

Development and pilot testing of an algorithm-based approach to anticholinergic deprescribing in older patients

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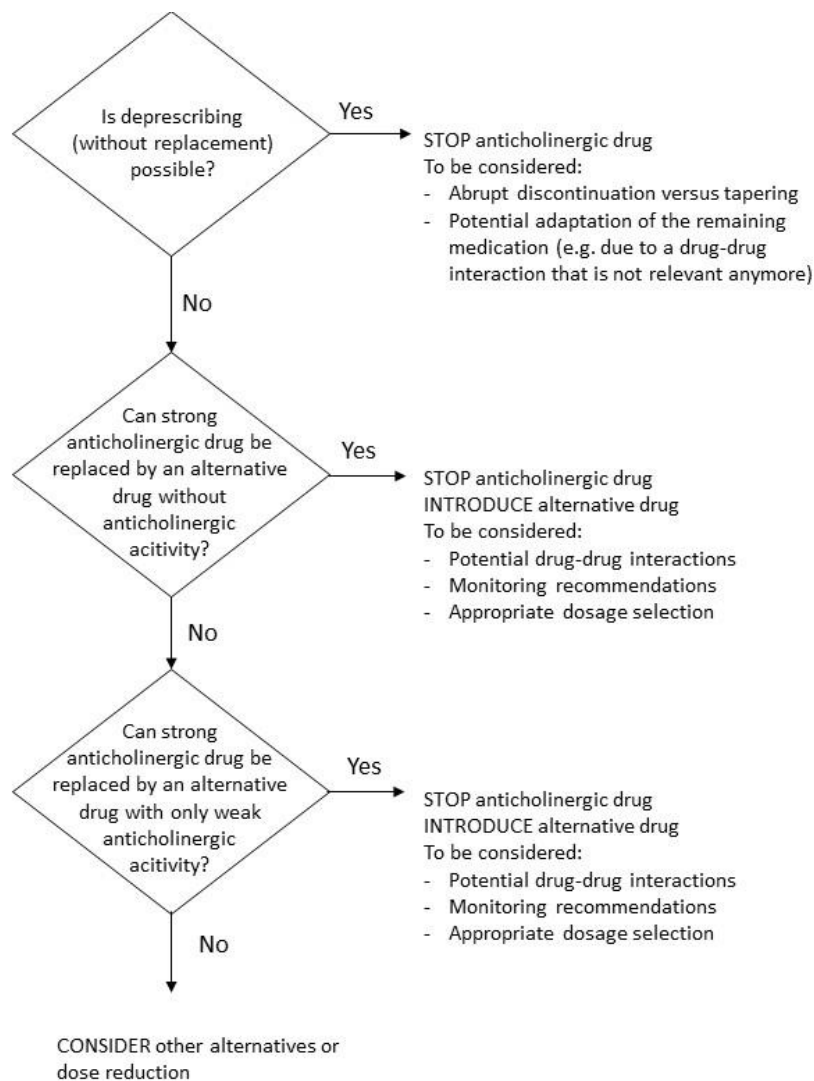
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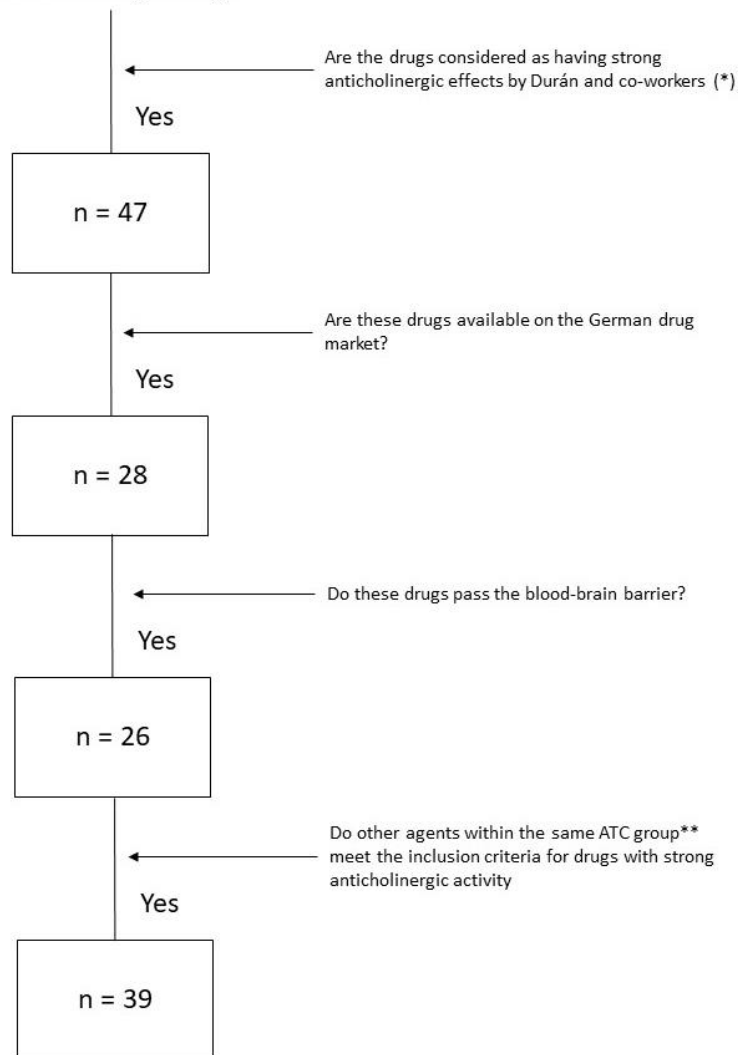
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Supplementary Figure 1: General structure of the deprescribing algorithm. Specific algorithms based on this structure were developed for 21 indications in which anticholinergic drugs are used.

