Quantifying Anticholinergic Burden and Sedative Load in Older Adults with Polypharmacy: A Systematic Review of Risk Scales and Models.

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Supplementary Text S1

1. ***Anticholinergic Drug Scale (ADS)*:** The ADS was developed in the U.S. in 2006. It is a 4-point scale (0−3) based on expert opinion and modification of the Clinician-rated Anticholinergic Scale (CrAS) developed based on experts' clinical experience and knowledge of the medication's properties.[1] A score of 0 indicates no known anticholinergic properties, while 1, 2, and 3 indicate drug have potentially anticholinergic, have occurrences of anticholinergic adverse events (usually at excessive doses), and are markedly anticholinergic, respectively. The scale includes a total of 520 drugs (403 drugs with 'no anticholinergic activity' score of 0) and with consideration of dose. The scale was developed through a cross-sectional observational study among older adults' patients in long-term care facilities. The ADS scale has been widely used and validated in populations of long-term care residents, hospital inpatients, nursing home residents, outpatient community residents and Australian veterans. It has been used to investigate associations between anticholinergic use and specific adverse events [2, 3]. This scale was first known as the CrAS modified version and the name was changed to ADS [3]. The adverse anticholinergic outcomes reported in these settings were cognitive dysfunction, risk of hospitalization, and mortality [4-6]. While the ADS reported a high number of medications, 117 drugs only showed anticholinergic activity and the remaining were classified as "No activity score" with a score of 0.
2. ***Anticholinergic Burden Classification (ABC)*:** The ABC was developed in France in 2006. It is a 4-point scale (0−3) based on expert opinion and extensive literature review of medications properties, available studies associating drugs with their serum anticholinergic activity through radioreceptor assays, route of administration, potential drug interaction effects and potential blood-brain barrier permeability. It includes a total of 27 medications with anticholinergic activity, without consideration of dose. The original publication includes drugs scored 2 and 3 on the ABC scale. The scale was developed through a longitudinal study in an outpatient population of older adults aged >60 years without senile dementia at baseline through 63 randomly selected general practitioners in France. The ABC scale was used to examine the associations between use of anticholinergic drugs and cognitive impairment in older adults and has been validated as described in Table S4 [7]. Patient drug burden was classified as 0 if they took no anticholinergic drugs, 1 if they took drugs with no likely effect, 2 if patient took drugs with low anticholinergic effect, and 3 if patient took drugs with high anticholinergic effect.
3. ***Anticholinergic Risk Scale (ARS)*:** The ARS was developed in the U.S. in 2008. It is a 4-point scale (0−3) based on expert opinion and extensive literature review of the 500 most prescribed medications within the Veterans Affairs Boston Healthcare System for their affinity for the muscarinic receptor, experimental reporting of anticholinergic activity, and literature review on anticholinergic adverse effects. The ARS includes 49 medications with consideration of dose. A score of 0 indicates no or limited anticholinergic potential and those drugs were not reported in the final ARS table, while 1, 2, and 3 indicate moderate, strong, and very strong anticholinergic potential, respectively. The scale was developed through 2 cohorts, retrospective cohort and a prospective cohort both included older adults. It has been validated in various populations of hospital patients, community dwelling patients, and veterans. It has been used to evaluate the associations between anticholinergic use and cognitive dysfunction or other anticholinergic adverse events [8].
4. ***Anticholinergic Cognitive Burden (ACB) scale***: The ACB scale was developed in the U.S. in 2008. It is as 3-point scale (1−3) based on literature review and expert opinion. It includes a total of 88 medications but with no consideration of dose. A score of 1 indicates drugs with possible anticholinergic effects (as demonstrated by serum anticholinergic activity or *in vitro* affinity to muscarinic receptor*)* but with no clinically relevant cognitive effects, while 2 or 3 indicate drugs with established, clinically relevant cognitive effects based on the drug blood-brain barrier permeability and its association with delirium. The scale was developed among a cohort of older adults attending primary care in Indianapolis, USA. The ACB has be widely used as is or with modifications based on the country and has been validated in a wide range of populations of older adults of different age-groups, with and without dementia, and who were receiving care in long-term care residents, hospital inpatients, nursing home residents, outpatient community residents. It has been used to investigate associations between anticholinergic use and specific adverse events [3, 9, 10].
5. [1]***Anticholinergic Activity Scale (AAS)*:** The AAS was developed in Norway in 2010. It is a 5-point scale (0−4) based on modifying the descriptive categorical score described in Chew's list of 107 drugs with measured anticholinergic activity and on expert opinion [11, 12]. It includes a total of 99 medications but with no consideration of dose. A score of 0 indicates no anticholinergic activity; while 1indicate none or minimal anticholinergic activity, 2, 3 and 4 indicates 0.5−5pmol/mL, 5−15pmol/mL, and >15pmol/mL of serum anticholinergic activity, respectively. The AAS scale was developed in a longitudinal community cohort of Parkinson's disease patients. It was used to evaluate the associations between anticholinergic use and cognitive dysfunction in this patient population but the scale has been validated as described in Table S4 [12].
6. ***Anticholinergic Loading Scale (ACL/ALS)*:** The ACL was developed in Australia in 2011. It is a 4-point scale (0−3) based on methods for calculation of anticholinergic load described in the ABC scale, the clinician-rated anticholinergic scores (CrAS). The authors used the previously published anticholinergic score for a medication and transformed to an ordinal scale (0-3) and expert opinion for any medication that has not been classified previously. The ACL includes a total of 292 medications with no consideration of dose. A score of 0 indicates no anticholinergic effect, and a score of 1,2 and 3 indicates low, moderate and strong anticholinergic effect respectively. The scale was developed through a multidisciplinary longitudinal study of aging, integrating expertise in neuroimaging,

biomarkers, clinical and neuropsychological research and lifestyle of older adults' participants of the Australian Imaging, Biomarkers and Lifestyle study of individuals. It was used to evaluate the associations between anticholinergic use and cognitive dysfunction and has been validated as described in Table S4 [13].

7. ***Anticholinergic effect on cognition (AEC)*:** The AEC was developed in the United Kingdom in 2016. It is a 4-point scale (0-3) based on a transparent and systematic evidence-based approach reviewing all British National Formulary (BNF) drug categories commonly used in older people for their *in-vitro* anticholinergic potency, capacity to cross the blood brain barrier and statements made in standard texts reviewed. A total of 165 drugs were examined and were able to classify 122 drugs without consideration of the dose, while 46 drugs were removed due to insufficient information. Individual drugs are ranked on their individual properties, so that different drugs from the same class may be allocated different AEC scores [14]. The scale has been recently validated in a retrospective study of patients with dementia using anonymized mental health records linked with mortality and hospitalization data [15].
8. ***German Anticholinergic Burden Scale (German ACB):*** This scale was developed in Germany in 2018. It is a 4-point scale (0−3) based on expert opinion and literature review that included 504 drugs approved in Germany without consideration of dose. A score of 0 indicates no anticholinergic potential, while 1, 2, and 3 indicate low, moderate, and high anticholinergic potential, respectively[16]. The German ACB has been recently validated in a multicentered observational cohort study in Germany and was compared with the ADS scale. The study found that increasing German ACB and ADS and was associated with reduced cognitive function, the German ACB generated comparable outcomes with the ADS score.[17]
9. ***Brazilian anticholinergic activity drug scale:*** This scale was developed in Brazil in 2019. It is a 3-point scale (1−3) based on expert opinion and literature review that considers 125 drugs approved in Brazil, with at least some anticholinergic activity and without consideration of the dose. The validation of this scale in different healthcare settings have not been done yet [18].
10. ***Korean Anticholinergic Burden Scale (KABS):*** The KABS was developed in Korea in 2019. It is a 4-point scale (0−3) based on expert opinion and literature review that generated a composite list of 655 medications with anticholinergic scores extracted from 10 existing scales and additional medications not rated previously and available in Korea were added to the list. A final list of 494 medications were deemed suitable for a Korean-specific scale without consideration of dose. A score of 0 indicates no anticholinergic potential, while 1, 2, and 3 indicate low, moderate, and high anticholinergic potential, respectively [19]. The KABS has been recently validated as described in Table S4.
11. ***Modified anticholinergic burden scale (mACB):*** The mACB scale was developed in Australia in 2019 based on modifying the original ACB scale developed by the Aging Brain Program of the Indiana Center for Aging Research ACB scale and Anticholinergic Risk Scale (ARS). The following approach for the modifications; first when a drug had different scores in the two scales used, the higher score was assigned. When a drug was only listed in one scale then the score for that scale was used. The modifications in this scale include only medications approved and in current use in Australia. It is as 3-point scale (1−3) that included a total of 82 drugs without consideration of the dose. The scale was developed and validated in a prospective quasi-experimental pre/post-controlled trial in sample population of 277 participants with dementia or cognitive impairment in Australia but the results are still under peer-review [20, 21].
12. ***Sedative Load Model:*** Published in 2003, the Sedative Load Model (SLM) was the first attempt to present a detailed classification of the sedative effects of drugs [22]. The model was developed by reviewing the product characteristics summary for all available drugs in Finland from 1998 to 2001 [23, 24]. Medications were categorized by a team of experts as: primary sedatives (group 1; scored 2), drugs with sedation as a prominent side effect (group 2; scored 1), drugs with sedation as a potential side effect (group 3; scored 0), and drugs with no sedative effect (group 4; scored 0) [23]. The SLM model has been extensively utilized and validated as described in Table S4.
13. ***Sloane Model:*** The Sloane Model has been derived from the SLM scale. Modifications to the SLM were introduced by Sloane *et al*. in 2008 for drugs used in their clinical trial [25]. First, drugs were scored from 0 to 6 (instead of 0-2) and reclassified to include only benzodiazepines, diphenhydramine, phenelzine, molindone, and chloral hydrate in group 1, with the highest score set at 6. All other drugs from Sloane's group 1 (*e.g*., amitriptyline, amoxapine, desipramine, doxepin and imipramine) were moved to group 2, with a score of 3. Drugs with sedation as a potential side effect were assigned a score of 1 (group 3), whereas drugs with no sedation were scored 0 (group 4) [25]. The sedative Sloane model has not been validated yet; few studies validated the Slone analgesic model.[26, 27]

Supplementary Table S1 Quality assessment scores for included papers (n=13)

Model/ Scale	Abstract and Title	Intro and Aims	Methods and Data	Sampling	Data analysis	Ethics and Bias	Findings and Results	Transferability and Reliability	Implications and Usefulness	SUM/36
Sedative										
SLM	4	2	4	4	3	1	4	4	4	30/36
Sloane model	4	4	4	4	4	1	4	4	4	33/36
Anticholinergic										
AAS scale	4	4	4	4	4	4	4	3	4	35/36
ABC scale	4	4	4	4	3	4	4	3	4	34/36
ACB scale	3	4	3	3	4	1	3	4	4	29/36
mACB scale	3	4	4	4	4	4	4	3	4	34/36
ADS scale	4	2	4	4	4	1	4	4	4	31/36
ARS scale	4	4	4	4	4	1	4	4	4	33/36
ARS/ACL scale	4	4	4	4	4	4	4	3	4	35/36
KABS scale	4	4	4	3	4	4	4	4	4	35/36
German ACB scale	4	4	4	4	3	4	3	3	4	33/36
Brazilian scale	4	4	4	3	3	1	3	4	3	29/36
AEC scale	4	4	4	3	2	1	4	4	4	30/36

Key: ADS: Anticholinergic Drug Scale; ABC: Anticholinergic Burden Classification; ARS: Anticholinergic Rating Scale; ACB: Anticholinergic Cognitive Burden; AAS: Anticholinergic Activity Scale; ALS: Anticholinergic Load Scale; AEC: Anticholinergic Effect on Cognition, KABS: Korean Anticholinergic Burden Scale, mACB: modified Anticholinergic Cognitive Burden scale, SLM: Sedative Load Model

Supplementary Table S2. The AntiCholinergic and Sedative Burden Catalog (ACSBC): a cumulative review table to classify medications for their anticholinergic and sedative properties (N = 642)

