This may be explained by the great difference between the ABC and the other scales in terms of the proportion of patients categorized as high risk. According to the ABC, practically, all patients treated with drugs with anticholinergic effects are classified as high risk, which makes this scale quite different from the others.

Limitations

Like any other study, ours also has some limitations that should be considered. First, not having conducted patient interviews to verify the treatment received and the patients' adherence could be a limitation. The results obtained are based on the theoretical treatments of each patient, which were extracted from the prescriptions listed in the e-prescribing program of the Andalusian health service, and on the assumption of good adherence to all the prescribed treatments. However, this approach may not correspond to reality.

In addition, the patients included in our study were drawn from only 1 region of Spain, which may limit generalizability to more diverse populations. However, from another perspective, this could be considered an advantage when trying to determine the scales that are most suitable for this specific population.

CONCLUSIONS

Although different scales are available for assessing anticholinergic risk, the results obtained should be evaluated with caution. The only scales that showed substantial agreement were the AAS-Chew, CrAS-Duran, and AAS-ACB pairs. In the rest of the cases, the scales are not interchangeable. From a clinical applicability point of view, great care should be taken when assessing anticholinergic drug exposure using existing scales because of the wide variability among them. More health outcomes research is necessary to identify the criterion standard that provides the most accurate and safest outcomes.

ACKNOWLEDGMENTS

The authors thank the following researchers who participated in the study: Alberto Caro Gutiérrez and Jose María Pérez Gata (Valme Hospital Clinical Documentation Department), for their contribution in data collection, and Emilio García Cabrera (Delos Clinical, SL) for his collaboration in the elaboration of statistics data.

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