

Stewart, C., Gallacher, K. , Nakham, A., Cruickshank, M., Newlands, R., Bond, C., Myint, P. K., Bhattacharya, D. and Mair, F. S. (2019) Barriers and facilitators to reducing anticholinergic burden from the perspectives of patients, their carers, and healthcare professionals: a protocol for qualitative evidence synthesis. *Journal of Evidence-Based Medicine*, 12(3), pp. 227-231.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

This is the peer reviewed version of the following article:

Stewart, C., Gallacher, K. , Nakham, A., Cruickshank, M., Newlands, R., Bond, C., Myint, P. K., Bhattacharya, D. and Mair, F. S. (2019) Barriers and facilitators to reducing anticholinergic burden from the perspectives of patients, their carers, and healthcare professionals: a protocol for qualitative evidence synthesis. *Journal of Evidence-Based Medicine*, 12(3), pp. 227-231.

This article may be used for non-commercial purposes in accordance with [Wiley Terms and Conditions for Self-Archiving](#).

<http://eprints.gla.ac.uk/191857/>

Deposited on: 05 August 2019

Short Title: Qualitative review anticholinergic reduction

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 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

This review is funded by The Dunhill Medical Trust (RPGF1806/66) as part of a series of work building an evidence synthesis suite to inform a future randomised trial of reducing anticholinergic related harm in older adults. The funding sponsors had no role in the design, execution, interpretation or writing of the study. The authors declare no conflict of interest.

Author Contributions: Conceptualisation: C.S., K.G., A.N., M.C., R.N., C.B., P.K.M., D.B. and F.S.M.; Funding acquisition: K.G., P.K.M., D.B. and F.S.M.; Investigation: C.S., K.G., A.N., M.C., R.N., C.B., P.K.M., D.B. and F.S.M.; Methodology: C.S., K.G., A.N., M.C., R.N., C.B., P.K.M., D.B. and F.S.M.; Project administration: C.S. AND F.S.M.; Resources: C.S., K.G., A.N., M.C., R.N., C.B., P.K.M., D.B. and F.S.M.; Supervision: F.S.M.; Writing- original draft: C.S. ; Writing- reviewing and editing: C.S., K.G., A.N., M.C., R.N., C.B., P.K.M., D.B. and F.S.M.; Study guarantor: F.S.M.

Supplementary Materials: Table S1: Database Search Strategies.

References

1. Gerretsen, P., & Pollock, B. G. Cognitive risks of anticholinergics in the elderly. *Aging Health* 2013, 9, 159-166.
2. Kouladjian O'Donnell, L., Gnjjidic, D., Nahas, R., Bell, J. S., & Hilmer, S. N. Anticholinergic burden: considerations for older adults. *J Pharm Prac Res* 2017, 47, 67-77.
3. Vardanyan, R. S., & Hruby, V. J. Anticholinergic drugs. In *Synthesis of essential drugs*, 1st ed.; Vardanyan, R.S. & Hruby, V.J., eds.; Elsevier: The Netherlands, 2006, pp 195-208.
4. Lampela, P., Lavikainen, P., Garcia-Horsman, J. A., Bell, J. S., Huupponen, R., & Hartikainen, S. Anticholinergic drug use, serum anticholinergic activity, and adverse drug events among older people: a population-based study. *Drugs Aging* 2013, 30, 321-330.
5. Merchant, R. A., Li, B., Yap, K. B., & Ng, T. P. Use of drugs with anticholinergic effects and cognitive impairment in community-living older persons. *Age Ageing* 2008, 38, 105-108.
6. Sittironarit, G., Ames, D., Bush, A.I., Faux, N., Flicker, L., Foster, J., *et.al.* Effects of anticholinergic drugs on cognitive function in older Australians: results from the AIBL study. *Dement Geriat Cogn Disord* 2011, 31,173-178.
7. Kersten, H., & Wyller, T. B. Anticholinergic drug burden in older people's brain - how well is it measured? *Basic Clin Pharmacol Toxicol* 2014, 114, 151-9.