Drug Name	Anticholinergic Activity	Sedative Activity	FDA Approved
Abemaciclib	No*	Low [22]	Yes
Acamprosate	No*	Low [22]	Yes
Acarbose	No [2, 16, 19]	No*	Yes
Acetaminophen	No [2, 19]	No [22]	Yes
Acetazolamide	No [2, 16, 19]	Low [22]	Yes
Acetylsalicylic Acid / Aspirin	No [2, 16, 19]	No [22]	Yes
Acitretin	No [16, 19]	No*	Yes
Acrivastine	No*	Low [22]	DXD
Activated Charcoal	No [16, 19]	No*	Yes
Acyclovir	No [2, 16, 19]	No*	Yes
Afatinib	No*	Low [22]	Yes
Albuterol	No [2]	No*	Yes
Alectinib	No*	Low [22]	Yes
Alendronate	No	No*	Yes
Alitretinoin (isotretinoin)	No*	Low*	Yes
Allopurinol	No	Low*	Yes
Almotriptan	Low*	Moderate*	Yes
Alprazolam	Low [2, 10, 13, 29]	High [22]	Yes
Aluminum Hydroxide	No [2, 16, 19]	No*	Yes
Amantadine	Moderate [8, 10, 13]	Low [22]	Yes
Amiloride	No [2, 16, 19]	Low [22]	Yes
Amiodarone	No [2, 16, 19]	No*	Yes
Amitriptyline	High [2, 7, 8, 10, 12, 13, 16, 19, 29]	High [22]	Yes
Amlodipine	No [2, 16, 19]	Low [22]	Yes
Ammonium	No [2]	No*	Yes
Amoxapine	High [7, 10, 19]	Moderate [22, 25]	Yes
Amoxicillin	No [2, 16, 19]	No*	Yes
Amoxicillin-Clavulanate	No	No*	Yes
Ampicillin	Low [2, 16, 18, 30, 31]	No*	Yes
Anagrelide	No [2, 16, 19]	Low [22]	Yes
Anastrozole	No [2, 19]	No*	Yes
Apixaban	No [16]	No*	Yes
Apraclonidine	No*	No*	Yes
Aripiprazole	Low [10, 16, 19]	Moderate [25]	Yes
Artemether	No*	Low [22]	Yes
Ascorbic Acid	No [2, 16, 19]	No*	Yes
Asenapine	Low [10, 16]	Moderate [22]	Yes
Atenolol	Low [10]	Low [22]	Yes
Atorvastatin	No [2, 16, 19]	Low [22]	Yes
Atovaquone	No*	Low [22]	Yes
Atropine	High [8, 13, 18, 19, 29, 31-33]	Moderate [25]	Yes
Axitinib	No*	Low [22]	Yes
Azathioprine	Low [2, 16, 18, 31, 34]	No*	Yes
Azithromycin	No [2, 16, 19]	No*	Yes
Bacitracin	No [2]	No*	Yes
Baclofen	Moderate [3, 8, 18, 29, 31, 32, 34-36]	Moderate [22]	Yes
Beclomethasone	No*	No [22]	Yes
Benazepril	No [2, 19]	Low [22]	Yes
Benzatropine/ Benztropine	High [2, 8, 10, 13, 18, 19]	Moderate [22, 25]	Yes
Benzonatate	No [2, 19]	Moderate*	Yes
Bepotastine	No [19]	No [37]	Yes
Betaine	No [16, 19]	No*	Yes
Betamethasone	No [2, 16]	No [22]	Yes
Betaxolol	Low [16, 29, 34]	Low [22]	Yes
Bethanechol	No [2, 16, 19]	No*	Yes
Bexarotene	No*	Low [22]	Yes
Bicalutamide	No [2, 16, 19]	No*	Yes
Bimatoprost	No [16]	No*	Yes
Binimetinib	No*	Low [22]	Yes
Bisacodyl	No [2, 19]	No*	Yes
Bismuth Subsalicylate	No [2]	No*	Yes
Bisoprolol	No [2, 16, 19]	Low [22]	Yes
Bosutinib	No*	Low [22]	Yes
Brigatinib	No*	Low [22]	Yes
Brivaracetam	No*	Moderate [22]	Yes
Bromhexine	No [16, 19]	Moderate [22]	No
Bromocriptine	Low [2, 16, 34]	Low [22]	Yes
Brompheniramine	High [2, 3, 10, 18, 19, 32, 35, 36]	Moderate [22]	Yes
Budesonide	No [2, 16]	No [22]	Yes
Bumetanide	No [2]	Low [38]	Yes
Buprenorphine	Low [16, 19]	Moderate [22]	Yes
Bupropion	Low [10, 16, 18, 19, 29, 31, 34]	Moderate [25]	Yes
Buspirone	No [2, 16, 19]	Moderate [22]	Yes
Butabarbital	No [2]	High [22]	DXD
Butalbital	No [2]	High [22]	Yes
Cabergoline	No [16]	Low [22]	Yes
Caffeine	No [2, 19]	No*	Yes
Calamine, Topical	No [2]	No*	Yes
Calcipotriene, Topical	No [2]	No*	Yes
Calcitriol	No [2, 16, 19]	Low*	Yes
Calcium	No [2, 16, 19]	No*	Yes
Camphor-Menthol, Topical	No [2]	No*	Yes
Candesartan (cilexetil)	No [2, 16, 19]	Low [22]	Yes
Cannabidiol	No*	Moderate [22]	Yes
Capecitabine	Low*	Low [22]	Yes
Captopril	Low [2, 10, 16, 18, 31, 34]	Low [22]	Yes
Carbamazepine	Low [11, 12, 29, 33]	Moderate [22]	Yes
Carbidopa	Low [8, 13, 18, 29, 31]	Low [22]	Yes
Carbinoxamine	High [2, 3, 10, 18, 19]	Moderate [22]	Yes
Cariprazine	No*	Moderate [22]	Yes
Carisoprodol	High [3, 8, 18]	Moderate [22]	Yes
Carmellose Sodium	No [16]	No*	No
Carnitine	No [16, 19]	No*	Yes
Carvedilol	No [2, 16, 19]	Low [22]	Yes
Castol Oil	No [2, 16]	No*	Yes
Cefaclor	No [2, 16, 19]	Low [22]	Yes
Cefadroxil	No*	Low [22]	Yes
Cefixime	No [2, 16, 19]	Low [22]	Yes
Ceftibuten	No [2, 16, 19]	Low [22]	DXD
Ceftriaxone	No [2, 16, 19]	Low [22]	Yes
Cefuroxime	No [2, 16, 19]	Low [22]	Yes
Celecoxib	Low [13, 16, 34]	Low [22]	Yes
Cephalexin	No[2, 16, 19]	Low [22]	Yes
Ceritinib	No*	Low [22]	Yes
Cetirizine	Moderate [8, 13, 29]	Low [22]	Yes
Cetylpyridinium	No [2]	No*	No
Chlorambucil	No [2, 16, 19]	No*	Yes
Chloramphenicol	No [16]	No*	Yes
Chlordiazepoxide	Low [2, 16, 19, 29]	High [25]	Yes
Chlorhexidine	No [2]	No*	Yes
Chloroquine	Low*	Low [22]	Yes
Chlorothiazide	No [2, 16, 34]	Low [22]	Yes

Drug Name	Anticholinergic Activity	Sedative Activity	FDA Approved
Chlorphenamine/ Chlorpheniramine	High [2, 3, 7, 8, 10, 13, 16, 18, 19, 29, 32, 33, 35, 36]	Moderate [22]	Yes
Chlorpromazine	High [2, 10, 19]	Moderate [25]	Yes
Chlorthalidone/ Chlortalidone	Low [2, 10, 16, 18, 20, 31]	No*	Yes
Chlorzoxazone	No [2, 19]	Low*	Yes
Cholestyramine	No [2, 16, 19]	No*	Yes
Cilostazol	No [2, 16, 19]	Low*	Yes
Cimetidine	Moderate*	Low [22]	Yes
Ciprofloxacin	No [2, 16, 19]	Low [22]	Yes
Citalopram	Low*	Moderate [22]	Yes
Clarithromycin	No [2, 16, 19]	No*	Yes
Clemastine	High [2, 3, 10, 16, 18, 19, 32, 35, 36]	Moderate [22]	Yes
Clidinium	Low*	Moderate [22]	Yes
Clindamycin	Low [2, 16]	No*	Yes
Clobazam	No [2, 16, 19]	High [22]	Yes
Clomipramine	High [2, 3, 7, 10, 16, 18, 19]	High [22]	Yes
Clonazepam	Low [2, 13, 16, 18, 19, 31]	High [25]	Yes
Clonidine	No [2, 16, 19]	Low [25]	Yes
Clopidogrel	No [2, 16, 19]	No*	Yes
Clorazepate	Low [2, 10]	High [25]	Yes
Clotrimazole	No [2, 16]	No*	Yes
Clozapine	High [10, 16, 18-20]	Moderate [22]	Yes
Cobimetinib	No*	Low [22]	Yes
Codeine	Low [10]	Moderate [22]	Yes
Colchicine	Low [2, 16, 19]	No*	Yes
Colestipol	No [2]	No*	Yes
Collagenase	No [2]	No*	Yes
Crizotinib	No*	Low [22]	Yes
Cromolyn	No[2]	No*	Yes
Cyclobenzaprine	Moderate [2, 8, 10]	Moderate [22]	Yes
Cyclophosphamide	No [2, 16, 19]	Low [22]	Yes
Cycloserine	Low [2]	No*	Yes
Cyclosporine	Low [2, 16, 31]	No*	Yes
Cyproheptadine	High*	Moderate [22]	Yes
Dabigatran	No [16]	No*	Yes
Dabrafenib	No*	Low [22]	Yes
Dacomitinib	No*	Low [22]	Yes
Danazol	No [2, 19]	No*	Yes

Drug Name	Anticholinergic Activity	Sedative Activity	FDA Approved
Dantrolene	No [2, 16, 19]	Moderate*	Yes
Darifenacin	High*	Low [22]	Yes
Dasatinib	No*	Low [22]	Yes
Deferasirox	No [16, 19]	No*	Yes
Delafloxacin	No*	Low [22]	Yes
Demeclocycline	No [2]	No [22]	Yes
Desipramine	High [2, 10]	High [22]	Yes
Desloratadine	Low [3, 10, 16, 18-20, 36]	Low [22]	Yes
Desmopressin	No [2, 16, 19]	Low*	Yes
Desonide	No [2]	No [22]	Yes
Desoximetasone	No [2]	No [22]	Yes
Desvenlafaxine	Moderate [39]	Moderate [22]	Yes
Dexamethasone	Low [2, 16, 18, 31]	No [22]	Yes
Dexchlorpheniramine	High [3, 10, 13, 18, 19, 31-33, 35, 36]	Moderate[22]	Yes
Dexlansoprazole	No*	Low [22]	Yes
Dextromethorphan	Low [16, 19, 29],	Moderate [25]	Yes
Diazepam	Low [2, 10, 12, 13, 29]	High [22]	Yes
Diclofenac	No [2, 16]	Low [22]	Yes
Dicyclomine	High [2, 8, 10, 16]	Moderate[22]	Yes
Diflunisal	No [2]	No*	Yes
Digoxin	Low*	No [22]	Yes
Dihydrocodeine	No*	Moderate [22]	Yes
Diltiazem	Low [2, 16, 18, 31]	Low [22]	Yes
Dimenhydrinate	High [2, 3, 10, 16, 18, 19, 31]	Moderate[22]	Yes
Diphenhydramine	High [2, 3, 8, 10, 16, 18, 19, 29, 31-33, 35, 36]	High [25]	Yes
Diphenoxylate	No [2]	Moderate [25]	Yes
Dipyridamole	Low [2, 10, 16, 18-20]	No [22]	Yes
Disopyramide	Moderate [2]	No*	Yes
Disulfiram	No*	Low [22]	Yes
Divalproex sodium	Low [2]	Moderate [22]	Yes
Dobutamine	No [2, 16, 19]	No*	Yes
Docusate	No [2, 16, 19]	No*	Yes
Donepezil	No [2, 16, 19]	Low [22]	Yes
Dopamine	No [2, 16, 19]	No*	Yes
Doxazosin	No [2, 16, 19]	Low [25]	Yes
Doxepin	High [2, 10, 12, 13, 16, 19, 29]	Moderate [25]	Yes
Doxycycline	No [2, 16]	No [22]	Yes

