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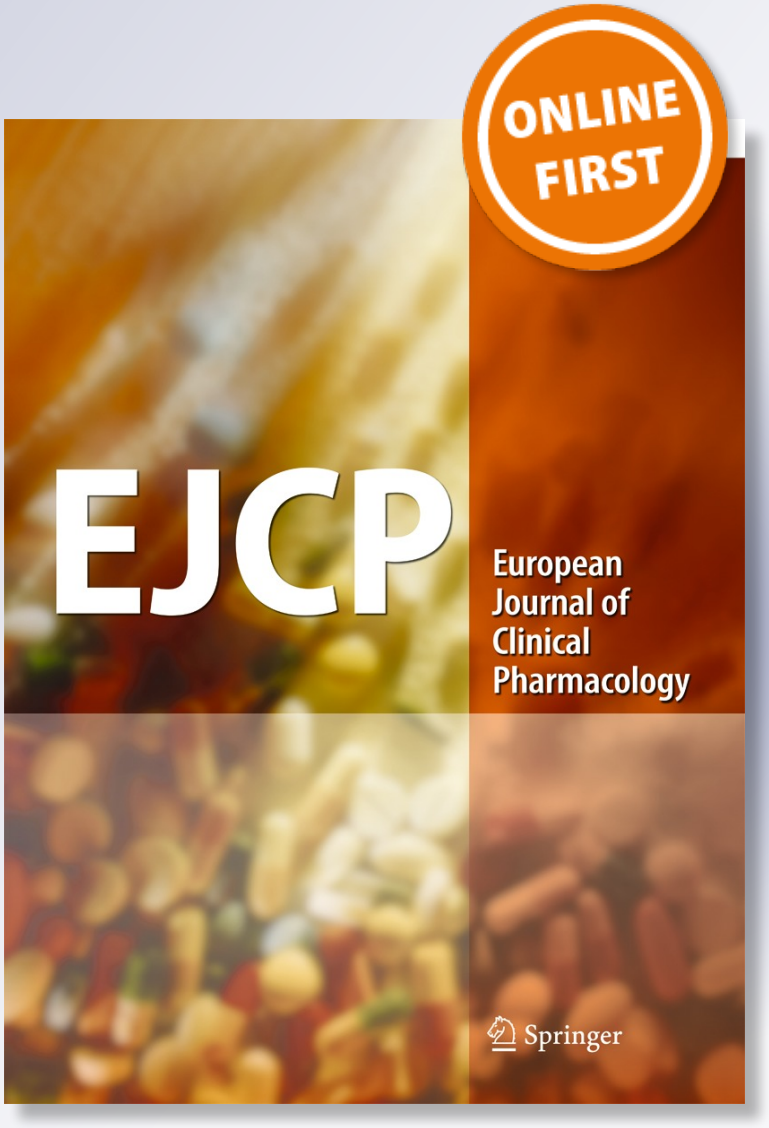

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Systematic review of anticholinergic risk scales in older adults

Carlos E. Durán · Majda Azermai · Robert H. Vander Stichele

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Abstract
Background Anticholinergic drugs are often involved in explicit criteria for inappropriate prescribing in older adults. Several scales were developed for screening of anticholinergic drugs and estimation of the anticholinergic burden. However, variation exists in scale development, in the selection of anticholinergic drugs, and the evaluation of their anticholinergic load. This study aims to systematically review existing anticholinergic risk scales, and to develop a uniform list of anticholinergic drugs differentiating for anticholinergic potency.
Methods We performed a systematic search in MEDLINE. Studies were included if provided (1) a finite list of anticholinergic drugs; (2) a grading score of anticholinergic potency and, (3) a validation in a clinical or experimental setting. We listed anticholinergic drugs for which there was agreement in the different scales. In case of discrepancies between scores we used a reputed reference source (Martindale: The Complete Drug Reference®) to take a final decision about the anticholinergic activity of the drug.
Results We included seven risk scales, and evaluated 225 different drugs. Hundred drugs were listed as having clinically relevant anticholinergic properties (47 high potency and 53 low potency), to be included in screening software for anticholinergic burden.
Conclusion Considerable variation exists among anticholinergic risk scales, in terms of selection of specific drugs, as well as of grading of anticholinergic potency. Our selection of 100 drugs with clinically relevant anticholinergic properties needs to be supplemented with validated information on dosing and route of administration for a full estimation of the anticholinergic burden in poly-medicated older adults.

Keywords Anticholinergic drugs · Risk scale · Aged · Anticholinergic activity

Introduction

There are over 600 medicinal products recognised to have anticholinergic activity [1], with broad therapeutic action as well as adverse effect profile.