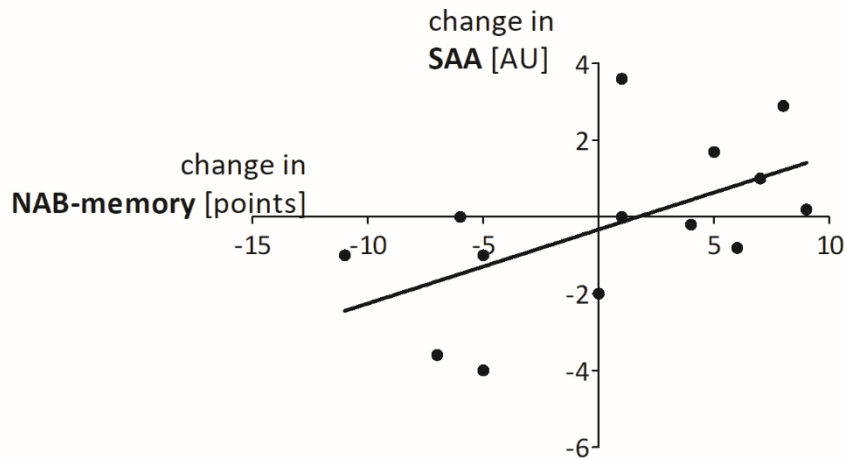
Identifying strong anticholinergic drugs



*Duran CE, Azermay M, VanderStichele RH. Systematic review of anticholinergic risk scales in older adults. European journal of clinical pharmacology. 2013;69(7):1485-96.

**ATC = anatomical therapeutic chemical group

Supplementary Figure 2: Selection of drugs with strong anticholinergic activity.



Supplementary Figure 3: Correlation of changes in memory test scores (Neuropsychological Assessment Battery - Memory, NAB-memory) with changes in measured SAA (Serum Anticholinergic Activity) between baseline and follow-up assessment (Pearson $r^2 = 0.36$; $p = 0.03$). With regard to SAA, the intraindividual difference between baseline and follow-up assessment was used with positive values indicating an improvement over time and negative values indicating deterioration. AU = atropine unit, NAB = neuropsychological assessment battery.

Supplementary Table 1: Tests for detecting symptoms potentially related to anticholinergic adverse drug reactions.

