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SYSTEMATIC REVIEW

Anticholinergic Drug Burden Tools/Scales and Adverse Outcomes in Different Clinical Settings: A Systematic Review of Reviews

Tomas J. Welsh[1,2,6] · Veronika van der Wardt[3] · Grace Ojo[3] · Adam L. Gordon[3,4] · John R. F. Gladman[3,5,7]

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Abstract

Background Cumulative anticholinergic exposure (anticholinergic burden) has been linked to a number of adverse outcomes. To conduct research in this area, an agreed approach to describing anticholinergic burden is needed.

Objective This review set out to identify anticholinergic burden scales, to describe their rationale, the settings in which they have been used and the outcomes associated with them.

Methods A search was performed using the Healthcare Databases Advanced Search of MEDLINE, EMBASE, Cochrane, CINAHL and PsycINFO from inception to October 2016 to identify systematic reviews describing anticholinergic burden scales or tools. Abstracts and titles were reviewed to determine eligibility for review with eligible articles read in full. The final selection of reviews was critically appraised using the ROBIS tool and predefined data were extracted; the primary data of interest were the anticholinergic burden scales or tools used.

Results Five reviews were identified for analysis containing a total of 62 original articles. Eighteen anticholinergic burden scales or tools were identified with variation in their derivation, content and how they quantified the anticholinergic activity of medications. The Drug Burden Index was the most commonly used scale or tool in community and database studies, while the Anticholinergic Risk Scale was used more frequently in care homes and hospital settings. The association between anticholinergic burden and clinical outcomes varied by index and study. Falls and hospitalisation were consistently found to be associated with anticholinergic burden. Mortality, delirium, physical function and cognition were not consistently associated.

Conclusions Anticholinergic burden scales vary in their rationale, use and association with outcomes. This review showed that the concept of anticholinergic burden has been variably defined and inconsistently described using a number of indices with different content and scoring. The association between adverse outcomes and anticholinergic burden varies between scores and has not been conclusively established.

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✉ Tomas J. Welsh
tomas.welsh@nhs.net

1 Research Institute for the Care of Older People (RICE), Royal United Hospital, Combe Park, Bath BA1 3NG, UK

2 Royal United Hospital Bath NHS Foundation Trust, Bath, Somerset, UK

3 University of Nottingham, Nottingham, Nottinghamshire, UK

4 Derby Teaching Hospitals NHS Foundation Trust, Derby, Derbyshire, UK

5 Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East Midlands, Leicester, UK

6 University of Bristol, Bristol, UK

7 NIHR Nottingham Biomedical Research Centre, Nottingham, Nottinghamshire, UK

Key Points

There are multiple available methods to quantify anticholinergic burden.

The available methods vary in their derivation and association with outcomes.

An agreed method of quantifying anticholinergic burden is needed to aid future potential research in this field.

1 Introduction

1.1 Rationale

Medications with anticholinergic properties are widely used for a variety of indications. Such products may not be used primarily for their anticholinergic effect and may not be routinely identified as having anticholinergic activity by practicing clinicians [1]. However, the cumulative effect of multiple medications with anticholinergic effects, known as anticholinergic burden, is potentially significant and is an area of specific concern in the literature [2]. Anticholinergic burden scales are designed to quantify the cumulative exposure to anticholinergic activity [3]. A number of scales have been developed and have been used in a number of clinical settings including inpatients, [4] community dwellers [5] and institutional care [6]. They are referred to by a number of terms, but for simplicity throughout the article 'anticholinergic burden scale' will be used.

Older people, with a higher rate of multimorbidity and subsequent polypharmacy, are at higher risk of experiencing anticholinergic burden compared with younger people and with age-related changes to pharmacokinetics and pharmacodynamics are at higher risk of anticholinergic side effects for a given anticholinergic burden [7]. This applies all the more in the frailest groups such as care home residents and people with dementia, where the risk of multimorbidity and polypharmacy is high [8].

Previous reviews have identified that all anticholinergic burden scales in use show an association between anticholinergic burden and at least one adverse outcome [2] and researchers have therefore called for interventions to reduce anticholinergic burden [9]. Clearly, a starting point for such interventions is a clear and consistent understanding of how to quantify and measure anticholinergic burden. Preliminary reading of the published reviews, however, showed variation in the type and number of scales/tools identified, with Salahudeen et al. [1] identifying seven and Mayer et al. [10] identifying 12. In addition there was variation in the authors' views on the appropriateness of the different scales/tools, with Cardwell et al. [2] advocating the use of the Drug Burden Index while Salahudeen et al. [1] identified the Anticholinergic Cognitive Burden Scale as the most frequently validated scale. To help clarify this divergence of view, a review of reviews was proposed to comprehensively identify anticholinergic burden scales and tools.