Although it has been argued that inter-individual variability could have a greater role than age-related variability to determine the response rate to pharmacotherapy in older adults [2], it is possible to assume, as a generalization, that older adults are more sensitive to anticholinergic effects, because of changes in pharmacokinetics and pharmacodynamics [3, 4]. However, drugs with anticholinergic properties are widely used among nursing home residents and community dwelling older adults [5–7]. The muscarine receptor blocking properties of anticholinergic drugs result in a variety of adverse effects; the most frequently cited include dry mouth, dry eyes, constipation, blurred vision and increased heart rate (peripheral adverse effects). Dizziness, sedation, confusion, delirium and even cognitive impairment have been reported as central adverse effects of anticholinergic drugs [1, 8]. Furthermore, anticholinergic drug use is closely related with serious negative outcomes on the

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older adults' health status, with increased risk of falls [9] and higher mortality rates [10].

Several attempts have recently been made to produce reliable lists of drugs with a measure for the anticholinergic load, and consequently the potential to produce adverse effects. These approaches are based on tests of the affinity of the drug to the muscarinic receptor, on experts' consensus, or on a combination method. Anticholinergic risk scales are proposed to give physicians a practical tool to anticipate anticholinergic-related adverse effects in an old population. All these scales have demonstrated positive results in clinical settings [11–17]. However, considerable variation exists in the methodology of anticholinergic risk scale development, in the selection of drugs with anticholinergic properties, and even more when the strength of the load is taken into account.

Therefore, the aim of our study was to systematically review existing anticholinergic risk scales, and to develop a uniform list of anticholinergic drugs, expressed in an international drug classification, with differentiation in anticholinergic potency.

Methods

Search strategy

In November 2011 we performed a systematic search in MEDLINE using the Medical Subject Headings (MeSH) and free text terms: ("cholinergic antagonists" OR "muscarinic antagonists") AND ("adverse effects" OR "drug toxicity") AND "aged". We also retrieved additional pertinent publications from the reference list of the selected articles (snowballing). All selected studies retrieved in the MEDLINE search were used as a starting point for the "related citation" strategy of Pubmed (automatic retrieval of references with similar content). In addition, we used Google Scholar and Web of Science to perform a citation analysis of the selected studies, with a check of the content of the relevant retrieved citations. We had no language or date restrictions. In September 2012 we updated the search in order to identify any new publication in the field.

The systematic search for relevant publications was performed by the first author (CD), and independently checked by a second author (RVS). In case of conflict, decisions were to be made in consensus with a third author (MA).

In Fig. 1, a flowchart of the search strategy is presented.

Inclusion and exclusion criteria

We only included studies that provided (1) a finite list of anticholinergic drugs; (2) a grading score of anticholinergic potency; (3) validation in a clinical or experimental setting. Studies where the anticholinergic drug were not listed by full active ingredient name but by unspecified medication group names (e.g., antipsychotics) were excluded. We excluded studies that did not use a scale or an indicator of the anticholinergic load, and did not relate this scale to a measured outcome (experimental or clinical). Studies performed in other populations than older adults were excluded, as well as case studies, case series, editorials, and narrative reviews.

Data extraction

First, from the included studies we listed anticholinergic drugs for which there was agreement among the anticholinergic risk scales on high potency.

Second, we repeated the first step and grouped all drugs for which there was agreement among anticholinergic risk scales on their lack of anticholinergic potency (non-anticholinergic).

For all scales, we extracted the quantitative grading scores proposed by the authors, usually from 0 (*no anticholinergic*) to 3 (*high potency*). When there were discrepancies between the different drug scales in the evaluation of the anticholinergic nature of the drug, we used a well reputed reference source (Martindale: The Complete Drug Reference®) [18] to confirm any previous report about anticholinergic properties or adverse effects. Martindale® was used with the aim to improve the decision cut-off level only in cases where there was found discrepancies, not in positive cases.

The drugs for which anticholinergic action could be confirmed were selected and classified in two separate collections, based on their scores in the different risk scales: one collection of drugs with confirmed high anticholinergic potency; one collection of drugs with confirmed low anticholinergic potency (see *data synthesis* for criteria).

The remaining drugs, for which the check in the reference source was negative, were classified as drugs with improbable anticholinergic action.

Each drug was coded according to the Anatomical, Therapeutic and Chemical (ATC) Classification from the World Health Organization (WHO), version 2011.

Data synthesis

High potency anticholinergics

High-potency anticholinergic drugs were selected when there was a sufficient level of agreement among the scales' grading scores. Agreement was found when drugs scored 3 in two or more risk scales or when drugs scored 3 in one scale and 2 in one or more scales. These drugs were directly pooled as high potency anticholinergics.

