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Anticholinergic burden in older adults

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Abstract

Introduction

The world's older population, often defined as people aged ≥ 65 , is growing rapidly. With advancing age, there is an increased likelihood of adverse effects from medicines. Medications possessing anticholinergic properties are commonly used for a variety of medical conditions. The accumulation of these anticholinergic effects (the anticholinergic burden) has been reported to increase the risk of adverse outcomes such as cognitive impairment, falls, physical impairment and mortality. About 25% of the overall population and 50% of the older population could be at risk of these adverse outcomes. To reduce the risk of adverse outcomes in this population, pharmacists need to identify and make recommendations to deprescribe inappropriate medicines. Existing guidelines on deprescribing are limited. They are often bulky, not tailored to pharmacists' workflow, do not address barriers to deprescribing, and do not guide pharmacists through what to do after identifying problem areas. Consequently, they are often ignored, resulting in lost opportunities to deprescribe or switch to safer alternatives, and frail older adults continue to be prescribed numerous medications that increase their anticholinergic burden. Therefore, this thesis aimed to develop an intervention to reduce anticholinergic burden in older adults.

Method

A study design involving both qualitative and quantitative methods was used. The thesis initially examines the evidence linking anticholinergic burden to adverse outcomes, including a systematic review of the literature on the strength of the association between anticholinergic burden, cognitive impairment, and mortality (Chapter 2). Then, a service evaluation was conducted to evaluate current practice regarding anticholinergic burden in a UK hospital (Chapter 3). Afterwards, a qualitative interview study with pharmacists was aimed to identify barriers and facilitators to deprescribing and decision-making among pharmacists (Chapter 4). Finally, the Behaviour Change Wheel (BCW), incorporating the Capability Opportunity Motivation Behaviour model (COM-B) and Theory Domains Framework (TDF), was used as the theoretical basis for developing a decision support tool for pharmacist users. The tool was refined iteratively to improve its usability (Chapter 4).

Results

The systematic review and meta-analysis included 19 studies and established the evidence linking anticholinergic burden and adverse outcomes. The results from the meta-analysis of 6 studies on mortality showed that patients with low, and moderate to high, anticholinergic burden had a statistically significant 29% and 94% increase in the risk of mortality, respectively, compared to those with no anticholinergic burden (Chapter 2). The evaluation of a hospital frailty service including a pharmacist included 110 hospitalised patients showed that there was no significant difference between anticholinergic burden on admission and at discharge. Some drugs with anticholinergic properties were stopped during hospitalisation, but there was considerable scope for further reduction in anticholinergic burden. There were also missed opportunities to avoid increasing anticholinergic burden in patients who were started on new drugs, where alternatives with lower burden were available (Chapter 3).

Given the importance of reducing anticholinergic burden, the potential to do so, and the failure to do so, eight pharmacists' interviews provided insight into the barriers and facilitators to deprescribing. These barriers and facilitators fit within three target behaviour domains from the COM-B model. They included physiological capability, reflective motivation, and physical opportunity. These were mapped to 5 behavioural change techniques; action planning (e.g. through providing guidance on what to say to prescribers and patients to facilitate planned communication), information on health consequences (e.g. through providing information on the consequence of increased anticholinergic burden in older adults), credible source (e.g. through providing evidence-based guidance), prompts/clues (e.g. through providing a checklist of things to consider with the purpose of cueing deprescribing) and restructuring the physical environment (e.g. introducing the tool). From insights gained from the interviews, a 3-step anticholinergic burden decision support tool was designed. The tool comprised a checklist to identify patients at more risk of anticholinergic burden, an ACB score table, instructions on calculating anticholinergic burden and a medication review section.

Conclusion

In summary, this thesis describes a multifaceted approach, including an exploration of current practice and an evaluation of theoretical determinants of behaviour resulting in the design of a decision support tool to improve consideration of anticholinergic burden among pharmacists. This study has important implications for patients, health care professionals, research, and the healthcare system. Reducing anticholinergic burden could

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improve the quality of life for patients and reduce the financial burden on the NHS. This thesis also highlights the need for decision support to aid pharmacists in participating more in the deprescribing process. Further research is needed to pilot this tool before testing in a big trial.

List of Terms and Abbreviations

AAS	Anticholinergic Activity Scale
ABC	Anticholinergic Burden Classification
ACB	Anticholinergic Cognitive Burden
Ach	Acetylcholine
AChE-I	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADE	Adverse drug events
ADS	Anticholinergic Drug Scale
ARS	Anticholinergic Risk Scale
BCTs	Behaviour Change Techniques
BCW	Behavioural Change Wheel
BNF	British National Formulary
CCI	Charleston Comorbidity Index
CGA	Comprehensive geriatric assessment
CNS	Central nervous system
COM-B	Capability Opportunity Motivation Behavioural model
COPD	Chronic obstructive pulmonary disease
CrAS	Clinician-rated Anticholinergic Score
CVLT	California Verbal Learning Test
DBI-Ach	Anticholinergic component of the Drug Burden Index
DBI	Drug Burden Index
ED	Emergency department
ERIC	Expert Recommendations for Implementing Change
FEAT	Frail Elderly Assessment Team
GP	General Practitioner
HCP	Health care professional
HR	Hazard ratio
HVRT	Hopkins Verbal Recall Test
ICM	ISOFT clinical manager
MARANTE	Muscarinic Acetylcholinergic Receptor ANTagonist exposure scale
MAU	Medical Admissions Unit
MCI	Mild cognitive impairment
MDT	Multidisciplinary team
MMSE	Mini-Mental State Exam
3MS	Modified MMSE

MoCA	Montreal Cognitive Assessment
MRC	Medical Research Council
MUR's	Medicines use review
N/R	Not reported
NICE	National Institute for health and Care Excellence guideline
NOS	Newcastle-Ottawa Scale
PCNs	Primary care network
PIMs	Potentially inappropriate medications
PNS	Peripheral nervous system
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analysis
PRN	<i>Pro re nata</i> "When required"
Q-Coh	Quality of Cohort studies
RCI	Reliable Change Index
RL/RI	Free and cued recall
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
SAA	Serum anticholinergic activity
SIGN	Scottish Intercollegiate Guidelines Network
SRB	Standardized Regression-Based measure
TCA	Tricyclic antidepressant
TDF	Theory Domains Framework
UK	United kingdom
USA	United States of America

Chapter 1: Overview of Anticholinergics, Mechanism of Action, and Side Effects

This introductory section provides an overview of the background and rationale for research into anticholinergic burden in older adults; it then describes the structure of the thesis. The main topic areas covered are increased susceptibility to adverse effects in older adults, potentially inappropriate medications, the concept of anticholinergic burden, and adverse effects associated with it. For this thesis, the term 'anticholinergic medicines' will be used to refer to medicines that are traditionally recognised as anticholinergic drugs and are used for their anticholinergic properties. However, the term 'medicines with anticholinergic properties' will be used to describe both traditional anticholinergic drugs and those that are not primarily used for their anticholinergic properties.

I made minimal contributions to reference "58" titled "Anticholinergic Drug Burden Tools/Scales and Adverse Outcomes in Different Clinical Settings: A Systematic Review of Reviews". The reference is used in the present chapter.

Introduction

A changing demographic

The population of adults aged 65 and over is growing considerably and is estimated to reach 17% of the world's population by 2050, compared with 7% in 2002 (1). The dramatic change to the structure of the world's population is attributed to factors such as decreased mortality of older adults, improved survival of younger people and a corresponding decrease in fertility rates occurring in almost all countries of the world (2). Improved socio-economic development leading to improved access to healthcare, living conditions, and a focus on a healthier lifestyle is reported to promote these factors and thus, lead to an improved life expectancy (2).

Though older adults are living longer, this does not necessarily translate to an extended period of good health (3). If the older population has an extended period of good health, they would have an improved quality of life and greater contribution to society (e.g. extended period in the workforce), which would mean less burden on the health care system (2). In contrast, where older adults live longer but in poor health, presenting either as a decline in mental or physical capacity, at the same or greater rates as their parents,

this would translate to increased demand for health and social care services, increasing pressure on health care resources (2).

Ageing, multimorbidity, frailty, and susceptibility to adverse outcomes

The ageing process is associated with various biological mechanisms, including oxidative damage to mitochondrial and nuclear DNA caused by severe oxidative stress, increased lipid peroxidation, telomere shortening, mitochondrial gene alterations, and upregulation of cell apoptosis (4, 5). These mechanisms result in changes in body composition and organ function, which lead to alterations to pharmacokinetics (e.g., alterations to drug absorption, distribution, metabolism and elimination) and pharmacodynamics (e.g., alterations to organ systems like cardiovascular and the central nervous system), resulting in an increased risk of adverse outcomes (4, 6). Some important pharmacokinetic alterations might include increased bioavailability for drugs with extensive first-pass metabolism, increased serum concentration for water-soluble drugs, a prolonged half-life for lipid-soluble drugs, reduced clearance for renally excreted drugs, and reduced clearance for many drugs with a high extraction ratio (7-12).

Multimorbidity is defined as the co-existence of 2 or more chronic conditions in an individual (13, 14). With advancing age, individuals are at an increased risk of having multiple chronic conditions leading to polypharmacy, decreased quality of life, and various adverse events (13, 15). In addition, multimorbid older patients are increasingly seen by a diverse group of health care professionals in various settings with insufficiently coordinated work, further increasing the risk of polypharmacy and hence adverse drug events (16). Adverse drug events (any injury that occurs during drug therapy) and adverse drug effects (an unintended and harmful effect of a drug) are important health concerns in older adults. A systematic review of 25 prospective observational studies involving 106,586 hospitalised patients demonstrated that 6.3% of younger participants below 60 experienced an adverse effect compared with 10.7% of older adults (17). Furthermore, in a prospective study on 332 residents in 2 nursing homes, 67.4% of residents experienced at least one adverse effect over four years (18). Adverse effects are also the cause of a considerable proportion of hospital admissions in older adults, with people aged 65 and over four times more likely to be hospitalised for an adverse effect compared to younger individuals (19). In addition, 88% of these unintended effects in older adults are reported to be preventable compared with 24% in younger people (19). Apart from being mostly preventable, these events are costly and can lead to increased disability and reduced quality of life (20-22).

Older adults with frailty are even more susceptible to adverse outcomes compared to non-frail older adults (23). Frailty is a complex age-related syndrome characterised by an accumulation of physiological and psychological deficits across multiple organ systems, leading to decreased homeostatic reserve, and heightened vulnerability to stressors (23-25). The increase in the population of older adults has led to a subsequent rise in the number of older adults with frailty (24, 26). Thus, interventions to reduce preventable adverse effects in frail older adults are a key health care concern.

Potentially inappropriate medications (PIMs)

Given the increased susceptibility of older adults to adverse effects, improving the appropriateness of prescribed medicines is an important strategy to improve drug safety in this population. Beer *et al.* defined explicit criteria to identify high-risk drugs using a list of potentially inappropriate medications (PIMs) to avoid or use with caution in older adults (27). PIMs were identified through an expert panel review, where the risk of an adverse event outweighs the therapeutic benefit, particularly when a safer alternative exists. As an approach to improving drug safety, Beer's criteria recommends that the use of anticholinergic drugs, including medicines for urinary incontinence (e.g., oxybutynin and tolterodine), and skeletal muscle relaxants (e.g., methocarbamol and orphenadrine) be avoided in older adults (27). Other guidance, such as the Scottish polypharmacy guidance 2018, highlights anticholinergic medicines as a poorly tolerated class in older adults (28).

Anticholinergic medicines are commonly prescribed to manage different conditions, including intestinal motility disorders, overactive bladder, chronic obstructive pulmonary disease (COPD), nausea, and vomiting. They work by competing with the naturally occurring neurotransmitter acetylcholine (ACh) and other muscarinic agonists for binding sites. The competition results in the inhibition of parasympathetic activities in the gastrointestinal tract, respiratory tract, urinary tract, eye, and heart (29-32). Muscarinic receptor antagonists would be a more accurate term to describe these drugs since they act primarily at the muscarinic receptors. However, to harmonise the terminology used in literature, they will be referred to as anticholinergic drugs throughout this thesis.

The extensive distribution of muscarinic acetylcholine receptors throughout the body accounts for the variety of adverse effects observed with anticholinergic drugs (33-35). Reported peripheral nervous system (PNS) effects include constipation, dry mouth, dry eyes, tachycardia, and urinary retention (36-38). Central nervous system (CNS) effects may include hallucinations, agitation, confusion, falls, cognitive impairment, and delirium

(39-41). Five subtypes of muscarinic receptors have been identified, including M1, M2, M3, M4, and M5. They are responsible for various physiological responses depending on their location in the body (42). The mnemonic below summarises the presentation of anticholinergic reactions and implicated receptors (43):

- Mad as a hatter (e.g., delirium predominantly through M1)
- Blind as a bat (e.g., ocular effect predominantly through M3)
- Dry as a bone (e.g., dry mouth predominantly through M1 and M3)
- Hot as a hare (e.g., decreased ability to dissipate heat mostly through M3)
- Bloated as a toad (e.g., constipation predominantly through M2 and M3)
- The heart runs alone (e.g., tachycardia predominantly through M2)
- Full as a flask (e.g., urinary retention predominantly through M3)
- Red as a beet (e.g., cutaneous vasodilation of the skin in a complex process likely involving M3)

All five receptors are present in the brain; however, the M1 and M2 receptors are responsible for cognitive processes. Thus, their antagonism results in impaired memory and learning ability (43, 44). The antagonism of M3 receptors does not affect behaviour or cognition due to their low concentration in the brain. However, antagonism of M4 and M5 subtypes results in alteration of neurotransmitters like dopamine (33, 45). Targeting specific subtypes of receptors within an organ might reduce unwanted effects. However, complete selectivity has not yet been achieved.

Anticholinergic Burden

Anticholinergic properties have also been identified in many drugs other than those primarily used for their anticholinergic effects (46-48) (Table 1). In addition, previous studies suggest that adverse effects may not arise entirely from drugs with potent anticholinergic activity but also from the accumulation of drugs with mild to moderate anticholinergic activities (46, 48, 49). The anticholinergic burden is defined as the cumulative effect of all anticholinergic activities an individual is exposed to (48, 50). For example, the anticholinergic burden for patients taking a traditional anticholinergic medication like oxybutynin (possessing very strong anticholinergic properties) and prednisolone (possessing mild anticholinergic properties) would be the cumulative effect of both drugs (51).

A large proportion of older adults take medicines with various anticholinergic properties. In a cohort study involving 13004 community-dwelling and institutionalised participants in the UK, 51% of participants aged 65 and over regularly used medicines with various anticholinergic properties (52). Another study on 1,652 community-dwelling participants in America also demonstrated that 64% of participants over the age of 70 were exposed to medicines with various anticholinergic properties (49). Table 1 below presents a summary of some medications with various anticholinergic properties.

Table 1 Drugs with various anticholinergic properties (51)

Minor anticholinergic effects	
Pain medicines	Morphine, codeine, and fentanyl
Benzodiazepine	Diazepam
Some blood pressure medicines	Metoprolol, hydralazine, and nifedipine
Steroids	Prednisone and hydrocortisone
Diuretic	Furosemide
Moderate anticholinergic effects	
Antiparkinsonian	Amantadine
Antiepileptics	Carbamazepine and oxcarbazepine
Pain medicine	Nefopam
Sedating antihistamine	Cyproheptadine
Antipsychotic	Pimozide
Strong anticholinergic effects	
Tricyclic antidepressants	Amitriptyline, Imipramine, and doxepin

Anticholinergic burden and adverse outcomes

There is growing evidence that the use of drugs with anticholinergic properties may increase the risk of dementia. For example, a previous meta-analysis of studies reporting strong anticholinergic medicines to treat overactive bladder over three months reported an increase in the risk of dementia on average by 46% in users compared to non-users (53). This suggests that long-term exposure to drugs with anticholinergic properties can lead to sustained deficits in cognition rather than a reversible effect as previously thought (54, 55). A plausible explanation may be that the long-term use of these medications may lead to Alzheimer like pathology (56, 57): Higher densities of amyloid plaque and neurofibrillary tangles have been observed in patients treated with anticholinergic

medication (56). However, despite these reports, a systematic review did not confirm conclusively an association between anticholinergic burden and dementia (58).

Mild cognitive impairment (MCI) is a noticeable cognitive decline from previous performance, which is not severe enough to be classified as dementia (59, 60). The prevalence of MCI in adults over the age of 70 is 16-22% (61, 62). Furthermore, the estimated annual conversion rate of MCI to dementia is around 11.7% (62). Therefore, it is a disorder that may or may not progress to dementia. Previous studies have evaluated the association between sustained exposure to anticholinergic burden and cognitive impairment. Though association does not mean causation, the possibility of causal association is strengthened by underlining biological hypotheses that could explain the findings. A plausible explanation of the relationship between anticholinergic burden and cognitive impairment could be because anticholinergics work predominately by blocking the M1 muscarinic receptors, which are more abundant in the cerebral cortex, neostriatum, and hippocampus and are reported to be involved in executive function and episodic memory (63, 64). Another plausible pathway is the report that anticholinergic use may lead to brain changes resembling Alzheimer like pathology, leading to a degeneration of the basal forebrain, which produces acetylcholine and plays an important role in cognitive processes (64, 65). However, reports have been inconsistent. In a systematic review of reviews that included 69 research articles, the authors reported that the majority of studies on cognitive function showed no association with anticholinergic burden (56, 58).

Beyond deficits in cognition, anticholinergic agents may have additional consequences. In a cohort study involving 1380 participants aged 65 and over in Italian geriatric wards, anticholinergic burden was associated with impairment of basic activities of daily living (66). Other adverse outcomes that have been reported include falls, delirium, physical impairment, and increased risk of hospitalisation (58). Anticholinergic burden has also been found to predict the risk of death in some studies. For example, in 537,387 participants aged 65 years and over living in New Zealand, anticholinergic burden was associated with fall-related hospitalisation, a greater number of GP visits and a higher risk of mortality (67). A few possible mechanisms may explain why anticholinergic burden may increase the risk of mortality. One explanation is that a high anticholinergic burden is associated with an increased risk of falls and fractures, which are major causes of morbidity and mortality among older adults (68). In addition, anticholinergic burden is also associated with reduced physical function and cognitive impairment, which are independent predictors for increased risk of injury from a fall (69). Another plausible explanation is that recent studies suggest that anticholinergic drugs are pro-arrhythmic

and pro-ischaemic, increasing the risk of cardiovascular death (70). In addition, drugs like clozapine and imipramine have been reported to decrease heart rate variability, likely contributing to adverse cardiovascular events and mortality (71). Nonetheless, the inconsistent reports on the association between anticholinergic burden and mortality need to be clarified (58).

The consequence of adverse effects from increased anticholinergic burden could translate to reduced quality of life, increased disability, and increased cost on the NHS (72, 73). A recent study was conducted to examine the link between clinical characteristics of people with Alzheimer's disease living in the community, their likelihood of institutionalisation or hospital admission, and associated cost. The study demonstrated that cognitive and functional impairment predicted the increased probability of hospital, care home admission and associated costs (74). Improving the appropriateness of prescribed medicines is a strategy to reduce the risk of adverse effects and associated costs in older adults. There is a need for the development of interventions to do this. However, to justify further intervention development work, the relationship between cognitive impairment/mortality and anticholinergic burden needs to be clarified, using the best available evidence in a systematic way. This process is detailed in a systematic review and meta-analysis in Chapter 2.

Measures of anticholinergic burden

Consideration of the impact of anticholinergic drugs led to the development of several scales to measure anticholinergic burden. The purpose of these scales is to quantify anticholinergic drug exposure for an individual. Anticholinergic burden scales have been applied in different clinical settings and used to demonstrate the link between anticholinergics and adverse outcomes such as the increased risk of falls, reduced quality of life, increased hospitalisation, mortality, delirium, cognitive and physical impairment (39, 52, 66, 75-77). However, studies have reported considerable heterogeneity between the scales. Duran *et al.* systematically compared seven different anticholinergic burden scales to develop a uniform anticholinergic drug list (78). Of the 100 drugs selected by the end of the study, there was agreement among the scales for anticholinergic potency for 50 drugs (78). The authors found significant differences between anticholinergic scales in the selection of drugs and quantification of anticholinergic potency.

Furthermore, a systematic review of reviews was done to identify different anticholinergic burden scales, the settings in which they have been used, and the adverse outcomes

associated with them (58). The review identified 18 different anticholinergic burden scales developed by different methods, including a radio-receptor bioassay to measure the serum anticholinergic activity (SAA), literature, equations, expert-based opinion, or a combination of methods (50, 78-81). This heterogeneity in the development of scales likely contributes to variability in content and results of studies. Anticholinergic burden scales that have been used in mortality and cognitive impairment studies and their differences are explored in Chapter 2.

It merits noting that questions have arisen concerning the usefulness of some methods of measuring anticholinergic burden in clinical practice. For example, though the anticholinergic activities of many drugs have been determined using an in vitro method to measure serum anticholinergic activity (SAA), it is not suitable for estimating the overall anticholinergic burden in the brain (42). This is because it measures the peripheral circulating anticholinergic compounds and does not reflect the concentrations in the brain. Thus, the association between SAA and centrally-mediated anticholinergic effects might be difficult to demonstrate (42). Therefore, other methods of quantifying anticholinergic burden are sometimes preferred in research and clinical practice.

Anticholinergic burden in routine clinical practice

Medications are one of the pillars of management and treatment of many chronic and acute conditions in older adults. Thus, the selection of appropriate pharmacotherapy in older adults is crucial (82). Though guidance on the use of medicines with anticholinergic properties exists, numerous studies have reported a high rate of inappropriate prescribing of these medicines in older adults (83). The STOPP/START criteria is a tool that provides guidance on identifying potentially inappropriate prescribing in older adults and has been extensively used in literature and clinical practice. Implementation of STOPP/START has been reported to improve medication appropriateness, reduce adverse drug reactions, polypharmacy, and cost of medication compared with usual pharmaceutical care (84). However, information on medications with anticholinergic properties in the criteria is minimal and would need to be supplemented by other materials. Findings from a study showed the scope of problems identified by pharmacists during a medication review encompassed various explicit criteria, including STOPP/START, Prescribing Indicators in Elderly Australians (PIEA), and Beers criteria (85). This was also seen with interventions to stop medicines with anticholinergic properties, suggesting that STOPP/START is more useful in combination with other tools when considering anticholinergic burden.

The STOPP/START tool has also been criticized for being nonspecific. A study to evaluate the clinical applicability of STOPP/START criteria in daily patient care reported that only 13 out of 80 STOPP criteria had high clarity for action, condition, and explanation. The findings also showed that recommendations for anticholinergic drugs were non-specific and needed clarity and more information (e.g., information on how to stop a medicine) to enhance clinical applicability (86). In addition, a systematic review of available prescribing appropriateness assessment tools reported that none of the 42 tools identified (including STOPP/START and Beers) provided both a rating regarding the level of polypharmacy (e.g., anticholinergic burden scale) and guidance around stopping inappropriate medications, limiting their clinical applicability for informing clinicians in practice. The authors recommended a holistic tool that provides structured guidance around inappropriate medication use and a scoring system to indicate the burden of polypharmacy and risk of harm (87). Other factors might limit the use of STOPP/START in reducing anticholinergic burden, including containing a limited number of medications with anticholinergic properties, alternative safer drugs not being suggested, and containing ambiguous wording.

With the increasing number of older adults, high rates of inappropriate prescribing and increased likelihood of adverse effects, there is a pressing need to develop optimal approaches to reduce anticholinergic burden in practice. However, before optimal approaches to reduce anticholinergic burden can be developed, one of the questions that need to be asked is what is already being done on anticholinergic burden in routine practice in the UK. To evaluate routine practice regarding anticholinergic burden, a population of elderly patients with a high prevalence of anticholinergic burden and adverse effects (e.g., falls and confusion) and in an environment where changes could be made and patients monitored was sought. The population identified were hospitalised frail patients in Royal Derby Hospital attended by a specialised multidisciplinary team involving doctors, nurses, and pharmacists. This exercise's rationale was to justify further work in this area and identify areas where the prescribing quality could be improved. This study, presented in Chapter 3, highlighted the need for the next step in the process: developing decision support for pharmacists to reduce anticholinergic burden in older adults.

Using theory in developing complex interventions

The MRC framework advocates the development of interventions in an iterative process before evaluation (88). The stages proposed by the framework include development, feasibility, piloting, and evaluation. The development phase comprises identifying the

evidence base, identifying or developing theory and modelling process and outcomes (88). The framework's development phase has been criticised for not being detailed enough, and other attempts have been made to improve it (89, 90). Bleijenberg et al. proposed combining the elements from the development phase of the MRC framework with additional elements from existing development models to improve the chances of developing a well-adopted and effective intervention (90). The resulting development phase elements include: identifying and defining the problem, systematically identifying the evidence base, identifying or developing theory, determining the needs, examining current practice, and modelling process and outcomes, leading to the intervention design. The application of the proposed elements to the present study is described below:

Identifying and defining the problem: This involves developing an understanding of the problem through various possible methods (e.g., existing literature, in-depth interviews or focus groups) (89, 90). This phase aims to provide insight into how the problem is perceived and the individual involved or affected. An increasing understanding of the problem may enable designing an intervention that reduces the impact of the problem (89). In the present thesis, the process of defining the problem is described in Chapter 4. In-depth interviews with pharmacists were the method of choice for understanding the problem.

Identifying the evidence base: The MRC proposes a thorough identification of relevant evidence base, ideally by conducting or identifying a systematic review or meta-analysis to provide insight into existing interventions to reduce anticholinergic burden in practice. In this case, it was not necessary to conduct a systematic review on interventions to reduce anticholinergic burden, as a recently published systematic review was identified (91). After evaluating included studies in the systematic review, no identified intervention was developed with theoretical bases, and the development process was not systematic or reported. Also, none of them answered the barriers identified in the in-depth interviews. Evidence of the effectiveness of intervention components was sought from studies not related to reducing anticholinergic burden to evaluate the present intervention's potential effectiveness.

Identifying or developing theory: The MRC framework advocates using theory rather than a pragmatic or empirical approach when developing interventions (88). This stage provides an understanding of the process of change. Specifically, what changes are expected and how change is to be achieved. Using theory helps identify modifiable determinants, providing information on how an intervention may affect the causal chain (90). In the present study detailed in Chapter 4, the Behavioural Change Wheel (BCW),

including the Capability, Opportunity, Motivation Behavioural model (COM-B) and Theory Domains Framework (TDF), was employed to develop the decision support tool.

Determination of the needs: This involves understanding the providers and recipients' needs and preferences using various methods, including qualitative and quantitative. This phase aims to ensure that the resulting intervention addresses the problem, is feasible, and fulfils the needs of its users (90). It provides information on aspects of the intervention that are likely to be adopted. In Chapter 3, interviews with pharmacists allowed the identification of barriers and facilitators to reducing anticholinergic burden, providing insight into their needs, and allowing decision support to be tailored to it. Also, the tool was developed in an iterative process that allowed pharmacists' preferences to be incorporated.

Examining current practice: Examining current practice is important to identify existing interventions. It also helps to judge the providers' competencies and can provide insight into how the intervention will be operationalised in practice (90). In the present study, Chapter 3 describes the process of examining the current practice regarding anticholinergic burden within a multidisciplinary frail assessment team in a UK hospital. This provided insight into how the anticholinergic burden of patients was modified during hospitalisation, health practitioners' involvement in stopping drugs and pharmacist's rationale for intervention on drugs with anticholinergic properties.

