

# A Review of Surreptitious Anticholinergics: Unknowingly Increasing Anticholinergic Burden in the Elderly

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## Objectives

To review surreptitious anticholinergics (anti-Ach) and the scales used to assess their harmful cognitive effects in elders.

## Methods

A literature search of the PubMed database from 1991 to May 2017 was conducted using key words: *cholinergic antagonists/adverse effects, aged, delirium, and cognition disorders*. References of identified studies were reviewed for relevant citations. Inclusion criteria identified English-language articles presenting measures of surreptitious anti-Ach activity (those not categorized as anti-Ach drugs but having anti-Ach activity) and scales to qualify and/or quantify the risk of these effects. Exclusion criteria consisted of studies examining elderly adults with additional psychiatric diagnoses. Drugs that were included to be evaluated were prescription and over the counter medications that are approved in the United States. Inactive ingredients, drugs withdrawn from the market, discontinued, and veterinary medications were excluded.

## Results

Initially, 559 drugs were investigated in four studies with 135 having detectable anti-Ach activity. For completeness, drugs listed on all scales were recorded to be evaluated. After removal of drugs meeting exclusion criteria, 574 drugs remained. Of the drugs having anti-Ach activity, 138 (72%) were surreptitious anti-Ach drugs. Surreptitious anti-Ach were dichotomized from the Camahan study where drugs ranked as a level 3 on the scale were determined to be known anti-Ach and drugs ranked as level 2 or 1 were surreptitious anti-Ach. Sixty-one additional drugs were considered to be surreptitious anti-Ach, as they were ranked 0 or not included on the Camahan study but were classified to have some activity by another study brining the total to 82%. Representative classes identified included histamine receptor antagonists, skeletal muscle relaxants, and selective serotonin reuptake inhibitors. Some drugs were recognized as either non- or anti-Ach depending on the source referenced. For example, carbamazepine, which is moderately anti-Ach on the anti-Ach drug scale (ADS), is not ranked on the anti-Ach activity scale (AAS) nor the anti-Ach load scale (ALS). Also, some drugs that were included on one scale were not evaluated on another. Of all the drugs evaluated, only 272 (47%) of drugs were included on two or more scales. Of the instances where a drug was listed on more than one scale, 109 (40%) of drugs had discrepancies on anti-Ach classification. This lack of congruency highlights the need for a more standardized system to evaluate surreptitious anti-Ach, and anti-Ach drugs as well.

## Results

Comparison of Evaluated Drugs Classified by Scale

Drug Class/Drug		Camahan (ADS) <sup>1</sup>	Ancefin (ABC) <sup>2</sup>	Boustani (ACB) <sup>3</sup>	Chew <sup>4</sup>	Duran <sup>5</sup>	Ehrt (AAS) <sup>6</sup>	Han (CrAS) <sup>7</sup>	Rudolph (ARS) <sup>8</sup>	Sittironnari (ALS) <sup>9</sup>	Tune (ng/mL) <sup>10</sup>
Antipsychotics	perphenazine	1	3	0	0	high	0	2	3		
	quetiapine	0		3	+	high	2	2	1		
Benzodiazepines	alprazolam	1	3	1	0			1		1	
	cetirizine	0			0	high		2	2	2	
Histamine Receptor Antagonists	cimetidine	2		1		high					0.86
	fexofenadine	0			0	high		2		2	
	loratadine	0			0	high		1	2	1	
	ranitidine	2			+	high	2	2	1	1	0.22
Opioids	codeine	1	2	1	0	high	0	1		1	0.11
	fentanyl	1		1	0/+	high				0	
	hydrocodone	0			0/+	high		2			
Skeletal Muscle Relaxants	baclofen	0			0	high		2	2		
	carisoprodol	0							3		
	cyclobenzaprine	2		2		high		1	2		
Selective Serotonin Reuptake Inhibitors	paroxetine	1		3	++	high	2	2	1	2	
Other	captopril	1		1			0			0	0.02
	colchicine	0	3	1						0	
	furosemide	1	3	1	0/+		1			0	0.22
	ipratropium	0				low	4				
	metformin	0			0/+					1	
	metoclopramide	0					0	3	1	1	
	theophylline	1	2	1		high	2			2	0.44
	warfarin	1		1	0		0			0	0.12

Drugs chosen for table can be found on top 200 drug list or Medicare top spending list. Select drugs are not on either list, but are listed due to discrepancy in rank or availability as over the counter products.

