Review Article

Anticholinergic Burden Measures Predict Older People's Physical Function and Quality of Life: A Systematic Review

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Abstract

Objectives

This systematic review (PROSPERO CRD42019115918) compared the evidence behind anticholinergic burden (ACB) measures and their ability to predict changes in older people's physical function and quality of life.

Design

Eligible cohort or case-control studies were identified systematically using comprehensive search terms and a validated search filter for prognostic studies. Medline (OVID), EMBASE (OVID), CINAHL (EMBSCO), and PsycINFO (OVID) databases were searched. Risk of bias, using Quality in Prognosis Studies tool, and quality of evidence, using the Grading of Recommendations, Assessment, Development and Evaluation ~~GRADE~~, were assessed.

Setting and Participants

People age 65 years and older from any clinical setting.

Measures

Any ACB measures were accepted (including the anticholinergic domain of the Drug Burden Index). Any global/ multidimensional measure for physical function and/ or quality of life was accepted for outcome.

Results

Thirteen studies reporting associations between ACB and physical function (n = 10) or quality of life (n = 4) were included. Exposure measures included Anticholinergic Cognitive Burden Scale, Anticholinergic Drug Scale, Anticholinergic Risk Scale, Clinician Rated Anticholinergic Score, and the anticholinergic domain of the Drug Burden Index. All studies were rated moderate risk of bias in ≥2 ~~QUIPS~~Quality in Prognosis Studies categories with 5 rated high risk in ≥1 categories. Seven of 10 studies (5251 of 7569 participants) reported significant decline in physical function with increased burden. All 4 studies (2635 participants) reporting quality of life demonstrated similar association with increased burden. High risk of biases and inadequate data reporting restricted analysis. There was no evidence to support one measure being superior to another.

Conclusions and Implications

The evidence supports association between increased ACB and future impairments in physical function and quality of life. No conclusion can be made regarding which ACB measure has the best prognostic value. Well-designed longitudinal studies are required to address this. Clinicians should be aware of patient's anticholinergic burden and consider alternative medications where appropriate.

Keywords: Anticholinergics; adverse outcomes; prognostic study; older adults; measurement scales

Physical function and quality of life are 2 important health outcomes for older people.[1] Physical function focuses upon an individual's activities and participation, particularly in relation to what would be considered normal general daily tasks, self-care activities, and participation in community and social interactions.[2] Quality of life overlaps this, defined as “a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships, and their relationship to salient features of their environment.”[3] Quality of life is concerned more with the impact of activity and participation limitations upon well-being.[4] Both outcomes are considered key research priorities by both older people and health professionals.[1]

Understanding what influences these outcomes is important; factors which are modifiable can be targeted to improve older people's physical function and quality of life. One potentially important factor is anticholinergic burden (ACB),[5,6] the accumulation of anticholinergic effects from one or more anticholinergic medications.[7,8] Medications with anticholinergic properties are prescribed for a range of common problems in older age, including urinary incontinence, depression, and gastrointestinal complaints.[8,9] Side-effects include confusion, constipation, delirium, dizziness, drowsiness, and dry mouth.[8,9] Studies estimate up to 50% of community-dwelling older adults use one or more anticholinergic medications.[10,11] However, in addition to being the greatest consumers of anticholinergic medications, older people are more susceptible to side effects and adverse outcomes.[8] To date, although a number of reviews in this area have included older people, few reviews have specifically restricted inclusion and analysis to older people. Therefore, there is an urgent need to understand anticholinergic use and its consequences within the older adult population.

Several factors presently limit advancing knowledge in this area, not least study design and choice of ACB measure. Our previous (unpublished) research identified 14 ACB measures reported in the literature. The variation in ACB measures makes interpretation challenging; the ACB measures differ substantially.[12,13] The number of medications assessed in each scale varies from 27 in the ACB Classification to 117 in the Anticholinergic Drug Scale (ADS).[13] The potency score for individual medications also varies between scales.[13] For example, Nortriptyline is rated as having high anticholinergic activity by Boustani et al (2008) in the Anticholinergic Cognitive Burden Scale[14] but moderate by Rudolph et al (2008) in the Anticholinergic Risk Scale (ARS).[15] As yet no evidence provides clear rationale to support use of one measure above another. In addition, many reviews have included cross-sectional study designs, restricting our understanding of the temporal relationship between ACB and future outcomes. There is a need to explore the ability of individual ACB measures to predict these outcomes and identify if one ACB measure performs better than another. Understanding the prognostic utility of ACB measures will enhance future outcome reporting for trials seeking to reduce ACB.

This systematic review aims to describe the association of individual ACB measures with physical function and quality of life, and to compare the prognostic utility of ACB measures.