1.2 Objectives

The primary objective of this systematic review of reviews was to identify scales/tools that have been used to quantify anticholinergic burden. The secondary objectives of this review were (1) to describe the rationale of the identified scales; (2) to describe the settings in which the identified scales have been used; and (3) to describe any associations between anticholinergic burden, as quantified by the identified anticholinergic burden scales, and adverse outcomes.

2 Methods

2.1 Eligibility and Exclusion Criteria

Systematic reviews describing the use of scales or tools to quantify anticholinergic burden were deemed eligible. For the purposes of this review, articles that stated that they were planned and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [11] were deemed to be systematic. No publication date or age of participant restrictions were imposed but the search was limited to reviews and English language articles. Reviews marked as narrative or clinical were excluded as were reviews that sought to test the association between prespecified anticholinergic burden scales and outcomes.

2.2 Information Sources and Study Selection

An electronic literature search was performed using a Healthcare Databases Advanced Search of MEDLINE, EMBASE, Cochrane, CINAHL and PsycINFO from inception to October 2016 for relevant articles. The last full search was run on 24 October, 2016.

2.3 Search

The following terms, a mixture of MeSH and free text, were used:

Anticholinergics OR cholinergic receptor blocking agents OR cholinergic antagonist OR antimuscarinics OR

muscarinic receptor blocking agents OR muscarinic antagonist AND risk OR risk measure OR risk scale OR rating scale OR risk tool OR load OR drug burden index. An example search (MEDLINE) is given in Appendix S1 of the Electronic Supplementary Material (ESM). The reference lists of included reviews were searched for additional relevant studies (snowballing).

2.4 Study Selection

The titles and abstracts of the identified articles were screened to see whether they met the inclusion criteria. Where there was uncertainty, full-length articles were evaluated before a final decision on inclusion was made. A list of excluded studies is included in Table S1 of the ESM.

2.5 Data Collection

Full-text copies of included articles were reviewed and data were extracted and entered into a structured Microsoft Excel (Redmond, WA, USA) database. For each article, the following variables were populated: (1) the anticholinergic burden scales used; (2) information on the scales' rationale; (3) the number of participants evaluated using the different scales; (4) the use of the scales in different settings [hospital, community, care home (including nursing homes, long-term care facilities and homes for the aged), database studies and in people with dementia]; and (5) (where available) adverse events associated with anticholinergic burden as defined by different anticholinergic burden scales.

2.6 Assessment of Risk of Bias

The ROBIS tool was used to assess the risk of bias for each systematic review [12]. The ROBIS tool is a method to assess bias in systematic reviews that is completed in three phases: (1) assessing relevance; (2) identifying concerns with the review process; and (3) judging risk of bias in the review. Phase two involves assessing the review across four domains: (1) study eligibility criteria, (2) identification and selection of studies, (3) data collection and study appraisal; and (4) synthesis and findings. In phase three, the findings of phase two and signalling questions are used to evaluate the overall risk of bias. Table 1 summarises the risk of bias for each review.

3 Results

The search identified 4656 articles. After limiting the search to review articles in English, 906 citations remained. The abstracts of these remaining articles were screened and 14 full-text papers were identified and subsequently reviewed for inclusion. From this group, a final total of five were included after a detailed review revealed that nine articles did not meet the inclusion criteria (Fig. 1).

3.1 Characteristics of Included Reviews

Four of the review articles aimed to identify anticholinergic burden scales and to test their association with clinical outcomes [1, 2, 7, 10]. Two produced an anticholinergic burden scale by combining pre-existing scales, [1, 3] and one aimed to identify the most useful scale for longitudinal research [2].

The five reviews cited a combined total of 62 original research articles. They included variable numbers of primary studies: Cardwell [2] 13 studies, Durán et al. [3] 7 studies, Mayer [10] 55 studies, Salahudeen [1] 38 studies and Villalba-Moreno [7] 25 studies. All reported on an association with adverse outcomes. The characteristics of the cited studies are summarised in Table 2. Sixty of the articles reported on observational studies, while the remaining two reported on randomised controlled trials. Of the 60 observational studies, 30 were cross-sectional and 30 longitudinal (including 4 database studies using primary care data). In total, 699,792 people were studied in the 62 articles, with 22,555 people recruited from the community, 6172 from a hospital (inpatients), 4253 from outpatients and 5316 from care homes or equivalents. Database studies reported data from 661,496 participants across a variety of settings. The findings of each study are summarised in Table 2.

3.2 Synthesis of Reviews

3.2.1 Anticholinergic Burden Scales

Eighteen different anticholinergic burden scales were identified between the five reviews. No single review identified all 18 anticholinergic burden scales. Nine were developed by teams in USA [30, 38, 51, 53, 67, 73, 75, 76], eight were produced by teams based in the UK [74], Israel [13], Norway [14], France [5], Italy [50], Ecuador [3] and New Zealand, [1] while one scale aimed to be international in outlook [70]. The evidence used to develop the scales varied between in vitro receptor binding testing to expert opinion and is summarised in Table 3.