Drug Name	Anticholinergic Activity	Sedative Activity	FDA Approved
Doxylamine	High [3, 10, 16, 18, 19, 32, 33, 35, 36]	Moderate [22]	Yes
Dulaglutide	No [16]	No*	Yes
Duloxetine	No [2, 16, 19]	Moderate [22]	Yes
Dydrogesterone	No [16, 19]	Low [22]	DXD
Edoxaban	No [16]	No*	Yes
Empagliflozin	No [16]	No*	Yes
Enalapril	No [2, 16, 19]	Low [22]	Yes
Enasidenib	No*	Low [22]	Yes
Encorafenib	No*	Low [22]	Yes
Enoxaparin	No [2, 16, 19]	No*	Yes
Entacapone	Low [8, 16, 19, 20]	Low [22]	Yes
Eperisone	No [19]	Moderate [22]	No
Epinephrine	No [19]	No*	Yes
Eplerenone	No*	Low[22]	Yes
Epoetin Alfa	No [2, 16, 19]	No*	Yes
Eprosartan	No [16, 19]	Low [22]	DXD
Ergocalciferol	No [2, 16, 19]	No*	Yes
Ergoloid	No [2]	No*	Yes
Ergoloid Mesylates	No [19]	No*	Yes
Ergotamine	No*	No*	Yes
Erlotinib	No*	Low [22]	Yes
Erythromycin	No [2, 16, 19]	No*	Yes
Escitalopram	Low [13, 16]	Moderate [22]	Yes
Eslicarbazepine	Low*	Moderate [22]	Yes
Esomeprazole	No [2, 16, 19]	Low [22]	Yes
Estazolam	Low [2, 19]	High [22]	Yes
Esterified Estrogens	No [2, 19]	Low [22]	Yes
Estradiol	No [2, 16, 19]	Low [22]	Yes
Estramustine	No*	Low [22]	Yes
Estrogen (estradiol)	No [2, 16, 19]	Low [22]	Yes
Estropipate; Estrone Sulfate	No [2, 19]	Low [22]	Yes
Eszopiclone	No*	High [25]	Yes
Ethambutol	No [2, 16, 19]	No*	Yes
Ethosuximide	No*	Moderate [22]	Yes
Ethotoin	No*	Moderate [22]	Yes
Etidronate	No [2, 16, 19]	No*	Yes
Etodolac	No [2, 19]	Low [22]	Yes
Everolimus	No*	Low [22]	Yes
Ezetimibe	No [16, 19]	No*	Yes

Drug Name	Anticholinergic Activity	Sedative Activity	FDA Approved
Famciclovir	No [16, 19]	No*	Yes
Famotidine	Low [2, 16, 18, 31]	Low [22]	Yes
Felbamate	No [2, 16]	Moderate [22]	Yes
Felodipine	No [2, 16, 19]	Low [22]	Yes
Fenofibrate	No [2, 16, 19]	Low[22]	Yes
Fenoprofen	No*	Low [22]	Yes
Fenoterol Inhalation	No [16]	No*	No
Fentanyl	Low [10, 14, 16, 18-20, 31, 40]	Moderate[22]	Yes
Ferrous Gluconate	No [2, 16]	No*	Yes
Ferrous Sulfate	No [16]	No*	Yes
Fesoterodine	High [10]	Low [22]	Yes
Fexofenadine	Moderate [19]	Low [22]	Yes
Filgrastim	No [2, 16, 19]	No*	Yes
Finasteride	No [2, 16, 19]	No [22]	Yes
Fish Oil	No [16, 19]	No*	Yes
Flavoxate	High [2, 10, 16, 19]	Low [22]	Yes
Flecainide	No [2, 16, 19]	No*	Yes
Fluconazole	No [2, 16, 19]	No*	Yes
Fludarabine	No*	Low [22]	Yes
Fludrocortisone	No [2, 16, 19]	No [22]	Yes
Flunisolide	No [2, 16]	No [22]	Yes
Fluoxetine	Low [2, 12-14, 16, 18, 19, 29, 31, 40]	Moderate [22]	Yes
Fluphenazine	Moderate*	High [22]	Yes
Flurazepam	Low [2, 16, 19]	High [22]	Yes
Flurbiprofen	No*	Low [22]	Yes
Flutamide	No [2, 16, 19]	No*	Yes
Fluticasone	No [2, 16]	No [22]	Yes
Fluvastatin	No [2, 16, 19]	Low [22]	Yes
Fluvoxamine	Low [2, 12, 13, 16, 18-20, 31]	Moderate [22]	Yes
Folic Acid	No [2, 16, 19]	No*	Yes
Formoterol Inhalation	No [16]	No*	Yes
Fosinopril	No [2, 16, 19]	Low [22]	Yes
Frovatriptan	No*	Moderate [22]	Yes
Furosemide	Low [10, 16, 18-20]	Low [22]	Yes
Gabapentin	No [2, 16, 19]	Moderate [22]	Yes
Galantamine	No [2, 16, 19]	Low [22]	Yes
Gefitinib	No*	Low [22]	Yes
Gemfibrozil	No [2, 16, 19]	Low [22]	Yes
Gemifloxacin	No*	Low [22]	Yes
Ginseng	No [16, 19]	No*	No
Glimepiride	No [2, 16, 19]	Low [22]	Yes
Glipizide	No [2, 16, 19]	Low [22]	Yes
Glucagon	No [2, 16, 19])	No*	Yes
Glucosamine	No [2, 16, 19]	No*	No
Glucose (Dextrose 5%)	No [16, 19]	No*	Yes
Glyburide/ Glibenclamide	No [2]	Low [22]	Yes
Glycerin, Topical	No [2]	No*	Yes
Goserelin Acetate	No [16, 19]	No*	Yes
Guaifenesin	Low [16, 19, 29]	No*	Yes
Guanfacine	No [16, 19]	Moderate*	Yes
Halcinonide, Topical	No [2]	No*	Yes
Haloperidol	No [2]	Moderate [25]	Yes
Heparin	No [2, 16, 19]	No*	Yes
Hydralazine	Low [2, 10, 16, 18-20]	No*	Yes
Hydrochlorothiazide	No [2, 16, 19]	Low [22]	Yes
Hydrocodone	No [2]	Moderate [22]	Yes
Hydrocortisone	Low [2, 10, 16, 18-20, 31]	No [22]	Yes
Hydromorphone	No [2, 16, 19]	Moderate [22]	Yes
Hydroxychloroquine	No [2, 16, 19]	Low [22]	Yes
Hydroxypropyl, Ophthalmic	No [2]	No*	Yes
Hydroxyurea	No [2, 16, 19]	Low [22]	Yes
Hydroxyzine	High [2, 3, 7, 8, 10, 13, 18, 19, 29, 31]	Moderate [25]	Yes
Hyperici Herba (St John's Wort)	No*	Moderate [22]	No
Ibrutinib	No*	Low [22]	Yes
Ibuprofen	No [2, 16, 19]	Low [22]	Yes
Icodextrin	No [2]	No*	Yes
Idelalisib	No*	Low [22]	Yes
Iloperidone	Low [10]	Moderate [22]	Yes
Imatinib	No*	Low [22]	Yes
Imipramine	High [2, 3, 7, 8, 10, 13, 16, 18, 19, 29, 31-33, 35, 36]	Moderate [25]	Yes
Indapamide	No [2, 16, 19]	Low [22]	Yes
Indomethacin	No [2, 16]	Moderate [25]	Yes
Influenza Virus Vaccine	No [16, 19]	No*	Yes
Inositol	No [16]	No*	No
Irbesartan	No [2, 16, 19]	Low [22]	Yes
Iron	No [2, 19]	No*	Yes
Isoniazid	No [2, 16, 19]	No*	Yes
Isosorbide	Low [10]	No*	Yes
Isradipine	No [2, 16, 19]	Low [22]	Yes
Ixazomib	No*	Low [22]	Yes
Ketoprofen	No [2, 16, 19]	Low [22]	Yes
Ketorolac	Low [16, 29]	Low [22]	Yes
Labetalol	No [19]	Low [22]	Yes
Lacosamide	No	Moderate [22]	Yes
Lactase; Tilactase	No [16, 19]	No*	Yes
Lactic Acid Bacteria	No [19]	No*	Yes
Lactobacillus Rhamnosus	No [41]	No*	Yes
Lactulose	No [2, 16, 19]	No*	Yes
Lamotrigine	No [2, 16, 19]	Moderate [22]	Yes
Lanolin-Mineral Oil, Topical	No [2]	No*	Yes
Lansoprazole	Low [2, 19]	Low [22]	Yes
Lapatinib	No*	Low [22]	Yes
Lenvatinib	No*	Low [22]	Yes
Leuprolide	No [2, 16, 19]	No*	Yes
levetiracetam	No [2, 16, 19]	Moderate [22]	Yes
Levocabastine	No [16]	No*	Yes
Levocetirizine	Low [10]	Low [22]	Yes
Levodopa	No [2]	Low [22]	Yes
Levofloxacin	No [2, 16, 19]	Low [22]	Yes
Levothyroxine	No [2, 16, 19]	No[22]	Yes
Lidocaine	No [2, 16, 19]	No*	Yes
Liothyronine	No [2, 16, 19]	No[22]	Yes
Lisinopril	No [2, 16, 19]	Low [22]	Yes
Lithium	Low [12-14, 16, 18, 31]	High [22]	Yes
Lomustine	No*	Low [22]	Yes
Loperamide	Low [10]	Moderate [22]	Yes
Loratadine	Low [10]	Low [22]	Yes
Lorazepam	Low [2, 16, 18, 19, 31]	High [22]	Yes
Lorlatinib	No*	Low [22]	Yes
Losartan	No [2, 16]	Low [22]	Yes
Lovastatin	No [2, 16]	Low [22]	Yes
Loxapine	Moderate [2, 10, 16, 19, 34]	High [22]	Yes
Lurasidone	No [42]	High [22]	Yes
Lysine	No [2, 16]	No*	Yes
Magnesium	No [2, 16, 19]	Low*	Yes