Modelling process and outcomes: The MRC framework recommends that optimal complex intervention be tailored to local and intended contexts rather than being completely standardised (88). In the present study, the tool was specifically developed for pharmacists, considering their needs and preferences. Additional pharmacists were also recruited to provide further insight, and the tool modified iteratively. The framework also encourages researchers to start thinking about implementation during the development process. Questions to ask include is it usable? In whom? By whom? In what setting? Etc. This has been described as being similar to presenting a 'manual' for the intervention, making it easy for someone else to implement the intervention in their practice. In the present study, aspects of the BCW allowed some degree of specification. However, the Proctor specification enabled the intervention to be further specified (92).

Intervention design: All previous steps lead to designing the intervention. Here, choices concerning what to include, ingredients, intensity and dose are made (90). In the present study, the intervention was designed using Behaviour Change Techniques (BCTs) identified

from the analysis of the interviews. In addition, subsequent iterations allowed the intervention design to be improved.

Thesis aim and structure

In summary, the thesis aimed to; (1) evaluate the strength of the association between anticholinergic burden and cognitive impairment/mortality; (2) evaluate normal practice regarding anticholinergic burden in frail hospitalised patients; and (3) describe the development of a clinical decision-making tool to reduce anticholinergic burden in older adults.

The overall structure of the study takes the form of five chapters, including this introductory chapter. Chapter 2 describes a systematic review and meta-analysis that seeks to clarify the strength of the relationship between anticholinergic burden, cognitive function, and mortality. The third chapter presents the research findings evaluating normal practice regarding anticholinergic burden within a specialised frailty team. The fourth chapter describes the co-development of a pharmacists' decision-making tool to improve consideration for anticholinergic burden in older adults. The final chapter drew upon the entire thesis, tying up the various strands to put the findings in perspective, discussing the implication of the findings and identifying areas for further research.

Chapter 2: The Long-term Impact of Anticholinergic Burden on Cognitive Function and Mortality: a Systematic Review and Meta-analysis

Background

As discussed in Chapter 1, many drugs other than those primarily used for their anticholinergic properties can contribute to anticholinergic burden. Anticholinergic burden has been reported to be associated with mortality. For example, a study on community-dwelling patients over 65 reported a dose-response relationship between anticholinergic and sedative burden and mortality in people with and without Alzheimer's disease (AD) (93). In contrast, anticholinergic burden was not associated with mortality in residents of a long-term care ward in Finland (94). Given the seemingly inconsistent findings, a systematic review and meta-analysis are needed to investigate the association between anticholinergic burden and mortality.

The Bradford Hill criteria for causation proposed nine criteria for inferring causality to associations in epidemiological studies. The criteria include the strength of the association between the exposure and outcome, the consistency of the research findings, the presence of specificity in the outcomes produced by the exposure, the demonstration of the appropriate temporal relationship (whereby the exposure occurs before the outcome), the presence of a dose-response, the demonstration that the association is biologically plausible, coherence of the findings, the demonstration of experimental evidence, and evidence from similar conditions (95). Temporality is considered one of the most important Bradford-Hill criteria with universal consensus (96). Therefore, study designs which allow a temporal progression between the exposure and outcome are more persuasive in causal inference (97).

Previous systematic reviews have included various study designs, including retrospective and cross-sectional studies, to evaluate the risk of increased mortality in older adults with anticholinergic burden (98, 99). However, cross-sectional studies do not allow for the temporal relationship between exposure and outcome to be examined and cannot evaluate the cause and effect relationship (100). It is also difficult to establish the temporal sequence in retrospective studies due to bias (e.g. recall bias) and confounding, limiting the inference of causality to an association (100). Prospective studies, however, ensure a temporal progression by allowing the participants to be studied at baseline and then followed over time and are the best way to establish a temporal sequence.

The short term impact of anticholinergic effect on cognition has been well reported in literature (101-103). However, In 2009, a literature review reported that few longitudinal studies evaluated the association between increased anticholinergic drug use and cognitive impairment over time (104). Therefore, the relationship between cumulative anticholinergic burden and cognitive impairment remained unclear. Since then, more studies have examined this relationship with varying results. A two-year study on community-dwelling and institutionalised participants aged 65 and over found an association between increased anticholinergic activity and a 0.33-point greater decline in the Mini-Mental State Exam (MMSE) score over time (95% confidence interval (CI)=0.03-0.64, P= 0.03) (52). In contrast, another study on community-based young-old participants aged 60–64 found that increased anticholinergic burden was not associated with an increased risk of cognitive decline over four years (105). These inconsistencies might be because of how the outcome is measured, dose, duration of treatment and the different scales used to quantify anticholinergic burden in literature.

Different scales that quantify anticholinergic burden have been reported to vary significantly in their development process, the drugs they contain and how they classify them. (106). Kashyap *et al.* compared the effect of using different anticholinergic drug scales and cognition measures to predict cognitive decline over time. (107) The authors found that the frequency of identifying an increase in anticholinergic burden varied between four scales, including the Anticholinergic component of the Drug Burden Index (DBI-Ach), Anticholinergic Cognitive Burden (ACB), Anticholinergic Drug Scale (ADS), and Anticholinergic Risk Scale (ARS). This variation in scales has been reported to affect the frequency of identifying an increase in anticholinergic burden and subsequently impact the results of studies (107). There is currently no gold standard anticholinergic burden scale, and the variability of the scores is a limitation in research and clinical practice. Improving understanding of scales with the best predictive value in prospective studies for mortality and cognition will inform clinical practice and enhance the quality of future research.

The measure of cognition has also been reported to impact the frequency of identifying cognitive decline. For example, in the study above, the authors also reported that the study results varied depending on the method used to measure cognitive decline (107). Therefore, consideration should be given to the measure of cognitive outcome used in research and clinical practice, as it may impact the result of studies. In older adults, understanding which cognitive domains change due to anticholinergic burden and the most sensitive measures to detect change over time is important for developing interventions focused on improving or maintaining cognitive function.

Though an association is not necessarily a causal relationship, ascertaining the temporal relationship between the exposure (to increased anticholinergic burden) and the outcome (cognitive impairment or decline and mortality), as well as a dose-response relationship, provides stronger evidence of a causal relationship. Furthermore, in the absence of a cure for dementia, identifying modifiable risk factors for cognitive impairment could lead to improved quality of life, and thus is of particular importance in older adults. This systematic review aimed to evaluate studies that have addressed the prospective relationship between anticholinergic burden, cognitive impairment, and mortality. The objectives are listed below.

Objectives

The primary objective of this systematic review was to examine the strength of the association between anticholinergic burden, cognitive impairment, and mortality; The secondary objectives were (1) to identify the differences between measures of anticholinergic burden that have been used to predict the risk of mortality and cognitive impairment in prospective cohort studies; (2) to identify the measures of anticholinergic burden that are associated with the greatest risk of adverse outcomes; and (3) to identify measures of cognition that are most likely to detect cognitive impairment due to increased anticholinergic burden in prospective cohort studies.

Methods and methodology

Search strategy

A systematic review protocol (PROSPERO registration number: CRD42017076787) was developed using the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidance. The search strategy was developed in terms of the population (P), interventions (I) or exposure (E), comparators (C), and outcomes of the studies (O); a framework used to plan literature search strategies (Table 2). PICO is useful when developing answerable clinical or healthcare-related questions in evidence-based practice.

Table 2 PICO plan for search strategy

Acronym	Definition	Main search term or comment
P	Patient, population, or problem: this was defined as older adults in care homes, hospitals, or community	The population (e.g. age) was not specified in the search term to minimise the exclusion of some potentially important articles
I/E	Exposure: this was defined as taking one or more drugs with anticholinergic properties quantified by a measure of anticholinergic burden	Anticholinergic and Risk measure
C	Comparator/control: this was defined as having minor or no exposure to anticholinergic drugs	This was not included as a search term to allow for a broader search
O	Outcome: the outcomes of interest were mortality and cognitive impairment	Cognitive impairment and death

A literature search (with no restriction on publication period) was performed in PubMed, EMBASE, and PsycINFO from May 2017 to identify eligible studies using a combination of the following keywords and mesh terms; Anticholinergic OR cholinergic receptor blocking agents OR "cholinergic antagonist"[Mesh] OR antimuscarinic OR muscarinic receptor blocking agents OR muscarinic antagonist AND Risk OR risk measure OR risk scale OR rating scale OR risk tool OR drug burden index OR "risk assessment "[Mesh] AND Cognitive function OR cognitive disorder OR cognitive impairment. To identify studies on mortality, the following keywords and mesh terms "Death"[Mesh]) AND "mortality"[Mesh] were combined with the search terms describing "Anticholinergic" above. The last full search was conducted in March 2018.

Following the primary literature search, a manual search of reference lists of previous systematic reviews was done to identify additional relevant studies.

Information sources and search

The three databases (PubMed, EMBASE, and PsycINFO) were selected to increase the chances of identifying all the relevant studies. In 2008, a study compared commonly used medical databases to describe their scope, content, and organisation. The author reported that Ovid MEDLINE and PubMed produced the most references (108). Though Ovid MEDLINE frequently identified the same articles as PubMed, the latter was chosen as one of the databases for this search strategy because, unlike Ovid MEDLINE, its default setting searches by text word and MESH term simultaneously, leading to the generation of a wide range of articles (108).

PsycINFO was selected as the second database in the search strategy for this review because of its ability to discover unique studies. PsycINFO indexes a greater proportion (73%) of leading psychiatry journals than EMBASE (67%) and Ovid MEDLINE (47%). (109) Also, of the three databases (EMBASE, Healthstar, PsycINFO) used in combination with Ovid MEDLINE, PsycINFO produced the most distinct articles to those generated by Ovid MEDLINE (108). PsycINFO was also reported to be the most useful database in producing additionally relevant articles compared to EMBASE and Cochrane library (19, 6 and 3 respectively) after articles that MEDLINE also generated were removed (110). Furthermore, the number of journals indexed by PsycINFO (73%) increased to 91% when it was combined with EMBASE, compared with 85% (PsycINFO and MEDLINE) and 86% (PsycINFO and BIOSIS) (109). This finding informed the decision to use EMBASE as the third database. Additionally, in 2010, EMBASE expanded to include all MEDLINE citations (111). Therefore a search in EMBASE should cover every record in both databases, making EMBASE a more comprehensive database.

Other databases such as Google Scholar and CINAHL were considered for the search strategy. However, it was anticipated that they might not produce additional benefits. Compared to Ovid databases, Google Scholar does not possess adequate features to narrow searches and might lead to an overload of information and false hits (112). Besides, PubMed searches were found to have better precision than advanced Google Scholar searches for both overall search results (13% vs 0.07%, $P < 0.001$) and full-text results (8% vs 0.05% $P < 0.001$) (113). Though previous studies have suggested that searches on CINAHL could add a considerable amount of literature when used in

combination with other databases in nursing subjects, it was unclear how useful it would be in other topic areas (114, 115). Moreover, In addition to the three databases, a manual search of reference lists of previous systematic reviews was done to ensure that the risk of missing eligible studies was mitigated.

Eligibility Criteria

Prospective cohort studies examining the association between anticholinergic burden, cognitive impairment, and mortality were considered eligible. Eligible studies also included studies that assess exposure to anticholinergic drugs at baseline and follow-up, studies that used a scale or equation to quantify anticholinergic burden, the presence of a measure of the outcome at follow-up for studies on cognition and human studies. There was no restriction on publication date, age, or language for included studies.

Review Team

The review team included the main reviewer, Grace Ojo (G.O); other reviewers included Tomas Welsh (TW) and Haiquan Wang (HW).

Study selection

Citations from the electronic searches were collated and duplicates removed. The titles and abstracts were initially screened by a single researcher (G.O) to exclude unrelated studies. The papers were not excluded at this stage if they were judged as having insufficient detail in the title or abstract.

The next stage involved two reviewers (G.O and T.W) independently screening the full text using a checklist developed from the present study's eligibility criteria (Appendix 1). Subsequently, the list of all full articles included and excluded by both reviewers were compared by G.O. Both reviewers agreed on including 19 articles but disagreed on three studies. The disagreements were resolved through discussion, resulting in the three studies being excluded. The results of the search were presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (116) (Figure 1). Reasons for the exclusion of all full-text studies were also presented.

Data extraction

A data extraction template was developed by G.O (Appendix 1) following guidance from the Cochrane Prognostic Review Group (117). To develop the template, a researcher (G.O) collated relevant aspects of the group's data collection checklist. This exercise aimed to aid the data extraction process and provide a clear and consistent description of the included studies. Data extracted included population descriptive, study characteristics (e.g., publication, country, year, study setting), anticholinergic burden scales used, covariates adjusted for, exposure at baseline, outcome measures, and the summary of findings. Two independent reviewers (G.O) and (H.W) used the data collection table and extracted data from included studies. After that, data were transferred to a Microsoft Excel database.

Risk of bias

The methodological quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS), a nine-item scoring scale (118). Each study was judged on the selection of participants, comparability of the exposed and nonexposed participants, and the assessment of outcomes. An increased number of points for a study was indicative of a reduced risk of bias. A maximum of nine points could be allocated. Cohort studies with 9, 8-7, 5-6, and 1-4 points were identified as having a low, moderate, high, and very high risk of bias, respectively.

There is no established gold standard for assessing the quality of cohort studies; however, the NOS is the most frequently used risk of bias tool in systematic reviews involving observational studies (119). Other risks of bias assessment tools include the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) and Quality of Cohort studies (Q-Coh) tools, which are based on bias domains alone and not a scoring scale. Although the NOS is widely used in medical research, it has been criticised for being over-simplified (120). However, compared to the ROBINS-I and the Q-Coh, the NOS has been reported to possess a higher degree of interrater reliability and usability in terms of clarity of instructions (120). This finding informed the decision to use the NOS as the risk of bias tool in this study. The risk of bias for each study was assessed by G.O and checked by a second reviewer H.W, and any disagreements were resolved through discussion.

Data analysis

Strength of the association between anticholinergic burden, cognitive impairment, and mortality

Where homogeneity of study design and outcome measures allowed, a meta-analysis was conducted for included studies; otherwise, the individual results were narrated. The hazard ratio (HR) was considered as the common risk estimate for the associations between anticholinergic burden and mortality. Studies were included in the meta-analysis if they controlled for confounding, reported hazard ratios, or reported results from which the HR could be estimated, and reported findings that could be put into the anticholinergic burden categories described below.

The included studies reported different exposure categories and used different anticholinergic scales; thus, it was necessary to pool reported risk estimates of different levels of anticholinergic burden that were common to the studies. A low anticholinergic burden was categorised as a score of 1 (ARS and ACB), 0-0.5 (DBI), and 0.5-1 (MARANTE). Moderate to high anticholinergic burden scores were classified as a score of 2 and above on all scales, excluding the DBI (>0.5) (Appendix 1. Table 20). The categories were derived from grading scores proposed by the authors in a previous systematic review of rating scales which mostly classified drugs from 0 to 3 (78). Scores on the rating scale represent 0 (no anticholinergic burden), 1 (mild anticholinergic burden), 2 (moderate anticholinergic burden), and 3 (severe anticholinergic burden) (78). All meta-analysis data presented compared ACB = 0 with ACB >0 (low or moderate-high categories).

Before the data were meta-analysed, hazard ratios were recalculated from the confidence intervals, and all values were transformed to their natural logarithms to normalise the distributions. The standard errors were then derived by subtracting the natural logs of the confidence intervals and dividing the value by 3.92 (95% CL) for each study (121). All estimates were then combined using inverse variance-weighted averages of logarithmic HRs in both fixed and random-effects models. Random effect models are preferred for the meta-analysis of studies with heterogeneity. This is because the random effect model assumes that effect estimates across individual studies differ, thus providing a more conservative estimate of the combined effect and allowing the effect of heterogeneity to be integrated into the meta-analysis (122).

Therefore, where significant statistical heterogeneity was identified, the random effects estimate was used preferentially to summarise the included studies. Between-study heterogeneity was analysed using chi-squared (χ^2) tests and I² value, which describes the percentage of total variation across studies due to heterogeneity rather than chance. The I² is the most commonly used heterogeneity measure and can be calculated as $(Q-df)/Q \times 100\%$ (Q denotes Cochran's homogeneity test statistic, and df is the degrees of freedom, which is the total number of studies minus 1) (123). The I² values ranges between 0-100%. Heterogeneity between studies was considered low, moderate and high for the I² values of 25, 50, and 75% (124). In addition, sensitivity analyses were performed to examine each study's contribution to the pooled estimate by sequentially excluding individual studies and recalculating the pooled HR estimates for the remaining studies (Appendix 1; Table 18 and 19).

All analyses were conducted using Review Manager Version 5.3.

Identifying the differences between measures of anticholinergic burden

The variation between the scales was demonstrated by comparing the identified scales to the ACB scale. First, the scores for very strong anticholinergic drugs listed on the ACB scale (score = 3) were compared to the scores on the other scales. The process was then repeated for all other drugs on the ACB scale. In addition to tabulating the results, a chart was produced to summarise the differences between the scales.

Identifying the measures of exposure and outcome that are associated with the greatest risk of adverse outcomes

The studies on mortality and cognition were summarised in different summary tables. Anticholinergic scales that were successfully used to predict cognitive impairment or mortality were reported. Measures of cognitive function that detected change in cognition were also reported. Given that many studies used more than one measure of cognitive function, a study was said to have found an association if any measure of cognition detected a noticeable change in cognition from a previous performance at follow-up.

Results

In total, 1299 citations were identified by the electronic searches of PubMed, EMBASE, and PsycINFO (Figure.1). Of these, 1285 were excluded, leaving 14 studies that matched the eligibility criteria. A manual search of the references for previous systematic reviews produced five additional studies, giving a total of 19 publications. Six of which were included in the meta-analysis.

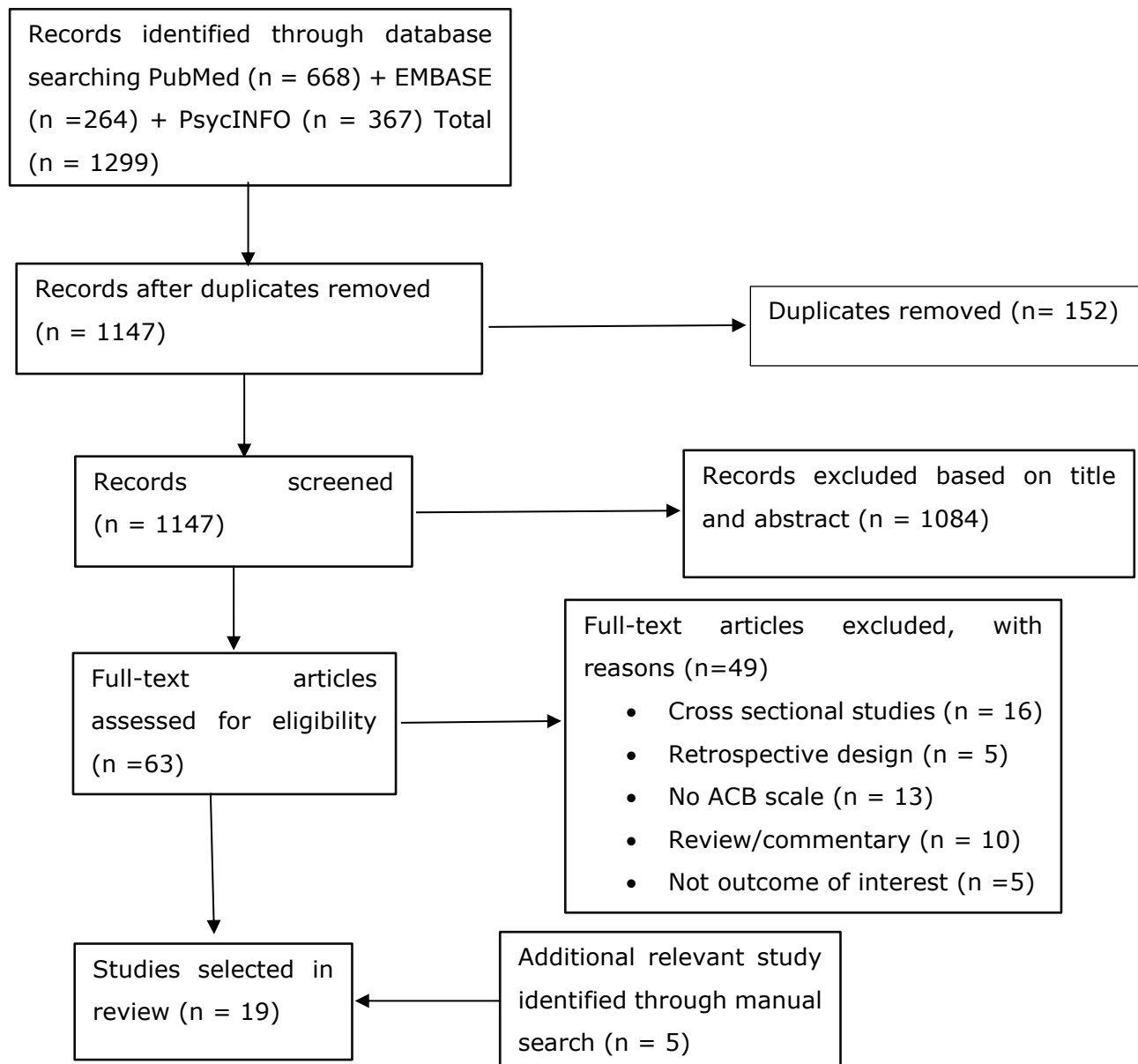


Figure 1 PRISMA flow diagram of study selection results

Demographic characteristics of included studies

In total, 47,990 participants were included in 19 cohort studies, with sample sizes ranging from 102 to 21,636 (Table 3 and 4). Of the 19 studies, two included only women (125, 126), two included only men (127, 128), and one study included only African-Americans (49). Nine studies were conducted in community settings (49, 105, 125-131), six in the hospital (94, 107, 132-135), one in a community and outpatient setting (136), and three studies in both community and care home settings (52, 137, 138).

Methodological quality appraisal

A maximum of nine points was allocated to included studies (Figure 2). A higher score was indicative of a lower risk of bias. Of the 19 studies, 16 had a moderate risk of bias (7-8 points), and 3 had a high risk of bias (5-6). In studies with a higher risk of bias, the recruitment method, control for confounding, and reporting of procedure for assessment of outcome were not appropriate. For example, in some studies, there was no control for confounders, the way the outcome was assessed was not described, and participants were volunteers or a selected group of participants (e.g., male veterans) (127, 132, 136). Of the 16 studies with a moderate risk of bias, 2 reported no negative association between anticholinergic burden, mortality, or cognitive impairment over time (94, 138). Of the three studies with a higher risk of bias, 2 found no association (132, 136). Figure 2 below presents the results obtained from the risk of bias analysis.

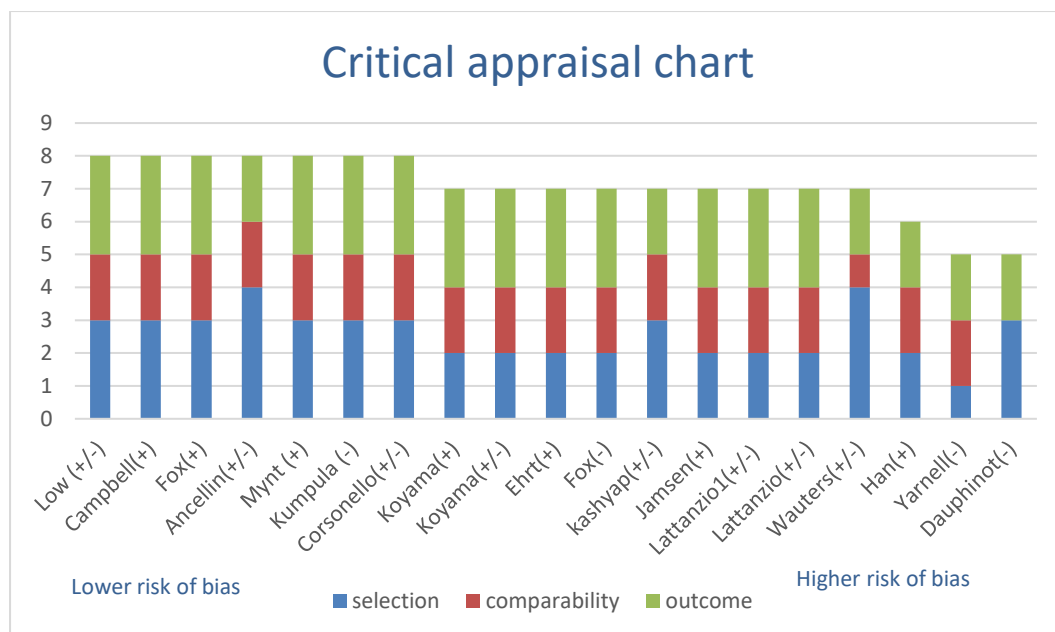


Figure 2 Critical appraisal of included studies using NOS. (+) statistical significant association, (-) no statistically significant association, and (+/-) mixed results depending on the measure of exposure, outcome, or dose. Selection (max 4 points): (1) when the none exposed cohort is drawn from the same community as the exposed, (1) when the ascertainment of the exposure was by a secure record or a structured interview, (1) when the outcome of interest was not present at the start of the study, (1) when the exposed cohort is not a selected group of participants. Comparability (max 2 points): (2) when the study controlled for at least two important covariates. Outcome (max 3 points): (1) when the outcome was assessed through independent blind assessment or secure record linkage, (1) awarded for any length of follow-up, (1) when there was adequate account for subjects lost at follow-up

Table 3 Characteristics of longitudinal observational studies assessing cognitive function

Study	Design, size	Country	Duration	Adjustment's	Participant characteristics	Anticholinergic Scale (+/-)*	Cognitive tool, (+/-)*	Exposure to anticholinergic drugs	Results
Low 2008 (105)	Cohort study, n=2058	Australia	4 years	Age, gender, education, depression, and self-rated health	Community-dwelling adults aged 60-64	ADS (+)	The symbol digit modalities test(+), CVLT-I immediate recall and recall (-), digits backwards (-), Mini-Mental State Exam(-), and simple and choice reaction time (-)	At baseline, 1730 (84.1%) had ADS scores of 0, 197 (9.6%) had scores of 1, 74 (3.6%) had scores of 2, and 57 (2.6%) had scores between 3 and 8.	Poorer complex attention was found in anticholinergic users averaged across time points (p < 0.005). However, no test demonstrated that the use of anticholinergic medication was associated with a greater decline over time.
Koyama 2013 (125)	Cohort study, n=1429	USA	5 years	Age, race, education, smoking, physical activity CCI, and cognitive score.	Community-dwelling older women aged 83.2±3.3	ACB (+)	Trails B (-), MMSE (3MS)(-), CVLT-II immediate recall (+), CVLT-II delayed recall (-), category fluency (+), verbal fluency (-), and backward digit span (-)	At baseline, there were 395 PIM users (27.6%), and the mean ± SD ACB score was 1.6 ± 1.9	ACB score was significantly associated with poorer Immediate recall (p <0.03) and category fluency (p <0.02) at follow up
Koyama 2013 (126)	Cohort study, n=1484	USA	10 years	Age, race, education, modified CCI, GDS score, BMI, and physical activity	Community-dwelling women aged 75 and over	ACB (+)	Modified MMSE, (3MS) (+)	Anticholinergics use was reported by 226 (15.2%) participants at baseline	A higher ACB score was significantly associated with poorer cognitive function (p<0.001) at the 10-year follow-up.