3.2.2 Agreement between Scales

Salahudeen et al. [1] compared the drugs included in the Anticholinergic Drug Scale, Anticholinergic Burden Classification, Clinician-Rated Anticholinergic Score, Anticholinergic Risk Scale, Anticholinergic Cognitive Burden Scale, Anticholinergic Activity Scale and Anticholinergic

Table 1 ROBIS [12] assessment of risk of bias in included reviews

Review, year	Phase 2				Any concerns identified?	Phase 3
	(i) Study eligibility criteria	(ii) Identification and selection of studies	(iii) Data collection and study appraisal	(iv) Synthesis and findings		Risk of bias
Cardwell et al. 2015 [2]	Low	Low	Low	Low	No additional search over and above the electronic search was conducted. However, 6 databases were searched, reducing the risk of missed studies	Low
Durán et al. 2013 [3]	Low	Low	Low	Low	No formal risk of bias assessment was carried out	Low
Mayer et al..2015 [10]	Low	Low	Low	Low	Only one database used for the electronic search and no formal risk of bias assessment was made. However, these issues were appraised during the authors' discussion	Low
Salahudeen et al. 2015 [1]	Low	Low	Low	Low	No	Low
Villalba-Moreno et al. 2016 [7]	Low	Low	Low	Low	No formal risk of bias assessment carried out	Low

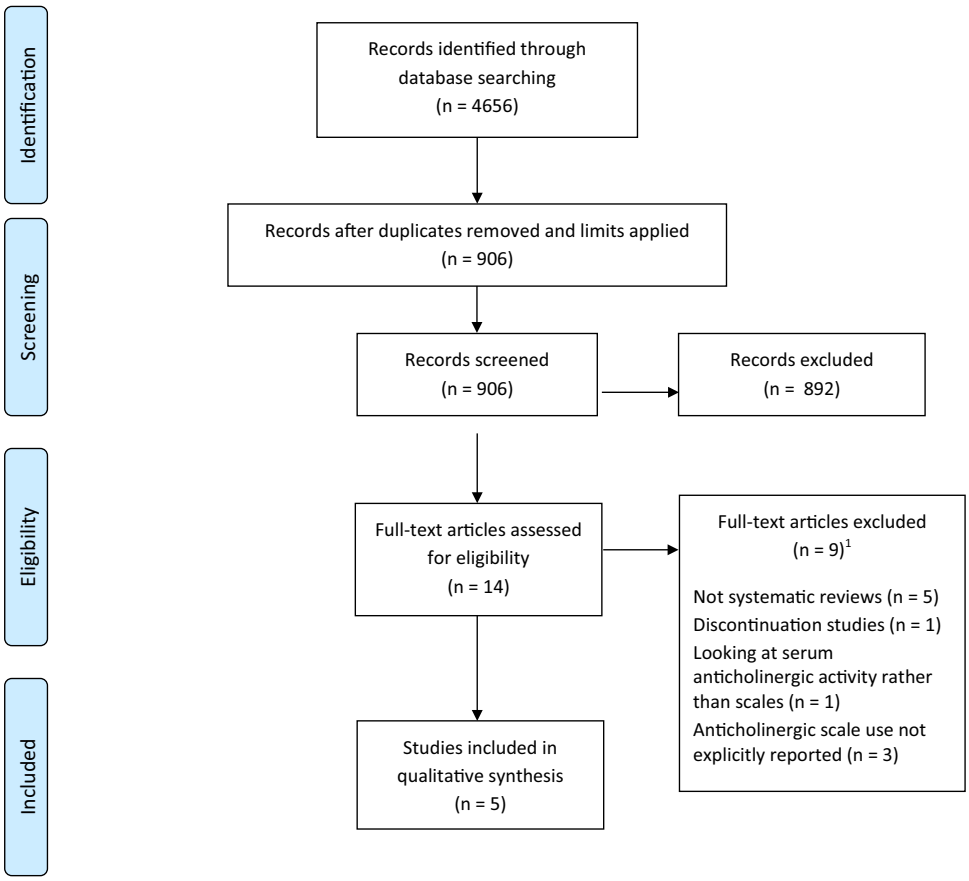

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search and study selection flowchart [11]