Methods

This PROSPERO registered systematic review (CRD42019115918, Available at: http://www.crd.york.ac.uk/PROSPERO) was conducted using the Cochrane Prognostic Review Group Framework for Prognostic Reviews (https://methods.cochrane.org/prognosis/our-publications)[16] and reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Supplementary File 1 for PRISMA Checklist).

Literature Search Strategy

The search strategy was developed following extensive scoping searches to identify appropriate MeSH and other controlled vocabulary for ACB and ACB measures. We employed a validated search filter for the identification of prognostic studies.[17] The strategy was modified to suit each database searched [MEDLINE (Ovid), EMBASE (Ovid), CINAHL (EBSCO), and PsycINFO (Ovid)]. Searches were from January 1, 2006 to March 4, 2020. The 2006 inception was chosen as the time when ACB was first conceptualized and studied. The full strategy is reported in our Supplementary File 1.

Inclusion Criteria

The following criteria were applied to identify appropriate studies: (1) Report a prospective or retrospective observational study (longitudinal cohort or case-control); (2) Involve adults age ≥65 years (or mean age ≥65 years); (3) Assess ACB exposure using any ACB measure [to include anticholinergic (Ach) domain of the Drug Burden Index (DBI)]; (4) Any length of follow-up period; and (5) Report any global/ multi-dimensional measure of physical function and/ or quality of life as an outcome.

Exclusion Criteria

The following exclusion criteria were applied: (1) Studies restricted to measuring classes of or specific anticholinergic medications (eg, psychotropics); and (2) Measure of medications not specifically directed at anticholinergic drugs (eg, Beers criteria).

Study Selection Process

Searches were conducted on the November 16, 2018, then updated on March 4, 2020 and identified studies transferred to Covidence systematic review software 2019 (Veritas Health Innovation Ltd,Melbourne Australia, www.covidence.org). After duplicates were removed, 13,394 studies remained. These were then screened by title and abstract by 2 independent reviewers (shared between C.S., K.Y., M.K.). Both primary reviewers had to agree upon exclusion and, where this was not the case, a third independent reviewer made the final decision (T.Q.). The full text of remaining studies (n = 124) were screened by 2 independent reviewers (shared between C.S., K.Y., M.K.). Again, a third independent reviewer resolved any disagreements (T.Q.). Exclusion reasons are reported in the identified PRISMA flow chart (Supplementary File 1). Reference lists of included studies were searched, and citations via PubMed reviewed, to check for studies our search had omitted. Reference lists and citations of recent seminal articles[13,18] were also searched. No additional studies for inclusion were identified. Thirteen articles remained that reported physical function or quality of life as an outcome.

Data Collection and Extraction

A data extraction template was developed in accordance with guidance by the Cochrane Prognostic Review Group framework (https://methods.cochrane.org/prognosis/our-publications).[16] This included study characteristics (eg, year of publication, country, study setting), measures assessed, timing and methods of assessments, statistical plan, confounders/ adjustments and results. Two reviewers (shared between C.S., K.Y., M.K.) independently extracted data and a third reviewer arbitrated any disagreements (T.Q.). Data were then transferred to a Microsoft Excel 2016 (Microsoft Corporation, California, USA, https://products.office.com/en-gb/excel) sheet and imported to Comprehensive Meta-Analysis v 3.3.070 (Biostat, New Jersey, USA, https://www.meta-analysis.com/) for analysis.

Risk of Bias

Risk of bias for each included study was assessed using the Quality in Prognosis Studies tool, developed by the Cochrane Prognosis Methods Group (QUIPS, Available at: https://methods.cochrane.org/sites/methods.cochrane.org.prognosis/files/public/uploads/QUIPS%20tool.pdf).[19] Risk of bias is assessed across 6 domains: study participation, attrition, prognostic measurement, outcome measurement, study confounding, and statistical analysis. As recommended, we took the QUIPS anchoring statement and modified the wording to suit our review question. We agreed to accept any baseline measure of ACB and for statistical analysis we agreed within the research team a minimum level of adjustment (set of confounders) that would constitute high quality (discussed further below). Assessments were conducted by those who completed data extraction (C.S., K.Y., M.K.) and any disagreements arbitrated by a third reviewer (T.Q.). Publication bias was planned to be assessed by way of funnel plot.

Analysis

All included studies underwent narrative analysis following the guidance provided by the European Social Research Council.[20] Findings were assessed qualitatively considering clinical heterogeneity and the risk of biases. Patterns of associations across the studies were also explored and described. Association data extracted included odds ratios, risk ratios, their respective confidence intervals, β values, standard error, and *P* values, where reported. Baseline and follow-up scores for ACB and relevant outcome were recorded if reported. Pooled analysis was planned with summary statistics where possible for both adjusted and unadjusted data.

