**Abstract:**
Anticholinergic drugs are prescribed for a range of conditions including gastrointestinal disorders, overactive bladder, allergies, and depression. While in some circumstances anticholinergic effects are therapeutic, they also pose many undesired or adverse effects. The overall impact from concomitant use of multiple medications with anticholinergic properties is termed “anticholinergic burden” (ACB). Greater ACB is associated with increased risks of impaired physical and cognitive function, falls, cardiovascular events and mortality. This has led to the development of interventions aimed at reducing ACB through the deprescribing of anticholinergic drugs. However, little is known about the implementation issues that may influence successful embedding and integration of such interventions into routine clinical practice. In this paper we present the protocol for our systematic review that aims to identify the qualitative evidence for the barriers and facilitators to reducing ACB from the perspectives of patients, carers and healthcare professionals. A comprehensive search strategy will be conducted across OVID Medline, EMBASE, PsycInfo and CINAHL. The review will be conducted in accordance with ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research) and has been registered with PROSPERO (Registration CRD42018109084). Normalization Process Theory (NPT) will be used to explore, understand and explain qualitative data in relation to factors that act as barriers or facilitators to ACB reduction.

**Keywords:** Anticholinergics; deprescribing; systematic review; qualitative research; intervention development

**Introduction**
Anticholinergic drugs block the actions of acetylcholine and prevent parasympathetic nerve activity [1]. In some circumstances these anticholinergic actions have intended therapeutic effects, for example, the use of amitriptyline in the treatment of chronic pain, but in others, they are a side effect of a drug used primarily for other pharmacological actions, such as Atenolol [2]. Anticholinergic drugs are prescribed for a wide range of conditions including gastrointestinal disorders, overactive bladder, allergies, depression, psychosis and cardiovascular disease [1-3] resulting in a high overall prevalence of these medications. Anticholinergic drugs have many adverse effects that include dry mouth, constipation, increased heart rate, confusion, and increased risk of falls [1-2]. Older people are more susceptible to these side effects [2]. The prescribing of multiple medicines for older adults in response to managing multiple morbidities in later life places them at greater risk of being exposed to anticholinergic drugs [2].

Population surveys suggest that up to 50% of community dwelling older adults may be taking one or more medications with anticholinergic effects [4-6]. The potential impact of anticholinergics on an individual is termed as “anticholinergic burden” (ACB) [2], and concomitant use of multiple medications with anticholinergic properties has a cumulative effect [2,7]. Several scales to assess ACB have been developed, such as the Anticholinergic Drug Scale [8], Anticholinergic Cognitive Burden Scale [9] and the Anticholinergic Risk scale [10]. Several recent systematic reviews have reported that greater ACB is associated with increased risk of impaired physical and cognitive function, falls, cardiovascular events and mortality [11-15]. These findings have led to the development of interventions aimed at reducing ACB through either stopping anticholinergic medications (deprescribing) or changing them to medicines that do not have anticholinergic properties. Therefore, understanding factors that will influence efforts to reduce this burden would be an important step forward.
Our recent systematic review identified eight studies that aimed to reduce ACB reduction amongst older adults (PROSPERO registration CRD42018089764). Interventions varied widely regarding their design and setting (e.g. community, nursing homes, acute care), person delivering the interventions (e.g. pharmacist, pharmacologist, physician), and how recommendations were identified and made (e.g. face to face, over the telephone or virtually). Seven of the eight studies reported positive improvements regarding ACB. Despite interest in conducting ACB reduction interventions, little is known about implementation issues. Specifically, what factors increase or decrease successful embedding and integration of such interventions. The current evidence base is limited to specific population groups, such as those on particular types of anticholinergic medications such as antipsychotics [2]. In relation to ‘deprescribing’ in general, several systematic reviews have revealed common barriers and facilitators [16-19]. There is overlap between factors reported by patients and prescribers including fears of negative consequences arising from stopping medications, and a lack of ongoing support [16-19]. Conversely, patient motivation, support for the prescriber and patient, and beliefs that deprescribing is the right thing to do, all support the deprescribing process [16-19]. However, it is unknown if the barriers and facilitators towards reducing use of anticholinergic drugs are different from those for general deprescribing of inappropriate medications, or if anticholinergic drugs and medical conditions associated with their use, may present unique challenges. Investigating barriers and facilitators to anticholinergic deprescribing is essential to inform the development and design of ACB reduction interventions [20]. To the best of our knowledge, this is the first study to systematically review primary qualitative studies exploring the barriers and facilitators to ACB reduction. Our aim is to identify and describe the evidence regarding such factors from the perspectives of patients, their carers (or proxy respondent on behalf of the patient) and healthcare professionals.

Our specific research questions are:
1. What are the barriers and facilitators to reducing patient ACB from the perspective of healthcare professionals?
2. What are the barriers and facilitators to reducing patient ACB from the perspective of patients and carers?

Methods

A systematic literature search and evidence synthesis of published papers that contain qualitative data is being conducted based on the general principles of the Cochrane Handbook for Systematic Reviews of Interventions [21], and ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research) [22]. This review has been registered with PROSPERO (Registration CRD42018109084). Any methodological changes made will be recorded in revisions of the study protocol and updated in PROSPERO.

Eligibility:

This review will use a modified PICO (population, intervention, control and outcome) framework to describe our inclusion and exclusion criteria [23]. Eligibility criteria are presented in Table 1. Language exclusions will be conducted by hand upon screening of identified studies.