Table 2 Characteristics and findings of included studies

Scale	Study, year	Study design	Population	Dementia	*N*	Age (y)[a]	Duration (y)	Adverse outcome(s) studied	Association? Present (+) Absent (−)
Aizenberg's Anticholinergic Burden Scale	Aizenberg et al. 2002 [13]	Prospective	Hospital	No	414	>65	4	Falls	+
Anticholinergic Activity Scale	Ehrt et al. 2010 [14]	Longitudinal cohort	Community (PD)	No	78	74.7	8	Cognitive function	+
Anticholinergic Burden Classification	Ancelin et al. 2006 [5]	Longitudinal study	Nursing home	No	372	>60	U	Cognitive function	+
Anticholinergic Cognitive Burden Scale	Kolanowski et al., 2009 [15]	Cross sectional	Nursing home	Yes	87	>66	2.17	Quality of life	−
	Campbell et al. 2010 [16]	Longitudinal	Community	No	1652	>70	6	Cognitive function	+
	Campbell et al. 2011 [17]	Observational cohort	Hospital	No	147	>65	U	Delirium	−
	Fox et al. 2011 [18]	Longitudinal cohort	Nursing, residential, day hospital, inpatients	Yes, Alzheimer's disease	224	81 ± 7.4	1.5	Cognitive function	−
	Fox et al. 2011 [19]	Longitudinal cohort	Community dwelling and institutional	No	1304	>65	2	Cognitive function	+
								Mortality	+
	Cai et al. 2013 [20]	Retrospective cohort	Primary care clinic	No	3690	>65	1	Cognitive function	+
	Koyama et al. 2014 [21]	Prospective	Community (women)	No	1429	>75	5	Function	+
								Cognition	−
	Koyama et al., 2013 [22]	Longitudinal	Community (women)	No	1484	>75	10	Cognitive function	+
								Dementia	+
	Pasina et al. 2013 [23]	Cross sectional prospective	Hospital	No	1380	>65	0.25	Cognitive function	+
								Physical function	+
	Shah et al. 2013 [24]	Cohort study	Community (catholic clergy)	No	896	>65	10	Cognitive function	+
	Kidd et al. 2014 [25]	Retrospective	Hospital	No	419	>90	0.25	Mortality	−
								Length of stay	−
	Kashyap et al. 2014 [26]	Longitudinal cohort	Outpatient	No	102	71.9 ± 7.3	1	Cognitive function	+
	Mangoni et al. 2013 [27]	Cross-sectional	Hospital	No	71	84 ± 6	1	Mortality	−
	Lanctot et al. 2014 [28]	Cross-sectional	Outpatients with coronary artery disease	No	U	64.2 ± 9.1	NA	Attention, speed, executive function	+

Table 2 continued

Scale	Study, year	Study design	Population	Dementia	*N*	Age (y)[a]	Duration (y)	Adverse outcome(s) studied	Association? Present (+) Absent (−)
Anticholinergic Loading scale	Sittironnarit et al. 2011 [29]	Cross-sectional	Community	Yes, Alzheimer's disease	133	78 ± 8.6	1.83	Psychomotor speed and executive function	+
Anticholinergic Drug Scale	Carnahan et al. 2002 [6]	Cross-sectional	Nursing home	No	U	U	NA	SAA	+
	Carnahan et al. 2006 [30]	Cross-sectional	Long-term care residents	No	279	86	0.08	SAA	+
	Kersten et al. 2013 [31]	RCT	Nursing home	No	64	85	0.92	Cognitive function	−
	Kersten et al. 2013 [32]	Cross-sectional	Nursing home	No	87	73	1	Cognitive function	−
								Function	−
	Lampela et al. 2013 [33]	Cross-sectional	Community	No	621	>75	3	Adverse events	+
								Cognitive function	+
								Function	+
	Low et al. 2009 [34]	Longitudinal	Community	No	2058	60–64	4	Cognitive function	+
	Kashyap et al., 2014 [26]	Longitudinal cohort	Outpatient	No	102	71.9 ± 7.3	1	Cognitive function	+
	Juliebø et al. 2009 [35]	Prospective	Hospital (with hip fracture)	No	364	>65	0.01	Delirium	−
	Drag et al. 2012 [36]	Cross-sectional	Hospital	No	450	67.9 ± 10.5	0.08	Cognitive function	−
	Mangoni et al. 2013 [27]	Cross-sectional	Hospital	No	71	84 ± 6	1	Mortality	−
	Kalisch et al. 2014 [37]	Retrospective	Community (Australian veterans)	No	36,015	80	2	Risk of hospitalisation for delirium or dementia	+
Anticholinergic Risk Scale	Rudolph et al. 2008 [38]	Retrospective and prospective cohort	Hospital	No	132	>65	0.75	Central adverse effect (confusion, dizziness, falls)	+
	Rudolph et al. 2008 [38]	Retrospective and prospective cohort	Long-term care	No	117	>65	0.83	Central adverse effect (confusion, dizziness, falls)	+
	Kumpula et al. 2011 [39]	Prospective cohort	Hospital and Long-term care	No	1004	81.3	1	Mortality	−
	Lowry et al. 2011 [40]	Prospective cohort	Hospital	No	362	83.6 ± 6.6	0.42	Activities of daily living	−
								Mortality	−
								Length of stay	+
	Lowry et al. 2011 [41]	Cohort study	Hospital	No	362	83.6 ± 6.6	0.42	Institutionalisation and comorbidities	+
	Koshoedo et al. 2012 [42]	Cohort study	Rehab unit	No	117	79 ± 7	0.75	Activities of daily living	+