Which factors and what constitutes minimum adjustment were determined by consensus, using a Delphi approach involving the senior authors (C.S., R.S., Y.L., P.M.). It was agreed after one round that minimum adjustment would be age and sex and ≥1 comorbidities (or a global measure of the number of comorbidities). Where possible forest plots and meta-analyses using random effects modeling techniques were planned to graphically and statistically demonstrate the body of evidence. Results were analyzed according to our hierarchy of research questions: (1) Prognostic utility of individual ACB measures for each outcome of interest (all measures for either physical function or quality of life combined); and (2) Comparison of prognostic utilities of ACB measures for each outcome of interest (all measures for either physical function or quality of life combined)

Quality Assessment

The the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) assessment tool was used to determine the quality of the body of evidence for each scale and outcome. The GRADE approach assesses the evidence across all studies analyzed for a given outcome, rather than assessing the evidence from each study individually.[21] The GRADE framework allows the quality of the evidence to be judged across criteria known to limit the quality of evidence.[21] Guidance for applying GRADE to prognostic studies was taken from Huguet et al (2013).[22] Quality was assessed across 7 criteria; study limitations, inconsistency, indirectness, imprecision, publication bias, effect size, and dose-effect. Further details regarding these criteria can be found on the GRADE website (http://www.gradeworkinggroup.org).

Results

Of the 13 studies,[23–35] 10 reported associations between ACB and physical function[23,24,26,27,29–34] and 4 reported associations with quality of life.[23,25,28,35] One study[23] is reported twice as it reports both outcomes. Five measures for ACB exposure were included Anticholinergic Cognitive Burden Scale (ACBS), ADS [modified Clinician Rated Anticholinergic Score (mCRAS)], ARS, CRAS, and the DBI-Ach. Each scale was developed within the United States. The ACBS assesses 88 medications considered by expert opinion to have anticholinergic properties which have significant impact upon cognition.[24] The ADS assesses 117 medications which are scored based on each medications serum anticholinergic activity as published in the existing literature.[13,35] The ADS was originally known as the modified Clinician Rated Anticholinergic Score.[13] The ARS assesses 49 medications considered to have anticholinergic properties which have significant impact on both cognitive and physical function.[24] The Clinician Rated Anticholinergic Score assess 60 medications, identified from several ACB scales, considered strongly implicated in the development of delirium.[13,26] The anticholinergic domain of the DBI is somewhat different from other ACB measures in that it considers dose and duration of use of individual anticholinergic medications.[28] It was also developed based upon existing literature and expert opinion.[28]

Physical Function

Descriptive details for each study are presented in Table 1. In total 7569 older people participated across the 10 studies, with mean (± standard deviation) ages ranging from 71.9 (12.0) years[23] to 86.1 (6.8) years.[29] Three studies were conducted in Italy,[24,32,34] 3 in the US,[26,29,31] and 1 each from Australia,[23] Israel,[27] Spain,[33] and the United Kingodm.[30]

Table 1 Characteristics of Studies Reporting Association Between ACB and Physical Function (n = 10) and QoL (n = 4)

Studies	Design	n	Age, y (Mean, SD)	Sex Male (n, %)	Country	Setting	Follow-Up Duration	ACB Measure	Function Measure	QoL Measure
Agar et al 2009[23]	Prospective	461*	71.9 (12.0)	232 (50.0)	Australia	Palliative care	Death (mean 107 d)	CRAS	AKPS	MQoL
Brombo et al 2018[24]	Retrospective	1123	81.0 (7.4)	494 (44.0)	Italy	Acute care (hospital)	1 y	ARS and ACBS	ADL (Katz)	–
Cossette et al 2017[25]	Prospective	1793	74.4 (4.2)	853 (48)	Canada	Community	36 mo	ACBS, ADS and ARS	–	SF-36
Han et al 2008[26]	Prospective	544	74.4 (5.2)	544 (100.0)	USA	Primary care clinic	1 y	mCRAS	IADL (OARS)	–
Hershkovitz et al 2018[27]	Retrospective	869	83.4 (6.9)†	41 (20.2)	Israel	Geriatric rehabilitation center	Discharge (mean NR)	ACBS	FIM	–
Ie et al 2017[28]	Retrospective	426	78.6 (6.72)	48 (11.3)	USA	Care homes and Community	12 mo	ACBS and DBI-Ach	–	EQ-5D
Kolanowski et al 2015[29]	Prospective	99	86.1 (6.8)	22 (32.0)	USA	Post-acute care (hospital)	Discharge (mean NR)	ACBS	BI	–
Koshoedo et al 2012[30]	Prospective	105	79.0 (7.0)	29 (25.0)	UK	Orthopedic rehabilitation unit	Discharge (mean 15 d)	ARS	BI	–
Koyama et al 2014[31]	Prospective	1429	83.0 (3.1)	0 (0.0)	USA	Community	5 y	ACBS	IADL (NS)	–
Landi et al 2014[32]	Prospective	1490	83.6 (65.1_106.4)‡	425 (28.5)	Italy	Nursing home	1 y	ARS	ADL (MDS-HC)	–
Lopez-Matons et al	Retrospective	126	80.0 (6.7)	28 (27.8)	Spain	Geriatric clinic (hospital)	1 y	ACBS	BI	–