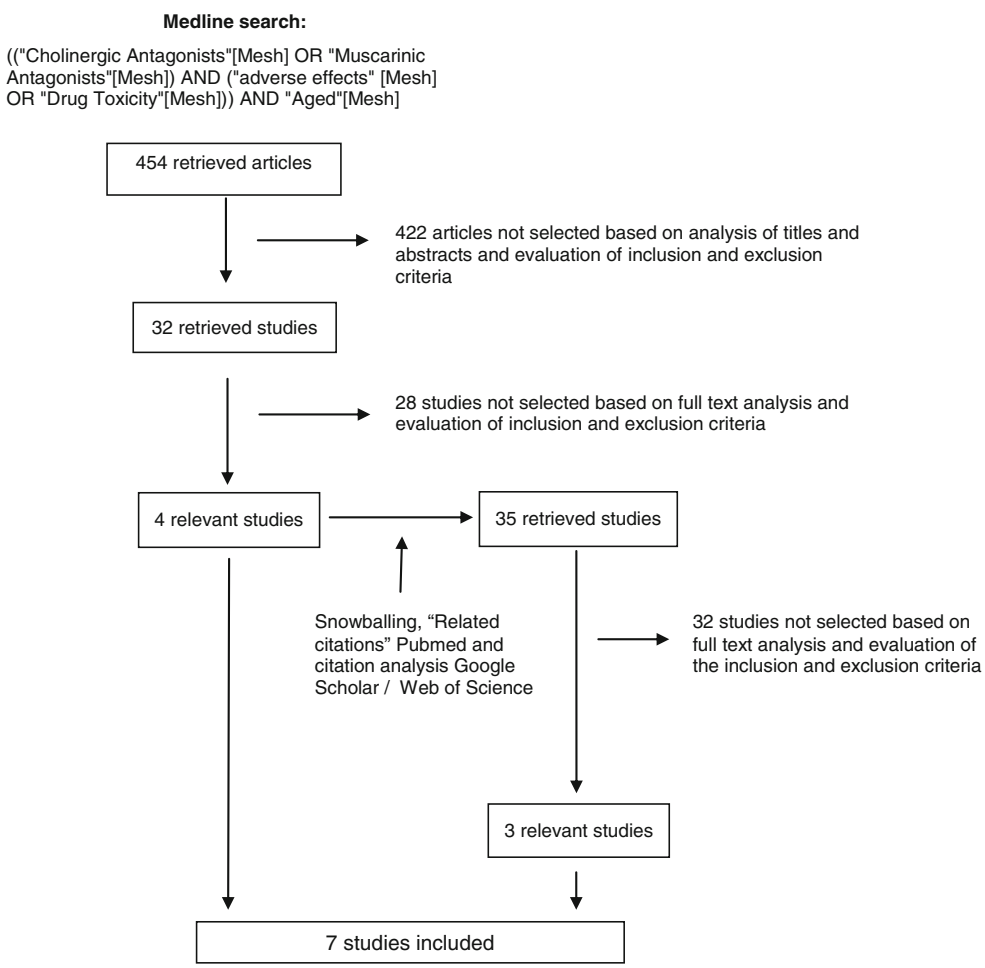

Fig. 1 Flowchart of the systematic search

Second, we checked the Martindale® for drugs for which there was disagreement. Disagreement was found when a drug scored 3 in at least one list but an explicit 0 was given in another risk scale, or when a drug scored 3 in one list but was not scored in any other list. In case the anticholinergic action was confirmed in the Martindale®, we selected the drug as a high potency anticholinergic.

Low potency anticholinergic

Low potency anticholinergic drugs were selected when there was a sufficient level of agreement among the scales' grading scores. Agreement was found when drugs scored 2 or 1 in two or more risk scales, or when drugs scored 2 in one risk scale and 1 in one or more scales.

Disagreement was found when a drug scored 2 or 1 in one or more list but an explicit 0 was given in other list, or when a drug scored 2 or 1 in only one list without confirmation in any other list. In these cases, we followed the same approach as with the high potency anticholinergics. In case the anticholinergic action in Martindale was found to be lacking, we classified the drug as part of the list of improbable anticholinergics. When the check in Martindale was positive the drugs were classified as part of the low potency anticholinergics.

Results

Systematic search

The broad search for relevant publications in the Medline database resulted in 454 retrieved articles. We screened these articles for our inclusion and exclusion criteria by title and abstract, and retained 32 studies which were analysed in full. Four studies were selected based on our inclusion and exclusion criteria. Through a manual review of additional pertinent publications identified through the reference list of selected articles (snowballing method), by using the "related citations" tool in PUBMED, and by performing a citation analysis of the selected articles in Google Scholar and Web of Science, we additionally identified 35 potentially eligible studies. In this second round, these articles were also analysed in full and evaluated for our inclusion and exclusion criteria. Three additional studies were included. Hence, in total, seven publications were selected [Carnahan 2006,

Ancelin 2006, Chew 2008, Rudolph 2008, Han 2008, Ehrt 2010, Sittironnarit 2011] for data extraction [11–17]. All the selected risk scales but one used a 4-point grading (0 to 3). Ehrt U, et.al. [16] used a 5-point grading (0 to 4). For the sake of congruence, we changed the ratings in this scale (4 into 3, 3 into 2, 2 and 1 into 1, and 0 remained 0).