Table 2 continued

Scale	Study, year	Study design	Population	Dementia	*N*	Age (y)[a]	Duration (y)	Adverse outcome(s) studied	Association? Present (+) Absent (−)
	Lampela et al. 2013 [33]	Cross-sectional	Community	No	621	>75	3	Adverse events	+
								Cognitive function	+
								Function	+
	Landi et al. 2014 [43]	Cohort study	Nursing homes	No	1490	>65	1	Functional decline	+
								Falls	+
								Delirium	+
	Pasina et al. 2013 [23]	Cross sectional prospective	Hospital	No	1380	>65	0.25	Cognitive function	+
								Physical function	+
	Kashyap et al. 2014 [26]	Longitudinal cohort	Outpatient	No	102	71.9 ± 7.3	1	Cognitive function	+
	Mangoni et al. 2013 [27]	Cross-sectional	Hospital	No	71	84 ± 6	1	Mortality	−
	Huang et al. 2012 [44]	Retrospective	National Health Insurance database	No	54,888	>65	1.5	Emergency visit	+
								Hospitalisation	+
								Constipation	+
								Delirium	+
								Cardiac arrhythmia	+
								Cognitive impairment	−
	Kalisch et al. 2014 [37]	Retrospective	Community (Australian veterans)	No	36,015	80	2	Risk of hospitalisation for delirium or dementia	+
	Bostock et al. 2013 [45]	Prospective observational	Hospital	No	271	U	U	Activities of daily living	+
								Cognitive function	−
	Dispennette et al. 2014 [46]	Retrospective	Vulnerable patients	No	229	>65	NA	Risk of readmission	+
	Teramura-Gronblad et al. 2011 [47]	Cross-sectional	Nursing homes	No	1475	81.7 ± 7.6	NA	Psychological well-being	+
	Zimmerman et al. 2014 [4]	Cross-sectional	Inpatients (palliative)	No	217	72.9 ± 12.8	NA	Delirium	+
	Walter et al. 2014 [48]	Retrospective	Outpatients	No	125	?	NA	Failed post-operative void trial	+
Cancelli's Anticholinergic Burden Scale	Cancelli et al. 2008 [49]	Retrospective	Dementia centre (outpatients)	Yes, Alzheimer's disease	230	77 ± 6	NA	Psychosis	+
	Cancelli et al. 2008 [50]	Cross-sectional	Community	No	750	>65	NA	Cognitive impairment	+
Chew's list	Lampela et al. 2013 [33]	Cross-sectional	Community	No	621	>75	3	Cognitive function	+
								Function	+
	Chew et al. 2008 [51]	Cross-sectional	In vitro	No	107	NA	NA	Anticholinergic activity in vitro	
	Jessen et al. 2010 [52]	Cohort	Community	No	2605	>75	4.5	Dementia risk	+

Table 2 continued

Scale	Study, year	Study design	Population	Dementia	*N*	Age (y)[a]	Duration (y)	Adverse outcome(s) studied	Association? Present (+) Absent (−)
Clinician-Rated Anticholinergic Score	Han et al. 2008 [53]	Prospective cohort	Community	No	544	>65	2	Cognitive function	+
								Function	+
	Agar et al., 2009 [54]	RCT	Palliative care	No	461	71	0.17	Quality of life	+
								Functional outcome	+
	Yeh et al. 2013 [55]	Prospective cohort	Veteran dementia care home	Dementia	53	83.4	0.23	Cognitive function	−
	Han et al. 2001 [56]	Longitudinal observational study	Hospital	No	278	83.4 ± 7.3	0.06	Delirium symptom	−
								Dementia diagnosis	−
Drug Burden Index	Best et al. 2013 [57]	Cross-sectional	Hospital	No	329	>65	NA	Delirium	+
	Gnjidic et al. 2009 [58]	Cross-sectional	Community	No	1705	76.9 ± 5.5	NA	Physical function	+
	Gnjidic et al. February 2012 [59]	Cross-sectional	Self-care retirement homes	No	115	>70	NA	Physical function	+
	Gnjidic et al. April 2012 [60]	Cross-sectional	Community	No	887	>70	NA	Cognitive function	−
	Gnjidic et al. August 2012 [61]	Cross-sectional	Community	No	700	>75	NA	Physical function	+
	Gnjidic et al. 2014 [62]	Retrospective cohort	Community/database	Yes, 16,603 with Alzheimer's disease	33,206	>65	U	Mortality	+
								Hospitalisation	+
	Wilson et al. 2012, 2011, 2010 [63–65]	Retrospective	Nursing home	No	602	>70	NA	Mortality	−
								Falls	+
								Balance and walking speed	−
	Bostock et al. 2013 [45]	Prospective observational	Hospital	No	271	U	U	Activities of daily living	+
								Cognitive function	−
	Cao et al. 2008 [66]	Cross-sectional	Community	No	932	>65	NA	Physical performance	+
	Hilmer et al. 2007 [67]	Cross-sectional	Community	No	3075	>70	NA	Physical status	+
								Cognitive function	+
	Dispennette et al. 2014 [46]	Retrospective	Vulnerable patients	No	229	>65	NA	Risk of readmission	+
	Mangoni et al. 2013 [27]	Cross-sectional	Hospital	No	71	84 ± 6	1	Mortality	−
	Lowry et al. 2012 [68]	Prospective cohort	Hospital	No	362	83.6 ± 6.6	0.42	Activities of daily living	−
								Mortality	−
								Length of stay	+