2018[33]										
Pasina et al 2013[34]	Retrospective	1323	79.9 (7.3)†	51 (49.7)	Italy	internal medicine and geriatric wards (hospital)	3 mo	ARS and ACBS	BI	–
Sura et al 2016[35]	Retrospective	112	Age 65.00 – 79.0 (n = 59) Age ≥80 (n = 53)	48 (42.9)	USA	Community	24 mo	ADS	–	SF-12

ADL, activities of daily living; AKPS, Australian-Modified Karnofsky Performance Status; BI, Barthel Index; EQ-5D, EuroQol 5D; FIM, Functional Independence Measure; IADL, instrumental activities of daily living; MDS-HC; Minimum Data Set for Home Care; MQoL, MacGill Quality of Life Score; NR, not reported; NS; not specified; OARS, Older American Resources and Services; QoL, quality of life; SD, standard deviation; SF-12, Short Form Health Survey 12.

* 461 participants recruited but QoL analysis conducted with 304 participants who died during study follow-up.

† Mean age for ACB users within sample.

‡ Median and interquartile range presented instead of mean (SD).

Risk of bias for each study (n = 10) is presented in Figure 1. Of the 10 studies, 4 papers were considered high risk of bias ≥1 QUIPS categories.[23,29,31,34] High risk of bias arose most commonly from issues around participation, including poor descriptions of sample group,[23] inadequate description of those excluded,[31] or little information regarding participation rate.[29] Moderate risks of bias were common throughout all studies; attrition (the number, reasons for or exploration of outcome factors in those lost) was rarely addressed. A funnel plot for assessing publication bias was not possible due to variation in statistical effect sizes presented and too few studies.

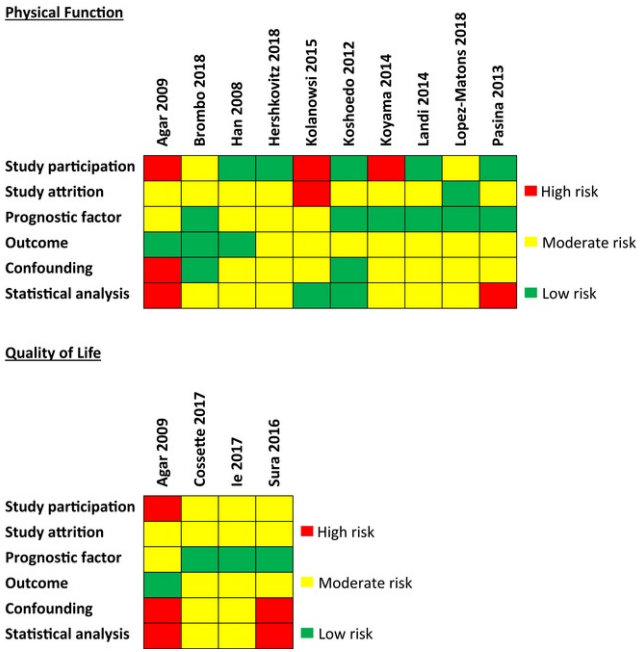

Fig. 1 QUIPS Risk of bias assessment of studies reporting association between ACB and physical function (n = 10) and quality of life (n = 4).

ACB Scale and Physical Function

Six studies, with sample sizes ranging from n = 99[29] to n = 1429[31] explored the relationship between baseline ACB and future physical function using the ACBS (Table 2). Three studies reported significant associations between increased ACB and impaired physical function[24,29,31] with little difference between unadjusted and adjusted results. Brombo et al 2018[24] reported the strongest association between increased ACBS score and a decline in activities of

daily living scores [2.77, 95% confidence interval (CI) 1.39, 5.54]. Inconsistencies between studies regarding statistical analysis and data presented limited further analysis. For example, as shown in Table 2 the 6 studies utilized 4 different physical function outcome measures and varied in comparison groups (eg, ACBS = 0 vs ACBS ≥1 or ACBS ≤ 1 vs ACBS ≥2).