Drug Name	Anticholinergic Activity	Sedative Activity	FDA Approved
Mannitol	No [2, 16, 19]	No*	Yes
Maprotiline	High [10]	High [22]	Yes
Mebeverine	No [16]	No*	Yes
Meclizine	High [3, 8, 18, 19, 29, 31]	Moderate [22]	Yes
Medroxyprogesterone	No [2, 16, 19]	Low [22]	Yes
Mefenamic Acid	No*	Low [22]	Yes
Mefloquine	Low [43]	Low [22]	Yes
Megestrol	No [2, 16, 19]	Low [22]	Yes
Melatonin	No [16, 19]	High [22]	Yes
Meloxicam	No [16, 19]	Low [22]	Yes
Memantine	No [16, 19]	Low [22]	Yes
Meperidine (Pethidine)	Moderate [2, 10]	Moderate [22]	Yes
Meprobamate	No [2]	Moderate [22]	Yes
Mercaptopurine	No*	Low [22]	Yes
Mesalamine (Mesalazine)	No [2, 19]	No*	Yes
Metamucil (Psyllium)	No [16]	No*	Yes
Metaxalone	No [2]	Moderate [22]	Yes
Metformin	No [13, 16]	No*	Yes
Methadone	Moderate [16, 18, 29, 31, 34]	Moderate [25]	Yes
Methazolamide	No [2, 19]	Low [22]	Yes
Methenamine	No [2, 16]	No*	Yes
Methocarbamol	Low [8, 16, 19, 29]	Moderate [22]	Yes
Methotrexate	No [2, 19]	Low [22]	Yes
Methyclothiazide	No [2]	Low [22]	Yes
Methylcellulose	No [2, 19]	No*	Yes
Methyldopa	No [2, 16, 19]	Low [22]	Yes
Methylene Blue	No [2, 16, 19]	No*	Yes
Methylphenidate	No [2, 16, 19]	No*	Yes
Methylprednisolone	Low [2, 16, 18, 31]	No [22]	Yes
Methyltestosterone	No [2, 19]	Low [22]	Yes
Metoclopramide	No [19]	Moderate [22]	Yes
Metolazone	No [2, 19]	Low [22]	Yes
Metoprolol	Low [10, 16, 18, 20, 29, 31]	Low [22]	Yes
Metronidazole	No [2, 16, 19]	Low [22]	Yes
Mexiletine	No [2, 19]	No*	Yes
Midazolam	Low [2, 16, 18, 20, 31]	High [22]	Yes
Midodrine	No [2, 16, 19]	No*	Yes
Midostaurin	No*	Low [22]	Yes
Milnacipran	No*	Moderate [22]	Yes
Miltefosine	No*	Low [22]	Yes
Mineral Oil	No [2]	No*	Yes
Minocycline	No [2, 16, 19]	No [22]	Yes
Mirabegron	No	Low [22]	No
Mirtazapine	Low [8, 12, 14, 16, 18-20, 31, 40]	Moderate [22]	Yes
Misoprostol	No [2]	Low*	Yes
Mitotane	No*	Low [22]	Yes
Modafinil	No [16, 19]	No*	Yes
Moexipril	No [2, 16, 19]	Low [22]	Yes
Molindone	Moderate [2, 10, 19]	High [25]	Yes
Mometasone Furoate	No [16]	No [22]	Yes
Montelukast	No [2, 16, 19]	Low [22]	Yes
Morphine	Low [2, 7, 10, 12, 16, 18-20, 29, 31, 40]	Moderate [22]	Yes
Moxifloxacin	No [2, 16, 19]	Low[22]	Yes
Multivitamin	No [2, 16, 19]	No*	Yes
Mupirocin, Topical	No [2]	No*	Yes
Nabumetone	No [2, 16, 19]	Low [22]	Yes
N-Acetyl-L-Cysteine	No [16, 19]	No*	Yes
Nadolol	No [2]	Low [22]	Yes
Naltrexone	Low*	Low [22]	Yes
Naproxen	No [2, 16, 19]	Low [22]	Yes
Naratriptan	Low [13, 16, 19]	Moderate [22]	Yes
Nateglinide	No [2, 16, 19]	No*	Yes
Nefazodone	Low [29]	Moderate [22]	Yes
Neratinib	No*	Low [22]	Yes
Niacin	No [2, 16, 19]	No*	Yes
Nicardipine	No*	Low [22]	Yes
Nifedipine	Low [2, 10, 16, 18, 20, 31]	Low [22]	Yes
Nilotinib	No*	Low [22]	Yes
Nimodipine	No*	Low [22]	Yes
Nintedanib	No*	Low [22]	Yes
Niraparib	No*	Low [22]	Yes
Nisoldipine	No [2, 16, 19]	Low [22]	Yes
Nitazoxanide	No*	Low [22]	Yes
Nitrofurantoin	No [2, 16, 19]	No*	Yes
Nitroglycerin	No [2, 19]	No*	Yes
Nizatidine	Low [2]	Low [22]	Yes
Norepinephrine	No [2, 16, 19]	No*	Yes
Norethisterone	No [16, 19]	Low [22]	Yes
Norfloxacin	No [16, 19]	Low [22]	Yes
Nortriptyline	High [2, 10, 29]	High [22]	Yes
Nystatin	No [2, 16, 19]	No*	Yes
Octreotide	No [2, 16, 19]	No*	Yes
Ofloxacin	No [2, 16, 19]	Low [22]	Yes
Olanzapine	Moderate [8, 29]	Moderate [22]	Yes
Olaparib	No*	Low [22]	Yes
Olmesartan	No [16, 19]	Low [22]	Yes
Omega-3	No [16, 19]	No*	Yes
Omeprazole	No [2, 16, 19]	Low [22]	Yes
Orphenadrine (citrate)	High [2, 3, 7, 10, 12, 16, 18, 19, 34]	Moderate [22]	Yes
Osimertinib	No*	Low [22]	Yes
Oxaprozin	No*	Low [22]	Yes
Oxatomide	No [19]	Moderate [22]	No
Oxazepam	Low [2, 13, 16]	High [22]	Yes
Oxcarbazepine	Moderate [2, 10, 16, 19, 31, 34]	Moderate [22]	Yes
Oxybutynin	High*	Low [22]	Yes
Oxycodone	Low [2, 13, 16, 18, 19, 29, 31, 40]	Moderate [22]	Yes
Palbociclib	No*	Low [22]	Yes
Paliperidone	Low [10, 16, 19, 20]	Moderate [22]	Yes
Pamidronate	No [19]	No*	Yes
Pancrelipase	No [13]	No*	Yes
Panobinostat	No*	Low [22]	Yes
Pantoprazole	No [2, 16, 19]	Low [22]	Yes
Paracetamol; Acetaminophen	No [16]	No [22]	Yes
Paroxetine	Moderate [13, 29]	Moderate [22]	Yes
Pazopanib	No*	Low [22]	Yes
Penicillin	No [2, 19]	No [22]	Yes
Pentazocine	No [16, 19]	Moderate [22]	Yes
Pentoxifylline	No [2, 16, 19]	No [22]	Yes
Perampanel	No*	Moderate [22]	Yes
Pergolide	No [2, 16]	Moderate [25]	Yes
Perindopril	No [2, 16, 19]	Low [22]	Yes
Perphenazine	Moderate [29]	High[22]	Yes
Phenazopyridine	No [2]	No*	Yes
Phenelzine	Low [2]	High [22]	Yes

Drug Name	Anticholinergic Activity	Sedative Activity	FDA Approved
Phenobarbital	Low [12, 16, 18, 29]	Moderate [22]	Yes
Phenprocoumon	No [16]	No*	Yes
Phenylephrine	No [2, 16, 19]	No*	Yes
Phenytoin	No [2, 16, 19]	Moderate [22]	Yes
Phytonadione	No [2]	No*	Yes
Pilocarpine	No [16, 19]	No*	Yes
Pimavanserin	No*	Moderate [22]	Yes
Pimozide	Moderate [2, 10, 16, 18, 19, 31, 34]	Moderate [22]	Yes
Pindolol	No [2, 16]	Low [22]	Yes
Pioglitazone	No [2, 16, 19]	No*	Yes
Piroxicam	No [2, 16, 19]	Low [22]	Yes
Pitavastatin	No*	Low [22]	Yes
Pivampicillin	No [2]	No*	No
Polyethelene Glycol	No [2, 16]	No*	Yes
Polymyxin B, Ophthalmic	No [2]	No*	Yes
Polyvinyl Alcohol	No [16]	No*	Yes
Ponatinib	No*	Low [22]	Yes
Potassium Bicarbonate	No [16]	No*	Yes
Potassium Chloride	No [16]	No*	Yes
Potassium Citrate	No [16]	No*	Yes
Pramipexole	Low [8, 16, 18, 31]	Low [22]	Yes
Pravastatin	No [2, 16, 19]	Low [22]	Yes
Prazosin	No [2, 19]	Low [25]	Yes
Prednisolone	Low [2, 14, 16, 18, 20, 31]	No*	Yes
Prednisone	Low [2, 10, 16, 18, 20, 31]	No [22]	Yes
Pregabalin	Moderate*	Moderate [22]	Yes
Primaquine	Low*	Low [22]	Yes
Primidone	No [2, 16, 19]	Moderate [22]	Yes
Probenecid	No [2, 16]	No*	Yes
Procainamide	No [2]	No*	Yes
Prochlorperazine	Moderate [8, 13, 29]	High [22]	Yes
Procyclidine	High [16, 19]	Moderate [22]	Yes
Progesterone	No [2, 16, 19]	Low [22]	Yes
Proguanil	No*	Low [22]	Yes
Promethazine	High [2, 8, 10, 16, 18, 31, 34]	Moderate [25]	Yes
Propafenone	No [2, 16, 19]	No*	Yes
Propoxyphene chloride (Dextro-propoxyphene)	Moderate [29]	Moderate [22]	Yes
Propranolol	No [2, 16, 19]	Low [22]	Yes
Propylene Glycol	No [16]	No*	Yes
Propylthiouracil	No [2, 16, 19]	No*	Yes
Protamine	No [16, 19]	No*	Yes
Protriptyline	High [2, 13]	High [22]	Yes
Pseudoephedrine	Moderate [3, 8, 13, 31]	No*	Yes
Psyllium	No [2, 16, 19]	No*	Yes
Pyrazinamide	No [2, 16, 19]	No*	Yes
Pyridostigmine	No [2, 16, 19]	No*	Yes
Pyridoxine	No [16, 19]	No*	Yes
Pyrilamine (Mepiramine)	High [2, 19]	Moderate [22]	DXD
Pyrimethamine	No*	Low [22]	Yes
Quazepam	No*	High [22]	Yes
Quetiapine	Moderate [29]	Moderate [22]	Yes
Quinapril	No [2, 16, 19]	Low [22]	Yes
Quinidine	Low [10, 16, 20]	No*	Yes
Quinine	No [2, 19]	Low [22]	Yes
Rabeprazole	No [2, 16, 19]	Low [22]	Yes
Raloxifene	No [2, 16, 19]	No*	Yes
Ramelteon	No*	High [25]	Yes
Ramipril	No [2, 16, 19]	Low [22]	Yes
Ranitidine	Low [2, 8, 12, 13]	Low [22]	DXD
Rasagiline	No*	Low [22]	Yes
Regorafenib	No*	Low [22]	Yes
Repaglinide	No [2, 16, 19]	No*	Yes
Ribociclib	No*	Low [22]	Yes
Rifampin	No [2, 16]	Low [22]	Yes
Rimantadine	No [2]	No*	Yes
Risedronate	No [2, 16, 19]	No*	Yes
Risperidone	Low [8, 10, 13, 16, 18-20, 29, 31, 40]	Moderate [22]	Yes
Rivastigmine	No [16, 19]	Low [22]	Yes
Rofecoxib	No [2]	Low [22]	DXD
Ropinirole	No [2, 16, 19]	Low [22]	Yes
Rosiglitazone	No [2, 19]	No*	Yes
Rosuvastatin	No [16, 19]	Low [22]	Yes
Rucaparib	No*	Low [22]	Yes
Rufinamide	No*	Moderate [22]	Yes
Ruxolitinib	No*	Low [22]	Yes
Saccharomyces Boulardii	No	No*	Yes
Safinamide	No*	Low [22]	Yes
Salbutamol; Albuterol	No [16, 19]	No*	Yes
Salicylic, Topical	No [2]	No*	Yes
Salmeterol	No [2, 16]	No*	Yes
Salsalate	No [2, 19]	No*	No
Scopolamine (Hyoscine/ Hyoscamine)	High [2, 8, 10, 16, 19, 20, 32, 33]	Moderate [22]	Yes
Secobarbital	Moderate*	High [22]	Yes
Selegiline	Low [8, 16, 18, 29, 31]	Low [22]	Yes
Senna (Leaf); Sennosides A & B; Senokot	No [16]	No*	Yes
Sertraline	Low [2, 8, 16, 18, 29, 31]	Moderate [22]	Yes
Sevelamer	No [16]	No*	Yes
Sildenafil	No [16, 19]	No*	Yes
Simethicone	No [2, 16, 19]	No*	Yes
Simvastatin	No [2, 16, 19]	Low [22]	Yes
Sitagliptin	No [16]	No*	Yes
Sodium Bicarbonate	No [16, 19]	No*	Yes
Sodium Chloride	No [16, 19]	No*	Yes
Sodium Phosphate	No [16]	No*	Yes
Solifenacin	High [10, 16, 18, 19, 31-33]	Low [22]	Yes
Sonidegib	No*	Low [22]	Yes
Sorafenib	No*	Low [22]	Yes
Sotalol	No [2, 16, 19]	Low [22]	Yes
Spironolactone	No [2, 16, 19]	Low [22]	Yes
Stiripentol	No*	Moderate [22]	Yes
Succinylcholine	No [2, 16, 19]	No*	Yes
Sucralfate	No [2, 16, 19]	No*	Yes
Sulfamethizole	No [2]	No*	DXD
Sulfamethoxazole	No [2, 16, 19]	No*	Yes
Sulfasalazine	No [16, 19]	No*	Yes
Sulindac	No [2, 19]	Low [22]	Yes
Sumatriptan	Low [13, 16]	Moderate [22]	Yes
Sunitinib	No*	Low[22]	Yes
Suvorexant	No*	High [22]	Yes
Tadalafil	No [16, 19]	No*	Yes
Talazoparib	No*	Low [22]	Yes
Tamoxifen	No [2, 16, 19]	Low [22]	Yes
Tamsulosin	No [2, 16, 19]	No*	Yes
Tapentadol	No*	Moderate [22]	Yes