Table 2 continued

Scale	Study, year	Study design	Population	Dementia	*N*	Age (y)[a]	Duration (y)	Adverse outcome(s) studied	Association? Present (+) Absent (−)
	Lönnroos et al. 2012 [69]	Prospective observational cohort	Community	No	339	81.0 ± 6.6	1	Hospitalisation	+
	Dauphinot et al. 2014 [70]	Longitudinal observational cohort	Hospital	No	337	85.4 ± 6.6	0.97	Mortality	−
								Falls	+
	Nishtala et al. 2014 [71]	Cross-sectional	Community/database	No	537,387	>65	NA	Falls-related hospitalisation	+
								GP visits	+
								Mortality	+
	Bosboom et al. 2012 [72]	Cross-sectional	Care homes	Yes	351	>65	NA	Quality of life	+
Drug Burden Index—World Health Organization	Dauphinot et al., 2014 [70]	Longitudinal observational cohort	Hospital	No	337	85.4 ± 6.6	0.97	Mortality	−
Minzenberg—Clinical Index and Pharmacological Index	Minzenberg et al. 2004 [73]	Cross-sectional	Outpatients with schizophrenia	No	106	39.9 ± 11.3	NA	Simple attention	−
								Complex attention	+
								Short-term memory	+
								Delayed recall	+
								Semantic memory	+
								Working memory	−
								Executive functions	−
								Factor scores (declarative memory)	+
Summers' drug risk number	Han et al. 2001 [56]	Longitudinal observational study	Hospital	No	278	83.4 ± 7.3	0.06	Delirium symptom	−
								Dementia diagnosis	−
Whalley's Anticholinergic Burden Scale	Whalley et al. 2012 [74]	Longitudinal observational study	Community	No	281	77–78	10	Cognitive impairment	+
								Developing dementia	−

Data are mean ± standard deviation unless stated otherwise

GP general practitioner, *NA* not applicable, *RCT* randomised controlled trial, *SAA* serum anticholinergic activity, *U* unknown or data unavailable

Table 3 Characteristics of and rationale behind the identified anticholinergic burden scales

Scale	Study, year	Country	Scoring range	Scoring criteria				
				Receptor bonding/serum anticholinergic activity	Laboratory data	Anticholinergic effect	Expert opinion	Systematic review + synthesis
Aizenberg's Anticholinergic Burden Scale	Aizenberg et al. 2002 [13]	Israel	0–5			X		
Anticholinergic Activity Scale	Ehrt et al. 2010 [14]	Norway	0–4	X			X	
Anticholinergic Burden Classification	Ancelin et al. 2006 [5]	France	0–3	X			X	
Anticholinergic Cognitive Burden Scale	Boustani et al. 2008 [75]	USA	0–3	X		X	X	
Anticholinergic Loading Scale	Sittironnarit et al. 2011 [29]	Australia	0–3	X			X	
Anticholinergic Drug Scale	Carnahan et al. 2006 [30]	USA	0–3			X		
Anticholinergic Risk Scale	Rudolph et al. 2008 [38]	USA	0–3			X	X	
Cancelli's Anticholinergic Burden Scale	Cancelli et al. 2008 [50]	Italy	0–3			X	X	
Chew's list	Chew et al. 2008 [51]	USA	0–4	X				
Clinician-Rated Anticholinergic Score	Han et al. 2008 [53]	USA	0–3		X	X	X	
Drug Burden Index (anticholinergic component)[a]	Hilmer et al. 2007 [67]	USA	0–1					
Drug Burden Index—World Health Organization[a]	Dauphinot et al. 2014 [70]	International	0–1					
Durán's Anticholinergic Burden Scale	Durán et al. 2013 [3]	Ecuador	0–3					X
Minzenberg—Clinical Index and Pharmacological Index	Minzenberg et al. 2004 [73]	USA	1–228			X	X	
Minzenberg—Clinical Index and Pharmacological Index	Minzenberg et al. 2004 [73]	USA	0.7–1470	X				
Salahudeen's Anticholinergic Burden Scale	Salahudeen et al. 2015 [1]	New Zealand	High, moderate, low	X				X
Summers' Drug risk number	Summers et al. 1978 [76]	USA	0–3	X				
Whalley's Anticholinergic Burden Scale	Whalley et al. 2012 [74]	UK	0–3	X			X	