Table 2 Summary of Results for Studies Exploring Prognostic Relationships Between ACB Scale and Physical Function (n = 10)

Scale/Outcome	Studies	ACB (Baseline)	Physical Function (Baseline)	Statistical Approach	Results (Unadjusted)	Results (Adjusted)
ACBS (Range 0–3)						
ADL (≥1 ADL)	Brombo et al 2018[24]	ACBS ≤1: 381 (33.9%)	Any ADL: 542 (48.3%)	Multivariable logistic regression OR 95% CI (ACBS ≥1 vs ACBS = 0)	2.38 (1.37,4.13) $P = .002$	2.77 (1.39, 5.54) $_P = .004$*
		ACBS ≥2: 348 (31.0%)				
BI (Range 0–100)	Kolanowski et al 2015[29]	ACBS Mild: 81 (81.8%)	NR	Multiple linear regression β (SE)	NR	Mild: _3.41 (2.14) $_P$ = NS†
		ACBS Mod/Sev: 25 (25.2%)				Mod/sev: 5.76 (1.99) $P \leq .05$
	Lopez-Matons et al 2018[33]	ACBS ≥1: 26.4%	BI (Mean, SD): 88.9 (18.5)	Difference in the BI scores between exposed and unexposed patients Mean (SD) (95% CI)	−4.3 (3.3) (−10.8, −2.2)	−4.0 (4.5) (−12.9, 4.9)‡
	Pasina et al 2013[34]	ACBS ≥1: 724 (58.8%)	NR	Correlation Pearson coefficient	0.004, $P = .91$	NR
FIM (Range 18–126)	Hershkovitz et al 2018[27]	ACB ≤1: 666 (76.6%)	60.5 (17.8)	Multiple linear regression β (SE)	NR	_0.03 (0.85) $_P = .02$§
		ACB ≥2: 203 (23.4%)	56.3 (18.7)			
IADL (Range 0–8)	Koyama et al 2014[31]	ACBS Mean (SD): 1.6 (1.9)	NR	Multiple logistic regression OR (95 % CI)	1.11 (1.04, 1.18) P = NR	1.11 (1.04, 1.19)‖ $_P$ = NR
ARS (Range 0–3)						
ADL (Range 0–28)	Brombo et al 2018[24]	ARS ≥1: 208 (18.5%)	ADL any: 542 (48.3%)	Multivariable logistic regression OR 95% CI	2.43 (1.26,4.68) $P = .008$	1.49 (0.60, 3.70) $_P = .38$*
	Landi et al 2014[32]	ARS ≥1: 721 (48.4%)	ADL Mean (SD): 15.4 (10.3)	Multivariable logistic regression OR (95% CI)	NR	1.13 (1.03, 1.23) $_P = .01$**
BI (Range 0–100)	Koshoedo et al 2012[30]	ARS Median	BI Median (IQR): 55 (40–60)	Poisson	NR	0.97 (0.95, 0.99) $_P = .008$††

		(IQR): 0 (0–1)		regression IRR (95% CI)		
	Pasina et al 2013[34]	ARS ≥1: 112 (9.1%)	NR	Correlation Pearson coefficient	−0.06 $P = .15$	NR
CRAS/mCRAS (Range 0–3)						
AKPS (Range 0–100)	Agar et al 2009[23]	NR	AKPS (Mean, SD): 61.0 (13.8)	Logistic regression OR (95% CI)	*NR*	0.85 (0.81, 0.90) $_P = _{NR}$‡‡
IADL (Range 0–8)	Han et al 2008[26]	CRAS Mean (SD): 1.3 (1.5)	IADL Mean (SD): 6.5 (1.07)	Mixed effects linear regression Effect estimate (95% CI)	0.16 (0.11, 0.25) $P = .001$	0.10 (0.04, 0.17) $_P = .001$§§

ADL, activities of daily living; AKPS, Australian-Modified Karnofsky Performance Status; BI, Barthel Index; FIM, Functional Independence Measure; IADL, instrumental activities of daily living; IRR, Incident Rate Ratio; NR, not reported; NS, not significant; OR, odds ratio; SD, standard deviation; SE, standard error.

* Adjusted for age, sex, education, smoking, mini-mental state examination score, ACBS score at first follow-up, hypertension, coronary heart disease, renal failure, anemia, and infectious diseases.

† Adjusted for sex, ethnicity, Charlson comorbidity index, clinical dementia rating, age, Apolipoprotein E status, education, and previous weekly function performance.

‡ Adjusted for age, sex, body mass index, smoking, high blood pressure, diabetes, dyslipidemia, heart disease, stroke, and dementia.

§ Adjusted for age, sex, time from surgery to rehabilitation, admission albumin level, education, presence of caregiver, residency, mini-mental state examination score, admission FIM, ischemic heart disease, congestive heart failure, diabetes, hypertension, cardiovascular disease, depression, Parkinson's, and chronic obstructive pulmonary disease.

‖ Adjusted for age, race, years of education, smoking, physical activity, and Charlson comorbidity index.

** Adjusted for schizophrenia, depression, cognitive performance scale score, age, sex, cumulative index rating scale, and ADL (baseline).

†† Adjusted for age, sex, Charlson comorbidity index, abbreviated mental test, total of other medications, and Barthel index at admission.

‡‡ Adjusted for time before death.