Study	Design, size	Country	Duration	Adjustment's	Participant characteristics	Anticholinergic Scale (+/-)*	Cognitive tool (+/-)*	Exposure to anticholinergic drugs	Results
Kashyap 2014 (107)	Cohort study, n=102	Canada	1 year	Practice effects, regression to the mean, and age-associated normal cognitive decline	Outpatients aged 71.9±7.3 without dementia or depression	DBI-Ach (+), ACB (+), ADS (+), ARS (+).	Mattis dementia rating scale(-), MMSE (-), Montreal Cognitive Assessment (MoCA) (-), Rey-Osterrieth Complex Figure Test recall (-), Stroop test (-), free and cued recall (RL/RI) (+), digit symbol-coding WAIS (-), and the trail-making test (+)	23 (22.5%) participants had a baseline mean ACB score ± SD of 0.6 ± 1.0 (range = 0–4)	Decline in free and cued recall (RL/RI) was significantly associated with ACB score (odds ratio (OR) = 5.3, 95% CI = 1.1–25.8), ADS (OR = 5.7, 95% CI = 1.1–27.7), and ARS (OR = 6.5, 95% CI = 1.34–32.3) scores at follow up. DBI-Ach score was associated with poorer performance on RL/RI (OR = 4.2, 95% CI = 1.8–15.4) and Trail-Making Test Part B (OR = 2.2, 95% CI = 1.1–8.0).
Han 2008 (127)	Cohort study, n=544	USA	2 years	Age, education, cognition, physical function, comorbidities, and hypertension severity	Community-dwelling men, aged 74.4±5.2 with diagnosed hypertension	CRAS (+)	Hopkins Verbal Recall Test (HVRT) (+)	342 (62.9%) participants were using anticholinergic medications, with a mean anticholinergic score of 1.3 ± 1.5	A 1-unit increase in the cumulative anticholinergic burden per 3 months was significantly associated with a memory decline (0.32, 95% CI = 0.05–0.58)
Ehrt 2010 (129)	Cohort study, n=235	Norway	8 years	Gender, education, age, baseline	Community-dwelling patients aged 68.7±8.4 with	AAS (+)	Mini-Mental State Exam (MMSE) (+)	At baseline, 102 (43.4 %) received at least one drug with anticholinergic activity	AAS score was associated with a decline in cognitive function (p<0.04).

				cognition and depression	Parkinson's disease				
Study	Design, size	Country	Duration	Adjustment's	Participant characteristics	Anticholinergic Scale (+/-)*	Cognitive tool, (+/-)*	Exposure to anticholinergic drugs	Results
Ancelin 2006 (137)	Cohort study, n=372	France	8 years	Age, sex, and education level	Community and institutionalised people over 60 without dementia	ABC (+)	Psychomotor speed (+), primary and secondary visuospatial memory (+), narrative recall (+), visuospatial construction (+), implicit memory (-)	14% were taking at least one anticholinergic drug at the start of the study	Anticholinergic drug was associated with mild cognitive impairment (OR=5.12, 95% CI=1.94-13.51)
Fox 2011 (52)	cohort study, n=13004	UK	2 years	Age, sex, education, social class, the number of non-anticholinergic medications, and some comorbidities.	Community and institutionalised participants aged 65 and older	ACB (+)	MMSE (+)	47% of the participants used medication with possible anticholinergic properties, and 4% used a drug with definite anticholinergic properties	Participants taking definite anticholinergics had a 0.33-point greater decline in the MMSE score (95% CI=0.03-0.64) than when not taking anticholinergics. For participants taking Possible anticholinergics, there was no association with a further decline (0.02, 95% CI=-0.14-0.11)
Campbell 2010 (49)	Cohort study, n=1652	USA	6 years	Age, gender, educational level, and baseline cognitive performance	Community-dwelling African-American participants over 70 with normal cognitive	ACB (+)	Neuropsychological battery adapted from (CERAD), The clinician home-based Interview to assess	53% of the population used a possible anticholinergic, and 11% used a definite anticholinergic	Definite anticholinergics were associated with an increased risk of cognitive impairment (odds ratio [OR] 1.46, 95% confidence

					function at baseline		function, and standardised neurological exam and a structured interview with a relative) (+)		interval [CI] 1.07–1.99). Whereas the number of possible anticholinergics at baseline did not increase the risk (OR 0.96, 95% CI 0.85–1.09).
Study	Design, size	Country	Duration	Adjustment's	Participant characteristics	Anticholinergic Scale (+/-)*	Cognitive tool, (+/-)*	Exposure to anticholinergic drugs	Results
Yarnall 2015 (136)	Cohort study, n=318	UK	18 months	age, gender, years of education, disease duration	Newly diagnosed patients with Parkinson's disease (PD) from community and outpatient clinics + unrelated control population	ADS (-)	MoCA (-), MMSE (-)	83 (43%) PD participants had ADS scores of ≥1, and 112 (89%) PD participant had ADS scores of zero	The proportion of patients with cognitive impairment and PD were similar in those with and without anticholinergic drug use
Fox 2011 (139)	Cohort study, n=224	UK	18months	cognition, age, gender, and cholinesterase inhibitor	Participants with AD, aged over 55 years living in North London community and institution	ACB (-)	MMSE (-), Severe Impairment Battery (SIB) (-)	the mean anticholinergic load was 1.1 (SD 1.4)	There was no significant association between ABS score and cognition at baseline, 6, or 18 months in patients with Alzheimer's disease

AAS = Anticholinergic Activity Scale ABC = Anticholinergic Burden Classification ACB = Anticholinergic Cognitive Burden Scale ADS=Anticholinergic Drug Scale ARS = Anticholinergic Risk Scale CrAS = Clinician-rated Anticholinergic Score DBI = Drug Burden index, N/R = not reported, California verbal learning test = CVLT, Mini-Mental State Exam = MMSE, potential inappropriate medicine = PIM, The Reliable Change Index (RCI) and the Standardized Regression-Based measure (SRB), * significant /non-significant longitudinal association (+/-).

Table 4 Characteristics of longitudinal observational studies assessing mortality

Study	Design, size	Country	Duration	Adjustment for cofounders	Participant characteristics	Anticholinergic Scale (+/-)*	Result
Kumpula 2011 (94)	Cohort, n=1004	Finland	1 year	Age, sex, and nutritional status	Long-term care ward in a hospital, aged 81.3±10.9	ARS(-)	High ARS scores were not associated with mortality. Higher ARS scores were not associated (ARS score 1–2: hazard ratio 1.08, 95% CI 0.84-1.41; ARS score ≥3: hazard ratio 1.05, 95% CI 0.75-1.46).
Dauphinot 2014 (132)	Cohort study, n=337	France	11.6 months	No	Hospital patients aged 85.4±6.6	DBI-WHO, DBI (-)	The Increase in DBI during hospital stay was not related to the risk of mortality (Hazard ratio (1.90; 0.8-4.4)
Fox 2011 (52)	longitudinal cohort, n=1304	UK	2 years	Age, sex, education, social class, the number of non-anticholinergic medications, and the number of comorbidities.	Community and institutionalised participants, 75.2 ± 6.8.	ACB (+)	Two-year mortality was greater for those taking definite (OR=1.68; 95% CI=1.30–2.16) and possible (OR=1.56; 95% CI=1.36–1.79) anticholinergics.
Myint 2015 (140)	Cohort, n=21,636	UK	10 years	Age, smoking status, alcohol consumption, systolic blood pressure and prevalent conditions	Community-dwelling participants aged 40-79	ACB (+)	There was a dose-response relationship between increasing ACB and mortality. People with total ACB ≥3, 2-3, 1 and 0 from medications had hazard ratios of 1.83 (1.53, 2.20), 1.65 (1.49–1.82), 1.28 (1.18–1.39), 1, respectively.
Jansen 2016 (128)	Cohort, n= 1705	Australia	5 years	Age, dementia, or mild cognitive impairment (MCI) diagnosis at baseline, comorbidity, education level, and living status	community-dwelling men aged 70 and older	DBI (+)	Each one-unit increase in DBI was associated with a 2.75 times greater risk of death (95% CI = 1.60–4.75)
Lattanzio 2018 (134)	Cohort, n=807	Italy	1 year	age, sex, cognitive impairment, depression, number of lost BADL, number of medications, hypertension(HBP), heart failure, diabetes, coronary artery disease, atrial fibrillation, peripheral arterial	Hospitalised older adults aged 65 and older	ACB (+)	Discharged patients' ACB score of ≥ 2 was significantly associated with mortality: ACB score ≥ 2: HR 1.69 (1.09–2.65), but not those with ACB scores of 1: ACB score 1: HR 1.19 (0.75–1.90).

				disease, stroke, COPD, and cancer			
Study	Design, size	Country	Duration	Adjustment for cofounders	Participant characteristics	Anticholinergic Scale (+/-)*	Result
Lattanzio 2018 (135)	Cohort, n=807	Italy	1 year	Age, sex, cognitive impairment, depression, history of falls, number of medications, HBP, stroke, atrial fibrillation, heart failure, COPD, diabetes, and cancer	Hospitalised older adults aged 65 and older	ACB (+)	ACB score 2 or more was significantly associated with mortality in dependent patients 2.25 95% confidence (CI) 1.22–4.1. No association was found in independent patients HR 1.06 95% CI 0.50–2.34). There was no significant association between an ACB score of 1 and mortality in both groups. In the independent group, ACB score of 1= 0.92 (0.45–1.89), and in the dependent group 1.50 (0.81–2.73).
Wauters 2017 (131)	Cohort, N= 503	Belgium	1.5 years	the number of medications taken at baseline and with the level of multi-morbidity	Community-dwelling older adults aged 80 and older without dementia	MARANTE (+)	MARANTE score ≥ 2 : HR 2.20 (1.03–4.67) Low: 0.5–1.5 : 1.31 (0.57–3.02) not significant increased risks of mortality in those with high anticholinergic exposure but not in those with low
Corsonello 2018(133)	Cohort, N= 576	Italy	1 year	Age and gender	Hospitalised older adults aged 65 and over	ACB (+)	A dose-response relationship between ACB score and mortality was reported in age and gender-adjusted model. ACB score 1:HR1.70(0.86–3.63), ACB score 2 :HR 3.32 (1.67–6.60),ACB score 3: HR 3.31 (1.45–7.56),ACB score 4: HR 4.16 (1.46–11.5) ACB score 5: HR 6.38 (1.41–28.9)

AAS = Anticholinergic Activity Scale. ABC = Anticholinergic Burden Classification ACB = Anticholinergic Cognitive Burden Scale ADS=Anticholinergic Drug Scale ARS = Anticholinergic Risk Scale CrAS = Clinician-rated Anticholinergic Score DBI = Drug Burden index N/R = not reported, Charleston comorbidity Index = CCI4 COPD = Chronic Obstructive Pulmonary Disease

MARANTE = Muscarinic Acetylcholinergic Receptor ANTagonist Exposure scale * significant /non-significant longitudinal association (+/-).

Anticholinergic burden scales

Nine measures of anticholinergic burden were identified. They included the following:

1. The Anticholinergic Cognitive Burden Scale (ACB) quantified the anticholinergic potency of 88 drugs, with scores from 0-3 and was developed through expert opinion and literature (51).
2. The updated Clinician-rated Anticholinergic Scale (CrAS) quantified the anticholinergic potency of 60 drugs, with scores from 0-4 and was developed through expert opinion and literature (127).
3. The Anticholinergic Burden Classification (ABC) quantified the anticholinergic potency of 27 drugs, scores 0-3 and was developed through expert opinion and receptor binding data (SAA) (137).
4. The Anticholinergic Risk Scale (ARS) quantified the anticholinergic potency of 49 drugs, with scores from 0-3 and was developed through expert opinion and literature review (141).
5. The Anticholinergic Drug Scale (ADS) quantified the anticholinergic potency of 117, with scores from 0-3 and was developed by evaluating available literature (142).
6. The Anticholinergic Activity Scale (AAS), which quantifies the anticholinergic potency of 99 drugs, scores from 0-4, and was developed through expert opinion and receptor binding data (SAA) (129)
7. The Drug Burden Index (DBI) is a dose-dependent equation and does not quantify a specified number of drugs. The normal scores range from 0-1. The equation is:

$$DBI = \sum \frac{D}{\delta + D}$$

The equation was developed using data from existing literature and involved consideration for the daily dose (D) and recommended minimum daily dose (δ) as approved by the US Food and Drug Administration (143)

8. The DBI-World Health Organization (DBI-WHO) was developed because recommended daily doses can vary across different countries. Thus, the daily dose (δ) needed to be defined according to local contexts. Here, δ represents the defined daily dose (DDD), the estimated average daily maintenance dose (defined by the WHO) for a drug used for its main indication in adults. The DDD is based on a review of doses used in various countries (132, 144).
9. The Muscarinic Acetylcholinergic Receptor ANTagonist Exposure (MARANTE) scale quantifies 41 drugs, scores from 0-2, and was developed through systematic review, expert opinion and calculations of potency and daily dose (145)

Anticholinergic burden scales that predicted an increased risk of adverse outcomes

The Anticholinergic Cognitive Burden Scale (ACB) was the most frequently used scale in this review. Five of 6 studies that used the ACB scale to measure anticholinergic exposure reported an increased risk of impaired cognitive function over time. Studies that used the Anticholinergic Activity Scale (AAs), Clinician-Rated Anticholinergic Score (CrAs), Anticholinergic Burden Classification (ABC), Drug Burden Index (DBI), and Anticholinergic Risk Scale (ARS) also demonstrated an increased risk of cognitive impairment. However, studies that used the Anticholinergic Drug Scale (ADS) gave inconsistent results depending on the cognitive tool.

The ACB, DBI and MARANTE were the only scales that predicted an increased risk of death. Studies that used the ACB (n=5), MARANTE (n=1), and DBI (n=1) showed a negative association with mortality. The ARS and DBI-WHO were not associated with death.

Differences between measures of anticholinergic burden

The anticholinergic burden scales (ADS, ARS, CrAs, ABC, MARANTE and AAs) were compared to the ACB scale, as it was the most frequently used scale identified in this review. The ACB scale comprises 88 drugs quantified based on their anticholinergic potency. Of all 88 drugs on the ACB scale, CrAs, ABC, ARS, ADS, AAS, and MARANTE quantified the anticholinergic potency for only 31, 21, 30, 71, 21, and 29 drugs, respectively. Figure 3 below illustrates the difference between the scales.

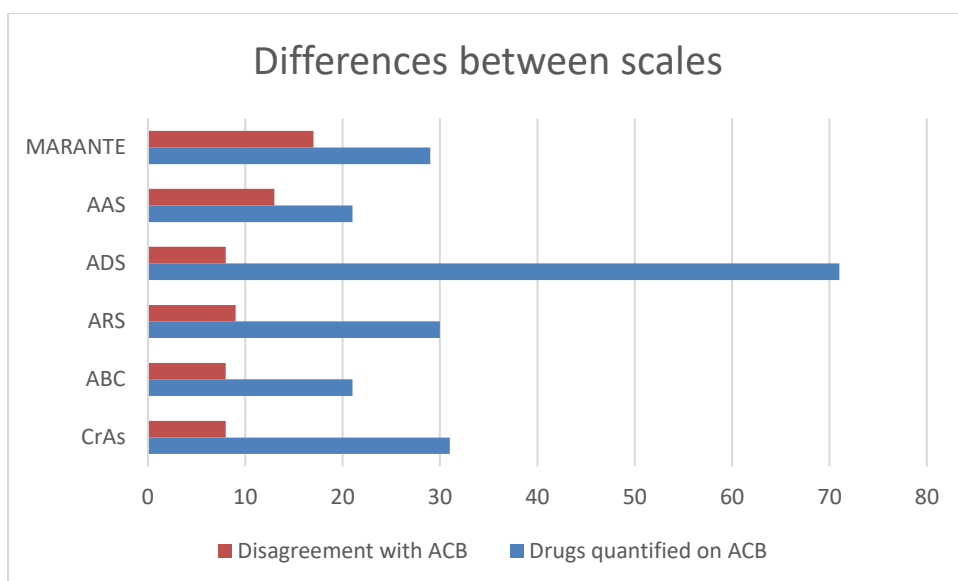


Figure 3. Summary of the differences between the scales

The ABC disagreed with the ACB on anticholinergic scores of 10 of 21 (47%) drugs, including cyproheptadine, alimemazine, alverine, codeine, theophylline, furosemide, digoxin, colchicine, clorazepate, and alprazolam. The CrAs disagreed with the ACB on 8 of 31 (26%) drugs, including paroxetine, perphenazine, propantheline, quetiapine, belladonna, carbamazepine, cyclobenzaprine, and ranitidine. The ARS disagreed with the ACB on the anticholinergic potency for 8 of 30 (27%) drugs, including clozapine, nortriptyline, olanzapine, paroxetine, quetiapine, cyproheptadine, cimetidine, and loperamide (Appendix 1. Table 17).

The ADS disagreed with the ACB on the anticholinergic potency for 9 of 71 (13%) drugs, including thioridazine, perphenazine, paroxetine, olanzapine, amantadine, ranitidine, disopyramide, cimetidine, and brompheniramine. The AAS disagreed with the ACB on the anticholinergic potency for 13 of 21 (62%) drugs, including benztropine, clozapine, doxepin, orphenadrine, scopolamine, tolterodine, trifluoperazine, trihexyphenidyl, trimipramine, quetiapine, fluvoxamine, ranitidine, and theophylline.

The MARANTE disagreed with the ACB on the anticholinergic potency for 17 of 29 (59%) drugs, including amantadine, belladonna, clozapine, doxepin, nortriptyline, olanzapine, paroxetine, quetiapine, tolterodine, trifluoperazine, amitriptyline, clomipramine, diphenhydramine, hydroxyzine, imipramine, oxybutynin, and promethazine. Appendix 1. Table 17 presents the result from the comparison of anticholinergic burden scales.

The DBI could not be directly compared to the ACB scale because it is an equation and does not rely on a specific drug list to estimate the anticholinergic burden. The DBI-Ach

was associated with an increased risk of a negative outcome (cognitive impairment), but both scales found no association in mortality studies.

Cognitive impairment and anticholinergic burden

Of the 11 studies that assessed cognitive function, eight reported a significant increase in the risk of cognitive impairment in patients exposed to anticholinergic burden over time (Table 3). One study on younger patients found a significantly lower level of complex attention but no evidence of greater cognitive decline, and two studies found no association. The studies that found no significant association involved patients with Alzheimer's (138) or short duration and small sample (136).

In addition, except for Kashyap et al., studies on cognitive function were more likely to show no association when they had fewer participants and a shorter duration (Table 5). There was little scope for the meta-analysis of studies on cognitive function due to considerable heterogeneity in study design and outcome measures

Table 5. Table of sample size, study duration for studies on cognition

Study	Sample Size	Time (years)
Koyama 2013 (+)	1484	10
Ancelin 2006 (+)	372	8
Ehrt 2010 (+)	235	8
Campbell 2010 (+)	1652	6
Koyama 2013 (+)	1429	5
Low 2008(+)	2058	4
Fox 2011 (+)	13004	2
Han 2008 (+)	544	2
Yarnall 2015 (-)	318	1.5
Fox 2011 (-)	224	1.5
Kashyap 2014 (+)	102	1

(+) association found, (-) no association found.

Anticholinergic burden and mortality

Of the nine studies that assessed mortality, two found no association between anticholinergic burden and death over time (Table 4). One of the studies that found no association had a smaller sample size and shorter duration (132). In general, studies with a longer duration of over a year all reached significance (Table 7).

Table 6. Table of sample size, study duration for studies on mortality

Study	Sample size	Duration (years)
Myint 2015 (+)	21636	10
Jansen 2016 (+)	1705	5
Fox 2011 (+)	1304	2
Kumpula 2011 (-)	1004	1
Dauphinot 2014 (-)	337	0.96
Lattanzio 2018 (+)	807	1
Lattanzio 2018 (+)	807	1
Wauters 2017 (+)	503	1.5
Corsonello 2018 (+)	576	1

(+) association found, (-) no association found.

Measures of outcome that are associated with the greatest risk of adverse outcomes

An increase in the risk of cognitive impairment with prolonged exposure to anticholinergic burden was observed when cognition was evaluated with symbol digit modalities test, CVLT-II immediate recall, category fluency, free and cued recall (RL/RI), digit symbol-coding WAIS, the trail-making test-B, Hopkins Verbal Recall Test (HVRT), psychomotor speed, primary and secondary visuospatial memory, narrative recall, visuospatial construction, neuropsychological battery adapted from (CERAD), the clinician home-based Interview to assess function, and standardised neurological exam and a structured interview with a relative

However, no significant association was observed between increased anticholinergic burden and cognitive impairment when cognition was evaluated with; California verbal learning test I (one trial), digits backwards test, simple and choice reaction time, trails B, CVLT-II delayed recall, Mattis dementia rating scale, Rey-Osterrieth Complex Figure Test recall, Stroop test, implicit memory, and logical reasoning ability, Severe Impairment Battery (SIB), and digit symbol-coding WAIS. Table 6 presents the cognitive outcome measures and corresponding domain.

The MMSE was applied to evaluate cognition more frequently than any other tool identified in this review. However, studies using the MMSE demonstrated inconsistent results. In two studies (52, 129), increased anticholinergic burden was significantly associated with lower MMSE scores, but not in four studies (105, 107, 136, 138). For the modified MMSE (3MS), one of two studies demonstrated significantly reduced 3MS scores with increasing anticholinergic burden, while the other study did not (125, 126). The Montreal cognitive assessment (MoCA) did not detect cognitive impairment in the two studies that used it to measure cognitive function (107, 136).

In summary, 5 of 8 memory tests, 1 of 4 tests for attention, 2 of 7 tests for executive function and 4 of 12 measures of global function showed a negative association with anticholinergic burden.

Table 7. Table of cognitive tests and what they measure

Cognitive outcome measure	Domain	Studies(+/-)
Primary and secondary visuospatial memory	Memory	Ancelin 2006 (137) (+)
Narrative recall	Memory	Ancelin 2006 (137) (+)
California verbal learning test I immediate recall	Memory	Low 2008 (105) (-)
CVLT-II immediate recall	Memory	Koyama 2013 (125) (+)
CVLT-II delayed recall	Memory	Koyama 2013 (125) (-)
Free and Cued Recall (RL/RI)	Memory	Kashyap 2014 (107) (+)
Implicit memory	Memory	Ancelin 2006 (137)(-)
Hopkins Verbal Recall Test (HVRT)	Memory	Han 2008 (127) (+)
The symbol digit modalities test	Attention	Low 2008 (105) (+)
Simple and choice reaction time	Attention	Low 2008 (105) (-)
Digits backwards	Attention	Low 2008 (105) (-)
Backward digit span	Attention	Koyama 2013 (125) (-)
The Trail-Making Test-B	Executive function	Koyama 2013 (125) (-), Kashyap 2014 (107) (+)
Digit symbol-coding WAIS	Executive function	Kashyap 2014 (107) (-)
Rey-Osterrieth Complex Figure Test recall	Executive function	Kashyap 2014 (107) (-)
Stroop test	Executive function	Kashyap 2014 (107) (-)
Category fluency	Executive function	Koyama 2013 (125) (+)
Verbal fluency	Executive function	Koyama 2013 (125) (-)
Severe impairment battery (sib)	Global function	Fox 2011 (139) (-)
Mattis dementia rating scale	Global function	Kashyap 2014 (107) (-)
MMSE	Global function	Kashyap 2014 (107) (-), Ehrt 2010 (129) (+), Yarnall 2015 (136) (-) ,Fox 2011 (139) (-),Fox 2011 (52) (+)
3Ms	Global function	Koyama 2013 (125) (-), Koyama 2013 (126) (+)
MOCA	Global function	Kashyap 2014 (107) (-), Yarnall 2015 (136) (-)
Psychomotor speed	Psychomotor	Ancelin 2006 (137) (+)
Visuospatial construction	Visuospatial	Ancelin 2006 (137) (+)
Neuropsychological battery from CERAD	Assessment	Campbell 2010 (49) (+)
Logical reasoning ability	Intellectual Ability	Ancelin 2006 (137) (-)

(+) association found, (-) no association found

Meta-analysis of studies on mortality

Of all studies on mortality included in the systematic review, only studies that reported enough information to estimate the hazard ratio and controlled for confounding were included in the meta-analysis (n=6). Three studies were excluded from the meta-analysis. One did not specify the anticholinergic burden class and did not control for confounding (132). The second study was excluded to avoid using the same cohort twice (135), and the third study used odds ratio (52).

Considerable variability in reporting of results posed difficulties in the analysis. Therefore, it was not possible to analyse moderate and high anticholinergic burden separately. All meta-analysis data presented compared no anticholinergic burden (ACB = 0) with low (ACB= 1) or moderate to high anticholinergic burden (ACB≥2). After stratifying the relevant data, it was still not possible to include all data in these categories. Thus, some results were excluded. Priority was given to the lower burden score that could fit within a category to avoid overestimating the effect size. For example, one study reported the risk of death in patients with an anticholinergic score of 1, 2-3 and over 3 (140). In this case, hazard ratios of patients with 1 (low) and 2-3 (moderate to high category) were included in the meta-analysis. The results of patients with scores above 3 were excluded from the analysis to avoid including the same study multiple times within a category. Appendix 1 Table 20 provides a summary of excluded and included data.

In total, the meta-analysis included 26,231 patients. Of the 6 studies included in the meta-analysis, only 5 presented results that could be pooled for the moderate to high burden. The pooled HR for five studies in the moderate to high category (ARS and ACB ≥2, MARANTE scale ≥ 2 or DBI >0.5) demonstrated that anticholinergic burden was associated with a statistically significant increase in mortality (HR 1.94; CI 1.35-2.77; $p<0.0003$) with significant heterogeneity between risk estimates (I^2 77; χ^2 $p=0.002$) (Figure. 4). There was a difference in the pooled result from the fixed-effects modelling 1.65 (1.51, 1.81). Sensitivity analysis did not show any results that were not significant (Appendix 1. Table 18).

Of the 6 studies included in the meta-analysis, only 4 presented results that could be pooled for the low burden (ARS or ACB 1, MARANTE 0.5–1.5 and DBI 0.5). However, since participants might have overlapped in two studies, only three studies could be analysed at a time. A pooled analysis of all three studies for low burden demonstrated that anticholinergic burden was associated with a statistically significant increase in mortality (HR 1.29; CI 1.19-1.39; $p<0.00001$) with insignificant heterogeneity between risk

estimates (I^2 0; χ^2 $p=0.42$). Figure 5 presents the meta-analysis results for low vs no burden. During sensitivity analysis, the greatest change in the overall risk estimate occurred after the largest study was excluded (146). The results showed a non-significant increase in the risk of death HR 1.33 (0.94-1.88) with no significant heterogeneity (I^2 0; χ^2 $p=0.42$) (Appendix 1. Table 19).

Only two studies could be pooled for the ACB scale in the low and moderate to high categories. The results showed a significant association with 1.29 [1.19, 1.39] and 2.15 [1.10, 4.19] for low and moderate to high categories. ARS, MARANTE and DBI could not be meta-analysed.