Method	Outcome	Test	Description	Reference range
(i) Test battery	Impairment of memory	Neuropsychological Assessment Battery (1)	- Repeating two different lists, each consisting of 12 words - Repeating numbers in the right sequence	- ≤ 19 points = severe impairment; 20-29 points = moderate impairment; 30-39 points = mild impairment; ≥ 40 points = no impairment (1)
	Impairment of attention	Neuropsychological Assessment Battery (1)	- Crossing out letters and numbers - Summation of numbers	- See reference range of memory impairment
(ii) Questionnaires	Constipation	Bowel Function Index (2)	- Three questions - Rating between 0 (no problem) and 100 (great problem) points - Result is the mean value of the rated questions	- No constipation: up to 28.8 points (3) - Clinically meaningful change: 12 points (2)
	Urinary difficulties	International Prostate Symptom Score (4)	- Seven questions - Likert scale with six possible answers - Rating of 0-5 points per answer - Result is the sum of points	- 0-7 points = no or mild difficulties; 8-19 points = strong difficulties; 20-35 points = great difficulties (4)
	Xerostomia	Summated Xerostomia Inventory (5)	- Five questions - Likert scale with three possible answers - Rating of 1-3 points per answer - Result is the sum score	- Older patients usually have a result of 8 points (5) - Clinically meaningful change: 4 points (6)
(iii) Practical test	Xerostomia	Stimulated saliva flow (7)	- Chewing a paraffin gum for 5 min - During chewing, the saliva is collected in a mug - Saliva volume is the endpoint	- < 3.5 ml = very poor saliva flow; 3.5-5 ml = poor saliva flow; > 5 ml = normal saliva flow (8)
(iv) Blood sample	Biomarker	Serum Anticholinergic Activity (SAA)	- Displacement of a radioactive marker in a rat brain membrane by the anticholinergic agent is measured in plasma (based on (9))	- < 0.5 pmol/ml of atropine unit (AU) = no or minimal activity; 0.5-5 pmol/ml of atropine unit (AU) = low activity; 5-15 pmol/ml of atropine unit (AU) = moderate activity; > 15 pmol/ml of atropine unit (AU) = high activity (10)
		Acetylcholinesterase, butyrylcholinesterase	- Enzyme activity hydrolyzing acetylcholine is measured in whole blood (11-13)	- Not available

References of the supplementary material

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Supplementary Table 2: Strong and weak anticholinergic drugs in the patients' medication for that no alternatives were recommended.

Patient	Anticholinergic drug	Intervention	Chosen alternative drug	No recommendation letter was issued, because...		
				...treatment should only be modified by a specialist.	...no alternative drugs with less anticholinergic activity were available.	...the anticholinergic activity of the drug was unclear. [#]
10	Clozapine	↓	None	X		
11	Biperiden	=		X		
3	Hydromorphone ⁺	=				x
2, 9, 10	Oxycodone ⁺	=				x
6	Oxycodone ⁺	↓	Hydromorphone ⁺			x
5	Tapentadol ⁺	=				x
2, 6	Tiotropium ⁺	=			x	
8	Trospium ⁺	=			x	

↓: stopped, =: no change, x: appropriate, #: applicable to the (entire) drug class of opioids (potential weak anticholinergic), +: weak anticholinergic drugs.

Supplementary Table 3: Differences between patient groups regarding cognitive and peripheral outcomes and blood biomarkers at follow-up assessment.

Characteristic	Patients with reduced anticholinergic load			Patients with constant anticholinergic load	Control group with no anticholinergic load
	Patients with (completely or partly) reduced anticholinergic load	Subgroup 1: patients with completely reduced anticholinergic load	Subgroup 2: patients with partly reduced anticholinergic load		
Participants: n	6	2	4	3	5
Cognitive outcomes					
Neuropsychological Assessment Battery (NAB) - Memory [Score (± SD)]	6 (± 3)*	4 (± 4)	7 (± 2)	-1 (± 6)	-5 (± 4)
Neuropsychological Assessment Battery (NAB) - Attention [Score (± SD)]	2 (± 4)	4 (± 1)	1 (± 6)	0 (± 2)	2 (± 6)
Peripheral outcomes					
Constipation [Score (± SD)]	16 (± 25)	7 (± 14)	21 (± 34)	1 (± 5)	-7 (± 12)
Urinary difficulties [Score (± SD)]	0 (± 2)	-2 (± 4)	0 (± 1)	0 (± 1)	1 (± 5)
Xerostomia [Score (± SD)]	1 (± 2)	2 (± 1)	1 (± 3)	0 (± 1)	1 (± 2)
Rate of salivary flow [ml (± SD)]	-1 (± 1)	-2 (± 0)	-1 (± 1)	1 (± 0)	2 (± 4)
Biomarkers					
Serum Anticholinergic Activity (SAA) [AU]	1 (± 1)	1 (± 1)	1 (± 2)	0 (± 4)	-2 (± 2)
Acetylcholinesterase [U/gHb]	0 (± 6)	-1 (± 8)	1 (± 6)	-4 (± 6)	5 (± 7)
Butyrylcholinesterase [U/l]	-790 (± 1643)	-668 (± 1976)	-851 (± 1784)	-385 (± 678)	-56 (± 287)

Reported are mean and standard deviation of the results on the respective outcome measures (difference between baseline and follow-up assessment; positive values indicate improvement, negative values indicate deterioration). *significant difference between patients with reduced anticholinergic load compared to patients with unchanged anticholinergic load or without anticholinergic load ($p < 0.05$), n = number, SD = standard deviation. AU = pmol/ml of atropine unit.