§§ Adjusted for age, race, education, living arrangement, follow-up year, baseline value of the outcome, ADL, center-epidemiologic studies depression scale, smoking, alcohol use, Charlson comorbidity index, and hypertension.

ARS and Physical Function

Four studies with sample sizes ranging from n = 105[30] to n = 1490[32] explored relationships between ACB and physical function using the ARS (Table 2). Studies varied in statistical analysis and findings; 2 of 4 studies reported significant association between baseline ARS and future functional decline.[30,32] Notably, Brombo et al 2018,[24] in contrast to their findings using the ACBS, failed to find a positive association between function and ACB using the ARS measure (odds ratio 1.49, 95% CI 0.60, 3.70).

Clinician Rated Anticholinergic Score and Modified Clinician Rated Anticholinergic Score and Physical Function

Two studies explored relationships between ACB and physical function using the Clinician Rated Anticholinergic Score (CRAS) or modified CRAS (mCRAS).[23,26] Sample sizes ranged from n = 461[23] to n = 544.[26] Agar et al (2009)[23] reported an odds ratio 0.85 (95% CI 0.81, 0.90) between the baseline CRAS of older palliative care patients and a decrease in Australian-Modified Karnofsky Performance Status category; those with higher ACB were less likely to be classed as independent at follow-up. Han (2008)[26] reported an effect estimate of 0.10 (95% CI 0.04, 0.17) suggesting for every unit increase in mCRAS score there is a 10% reduction in IADL (ie, lower independence).

Comparison of Prognostic Ability of ACB Measures to Predict Future Physical Function

Only 2 studies directly compared >1 ACB measures in the same population; Brombo et al (2018)[24] and Pasina et al (2013)[34] both compared the ACBS and ARS abilities to predict future physical function. Brombo et al (2018)[24] reported associations with the ACBS but not ARS, while Pasina (2013)[34] failed to find a significant relationship with either the ACBS or ARS.

Quality of Life Outcome Studies

In total 2635 older people participated across the 4 studies, with mean (standard deviation) ages ranging from 71.0 (12.0) years[23] to 78.6 (6.7) years.[28] Two studies were conducted in the United States.[28,35] and 1e each from Australia[23] and Canada.[25] Further details of each study are presented in Table 1.

Risk of bias for each study (n = 4) is presented in Figure 1. Of the 4 studies, 2 papers were considered high risk of bias in ≥1 QUIPS categories.[23,35] High bias risks arose from a lack of reporting of, or adjustment for, confounders and unclear analysis plans.[23,35] Moderate risks of bias were common throughout; Participation rates were rarely reported, the number, reasons for or exploration of those lost to follow-up was rarely addressed, along with non-reporting of missing data. A funnel plot for assessing publication bias was not possible due to variation in statistical effect sizes presented and too few studies.

ACBS and Quality of Life

Two studies, with sample sizes ranging from n = 426[28] to n = 1793[25] explored the relationship between baseline ACB and quality of life using the ACBS. Table 3 summarizes results. Cossette (2017) identified a significant association between baseline ACB and the physical domain of the Short Form Health Survey 36 (SF-36) [β −0.50 (95% CI −0.31, −0.68) $P < .001$)] but not the mental domain [β 0.19 (95% CI 0.01,0.37) P = ns].[25] Conversely, using the EuroQol 5D, Ie et al (2017) did not identify any association with ACBS score over 12 months [β 0.006 (95% CI −0.01 to 0.02) P = ns)].[28] Cossette (2017) do not present results combining the domains of the SF-36 making it difficult to compare the 2 sets of results.[25]

Table 3 Summary of Results for Studies Exploring Prognostic Relationships Between ACB and QoL (n = 4)

Scale/Outcome	Study	ACB (Baseline)	QoL (Baseline)	Statistical Approach	Results (Unadjusted)	Results (Adjusted)
ACBS (Range 0–3)						
SF-36 PCS (Range 0–100)	Cossette et al 2017[25]	ACBS ≥1: 33%	SF-36 PCS (Mean, SD): 49.0 (8.2)	Multiple linear regression β (95% CI)	NR	−0.50 (−0.31, −0.68) $P < .001$*
EQ-5D (Range 0–1)	Ie et al 2017[28]	ACBS Mean (SD): 0.55 (0.87)	EQ-5D (Mean, SD): 0.82 (0.14)	Multiple linear regression β, SE (95% CI)	NR	0.006, .009 (−0.01, 0.02) P = NR†
ADS (Range 0–3)						
SF-36 PCS (Range 0–100)	Cossette et al 2017[25]	ACBS ≥1: 33%	SF-36 PCS (Mean, SD): 49.0 (8.2)	Multiple linear regression β (95% CI)	NR	−0.30 (−0.10, −51) $P < .01$*
SF-12 PCS (Range 0–100)	Sura et al 2016[35]	Ach user: 17 (15.2%)	NR	Multiple linear regression Parameter estimate (95% CI)	NR	−7.48 (−12.57, −2.39) $P < .01$‡
ARS (Range 0–3)						
SF-36 PCS (Range 0–100)	Cossette et al 2017[25]	ACBS ≥1: 33%	SF-36 PCS (Mean, SD): 49.0 (8.2)	Multiple linear regression β (95% CI)	NR	−0.43 (−0.69, −0.17) $P < .01$*
mCRAS (Range 0–3)						
MQoL (Range 0–10)	Agar et al 2009[23]	NR	McGill QOL Mean (SD): 6.0 (2.0)	Generalized linear models OR (95% CI)	NR	0.90 (0.85, 0.95) P = NR§
DBI-Ach (Range 0–3)						
EQ-5D (Range		DBI-Ach (Mean, SD): 0.05 (0.14)	EQ-5D (Mean, SD): 0.82	Multiple linear regression	NR	