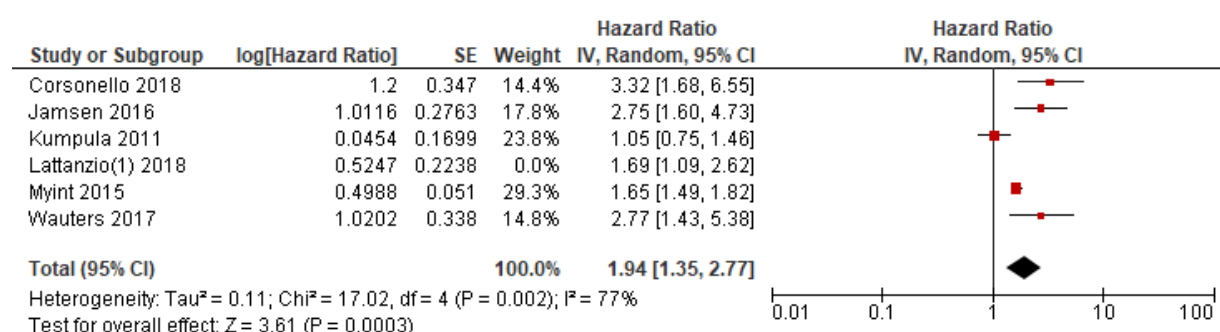


Figure 4. Mortality of patients with moderate to high anticholinergic burden vs no burden (excluding lattanzio1)

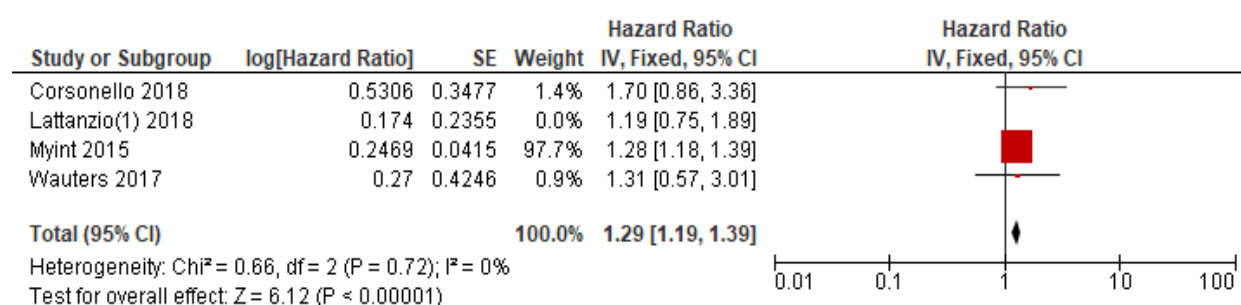


Figure 5 Mortality of patients with low anticholinergic burden vs no burden (excluding lattanzio1)

Strength of the association between anticholinergic burden, cognitive impairment, and mortality

As mentioned above, a causal relationship is more plausible where there is a dose-response relationship. Few studies examined reported on the anticholinergic dose relationship with cognition and mortality. Han et al. reported that a 1-unit increase in the cumulative anticholinergic burden per 3 months was significantly associated with memory decline (0.32, 95% CI = 0.05–0.58) (127). Fox et al. reported a dose-response relation observed between greater total ACB score and MMSE decline, with those who scored 4 or greater on the ACB declining by 0.34 (95% CI=0.01–0.67) more points on the MMSE than those not taking anticholinergics. However, participants taking possible anticholinergics did not experience a further decline in cognition (0.02, 95% CI=–0.14–0.11) (52). Campbell et al. also reported that drugs with ACB scores 2 or 3 were associated with an increased risk of cognitive impairment (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.07–1.99). In comparison, drugs with an ACB score of 1 at baseline did not increase the risk (OR 0.96, 95% CI 0.85–1.09; $p < 0.55$).

For studies on mortality, Fox et al. reported that mortality was greater for those taking drugs with an ACB score of 2 or 3 (OR=1.68; 95% CI=1.30–2.16; $P < 0.001$) and drugs with an ACB score of 1 (OR=1.56; 95% CI=1.36–1.79; $P < 0.001$) compared to those with an ACB score of 0 (52). Myint et al. reported that people with total ACB ≥ 3 , 2–3, 1 and 0 from medications had hazards ratios of 1.83 (1.53–2.20), 1.65 (1.49–1.82), 1.28 (1.18–1.39), 1 respectively ($p < 0.00001$) (140). Jansen et al. reported that each one-unit increase in DBI was associated with a 2.75 times greater risk of death (95% CI = 1.60–4.75) (128).

Furthermore, three studies reported that mortality was greater for those with ACB scores of 2 and over (133–135). With one of these reporting a further dose relationship with ACB score 1: HR 1.70 (0.86–3.63), ACB score 2: HR 3.32 (1.67–6.60), ACB score 3: HR 3.31 (1.45–7.56), ACB score 4: HR 4.16 (1.67–6.60) and ACB score 5: HR 6.38 (1.41–28.9) (133).

Discussion

This is the first systematic review to examine prospective studies that allow the temporal relationship between anticholinergic burden, cognitive impairment, and mortality in older adults to be established. This is also the first study on the meta-analysis of prospective studies on mortality. The review evaluated 19 studies that used a measure of anticholinergic burden at baseline and follow-up. This systematic review's main finding was the evidence of the temporal relationship between sustained exposure to anticholinergic burden, cognitive impairment, and mortality.

Anticholinergic burden and mortality

Of the 9 studies on mortality, 7 reported an increased risk of mortality with anticholinergic burden, and 2 did not. The studies with follow-up of >1 year were more likely than those with shorter duration (100 vs 60%) to show a significant association between anticholinergic burden and mortality. This finding further supports the hypothesis that the short duration of studies on mortality could impact their ability to reach significance (79). Furthermore, during sensitivity analysis, the greatest change in the overall risk estimate of the low vs no burden group occurred after the study with the longest duration was excluded, demonstrating a non-significant trend toward increased risk of mortality (Appendix 1. Table 19) (140).

The anticholinergic burden classification categories used in the present systematic review were similar to those used in a previous systematic review (78). Based on the meta-analysis of all 3 studies for low burden (ARS or ACB 1, MARANTE 0.5–1.5 and DBI 0.5) using a non-conservative estimate, there was a 29% increase in the risk of mortality in this group compared to those who had no exposure to anticholinergic burden. There was no evidence of heterogeneity between the risk estimates.

The conservative estimate for pooled HR for the moderate to high category (ARS, ACB and MARANTE ≥ 2 or DBI >0.5) in 5 studies demonstrated a statistically significant 94% increase in mortality, with statistically significant heterogeneity between studies. There was some evidence of a dose-response in that the pooled HR was higher for the moderate to high categories 1.94 (CI 1.35-2.77) than for the low-moderate categories 1.29 (CI 1.19-1.39). In addition, a dose-response relationship was reported in a study that could not be included in the meta-analysis (52). These findings demonstrate evidence of a temporal relationship between mortality and anticholinergic burden. Also, the dose-response seen provided some evidence of a gradient in the expected direction.

However, the evidence of dose-response should be interpreted with caution. The confidence intervals for both categories slightly overlap, suggesting the true HR could be the same for the two groups relative to none. A possible explanation of this finding may be the exclusion of patients with scores above 3 in the largest study, eliminating a large proportion of patients in the moderate to high category and impacting the strength of the results. In addition, fewer studies were meta-analysed in the low category because of how they were reported. There is a possibility that including other studies could have significantly impacted the results. It merits noting that with the non-conservative estimate for the high category, there was a 65% increase in the risk of death devoid of overlapping confidence intervals (1.51-1.81).

A systematic review that did not include a meta-analysis found that most studies on mortality did not find an association (147). While the study had different inclusion criteria and involved cross-sectional and case-control study designs, it is of value to note that the majority of the studies on mortality that did not show an association possessed smaller sample sizes than studies that reached significance in the present review (148-151). This might be because smaller studies might be inadequately powered to show a meaningful difference.

The present study's findings support the findings from a meta-analysis by Ruxton et al. on the association between anticholinergic burden and mortality (98). The authors reported a 106% increase in the odds of mortality for each additional score on the ACB scale. However, the review included retrospective cohort studies that do not allow for the temporal relationship between event and outcome to be reliably established, thus providing less scope for inference of causal association. In addition, the odds ratios used in the previous study are not appropriate for the meta-analysis of time-to-event outcomes (121). This might explain the large effect seen in the above study.

Anticholinergic burden and cognition

Only 8 of the 11 studies that evaluated cognition reported a negative association with anticholinergic burden over time on any measure of cognition. Global measures of cognition and specific neuropsychological domains such as memory, attention, and executive function, were used to measure cognition in the included studies. Notably, most (64%) studies on cognition relied on multiple measures of cognitive function. However, the authors reported finding an association with some, but not other measures of cognitive function. For example, one study reported no negative association with global measures

of cognitive function such as Mattis dementia rating scale, MMSE and MOCA, but reported deficits in memory and attention measured by free and cued recall and the trail-making test-b, respectively (107).

Generally, global cognitive tests were used more often than neuropsychological tests that measured one specific cognitive domain. The MMSE and modified MMSE (3MS) was used to evaluate cognition in seven studies and demonstrated inconsistent results, with only 3 demonstrating a negative association. Interestingly, most of the studies that did not detect a significant difference in MMSE with exposure to anticholinergic medicines identified deficits in cognition with specific neuropsychological tests (free and cued recall, visual attention and task switching, verbal and learning memory, and semantic memory). One of the criticisms of MMSE is limited sensitivity to subtle changes in cognition, and ceiling effect, which may have prevented the detection of subtle changes (152). Though many practitioners rely on global measures like MMSE and MOCA to evaluate cognitive performance, the results of this review indicate that global tests of cognitive function might not be sensitive or specific enough to detect changes in some populations exposed to anticholinergic burden. Overall, specific neuropsychological tests of memory on older adults were more likely to detect a significant difference from a previous performance. However, there was considerable heterogeneity in the neuropsychological test used in the included studies precluding meaningful meta-analysis.

Overall, studies with longer duration were more likely to report an association. This finding implies that prolonged exposure, rather than short-term exposure to anticholinergic burden, increases the risk for cognitive impairment. It is not clear how long an older adult will need to be exposed to anticholinergic burden to see a decline in function since the included studies did not follow patients from the start of the therapy or monitor adherence, potentially impacting the results of studies. It also merits noting that individual pharmacokinetic differences resulting from sex, health status, lifestyle and genetic variations may cause variation or impact an individual's susceptibility to these adverse effects. Explaining why the same dose of a drug in an older adult may not always produce a similar effect even in an identical population (153). Thus the period before an adverse outcome is seen may vary among individuals.

In addition to a relatively small sample size and short duration, one study that found no association included patients with Alzheimer's disease and used MMSE as a measure of cognition (139). This finding is consistent with reports from a previous study which demonstrated that anticholinergic burden was not associated with a decline in MMSE score in participants with dementia. However, the study demonstrated an association in

participants without dementia(154). This finding also supports the previous reports of the floor effect of MMSE, making it inefficient at detecting small changes in patients with advanced stages of dementia (155).

In a few studies, the amount of anticholinergic exposure and the corresponding degree of cognitive decline observed was reported. Han *et al.* reported that in older community-dwelling men with hypertension, a 4-unit increase in total anticholinergic burden per year corresponded with a 0.32 point deficit in memory. Similarly, Fox *et al.* reported that an anticholinergic score of 4 corresponded with a 0.34 point decline in cognition. The presence of a dose relationship in long-term studies is an important predictor of a causal relationship. However, it is important to note that the presence of inadequate control for confounding could lead to false positives. For example, no study controlled for frailty, an important consideration in older populations. In addition, only 1 study on cognition controlled for smoking, an identified risk factor of cognitive impairment (125, 156). Across the board, control for potential confounders such as co-morbidities and disease severity was poor.

Temporality

One of the widely accepted principles of causality is that exposure should precede outcome. Temporality was achieved by the inclusion of studies with a prospective cohort design. Though some studies included participants that were not cognitively normal at the start, this did not necessarily invalidate the presence of a temporal relationship, which was in this case established with new cases of the outcome or worsening cognitive impairment. Thus, the studies for cognition showed a temporal relationship between anticholinergic burden and cognitive impairment. In addition, the results from the meta-analysis also demonstrated a temporal relationship between anticholinergic burden and mortality. Temporality adds to the evidence of a causal relationship; however, the presence of residual confounding in some or all of the studies limits the inference of causality.

Anticholinergic burden scales

The anticholinergic cognitive burden scale (ACB) was the most frequently used scale in this review (51). Similarly, Salahudeen *et al.* reported that the ACB was the most frequently validated anticholinergic scale on adverse clinical outcomes (157). Also, 5 of 6 that applied the ACB scale reported a significant negative association with cognitive impairment. Kashyap *et al.* reported that the ACB scale was more sensitive at identifying

individuals with an increase in anticholinergic burden compared to other scales (DBI-Ach, ADS, and ARS) that were applied (107). The authors attributed the differences in sensitivity between the scales to the quantification of certain drugs on the ACB scale compared to the others (e.g., paroxetine ACB score = 3, ARS score =1, ADS score = 1) (107).

A high percentage of disagreement was also identified in this review, with CrAs disagreeing with the ACB scale on 26% of drugs, ARS on 33%, ADS on 13%, and AAS on 62% of drugs. The variation between the scales could affect the estimate of anticholinergic exposure and subsequently affect the results of studies. For example, suppose a patient was on a combination of drugs, including quetiapine, carbamazepine, ranitidine, and theophylline. In that case, a clinician might calculate the anticholinergic burden score differently depending on the scales used. The anticholinergic potency for the combination of drugs would be 7 (ACB), 5 (CRAs), 2 (ABC scale), 2 (ARS scale), 5 (ADS scale), and 6 (AAS). The difference in anticholinergic burden score is not only influenced by the variation in the quantification of anticholinergic potency between the scales but also by the absence of many drugs from the scales. Clinicians and researchers who use the anticholinergic burden scales might not consider the anticholinergic effect of drugs that have not been quantified, resulting in an underestimation of anticholinergic activity. Also, the type of drugs used in certain populations might limit the usefulness of a scale. Thus, in the absence of a gold standard, the choice of scale may depend upon the population being studied. Clinicians and researchers estimating the anticholinergic burden should consider using larger scales which are more likely to quantify more of the patient's drugs and give a more accurate picture of anticholinergic burden (e.g., ACB and ADS). Also, consideration should be given to clarifying the anticholinergic activity on more than one scale.

Meta-analysis of low and moderate to high categories measured by the ACB scale in mortality studies demonstrated a 29% and 215% increase in the risk of death. It is not clear how useful the meta-analysis of the two studies is since meta-analysis of 2 studies often performs poorly, particularly in the estimation of heterogeneity (158). Thus, the risk of death may be overestimated in this case. A recently published meta-analysis of mortality reported that pooled prospective and retrospective studies showed a 39% increase in the HR of low anticholinergic exposure measured with the ACB scale (95%CI 1.1–1.75). The "high" ACB category showed a 47% increase in HR (95%CI 1.19–1.81) (159).

Despite the considerable variability between the scales, all the scales included in this study were able to predict an adverse outcome. These findings demonstrate that anticholinergic

burden scales are useful in predicting the adverse effects of medicines with anticholinergic properties in research and clinical practice.

Quality of included studies

Included studies had a moderate to high risk of bias, which did not seem to affect the study outcome. However, the moderate to high risk of bias in each study in this review reduces confidence in the results obtained. Though most studies in the review adjusted for confounding (18 of 19), it might be difficult to control all potential confounders adequately. Therefore, the risk of residual confounding is a limitation of the studies selected for this review and reduces confidence in the results of the present study. Also, no study controlled for mortality as a potential confounder. Fox *et al.* reported no evidence of an association between anticholinergic use and cognitive decline in those with already significantly impaired cognition. The authors noted that 24% of this group died before the follow-up assessment. They highlighted the possibility that cognitive decline associated with anticholinergic medication use might have occurred in this group before death but was not captured in the study (52). Future studies of cognition should consider mortality as a potential confounder. Notably, the study by Myint *et al.* that demonstrated a temporal relationship did not control for comorbidities such as dementia and malignant diseases. In addition, no study controlled for frailty, an important consideration in older adults.

The possible presence of publication bias was not assessed using funnel plots due to the small number of studies in the meta-analysis resulting in a possible misleading interpretation of funnel symmetry (160).

Strengths and Limitations of the review

The electronic search conducted for this systematic review was wide-ranging, in that three different databases were searched. In addition, a subsequent manual search was conducted on previous systematic reviews to identify additional studies. Another strength of the study was that the search did not limit studies by language to reduce the possibility of excluding a large body of knowledge. Nevertheless, it is possible to miss a small number of studies and publication bias may have made it easier to find studies with a “positive” result. Also, authors may have selectively reported results that demonstrate desired outcomes.

Secondly, substantial heterogeneity precluded meta-analysis of studies on cognition, and pooled mortality studies were too few to evaluate publication bias. This meant publication bias could not be considered and may have impacted the results of this review. Thirdly the studies varied in their reporting of the results, meaning that some groups within the studies could not be included in the analysis. This potentially had an impact on the results of the review. Fourthly, combining all the anticholinergic scales in the meta-analysis is a potential limitation of the study, given the variability in the development of scales. However, the analysis only showed heterogeneity in one group (moderate to high vs no ACB) but not in the other (low vs no ACB).

Another limitation was the selection process for this systematic review. Ideally, titles, abstracts, and full-text articles should be independently reviewed for inclusion and exclusion to minimize bias. However, a single researcher first reviewed the titles and abstract before presenting the articles to another reviewer for independent selection. The eligibility criteria were straightforward, and articles were easily selected, but there is a possibility that relevant publications might have been excluded from the study.

Conclusion

This review's findings showed evidence of a temporal relationship between anticholinergic burden and cognitive impairment. There was also evidence of a temporal relationship between increased anticholinergic burden and mortality over time. Despite the considerable variability between anticholinergic burden scales, they all demonstrated the ability to predict the risk of cognitive impairment.

Given the evidence for a plausible causal relationship between exposure to anticholinergic burden and adverse outcomes, improvement or prevention of adverse outcomes could be expected from clinical interventions to reduce anticholinergic burden. Future research should be conducted on developing interventions that could be applied to clinical practice to minimise anticholinergic burden. However, before a further investigation to develop optimal interventions, the current practice regarding anticholinergic burden in older adults needs to be understood in detail. This understanding will inform intervention development work and help to improve clinical practice.

The next chapter will present a cohort study set out to describe the current practice regarding anticholinergic burden in a UK hospital

Chapter 3: The Impact of a Frail Elderly Assessment Team on the Anticholinergic Burden of Frail Older People During Hospitalisation

Chapter 1 introduced the concept of anticholinergic burden and the adverse effects associated with it. Chapter 2 presented evidence to clarify the temporal relationship between anticholinergic burden, cognitive function, and mortality. This chapter will inform intervention development work by describing current practice regarding anticholinergic burden within a multidisciplinary frail assessment team in a UK hospital.

Introduction

Comprehensive geriatric assessment (CGA) is the foundation of geriatric care. CGA is defined as a multidisciplinary and multidimensional treatment and diagnostic process that focuses on identifying medical, psychological, and functional issues affecting a frail older adult to produce a coordinated plan to tackle them (161). Multidisciplinary teams play a pivotal role in geriatric medicine (a medical and academic speciality that deals with all aspects of illness in old age) (162). The presence of frailty, including numerous comorbidities and other problems across various domains in some older adults, makes medical care complex and multifaceted (162). This means that medical care for older adults must rely on the distinct and complementary skills of various health care professionals within a team to address these issues simultaneously (163).

The multidisciplinary team (MDT) approach adopted during a comprehensive geriatric assessment (CGA) provides optimal medical care through a collaboration of healthcare professionals of various disciplines in a coordinated and effective manner (164). Multidisciplinary teams consist of doctors, pharmacists, nurses, physiotherapists, occupational therapists, and other health care professionals. Traditionally, doctors within the teams were the prescribers; however, In recent times, the roles of pharmacists, nurses and physiotherapists have been extended to include non-medical prescribing (165, 166). Non-medical prescribing refers to specially trained pharmacists, physiotherapists, and nurses that work as independent or supplementary prescribers within their clinical competence (165).

Pharmacists play vital roles within multidisciplinary teams and have been reported to identify drug-related problems within the teams (167). Pharmacists within these teams have also improved the quality of prescribing (168). For example, when multidisciplinary

team interventions were applied, it improved the quality of psychotropic drug prescribing, which might otherwise have contributed to an increased anticholinergic burden (169, 170). This demonstrates that a multidisciplinary health care team involving a pharmacist might be an effective strategy for improving the quality of anticholinergic drug prescribing and medication safety in older adults.

Many older people with frailty and cognitive impairment are admitted to hospital (171-174). These patients may be exposed to even more anticholinergic medicines as a consequence of hospital admission (175). Given that frail older adults are at even more risk of adverse effects than non-frail older adults, reducing anticholinergic burden in this population should be a priority (176). This also makes them an ideal population to focus on in future interventions. Evaluating regular practice in frail older adults within a hospital may be particularly helpful because hospital admission presents a valuable opportunity to recognise anticholinergic burden, review and modify patients' medications before discharge. Also, the effects of de-prescribing or prescribing can be monitored and assessed, and the risk and benefits of continuing these medicines can be evaluated.

Modern hospitals are increasingly developing services and assembling multidisciplinary teams that provide specialised care for those with frailty (177). However, there is no data on the impact of these specialised multidisciplinary teams on anticholinergic burden of hospitalised patients in the UK. In addition, it is unclear if they already consider anticholinergic burden as part of routine practice. Evaluation of normal practice can help make informed decisions about whether further work to develop tools to reduce anticholinergic burden will benefit this population. Clearly, if current practice in this setting is optimal, it would be difficult to justify further interventional development work to modify the anticholinergic burden in this population.

Additionally, there is also limited evidence on how the involvement of a pharmacist within a CGA focused MDT might impact the anticholinergic burden during hospitalisation. This project aimed to describe current practice regarding anticholinergic burden within a frailty team in a UK hospital, as well as a detailed examination of pharmacists' recommendation to deprescribe medicines with anticholinergic properties. This project's results will inform practice and improve clinical decision-making by identifying areas for quality improvement.

Overview of a frail elderly assessment team (FEAT)

At Derby Teaching Hospitals, a group of representatives from acute and community services came together in March 2013 to develop services for frail older people admitted to the emergency department and the Medical Admissions Unit (MAU). They worked to define appropriate assessments for frail older people and understand the pathway and barriers to timely discharge from the hospital. To reduce the risk of readmission and promote timely assessment and discharge of frail older patients, they assembled a Frail Elderly Assessment Team (FEAT) based at the Royal Derby Hospital's Medical Admissions Unit (MAU).

FEAT included doctors, pharmacists, speech and language therapists, dieticians, discharge facilitators and a psychiatry liaison team. The team also worked alongside geriatricians, other speciality physicians, and acute physicians to provide a timely, comprehensive geriatric assessment (CGA). To identify older people with frailty, the team developed and validated four screening criteria to identify patients with a high risk of frailty. The criteria were:

- ≥ 65 years old in a care home
- ≥ 75 years old presenting with a fall
- ≥ 75 years old presenting with confusion
- ≥ 85 years old with four or more comorbidities

According to the team's data, more than 1200 patients had been seen by FEAT from January 2018 to June 30th 2018, with 71% of the patients getting home on the same day if medically fit.

Project questions

1. Does the FEAT modify patients' anticholinergic burden as part of routine practice?
2. In what way is the anticholinergic burden modified?
3. To what extent is any reduction in anticholinergic burden due to pharmacist recommendations?
4. What proportion of drug changes by pharmacists have anticholinergic adverse effects documented as part of the rationale for change?
5. Was there any scope for improvement?

Inclusion Criteria

Participants that have been admitted to the medical assessment unit and seen by the FEAT

Exclusion criteria

Participants receiving palliative care during admission

Method and methodology

Sample Size Calculation

The sample size calculation was based on the objective of including a sufficient number of participants to detect a true effect without being too large and hence wasteful of time. Data from previous studies were used to estimate the minimum number of required participants to see a moderate difference of 22% in the ACB score of participants in the present study. The effect size was chosen because a previous study reported reducing the ACB score by 22% in hospitalised older adults (168).

The significance level was set to 5%, 95 confidence interval (CI) and power to 80%. It was estimated that at 80% power (at 95% CI), to detect a 22% difference in anticholinergic burden, a minimum of 80 patients would be needed for analysis. Missing data are more common in retrospective studies, where collected data are used for a different purpose than originally intended (178, 179). Increasing the target sample size is advised to allow for losses where expected (178). In addition, given that the present study involved an older cohort with frailty, it was important to anticipate that additional records may be incomplete due to various reasons (e.g., deaths and patients started on palliative care). In the present study, a total of 110 patients were identified for data extraction.

The number of participants required for the evaluation was estimated using the equation below (180).

$$N = \frac{2(Z_{\alpha} - Z_{1-\beta})^2 \times \sigma^2}{\Delta^2}$$

Where N = sample size

Z_{α} = 1.96 for two-tailed hypothesis at 5% level of significance (i.e., 95% confidence level)

$Z_{1-\beta} = 0.8416$ it is the constant set by convention according to the power of the study (80%)

$\Delta = 22.2\%$ (0.222) effect size of geriatric-pharmaceutical practice on the anticholinergic burden in a multidisciplinary ward, from a previous study (168)

$\Sigma = 0.5$ estimated standard deviation of the anticholinergic score in the reference population from a previous study (181)

Selection of participants, data sources, and data collection

Data for this study were retrospectively collected from the iSOFT clinical manager (ICM) database in Royal Derby Hospital. The ICM is a comprehensive assessment database system used to compile information and highlight patients that meet the FEAT frailty criteria. The database comprises data including patient demographic information, past medical history, details of pharmacist and clinician intervention, discharge letter, and comprehensive geriatric assessment report.

Given that the eligibility criteria required patients to have been assessed by FEAT, patients were initially identified from a FEAT summary document. The document comprises a list of patients the team assessed each month. A search was conducted on the ICM database using their unique hospital identification number to retrieve the required information for individual patients. The patient records retrieved were from between the 1st and 27th June 2018. Only data from the first visit was retrieved for analysis where patients were admitted multiple times. This was to ensure that change during hospital admission in patients with multiple visits and those without was captured and treated in the same way.

After the records were identified and the first visits selected, both regular and “when required” or *pro re nata* (PRN) medicines recorded by the attending pharmacist during medicines reconciliation were manually entered into an excel database from the clinical record section on the ICM. In addition to demographic information, this section listed all patients' medication, including those started temporarily in hospital (e.g., enoxaparin), and what medicines patients were admitted and discharged on. Medicines denoted “admitted on” on the clinical record section of the ICM were copied into an excel column labelled “medicines of patients on admission”. Medications marked “discharged with” were copied into the excel column labelled “medicines of patients on discharge”.

The medicines management checklist was a section of the ICM comprised of summary information on co-morbidities, pharmacist intervention and pharmacist notes. This section

was used to extract pharmacists' rationale for stopping medications. The present study was retrospective and depended on existing records that were sometimes incomplete or missing. Therefore the data collection approach evolved, and data had to be collected a second time to improve the data collection accuracy. In the first round of data collection, the clinical record section and the medicines management checklist were used as the primary sources of data collection. However, after errors were identified in the extracted data, an explicit data extraction protocol was developed to include the above data sources and additional sources like the discharge summary and comprehensive geriatric assessment section. The data collection protocol was created to improve the consistency and clarity of data extraction.