Drug Name	Anticholinergic Activity	Sedative Activity	FDA Approved
Tasimelteon	No*	High [25]	Yes
Telmisartan	No [16, 19]	Low [22]	Yes
Temazepam	Low [2, 8, 13, 16, 19]	High [25]	Yes
Temozolomide	No*	Low [22]	Yes
Terazosin	No [2, 16, 19]	Low [25]	Yes
Terbinafine	No [16, 19]	No*	Yes
Terbutaline	No [2, 16]	No*	Yes
Teriparatide	No [16]	No*	Yes
Tetracycline	No [2, 16, 19]	No [22]	Yes
Theophylline	No*	Moderate [22]	Yes
Thiamazole (Methimazole)	No [16]	No*	Yes
Thiamine	No [2, 16, 19]	No*	Yes
Thioridazine	High [3, 8, 10, 12, 16, 18, 19, 34]	High [22]	Yes
Thiothixene	Low [2]	No*	Yes
Thyroid Desiccated	No [2]	No [22]	Yes
Tiagabine	No*	Moderate [22]	Yes
Tianeptine	No [19]	Moderate [22]	No
Tiaprofenic Acid	No [16, 19]	Moderate [22]	No
Ticlopidine	No [2, 16, 19]	No*	Yes
Timolol	No [8, 16, 19]	Low [22]	Yes
Tinidazole	No*	Low [22]	Yes
Tizanidine	High [3, 8, 16, 31, 34]	Moderate [22]	Yes
Tocopherol, Vitamin E	No [19]	No*	Yes
Tolazamide	No*	Low [22]	Yes
Tolbutamide	No [2, 16]	Low [22]	Yes
Tolcapone	No [2, 16]	Low [22]	Yes
Tolmetin	No*	Low [22]	Yes
Tolterodine	High [10, 11, 13, 16, 18-20, 29, 31]	Low [22]	Yes
Topiramate	No [2, 16, 19]	Moderate [22]	Yes
Torsemide	No [2, 16, 19]	No*	Yes
Tramadol	Moderate [13, 16, 29]	Moderate [22]	Yes
Trametinib	No*	Low [22]	Yes
Trandolapril	Low [16, 29, 34]	Low [22]	Yes
Travoprost	No [16]	No*	Yes
Trazodone	Low [8, 10, 16, 18, 19, 29, 31, 40]	Moderate [22]	Yes
Triamterene	Low [2, 10, 16, 18, 20, 31]	Low [22]	Yes
Triazolam	Low [2, 16, 19, 20, 29]	High [22]	Yes
Trichlormethiazide	No [2]	No*	Yes
Trifluoperazine	High [8, 10]	High [22]	Yes
Trihexyphenidyl	High [2, 7, 10, 12, 16, 18-20, 29, 31-34]	Low [22]	Yes
Trimethoprim	No [2, 16]	No*	Yes
Trimipramine	High [2, 7, 12, 16, 34]	High [22]	Yes
Triprolidine	High [18, 33]	Low [22]	Yes
Trospium	High [10, 16, 19]	Low [22]	Yes
Tuberculin Purified Protein Derivate	No [2, 16, 19]	No*	Yes
Ubidecarenone	No [16, 19]	No*	Yes
Urea	No [2]	No*	Yes
Ursodiol	No [2, 16, 19]	No*	Yes
Valproic acid	Low [2, 16, 18, 31]	Moderate [22]	Yes
Valsartan	No [2, 16, 19]	Low [22]	Yes
Vancomycin	Low [2, 16, 18, 31]	No*	Yes
Vandetanib	No*	Low [22]	Yes
Vardenafil	No [16, 19]	Low*	Yes
Varenicline	No [16, 19]	No*	Yes
Vecuronium	No [2, 16, 19]	No*	Yes
Vemurafenib	No [16]	Low [22]	Yes
Venetoclax	No*	Low [22]	Yes
Venlafaxine	Low [10, 13, 16, 18-20, 29]	Moderate [22]	Yes
Verapamil	No [2, 16, 19]	Low [22]	Yes
Vigabatrin	No*	Moderate[22]	Yes
Vismodegib	No*	Low [22]	Yes
Vitamin E	No [2, 16]	No*	Yes
Vitamin K	No [19]	No*	Yes
Vorinostat	No*	Low [22]	Yes
Vortioxetine	No*	Moderate [22]	Yes
Warfarin	Low [2, 16, 18-20, 31]	No*	Yes
Zafirlukast	No [2, 19]	Low [22]	Yes
Zaleplon	No [2, 16]	High [25]	Yes
Zinc	No [2, 16, 19]	No*	Yes
Ziprasidone	Low [8, 16, 19]	High [22]	Yes
Zolmitriptan	No [19]	Moderate [22]	Yes
Zolpidem	No [2, 16, 19]	High [25]	Yes
Zonisamide	Low*	Moderate [22]	Yes
Zuclopenthixol	Low*	High [22]	No

*Indicates Monograph or Drug Label

Color key: No activity, Low activity, Moderate activity, High activity

DXD = Discontinued

Supplementary Table S3 Scales detailed citation analysis

			Web of Science (YTD)																
Scale	**Google Scholar**	**Web of Science (Total Citations)**	Average per Year	1900-2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
ARS	**600**	**359**	27.62	0	0	0	0	10	10	7	24	24	22	34	34	25	41	46	55	27
ABC	**577**	**332**	22.13	0	0	10	12	37	32	15	27	18	21	20	25	22	28	18	30	17
ADS	**481**	**295**	19.67	0	0	0	0	3	12	9	21	19	24	24	28	30	37	23	(Kiesel et al, 2018)	27
ACB	**429**	**NA**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
AAS	**172**	**96**	8.73	0	0	0	0	0	0	2	7	6	5	6	7	6	10	11	23	13
ALS	**84**	**56**	5.6	0	0	0	0	0	0	0	1	4	3	1	6	7	6	9	12	7
AEC	**26**	**12**	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	4	5
German ACB	**8**	**5**	1.67	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	3
KABS	**6**	**3**	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
mACB	**5**	**2**	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2
Brazilian ACB	**1**	**0**	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SLM	**46**	**27**	1.59	0	1	2	0	2	2	2	4	3	0	2	1	2	3	2	1	0
Sloane	**26**	**19**	1.46	0	0	0	0	0	1	3	1	1	0	4	2	2	2	1	0	2

Key: YTD: Year -To-Date, ADS: Anticholinergic Drug Scale; ABC: Anticholinergic Burden Classification; ARS: Anticholinergic Rating Scale; ACB: Anticholinergic Cognitive Burden; AAS: Anticholinergic Activity Scale; ALS: Anticholinergic Load Scale; AEC: Anticholinergic Effect on Cognition, KABS: Korean Anticholinergic Burden Scale, mACB: modified Anticholinergic Cognitive Burden scale, SLM: Sedative Load Model, NA: Not Available.

Table S4: A summary of selected validation studies that evaluated the different rating scales in older adults

Scale/Model	Validation study design / duration	Study population	Measured outcomes	Results and clinical outcomes
ADS	Cross-sectional, observational study / 1 month [2]	Long-term care facility residents in the USA (n= 201, mean age 86 ± 7 years)	Serum anticholinergic activity (SAA)	A significant association was reported between the ADS scores and the measured SAA
	Cross-sectional, randomized controlled trial / 2 years [44]	Nine rural municipalities with 70 000 inhabitants in Northern Norway (n=387, mean age 76 ± 6 years)	Comorbidity score and current drug use in participants with and without AD	This study included ADS level 2 and 3 drugs only. AD participants had a higher co-morbidity score not clinically significant when adjusted to dose and gender. AD participants had almost two-fold use of drugs and higher percentage of inappropriate use of anticholinergic, anxiolytic-hypnotic and antidepressants.
	Analyses of data collected from the AGP (Ageing in General Practice) study, a cluster randomized clinical trial / 2 years [45, 46]	Patients who could speak English, aged ≥ 75 years and had visited the GP within the last 12 months in Australia (n=1044, mean age 81.3 ± 4.2 years)	The Geriatric depression scale (GDS), the Revised Cambridge Cognitive Examination (CAMCOG-R), and quality-of-life instrument	Dementia patients had significantly higher number of medications, higher anticholinergic load and consumed higher proportion of anticholinergic drugs compared to non-demented patients. Patient factors associated with increased anticholinergic load were polypharmacy, increased age, depression, lower physical quality of life and CAMCOG-R dementia. ADS level 1 drugs contributed around 70% of total burden followed by around 25% level 3 drugs and less than 10% of level 2 drugs.
	Analysis of data from the population-based Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) Study/ 3 years [47]	Randomly selected persons aged ≥ 75 years in Finland. (n=621, mean age 81.7 ± 4.9 years)	SAA, vision, cognitive function, mood, and functional capacity	Measurement of SAA was not associated with anticholinergic adverse events. In contrast, anticholinergic burden calculated using the ADS, ARS and Chew's list was inversely associated with short-distance vision, activities of daily living (ADL) and instrumental ADL. The strongest association was found when using ADS and Chew. The ADS covered more than 88% of drugs used compared to 55% and 5% covered by Chew's list and ARS respectively.
	Randomized clinical interventional trial / 8 weeks [48]	Patients actively enrolled in a cohort at the Alzheimer's Disease Center at University of Kentucky in USA, aged ≥ 65 years reporting ≥ 1 anticholinergic drug. (n=50, mean age 77.7 ± 6.6 years)	Changes in the medication appropriateness index (MAI) and ADS score from baseline to the end of study	Pharmacist–physician targeted medication management interventions resulted in significant improvement in MAI, improvement in clinical dementia rating and reduction in ADS scores in the intervention group compared to control.
ACB	Cross-sectional, retrospective study 8 months [49]	Older patients admitted to the acute geriatric unit of the San Gerardo Hospital in Italy (n=477, mean age 84 ± 6.5 years)	Comorbidity Index, nutritional status, activities of daily living, dementia diagnosis, and ACB score	Th cumulative anticholinergic exposure measured using the ACB scale was only partially associated with delirium in a sample of hospitalized older adults. A dose-response relationship between anticholinergic burden and delirium was significant at univariate analysis only. Patients with a sum of ACB score of 0 to 2 had a plateau risk of delirium, patients who scored ≥3 had about 3 or 6 times the risk of delirium than those not taking anticholinergic drugs.
	Prospective cohort study / 4.7 years [50]	Community-dwelling older adults initially free of dementia, cardiovascular disease or any significant life-limiting diseases in Australia and the USA (n=19114, age 65+ years)	Cognitive assessments, dementia diagnosis, stroke diagnosis, and ACB score	Participants who were female, older in age, from the USA, had lower education, current or former smokers, or had diabetes, chronic kidney disease, depression, or hypertension, were more likely to have a higher ACB score. Dementia and incident stroke rates were higher in participants with an ACB score of ≥ 3 compared to score 0 and were more likely to be diagnosed with possible AD dementia. No association between anticholinergics and probable Alzheimer's dementia was observed.
	Longitudinal cohort study / 2 years [51]	Community-dwelling and institutionalized participant in five study centers in England and Wales (n=13004, age 65+ years)	Cognitive measures, activities of daily living, medication use, and ACB score	An inverse correlation was observed between total ACB score and cognitive function score. For every additional point scored on the ACB, the odds of dying increased by 26%. Overall, the use of medications with anticholinergic activity increased the risk of cognitive decline and mortality over 2 years in participants with normal or mildly impaired cognition.