An overview of the included studies is presented in Table 1.

Four of the risk scales [Carnahan 2006, Chew 2008, Ehrt 2010 and Sittironnarit 2011] provided an extra list of drugs explicitly considered as having no anticholinergic properties.

Selection of anticholinergic drugs

High and low potency anticholinergics

We selected 47 drugs as high potency anticholinergics (see Table 2). There was agreement among the scales for 30 drugs. An additional 17 drugs were selected after consulting the Martindale®.

We selected 53 drugs as *low potency anticholinergics* (see Table 3). There was agreement among scales for 20 drugs. An additional 33 drugs were selected after consulting the Martindale®.

In total, 100 drugs were selected. The nervous systems drugs were the most frequent on the list (n=58/N=100), followed by drugs for the respiratory system (n=19), alimentary tract and metabolism (n=10), genitourinary system (n=5), musculoskeletal system (n=5), cardiovascular system (n=2) and sensory organs (n=1). No ATC code was available for aceprometazine and carbidopa. We considered them as nervous system drugs.

Drugs with improbable or no anticholinergic action

In Table 4 is presented a first sublist of 12 drugs, which were assigned with the highest grade in one risk scale, but with no confirmation neither in other risk scales nor in Martindale.

In a second sublist, we placed 68 drugs which were scored 1 or 2 in at least one scale but without confirmation in Martindale. In a third sublist we placed 45 drugs which received an explicit 0 in at least 3 out of 4 scales. These sublists are available in the Annex.

Finally, we listed an additional 484 drugs which received an explicit 0 in only one or two risk scales (sublist available on request of the authors).

Discussion

To our knowledge, this is the first systematic review of anticholinergic risk scales in older adults. From the 7 identified scales we selected 100 active ingredients to be considered in screening of medication lists for anticholinergic properties.

In addition, we listed 80 drugs for which there was no consensus on the clinical relevance of alleged anticholinergic properties, and no confirmation in the reference source. Therefore, there is insufficient evidence to include them in routine screening work for epidemiologically and clinically relevant problems related to anticholinergic drug use.

The 100 drugs with clinically relevant anticholinergic properties were divided in 47 high potency and 53 low potency anticholinergics, based on a pooling of scores from the different risk scales. This is a reduction to a 3-point (0 to 2) classification of potency, compared to the usual 4-point (0 to 3) classification in individual risk scales. There was too much divergence in the grading of mild to moderate potency (2 and 1) in 4-point scales to reproduce this with a consistent algorithm in a pooled grading. For screening purposes, this simpler two grade classification might provide sufficient clinical sophistication, especially when dosing information is considered as separate issue.

We classified all the evaluated products into the international Anatomical Chemical Therapeutic Classification (ATC). This will enhance the cross national validity of quality assurance software to identify all relevant branded products with anticholinergic properties in the countries, participating in cross national comparison.

This study focused on anticholinergic burden in older people and did not look for studies in other population with potentially interesting additional information. However, as we only wanted to select information with some confirmation of relevance for the population of the elderly, these additional studies would not have been pertinent for our aim.

Our search strategy was more limited than a search for clinical trials in several bibliographic databases, as recommended by the Cochrane Collaboration.

The studies we selected and multiple other observational studies have shown the association between high anticholinergic burden and negative clinical outcomes, mainly related to cognitive decline [10, 16–19]. However, an association is not necessarily a causal relationship and can be confounded by indications such as Parkinson's disease. Furthermore, there is indeed little evidence from randomized clinical trials that interventions to reduce anticholinergic burden will result in better clinical outcomes for the patients. In a recently published study, the first attempt to do so was not convincing [20]. In this review, up to 58% of the anticholinergics belong to the nervous system group (mainly antidepressants, antipsychotics and drugs for Parkinson's disease). Moreover, cognitive impairment might also be possible in other indications treated with less well known and hence less well recognized anticholinergics. Consequently, our results contribute to expand the spectrum of anticholinergic drugs to be taken into account by physicians, guidelines developers and researchers to study further the anticholinergic adverse reactions in older adults.