The discharge summaries on the ICM were used to identify the drugs a patient was discharged with and those that were stopped during the hospital admission. The discharge summary also contained information on the length of hospital stay and who stopped what during hospitalisation. In cases where the discharge summary was missing or incomplete, other sections of the ICM were analysed to retrieve the required information. The discharge summary provided an up-to-date picture of the patient's medication list, what was stopped and who stopped it. After data was extracted from the discharge summary, the medication review file in the comprehensive geriatric assessment section was used to check if data from other sources were complete. Appendix 5 Table 28 summarizes each ICM data source used during data extraction.

Anonymization and quality control

Data was initially extracted by a single researcher (G.O). The data included demographic information (age and sex), medication on admission, medication on discharge, stopped medication, including who stopped it and rationale, and the total number of medications on admission and discharge. Following the data extraction, another researcher (A.G) independently extracted selected data (medication on admission, medication on discharge, and stopped medication) for 20 patients. Comparison of data revealed errors, including discrepancies in patients' medication lists. Anticholinergic burden scores for both extractions were compared and gave a 75% agreement. Upon discussion with the second researcher (A.G), it was agreed that discrepancies most likely resulted from an inconsistent approach to data collection due to unfamiliarity with the ICM and not considering discharge summaries. Therefore a clearly defined protocol for raw data collection was developed.

Following the development of an explicit data collection protocol, a second data collection was done by G.O and double-checked on a different week. Given the high error rate of the first data collection, selected data for all 110 patients, including medication on admission and discharge, anticholinergic scores, and data extraction protocol, were presented to A.G for audit. The researcher, following the protocol presented, compared extracted data against the database and verified the data. After the correctness of extracted data had been evaluated, all identifiable information were excluded from this database, and patients numbered from 1 to 110. The new anonymised database included patient medication lists, corresponding anticholinergic burden, and pharmacist recommendations on drugs with anticholinergic effect.

Data cleaning and missing records

The database was searched for duplicates using the hospital number in excel. Given that the objective was to evaluate ACB scores on admission and discharge, patients with missing data were excluded. The missing values for patients were coded into SPSS.

Does the FEAT reduce patients' anticholinergic burden as part of routine practice?

The anticholinergic burden of patients on admission and discharge was calculated as the sum of rankings for all medicines with anticholinergic properties prescribed. Medicines on admission and discharge were ranked on a scale of 0-3 depending on their anticholinergic potential (e.g., 0: none, 1: Mild or possible, 2: strong, and 3: very strong). The ACB scale was selected for this exercise following the systematic review of the literature in Chapter 2, identifying it as the most validated scale. After calculating the anticholinergic scores, they were analysed using the statistical tests described below.

Statistical methods and analysis

All data were analysed using the IBM SPSS V.23 statistical software. The Shapiro-Wilk test was used to test for normality. The Shapiro-Wilk test was chosen because it is reported to provide better power than the Kolmogorov-Smirnov test. It is also regarded by some researchers as the 'gold standard' for assessing normality of data sets (182). Median (IQR) were calculated for continuous data, and the Wilcoxon signed-rank was used to identify

significant differences between anticholinergic burden at admission and discharge. All statistical tests were two-tailed, with p values of <0.05 deemed significant.

In what way is anticholinergic burden modified?

To answer the research question: In what way is anticholinergic burden modified; first, the number of medications with anticholinergic burden added or stopped during admission, as well as the changes made to different classes of drugs, was recorded and reported.

The proportion of patients prescribed psychotropic drugs (e.g. tricyclic antidepressant amitriptyline), incontinence drugs (e.g. oxybutynin), blood pressure/cardiac drugs (e.g. nifedipine), pain medicines (e.g. codeine), and others (e.g. warfarin, ranitidine, prednisolone theophylline and loperamide) were recorded on admission and discharge. BNF 78 classification of drugs was used where possible (183).

To what extent is any reduction in anticholinergic burden due to pharmacist recommendations?

Pharmacists' notes and discharge records on individual patients were reviewed to evaluate how the pharmacist's involvement within the team may have influenced the anticholinergic burden. The health care professional (e.g., doctor, nurse and pharmacist) responsible for stopping each drug with an anticholinergic property was recorded and reported.

What proportion of drug changes by pharmacists have anticholinergic adverse effects documented as part of the rationale for change?

Pharmacists' notes were reviewed for the rationale for stopping medicines with anticholinergic burden. Recommendations to stop medications were considered to be made based on consideration for anticholinergic burden where pharmacists cited an anticholinergic adverse effect as the reason for stopping.

Was there any scope for improvement?

To identify any scope for improvement, a researcher (G.O) went through the medication on admission and discharge, including those amended during the hospital stay. This was

done to identify where additional stops could be made or where starting certain drugs was potentially inappropriate. The criteria for identifying a potentially inappropriate medicine with anticholinergic properties were adapted from the definition of PIMs as described by Beer's criteria (where the risk of an adverse event outweighs the therapeutic benefit, particularly when a safer alternative exists) and relevant parts of the NO-TEARS medication review tool (27). The NO-TEARS is a flexible medication review tool that can be tailored to fit different consultation styles. NO-TEARS is a mnemonic that prompts health care professionals conducting medication reviews to check for N (need and indication), O (ask open questions), T (tests and monitoring), E (evidence and guidelines), A (adverse events: checking for interactions, duplications, or contraindications), R (risk reduction or prevention), and S (simplification and switches) (184). It was chosen for this study because of its simplicity, previous use in developing other medication review checklists and favourable reports on usefulness from users in an earlier study (184, 185). The following criteria were used to identify PIMs:

1. Patients with ACB scores of 3 and over, where an alternative with a lower ACB score exists
2. Patients with dementia and on an anticholinergic drug
3. Patients with serious interactions involving medicines with anticholinergic properties
4. Patients started on an inappropriate new medication with anticholinergic properties
5. Therapeutic duplication
6. Patients on drugs that might not be needed

Where appropriate, simplification and switches were recommended using available guides and evidence, including the BNF, NICE guidelines, ACB scale and the STOPP/START criteria.

Ethical considerations and data management

The evaluation was conducted following the seven Caldecott principles, the principles of Good Clinical Practice and Records Management Code of Practice for Health and Social Care 2016. Approval was obtained from the Caldecott guardian for the study. The physical location of the anonymised data was an encrypted password-protected computer within the Medical school (UON), with frequent electronic and periodic physical backup.

Results

The Shapiro-Wilk test indicated that the ACB scores were not normally distributed (S-W $p < 0.05$); therefore, a choice was made to use non-parametric statistics (e.g. Wilcoxon signed-rank test). The results were reported as median (IQR) or as percentages where appropriate.

Demographic characteristics

Approximately 98% (108) of 110 patients included in the study had complete records and could be included in the data analysis. The median age (IQR) of the study population was 86 (9) years, and the population was almost evenly divided, with 49% of patients being female and 51% male.

The number of prescribed medicines increased from admission to discharge (897 vs 958). For example, four patients were on a single medication on admission; however, three were discharged with 2, 4 and 8 medications. Appendix 5, Table 29 presents the changes in the number of medications prescribed for different patients. The Wilcoxon signed-rank test for paired data showed a statistically significant increase in the median (IQR) number of medications prescribed on discharge 8(5) compared to admission 9(5) ($p < 0.004$). The proportion of persons exposed to polypharmacy (≥ 5 medications) was 80.7% at admission, which increased to 87.9% on discharge (Table 8).

Table 8. Summary of medication changes

Number of medicines prescribed on admission	Number of patients	%
1-4	21	20
≥ 5 (polypharmacy)	87	80
Number of medicines prescribed on discharge		
1-4	13	12
≥ 5 (polypharmacy)	95	88

Does the FEAT modify patients' anticholinergic burden as part of routine practice?

Based on the ACB scale, 78 (72%) patients were identified as using at least one medicine with anticholinergic properties at admission, and on discharge, the proportion increased slightly to 80 (74%). However, the Wilcoxon signed-rank test indicated there were no statistically significant differences ($p < 0.316$) between the median (IQR) anticholinergic burden at admission 1(3) and on discharge 1(3).

On admission, 32(31%) patients had an ACB of 3 and over, which decreased to 29 (27%) patients on discharge. In contrast, 17(16%) patients had an ACB of 2 at admission, which increased to 21(19%) on discharge. Similarly, 28(26%) patients had an ACB of 1 on admission compared with 30(28%) patients on discharge. Figure 6 illustrates the proportion of patients with various ACB scores at admission and discharge.

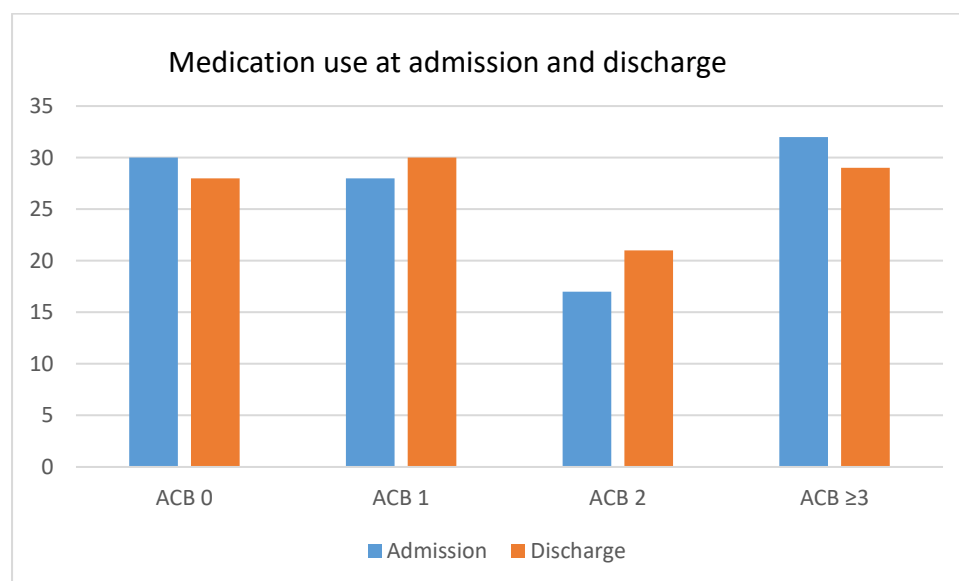


Figure 6. Proportion of patients with various anticholinergic properties at admission and discharge

In what way were drugs modified?

Though there was no statistical difference between anticholinergic burden at admission and discharge, some medicines with anticholinergic properties were stopped, while others were started. A total of 27 stops and 33 starts of drugs with anticholinergic properties were recorded.

The proportion of patients prescribed psychotropics (25 vs 20), blood pressure (54 vs 47), and incontinence drugs (9 vs 4) decreased on discharge from the hospital. In contrast, the proportion of patients prescribed opioids (21 vs 30) and H1 antihistamines (8 vs 11) increased.

The highest number of prescribed drugs with anticholinergic properties on admission were loop diuretics, opioids, tricyclic antidepressants, and antimuscarinics for urinary incontinence. Appendix 2, Table 21 illustrates the full list of different drug classes with ACB scores prescribed to patients on admission and discharge.

To what extent is any reduction in anticholinergic burden due to pharmacist recommendations?

According to records on the ICM, Healthcare professionals (doctors, nurses, and pharmacists) made 27 interventions that reduced anticholinergic burden. Of the 27 interventions, 16 were made by pharmacists, ten by doctors, and one by a nurse. Doctors and pharmacists stopped an equal number of drugs with an ACB score of 1, with a total of 8 interventions each. However, pharmacists were more likely to make interventions on drugs with an ACB score of 3 (8 of 9). Table 9 below shows the proportion and name of medicines with anticholinergic properties stopped by different healthcare professionals.

Table 9. Number of medications stopped by members of the FEAT

Medicine	Total number stopped	Total number stopped by a pharmacist	Total number stopped by a nurse	Total number stopped by a doctor
***Amitriptyline	4	3	0	1
***Tolterodine	3	3	0	0
***Solifenacin	1	1	0	0
***Oxybutynin	1	1	0	0
**Carbamazepine	1	0	0	1
*Diazepam	1	1	0	0
*Furosemide	5	4	0	1
*Digoxin	2	0	1	1
*Codeine	3	1	0	2
*Trazodone	1	1	0	0
*Fentanyl	1	0	0	1
*Warfarin	1	0	0	1
*Cetirizine	1	0	0	1
*Loperamide	2	1	0	1
Total	27	16	1	10

*ACB score=1, ** ACB score=2, *** ACB score=3

What proportion of drug changes by pharmacists have anticholinergic adverse effects documented as part of the rationale for change?

Pharmacists recorded various reasons for recommendations made during hospital admissions. Some recommendations to stop were based on an anticholinergic adverse effect (6 of 16), while others were not. Only recommendations citing dementia, confusion, delirium, and constipation were considered to be made based on anticholinergic adverse effects. The pharmacists did not give a high anticholinergic burden as a rationale for recommending any stop. Table 10 presents the drugs stopped and the corresponding rationale for discontinuation.

Eight patients with dementia were prescribed an acetylcholinesterase inhibitor on admission, and 5 of these were on medication with anticholinergic properties. This number reduced slightly to four upon discharge from hospital.

Table 10. medicine with anticholinergic property and rationales for medication stops

Drug	Reason for stopping
Oxybutynin	Dementia
Solifenacin	Dementia
Loperamide	Not appropriate
Diazepam	Confusion
Amitriptyline	Prolonged QTC, no indication or not needed
Tolterodine	Constipation, confusion, delirium, or dementia
Furosemide	No oedema, clinically dry, electrolytes or acute kidney injury
Codeine	Shortness of breath

Was there any scope for improvement?

Though many drugs were stopped and others started, some missed opportunities to reduce or prevent an increase in ACB scores were identified for some patients discharged from the hospital. For example, alternatives with no anticholinergic burden (e.g. antacids or lansoprazole instead of ranitidine) were identified for the four patients with dementia and on an anticholinesterase inhibitor. Fentanyl was contraindicated in one patient, and oral rehydration therapy and lifestyle amendment were suggested for loperamide. These opportunities to reduce anticholinergic burden were also identified for a newly started drug in two of these patients.

Opportunities were also identified to deprescribe drugs for urinary incontinence in two patients with an ACB score of 6 and 4 on discharge. For three frail patients with a benzodiazepine and an opioid combination, non-pharmacological alternatives were suggested for benzodiazepine. In total, theoretical recommendations were made for 18 patients. Appendix 2, Table 22 presents a table with identified opportunities to deprescribe.

Discussion

The findings in the present study showed no significant differences between the ACB scores of older adults seen by the multidisciplinary team at admission and discharge. The proportion of patients on medicines with high anticholinergic burden reduced at discharge, but those on medicines with low to moderate burden increased. Pharmacists made most of the interventions that reduced anticholinergic burden compared to nurses and doctors. However, opportunities to further reduce ACB scores were identified.

Polypharmacy

The median number of prescribed medications was significantly higher at discharge compared to admission (8 vs 9 $p < 0.04$). There was also a corresponding increase of patients with polypharmacy at discharge compared to admission (80.7% vs 87.9%). This finding is similar to a previous study in an acute geriatric unit that reported increased medication use (9.1 vs 10.1, $P < 0.001$) and polypharmacy (81 vs 88%) after hospitalisation (186). Another study also reported an increase in the proportion of polypharmacy patients during hospitalisation (87% vs 92%) (187). However, other studies have reported contrasting findings. For example, one study reported a reduction in polypharmacy from 87% to 82% at discharge from hospital (186). Also, a study on patients with dementia reported a reduction in patients with polypharmacy (94% to 90%) during hospitalisation (188). This finding implies that further reduction of polypharmacy in the present cohort might be possible. Although the present study did not aim to identify opportunities to reduce polypharmacy, reducing anticholinergic burden may contribute to reducing polypharmacy.

Does the FEAT modify patients' anticholinergic burden as part of routine practice

The frailty multidisciplinary team assessment did not significantly impact the anticholinergic burden during hospitalisation ($p < 0.316$). There is a possibility that the sample size was too small to detect a small effect. However, the findings were similar to those described in a recent multi-centre study to evaluate the changes in anticholinergic cognitive burden (ACB) of patients admitted to hospital with a diagnosis of cognitive impairment. The authors reported that there was no difference in scores on admission and discharge (189). In the above study, the proportion of patients with at least one

anticholinergic drug on admission was lower than in the present study (60.8 vs 72%) (189). A possible explanation for this is the slightly older age of participants in the present study (Median age: 85.4 vs 79.6) may have translated to higher comorbidities, polypharmacy, and a subsequent increase in the number of patients with anticholinergic burden.

In contrast to the findings in the present study, a similar study on 67 patients admitted to an acute multidisciplinary geriatric unit and undergoing routine care in Spain reported a 22% statistically significant reduction in anticholinergic scores between admission and discharge ($p < 0.047$) (168). These findings highlighted the possible scope for further reduction in anticholinergic burden for hospitalised patients in the present study.

In what way is anticholinergic burden modified?

Drugs with anticholinergic properties were discontinued in some patients, and other patients were prescribed new medications. On admission, more patients had an ACB score of 3 and over than at discharge (30 vs 27%). However, for other ACB scores (2 and 1), the proportion of patients increased on discharge. A possible explanation for this trend is that interventions by the team pushed patients with higher scores (ACB=3) into categories with lower scores (ACB=2-1) during hospitalisation, resulting in more patients with lower ACB scores.

Similar to reports from another study, the most frequently prescribed drugs were furosemide and codeine (189). Opioids and ranitidine were the most likely to be started in the hospital. Psychotropic medications made up the second-largest group of medications with anticholinergic properties at admission and the third-largest at discharge. This decrease was because pharmacists and doctors discontinued psychotropic medicines for 20% of patients. Amitriptyline was the most common in this group, with 8% and 5% of patients prescribed them at admission and discharge. This finding contrasts with a previous study that reported fewer patients on amitriptyline at admission (3%) (189). This finding suggests that amitriptyline might be overprescribed for this study population.

To what extent is any reduction in anticholinergic burden due to pharmacist recommendations?

There was evidence of collaboration between team members, as records were made in such a way that allowed team members to follow and action. In addition, various team members signed into the ICM database. It was beyond the scope of the present study to define the exact roles of pharmacists, nurses, or doctors within the team. However, it is recommended that within MDTs, the roles and responsibilities of each member and how they work together should be considered and agreed on (190). Notably, there was evidence that pharmacists took on the responsibility of conducting medication reviews. This is because only pharmacists completed and signed off the medication review section of the ICM.

A medication review is a structured examination of a patient's medicines to reach an agreement with the patient about treatment (191). The three types of medication reviews characterized by Medicines Partnership are; a prescription review (level 1: to identify medicines management issues, usually without patient involvement unless the review results in a change to prescribed medicines), a concordance and compliance review (level 2: a review to address issues relating to a patient's pattern of taking medicines, usually with patient involvement), and a clinical medication review (level 3: to address medication-related issues in the context of patient's clinical condition with patient involvement) (192, 193). The boundaries between the three review types are not clearly defined; however, unlike level 3, level 1 and 2 medication reviews can be done without full access to patients' medical notes.

Medication reviews were more likely an ongoing process after the initial assessment. The medication review section could be edited, meaning that additional information and interventions could be added at any point during the patient's stay. Though pharmacists did not report on what kind of reviews they did and could have done various levels of reviews on a single patient during their hospital stay, there was evidence that level 3 reviews were done. For example, pharmacists had full access to patients' medical notes and addressed medical-related issues in the context of patients' clinical conditions. However, level 3 reviews require that the patient is involved in the review process, and there were no notes on the medication review files identifying where patients had been involved in medication reviews. It is recommended that, where appropriate, family members or carers are involved in medication reviews (190).

Members of the team made interventions that led to a reduction in some patients' anticholinergic burden during hospitalisation. Specifically, pharmacists contributed to the discontinuation of 59% of medicines with anticholinergic properties, doctors 37% and nurses 4%. Also, pharmacists were more likely to make interventions on drugs with an ACB score of 3. An explanation for this could be that while there was collaboration between the team, pharmacists may have been expected to lead medication management. Previous studies have also reported pharmacists leading medication management within multidisciplinary teams (194-197). In the present study, doctors and nurses also made interventions that reduced anticholinergic burden, suggesting that while pharmacists were expected to take on a medication management role, the team was also interdependent to solve issues and carry out care plans.

What proportion of drug changes by pharmacists have anticholinergic adverse effects documented as part of the rationale for change?

Pharmacists made 16 interventions that impacted patients' ACB scores and were more likely than doctors or nurses to stop drugs with an ACB score of 3 in patients with dementia. They were also more likely to stop incontinence drugs than psychotropics (e.g. amitriptyline) in patients with dementia.

After analysing the pharmacists' notes, only rationales citing dementia, confusion, delirium, and constipation were judged to be made with anticholinergic consideration. 38% of identified rationales for discontinuation given by pharmacists fit these criteria. It is important to note that more ambiguous rationales such as not appropriate (13%) or not needed (6%) could have also involved consideration for anticholinergic burden. However, it was beyond the scope of this study to investigate further.

Despite the increased likelihood of pharmacists stopping incontinence drugs and other medicines with anticholinergic burden in patients with dementia, there was no evidence from records that patients' overall anticholinergic burden was considered. For example, anticholinergic burden scores were not cited as a rationale for discontinuation for any patient. Also, the only drug with an ACB score of 1 stopped for an anticholinergic adverse effect was diazepam. Discontinuation seemed to be based on a particular drug's adverse effect in isolation and not the patient's cumulative anticholinergic burden.

In the present study, health care was provided by specialised health care professionals with extensive experience in geriatric care, and thus, the results obtained might paint a

better picture than average. Kersten et al. found that in hospitalised older adults in the geriatric wards, PIMs, including drugs with anticholinergic properties, were more readily discontinued compared to other wards (198). This might also explain why the increase in anticholinergic burden on discharge reported by a previous study was not seen here (175).

Was there any scope for improvement?

Some patients with dementia who were on an acetylcholinesterase inhibitor (AChE-I) (e.g. rivastigmine, galantamine and donepezil) also had anticholinergic burden. Of the patients on AChE-I's, 62.5% had anticholinergic burden at admission. This finding is similar to the findings in a recent study which demonstrated that 54% of hospitalised patients on AChE-I's, were on drugs with anticholinergic properties (189). The concurrent prescribing of medicines with anticholinergic properties may counter the effect of AChE-I's and lead to more cognitive decline.

Furthermore, high risk of prescribing cascades in older adults involving AChE-I's and anticholinergics have also been highlighted by other studies (199, 200). For example, side effects of AChE-I's (e.g. urinary incontinence) being misinterpreted as part of the natural ageing process, and an anticholinergic medicine prescribed to manage it (199). In the present study, new drugs with anticholinergic properties were started for some patients on an AChE-I. Though many new drugs are started for good reason (e.g. new indication), more attention should be directed at not starting new drugs with anticholinergic burden in these patients.

Theoretical recommendations that could lead to reduced ACB scores were made for 18 patients. These recommendations were either on old or newly prescribed drugs. Notably, some theoretical interventions were made for new drugs started in patients with dementia and prescribed an AChE-I. Furthermore, opportunities were identified where benzodiazepines, fentanyl, ranitidine, furosemide, oxybutynin and solifenacin could be deprescribed (Appendix 2, Table 22). Due to the retrospective nature of this study, there was a limit to the number of recommendations made because of limited information. There is a possibility that more opportunities could have been identified for ineffective medications if patients were involved in the process. In addition, in the absence of patients' complete clinical notes, some recommendations might not be appropriate. For example, some recommended drugs with lower or no anticholinergic burden might be contra-indicated, might have been ineffective in the past or poorly tolerated by the patient.

However, alternative medications were only recommended when they did not interact with the patient's medication list.

Though there are opportunities to reduce anticholinergic burden in older adults admitted to hospital, an important concern is the transition of care. Ideally, undisrupted, consistent and coordinated care should be provided for patients despite their complex care needs and the involvement of different health care professionals in various settings. However, this is not often the case; changes made in hospitals are not always communicated to relevant health care professionals (201-203). This means that medications that are deprescribed could be erroneously continued in community due to poor or delayed communication between settings, limiting the impact of stopping medicines with anticholinergic properties in hospital. However, the new Discharge Medicine Service (DMS) introduced by the NHS in February 2021 could potentially minimize transition of care issues by providing an opportunity for community pharmacists to reconcile any changes made in hospital and update pharmacy records (204). Thus even in cases where the GP practice erroneously continues a drug with anticholinergic properties, this might be flagged during the DMS review.

Older adults with frailty are particularly vulnerable to adverse outcomes associated with anticholinergic burden. Thus, reducing anticholinergic burden in this population should be a priority. This study indicates that anticholinergic burden in older adults requires more targeted attention to reduce possible risks of adverse outcomes. Pharmacists can play a role in modifying anticholinergic burden; however, they do not always do this. This study's findings are consistent with previous reports highlighting the considerable scope for reducing anticholinergic burden in patients (205, 206). One strategy to tackle this problem could involve reducing barriers to considering anticholinergic burden during pharmacists' medication reviews by providing decision support. Opportunities remain for pharmacists to recommend alternatives to reduce anticholinergic burden, including drugs with little to no anticholinergic properties and non-pharmacological alternatives. Involving anticholinergic burden consideration in the medication review process may further improve prescribing and hence patient outcomes.

Strengths and limitations

The study's strength is its retrospective design, ensuring that doctors and pharmacists could not have been triggered to change practice. Therefore the findings obtained were probably an accurate picture of normal practice. However, a limitation of retrospective studies is that the researcher depends on the information documented, which could contain errors. In the present study, this was mitigated by clarifying the information from different records on the database.

Another limitation of this study was that it was conducted in a single hospital, limiting its generalizability. However, it was necessary to understand the process of deprescribing with sufficient granularity to provide answers to the rationale for deprescribing drugs and the consideration for anticholinergic burden among pharmacists. Thus, the study would have been less feasible if the study design had been multicentre. Another limitation of this study is the small sample size. The sample size was estimated to allow a moderate effect to be seen, based on results from a similar study. Therefore there is the risk that a small effect could have been missed.

Conclusion

This study aimed to describe current practice regarding anticholinergic burden within a specialised frailty team in a UK hospital. This is also the first study to evaluate the rationale for pharmacist stoppage of drugs with anticholinergic properties.

Current practice in a frail elderly assessment team was not effective at reducing anticholinergic burden during hospitalisation. Pharmacists made most of the interventions that reduced anticholinergic burden compared to doctors and nurses. Moreover, though pharmacists stopped the most number of drugs that reduced anticholinergic burden, there were lost opportunities for further reduction or avoidance of anticholinergic burden.

These results imply that even though pharmacists play a significant role in the deprescribing process of medications with anticholinergic properties, there is considerable scope for improving clinical practice. There is the possibility that improving consideration for anticholinergic burden among pharmacists during clinical practice could significantly impact the anticholinergic burden and translate to reduced falls, cognitive impairment, and hospitalisation, with a consequent alleviation of pressure on services. Further work is needed to develop interventions to improve consideration for anticholinergic burden among pharmacists. One strategy that could help is a decision support resource that considers the barriers to reducing anticholinergic burden in practice.

The next chapter sets out to report a study that details the process of developing a clinical decision-making tool that addresses barriers to improving consideration for anticholinergic burden among pharmacists in practice.