Criteria that Comprised the Creation of Evaluated Drug Scales

	Expert Opinion	Serum Assay	Literature/ Databases	Dose	Side Effects	Blood Brain Barrier	Route of Administration	Drug Interactions
Camahan (ADS)	+	+	+				+	
Ancefin (ABC)		+					+	+
Boustani (ACB)	+		+		+	+		
Chew		+						
Duran			+					
Ehrt (AAS)	+	+						
Han (CrAS)	+		+					
Rudolph (ARS)	+		+		+			
Sittironnari (ALS)	+	+	+					
Tune (ng/mL)		+						
Drug Burden Index				+	+		+	

+ indicates a variable used to create drug scale, \* indicates variable attributed to scale, but not explicitly defined: the Camahan ADS is a modified version of the CrAS.

## Results

Eleven articles presented drug scales. Two reported serum anti-Ach activity (SAA) relative to atropine activity which is highly associated with blockade in postsynaptic muscarinic receptors and impaired cognitive function. The drug burden index (DBI) calculates any anti-Ach or sedative drug based on given dose, recommended dose, and the summative load of the drugs. To use the index a provider must be able to identify that a drug falls into one of the former categories. Various criteria comprised the remaining scales including dose, route of administration, blood brain barrier permeability, expert opinion or existing drug references, accounting for the variability between sources. Even when evaluating side effects, one scale looked specifically at central side effects, while another gauged side effects as a whole. None of the studies recognized a specific value associated with their scale where harm from anti-Ach drugs was more likely to occur.

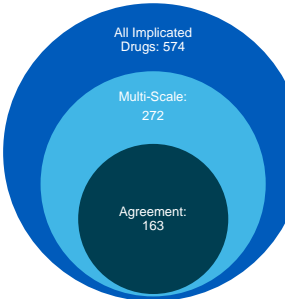
## Conclusion

Many commonly prescribed medications can increase the anti-Ach burden on older adults, even if not categorized as anti-Ach drugs. Geriatric clinical pharmacists can reduce potential patient harm by systematically identifying and qualifying surreptitious anti-Ach drugs in patients. However, caution must be exercised when using scaling systems as they currently exist, as some drugs may be classified as having low or no anti-Ach effect, but can cause a significant impact on a patient when used as part of a multi-drug regimen. While the scales can be used to estimate anti-Ach burden, currently there is no reported value which states when anti-Ach effects approach clinical importance. The discrepancies between scales can also create confusion when evaluating a patient's drug regimen for a potentially inappropriate or harmful drug. An opportunity for a standardized clinical decision support tool still exists.

## References

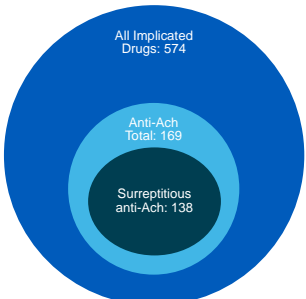
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Number of Drugs Classified the Same on 2 or More Scales



Multi-scale drugs are drug listed on more than one scale. Agreement indicates the same or similar classification when listed more than once. Partial agreement was counted as a discrepancy between scales. Of all drugs evaluated 28% were in complete agreement.

Number of Surreptitious anti-Ach Drugs



Surreptitious anti-Ach were 72% of total anti-Ach and 24% of all drugs reviewed.