	Longitudinal observational study / 6 years [52]	Community-dwelling African American subjects aged ≥ 70 years who were enrolled in the Indianapolis-Ibadan Dementia Project in the USA (n=1652, mean age 81 ± 5.3 years)	Cognitive function and ACB score	The use of definite anticholinergics (score of 2 or 3 on the ACB) alone may increase the risk of less severe forms of cognitive impairment.
	Nested case-control study utilizing data from the Clinical Practice Research Datalink/ 9 years [53]	Patients with a recorded diagnosis of dementia made between April 2006 and July 2015 from general practices in the UK (n=40770, patient age 65-99 years)	Incident dementia and ACB score	In this case-control study of older adults increasing average ACB score was associated with dementia. The risk of dementia increased with greater exposure to ACB score 3 antidepressant, urological, and anti-Parkinson drugs. This result was also reported for exposure 15-20 years before a diagnosis.
	Cross-sectional analysis utilizing baseline data from the prospective research on memory clinics / 3 years [54]	Community-dwelling patients with mild cognitive impairment or dementia in Australia (n= 964, mean age 77.6 years)	Medication use, potentially inappropriate medication related to cognitive impairment (PIMcog) and the ACB score	Clinically significant anticholinergic cognitive burden (ACB ≥3) was present in 11.7 % of patients. PIMcog use, ACB ≥3, and concomitant use of anticholinergic medications with cholinesterase inhibitors were prevalent in this population of patients attending memory clinics.
	Longitudinal, retrospective observational study/ 5 years [55]	Older adults residing in nursing homes in Italy (n= 3761, mean age 83 ± 7 years)	Comprehensive clinical and functional assessment, and ACB score	Older adult patients with and ACB score of 1 and ≥2 showed a higher hazard to develop the primary outcome of composite occurrence of overall mortality/first hospitalization compared with patients with no anticholinergic medications' exposure.
ARS	Retrospective cohort study (1 year) / Prospective cohort study (1 year) {Rudolph, 2008 #30}	Retrospective cohort (n=132, age ≥65 years) of older adults visiting the geriatrics clinics and prospective cohort (n=117, age ≥65 years) male subjects attending primary care clinic at the Veterans Affairs Boston Healthcare System in the USA	Clinical symptoms of anticholinergic toxic reaction and ARS score	A statistically significantly association between higher ARS scores and increased risk of anticholinergic side effects in older patients was reported.
	Analyses of data from the population-based Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS) Study/ 3 years [47]	Participants of the GeMS study, randomly selected individuals aged ≥75 years in Finland (n=621, mean age 81.7 ± 4.9 years)	SAA, vision, functional capacity, cognition, and mood	The ARS, ADS and Chew list were used in this study. The ARS covered 5% of drugs used by participants compared to 88% and 55% covered by ADS and Chew's list respectively. The ARS and ADS were not significantly associated with SAA results. Anticholinergic burden measured using the 3 scales was inversely associated with short-distance vision, activities of daily living and a higher ARS score predicted 3-month mortality.
	Retrospective, longitudinal cohort study / 6 years [56]	Participants discharged from the convalescence rehabilitation ward at Hitachinaka General Hospital in Japan (n=618, median age 79 years)	Onset of aspiration pneumonia (AP)	Increased anticholinergic load might be a prediction of AP, an increase in ARS score by 2 points and ≥3 points were correlated with almost 2-fold and >3-fold significant increase risk for AP respectively
	Population-based longitudinal cohort study utilizing data from Taiwan's National Health Insurance Research Database/ 10 years [57]	Taiwanese population (n= 116043, age ≥65 years)	Monthly ARS and ACB score over a 10-year period, adverse outcomes (hospitalization, emergency visits, fractures, and dementia)	Both ARS and ACB scores increased gradually over the 10-year period, but the changes differed significantly with more pronounced increase with the ACB score. Overall, the cumulative effects of multiple low anticholinergic activity anticholinergics were associated with higher odds of emergency department visits and hospitalization than the effect of a single high anticholinergic activity medication. In clinical practice, the ACB scale performed better than the ARS as an instrument for identifying high-risk patients needing early intervention.
	Prospective cross-sectional study in 2017 [58]	Older adults residing in long-term care facilities in Finland (n=2474, mean age 81.7 ±9.2 years)	ARS score, nutritional status, and health-related quality of life (HRQoL)	Initial analysis revealed an association between ARS score and HRQoL, this relationship disappeared after stratification by dementia, dependency, and nutritional status.
	Retrospective, observational study/ 4 years [59]	Older adults admitted to the emergency department at a university hospital in England (n=33360, mean age 78.9 ± 8.5 years)	Death within 30 days of admission, death within 30 days of discharge, Prolonged length of hospital stay (≥ 10days), hospital readmission withing 30 days, discharge to usual place of residence	Strong associations were found between ARS score 1 and increased odds of inpatient mortality, post-discharge mortality, and lower odds of discharge to usual residence, compared to no anticholinergic medications. A weaker association was also observed with ARS scores ≥ 2. A higher ARS scores also had increased odds of 30-day post-discharge readmission. No associations with prolonged hospital stay were reported.

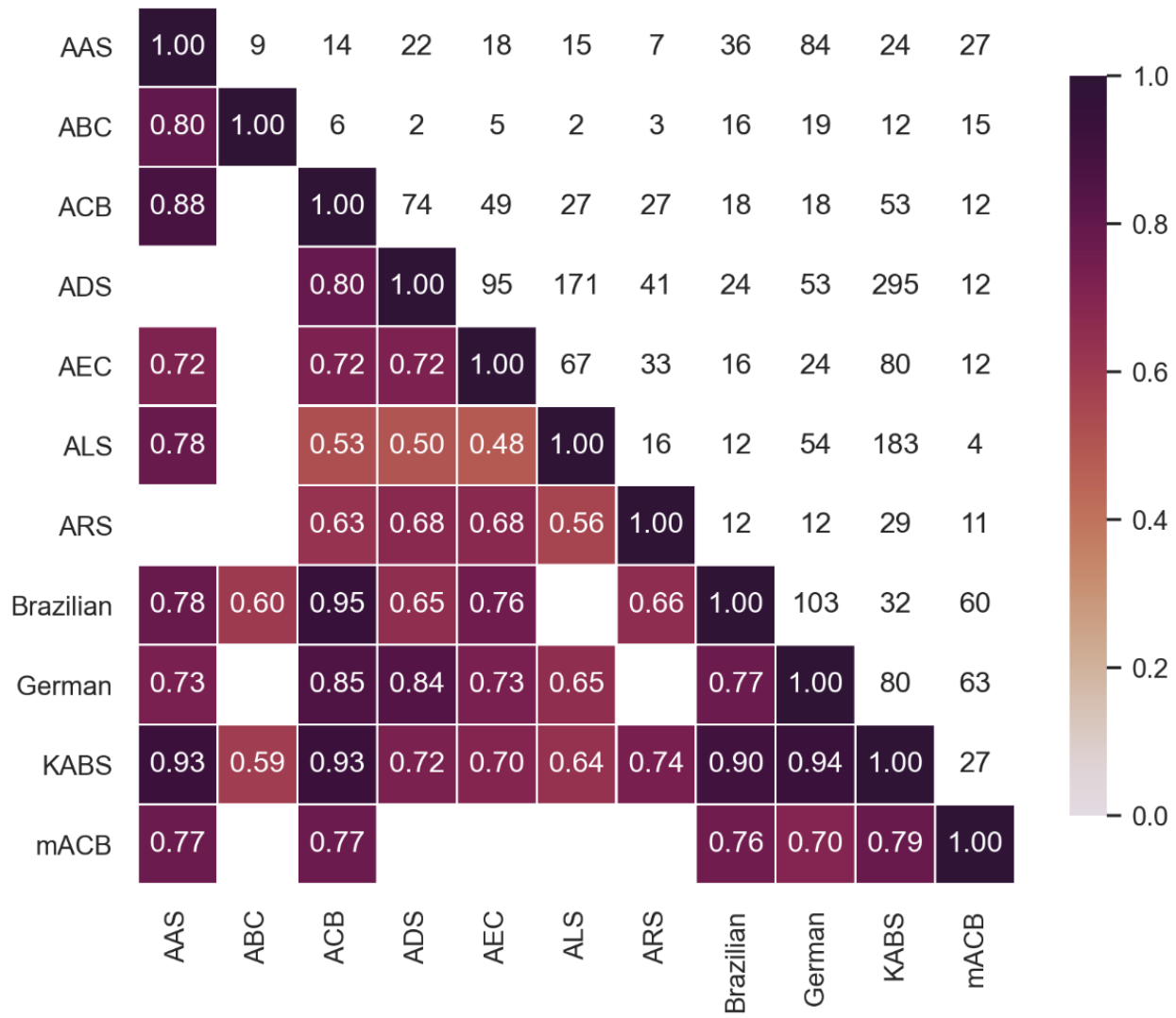
	Retrospective and longitudinal analysis of the criteria to assess appropriate medication use among elderly Complex Patients (CRIME) project/ 1-year follow-up [60]	Older hospitalized adults enrolled in seven acute care wards in Italy (n=1123, mean age 81 ± 7.5 years)	Cognitive function, activities of daily living, ARS and ACB scores	The ARS and ACB are moderately correlated. Adults with ARS S of ≥1 at discharge had significantly lower cognitive function score at baseline and a steeped cognitive decline during follow-up. Adults with an ACB of ≥1 at discharge had an almost 3-fold increased risk of developing disability.
	Prospective study/ 5 months [61]	Older adults admitted to 2 acute geriatric units in the UK (n=362, mean age 83.6 ± 6.6 years)	The Barthel Index (BI) for activities of daily living and ARS score	The ARS score was strongly associated with decreased physical function in older hospitalized adults and predicted in-hospital mortality in the case of hyponatremia.
ABC	Longitudinal cohort study/ 2 years [7]	Participants with no dementia at recruitment from 63 randomly selected general practitioners in France (n=372, mean age 77.8 ± 7.7 years)	Cognitive performance, mild cognitive impairment, dementia, and anticholinergic burden	The use of anticholinergic drug was a strong predictor of mild cognitive impairment, but no effect on overall dementia rates at 8-year follow-up.
	Pharmacoepidemiological population-based study using data from two large datasets in 2011 and 2012 [62]	Population aged 65 and older in New Zeeland (n = 537387, mean age 74.7 ± 7.6 years)	Morbidity, mortality, hospital length of stay, institutionalization, functional and cognitive decline, and anticholinergic burden	Anticholinergic burden exposure was measured using 9 different scales. The highest exposure was identified using the ADS and lowest exposure identified using the ABC scale.
AAS	Longitudinal prospective community-based prevalence study/ 8 years [12]	Patients diagnosed with Parkinson's disease on January 2003 in Norway (n=235, mean age 74.7 ± 8.4)	Cognitive function, anticholinergic load using the AAS	This study showed a significant association between anticholinergic medications use and the rate of cognitive decline. Patients who used anticholinergics reported a 6.5 times higher decline rate compared to non-users.
	Cross-sectional findings study from the Northern Finland Birth Cohort 1966 (NFBC1966) [63])	Individuals from the NFBC1966 who participated in a voluntary 46-year follow-up study recruited between 2012-2013 with complete dental status in Finland (n=1945, mean age 46 years)	Anticholinergic burden, oral hygiene practices and oral hygiene status	Anticholinergic burden was measured using 9 different scales. Overall, a higher likelihood of having more teeth with dental plaque was reported in participants with anticholinergic burden. The AAS, Chew's scale and ACB showed the strongest association with the number of teeth with dental plaque.
	Observational and cross-sectional study utilizing data collected between 2007-2014 by the Registry of Dementia of Girona [64]	Patients with incident cases of dementia diagnosed in 7 hospitals in Spain (n=5323, mean age 79.9 ±7.3 years)	Anticholinergic exposure, cognitive function, and dementia score	Anticholinergic burden was measured using 9 different scales and a large difference in clinical outcomes among the scales was found. Prevalence of annual anticholinergic exposure was calculated using different scales. The ABC, ARS, and AAS showed the lowest prevalence percentages.
ACL (ALS)	Cross-sectional study utilizing data collected from the multidisciplinary longitudinal Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging/ 22 months [13]	Healthy controls, patients with mild cognitive impairment and patients with Alzheimer's disease as part of the AIBL in Australia (n=1112, mean age 74.5± 7.7 years)	Cognitive performance and ACL score	A high ACL score within the healthy controls had a modest negative impact on cognitive performance in the area of the psychomotor speed and executive function and no impact on other areas of cognition.