Chapter 4: The Co-Development of a Clinical Decision-Making Tool to Reduce the Anticholinergic Burden in Older Adults

Chapter 3 described current practice regarding anticholinergic burden within a specialised frailty team in a UK hospital and highlighted the scope for further reduction of anticholinergic burden in older adults. The study also identified some classes of drugs with anticholinergic properties that were more likely to be prescribed to frail adults, around which interventions can be focused. The present chapter details the development of a clinical decision-making tool to assist pharmacists in reducing anticholinergic burden in older adults.

Introduction

Consideration of anticholinergic burden is an essential part of medication management in older adults (207). However, despite guidance on avoiding the use of anticholinergics in older adults (208), little consideration is given to anticholinergic burden as these medicines are still commonly prescribed, even in frail older populations with a high prevalence of falls, impaired physical function, dementia, and delirium (138, 209-211). This might be due to a lack of recognition of many drugs with anticholinergic properties, or adverse events that occur only after sustained exposure to these drugs, or limited knowledge about what can be done even if the issue is recognised. The risk of avoidable adverse events may be further increased when new drugs are prescribed to treat symptoms arising from an unrecognised adverse event related to an existing anticholinergic therapy (prescribing cascades) (199, 212, 213).

Pharmacists play an essential healthcare role by performing medicine reviews on older adults. NICE defines a medicines review as a “structured, critical examination of a patient’s medicines to reach an agreement with the patient about treatment, optimising the impact of medicines, minimising the number of medicine-related problems and reducing waste” (191). Recommendations developed during medicine reviews are usually communicated to the relevant prescriber for action. Examples of pharmacists' referrals to prescribers after reviews include recommendations to rectify inappropriate dosing, inappropriate medication, and unnecessary therapeutic duplication (214). Reports on the uptake of these recommendations by prescribers vary, with studies reporting 22-78% of uptake after reviews (215). Thus, if pharmacists can correctly identify anticholinergic burden and recommend strategies to reduce it, they may change patient prescriptions and potentially modify outcomes.

Previous studies have reported a lower risk of adverse effects following a reduction in anticholinergic burden. A prospective, single-centre study on 125 older patients (mean age 84.4 years) evaluated the impact of reducing anticholinergic burden on the frequency and severity of behavioural and psychological symptoms of dementia (BPSD). The authors reported that the reduction of the anticholinergic burden by 20% reduced the frequency and severity of BPSD (216). Another prospective study on 20 patients evaluated the effect of anticholinergic discontinuation on movement disorders, cognition, and general psychopathology after a 4-week taper in 20 outpatients with schizophrenia or schizoaffective disorder treated with antipsychotics. The authors reported that the discontinuation of anticholinergics led to a significant improvement in cognition (217).

The goals of deprescribing are to reduce the medication burden and maintain or improve quality of life. However, the clinical decision-making process around deprescribing medicines with anticholinergic properties can be complex and multifaceted. For example, deprescribing involves the process of systematically identifying and reducing or withdrawing medicines in individual patients where potential harm outweighs the possible benefit, after taking into consideration factors such as an individual's comorbidities, life expectancy, values and preferences (218). In addition, there can be difficulty in stopping medications, especially when they do not appear to be causing overt harm. Nevertheless, given the long term risks of anticholinergic burden (such as premature death or cognitive impairment), there needs to be proactive deprescribing of these medicines even in asymptomatic patients, especially where an alternative with a lower burden exists. Few pharmacists who perform medication reviews are experienced in geriatric pharmacotherapy, and even when they are, as seen in Chapter 2, there is considerable scope to improve anticholinergic prescribing. Furthermore, pharmacists will not alter anticholinergic burden if they do not know enough about it. Thus, there is a need for explicit clinical tools/resources that can simplify the process by guiding pharmacists through decision-making to improve the quality of drug treatment in older adults

Clinical decision-making tools have been used to support decision-making, convey health information/ improve knowledge, impact the process of care, and lead different health care professionals to the same set of diagnostic or therapeutic instructions (219, 220). A systematic review evaluated the impact of clinical decision support tools targeting pharmacists on physician prescribing, clinical and patient outcomes (221). All RCT's included in the systematic review reported at least one positive outcome (e.g., improved prescribing, improved patient outcomes, and improved clinical outcome), and two-thirds of studies found a statistically significant impact of the tools on a majority of outcomes (221).

The development of a clinical decision-making tool that addresses the challenges and barriers to decision-making and provides information to pharmacists on anticholinergic burden could simplify an otherwise complex process and lead to a change in practice. The existing ACB scales are useful in quantifying anticholinergic burden but do not provide recommendations to clinicians and hence are not decision-making tools. Though guidelines that provide recommendations on some drugs with anticholinergic properties exist, recommendations are usually embedded in lengthy documents that limit practical use in the busy routine clinical setting, provide vague recommendations, do not focus on deprescribing, and are not always tailored to pharmacists' workflow (28, 222, 223). In addition, multiple criteria-based strategies like Beers and STOPP/START have been developed to reduce inappropriate polypharmacy; however, they do not suggest alternative safer drugs or provide explicit support for incorporating patient preferences into decision-making (27, 222, 224, 225).

Clinically relevant, explicit recommendations delivered to the pharmacists offer one way to reduce inappropriate prescribing of medications with anticholinergic properties and ensure optimal medicines management for older patients. Factors that increase the usability and implementation of guidelines include ensuring it is easy to understand, can be easily used, which typically requires the target users to be involved in the development process (226). In addition, usability of decision support tools is improved if:

- the tool automatically provides decision support rather than requiring the user to undertake additional tasks.
- the tool is integrated into the clinician's workflow and practices rather than being an interruption to usual practice
- actionable recommendations are provided rather than just assessments which then require the user to determine lines of action
- the decision support is provided at the time and location of decision making (227).

Furthermore, positive professional behaviour change in healthcare interventions is improved when their implementation focusses on action or education (228).

The current chapter describes the systematic process employed to develop a decision-making tool to reduce anticholinergic burden in older adults using the Behaviour Change Wheel (BCW) (Figure 7). The BCW is a comprehensive framework that provides a systematic method for intervention development and presents intervention designers with various options to consider when designing interventions (229). This framework was chosen because it has been used to successfully design behaviour change interventions

(including decision support tools) (230-232), is coherent and has led to an improvement in practice in previous interventions (233, 234).

The wheel has three layers and was developed from a synthesis of 19 frameworks of behaviour change (235). At the core of the BCW sits the Capability (physical and physiological), Opportunity (social and physical), and Motivation (automatic and reflective) behaviour (COM-B) model. The COM-B model is the starting point for the development of interventions. Figure 7 below is a representation of the BCW

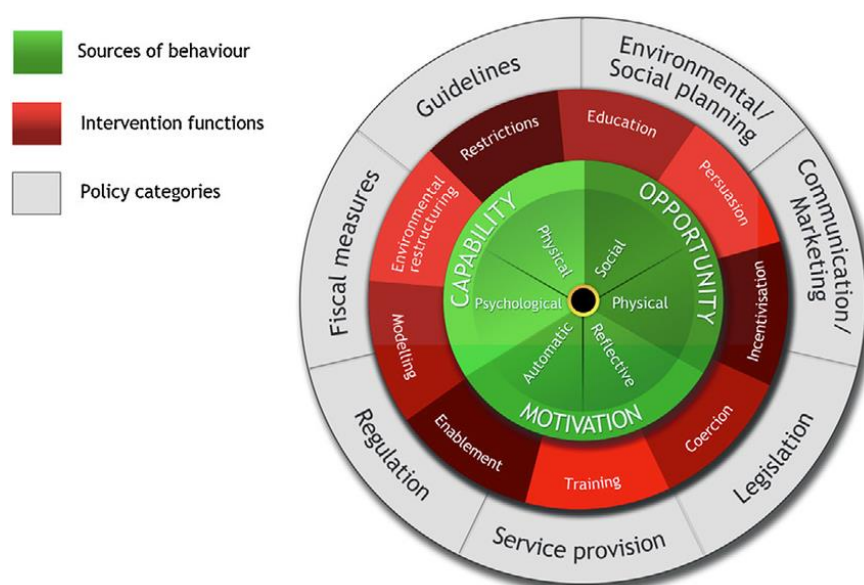


Figure 7 The Behaviour Change Wheel. From Michie 2011 (235)

The NICE guidance on behaviour change refers to the COM-B model in asserting that for a behaviour change intervention to be successful, an individual must be physically and physiologically capable, have the physical and social opportunity, and be more motivated to perform a given task (236). COM-B recognises that behaviour is part of an interactive system, where a behaviour change can be achieved by a shift in interacting components (e.g., change in motivation can lead to behaviour change). COM-B is supported by the Theory Domains Framework (TDF), enabling a comprehensive assessment of behavioural determinants in qualitative studies. TDF is a synthesis of 128 theoretical constructs derived from 33 behaviour change theories. The resulting framework consists of 14 distinct domains, each allowing the COM-B components to be further specified. These domains are knowledge, social/professional role and identity, beliefs about capabilities, reinforcement, intentions, goals, memory, attention and decision processes,

environmental context and resources, emotions, behavioural regulation, optimism, beliefs about consequences, skills, and social influences.

The second layer of the BCW comprises nine intervention functions (education, incentivisation, coercion, enablement, persuasion, modelling, environmental restructuring, restriction, and training) to address the barriers identified from the COM-B analysis. They are described as 'active ingredients' of behaviour change. The final layer of the BCW comprises policy categories, including communication/marketing, guidelines, fiscal measures, regulation, legislation, environmental/social planning, and service provision. Intervention designers who have access to policy levers are encouraged to consider policy options that could help deliver intervention functions (education, persuasion, incentivisation, coercion, training, restriction, environmental restructuring, modelling and enablement). Collectively, the interaction between these three layers is likely to bring about behaviour change.

Objectives

1. To develop a clinical decision-making tool to identify and reduce anticholinergic burden in older adults and
2. To specify the implementation strategy for the tool

Methods

Study Design

The objectives above were met using a participatory, action research methodology. This refers to a study design in which study participants reflect on issues and collaboratively devise strategies to overcome challenges through an iterative process (237). Participatory action was appropriate to ensure that a wide range of perspectives was explored during the development of the tool and that the tool was refined through progressive problem-solving (238). Initially, a sample of pharmacists was interviewed to identify themes and the context relevant to a decision support tool to assist pharmacists in reducing anticholinergic burden (stage 1). The findings of these interviews were then applied, alongside the author's background knowledge, in an analysis using the Behaviour Change Wheel principles (stage 2). From this, a draft decision support tool

(the Anticholinergic Burden Decision Support (ABDeS) tool) was devised (stage 3). The tool was then refined on the basis of user feedback from field testing (stage 4). Finally, based on the above experience, an implementation strategy for the application of the tool was devised (stage 5). Figure 8 below represents the study progression.

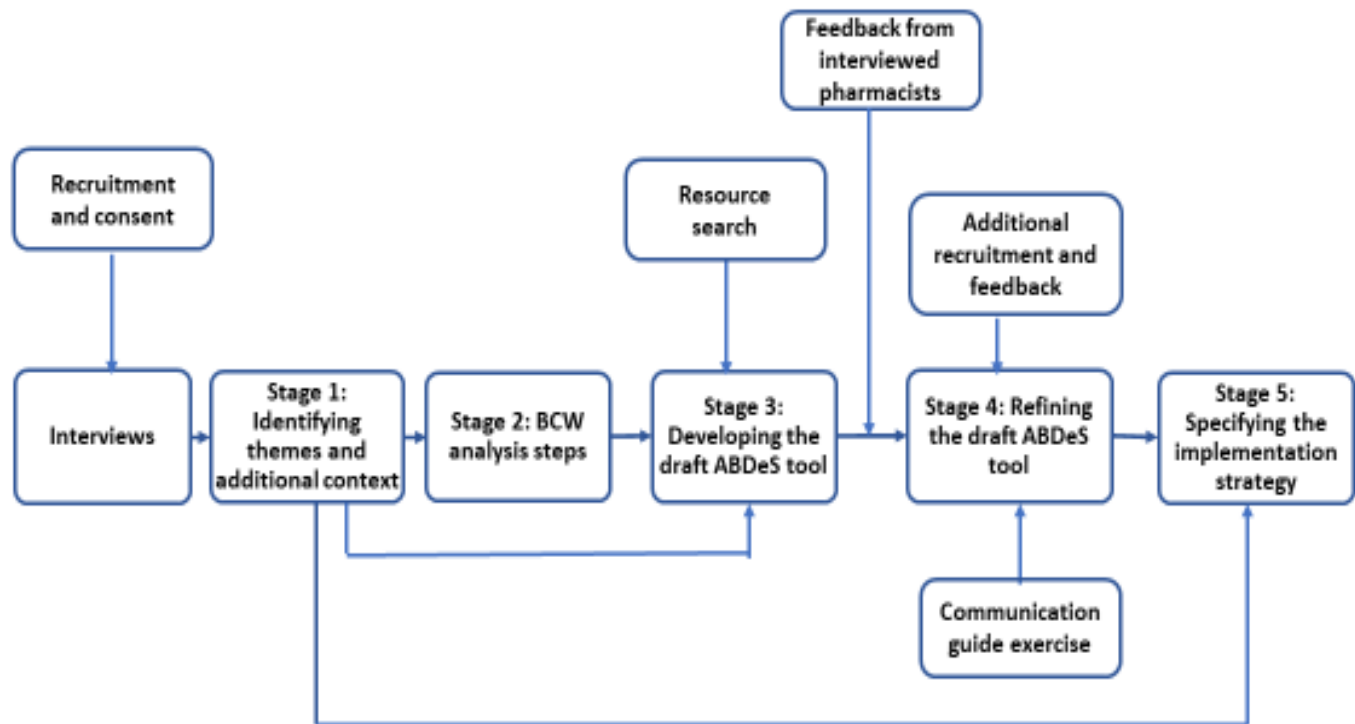


Figure 8 Schematic representation of study progression

Ethical considerations

Ethical approval was sought and granted by the Faculty of Medicine and Health Sciences Research Ethics Committee (NO 248-1902). The study was conducted following the ethical principles that have their origin in the Declaration of Helsinki, 1996 and the Department of Health Research Governance Framework for Health and Social Care, 2005.

Sample size

As this was a qualitative study, a formal sample size calculation was not conducted. For the initial interviews to develop the draft tool (stage 1), it was estimated that eight pharmacists needed to be interviewed to obtain the information required, similar to a previous study on developing an intervention using the BCW (237).

There is no clearly required sample size for field testing, and ideally, this process should be iterative, using larger or different samples each time. In the present study, the same pharmacists were invited to participate in the field testing of the draft decision support tool (stage 4). Because some were unable to do so for various personal reasons, a further sample of pharmacists who had not been involved in the initial interviews was recruited, aiming for a minimum of 8 in the ABDes tool refining phase. Expanding recruitment for field testing ensured an adequate sample size and enabled gathering feedback from pharmacists with a fresh perspective.

Recruitment of pharmacists for initial interviews (stage 1) and field testing to refine the tool (stage 4)

Pharmacists who were General Pharmaceutical Council (GPHC) registered, were accredited to perform medication reviews, and were directly involved in patient care were eligible for recruitment. Pharmacists were sought from various sectors, including community pharmacy, GP surgery, care home, and hospital across the UK, to ensure that multiple relevant perspectives informed the tool's development. Initially, participants were recruited to participate in the study using convenience sampling. Convenience sampling was used as a sampling technique for the study design, as it allowed for the recruitment of pharmacists according to their accessibility and availability (239). This sampling technique also provided a quick, inexpensive, and convenient method of participant recruitment.

The General Pharmaceutical Council (GPHC) maintains a comprehensive pharmacy register of all hospital and community pharmacy premises within the UK. Pharmacies were approached alphabetically, as they appeared on the registers until all participants were recruited. The study was promoted by delivering posters advertising the project to pharmacies in Nottingham. Pharmacists from other areas outside of Nottingham were contacted through word of mouth and email communication.

However, difficulties encountered in recruitment necessitated further development of the recruitment strategy. Though some pharmacists initially expressed interest in participating (n=13), only a few (n=4) returned emailed consent forms or replied to emails. As the data collection end date approached, it became clear that the recruitment rate needed to be accelerated in order to achieve the intended number of recruited pharmacists by the study's conclusion. Additionally, it was apparent that the interviewed pharmacists had limited knowledge about anticholinergic burden. While it was crucial to gather input from pharmacists unfamiliar with anticholinergic burden, it was equally important to capture the perspectives of those who were to gain a more comprehensive understanding of the barriers and facilitators to reducing anticholinergic burden in practice. The recruitment strategy was adapted to purposefully recruit pharmacists known to the researcher (G.O) or colleagues to consider anticholinergic burden in their practice to address these challenges. For example, those specialised in older adults' care (e.g. care home pharmacists). Adopting this flexible strategy allowed the recruitment of an informative sample of pharmacists across sectors while also allowing the required number of pharmacists to be recruited on time.

Consent forms and participant information sheets were sent out to those who expressed interest in the study. A signed and dated consent form was obtained from each participant before participation. Participants were made aware (via the information sheet and consent form) that should they withdraw, the data already collected may still be used in the final analysis. Participants were reassured that steps would be taken to ensure no material was made available to the public from which their identity could be inferred. Participants were identified using pseudonyms instead of names for quotations. Participant anonymity was maintained during the tape recording, transcribing, and analysing the data. Hard copies with raw data, such as interview notes and audiotapes, were kept securely in a key-locked filing cabinet that could only be accessed by a single researcher (G.O). Soft copies were kept on a password-protected computer.

After consent forms were returned, participants were contacted by email or telephone either to arrange an initial interview as part of stage 1 or (for those recruited after the draft tool was developed) to participate in field testing to refine the tool (stage 4).

Data collection (interviews)

Data was collected through semi-structured interviews and feedback from participants in an iterative process that informed the selection of content included in the tool. Semi-structured interviews were adequate to enable the interviewer to create follow-up questions based on the participants' responses. The interviews were conducted to understand how target patients can be identified and the processes involved in decision making around deprescribing anticholinergic medicines. The questions asked during interviews fit broadly into the categories outlined below:

1. Identification of patients with a higher risk of having an increased anticholinergic burden (e.g., Describe how patients with a higher risk of adverse events from anticholinergic burden can be identified?)
2. The process of decision making (e.g., what is your decision-making process after patient identification, or what do you consider before deciding on what to do?)
3. Barriers to reducing anticholinergic burden in older adults
4. What needs to be done differently?
5. Opportunities to deprescribe (e.g., when and where anticholinergic burden can be targeted?)

Other topics explored in the categories outlined above included the barriers to identifying these patients, activities that could reduce anticholinergic burden, information needs of health care professionals, information sources, non-pharmacological and pharmacological alternatives. The interview guide was initially developed using guidance from the BCW (e.g., who needs to do the behaviour/ when it needs to be done); however, questions were broadened as the interview progressed. The interview guide is presented in appendix 3.

A sole researcher (G.O) conducted the interviews, which were carried out either at the participant's workplace, the interviewer's office, or at an alternative location preferred by the participant. The interviews were recorded on a digital audio device and transcribed verbatim.

Data analysis

Stage 1: Identifying themes and additional context

Following transcription of recorded interviews, themes were identified following some of the steps advocated by Braun and Clarke 2006 (240). The aim of this stage was to use an inductive approach to identify themes (e.g., barriers and facilitators to reducing anticholinergic burden that could be mapped onto TDF to facilitate the COM-B analysis). The stage also aimed to identify additional contextual information that could assist in the development of the tool. An inductive approach was used to find themes that may have been obscured or left invisible if predefined TDF domain themes had been applied to the raw data set in a deductive approach. Further, this was also done to ensure that any additional context gained from an inductive approach was not lost by restricting the analysis to predefined domains (241).

Identifying the themes involved the following:

Becoming familiar with the data and generating initial codes

In the first stage of the analysis, the transcribed data were read and re-read for familiarisation with the content. Initial notes and impressions from the data were jotted down to generate an initial list of ideas about the data content and areas of interest. All the transcripts were read by G.O.

After generating an initial list of ideas, the next step involved producing initial codes from the data by G.O. Coding involved summarising and organising the data into meaningful groups. The data were examined line by line systematically to give full attention to each data item and to identify aspects of the data that may form the basis of themes across the data set. After the initial coding of the raw data was completed. A second coder, Olufunmilayo Agbesanwa (O.A), was given a sample of the raw text, and the categories developed with a description of categories in separate documents. The coder (O.A) labelled sections of the text with the developed categories. Discrepancies were resolved through discussion, and categories amended where necessary.

Searching for and reviewing themes

Data notes and codes were examined for patterns and connections by G.O. Codes were collated into categories, and all data relevant to each potential theme gathered. The categories were then reviewed, modified, and further combined to generate high-level themes by G.O. Coded data extracts for each theme were checked for coherence and reclassified if necessary. Where additional relevant information was identified, they were included under the broad themes identified where possible; otherwise, new themes were created to categorise additional information.

Defining themes and describing additional contextual data

Theme definitions that capture the meaning of each theme concisely were developed. Because there was an overlap of quotes and meaning within the data, themes were briefly discussed to highlight tensions and context not captured in the COM-B analysis. Similar to previous studies, barriers and enablers relating to identified behavioural target were mapped to relevant TDF domains and used to facilitate COM-B analysis (232, 242, 243). NVivo 12 software was used to facilitate data analysis.

Stage 2: BCW analysis steps

This stage involved framework analysis according to the BCW and was essential to developing the draft decision support tool. The stage aimed at identifying Behaviour Change Techniques to incorporate into the tool. The steps included:

1: Defining the problem in behavioural terms

The first step in the design process was identifying a specific problem and defining it in behavioural terms. This process involved identifying the problem, being specific about the population involved in the behaviour and the behaviour. A researcher (G.O) used the Interview data to define the problem in behavioural terms.

2: Selecting the target behaviours

Behaviours do not occur in isolation and take place within a system of other behaviours. Therefore, changing one behaviour can influence other behaviours performed by pharmacists. This step involved generating a list of potential target behaviours relevant to the problem of increased anticholinergic burden in older adults. Two researchers (G.O and A.G) went through the coded transcripts of the interviews and independently generated a list of potential target behaviours. After which, some target behaviours were reworded and then prioritised according to the Behavioural Change Wheel (BCW) criteria. As the BCW recommends a less is more approach and suggests that it is more beneficial to start with small changes and build on these incrementally, only a few potential behaviours were selected.

The results were presented to the participating pharmacists for feedback. Any disagreements were resolved through discussion.

The following criteria were used to select the target behaviours:

1. Likely impact of changing the behaviour on the desired outcome
2. The likelihood of changing the behaviour
3. How likely it is that the behaviour (or group of behaviours) will have a positive impact on other related behaviours
4. How easy it will be to measure the behaviour

3: Specifying the target behaviour

The third step of the BCW involved defining all the target behaviours identified in step 2 in detail. Therefore, for each target behaviour, a researcher (G.O) used the interview data to specify the behaviour in terms of 1) who needs to perform the behaviour? 2) What do they need to do differently? 3) When do they need to do it? 4) Where do they need to do it? and 5) with whom do they need to do it.

The results were presented to the participating pharmacists for member checking. Pharmacists were asked to comment on how fair they thought the results were, even where they might not agree. They were also asked to report any disagreements and general thoughts on the results from this step. Any disagreements were resolved through discussion and amendment of the results.

4: COM-B analysis

The next step was identifying what needs to change to achieve the desired change in behaviour using the COM-B model. The themes and categories derived from the thematic analysis were used to facilitate COM-B analysis.

According to the COM-B model, for a behaviour to occur, an individual must have the physical capability (e.g. skill), physiological capability (e.g. knowledge), physical opportunity (e.g. triggers, and time), social opportunity (e.g. what is socially acceptable), reflective motivation (e.g. beliefs about what is good and bad), and automatic motivation (e.g. reflex, responses, and desires).

The barriers and enablers identified from the inductive analysis were mapped onto the relevant TDF component and organised into COM-B components by a researcher (G.O). Tables including the theme, theme statement describing the theme, theme quote, relevant COM-B component, TDF context, and researcher's comments on what needs to change were produced for each relevant behaviour.

The results were presented to the participating pharmacists for member checking. Pharmacists were asked to comment on how fair they thought the results were, even where they might not agree. They were also asked to report any disagreements and general thoughts on the results from this step. Any disagreements were resolved through discussion.

5 and 6: Selecting relevant intervention functions and policy categories from the BCW

Having identified the relevant COM-B components related to pharmacist's behaviour that needed to change in Step 4, Intervention functions to address each of the barriers were identified for each COM-B component. Intervention functions are behaviour change instruments and include education, persuasion, incentivisation, coercion, training, restriction, environmental restructuring, modelling, and enablement. These intervention functions can be mapped to the corresponding COM-B components identified in Step 4 to facilitate the target behaviour. For example, if motivation was identified as a barrier, persuasion, enablement, and education are intervention function options from the BCW that could be specifically mapped to it.

The selection of intervention functions was based on the APEASE (affordable, practicable, effective, and cost-effective, acceptable, safe, and equitable) criteria. The APEASE criteria are suggested to help intervention designers make strategic judgements as to what might be most appropriate for the intervention in the context of a study. For example, an intervention that is effective with extensive resources may not be affordable or practical in clinical practice. Two researchers (G.O and O.A) discussed and applied the appease criteria to the relevant intervention function.

After selecting intervention functions, designers are encouraged to consider policy categories that would support the delivery of the intervention functions, e.g. guidelines that recommend or mandate practice, advertisement, and service provision. This research aims to develop a decision-making tool using the COM-B model and aspects of the Behaviour Change Wheel. Should the intervention be effective, then the study results could be written into guidelines or a regulatory framework. However, at this stage in intervention development and piloting, using policy categories on the BCW is impracticable.

7 and 8: Identify Behaviour Change Techniques to incorporate into the tool and mode of delivery

After selecting the relevant intervention functions, the next step was selecting Behaviour Change Techniques (BCTs) to incorporate in developing the tool. A BCT is defined as “an active component of an intervention designed to change behaviour”. Some BCTs include prompts, clues, goal setting, feedback and monitoring, shaping knowledge, feedback on behaviour and persuasion (244). The Behaviour Change Wheel Guide describes how each BCT is linked to intervention functions and provides a list of potential BCTs. Intervention designers are encouraged to select BCTs based on how appropriate they are for the population and location where the intervention will be conducted. BCTs were jointly selected by (G.O and O.A) based on their relevance, affordability, practicability, and effectiveness to this study. Upon identification of BCTs, steps were taken to embed these as features of the tool.

In addition to intervention content, designers are encouraged to decide the mode of delivery for the intervention. The interview data was used to specify the mode of delivery.

Stage 3: Developing the draft ABDeS tool

Searching for resources

To develop the tool, resources including evidence-based clinical guidelines, consensus documents, clinical decision support tools, and published literature were evaluated. These resources were identified by searching the websites of known guideline developers (e.g. Scottish Intercollegiate Guidelines Network (SIGN) and The National Institute for Health and Care Excellence (NICE)). Another strategy was conducting an Internet search. This was done because many guideline developers post their guidelines directly online. Further, consensus documents, tools, and guidelines familiar to pharmacists (e.g. STOPP/START and electronic medicines compendium) were retrieved, and bibliography's scanned to identify additional resources.