0–1)	Ie et al 2015[28]		(0.14)	β, SE (95% CI)		−0.09, .05 (−19, .002) $P < .05$ † §

EQ-5D, EuroQol 5D; MQoL, MacGill Quality of Life Score; NR, not reported; OR, odds ratio; QoL, quality of life; SF-12 PCS, Short Form Health Survey 12 Physical health Compo~~nent~~site Scores; SE, standard error; SF-36 PCS, Short Form Health Survey 36 Physical health Composite Scores. ~~Component.~~

* Adjusted for age, sex, education, income, living alone, frailty, number of comorbidities, modified mini-mental state examination, and Geriatric Depression Scale.

† Adjusted for age, sex, living with someone, income, number. of comorbidities, use of assistive devices, falls <12 months, baseline DBI ACH, baseline DBI-~~SED~~Sedatives, baseline ACBS, number of regular medications, and number of ~~BEER~~Beers list medications.

‡ Adjusted for predisposing factors such as age, race/ethnicity, sex, marital status, and education. Enabling factors included family income, health insurance coverage, region, and metropolitan status area. Need factors comprised of perceived general and mental health status, ADL, IADL, and cholinesterase inhibitors. The baseline P~~CS~~hysical health Composite Scores and M~~CS~~ental health Composite ~~summary~~ scores were used as additional need factors.

§ Adjusted for time before death.

ADS and Quality of Life

Two studies with sample sizes ranging from n = 112[35] to n = 1793[25] explored relationships between ACB and physical function using the ADS (Table 3). Both studies demonstrated moderate significant associations between increased ACB measured by the ADS and the physical domain of the SF-36 [β −0.30 (95% CI −0.10, −0.51) $P < .01$][25] and SF12 [est. −7.48 (95% CI −12.57, −2.39) $P < .01$],[35] respectively. Neither study detected association between the ADS and the mental domains of the SF-36 [β −0.07 (95% CI −0.28, 0.13) P = ns] or SF12 [Mean between group difference in SF12 scores −2.27 (95% CI −7.81, 3.27) $P = .43$].[25,35]

ARS and Quality of Life

Only 1 study explored relationships between ACB and quality of life using the ARS.[25] Results are detailed in Table 3, but again a significant association with the physical, but not the mental, domains of the SF-36 were identified.

DBI-Ach Subscale and Quality of Life

Only 1 study explored the relationship between DBI-Ach and quality of life,[28] which demonstrated a small but significant relationship with reduced quality of life measured by the EuroQol 5D (Table 3).[28]

mCRAS and Quality of Life

Only 1 study explored the relationship between mCRAS and quality of life,[23] which demonstrated significant association with the McGill Quality of Life score (Table 3). Those with higher ACB scores reported poorer quality of life at follow-up.[23]

Comparison of Prognostic Ability of ACB Measures to Predict Future Quality of Life

Only 2 studies directly compared different ACB measures in the same population sample; Cossette et al (2017)[25] compared 3 measures (ACBS, ADS ARS), whereas Ie et al (2016)[28] compared the ACBS and DBI-Ach, to predict quality of life. The ACBS demonstrated the strongest associations in comparison to the ADS and ARS.[25] Ie et al (2016) demonstrated a stronger relationship using the DBI-Ach than the ACBS, however associations were very small (β −0.095, $P < .05$).[28]

GRADE Assessment

All GRADE assessments conducted for each ACB scale and outcome combination resulted in an assessment of “very low,” meaning that we have little confidence in the results and further studies will likely change the results. Quality was commonly downgraded due to serious concerns regarding study biases, inconsistency in results, indirectness, potential for publication bias and small effect sizes (Supplementary File 1 for detailed GRADE assessments).