	Cross-sectional retrospective evaluation study [65]	Outpatients aged 60 and over in Turkey (n=420, mean age 73 ± 8.7 years)	Polypharmacy and anticholinergic burden scales including ACL	The ACL scale showed moderate correlation with polypharmacy. The highest correlation was found with the drug burden index (DBI) and the lowest was with the AAS.
	Retrospective analysis study/ 18 months [66]	Hospitalized patients at the long-term care facility in South Korea (n=216, mean age 81.0 ± 6.7 years)	Concordance between Beers' criteria and different anticholinergic scales for identifying potentially inappropriate medications and anticholinergics	When the Beers' Criteria 2015 was compared with the different anticholinergic scales for the proportions of anticholinergics identified, the ADS showed the highest concordance followed by the ACL, whereas the lowest concordance was found for AAS.
	Longitudinal analysis utilizing data from the UK Biobank community cohort/ 6.2 median follow-up years [67]	Participants of the UK biobank, a community-based cohort (502538, mean age 55 years)	All-cause mortality, major adverse cardiovascular event, hospital admission for fall, fracture, dementia, or delirium	Anticholinergic burden was calculated at baseline using 10 scales. The ACL identified the greatest number of participants taking medications with anticholinergic properties
AEC	Retrospective study utilizing data from the South London and Maudsley National Health Service Foundation Trust (SLaM) Clinical Record Interactive Search (CRIS) resource/ 9 years [15]	Patients with a first diagnosis of dementia in the UK (n=14093, mean age 79.8 ± 10.7 years)	Cognitive performance score and AEC score	Dementia patients with high AEC score appeared to have worse prognosis in terms of hospitalization risk, short-term cognitive function impairment and mortality. No long-term differences in cognitive decline were found.
	Longitudinal analysis utilizing data from the UK Biobank community cohort/ 6.2 median follow-up years [67]	Participants of the UK biobank, a community-based cohort (502538, mean age 55 years)	All-cause mortality, major adverse cardiovascular event, hospital admission for fall, fracture, dementia, or delirium	Anticholinergic burden was calculated at baseline using 10 scales. The AEC scale showed the greatest association for assessing the risk of neurocognitive complications and a great predictive accuracy for dementia and delirium.
German ACB	Multicentered observational cohort study/ 15 months [17]	Patients from 8 different primary care centers in Germany (n= 3189, mean age 74.4 ± 5.2 years)	Influence of anticholinergic burden on the cognitive function	Anticholinergic burden was measured according to the German ACB and ADS scales. Patients used 2750 and 1764 anticholinergic drugs according to the German ACB and ADS respectively. An increasing German ACB and ADS and was associated with reduced cognitive function. The German ACB generated comparable outcomes in this study with the ADS score.
Brazilian ACB	***No validation studies available***			
Korean ACB	Single-center retrospective descriptive study/ 8 months [68]	Patients visiting the nephrology clinic at Seoul National University Hospital in Korea (n=95, mean age 74.9 ± 7.3 years)	Change in Quality of Medication Use and anticholinergic burden	Pharmacist-led geriatric medication management service significantly decreased patient's anticholinergic burden measured using KABS and improved the quality of medication use in this population.

	Nested case-control study utilizing national claims data for validation KABS/ 6 months [69]	Older adult patient sample dataset provided by the health insurance review and assessment services in Korea (n=461,034, mean age 76.1 ± 7.1 years)	Associations between high anticholinergic burden, measured with the KABS, and emergency visits related to anticholinergic adverse events compared to ARS, ACB and ADS scales	Using KABS in older Korean adults for the measurement of anticholinergic burden is superior to the ARS, ACB and ADS for identifying patients with high anticholinergic burden with a stronger dose-response relationship for individual anticholinergic adverse effect and anticholinergic emergency visits.
	Retrospective case-control study/ 9 years [70]	Older adults diagnosed with dementia in 2012-2013 were selected from the Korea National Health Insurance Service Senior Cohort database (n=86,576, mean age 79 ± 4 years)	Average daily anticholinergic burden score measured using KABS and ACB for the last 9 years prior to dementia onset	Patients with high exposure according to KABS and ACB had a significantly higher risk for incident dementia and a dose response relationship was confirmed for the cumulative anticholinergic burden measured using KABS with incident dementia.
mACB	Quasi-Experimental Study/ 2 years (PREPRINT) [21]	Patients with dementia and older adults with memory problem or confusion visiting two hospitals in New South Wales, Australia (n=628, mean age 84 ± 8 years)	The effect of medication safety interventions on potentially inappropriate medications, polypharmacy, and anticholinergic burden scores	The study was completed, and the results are still under peer-review.
Sedative Load Model	Analysis study utilizing data from the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly (GeMS), a randomized comparative study [71]	Community-dwelling older adults living in Finland (n= 700, mean age 81.4 ± 4.4 years)	Sedative load using the SLM, instrumental activities of daily living (IADL), depressive symptoms	Cumulative sedative load was associated with female sex, poor overall health status, impaired IADL, and loneliness.
	Cross-sectional study [71]	Residents of 53 long-term care wards in Finland (n= 1052, mean age 80 years)	Sedative load using the SLM, dementia, cognitive performance, and comorbidity	Dementia patients were less frequent users of sedatives and hypnotics compared to non-dementia patients. Importantly, both groups had a similar sedative load indicating the use of medications not prescribed for intentional sedation.
	Analysis study using data from the EVIDEM-End of Life (EOL) prospective study / 2 years [72]	Older adults with dementia living in residential care homes in the UK (n=133, mean age 85.8 ± 6.8 years)	Sedative load using the SLM	One or more psychotropic medication(s) was used by more than 66% of residents. Throughout the study duration, administration of SLM category 2 medications outweighed SLM category 1 drugs
	Multicenter prospective cohort study/ 2 years [73]	Older hospitalized adults in France (n=315, mean age 87 years)	SLM, DBI, ADS, risk of falling, comorbidities, level of autonomy, cognitive functions, and physical and physiological health status	More than 56 % of patients included in this study had a SLM >0. No association was found between the SLM, ADS and DBI scores and risk of a falls.

	Retrospective cohort and cross-sectional analysis utilizing the Registry of Senior Australians National Historical Cohort / 8 years [74]	Older adults with a diagnosis of dementia using government-subsidized aged care in Australia (n = 373695, mean age 84.1 ± 6.9 years)	Four clinical quality indications: Sedative load using the SLM, dispensing of antipsychotics, dispensing of anti-dementia medications, dementia, and delirium-related hospitalizations	Among aged care users with dementia, a minimal change in the incidence rate of the four indicators of dementia care quality over five years was found.
	Analysis study utilizing data from NILVAD Study, an investigator-led phase III trial of the antihypertensive nilvadipine in mild–moderate Alzheimer's disease (AD) [75]	Community-dwelling older adults with mild-to-moderate AD from 23 different sites in Europe (n=510, mean age 72.8 ± 8.3 years)	Sedative load using the SLM and adverse events, unscheduled healthcare utilization, delirium, and falls	More than 55% of patients with mild-moderate AD were prescribed a regular SLM group 1 and 2 medications and around 22% of patients with SLM ≥3. Increased baseline SLM was associated with incidents of adverse events, unscheduled general practitioner visits and likelihood of incident delirium. No association between SLM and cognitive decline or AD progression.
Sloane Model	***No validation studies available using Slone sedative model. Few studies validated the Slone analgesic model [26, 27]***			

Supplementary Figure S1 Drug count between each pair of anticholinergic scales



Key: ADS: Anticholinergic Drug Scale; ABC: Anticholinergic Burden Classification; ARS: Anticholinergic Rating Scale; ACB: Anticholinergic Cognitive Burden; AAS: Anticholinergic Activity Scale; ALS: Anticholinergic Load Scale; AEC: Anticholinergic Effect on Cognition, KABS: Korean Anticholinergic Burden Scale, mACB: modified Anticholinergic Cognitive Burden scale.
Legend Heatmap showing Spearman's rank correlation coefficient and number of drugs in common between scores for medications common to each pair of scales.

References:

1. Han L, McCusker J, Cole M, Abrahamowicz M, Primeau F, Elie M. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med. 2001 Apr 23;161(8):1099-105.

2. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. J Clin Pharmacol. 2006 Dec;46(12):1481-6.

3. MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. BMC Geriatrics. 2015 2015/03/25;15(1):31.

4. Kersten HM, E.; Willumsen, T.; Engedal, K.; Bruun Wyller, T.; . Higher anticholinergic drug scale (ADS) scores are associated with peripheral but not cognitive markers of cholinergic blockade. Cross sectional data from 21 Norwegian nursing homes. British Journal of Clinical Pharmacology. 2013;75(3):842-9.

5. Amoros-Reboredo P, Soy D, Hernandez-Hernandez M, Lens S, Mestres C. Anticholinergic Burden and Safety Outcomes in Older Patients with Chronic Hepatitis C: A Retrospective Cohort Study. Int J Environ Res Public Health. 2020;17(11):3776.

6. Sevilla-Sánchez D, Molist-Brunet N, González-Bueno J, Solà-Bonada N, Espaulella-Panicot J, Codina-Jané C. Prevalence, risk factors and adverse outcomes of anticholinergic burden in patients with advanced chronic conditions at hospital admission. Geriatr Gerontol Int. 2018 Aug;18(8):1159-65.

7. Ancelin ML, Artero S, Portet F, Dupuy AM, Touchon J, Ritchie K. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. Bmj. 2006 Feb 25;332(7539):455-9.

8. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008 Mar 10;168(5):508-13.

9. Lozano-Ortega G, Johnston KM, Cheung A, Wagg A, Campbell NL, Dmochowski RR, et al. A review of published anticholinergic scales and measures and their applicability in database analyses. Archives of Gerontology and Geriatrics. 2020 2020/03/01/;87:103885.

10. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. Aging Health. 2008 2008/06/01;4(3):311-20.

11. Chew ML, Mulsant BH, Pollock BG, Lehman ME, Greenspan A, Mahmoud RA, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc. 2008 Jul;56(7):1333-41.

12. Ehrt U, Broich K, Larsen JP, Ballard C, Aarsland D. Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study. J Neurol Neurosurg Psychiatry. 2010 Feb;81(2):160-5.

13. Sittironnarit G, Ames D, Bush AI, Faux N, Flicker L, Foster J, et al. Effects of anticholinergic drugs on cognitive function in older Australians: results from the AIBL study. Dement Geriatr Cogn Disord. 2011;31(3):173-8.

14. Bishara D, Harwood D, Sauer J, Taylor DM. Anticholinergic effect on cognition (AEC) of drugs commonly used in older people. International Journal of Geriatric Psychiatry. 2017;32(6):650-6.

15. Bishara D, Perera G, Harwood D, Taylor D, Sauer J, Stewart R, et al. The Anticholinergic Effect on Cognition (AEC) Scale-Associations with Mortality, Hospitalisation and Cognitive Decline Following Dementia Diagnosis. International Journal of Geriatric Psychiatry. 2020.

16. Kiesel EK, Hopf YM, Drey M. An anticholinergic burden score for German prescribers: score development. BMC Geriatr. 2018 Oct 11;18(1):239.

17. Krüger C, Schäfer I, van den Bussche H, Bickel H, Fuchs A, Gensichen J, et al. Anticholinergic drug burden according to the anticholinergic drug scale and the German anticholinergic burden and their impact on cognitive function in multimorbid elderly German people: a multicentre observational study. BMJ Open. 2021 Mar 23;11(3):e044230.

18. Nery RT, Reis AMM. Development of a Brazilian anticholinergic activity drug scale. Einstein (Sao Paulo). 2019;17(2):eAO4435-eAO.

19. Jun K, Hwang S, Ah YM, Suh Y, Lee JY. Development of an Anticholinergic Burden Scale specific for Korean older adults. Geriatr Gerontol Int. 2019 Jul;19(7):628-34.

20. Kable A, Fullerton A, Fraser S, Palazzi K, Hullick C, Oldmeadow C, et al. Comparison of Potentially Inappropriate Medications for People with Dementia at Admission and Discharge during An Unplanned Admission to Hospital: Results from the SMS Dementia Study. Healthcare (Basel). 2019;7(1):8.

21. Kable A, Fraser S, Fullerton A, Hullick C, Palazzi K, Oldmeadow C, et al. Evaluation of the Effect of an Intervention on Potentially Inappropriate Medications (PIMS), Polypharmacy and Anticholinergic Burden Scores for People with Dementia; Results from the SMS Dementia Study†: A Quasi-Experimental Study. Research Square; 2020.

22. Linjakumpu T, Hartikainen S, Klaukka T, Koponen H, Kivelä SL, Isoaho R. A model to classify the sedative load of drugs. Int J Geriatr Psychiatry. 2003 Jun;18(6):542-4.

23. Taipale HT, Hartikainen S, Bell JS. A comparison of four methods to quantify the cumulative effect of taking multiple drugs with sedative properties. Am J Geriatr Pharmacother. 2010 Oct;8(5):460-71.

24. Linjakumpu TA, Hartikainen SA, Klaukka TJ, Koponen HJ, Hakko HH, Viilo KM, et al. Sedative drug use in the home-dwelling elderly. Ann Pharmacother. 2004 Dec;38(12):2017-22.

25. Sloane P, Ivey J, Roth M, Roederer M, Williams CS. Accounting for the sedative and analgesic effects of medication changes during patient participation in clinical research studies: measurement development and application to a sample of institutionalized geriatric patients. Contemp Clin Trials. 2008 Mar;29(2):140-8.

26. Tan EC, Visvanathan R, Hilmer SN, Vitry A, Emery T, Robson L, et al. Analgesic use and pain in residents with and without dementia in aged care facilities: A cross-sectional study. Australasian Journal on Ageing. 2016;35(3):180-7.