[a]The Drug Burden Index is calculated using prescribed and recommended doses of medications. The medications composing the anticholinergic component of the scale were identified using Mosby's Drug Consult [77] and the Physicians' Desk Ref. [78]

Table 4 Anticholinergic burden scales used in people with dementia

Scale	Total populations with dementia studied	Setting(s)	Association with outcome events	No association with outcome events
Anticholinergic Cognitive Burden Scale	1207	Care homes, inpatients	Cognitive function	Quality of life, cognitive function
Anticholinergic Loading Scale	133	Community	Psychomotor speed and executive function	
Cancelli's Anticholinergic Burden Scale	230	Outpatients	Psychosis	
Clinician-Rated Anticholinergic Score	53	Veteran home		Cognitive function
Drug Burden Index	351 (16.603)	Care homes, (database)	Mortality, hospitalisation, quality of life	

Loading Scale. Out of 195 medications, 34 (17%) were scored differently in different scales and 12 (6%) were scored as having low anticholinergic effect in at least one scale but having high anticholinergic activity in another.

3.2.3 Population Sizes

The Drug Burden Index was used to quantify the anticholinergic burden in the largest number of participants, followed by the Anticholinergic Risk Scale, Anticholinergic Drug Scale and Anticholinergic Cognitive Burden Scale while the Anticholinergic Activity Scale was applied in the smallest population. Table S2 of the ESM summarises the numbers of participants assessed using the different scales.

3.2.4 Population Settings

The reviews identified studies conducted in a number of different settings; with some conducted in multiple settings. These included the community [8, 14, 16, 18–22, 24, 29, 33, 34, 37, 52, 53, 58, 66, 67, 69, 74, 79] (21), hospital [4, 13, 17, 23, 25, 27, 35–41, 45, 46, 56, 57, 68, 70] (19), outpatients [18, 26, 28, 48, 49, 73] (6), care homes (or equivalents) [5, 6, 15, 18, 19, 30–32, 38, 39, 42, 43, 47, 55, 59, 63–65, 72] (19) and databases [37, 44, 62, 71] (4).

The Drug Burden Index was the most commonly used scale in the community and in database studies, while the Anticholinergic Risk Scale dominated in care homes and hospital settings. Table S3 of the ESM summarises the numbers of participants assessed using the different scales.

3.2.5 Dementia

Eight out of the 62 studies involved populations where all participants had dementia. The Drug Burden Index was the most commonly used scale followed by the Anticholinergic Cognitive Burden Scale. Table 4 shows a further breakdown.

3.2.6 Association with Adverse Outcomes

Of the studies reporting outcomes related to falls and hospitalisation, all reported an association with anticholinergic burden. Of the studies reporting mortality, delirium and physical function outcomes, the majority found an association with anticholinergic burden. Of the studies reporting on cognitive function, the majority showed no association with anticholinergic burden. Table 5 shows further details.

4 Discussion

This review of reviews has demonstrated that multiple different scales have been developed to quantify anticholinergic burden. These have been developed variously based on expert opinion, clinical anticholinergic effects and in vitro testing. They have been applied to outpatients, inpatients, community dwellers and care home residents and in database studies. The Drug Burden Index was the most frequently used scale/tool as reported by these studies. More studies reported an association between increasing anticholinergic burden and falls, hospitalisation, mortality and physical function than those that did not. Although more studies reported an association with cognitive function than those that did not, the studies reporting no association involved more participants.

This review identified studies using 18 different anticholinergic burden scales, more than any of the individual reviews, [1–3, 7, 10] suggesting that this approach has been more comprehensive. The individual studies identified as part of this review occurred in a number of different settings and included a number of large scale database/