Discussion

This systematic review included 13 studies reporting the prognostic value of 1 or more ACB measures in relation to physical function or quality of life in older people. Seven out of 10 studies reported a significant association between increased ACB and future impaired physical function, with the remaining studies showing a nonsignificant trend toward this. However, statistical and clinical heterogeneity prevents meta-analysis and our ability to recommend

one measure above another. In relation to quality of life, 4 studies reported the longitudinal relationships between ACB and quality of life among older people. Each study reported at least 1 significant association between ACB and quality of life, but again limited evidence prevents recommending one measure above another. At present, the evidence behind the ability of individual ACB measures to predict future physical function and quality of life is poor and does not permit informed decisions regarding which measure is best to assess ACB. We conclude that, in relation to older people, ACB shows a general trend toward impaired physical function and reduced quality of life but the question as to which ACB measure performs best remains unanswered.

In the review by Fox et al (2014),[5] studies which failed to associate ACB and physical function often focused upon single domain aspects of function (eg, walking ability). Our study excluded such outcomes to focus upon global measures that are more comparable between populations. However, it has been suggested that specific domains of physical function such as gait may play important mediating roles between ACB and other adverse outcomes such as falls.[36] Research focusing upon the temporal relationship between ACB and global physical function, specific physical abilities and how these relate to other outcomes are required to advance our understanding of the complexities of this relationship.

Our findings support a general trend for increased ACB being associated with a reduction in quality of life; however, the evidence is limited by few studies and low study quality. The divergence in results between domains of quality of life, demonstrating greatest associations with the physical domain of quality of life than the mental domain, is not unique to ACB. Similar results were recently published in relation to associations between multi-morbidity and quality of life where strong associations with physical, but not mental domains were also found.[37] Exploration of older peoples perspectives toward ACB and its impact upon quality of life is necessary to further understand what aspects, if any, ACB is perceived to impact upon, which may help explain this finding.

The number of, and variations between ACB measures, has been documented previously.[13,38] Many were developed to target specific adverse outcomes, most commonly cognitive impairment and dementia.[13,38] These may nevertheless be associated with the outcomes assessed in this review because cognitive impairment is associated with poorer physical function[39] and quality of life,[40] and because anticholinergics are well known to have many other adverse effects beyond cognitive impairment. Reliance upon expert rated anticholinergic potency is troublesome due to divergent views amongst clinicians.[13,38] Conversely attempts to rate anticholinergic potency objectively is not without its limitations, not least discordance between measurable biological markers and symptoms of anticholinergic properties.[13,38] Despite our intentions this present review cannot answer the question as to which ACB measure may be most suitable for predicting specific outcomes. The small number of studies, diverse range of outcome measures, and substantial differences in study characteristics means determining one ACB measure as being a better predictor of future physical function or quality of life is not possible. To improve prognostic research future research should be prospective longitudinal or case-control in design and sufficiently large, with sample size calculations appropriate for the outcome of interest and adjust for important confounding variables.

The strengths of this systematic review include its novelty in both focusing upon comparing ACB measures and being restricted to older people. Other strengths include its comprehensive search strategy using a validated search filter to identify relevant studies, reference list checks of all included studies and any seminal studies not included to ensure no eligible studies were omitted, and our decision to focus on longitudinal and case-control studies more suited to understanding adverse outcomes. However, this review also has some limitations. We did not include gray literature; while this can help avoid contaminating results with low quality non-peer reviewed evidence, we cannot say with certainty that its exclusion did not result in the omission of insightful and relevant papers. Finally, the small number of studies identified meant it was not possible to adequately assess for publication bias so we have to assume there is a possibility of this.

Conclusions and Implications

This systematic review identified 13 studies reporting the prognostic value of one or more ACB measures in relation to physical function or quality of life. The majority of studies show at least a general trend toward impaired function and reduced quality of life associated with increased ACB. At present the evidence behind individual ACB measures' ability to predict physical function and quality of life among older adults is poor and does not permit informed decisions regarding which is the best measure to use. Well-designed longitudinal studies are required to address this. However, the general consistency in our findings, alongside the wider body of evidence, suggests clinicians should continue to be aware of individual patients' ACB and consider alternatives to anticholinergic medications where appropriate.

Supplementary Data

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.jamda.2020.05.065.

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Supplementary Data

Multimedia Component 1

Supplementary File 1

Queries and Answers

Query: If there are any drug dosages in your article, please verify them and indicate that you have done so by initialing this query
Answer: There are no medication dosages. CS.

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Answer: Microsoft Corporation, California, USA; (Biostat, New Jersey, USA

Query: Please expand GRADE at first mention in text body.
Answer: Added, thank you. CS

Query: Table 2: Please expand IRR in footnote.
Answer: Incident Rate Ratio added. CS

Query: Please clarify subscript $P < .05$ $_{b}$.
Answer: Corrected to †, thanks. CS

Query: Table 3: Please expand SED, BEERs, PCS, and MCS in footnotes.
Answer: All corrected, thank you. CS

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