Data Sources:
Four electronic databases will be searched: Ovid MEDLINE, EMBASE, CINAHL and PsycINFO. The search strategy will be developed for Ovid MEDLINE and adapted as needed for other databases where appropriate. Scoping searches to identify appropriate subject headings, key words and text words, will be completed for each database. This will involve using the MeSH mapping tool to identify relevant and related search terms, and reviewing the indexing of, references within and citations for, known relevant and closely related manuscripts. Bibliographies of included publications will also be searched manually for additional potentially eligible papers. We will also review papers citing the included articles to check for further eligible studies.

Search strategy:

The search strategy will adopt a concepts-based approach, the concepts of interest being ACB, interventions to reduce ACB, and qualitative methods. A search strategy is presented in supplementary file S1.

Data collection and analysis:

Identified studies will be transferred into RefWorks (ProQuest LLC) [24] for bibliographic management and transferred to Covidence (Veritas Health Innovation Ltd) [25] for title and abstract screening. Two independent reviewers will screen article titles, abstracts and full papers using the inclusion and exclusion criteria shown in Table 1. Full-texts of potentially eligible studies will be obtained and study authors will be contacted where full-texts cannot be found. Any discrepancies in eligibility between the two reviewers will be resolved by an independent third reviewer.

A standardised data extraction form will be developed to ensure consistent data collection from all studies. Items from standard reporting checklists will be included in the form as follows: The Cochrane Handbook for Systematic Reviews of Interventions [21], and ENTREQ (Enhancing Transparency in Reporting the Synthesis of Qualitative Research) [22]. Two reviewers will be involved in data extraction and disagreements discussed and resolved within the wider research team.

Studies quality assessment:

Two reviewers will independently assess risk of bias of included studies using the relevant Critical Appraisal Skills Programme (2018) checklist [26].

Data synthesis:

Two reviewers will conduct data analysis with a third party for arbitration of disagreements. Qualitative data will be exported into NVivo, version 12, QSR International [27] to facilitate data analysis. Normalization Process Theory (NPT) will serve as the underpinning conceptual framework to explore, understand and explain the qualitative data in relation to factors that act as barriers or facilitators to ACB reduction. NPT is a well-developed theory for understanding such factors from the perspective of intervention implementation [28-32]. NPT consists of four constructs: coherence, which addresses the sense-making work that people participating in an intervention have to undertake; cognitive participation, the engagement work that is undertaken to ensure participants ‘buy into’ the intervention; collective action, the operational work and tasks that people have to do to enact the intervention; and reflexive monitoring, the appraisal work people undertake in relation to the intervention [29]. Data will be analysed using a framework underpinned by NPT. A coding sheet detailing and describing the themes required to be explored by NPT will be developed and agreed by the team. This will provide a framework for sorting and categorising the data, and exploring relationships between themes. The framework will be refined and adapted during data analysis and will be flexible to enable data that falls outside of our conceptual model to be captured.
Discussion

To date, the search strategies have been conducted and screening of identified articles is underway. The findings of this review will be used to inform development and design of a future trial examining the efficacy of an ACB reduction intervention. The Medical Research Council [20] recommends that interventions be developed from evidence accrued from systematic reviews. They also recommend examining this evidence to develop understanding of the theoretical underpinnings of the intervention [20]. This review will identify if there are key research gaps. For example, if the quantity and quality of identified evidence are found to be insufficient, future qualitative research may be required to answer outstanding implementation questions. Our use of a robust theoretical framework to underpin our data analysis will help us to move from a purely descriptive account to one that is more explanatory in nature. The use of such approaches is advocated when developing complex interventions [20]. Dissemination plans include one peer-reviewed manuscript and conference presentations and/or public engagement events.

Acknowledgements

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Supplementary Materials: Table S1: Database Search Strategies.

References


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<tr>
<th>Inclusion Criteria</th>
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<tr>
<td><strong>Population (Participants)</strong></td>
<td><strong>Exclusion Criteria</strong></td>
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<tr>
<td>• Persons aged ≥18 years of age</td>
<td>• Persons aged &lt; 18 years</td>
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<td>• Persons using one or more anticholinergic medications</td>
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<td>• Carer/proxy (e.g. a person answering on behalf of the patient) for an adult using one or more anticholinergic medications</td>
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<td>• Healthcare professional (e.g. physicians, nurses, pharmacists) involved in the care of adults using one or more anticholinergic medications</td>
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<td><strong>Setting</strong></td>
<td><strong>Exclusion Criteria</strong></td>
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<tr>
<td>• Primary care</td>
<td>• Acute care/inpatients</td>
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<td>• Community</td>
<td>• Palliative care</td>
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<td>• Nursing home</td>
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<td>• Outpatient clinics</td>
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<td>• Day hospitals/centres/care facilities</td>
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<td>• Rehabilitation services</td>
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<tr>
<td><strong>Intervention</strong></td>
<td><strong>Exclusion Criteria</strong></td>
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<tr>
<td>• Original research findings examining attitudes to deprescribing/medication switching in relation to anticholinergic medication</td>
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<tr>
<td><strong>Study Type / Design</strong></td>
<td><strong>Exclusion Criteria</strong></td>
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<tr>
<td>• Qualitative research (face-to-face or telephone approaches)</td>
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<td>• Full papers published in peer-reviewed journals</td>
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<td>• Published in English</td>
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<td><strong>Controls</strong></td>
<td><strong>Exclusion Criteria</strong></td>
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<tr>
<td>• None</td>
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<tr>
<td><strong>Outcome</strong></td>
<td><strong>Exclusion Criteria</strong></td>
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<tr>
<td>• Barriers and facilitators to deprescribing or medication switching in relation to anticholinergic medications</td>
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