PubMed and Google Scholar were also searched for published guidelines using keywords like practice guidelines, clinical practice guidelines and consensus statement, in addition to relevant drug class (e.g. opioids) and population (e.g. older adults). Similarly, literature underpinning recommendations were also searched using the topic-related keyword. The search was initially limited to reviews, meta-analysis and RCTs. Where these were not available, limits were removed to allow other studies to be identified. There were no limits on the language of publication or date of publication.

The objectives for reviewing the guidelines, guides, or consensus document include:

1. To identify existing guidance relating to reducing anticholinergic burden
2. To provide a concise summary of the relevant evidence and recommendations
3. To clarify vague recommendations.

Resources were scanned for recommendations that could potentially reduce anticholinergic burden and evidence underpinning the recommendation. Where a guideline, guide, or consensus document contained the relevant information, they were assessed for their methodological quality using the AGREE Global Rating Scale instrument (AGREE GRS) described below.

Applying AGREE

The AGREE Global Rating Scale instrument (AGREE GRS) was used to assess the methodological quality of referenced guidelines, consensus, and guidance documents. It was important to assess the quality of guidance documents because they are used by HCP's to inform clinical decisions and were assessed for recommendations that reduce anticholinergic burden in the present study. The AGREE GRS is a tool for evaluating the quality and reporting of practice guidelines. It is based on the AGREE II and was created to allow health care professionals, researchers, and policymakers to quickly assess the quality of guidelines, especially where limited time and resources preclude using the 23 items AGREE II tool. This tool was chosen for the present study because it was decided by two assessors (G.O and O.A; both with knowledge of evidence-based medicine) that the most important domain of the AGREE in this context was the overall quality of guideline recommendation (Domain 4). This is because, in most cases, recommendations were adapted from guidelines. The AGREE GRS includes four domains for assessment (Table 11).

Table 11. AGREE GRS domains

Domains	What to rate	What to consider
Domain 1 (PROCESS OF DEVELOPMENT)	Rate the overall quality of the guideline development methods.	Were the appropriate stakeholders involved in the development of the guideline? Was the evidentiary base developed systematically? Were recommendations consistent with the literature?
Domain 2 (Presentation style)	Rate the overall quality of the guideline presentation	Was the guideline well organized? Were the recommendations easy to find?
Domain 3 (Completeness of reporting)	Rate the completeness of reporting.	Was the guideline development process transparent and reproducible? How complete was the information to inform decision-making?
Domain 4; (Clinical validity)	Rate the overall quality of the guideline recommendations.	Are the recommendations clinically sound? Are the recommendations appropriate for the intended patients?

Two assessors (G.O and O.A) independently scored the retrieved guidelines and guidance documents on a scale from 1 to 7 (1 = strongly disagree; 7 = strongly agree). A score between 2 and 6 was assigned when the item did not meet the full criteria. Scores were

averaged and categorised as very good (7), good (6-5), fair (3-4), and poor (1-2). The aim of this exercise was not to exclude guidelines or consensus documents but to assess and report on the quality of guidelines that contained a recommendation that could reduce anticholinergic burden. A precedent of categorical reporting of items was set by previous studies (245, 246).

Collation and extraction of recommendations

G.O. extracted recommendations relevant to reducing anticholinergic burden from resources identified through the literature search. The recommendations were organised into summary tables categorised by medication class to provide a clear overview of the identified evidence-based recommendations.

Vague recommendations were clarified by G.O. to enhance interpretability and ensure the recommendations were actionable for pharmacists. Additionally, G.O. revised the wording of some recommendations for conciseness and clarity when needed. Some new recommendations were added, along with supporting evidence.

Established guidelines and consensus documents were consulted to identify treatment alternatives for indications covered by the priority drug classes. For each drug class, pharmacological alternatives suggested for indications were checked, and their anticholinergic burden was calculated using the ACB scale. Alternatives with lower ACB scores were then incorporated into the ABDeS tool. Furthermore, non-pharmacological alternatives were identified from relevant documents retrieved in the search and incorporated into the ABDeS tool.

Incorporating BCW analysis and relevant resources into the tool

The draft tool was developed using a combination of interview data, results from BCW analysis, and recommendations from consensus documents, tools, and guidelines. The BCW analysis identified Behaviour Change Techniques to incorporate into the tool. The literature offered evidence-based guidance on deprescribing and alternatives (pharmacological and non-pharmacological) for anticholinergic medication classes.

The draft ABDeS tool was designed as a 3-step tool in Microsoft PowerPoint.

Step 1 is a checklist for pharmacists to identify older patients at increased risk of adverse effects from anticholinergic burden. The categories for the checklist were informed by the qualitative interviews, where pharmacists provided perspectives on priority patients at an increased risk of anticholinergic burden. The purpose of Step 1 is to allow pharmacists to quickly flag higher risk patients during medication reviews so anticholinergic burden can be evaluated and managed. This step also aligned with the BCW focus on specifying the target population.

Step 2 is an anticholinergic burden calculation table extracted from the ACB scale to provide pharmacists with the 'resources' to quantify anticholinergic burden levels.

Step 3 of the draft ABDeS tool is the medication review section designed to guide pharmacists in identifying opportunities to deprescribe medicines with anticholinergic properties. This section was developed for priority drug classes with anticholinergic properties identified based on interview findings and results of the hospital study in Chapter 3. The classes are titled: Anticholinergic drugs for Urinary Incontinence, Antipsychotics, Tricyclic Antidepressants, Benzodiazepines, and Opioids for non-cancer pain.

Step 3 was developed to incorporate BCTs identified from the BCW analysis by using credible sources to provide actionable recommendations to pharmacists and using a checklist format to provide memory cues and prompt action. The checklist items in this section are based on the results of the thematic analysis of interview data.

In addition, step 3 incorporated evidence-based recommendations from established practice guidelines, review articles, meta-analyses, and other resources in the development of deprescribing triggers and recommended actions to reduce anticholinergic burden. Step 3 also includes taper guides adapted from established resources to facilitate safe deprescribing.

Stage 4: Refining the draft ABDeS tool

The draft tool was provided to a subset of the participating pharmacists who were available to evaluate it and provide feedback. They were asked to use it in their practice and to report:

1. If the information in the tool was clinically sound.
2. If they thought the tool was usable.
3. If the information was provided in a suitable format.
4. If they thought the recommendations were practical.
5. To suggest any recommendations for amendment.

Feedback responses were analysed and organised into summary themes. These themes guided refinements to the draft tool based on pharmacist perspectives.

Email exchanges and scheduled discussions facilitated revision clarifications when needed. Ten participating pharmacists provided feedback on the draft tool, with 5 pharmacists directly contributing to developing an added communication guide incorporated into the tool. This collaborative, iterative approach aimed to refine the draft ABDeS tool into one that was more aligned with pharmacists' needs and preferences to promote usability and adoption.

Trustworthiness

Qualitative researchers in clinical pharmacy are encouraged to use realist terminology to describe trustworthiness (e.g. dependability, credibility, conformability and transferability) rather than positivist terminology (e.g. reliability, internal validity, objectivity and generalizability) (247). Thus, realist terminology was used throughout this study.

Qualitative research is often subject to criticisms on lack of rigour, transparency, and justification of data analysis and collection methods (248). These concerns negatively impact the integrity of the research findings. A host of strategies for improving the trustworthiness of findings during the qualitative research process have been described extensively, including member checking and triangulation (247, 249).

Member checking

This technique has been described as the most important method to strengthen data credibility (249, 250). It is described as testing data, findings, or conclusions with the population that the data was initially obtained. In the present study, member checking was used as a method of strengthening the credibility of the findings. Results from steps 1-4 of the BCW analysis were presented to interviewed pharmacists for checking.

There have been some arguments about the usefulness of member checking in qualitative research. This is because study results are often a synthesis of different voices in focus groups or interviews. As a result, one may not necessarily find their voice in the results, impacting their ability to critique the findings (251). Thus, participants were not asked to find themselves in the data to mitigate this limitation. Instead, a more nuanced approach was taken. Participants were asked to check if the results made sense and if the findings were viewed as fair even if they did not completely agree with them (249). They were also asked to make a note of any disagreements.

Triangulation

Triangulation is described as a method that involves answering the same question using more than one strategy. In the present study, it was not practicable to use methodological triangulation (e.g. focus groups and interviews) because of pharmacists' anticipated scheduling issues. However, two researchers (G.O and A.G) independently read through the coded transcripts to generate a list of behaviours in step 2 of the BCW analysis (investigator triangulation). Researchers are not encouraged to use triangulation solely to establish credibility (249, 251). This is because it is difficult to obtain the same results from two independent researchers. Thus, this exercise aimed to ensure data analysis was rich and inclusive of insights and interpretations by different researchers in the present study. Besides, the inclusion of pharmacists from a wide range of backgrounds, including prescribing, non-prescribing, GP, Community, hospital and care home pharmacists, was done to ensure that a diversity of perspectives were captured.

In addition to these approaches, a check on the clarity of categories was conducted in the present study to strengthen trustworthiness. This refers to when categories and code decisions are communicated by clear definitions to allow an independent second coder to make similar coding decisions as the first coder (251, 252).

Stage 5: Specifying the implementation strategy

Apart from specifying the mode of delivery in the BCW step 8, how the tool will be introduced into clinical practice was specified following Proctor specification (92). To specify the implementation strategy, the following questions were answered

- 1) What is the name of the strategy (name it)?
- 2) What is the conceptual definition of the implementation strategy (define it)?
- 3) Who would use the tool (actor)?
- 4) What would need to be done (action)?
- 5) How should pharmacist choose whom to apply the tool?
- 6) When, where and how frequently could the tool be used?
- 7) How should the outcome be evaluated?

The naming and definitions provided by the Expert Recommendations for Implementing Change (ERIC) taxonomy were used in the present study to promote harmonisation of the terminology. The original classifications provided by Powell et al. were also considered. However, the ERIC was chosen because it was developed to refine the Powell taxonomy by systematically gathering input from a panel of implementation and clinical experts in a rigorous consensus development process (253). The ERIC strategy has been successfully used in previous studies (254).

Results

Thirteen pharmacists participated in this study, 8 of whom took part in initial in-depth interviews that were used to develop the draft tool (stages 1-3). All 8 pharmacists were asked to provide feedback on the draft tool; however, 3 pharmacists were not available to provide the feedback due to time constraints (n=1) and changing jobs (n=2). Thus, 5 additional pharmacists were recruited to participate in stage 4 (refining the draft ABDeS tool) of the study. In summary, a total of 13 pharmacists took part in the study, 8 in stages 1-3, and 10 (including 5 from stages 1-3 and 5 additional) in stage 4. Pharmacists practiced in various settings including, hospital (n=3), care home (n=2), general practitioner (GP) (n=3), community (n=4), and cross-sector community and hospital pharmacist (n=1). Table 12 summarises participant demographic information.

Table 12. Participating pharmacists' demographic information

Pharmacist label	experience (years)	Sector
S4*	6	Community
LB8*	10	Care home
T4*	5	Community
Fil6*	8	Hospital**
P2*	13	Hospital**
A1*	4	Hospital
Sa7*	9	Care home
Emm5*	11	GP
N2	5	GP **
Z2	5	Community
TA1	10	Hospital/community
RT1	11	GP
A2	5	Community

*Participated in initial interviews

**independent prescriber

Stage 1: Identifying themes and additional context from interviews

The in-depth interviews were summarised into four main themes and 15 categories. Two themes: 'limiting and enabling factors' were related to factors that pharmacists perceived were likely to act as barriers or facilitators to reducing anticholinergic burden in practice. The third theme: 'a holistic medicines review process' was concerned with processes and attitudes ideal for a well-rounded medicine review process.

The fourth theme: 'implementation considerations', explores essential aspects to consider when implementing the tool (e.g. pharmacist's view on what patients are more at risk of anticholinergic burden, opportunities to reduce ACB scores in practice, and the roles of health care professionals in this task). Themes were briefly described where they overlap with the BCW analysis. The summary of themes and categories is presented in Table 13 below.

Table 13. Themes and categories

Themes	Categories
A holistic medicines review process	<i>Medication appropriateness</i> <i>Discussion about change</i> <i>Amendments after review</i>
Implementation considerations	<i>During medication reviews,</i> <i>New medicines,</i> <i>In various settings,</i> <i>Identifying priority patients,</i> <i>Role of health care professionals.</i>
Limiting factors	<i>Lack of confidence</i> <i>Lack of tools and information</i> <i>Patient's resistance</i> <i>Limited time</i>
Enabling factors	<i>Behaviours that lower ACB scores,</i> <i>Patient involvement,</i> <i>Quick and easy to use decision support.</i>

The themes are further described below with supporting quotes

A holistic medicines review process

The process for a well-rounded medication review included:

Medication appropriateness

In general, pharmacists appeared to reflect on their own experience of what they did in practice rather than what they thought should be done. For example, when talking about 'medication appropriateness,' a pharmacist said

"I might look at how long they have been on it" LB8 (10 yrs qualified; care home).

Pharmacists indicated that inquiring about the patient's adverse effects and identifying the cause of the adverse effect were important aspects of a review. Also, looking at whether the benefit provided by the medication was more than the harm caused was an important consideration.

Another critical concern for *medication appropriateness* was if the patient needed the medication. Pharmacists considered lack of effectiveness, a resolved initial clinical complaint, an overextended duration of prescribing and non-adherence as signs that the medication was not appropriate.

"I think from talking to the patient. If they were started on a particular agent, which should have been short term, then you see that after a certain period of time, they are still taking it; obviously, that is something that you would be telling the prescriber" A1 (4 yrs qualified; hospital)

Other essential aspects identified were checking for drug interactions, therapy duplications and the initial indication to establish the prescribed medication's validity.

"It would be what is its indication and is that indication still valid first. So, what was it initiated for and have they still got that" LB8 (10 yrs qualified; care home).

Discussion about change

Pharmacists emphasised the inclusion of patients in the decision-making process to find solutions that would best suit patients.

"I think it always works hand in hand by talking to the patient, understanding how they are health-wise and also understanding how they feel about their medicines because a lot of the time patients are told to do a lot of things, and you see issues of compliance when the patients don't necessarily understand or believe that what they should be doing is what they need to do" A1 (4 yrs qualified; hospital)

An exception to involving a patient when considering medication appropriateness was where patients lacked capacity.

"Always get the patient involved in the decision making if possible unless they are confused then, in that case, no" P2 (13 yrs qualified; hospital; prescriber).

In cases where patients could not make decisions about their care, family members and carers were seen as an essential part of the decision-making process.

"I would say that, for me, my concern is with me is that it is difficult to assess the views and needs of the individual, from that individual moment and getting the information from carers. Occasionally, I can speak to family, but it is mainly from the carers" Emm5 (11 yrs qualified; GP)

Amendments after review

Amendments that could be enacted after a review included stopping or switching drugs, reducing the dose, and switching dose timing.

"So, if they need it and it's still working, is there an alternative that has a lower anticholinergic burden" LB8 (10 yrs qualified; care home).

This category is extensively covered in the BCW analysis

Implementation considerations

Role of health care professionals

Overall, participants agreed that pharmacists had a role in reviewing medication to reduce ACB scores; however, tensions were identified. For example, a pharmacist thought that prescribers could take more responsibility for reducing anticholinergic burden at the start of the therapy.

"Particularly prescribers when they are first starting these medicines to look at what other medicines they are on. Because it is easier to review something when it is started than later on" Sa7 (9 yrs qualified; care home)

However, another pharmacist mentioned that it was the pharmacists' responsibility to be reactive to adverse effect presentation and use that as an opportunity to reduce ACB scores in older adults.

"Pharmacist would be the first line, especially if it has been recently, the patient has been suffering from certain side effects. There is cognitive impairment. If we notice that the patient's cognition is declining, that would be one of the areas that we should start thinking about, because it is the main side effect". T4 (5 yrs qualified; community)

New medicines

Participants also identified the start of 'new medicines' as an opportunity for pharmacists to identify problematic medications and reduce ACB scores. However, tensions were identified where pharmacists took different views on when to make interventions to reduce anticholinergic burden. Some pharmacists had a 'post side effect' view of pharmacist interventions (deprescribing as a response to reported adverse effects). For example, a pharmacist stated that

"In community pharmacy, it is a little bit tricky to monitor such things, unless, of course, the patient comes in and starts describing that he has a lot of side effects. That would be a dry mouth or effect on the eye, dry skin. I guess it's just about recognising the side effects" S4 (6 yrs qualified; community)

Pharmacists that took a more proactive stance advocated planning a stop at the beginning or avoiding starting the medication in the first place.

"At the point of prescribing to say right, we need a review in three months' time so that they actually can see what the outcome of starting that medication is. Rather than them being admitted to hospital and then the medication review happening then because it's quite late on within their journey" Fil6 (8 yrs qualified; hospital; prescriber)

Another pharmacist added that pharmacists should be encouraged and supported to start considering anticholinergic burden at the start of therapy, rather than after patients have been on medication for a while.

"So, it's about not just doing the medication reviews because that's retrospective, you need to have a pathway that actually supports people thinking about it as a prospective" LB8 (10 yrs qualified; care home).

During medication reviews

Implementing the tool '*during medication reviews*' was seen as an important factor. This was because medication reviews were seen as an opportunity to identify problems and make changes.

"Medication review would still be the most important sort of parameter in this tool because that is the one that identifies the problem" S4 (6 yrs qualified; community)

In various settings

Pharmacists thought that interventions to reduce ACB scores could occur in various settings

"So, in my opinion, this can occur both in the community and in the hospital because GP's can start new drugs as well as doctors in a secondary setting" A1 (4 yrs qualified; hospital)

A pharmacist also suggested that an ideal implementation plan should involve embedding tool in normal pharmacist routine

"The best tool would be one linked to a system that's used regularly on a day to day basis". Sa7 (9 yrs qualified; care home)

Identifying priority patients

Pharmacists described priority patients as those with polypharmacy, co-morbidities, dementia, confusion, older, and frailty.

"So generally, it's the over 65 have other comorbidities, especially dementia"
Emm5 (11 yrs qualified; GP).

Limiting factors

Lack of confidence and lack of tools and information

Participants thought that pharmacists not feeling confident enough to make recommendations meant that they did not make recommendations to reduce ACB scores. This barrier was closely linked to another identified barrier, '*lack of tools and information*'. These two factors seemed to suggest that even when the pharmacists were aware of anticholinergic burden, they did not have the confidence to make those recommendations because they did not have enough information on what to do.

"If they had a tool that actually gave them some guidance on it, then they would. But I think because they do not really know how to, what recommendation that they would make, they don't have that information or background knowledge, so they don't feel confident within their role now to be able to make recommendations like that" Fil6 (8 yrs qualified; hospital; prescriber)

Some pharmacists spoke about less experienced pharmacists lacking in confidence and experience to lead deprescribing

"Pharmacists that haven't been around in the hospital for some time, they might find it a bit difficult because of lack of confidence" T4 (5 yrs qualified; community)

However, others seemed to reflect on their practice and the difficulty a '*lack of tools and information*' presented

"My example might be, I don't know, say the amitriptyline or the oxybutynin, but it flags it, but it doesn't, it says review, it doesn't talk you through that. It relies on somebody knowing that that is the right thought process" LB8 (10 yrs qualified; care home)

Barriers to reducing anticholinergic burden are further explored in the BCW analysis

Enabling factors

Behaviours that lower ACB scores

Pharmacists perceived that behaviours like *"raising awareness"* by providing information on the concept of anticholinergic burden were enabling factors to reduce anticholinergic burden.

"I think more awareness of it (reducing anticholinergic burden). Increased awareness means that you pay more attention to it. So, I would say if it's a topic that a lot more people speak about or if there was a lot more information about it, then maybe people would know of it and actually put it into practice" A1 (4 yrs qualified; hospital)

Identifying patients for reviews was also a behaviour that lowers the ACB score. It was seen as an opportunity to make recommendations to reduce anticholinergic burden

"I would say that every patient that you come across on the ward is a candidate because you're looking at the medicines they are on, you're looking at the condition that they are currently in, their reason for admission to hospital, and you're trying to optimise their treatment, by making sure that all the medicines that they are on are appropriate" Fil6 (8 yrs qualified; hospital; prescriber)

Other behaviours included communication with health professionals and encouraging uniform practice

"And there are certain medicines that I would look at a chart and stop if a patient is going through certain things, but I've sat down with other pharmacists, and they can be presented with a very similar situation, and they wouldn't hold those medicines" A1 (4 yrs qualified; hospital)

Enablers to reducing anticholinergic burden (e.g. quick and easy to use decision support) are further explored in the BCW analysis.

After identifying relevant themes and categories, the next, second, stage was to identify target behaviours and behavioural change techniques to incorporate into the tool using the BCW analysis.

Stage 2: BCW analysis steps

1: Defining the problem in behavioural terms

The issue (anticholinergic burden in older adults) is already known; however, as prescribed by the BCW framework, the problem needed to be defined in behavioural terms. A key factor identified during thematic analysis was *'behaviours that lower ACB scores'*. Participants thought that pharmacists needed to be more aware of anticholinergic burden at the start of a new therapy and during medication reviews to make interventions to reduce it. Therefore raising awareness on the potential risk of anticholinergic burden in older adults was seen as an enabler.

"So, some of it is being aware at the start, and I think that needs to be supported too, not to be forgotten about. To raise awareness to have the tools out there, and it is to promote it so that if the tool is out there, it's actually used because, at the end of the day, you can't make somebody do something. So, you need to make it as easy as it can be" LB8 (10 yrs qualified; care home)

Another key category (lack of tools and information) was identified during thematic analysis and is related to the theme limiting factors. Here, pharmacists expressed that a *'lack of tools and information'* meant that some pharmacists did not have the *confidence* to make decisions to reduce anticholinergic burden.

"If they had a tool that actually gave them some guidance on it, then they would. But I think because they don't really know how to, what recommendation that they would make, they don't have that information or background knowledge, so they don't feel confident within their role now to be able to make recommendations like that" Fil6 (8 yrs qualified; hospital; prescriber)

Further, participants reflected on their own practice and mentioned not thinking about anticholinergic burden.

"To be completely honest with you, I can't say I have. I'm just thinking back to some of my reviews, and I don't think I've paid as much attention to them as I might have". A1 (4 yrs qualified; hospital)

Another pharmacist added that they did not prioritise anticholinergic burden

"I have heard of anticholinergic burden, but it is more of an afterthought. It is not really brought up to the forefront. But I think that is something that needs to be talked about more". T4 (5 yrs qualified; community)

In addition to the thematic analysis results, the results from Chapter 2 showed that more could be done to reduce anticholinergic burden in practice. Therefore, the behavioural problem of interest, in this case, was defined as inadequate consideration of anticholinergic burden among pharmacists in older adults. After further discussion with pharmacists, it was agreed that the behavioural problem definition was appropriate. Thus, this exercise aims to identify how the tool could be developed to improve the consideration of anticholinergic burden among pharmacists to reduce anticholinergic burden in older adults.

2: Selecting the target behaviours

After two independent researchers (G.O and A.G) read the coded interview transcripts, ten modifiable potential target behaviours relating to reducing anticholinergic burden in older adults were identified. They include: Stopping or recommending to stop drugs that unnecessarily contribute to anticholinergic burden, switching/recommending to switch an alternative with lower anticholinergic burden, identifying patients with high anticholinergic burden during medicines reviews (scoring anticholinergic burden), checking that medication with anticholinergic properties are appropriate, triggering reviews in the context of an acute decline, tapering dose with the aim to stop, revising in light of any adverse outcomes, triggering routine reviews, communicating with other health professionals and gathering prescribing history. Figure 9 illustrates how these behaviours might relate to each other.

Switching, stopping, and tapering the drug are activities that can directly lead to a reduced anticholinergic burden. However, these behaviours may depend on other interlinking

behaviours, e.g. triggering reviews and identifying patients with anticholinergic burden during medicine reviews. Pharmacists that participated in the member checking exercise (n=4) agreed with the results from this exercise.

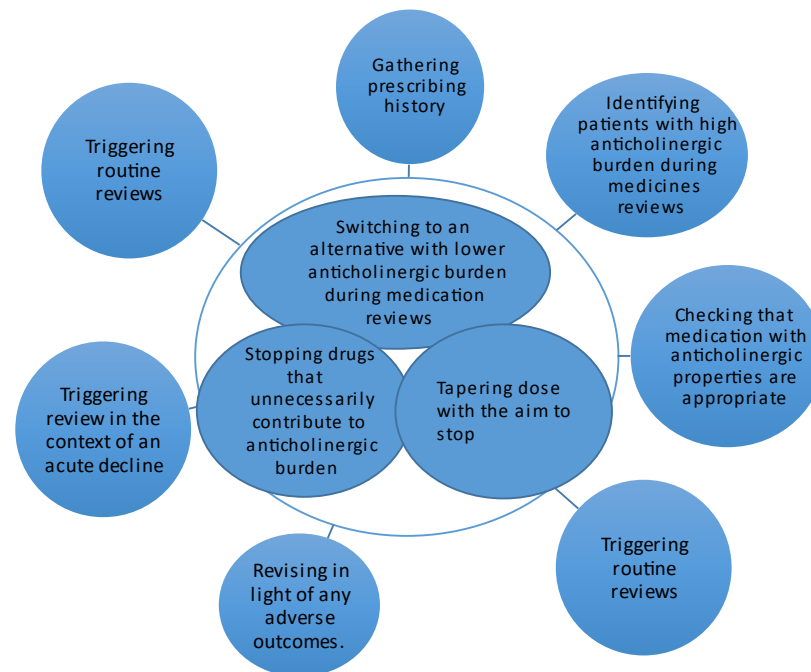


Figure 9 Behaviours relevant to reducing anticholinergic burden in older adults

Prioritising potential target behaviour

Though the BCW recommends a less is more approach and suggests that it is more beneficial to start with small changes and build on these incrementally, however, multiple potential behaviours were selected because of their likely spillover effect (how interrelated behaviours are) (255). For example, a pharmacist would need to identify a patient with anticholinergic burden before deciding what to switch, taper or stop. These behaviours were also selected based on the likelihood of changing behaviour, likely impact of behaviour change and how easy it might be to measure behaviour.

After prioritising the potential target behaviours. The target behaviours selected were;

1. Stopping/recommending to stop drugs that unnecessarily contribute to anticholinergic burden
2. Switching/recommending to switch to an alternative with a lower anticholinergic burden
3. Identifying patients with high anticholinergic burden during medicines reviews (scoring anticholinergic burden)
4. Checking that medication with anticholinergic properties are appropriate
5. Tapering drug dose with the aim to stop
6. Revising in light of any adverse outcomes and
7. Communicating with other health professionals

Behaviours like gathering drug history, triggering reviews in the context of an acute decline and triggering routine reviews were not selected as target behaviours because they were judged as less promising targets. When pharmacists were presented with this exercise's results for member checking, they unanimously indicated that they thought it was a fair and detailed assessment and selection. One pharmacist mentioned that a rejected target (*triggering routine review*) "*may not work in community, but could be suggested in the hospital*" T4 (5 yrs qualified; community) (Table 27. Appendix 4). The result summary was updated to reflect this. Table 14 presents the results from prioritizing the target behaviours and summarizes the reason for choosing each behaviour.

