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REVIEW ARTICLE

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A systematic review of interventions to reduce anticholinergic burden in older people with dementia in primary care

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Abstract

Objective: This systematic review aimed to assess the types and effectiveness of interventions that sought to reduce anticholinergic burden (ACB) in people with dementia (PwD) in primary care.

Methods: One trial registry and eight electronic databases were systematically searched to identify eligible English language studies from inception until December 2021. To be eligible for inclusion, studies had to be randomised controlled trials (RCTs) or non-randomised studies (NRS), including controlled before-and-after studies and interrupted time-series studies, of interventions to reduce ACB in PwD aged ≥65 years (either community-dwelling or care home residents). All outcomes were to be considered. Quality was to be assessed using the Cochrane Risk of Bias tool for RCTs and ROBINS-I tool for NRS. If data could not be pooled for meta-analysis, a narrative synthesis was to be conducted.

Results: In total, 1880 records were found, with 1594 records remaining after removal of duplicates. Following title/abstract screening, 13 full-text articles were assessed for eligibility. None of these studies met the inclusion criteria for this review. Reasons for exclusion were incorrect study design, ineligible study population, lack of focus on reducing ACB, and studies conducted outside the primary care setting.

Conclusions: This 'empty' systematic review highlights the lack of interventions to reduce ACB in PwD within primary care, despite this being highlighted as a priority area for research in recent clinical guidance. Future research should focus on development and testing of interventions to reduce ACB in this patient population through high-quality clinical trials.

KEYWORDS

anticholinergic burden, dementia, inappropriate prescribing, older people, primary health care, systematic review

Key points

- Anticholinergic burden (ACB) remains high among people with dementia (PwD) despite known risks to physical and cognitive functioning. Reducing ACB in PwD is essential to improve quality of life and reduce negative outcomes.
- The literature was systematically reviewed to assess the types and effectiveness of interventions to reduce ACB among PwD in primary care.
- However, no studies met the inclusion criteria for this review, highlighting the lack of high-quality evidence in this area.
- There is a clear need for future studies to develop and test interventions to reduce ACB in PwD, particularly in the primary care setting, using robust study designs.

1 | INTRODUCTION

Dementia is defined as a chronic and progressive functional and cognitive decline and it is considered a global challenge for health and social care systems.[1] Worldwide, there are currently more than 55 million people living with dementia.[2] A number of factors are acknowledged to increase a person's risk of developing dementia, such as increasing age, a positive family history, a history of other medical conditions such as hypertension and diabetes, and lifestyle factors such as smoking and excessive alcohol consumption.[3] Reducing a person's exposure to modifiable risk factors may be the most effective approach to prevent or delay dementia.[1,3,4]

Anticholinergic drugs are commonly used in older people for the management of several medical conditions, such as Parkinson's disease, overactive bladder, gastrointestinal disorders, depression, and cardiovascular diseases. Drugs with anticholinergic activity act by blocking parasympathetic nerve action,[5,6] and can cause a wide range of side-effects including drowsiness, blurred vision, dry mouth, confusion, and hallucinations. Anticholinergic drugs are acknowledged to cause impairments in cognitive function, with deficits in attention, information processing, and increased brain atrophy reported.[7–9] In recent years, there has been mounting evidence that anticholinergic drug use is associated with an increased risk of incident dementia.[10–13] Therefore, anticholinergic prescribing in older people is considered potentially inappropriate by tools such as the Beers criteria and Screening Tool of Older Person's Prescriptions, and clinical guidelines recommend minimising the use of anticholinergic drugs in people with dementia (PwD) and those with suspected dementia.[14–16]

Despite well-publicised risks, anticholinergic drug use among PwD remains widespread and has been increasing over recent decades.[17–21] Furthermore, studies have shown that PwD often experience a high anticholinergic burden (ACB), which refers to the cumulative effect of using multiple medications with anticholinergic properties concomitantly.[17,22–24] Various scales have been developed to assess ACB (e.g. the Anticholinergic Cognitive Burden Scale,[25] the Anticholinergic Risk Scale,[26] the Anticholinergic Drug Scale,[27] and the Drug Burden Index).[28] The use of drugs with anticholinergic activity and high ACB is linked to adverse events such as reduced physical functioning, falls, reduced quality of life, hospitalisation, and mortality among PwD.[29–34] Reduction of anticholinergic drug use and ACB in PwD has therefore been highlighted as a research priority.[14]