Table 1 Overview of study characteristics in the included studies

Study ID	Study design	N	Participants	Grading system and methodology	Outcome studied
Carnahan 2006 USA (*AnticholinergicDrugScale*)	Cross-sectional study	279	Residents of long-term care facilities (mean age 86 y)	Scores : 4-point scale (0 to 3) Basis: Expert opinion Number of drugs: 117	Serum anticholinergic activity
Ancelin 2006 France	Cohort study (2 years follow-up)	372	Subjects >60 years without dementia at the recruitment	Scores: 4 point scale (0 to 3) Basis: serum anticholinergic activity and expert opinion. Number of drugs: 27	Cognitive performance and mild cognitive impairment
Han 2008 USA	Cohort study (2 years follow-up)	544	Hypertensive men >65 years	Scores: 4-point scale (0 to 3) Basis : previous published anticholinergic scale and expert opinion Number of drugs: 60	Memory performance and executive function
Rudolph 2008 USA (*Anticholinergic Risk Scale ARS*)	One retrospective cohort. One prospective cohort study	132/ 117	Males over 65 years 1st. Cohort: patients in geriatric clinics 2nd. Cohort: patients attending primary care clinics.	Scores: 4 points scale (0 to 3) Basis: detailed literature review and expert opinion. Number of drugs: 49	Frequency of anticholinergic adverse effects
Chew 2008 USA	Cross-sectional study	107	Drugs commonly used in older adults	Scores : 4-point scale Basis: radioreceptor assay Number of drugs : 22	Anticholinergic activity *in vitro*
Ehrt 2010 Norway	Cohort study (8 years follow-up)	78	Subjects (mean age 68.7 y) with diagnosis of Parkinson's disease.	Scores: 5-point scale (0 to 4) Basis: Chew 2008 and expert opinion. Number of drugs: 29	Long-term cognitive decline
Sittironnarit 2011 Australia (*Anticholinergic Loading Scale*)	Cross-sectional study	1112	Subjects >60 years (211 Alzheimer's disease; 133 mild cognitive impairment; 768 healthy controls)	Scores: 4-point scale (0–3) Basis: Ancelin 2006, Han 2008, Chew 2008, Rudolph 2008 and expert opinion. Number of drugs: 49	Psychomotor speed and executive function

Table 2 High potency anticholinergics

N	Drug name	ATC 5th level	Carnahan 2006 USA	Ancelin 2006 France	Chew 2008 USA	Rudolph 2008 USA	Han 2008 USA	Ehrt 2010 Norway	Sittironnarit 2011 Australia
• High potency anticholinergics									
1	Amitriptyline	N06AA09	3	3	3	3	3	3	3
2	Atropine	A03BA01	3		3	3	3		3
3	Belladona alkaloids	A03BA04		3			3		
4	Benzatropine	N04AC01	3			3		3	
5	Chlorphenamine	R06AB04	3	3		3	3		3
6	Chlorpromazine	N05AA01	3		2	3	3		
7	Clomipramine	N06AA04	3	3					
8	Clozapine	N05AH02	3		3	2		3	
9	Cyproheptadine	R06AX02	2			3			3
10	Desipramine	N06AA01	3			2	2		
11	Dexchlorpheniramine	R06AB02		3					3
12	Dicyclomine	A03AA07	3		3	3			
13	Diphenhydramine	R06AA02	3		2	3	3		
14	Doxepin	N06AA12	3		3		3	3	
15	Fluphenazine	N05AB02	1			3			3
16	Hydroxyzine	N05BB01	3	3		3			
17	Hyoscyamine	A03BA03	3		3	3			
18	Imipramine	N06AA02	3	3		3	3		3
19	Levomepromazine	N05AA02	2	3					
20	Meclozine	R06AE05	3			3			
21	Nortriptyline	N06AA10	3		2	2	3	2	
22	Orphenadrine	N04AB02	3	3				3	
23	Oxybutynin	G04BD04	3	3	2	3		3	2
24	Propantheline	A03AB05	3				2		
25	Protriptyline	N06AA11	3						3
26	Scopolamine (Hyoscine)	A04AD01	3				3		
27	Thioridazine	N05AC02	3		3	3	3	3	
28	Tolterodine	G04BD07	3		3	2	3		3
29	Trihexyphenidyl	N04AA01	3	3			3	3	
30	Trimipramine	N06AA06	3	3				3	
• High-potency anticholinergics after review in Martindale: The Complete Drug Reference									
31	Acepromazine	N05AA04		3					
32	Aceprometazine	N/A		3					
33	Brompheniramine	R06AB01	3						
34	Carbinoxamine	R06AA08	3						
35	Clemastine	R06AA04	3						
36	Darifenacin	G04BD10	3						
37	Dimenhydrinate	R06AA02	3						
38	Emepronium	G04BD01						3	
39	Flavoxate	G04BD02	3						
40	Homatropine	S01FA05					3		
41	Ipratropium	R03BB01	0					3	
42	Procyclidine	N04AA04	3						
43	Promethazine	R06AD02	3			3			0
44	Pyrilamine	R06AC01	3						
45	Thiothixene	N05AF04	1			3			
46	Tizanidine	M03BX02				3			
47	Tropatepine	N04AA12		3					

