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**Anticholinergic drug burden tools/scales and adverse outcomes in different clinical settings: a systematic review of reviews**

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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 (HDAS) 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 pre-defined 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. 18 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. Association between anticholinergic burden and clinical outcomes varied by index and study. Falls and hospitalisation were consistently found to associate 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.

**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 research 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 to 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 and colleagues identifying seven[1] and Mayer and colleagues identifying 12[10]. In addition there was variation in the authors’ views on the appropriateness of the different scales/tools with Cardwell and colleagues advocating the use of the Drug Burden Index[2] while Salahudeen and colleagues identified the Anticholinergic Cognitive Burden Scale as the most frequently validated scale[1]. In order 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:

1. 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.
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 (PRISMA)[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 Healthcare Databases Advanced Search (HDAS) of Medline, Embase, Cochrane, CINAHL and PsycINFO from inception to October 2016 for relevant articles. The last full search was run on the 24th of 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 Electronic Supplementary Material Appendix S1. 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 Electronic Supplementary Material Table S1.

**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: (i) the anticholinergic burden scales used (ii) information on the scales’ rationale (iii) the number of participants evaluated using the different scales (iv) 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) (v) (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 which 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: (i) study eligibility criteria, (ii) identification and selection of studies, (iii) data collection and study appraisal and (iv) 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**

4656 articles were identified by the search. 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 5 were included after detailed review revealed that 9 articles did not meet the inclusion criteria (Figure 1).

**Figure 1** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) literature search and study selection flow chart[11]

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

|  |  |  |  |
| --- | --- | --- | --- |
| Review | 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.[2] (2015) | 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 |
| Duran et al.[3] (2013) | Low | Low | Low | Low | No formal risk of bias assessment was carried out. | Low |
| Mayer et al.[10] (2015) | 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. [1] (2015) | Low | Low | Low | Low | No | Low |
| Villalba-Moreno et al. [7] 2016 | Low | Low | Low | Low | No formal risk of bias assessment carried out. | Low |

**3.1 Characteristics of included reviews**

Four of the review articles set out 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 set out 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, Duran[3] 7 studies, Mayer[10] 55 studies, Salahudeen[1] 38 studies and Villalba-Moreno[7] 25 studies. All reported on association with adverse outcomes. The characteristics of the cited studies are summarised in table 2. 60 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). 699,792 people were studied in the 62 articles. 22,555 people were recruited from the community, 6172 from 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.

**Table 2 Characteristics and findings of included studies**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Scale** | **Study** | **Study design** | **Population** | **Dementia** | **N** | **Age (years)a** | **Duration (years)**  | **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 a. 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 | + |
| **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  | 36015 | 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  | + |
| 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  | 54888 | >65 | 1.5 | Emergency visit | + |
| Hospitalisation | + |
| Constipation | + |
| Delirium | + |
| Cardiac arrhythmia | + |
| Cognitive impairment | - |
| Kalisch et al. 2014[37] | Retrospective | Community (Australian veterans) | No  | 36015 | 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 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 | + |
| **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 Feb 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 Aug 2012[61] | Cross-sectional | Community | No  | 700 | >75 | NA | Physical function | + |
| Gnjidic et al 2014[62] | Retrospective cohort | Community / database | Yes - 16603 with Alzheimer’s disease | 33206 | >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 | + |
| 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  | 537387 | >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 Organisation**  | 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 ± SD unless stated otherwise

Key: NA= Not applicable, SAA= serum anticholinergic activity, U= Unknown or data unavailable.

**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 the 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.

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Scale** | **Study** | **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)\*** | Hilmer et al.2007[67] | USA | 0-1 |  |  |  |  |  |
| **Drug Burden Index – World Health Organisation\***  | Dauphinot et al. 2014[70] | International | 0-1 |  |  |  |  |  |
| **Duran’s Anticholinergic Burden scale**  | Duran 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 |  |

\* 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 Reference[78].*

**3.2.2 Agreement between scales**

Salahudeen and colleagues 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 Loading Scale[1]. 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. Electronic Supplementary table S2summarises the numbers of participants assessed using the different scales.

**3.2.4 Population settings**

The reviews identified studies which were 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. Electronic Supplementary table S3 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 further breakdown.

**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(16603) | Care homes, (database) | Mortality, hospitalisation, quality of life. |  |

**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.

**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 Burdenscale Anticholinergic Risk Scale Drug Burden Index  | 7 | 7, 540479 | 0,0 |
| **Hospitalisation** | Anticholinergic Drug Scale Anticholinergic Risk Scale Drug Burden Index  | 8 | 8,698308 | 0,0 |
| **Mortality** | Anticholinergic Cognitive Burden scale Anticholinergic Drug Scale Anticholinergic Risk Scale Drug Burden Index – World Health Organisation Drug Burden Index  | 9 | 3,571897 | 6,2193 |
| **Delirium** | Anticholinergic Cognitive Burden scale Anticholinergic Drug Scale Anticholinergic Risk Scale Cancelli’sAnticholinergic Burden scale Clinician-rated Anticholinergic ScoreSummers’ Drug Risk Number Drug Burden Index  | 8 | 5,57154 | 3,789 |
| **Cognitive function** | Anticholinergic Activity Scale 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 | 24 | 16,17666 | 8,58082 |
| **Physical function**  | Anticholinergic Cognitive Burden scale Anticholinergic Drug Scale Anticholinergic Risk Scale Chew’s listClinician-rated Anticholinergic Score Drug Burden Index  | 16 | 12,12840 | 4,1051 |

**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, 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/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 the 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 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 interpretation of any findings. The different scales include different drugs and attribute markedly different anticholinergic activity to the same drugs[3]. Salahudeen and colleagues[1] and Duran[3] and colleagues 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 due to 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 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 which 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 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 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. Firstly, 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. Secondly, 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.

6. Compliance with Ethical Standards

6.1 Funding

No sources of funding were used to assist in the preparation of this article.

6.2 Conflicts of Interest

Tomas Welsh, Veronika Van der Wardt, Grace Ojo, Adam Gordon and John Gladman declare that they have no conflicts of interest relevant to the content of this review.

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