Following diagnosis, PwD will be predominantly managed and supported within primary care settings.[35] It is therefore important that evidence-based interventions to reduce ACB in PwD are developed to be delivered within primary care, which may help to delay cognitive deterioration and improve quality of life for this patient population.[14,36] A recent systematic review described the effectiveness of interventions to reduce ACB in older people.[37] Whilst eight studies were included, none of these studies involved PwD, highlighting a critical gap in the evidence base.[37] Little is known about what interventions have been developed and implemented in primary care to reduce ACB in PwD and the impact of such interventions. Therefore, the aim of this study was to systematically review the literature to identify the types, and assess the effectiveness of, interventions to reduce ACB in older PwD in primary care.

2 | METHODS

This systematic review was guided by the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[38] It is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement[39] (Supplementary file 1). The review protocol was prospectively registered with PROSPERO (International prospective register of systematic reviews; CRD42020216085).

2.1 | Eligibility criteria

Studies that were randomised controlled trials (RCTs), non-randomised studies (NRS), controlled before-and-after studies, or interrupted time series studies were included in this review. Participants had to be aged 65 years or older, diagnosed with dementia (of any type), and be either community-dwelling or living in a care home (with or without nursing care). Participants with mild cognitive impairment were excluded, as they were outside the focus of the review. Studies had to involve an intervention that aimed to reduce ACB in PwD; any ACB scale that was used by the study investigators

was considered. The interventions had to be implemented in primary care. Interventions aimed at those who had a role in caring for PwD, such as carers (formal/informal) or healthcare professionals (HCP) were also considered eligible for inclusion. All outcomes (both primary and secondary) that were reported in included studies were to be considered, and studies were not excluded on the basis of outcomes stated. Only articles published in the English language were included. Review articles, conference abstracts, and editorials/letters were excluded.

2.2 | Data sources and search strategy

A broad literature search was performed to identify eligible studies published from date of inception to December 2021. Eight electronic databases [Cochrane Library, Cumulative Index to Nursing and Allied Health Literature Plus (CINAHL Plus), International Pharmaceutical Abstracts, Ovid Medline, Embase, PsycINFO, Scopus, Web of Science] were searched using a combination of MeSH terms and keywords. A search strategy was developed in Medline in consultation with a subject librarian (Supplementary file 2) and this was adapted for other databases. Three trial registries (Cochrane Central Register of Controlled Trials, Health Canada Clinical Trial Database, and World Health Organisation International Clinical Trials Registry Platform) were searched to identify ongoing or unpublished trials. In addition, the reference lists of included articles were to be hand-searched to identify additional relevant studies.

2.3 | Article selection

The references from all retrieved articles were downloaded into EndNote[40] and duplicates were removed. One reviewer Bara'a Shawaqfeh (BS) screened titles and abstracts of all studies for eligibility. Following removal of articles that did not meet the inclusion criteria, full texts were obtained and independently screened by two reviewers (BS and Heather E. Barry [HB]) for eligibility according to the inclusion/exclusion criteria described above. Reasons for exclusion were documented. Any disagreements regarding inclusion of studies were resolved through discussion within the research team.

2.4 | Data extraction, risk of bias assessment, and data analysis

We had planned for two reviewers (BS and HB) to independently extract the data from each included study using a standardised form which was based on the Cochrane data collection form.[38] The risk of bias of included studies was to be assessed using the Cochrane Collaboration Risk of Bias tool version 2[38] for RCTs and the ROBINS-I tool[38] for NRS. We planned to conduct a meta-analysis if the interventions in the included studies were similar enough in terms of participants, settings, interventions, comparison, and outcome measures to ensure meaningful conclusions from a statistically pooled result. If this was not possible, we planned to conduct a narrative synthesis of data.