8. Carnahan, R. M., Lund, B. C., Perry, P. J., Pollock, B. G., & Culp, K. R. The anticholinergic drug scale as a measure of drug-related anticholinergic burden: Associations with serum anticholinergic activity. *J Clin Pharmacol* 2006, 46, 1481-1486.
9. Boustani, M., Campbell, N., Munger, S., Maidment, I., & Fox, C. Impact of anticholinergics on the ageing brain: A review and practical application. *Aging Health* 2008, 4, 311-320.
10. Rudolph, J. L., Salow, M. J., Angelini, M. C., & McGlinchey, R. E. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med* 2008, 168, 508-513.
11. Cardwell, K., Hughes, C. M., & Ryan, C. The association between anticholinergic medication burden and health related outcomes in the 'oldest old': a systematic review of the literature. *Drugs Aging* 2015, 32, 835-848.
12. Fox, C., Smith, T., Maidment, I., Chan, W. Y., Bua, N., Myint, P. K., *et. al.* Effect of medications with anticholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age Ageing* 2014, 43, 604-615.
13. Ruxton, K., Woodman, R. J., & Mangoni, A. A. Drugs with anticholinergic effects and cognitive impairment, falls and all-cause mortality in older adults: a systematic review and meta-analysis. *Brit J Clinical Pharmacol* 2015, 80, 209-220.
14. Singh, S., Loke, Y. K., Enright, P., & Furberg, C. D. Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergic medications. *Thorax* 2013, 68, 114-116.
15. Zia, A., Kamaruzzaman, S., Myint, P. K., & Tan, M. P. (2016). Anticholinergic burden is associated with recurrent and injurious falls in older individuals. *Maturitas* 2016, 84, 32-37.
16. Anderson, K., Stowasser, D., Freeman, C., & Scott, I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ open* 2014, 4, 12.
17. Luymes, C. H., van der Kleij, R. M., Poortvliet, R. K., de Ruijter, W., Reis, R., & Numans, M. E. Deprescribing potentially inappropriate preventive cardiovascular medication: barriers and enablers for patients and general practitioners. *Ann Pharmacother* 2016, 50, 446-454.
18. Reeve, E., To, J., Hendrix, I., Shakib, S., Roberts, M. S., & Wiese, M. D. Patient barriers to and enablers of deprescribing: a systematic review. *Drugs Aging* 2013, 30, 793-807.
19. Turner, J. P., Edwards, S., Stanners, M., Shakib, S., & Bell, J. S. (2016). What factors are important for deprescribing in Australian long-term care facilities? Perspectives of residents and health professionals. *BMJ open* 2016, 6, e009781.
20. Medical Research Council Developing and evaluating complex interventions. Available online: <https://mrc.ukri.org/documents/pdf/complex-interventions-guidance/> [Accessed 20th November 2018]
21. Higgins, J. P. T., & Green, S. *Cochrane handbook for systematic reviews of interventions*, 1st ed.; John Wiley & Sons Ltd: West Sussex, 2008.
22. Tong, A., Flemming, K., McInnes, E., Oliver, S. and Craig, J., Enhancing transparency in reporting the synthesis of qualitative research: ENTREQ. *BMC Med Res Method* 2012, 12, 181.
23. Schardt, C., Adams, M.B., Owens, T., Keitz, S., Fontelo, P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007, 7, 16.

24. ProQuest LLC. RefWorks 2018. Available online: <https://refworks.proquest.com/>. (Accessed 11th December 2018)
25. Veritas Health Innovation Ltd. COVIDENCE. Available online: www.covidence.org (Accessed 11th December 2018)
26. Critical Appraisal Skills Programme CASP Qualitative Checklist. Available online: https://casp-uk.net/wp-content/uploads/2018/03/CASP-Qualitative-Checklist-2018_fillable_form.pdf (Accessed 10th December 2018).
27. NVivo version 12, QSR International. Available online: <https://www.qsrinternational.com/> (Accessed 11th December 2018).
28. Mair, F. S., May, C., O'Donnell, C., Finch, T., Sullivan, F., & Murray, E. Factors that promote or inhibit the implementation of e-health systems: an explanatory systematic review. *B World Health Organ* 2012, 90, 357-364.
29. May, C. R., Cummings, A., Girling, M., Bracher, M., Mair, F. S., May, *et. al.* Using Normalization Process Theory in feasibility studies and process evaluations of complex healthcare interventions: a systematic review. *Implement Sci* 2018, 13, 80.
30. McEvoy, R., Ballini, L., Maltoni, S., O'Donnell, C. A., Mair, F. S., & MacFarlane, A. A qualitative systematic review of studies using the normalization process theory to research implementation processes. *Implement Sci* 2014, 9, 2.
31. Murray, E., Treweek, S., Pope, C., MacFarlane, A., Ballini, L., Dowrick, C. *et. al.* Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. *BMC Med* 2010, 8, 63.
32. Simpson, R., Simpson, S., Wood, K., Mercer, S. W., & Mair, F. S. Using normalisation process theory to understand barriers and facilitators to implementing mindfulness-based stress reduction for people with multiple sclerosis. *Chronic Illn* 2018, doi/10.1177/1742395318769354.

Table 1 Study Eligibility Criteria

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