Table 3 Low-potency anticholinergics

N	Drug name	ATC 5th level	Carnahan 2006 USA	Ancelin 2006 France	Chew 2008 USA	Rudolph 2008 USA	Han 2008 USA	Ehrt 2010 Norway	Sittironnarit 2011 Australia
• Low-potency anticholinergics									
1	Amantadine	N04BB01	1			2			
2	Chlordiazepoxide	N05BA02	1				1		
3	Cimetidine	A02BA01	2			2			
4	Clonazepam	N03AE01	1						1
5	Cyclobenzaprine	M03BX08	2			2	1		
6	Diazepam	N05BA01	1		1			1	1
7	Digitoxin	C01AA04	1		1			1	
8	Fentanyl	N02AB03	1		1				
9	Fluoxetine	N06AB03	1		1		1	1	1
10	Fluvoxamine	N06AB08	1					1	1
11	Methocarbamol	M03BA03				1	1		
12	Olanzapine	N05AH03	1		2	2	1	2	
13	Oxycodone	N02AA05	1				1		1
14	Paroxetine	N06AB05	1		2	1	2	2	2
15	Propoxyphene	N02AC04			1		2	1	
16	Quetiapine (fumarate)*	N05AH04	0		1	1	2	1	
17	Ranitidine	A02BA02	2		1	1	2	1	1
18	Temazepam	N05CD07	1		1				1
19	Theophylline	R03DA04	1	2				1	2
20	Triazolam	N05CD05	1				1		
• Low-potency anticholinergics after review in Martindale—The Complete Drug Reference									
21	Alimemazine	R06AD01		2				0	
22	Baclofen	M03BX01	0		0	2	2		
23	Bromocriptine	N04BC01	1					0	
24	Carbamazepine	N03AF01	2		0		1	0	0
25	Cetirizine	R06AE07	0		0	2	2		2
26	Citalopram	N06AB04	0		1			1	1
27	Codeine	R05DA04	1	2	0		1	0	1
28	Disopyramide	C01BA03	2					0	0
29	Domperidone	A03FA03							1
30	Dosulepin	N06AA16							2
31	Entacapone	N04BX02	0			1			
32	Fexofenadine	R06AX26	0		0		2		2
33	Haloperidol	N05AD01	0		0	1			2
34	Hydrocodone	R05DA03	0		1		2		
35	Ketorolac	M01AB15					1		
36	Lithium	N05AN01	0		1				1
37	Loperamide	A07DA03	1		0	2	1		1
38	Loratadine	R06AX13	0		0	2	1		1
39	Loxapine	N05AH01	2						
40	Meperidine	N02AB02	2						
41	Methadone	N07BC02					2		
42	Mirtazapine	N06AX11	0		1	1			
43	Molindone	N05AE02	2						
44	Morphine	N02AA01	1		0		1		
45	Nefazodone	N06AX06	0				1		

Table 3 (continued)

N	Drug name	ATC 5th level	Carnahan 2006 USA	Ancelin 2006 France	Chew 2008 USA	Rudolph 2008 USA	Han 2008 USA	Ehrt 2010 Norway	Sittironnarit 2011 Australia
46	Oxcarbazepine	N03AF02	2						
47	Phenelzine	N06AF03	1						
48	Pimozide	N05AG02	2						
49	Prochlorperazine	N05AB04	1			2	2	0	2
50	Promazine	N05AA03						2	
51	Risperidone	N05AX08			0	1	1		1
52	Tramadol	N02AX02	1		0		2		2
53	Trazodone	N06AX05	0		0	1	1		

The validity of our selection of drugs with clinically relevant anticholinergic activity and the grading in high and low potency can be questioned. First, among the selected studies in this systematic review there was big variation in the criteria to assign anticholinergic drugs and the grades given to them. A 3-point grading approach, with only the distinction between low and high potency anticholinergics might be considered as rather crude. However, it was the only way we could operationalize a consistent pooling of the scores from the various lists.

The use of a secondary source of information (Martindale®) as a reference source could also be seen as a limitation. This was a *post-hoc* solution mainly because it was impossible to anticipate so much variation among the scales. Therefore, this source of information allowed us to expand the spectrum of selected anticholinergic drugs and decrease the probability to leave a drug with anticholinergic properties out.

We did not check borderline products with experimental or clinical methods. Special attention could be given to Table 4 with 12 products, all mentioned in one of the scales as high potency anticholinergic drugs, but not confirmed in other scales nor in our secondary reference source. Eight of these drugs (alprazolam, amoxapine, clorazepate, colchicine, digoxin, furosemide, maptroline, and opirpramol) are mentioned by Ancelin et.al. [12], and four of them (colchicine, amoxapine, maprotiline and opipramole) exclusively by this author. For future research, it is recommendable to clarify the real anticholinergic potency of drugs like alprazolam, colchine, digoxin, furosemide and metoclopramide (highly used among older adults) to be sure that excluding these drugs does not underestimate the anticholinergic burden.