3 | RESULTS

In total, 1400 articles were identified from database and trial registry searches until December 2020. The search was updated in December 2021 and an additional 480 articles were identified. Following removal of duplicates (n = 286 records), 1594 records progressed to title and abstract screening. Following this, 1581 articles were excluded. The 13 remaining articles subsequently underwent full-text review, however none of these met the inclusion criteria for this review. An overview of the article screening process is shown in Figure 1.

The 13 studies were excluded for various reasons: six studies[41-46] utilised an incorrect study design, two studies[47,48] included participants who did not have a diagnosis of dementia, in one study[49] the intervention did not aim to reduce ACB, and one study[33] was not conducted in a primary care setting. In addition, two conference abstracts[50,51] and one protocol paper[52] were excluded. The reasons for exclusion of each of these studies are described in more detail in Table 1.

4 | DISCUSSION

The aim of this study was to systematically review the literature to identify and assess the effectiveness of interventions to reduce ACB in older PwD in primary care. No studies were found to be eligible for inclusion in this systematic review – it is therefore an 'empty review'. This result is unexpected given that first, several studies have previously reported the risks of anticholinergic drug use and high ACB in PwD[11,29,32] and second, because evidence-based clinical guidance has emphasised the need for high-quality, clinical trials to evaluate interventions to reduce ACB among PwD.[14] Despite this being an empty review, we consider the findings to be important, as they highlight major gaps in the current evidence-base and provide some indication as to the direction future research should take to guide clinical practice.

In 2018, the National Institute for Health and Care Excellence emphasised the need for RCTs to be conducted to reduce ACB and the use of drugs with anticholinergic activity among PwD, without negatively affecting the management of the conditions for which these medicines are prescribed.[14] However, all the articles that were found in our searches failed to address the inclusion criteria for our systematic review for different reasons: almost half of the studies were excluded as they did not utilise the correct study design (two were prospective cohort studies, one was a retrospective observational study, one was a full audit cycle, one was a clinical review, and one was a quasi-experimental feasibility study). Some studies either did not include PwD or they actively excluded them as study