27. Tan ECK, Visvanathan R, Hilmer SN, Vitry AI, Quirke T, Emery T, et al. Analgesic use, pain and daytime sedation in people with and without dementia in aged care facilities: a cross-sectional, multisite, epidemiological study protocol. BMJ Open. 2014;4(6):e005757.

28. Hunt JN, Lallemand RC. Sedative properties of simple analgesics. Br J Pharmacol. 1969;37(2):450-8.

29. Han L, Agostini JV, Allore HG. Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. J Am Geriatr Soc. 2008 Dec;56(12):2203-10.

30. Koyama A, Steinman M, Ensrud K, Hillier TA, Yaffe K. Long-term cognitive and functional effects of potentially inappropriate medications in older women. J Gerontol A Biol Sci Med Sci. 2014 Apr;69(4):423-9.

31. Briet J, Javelot H, Heitzmann E, Weiner L, Lameira C, D'Athis P, et al. The anticholinergic impregnation scale: Towards the elaboration of a scale adapted to prescriptions in French psychiatric settings. Therapie. 2017 Sep;72(4):427-37.

32. Puustinen J, Nurminen J, Vahlberg T, Lyles A, Isoaho R, Räihä I, et al. CNS medications as predictors of precipitous cognitive decline in the cognitively disabled aged: a longitudinal population-based study. Dement Geriatr Cogn Dis Extra. 2012;2(1):57-68.

33. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019 Apr;67(4):674-94.

34. Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. European Journal of Clinical Pharmacology. 2013 2013/07/01;69(7):1485-96.

35. Nishtala PS, Salahudeen MS, Hilmer SN. Anticholinergics: theoretical and clinical overview. Expert Opin Drug Saf. 2016 Jun;15(6):753-68.

36. Hilmer SN, Mager DE, Simonsick EM, Ling SM, Windham BG, Harris TB, et al. Drug burden index score and functional decline in older people. Am J Med. 2009 Dec;122(12):1142-9 e1-2.

37. Takahashi H, Ishida-Yamamoto A, Iizuka H. Effects of bepotastine, cetirizine, fexofenadine, and olopatadine on histamine-induced wheal-and flare-response, sedation, and psychomotor performance. Clinical and Experimental Dermatology. 2004;29(5):526-32.

38. Koyama Y, Andoh T, Kamiya Y, Miyazaki T, Maruyama K, Kariya T, et al. Bumetanide, an Inhibitor of NKCC1 (Na-K-2Cl Cotransporter Isoform 1), Enhances Propofol-Induced Loss of Righting Reflex but Not Its Immobilizing Actions in Neonatal Rats. PloS one. 2016;11(10):e0164125-e.

39. Andrade C. Desvenlafaxine. Indian J Psychiatry. 2009 Oct-Dec;51(4):320-3.

40. Klamer TT, Wauters M, Azermai M, Durán C, Christiaens T, Elseviers M, et al. A Novel Scale Linking Potency and Dosage to Estimate Anticholinergic Exposure in Older Adults: the Muscarinic Acetylcholinergic Receptor ANTagonist Exposure Scale. Basic & Clinical Pharmacology & Toxicology. 2017;120(6):582-90.

41. Errington AC, Coyne L, Stöhr T, Selve N, Lees G. Seeking a mechanism of action for the novel anticonvulsant lacosamide. Neuropharmacology. 2006 2006/06/01/;50(8):1016-29.

42. Greenberg WM, Citrome L. Pharmacokinetics and Pharmacodynamics of Lurasidone Hydrochloride, a Second-Generation Antipsychotic: A Systematic Review of the Published Literature. Clin Pharmacokinet. 2017 May;56(5):493-503.

43. Speich R, Haller A. Central anticholinergic syndrome with the antimalarial drug mefloquine. N Engl J Med. 1994 Jul 7;331(1):57-8.

44. Andersen F, Viitanen M, Halvorsen DS, Straume B, Engstad TA. Co-morbidity and drug treatment in Alzheimer's disease. A cross sectional study of participants in the dementia study in northern Norway. BMC Geriatr. 2011;11:58-.

45. Mate KE, Kerr KP, Pond D, Williams EJ, Marley J, Disler P, et al. Impact of multiple low-level anticholinergic medications on anticholinergic load of community-dwelling elderly with and without dementia. Drugs Aging. 2015 Feb;32(2):159-67.

46. Pond CD, Brodaty H, Stocks NP, Gunn J, Marley J, Disler P, et al. Ageing in general practice (AGP) trial: a cluster randomised trial to examine the effectiveness of peer education on GP diagnostic assessment and management of dementia. BMC Family Practice. 2012 2012/03/07;13(1):12.

47. Lampela P, Lavikainen P, Garcia-Horsman JA, Bell JS, Huupponen R, Hartikainen S. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: a population-based study. Drugs Aging. 2013 May;30(5):321-30.

48. Moga DC, Abner EL, Rigsby DN, Eckmann L, Huffmyer M, Murphy RR, et al. Optimizing medication appropriateness in older adults: a randomized clinical interventional trial to decrease anticholinergic burden. Alzheimer's Research & Therapy. 2017 2017/05/23;9(1):36.

49. Pasina L, Colzani L, Cortesi L, Tettamanti M, Zambon A, Nobili A, et al. Relation Between Delirium and Anticholinergic Drug Burden in a Cohort of Hospitalized Older Patients: An Observational Study. Drugs Aging. 2019 Jan;36(1):85-91.

50. Lockery JE, Broder JC, Ryan J, Stewart AC, Woods RL, Chong TT, et al. A Cohort Study of Anticholinergic Medication Burden and Incident Dementia and Stroke in Older Adults. J Gen Intern Med. 2021 Jun;36(6):1629-37.

51. Fox C, Richardson K, Maidment ID, Savva GM, Matthews FE, Smithard D, et al. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. J Am Geriatr Soc. 2011 Aug;59(8):1477-83.

52. Campbell NL, Boustani MA, Lane KA, Gao S, Hendrie H, Khan BA, et al. Use of anticholinergics and the risk of cognitive impairment in an African American population. Neurology. 2010 Jul 13;75(2):152-9.

53. Richardson K, Fox C, Maidment I, Steel N, Loke YK, Arthur A, et al. Anticholinergic drugs and risk of dementia: case-control study. BMJ (Clinical research ed). 2018;361:k1315-k.

54. Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Ilomäki J, et al. Potentially Inappropriate Medications and Anticholinergic Burden in Older People Attending Memory Clinics in Australia. Drugs Aging. 2016 Jan;33(1):37-44.

55. Vetrano DL, La Carpia D, Grande G, Casucci P, Bacelli T, Bernabei R, et al. Anticholinergic Medication Burden and 5-Year Risk of Hospitalization and Death in Nursing Home Elderly Residents With Coronary Artery Disease. J Am Med Dir Assoc. 2016 Nov 1;17(11):1056-9.

56. Kose E, Hirai T, Seki T. Assessment of aspiration pneumonia using the Anticholinergic Risk Scale. Geriatr Gerontol Int. 2018 Aug;18(8):1230-5.

57. Hsu WH, Huang ST, Lu WH, Wen YW, Chen LK, Hsiao FY. Impact of Multiple Prescriptions With Anticholinergic Properties on Adverse Clinical Outcomes in the Elderly: A Longitudinal Cohort Study in Taiwan. Clin Pharmacol Ther. 2021 Feb 24.

58. Aalto UL, Finne-Soveri H, Kautiainen H, Öhman H, Roitto HM, Pitkälä KH. Relationship between Anticholinergic Burden and Health-Related Quality of Life among Residents in Long-Term Care. The journal of nutrition, health & aging. 2021 2021/02/01;25(2):224-9.

59. Herrero-Zazo M, Berry R, Bines E, Bhattacharya D, Myint PK, Keevil VL. Anticholinergic burden in older adult inpatients: patterns from admission to discharge and associations with hospital outcomes. Ther Adv Drug Saf. 2021;12:20420986211012592.

60. Brombo G, Bianchi L, Maietti E, Malacarne F, Corsonello A, Cherubini A, et al. Association of Anticholinergic Drug Burden with Cognitive and Functional Decline Over Time in Older Inpatients: Results from the CRIME Project. Drugs Aging. 2018 Oct;35(10):917-24.

61. Lowry E, Woodman RJ, Soiza RL, Mangoni AA. Associations between the anticholinergic risk scale score and physical function: potential implications for adverse outcomes in older hospitalized patients. J Am Med Dir Assoc. 2011 Oct;12(8):565-72.

62. Salahudeen MS, Hilmer SN, Nishtala PS. Comparison of anticholinergic risk scales and associations with adverse health outcomes in older people. J Am Geriatr Soc. 2015 Jan;63(1):85-90.

63. Tiisanoja A, Syrjälä AM, Anttonen V, Ylöstalo P. Anticholinergic burden, oral hygiene practices, and oral hygiene status-cross-sectional findings from the Northern Finland Birth Cohort 1966. Clin Oral Investig. 2021 Apr;25(4):1829-37.

64. Turró-Garriga O, Calvó-Perxas L, Vilalta-Franch J, Blanco-Silvente L, Castells X, Capellà D, et al. Measuring anticholinergic exposure in patients with dementia: A comparative study of nine anticholinergic risk scales. International Journal of Geriatric Psychiatry. 2018;33(5):710-7.

65. Okudur SK, Dokuzlar O, Aydin AE, Kocyigit SE, Soysal P, Isik AT. The evaluation of relationship between polypharmacy and anticholinergic burden scales. North Clin Istanb. 2021;8(2):139-44.

66. Park KH, Yang Y-M, Yoo JC, Choi EJ. Comparative Analysis Of Anticholinergics Prescribed To Elderly Patients At A Korean Long-Term Care Facility According To Beers Criteria 2003, 2012, And 2015 And Anticholinergic-Burden Rating Scales: A Cross-Sectional Retrospective Study. Clinical interventions in aging. 2019;14:1963-74.

67. Hanlon P, Quinn TJ, Gallacher KI, Myint PK, Jani BD, Nicholl BI, et al. Assessing Risks of Polypharmacy Involving Medications With Anticholinergic Properties. The Annals of Family Medicine. 2020;18(2):148-55.

68. Kim AJ, Lee H, Shin E-J, Cho E-J, Cho YS, Lee H, et al. Pharmacist-Led Collaborative Medication Management for the Elderly with Chronic Kidney Disease and Polypharmacy. Int J Environ Res Public Health. 2021;18(8):4370.

69. Hwang S, Chung JE, Jun K, Ah Y-M, Kim K-I, Lee J-Y. Comparative associations between anticholinergic burden and emergency department visits for anticholinergic adverse events in older Korean adults: a nested case-control study using national claims data for validation of a novel country-specific scale. BMC Pharmacol Toxicol. 2021;22(1):2-.

70. Suh Y, Ah Y-M, Han E, Jun K, Hwang S, Choi KH, et al. Dose response relationship of cumulative anticholinergic exposure with incident dementia: validation study of Korean anticholinergic burden scale. BMC Geriatrics. 2020 2020/07/29;20(1):265.

71. Bell JS, Taipale HT, Soini H, Pitkälä KH. Sedative Load among Long-Term Care Facility Residents with and without Dementia. Clinical Drug Investigation. 2010 2010/01/01;30(1):63-70.

72. Parsons C, Haydock J, Mathie E, Baron N, Machen I, Stevenson E, et al. Sedative load of medications prescribed for older people with dementia in care homes. BMC Geriatrics. 2011 2011/09/30;11(1):56.

73. Jean-Bart E, Moutet C, Dauphinot V, Krolak-Salmon P, Mouchoux C. Exposure to anticholinergic and sedative medicines as indicators of high-risk prescriptions in the elderly. Int J Clin Pharm. 2017 Dec;39(6):1237-47.

74. Cations M, Lang C, Ward SA, Caughey GE, Crotty M, Whitehead C, et al. Using data linkage for national surveillance of clinical quality indicators for dementia care among Australian aged care users. Sci Rep. 2021;11(1):10674-.

75. Dyer AH, Murphy C, Lawlor B, Kennelly SP. Sedative Load in Community-Dwelling Older Adults with Mild-Moderate Alzheimer's Disease: Longitudinal Relationships with Adverse Events, Delirium and Falls. Drugs Aging. 2020 Nov;37(11):829-37.