Finally, the observation that a drug highly scored in one risk scale is not mentioned at all in another one does not necessarily mean a disagreement about the anticholinergic potency of that particular drug. It could simply mean that this drug is not marketed in the country where the underlying study was made.

In our opinion, the tools to measure anticholinergic burden need further sophistication and standardization and our study is an attempt to start this process. It needs confirmation as to

Table 4 Strong discrepancies in highly-scored drugs, not confirmed in Martindale®

N	Drug name	ATC 5th level	Carnahan 2006 USA	Ancelin 2006 France	Chew 2008 USA	Rudolph 2008 USA	Han 2008 USA	Ehrt 2010 Norway	Sittironnarit 2011 Australia
1	Alprazolam	N05BA12	1	3	0		1		1
2	Amoxapine	N06AA17		3					
3	Carisoprodol	M03BA02	0			3			
4	Clorazepate	N05BA05	1	3					
5	Colchicine	M04AC01	0	3					0
6	Digoxin	C01AA05	1	3				1	1
7	Furosemide	C03CA01	1	3	1			1	0
8	Maprotiline	N06AA21		3					
9	Metoclopramide	A03FA01	0			1	3	0	1
10	Opipramol	N06AA05		3					
11	Perphenazine	N05AB03	1		0	3	2	0	
12	Trifluoperazine	N05AB06	1			3			

the completeness of the list of epidemiologically and clinically relevant anticholinergic drugs, confirmation of the scaling of intrinsic potency, and it needs to be completed with determination of clinically important dosage levels for each of the selected drugs. For the individual patient, anticholinergic burden results from the intrinsic potency of the anticholinergic drug(s) used, but also from the administered dose(s) and route of administration. The next step would be to determine for each of these 100 products the usual dose [3] for each relevant route of administration, the recommended dose in older people (often half the dose of the usual dose), and the maximum dose (twice or triple the recommended dose). This is a necessary prerequisite for building quality assurance software, capable of analysing medication charts of poly-medicated elderly patients for a prediction of an overall anticholinergic burden in individual patients. The best method to integrate grading of potency, dosing strength and route of administration should again be clinically evaluated in a data-driven analysis.

Conclusion

Considerable variation exists among anticholinergic risk scales, especially in terms of anticholinergic potency of drugs. We developed a uniform list of 100 drugs with clinically relevant anticholinergic properties, and provided a differentiation in anticholinergic potency to estimate the anticholinergic burden in medicated older adults.

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Conflict of interest None to declare

Annex

N	Drug name	ATC 5th level	Carnahan 2006 USA	Ancelin 2006 France	Chew 2008 USA	Rudolph 2008 USA	Han 2008 USA	Ehrt 2010 Norway	Sittironnarit 2011 Australia
• Sublist 1. Discrepancies in drugs that received low grades, not confirmed in Martindale® (improbable anticholinergic action)									
1	Alverine	A03AX08		2					
2	Amoxicillin	J01CA04	0		1				0
3	Ampicillin	J01CA01	1						
4	Azathioprine	L04AX01	1						
5	Benazepril	C09AA07	0				1		
6	Betaxolol	C07AB05					1		
7	Bisacodyl	A06AB02	0		0				1
8	Bupropion	N06AX12	0		0		1		
9	Captopril	C09AA01	1					0	0
10	Carbidopa	N/A	0		0	1	1		1
11	Cefalexin	J01DB01	0		1				0
12	Cefamandole	J01DC03	1						
13	Cefoxitin	J01DC01	1						
14	Celecoxib	M01AH01	0		1				1
15	Cephalotin	J01DB03	1						
16	Clindamycin	J01FF01	1						
17	Cortisone	H02AB10	1						
18	Cycloserine	J04AB01	1						
19	Cyclosporine	L04AD01	1						
20	Chlorthalidone	C03BA04	1						0
21	Dexamethasone	H02AB02	1						
22	Dextromethorphan	R05DA09					1		
23	Diltiazem	C08DB01	1		0				0
24	Diphenoxylate	A07DA01	0		1				0
25	Dipyridamole	B01AC07	1		0			0	