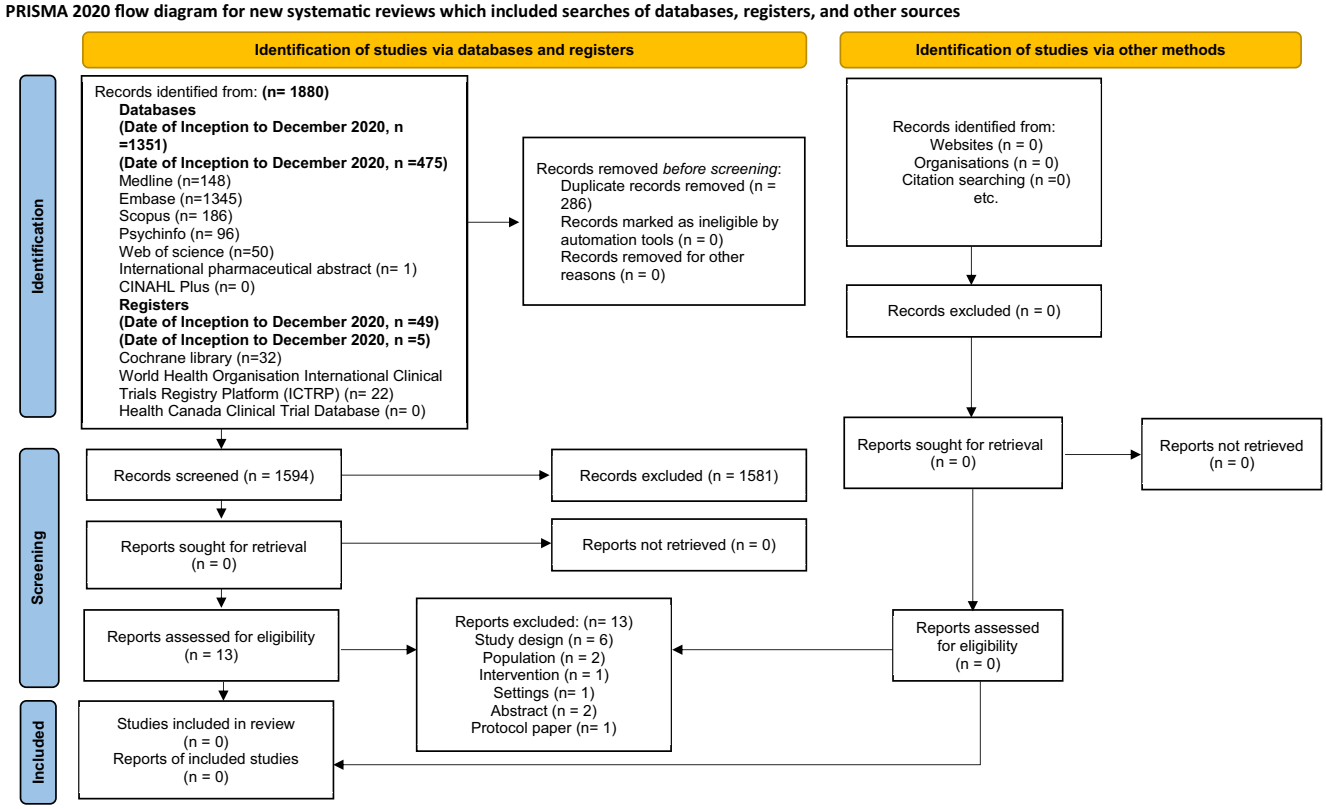

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram describing screening process and reasons for exclusion of studies. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

TABLE 1 A summary of papers excluded from the review and reasons for exclusion

Author	Exclusion reasons
Tay et al. (2014)[42]	Study design was excluded
Yeh et al. (2013)[43]	Study design was excluded
Wilchesky et al. (2018)[44]	Study design was excluded
Jaïdi et al. (2019)[45]	Study design was excluded
Fiss et al. (2013)[52]	Paper protocol design was excluded
Lee et al. (2018)[46]	Study design was excluded
Silva-Almodóvar et al. (2020)[41]	Study design was excluded
Arvisais et al. (2015)[47]	Participants were not recruited on the basis of dementia
Moga et al. (2017)[48]	Participants were not recruited on the basis of dementia
Rojo-Sanchís et al. (2017)[49]	Intervention did not aim to reduce anticholinergic burden
Jaïdi et al. (2018)[33]	Study was not conducted in primary care
Jaidi et al. (2016)[50]	Abstract
Harder et al. (2021)[51]	Abstract

participants (two studies were excluded for these reasons).[47,48] In addition, during our searches of clinical trial registries, many RCTs were found to be in progress, with most started after 2018.[53-59] Whilst these RCTs appear to be testing interventions which aim to reduce ACB, the study populations are largely frail older people, and only one registry entry was found for a study aiming to reduce ACB among PwD specifically.[43,53-59] However, this study is observational (a prospective cohort study).[43] Moreover, the review by Nakham and colleagues, which was published shortly before our searches were completed, highlighted the need for development and testing of high-

quality clinical trials with those who are community-dwelling as well as specific patient populations (such as PwD) at high risk of harm from ACB.[37]

The issue of involving PwD in research studies is one that has been deliberated in the literature.[60,61] Many barriers to including PwD in research exist; the complexity of study procedures may make it difficult for PwD to understand study information, fluctuations in mental capacity can make it challenging for PwD to provide informed consent, and they may have difficulty travelling to research sites, particularly as the condition progresses.[60,61] Furthermore, it is likely that PwD may be multimorbid or receiving polypharmacy – both of these factors are known to be common exclusion criteria in research studies.[62,63] Furthermore, consideration needs to be given as to how future research in this area can be more inclusive of PwD. Overcoming barriers to including PwD in research studies will ultimately contribute to the development of new clinical guidelines to assist prescriber decision-making and improve patients' quality of life.[64–66] Development of registers, platforms, or websites for dementia research (e.g. the UK-based Join Dementia Research service) might improve recruitment of PwD by helping to overcome recruitment barriers and raising awareness of dementia research.[67]