Table 5 Association between anticholinergic burden and outcomes

Outcome	Scale(s)	Studies	N studies; involving N participants (association)	N studies; involving N participants (no association)
Falls	Aizenberg's Anticholinergic Burden Scale	7	7; 540,479	0; 0
	Anticholinergic Risk Scale			
	Drug Burden Index			
Hospitalisation	Anticholinergic Drug Scale	8	8; 698,308	0; 0
	Anticholinergic Risk Scale			
	Drug Burden Index			
Mortality	Anticholinergic Cognitive Burden Scale	9	3; 571,897	6; 2193
	Anticholinergic Drug Scale			
	Anticholinergic Risk Scale			
	Drug Burden Index – World Health Organisation			
	Drug Burden Index			
Delirium	Anticholinergic Cognitive Burden Scale	8	5; 57,154	3; 789
	Anticholinergic Drug Scale			
	Anticholinergic Risk Scale			
	Cancelli's Anticholinergic Burden Scale			
	Clinician-Rated Anticholinergic Score			
	Summers' Drug Risk Number			
	Drug Burden Index			
Cognitive function	Anticholinergic Activity Scale	24	16; 17,666	8; 58,082
	Anticholinergic Burden Classification			
	Anticholinergic Cognitive Burden Scale			
	Anticholinergic Drug Scale			
	Anticholinergic Risk Scale			
	Cancelli's Anticholinergic Burden Scale			
	Clinician-Rated Anticholinergic Score			
	Drug Burden Index			
	Whalley's Anticholinergic Burden Scale			
Physical function	Anticholinergic Cognitive Burden Scale	16	12; 12,840	4; 1051
	Anticholinergic Drug Scale			
	Anticholinergic Risk Scale			
	Chew's list			
	Clinician-Rated Anticholinergic Score			
	Drug Burden Index			

population studies. Findings drawn from these data are therefore likely to be applicable in a number of different settings.

The chief limitation of the approach taken in this review is the potential for bias introduced by including only previous reviews, rather than seeking out newer empirical studies published in the interim. Some potentially pertinent studies may have been missed by this method and since the completion of this review we have become aware of one such example [80]. However, this potential has been mitigated to a degree by the number of reviews included and their recent publication dates. In addition, the primary focus of this review was to identify existent scales rather than to assess the association between anticholinergic burden and outcomes. We have chosen to present data on the association with outcomes where it has been reported in the included reviews. However, reviews whose principal aim was to examine this association were not included and this does potentially introduce bias. This is mitigated to a degree by the large number of included studies. Finally, the use of only a single reviewer was not ideal and this may have increased the risk of missing relevant studies. However, the fact that this review identified more anticholinergic burden scales than any of the individual reviews suggests this is unlikely to have been a significant problem.

Anticholinergic burden in older people has been studied extensively; [1, 3] however, the variation in anticholinergic burden scales used, the metrics used to assess outcomes and the outcomes themselves make it challenging to synthesise the data. The reviews all concluded that there is a lack of a universal approach to assessing anticholinergic burden, which handicaps the interpretation of any findings. The different scales include different drugs and attribute markedly different anticholinergic activity to the same drugs [3]. Salahudeen et al. [1] and Durán et al. [3] both propose new scales derived from synthesis of the existing scales but at the time of this review of reviews these had not been tested.

A larger population had been assessed using the Drug Burden Index than any other anticholinergic burden scale because of its use in database studies and it has been shown to be associated with a number of outcomes of interest [71]. However, the approach is more time consuming than other anticholinergic burden scales and copyright restrictions on the use of the 'Drug Burden Index Calculator', which limits its use to registered Australian healthcare practitioners, [81] inevitably curbs its potential widespread application. Discounting the Drug Burden Index, the Anticholinergic Risk Scale was the most frequently used scale in care home and inpatient studies, while the Anticholinergic Cognitive Burden Scale was the most frequently used in community dwellers and in people with dementia. Both the Anticholinergic Risk Scale and Anticholinergic Cognitive Burden Scale were associated with outcomes of interest, although within the studies examining people with dementia, the association between anticholinergic burden and outcomes was variable and inconsistent. The lack of a clear association between anticholinergic burden and cognitive outcomes was surprising and is an area that warrants closer investigation.

5 Conclusion

There are at least 18 anticholinergic burden scales. These scales vary in their derivation, content and rating of the anticholinergic activity of the same medications. Although the Drug Burden Index has been most extensively used, there are practical considerations that limit its implementation. Of the remaining scales, the Anticholinergic Risk Scale and Anticholinergic Cognitive Burden scale have the most experience in rating anticholinergic burden in care home residents and people with dementia, respectively. The Anticholinergic Risk Scale shows an association with relevant clinical outcomes while the data for the Anticholinergic Cognitive Burden scale in people with dementia are mixed.

Although the approach has been hampered by methodological issues, this review has suggested that the evidence of an association between anticholinergic burden and adverse outcomes is not as clear cut as some authors have suggested. Two avenues of enquiry will need to be pursued to help clarify the association between anticholinergic burden and outcomes. First, a formal systematic review of the use of anticholinergic burden scales as reported in original research articles with particular focus placed on the quality of the evidence is needed. Second, additional empirical research testing the use of the most evidence-based scales in their appropriate clinical context is needed to better understand whether the differences in classification and weighting of anticholinergic effects in different scales are justified. By combining these two approaches, greater clarity on the association between anticholinergic burden, as reported by anticholinergic burden scales, and outcomes will be achieved.

Compliance with Ethical Standards

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