N	Drug name	ATC 5th level	Carnahan 2006 USA	Ancelin 2006 France	Chew 2008 USA	Rudolph 2008 USA	Han 2008 USA	Ehrt 2010 Norway	Sittironnarit 2011 Australia
26	Duloxetine	N06AX21	0		1				0
27	Escitalopram	N06AB10	0		1				1
28	Estazolam	N05CD04	1						
29	Famotidine	A02BA03	1		0				0
30	Flunitrazepam	N05CD03						1	
31	Flurazepam	N05CD01	1						
32	Fluticasone-salmeterol	R03AK06	1						
33	Gentamicin	J01GB03	1						
34	Guaifenesin	R05CA03	0				1		
35	Hydralazine	C02DB02	1						0
36	Hydrocortisone	H02AB09	1						
37	Isosorbidedinitrate	C01DA08	1					0	0
38	Isosorbidemononitrate	C01DA14	1					0	0
39	Ketotifenophthalmic	S01GX08	1						
40	Lansoprazole	A02BC03	0		1			1	0
41	Levofloxacin	J01MA12	0		1				
42	Lorazepam	N05BA06	1		0				
43	Lumiracoxib	M01AH06							1
44	Metformin	A10BA02	0		1				1
45	Methotrexate	L04AX03	0						1
46	Methylprednisolone	H02AB04	1						
47	Midazolam	N05CD08	1						
48	Naratriptan	N02CC02							1
49	Nizatidine	A02BA04	1						0
50	Oxazepam	N05BA04	1		0			0	1
51	Pancuronium	M03AC01	1						
52	Phenobarbital	N03AA02	0				1	1	
53	Phenytoin	N03AB02	0		1				
54	Piperacillin	J01CA12	1						
55	Pramipexol	N04BC05	0			1		0	
56	Prednisolone	H02AB06	1					0	
57	Pseudoephedrine	R01BA02	0						2
58	Selegiline	N04BD01	0			1		0	
59	Sumatriptan	N02CC01							1
60	Topiramate	N03AX11	0		1				
61	Trandolapril	C09AA10	0				1		
62	Triamcinolone	H02AB08	1						
63	Triamterene	C03DB02	1						0
64	Valproatesodium	N03AG01	1						
65	Valproicacid	N03AG01	1		0				0
66	Vancomycin	J01XA01	1						
67	Ziprasidone	N05AE04			0	1			
68	Zolmitriptan	N02CC03							1
• Sublist 2. Drugs that received an explicit 0 in 3 out of 4 scales									
1	Acetylsalicylicacid	N02BA01	0		0			0	0
2	Allopurinol	M04AA01	0					0	0
3	Amlodipine	C08CA01	0		0			0	0
4	Atenolol	C07AB03	0		0			0	0

N	Drug name	ATC 5th level	Carnahan 2006 USA	Ancelin 2006 France	Chew 2008 USA	Rudolph 2008 USA	Han 2008 USA	Ehrt 2010 Norway	Sittironnarit 2011 Australia
5	Atorvastatin	C10AA05	0		0			0	0
6	Carbamazepine	N03AF01			0			0	0
7	Clopidogrel	B01AC04	0		0				0
8	Donepezil	N06DA02	0					0	0
9	Enalapril	C09AA02	0		0			0	0
10	Galantamine	N06DA04	0		0			0	0
11	Gemfibrozil	C10AB04	0						0
12	Glipizide	A10BB07	0		0			0	0
13	Haloperidol	N05AD01	0		0			0	
14	Hydrochlorothiazide	C03AA03	0		0			0	0
15	Ibuprofen	M01AE01	0		0			0	0
16	Insulin	A10A	0					0	0
17	Ketoprofen	M01AE03	0					0	0
18	Levodopa	N04BA01	0		0			0	0
19	Lisinopril	C09AA03	0		0			0	0
20	Losartan	C09CA01	0		0			0	
21	Metoprolol	C07AB02	0		0			0	0
22	Nifedipine	C08CA05			0			0	0
23	Nitroglycerin	C01DA02	0		0			0	0
24	Omeprazole	A02BC01	0		0			0	
25	Pantoprazole	A02BC02	0		0				0
26	Paracetamol	N02BE01	0		0			0	0
27	Pioglitazone	A10BG03	0		0				0
28	Piroxicam	M01AC01	0					0	0
29	Propranolol	C07AA05	0		0				0
30	Rabeprazol	A02BC04	0		0				0
31	Ropinirole	N04BC04	0					0	0
32	Rosiglitazone	A10BG02	0		0				0
33	Senna	A06AB06	0					0	0
34	Sertralin	N06AB06			0			0	0
35	Simvastatin	C10AA01	0		0			0	0
36	Spironolactone	C03DA01	0					0	0
37	Terbutaline	R03AC03	0					0	0
38	Timolol	C07AA06	0					0	0
39	Tamoxifen	L02BA01	0					0	0
40	Trimethoprim	J01EA01	0		0				0
41	Venlafaxine	N06AX16	0		0			0	
42	Verapamil	C08DA01	0					0	0
43	Warfarin	B01AA03			0			0	0
44	Zolpidem	N05CF02	0		0				0
45	Zopiclone	N05CF01	0					0	0

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