Recently, studies have focused on reducing ACB among the general older population.[43,53-59] Many of these interventions demonstrated an effective approach to reducing ACB and reported that pharmacists are well placed to implement such interventions.[43,53-59] Furthermore, a recent systematic review by Nakham and colleagues, which included eight studies of interventions to reduce ACB, reported that most of the included studies demonstrated a decrease in ACB following intervention delivery.[37] In our systematic review, one study was excluded as the intervention did not focus on reducing ACB.[49] Such a focus is needed as the development and testing of interventions to reduce ACB among PwD have the potential to improve the quality of life for older PwD.[14,37]

In 2016, the World Alzheimer Report recommended a task-shifted model of post-diagnostic dementia care, moving from secondary to primary care-led healthcare, comprising initial treatment and continuing support.[68] However, many barriers to conducting research with PwD in the primary care setting have been reported.[69] Barriers were found to be organisation-related (such as limited funding in general, lack of time to train staff, insufficient equipment or administrative support to perform additional data entry or deal with paperwork), healthcare professional-related (e.g. peer influences, a lack of confidence in one's own ability to carry out specific tasks and the feeling of not having sufficient authority or influence to conduct study procedures), and intervention-related (e.g. intervention complexity, increasing staff workload through intervention delivery).[69] Primary care is often patients' first point of contact with a healthcare system, and due to its accessibility and the continuity of care provided, primary care is a key setting for the delivery of effective interventions to reduce ACB among the older population and PwD specifically.[35,36,70] Many studies have shown that provision of care to PwD (such as regularly reviewing patient medications) by interdisciplinary teams in the primary care setting results in better adherence to dementia care guidelines,[71] less behavioural and psychological disturbances,[72] and a reduction in carer stress and depression.[72–74] In our systematic review, one study was excluded as it was implemented in a specialised tertiary care unit for Alzheimer's disease and related disorders.[33] The study reported a significant decrease in behavioural and psychological symptoms of dementia and caregiver burden following reduction of ACB among PwD; such outcomes might be observed if similar interventions were implemented in the primary care setting.[33] Two of the excluded studies were conducted in primary care settings.[43,52] The first study, using a prospective cohort design, reported a successful and safe reduction of ACB for residents with dementia in a Veteran home through an educational programme for primary care physicians. However, the long-term benefits were unclear.[43] The second article described the components of an intervention focusing on medicines management and home medication review to be delivered as part of the Life and Person-centred help in Mecklenburg-Western Pomerania, Germany (DelpHi) study.[52] However, a subsequent trial of this intervention only measured use of potentially inappropriate medication as one of the primary outcomes, and was not focused on ACB specifically.[75] Furthermore, developing positive relationships between primary HCP and patients, involving them in training workshops to improve their own confidence to carry out research-related tasks, and developing interventions that demonstrate clear and consistent clinical evidence of benefit or good applicability relevant to the setting, might help facilitate participant recruitment, as well as the quality and integration of clinical research with this patient population in primary care.[69]

4.1 | Strengths and limitations

This is the first systematic review that has sought to identify studies of interventions that aim to reduce ACB among PwD in primary care. We used a number of search terms for dementia, ACB, and medicines optimisation in our searches which facilitated the identification of a large number of published papers. Broad searches of multiple databases and trial registries were undertaken, and hand searching of reference lists of included studies was planned to be undertaken, but it is still possible that some unpublished or unindexed data might have been missed. A key strength of this study is that specific inclusion criteria were utilised; however, these may have been overly stringent. By choosing to only include certain study designs (RCTs, NRS, controlled before-and-after studies, and interrupted time-series studies), participants (PwD), and settings (primary care), we aimed to identify only high-quality evidence, although this approach resulted in no studies that met the inclusion criteria.

5 | CONCLUSION

This systematic review aimed to assess the effect of interventions to reduce ACB in older PwD in primary care. Whilst no studies were eligible to be included, resulting in an empty review, this study has

highlighted key areas on which future research should focus. There is a need for further work to focus on the development, implementation and evaluation of interventions to reduce ACB in this patient population, with a need for high quality evidence to be generated. Furthermore, strategies are needed to minimise and overcome barriers to recruitment of PwD in future research studies so that interventions can be fully evaluated with the target population.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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