Table 14 Potential target behaviours to reduce anticholinergic burden in older adults

Potential target behaviour	Likely Impact on reducing anticholinergic burden	Likelihood of changing behaviour	Likely spill over score*	Measurement score	Decision**
1. Identifying patients with high anticholinergic burden during medicines reviews (scoring anticholinergic burden)	Promising target. To make changes to reduce burden, pharmacists will have to first identify patients with high anticholinergic burden	Promising. As identified from the interviews, It is already done by some pharmacists and should be a fairly easy behaviour to encourage, particularly where pharmacists are provided with more information	Promising. There is evidence that identifying patients with high anticholinergic burden can lead to other behaviours on this list, such as stopping, switching and tapering medicines (256).	Promising, for example, this behaviour can be measured from medication review records	The behaviour appears very promising as a target behaviour. Selected
2. Checking that medications with anticholinergic properties are appropriate	Promising target. This was judged promising because if pharmacists check to verify the appropriateness of medicines, it might prompt interventions to reduce burden where they are not.	Promising. Pharmacists already routinely check the appropriateness of medicines in medication reviews. Thus getting them to check the appropriateness of medications, with a focus on anticholinergic burden, should be fairly easy.	Promising. Checking the appropriateness of medication is likely to lead to performing other anticholinergic reducing behaviours(257).	Promising can be assessed from pharmacist notes or self-report	The behaviour is quite promising as a target behaviour. Selected
3. Triggering reviews in the context of an acute decline	Unpromising. Pharmacists already routinely trigger reviews in acute decline. For example, medications of patients admitted to hospital will usually be reviewed by pharmacists. Thus targeting this behaviour in itself is unlikely to provide substantial change.	It is considered to be very promising in terms of the likelihood of change as it is thought that the behaviour is likely to be easy to change as it is already adopted widely by pharmacists and is a key function of hospital pharmacists.	Promising. It is estimated to have a likely impact on other target behaviours such as stopping, tapering, or communicating with other health care professionals (258).	Promising can be assessed from pharmacist notes	The behaviour appears unpromising but is worth considering as a target behaviour (particularly in hospital). Rejected
4. Stopping/recommending to stop drugs that unnecessarily contribute to ACB burden during reviews	Promising target. Stopping/recommendations to stop drugs that unnecessarily contribute will reduce anticholinergic burden. Evidence suggests that it is not always done (259).	Promising. Pharmacists already routinely recommend stopping medications. Therefore, encouraging this behaviour in terms of medicines with anticholinergic properties should be easy.	Promising. Pharmacist's recommendation to stop can spill over to behaviours such as communication with the prescriber (260).	Promising. It can be easily measured from patient records and pharmacy notes.	The behaviour appears very promising as a target behaviour. Selected
5. Switching/recommending to switch to an alternative with lower anticholinergic	Promising target. Switching/recommending a switch of drugs to alternatives with a lower burden will reduce anticholinergic burden. Evidence from the interview and previous	Promising. It is considered to be very promising in terms of the likelihood of change as it is thought that pharmacists already routinely recommend switching medications.	Promising. Previous report of pharmacist's recommendation to switch leading to behaviours such as communication with prescriber at the point of care (260)	Promising. It can be easily measured from patient records and pharmacy notes.	The behaviour appears very promising as a target behaviour. Selected

burden during medication reviews	studies suggests that it is not always done (259). Therefore, changing this behaviour is likely to have a big impact				
Potential target behaviour	Likely Impact on reducing anticholinergic burden	Likelihood of changing behaviour	Likely spill over score*	Measurement score	Decision**
6. Tapering drug dose with the aim to stop	Promising target. Tapering the dose with the aim to stop can reduce anticholinergic burden. Some pharmacists already do this; however, getting more pharmacists to recommend a taper of medicines with anticholinergic properties is likely to have a big impact. Some patients may not be keen on stopping the medication, especially when there is a withdrawal effect. Reassuring them that they can be tapered may have a positive impact.	Promising. It is considered to be very promising in terms of the likelihood of change as it is thought that pharmacists already recommend tapering to stop for some medications. Extending this behaviour to medications with anticholinergic properties should be fairly easy	Promising. Previous report of pharmacist's recommendation to reduce dose spilling over to communication with prescriber at the point of care (260).	Promising. Patient records and pharmacy notes.	The behaviour appears very promising as a target behaviour. Selected
7. Revising in light of anticholinergic adverse outcomes.	Promising target. Reviewing and changing medicines with anticholinergic properties when an adverse outcome is reported or observed will reduce anticholinergic burden. This is not always done, and some of these adverse effects might be mistakenly considered a consequence of ageing. Therefore changing this behaviour is likely to have a big impact	Promising. Pharmacists widely review and recommend changing some medications when adverse effects are observed or reported. Extending this behaviour to medications with anticholinergic properties should be fairly easy	Promising. There is evidence that revising medication in light of adverse effects, such as a fall, has led to other behaviours such as communication with prescribers (261).	It is estimated to be promising of ease of measurement as it would be fairly easy to monitor behaviour that is recorded in pharmacy and patient notes.	The behaviour appears very promising as a target behaviour. Selected
8. Triggering routine reviews	Unpromising but worth considering. Triggering routine reviews in itself is unlikely to have an impact. If pharmacists do not already consider anticholinergic burden during reviews, triggering more routine reviews is unlikely to have an impact.	Promising. Many pharmacists already trigger yearly reviews for patients within review criteria.	Promising. Some evidence that triggering routine reviews with a decision making resource led to other behaviours such as stopping medications with anticholinergic burden(168).	Promising, for example, pharmacists keep a record of reviews on the pharmacy database	The behaviour appears unpromising but is worth considering as a target Behaviour. Rejected

Potential target behaviour	Likely Impact on reducing anticholinergic burden	Likelihood of changing behaviour	Likely spill over score*	Measurement score	Decision**
9. Communicating with other health professionals	Communication between pharmacists and other health care professionals is very important. However, if pharmacists do not already consider anticholinergic burden, targeting communication is unlikely to impact their consideration. It is worth considering because the pharmacist would need to communicate with other professionals to action recommendations.	Promising. It is thought that the behaviour would have a good likelihood of change as it is already widely adopted, especially by pharmacists within teams.	Promising. Pharmacists – geriatrician collaboration has led to stopping medications with anticholinergic properties (262).	It is estimated to be unpromising but worth considering in terms of ease of measurement as it would be difficult to monitor all instances when pharmacists communicate with other health professionals	The behaviour is quite promising. Selected
10. Gathering prescribing history	Unpromising but worth considering. Gathering prescribing history is integral to medicines reviews. Since pharmacists already perform this behaviour, making it a target behaviour is unlikely to impact consideration for anticholinergic burden among pharmacists.	Promising. It is considered to be very promising in terms of the likelihood of change as it is thought that that behaviour is already widely adopted. Many pharmacists already gather prescribing history during medication reconciliation and reviews; thus, encouraging this behaviour should be easy.	Promising. Medicines reconciliation may promote communication between pharmacist and other health professionals (263).	Unpromising but worth considering, measuring if pharmacists adequately gathered prescribing history. There is a possibility that it could be measured by self-report.	The behaviour is unpromising but worth considering. Rejected

*Rated as unacceptable, unpromising but worth considering, promising, very promising

**The following options could be selected as the decision

1. The behaviour appears very promising as a target behaviour
2. The behaviour is quite promising as a target behaviour
3. The behaviour appears unpromising but is worth considering as a target behaviour
4. The behaviour is not acceptable as the target behaviour (it does not matter what it is like on the other criteria, this behaviour cannot be selected as the intervention target)

3: Specifying the target behaviours

Selected behaviours, such as identifying patients with a high anticholinergic burden and checking that medication with anticholinergic properties are appropriate, were specified to be conducted by pharmacists in various settings (e.g. community, hospital and care home) when new drugs are started and during medication reviews. The results from specifying selected target behaviours are presented in table 15 below.

When the results from specifying the behaviours from the interview data were presented to pharmacists (n=4), there was disagreement on who needed to perform the behaviours and what patients to prioritise. Two pharmacists thought that some behaviours could be expanded to include other health care professionals. This disagreement was resolved through discussion that because the study is centred on pharmacists and did not involve interviews with any other health care professionals, the resulting intervention would be limited regarding whose behaviour it can target. Another pharmacist “disagreed with using over 65 as the criteria to trigger interventions”. They believed that “overall frailty and polypharmacy” were more appropriate than picking a particular age. After discussion, it was agreed that some behaviours would be specified further to include polypharmacy, frailty, and an age trigger.

Table 15. Specification of the identified behaviours

Behaviour	Who needs to perform the behaviour	What do they need to do differently	When do they need to do it	Where do they need to do it	With whom do they need to do it?
1. Identifying patients with high anticholinergic burden during medicines reviews (scoring ACB)	Pharmacist	They need to identify drugs with anticholinergic properties, score them and calculate a patients total anticholinergic score	During medication reviews and when new drugs are prescribed	Community, hospital, and care home	In older patients aged ≥ 65 . Polypharmacy and/or on medicines with anticholinergic properties. Dementia Recent fall Confusion and/or frail
2. Checking that medication with anticholinergic properties are appropriate	Pharmacist	They need to check what the medication is for, that the medicine is needed, working, and will not potentially worsen a patient's presentation, does not interact with other medications, and that therapy is not duplicated.	During medication reviews and when new drugs are prescribed	Community, hospital, and care home	In older patients aged ≥ 65 . Polypharmacy and/or with an anticholinergic burden score of 3 and over. Frail older adults. Dementia, recent fall, and confusion
3. Stopping drugs that unnecessarily contribute to anticholinergic burden during reviews (making decisions about which drugs to stop)	Pharmacist	They need to make decisions about which drugs to stop	During medication reviews	Community, hospital, and care home	In older patients aged 65 and over with an anticholinergic burden score of 3 and over. In older adults with frailty and /or polypharmacy.
4. Switching to an alternative with a lower anticholinergic burden during medication reviews	Pharmacist	They need to identify possible switches and making decisions about what drugs to switch	During medication reviews	Community, hospital, and care home	In older patients aged 65 and over with an anticholinergic burden score of 3 and over. In older adults with frailty and /or polypharmacy
5. Tapering dose with the aim to stop	Pharmacist	They need to make decisions about which drugs with anticholinergic properties they want to taper down to stop	During medication reviews	Community, hospital, and care home	In older patients aged 65 and over with an anticholinergic burden score of 3 and over. In older adults with frailty and /or polypharmacy
6. Revising in light of any adverse outcomes.	Pharmacist	They need to make decisions on whether to stop a drug when a patient experiences an adverse effect	After a patient complaint, during an intervention review	Community, hospital, and care home	In older adults with frailty and /or polypharmacy Dementia Recent fall Confusion Chronic constipation

Behaviour	Who needs to perform the behaviour	What do they need to do differently	When do they need to do it	Where do they need to do it	With whom do they need to do it?
7. Communicating to all relevant professionals,	Pharmacist	They need to communicate their recommendations to other health care professionals when working independently (e.g. community or hospital pharmacist) or within a multidisciplinary team (e.g. hospital pharmacists)	During and after a medication review	Community, hospital, and care home	With nurses, doctors, and other prescribers in the hospital. With the GP in community and care homes.

4: COM-B analysis

The fourth step in the BCW involved identifying what it would take to bring about the desired behaviour changes in terms of capability, opportunity, and motivation. The themes and categories that emerged from the in-depth interviews were mapped to the COM-B and TDF domains. The result of this exercise, illustrative quotes and researcher's comment are presented in table 16 below.

For example, a key factor identified was a lack of confidence that limited consideration for anticholinergic burden, which led to a lack of reflective motivation in behaviour targets 4-7. Pharmacists identified that limited time and resources were barriers to reducing anticholinergic burden in practice, and these led to a lack of physical opportunity for behaviour targets 1, 2, 4, 5 and 6. Further, pharmacists perceived that raising awareness by providing anticholinergic burden information will enable physiological capability in behaviour targets 1-3.

When the COM-B analysis results were presented to pharmacists for member checking, they agreed with the results of the analysis. However, a pharmacist added that patient-friendly leaflets could help with patient's resistance to change and thus reflective motivation. The researcher's comments were updated to include this.

Table 16. COM-B analysis results

Com-b component (TDF context)	Theme (statement)	Illustrative quote	Comment
Behaviour Target 1: Identifying patients with high anticholinergic burden during medicines reviews (scoring anticholinergic burden)			
Physiological capability (knowledge)	Enabling factors (raising awareness)	<i>"So, I would say if it's a topic that a lot more people speak about or if there was a lot more information about it, then maybe people would know of it and actually put it into practice". A1 (4 yrs qualified; hospital)</i>	Pharmacists need to be provided information on anticholinergic burden in older adults in order to know more about why it is important
Physical opportunity (resources/tools)	Enabling factors (availability of tools that are quick and easy to use)	<i>"You need to make something that, whilst it might be robust, that it's quick and easy and that it is simple". LB8 (10 yrs qualified; care home)</i>	Tools that enable pharmacists to identify patients with high anticholinergic burden need to be provided to pharmacists
Behaviour Target 2: Checking that medication with anticholinergic properties are appropriate			
Physical opportunity (Time)	limiting factors (limited time)	<i>"Time, because most of the time you are the only pharmacist covering one ward of about, it depends on the ward, but sometimes you can have up to thirty patients on one ward. Particularly, I think, patients who might be more high risk, so in care of the elderly wards, you tend to have bigger wards and one pharmacist covering that bigger ward compared to a general ward, where it tends to be about twenty-four patients to one pharmacist". A1 (4 yrs qualified; hospital)</i>	Tools that enable pharmacists to quickly assess the appropriateness of stopping or continuing a medicine need to be provided to pharmacists.
Physiological capability (knowledge)	Enabling factors (raising awareness)	<i>"I think after hearing you explain it in-depth, even the ones that don't exert as much anticholinergic activity as I would assume, even all of that, working together leads to a higher burden, I can't say that I have particularly thought about that" S4(6 yrs qualified; community)</i>	Pharmacists need to be provided information on anticholinergic burden in older adults in order to encourage them to check medication appropriateness.
Behaviour Target 3 Revising in light of any adverse outcomes			
Physiological capability (knowledge)	Enabling factors (raising awareness)	<i>"So, I would say if it's a topic that a lot more people speak about or if there was a lot more information about it, then maybe people would know of it and actually put it into practice" A1 (4 yrs qualified; hospital)</i>	Pharmacists need to be provided information on anticholinergic burden in older adults in order to know more about why it is important to revise in light of any adverse outcomes
Behaviour Target 4: Stopping drugs that unnecessarily contribute to anticholinergic burden during reviews			
Reflective motivation (Believes consequences)	limiting factors (the belief that stopping the drugs is the right option)	<i>"Otherwise, you might get ... they might get withdrawal effects, particularly for amitriptyline. Depends on the dose. If they're only on 20 milligrams, you might consider just stopping it" Sa7 (9 yrs qualified; care home)</i>	Knowledge of when to stop and how to taper doses should be provided to pharmacists

Reflective motivation (Belief about one's capability)	limiting factors (lack of confidence)	<i>"I think people are quite hesitant to stop patients' medication because they think that if they've then, also they come into hospital, they get admitted with one symptom or problem, that they don't want to worsen that or cause any further harm by stopping another medication". Fil6 (8 yrs qualified; hospital; prescriber)</i>	Provide resources that simplify decision making to improve confidence
Physical opportunities (resources)	limiting factors (lack of tools)	<i>"If they had a tool that actually gave them some guidance on it, then they would. But I think because they don't really know how to, what recommendation that they would make, they don't have that information or background knowledge". Fil6 (8 yrs qualified; hospital; prescriber)</i>	Quick and easy tools
Reflective motivation (beliefs about consequence)	limiting factors (Patient resistance to change)	<i>"And of course, patients do not want to have their medications stopped". P2 (13 yrs qualified; hospital; prescriber)</i>	Patient, carer or family involvement in the decision making process. The risk vs benefit of continuing medication should be communicated to the patient. Refer to the patient information leaflet
Behaviour Target 5: Switching to an alternative with lower anticholinergic burden during medication reviews			
Reflective motivation (beliefs about capability)	limiting factors (lack of confidence)	<i>"They don't feel confident within their role now to be able to make recommendations like that" Fil6 (8 yrs qualified; hospital; prescriber)</i>	Improve education to improve confidence
Physical opportunity (Time)	limiting factors (limited time)	<i>"So, I would say the time aspect because you know that you have seen all your patients within a restricted period of time, you have to attend meetings, you have to go see the doctors, there's a lot to do in one day" A1 (4 yrs qualified; hospital)</i>	Quick and easy tools

Physical opportunities (resources)	limiting factors (lack of tools)	<i>"So, I think that's the difficulty is that these tools might highlight them, but it doesn't say what to do. So, it might say choose an alternative, but you've got to go back to find and look up well what are the alternatives and what are their scores? It doesn't further follow you through". LB8 (10 yrs qualified; care home)</i>	Quick and easy tools
Reflective motivation (beliefs about consequence)	limiting factors (Patient resistance to change)	<i>"if you've got somebody who has the capacity who doesn't want to change and has been on that medicine for a long time and actually quite settled on it, doesn't want to change, there's risk of concern that if it's working for them, to change to something else that's a lower anticholinergic burden score and lower risk, they might be reluctant to change if it is working". LB8 (10 yrs qualified; care home)</i>	Patient, carer or family involvement in the decision making process. The risk vs benefit of continuing medication should be communicated to the patient. Refer to the patient information leaflet
Behaviour Target: 6 Tapering dose with the aim to stop			
Reflective motivation (beliefs about capability)	limiting factors (lack of confidence)	<i>"They don't feel confident within their role now to be able to make recommendations like that" Fil6 (8 yrs qualified; hospital; prescriber)</i>	Provide resources to improve confidence
Physical opportunity (Time)	Professional level limiting factors (limited time)	<i>"I would say, thinking about it, I would say time" P2 (13 yrs qualified; hospital; prescriber)</i>	Quick and easy tools
Physical opportunities (resources)	limiting factors (lack of tools)	<i>"Yes, definitely. Because I know that there are quite a lot of medication review tools that you can use out there, but to be honest, I have used a few, but I can't say that anticholinergic burden is something that I've come across" A1 (4 yrs qualified; hospital)</i>	Quick and easy tools
Behaviour Target 7: Communicating with all relevant professionals			
Reflective motivation (beliefs about one's capability)	limiting factors (lack of confidence in capability)	<i>"Because sometimes it's a bit difficult to just say here, can you stop the medication? Or can you do this? And that? I do think there needs a bit more education in that area now. Building up confidence, to be like yes, please can we stop the medication" T4 (5 yrs qualified; community)</i>	Improve education to improve confidence

5 and 6: Identify intervention options and select policy categories

Of the nine intervention functions listed as options on the BCW, seven were relevant to reducing the anticholinergic burden in older adults. However, only 3 of these were relevant in the context of this study. They were persuasion (using communication to induce positive or negative feelings and stimulate), enablement (improving means and reducing barriers to encourage behaviour change) and environmental restructuring (changing the physical or social context). Two researchers (O.A and G.O) discussed and applied the APEASE criteria to the intervention functions during a meeting. Intervention functions like modelling (providing an example for pharmacists to imitate) and training (Imparting skills) were rejected due to not being practicable in the context of this study because of limited time and resources. The summary of the application of the APEASE criteria and the reasons for not selecting an intervention function are presented in appendix 4, table 23.

Regarding policy categories, fiscal measures (e.g. applying tax) and legislation (e.g. making laws) are not practicable or relevant and beyond the scope of this study. In addition, the creation of guidelines is unlikely to add extra value because they already exist. Should the tool be effective, then in the future, policy categories such as communication/marketing (e.g. using media to promote the resource) and service provision policy (delivering a service) could be applied. However, at this stage, using policy categories is impracticable.

7 and 8: selecting Behaviour Change Techniques (BCTs) to deliver intervention functions and mode of delivery

Ninety three behavioural change techniques, 20 commonly used BCTs mapped to the relevant intervention functions from step 5 were selected (244). Following this, two researchers (G.O, O.A) considered which of the 20 BCTs could be most appropriately and practically applied to address the identified barriers. A final shortlist of 5 BCTs were judged to be the most appropriate and practical.

The five techniques eventually selected were information about health consequences, prompts/cues, credible source, restructuring the physical environment, and action planning. A previous systematic review reported that some BCTs such as action planning, information on health consequences, credible source and restructuring the physical

environment, had reported intervention effectiveness for deprescribing (264). Appendix 4, Table 24, summarises the reason some BCTs were rejected.

The mode of delivery is a decision support tool provided from a distance, on an individual level through a link by mail or face to face. Apart from the mode of delivery, other dimensions of implementation were considered when specifying the implementation strategy below.

Stage 3: Developing a draft clinical decision-making tool to identify and reduce anticholinergic burden in older adults

Resources identified

After identifying BCTs to incorporate into the tool, the next stage was a search to identify resources including evidence-based clinical guidelines, consensus documents, clinical decision support tools, and published literature that contain recommendations that can reduce anticholinergic burden. Following the search, 77 resources were identified. 13 of these were guidelines, six guidance documents, 20 were systematic reviews with or without meta-analysis, 12 were other types of reviews (e.g. literature reviews and clinical reviews), three were randomized controlled trials, one consensus document and 22 were put in the “others” category (e.g. British National Formulary, MHRA warnings and observational studies).

AGREE results

The Agree GRS tool was used to evaluate the methodological quality of the 20 guidelines, consensus, and guidance documents identified. This exercise aimed not to exclude consulting poor quality guidelines or tools but to document the methodological rigour of evaluated guidelines. Two researchers (G.O and O.A), both with knowledge of evidence-based medicine, agreed that the AGREE GRS's most important domain was the overall quality of guideline recommendations (Domain 4). For this domain, guidelines (12 of 13) were more likely to be given ‘very good’ scores than guidance documents (1 of 6). In contrast, guidelines (4 of 13) were more likely to get average scores in Domain 2 (presentation style) compared to guides (1 of 6) which scored higher. Guides were rated higher because they were often easier to navigate and user friendly.

Furthermore, guidelines (12 of 13) were more likely than guidance documents (1 of 6) to involve relevant stakeholders in a systematic development process and thus were more likely to be given 'very good' scores in domain 1 (the process of development). Scores were averaged from the two researchers and rounded up. Appendix 4, Table 26 presents the scores for domains 1 to 4 for each guideline, guide, and the researcher's comments.

The draft ABDeS tool

This section provides an in-depth description of the draft tool's composition, outlining each section's origin. As mentioned above, the draft tool was developed based on the thematic analysis of semi-structured interviews with pharmacists, the Behaviour Change Wheel analysis, and evidence-based recommendations.

The BCTs identified from the BCW analysis described in stage 2 above were incorporated into the tool by:

1. Providing information on the health consequences of increased anticholinergic burden in the introduction section of the draft Abdes tool.
2. Introducing a checklist to identify patients and of things to consider and cue deprescribing.
3. Guiding communication with prescribers so that discussions can be planned.
4. Using credible sources to provide actionable recommendations.

During pharmacist interviews, it became evident that a lack of knowledge about anticholinergic burden was a major barrier to deprescribing. Some pharmacists were unfamiliar with the concept of anticholinergic burden and thus, did not prioritize it in reviews. To address this barrier to deprescribing, and enhance capability, an introductory overview explaining anticholinergic burden was added to the ABDeS tool. This introduction defines anticholinergic burden and highlights the increased risk of anticholinergic adverse effects in older adults. Equipping pharmacists with foundational knowledge aims to provide motivation and capability to then use the medication review steps to act on reducing anticholinergic burden. Figure A1 shows the introduction section of the draft ABDeS tool.

Introduction

Older adults may be more vulnerable to medicines' adverse effects because of important pharmacodynamic and pharmacokinetic changes that often accompany the natural ageing process. Anticholinergic medicines are commonly used for a variety of medical conditions. However, many other drugs not recognised as anticholinergics also possess anticholinergic properties. When multiple drugs are prescribed, the anticholinergic effect of these drugs can add up. The sum of these anticholinergic effects (the anticholinergic burden) has been reported to be associated with adverse reactions such as cognitive impairment, falls, physical impairment, and mortality (1, 2). Consequently, about 25% of the overall population and 50% of the older population could be at risk of these adverse outcomes (3).

Some current recommendations on reviewing anticholinergics

- **NICE guidance on the management of urinary incontinence in women (NICE NG123)** recommends that coexisting conditions (e.g. poor bladder emptying, cognitive impairment or dementia), current use of other medicines that affect total anticholinergic load and risk of adverse effects, including cognitive impairment should be considered when prescribing anticholinergic medicines to treat overactive bladder (4).

- **NICE guidance on falls in older people (CG161)** recommends that people who have had a fall or are at increased risk of falling should have their medication reviewed as part of a multifactorial risk assessment. It recommends that psychotropic medications (e.g. neuroleptics, sedatives and antidepressants) should be reviewed and if possible discontinued, reducing an older adults risk of falling (5)

- **NICE guidance on dementia (NG97)** recommends that people with suspected dementia are referred to a specialist dementia diagnostic service once reversible causes of cognitive decline have been investigated. These include delirium, depression, sensory impairment [such as sight or hearing loss], or cognitive impairment from medicines associated with anticholinergic burden. Also, It recommends considering minimising the use of medicines associated with increased anticholinergic burden, and where possible to look for alternatives during medication reviews (6)

Figure A 1. Introduction section of the draft ABDeS tool

In addition to the introduction, the draft ABDeS tool comprised of 3 steps described below.

Step 1 is a checklist to identify patients at increased risk of anticholinergic burden adverse effects, such as those aged ≥ 65 years, with polypharmacy, dementia, frailty, recent falls, confusion, and chronic constipation. The checklist items are highlighted under the theme 'Implementation considerations' and category 'identifying priority patients' in the thematic analysis results described above. In addition, the checklist is backed by existing literature. For example, medicines with anticholinergic properties have been shown to increase the risk of falls (265).

Pharmacists are expected to use the checklist to screen older adult patients and identify those at higher risk of anticholinergic burden who may benefit from review. If a patient fits into any of the categories highlighted in step 1 of the draft ABDeS tool, pharmacists were advised to go to step 2. Figure A2 shows step 1 of the draft ABDeS tool.

STEP 01

Cross-check patient profile:

Age

- 65 and over

Medical context

- Taking ≥ 5 medicines
- Recent fall (≤ 3 months)
- Dementia
- Mild cognitive impairment*
- Confusion
- Frailty**
- Chronic constipation

* Problems with memory, language, thinking and judgment that are more than expected with normal ageing (75)

**Three or more of the following: slow walking speed, weak grip strength, exhaustion, low physical activity level, and unintentional weight loss (76)

If your patient fits any of the options above, go to page 2 to calculate the anticholinergic burden score.

Figure A 2 Step 1 of the draft ABDeS tool (a checklist to identify patients who are at risk of anticholinergic burden)

Step 2 is an ACB calculation table that lists medications and their corresponding anticholinergic burden scores (1, 2 or 3). To use this step, the pharmacist would identify the patient's medications on the ACB scale and add up the scores to calculate their total ACB score. Incorporating the ACB scale aimed to provide pharmacists with a resource to identify patients with high anticholinergic burden during medicines reviews (target behaviour 1), addressing the lack of tools/resources barrier identified in the COM-B analysis (Table 16).

The draft version advises pharmacists to proceed to Step 3 for medication review if the patient had an elevated ACB score, without specifying a cutoff point. Figure A3 below represents step 2 of the draft ABDeS tool.

STEP 02

To calculate the patient's anticholinergic burden from the Anticholinergic cognitive burden (ACB) scale below, find the drug's ACB score from the relevant columns and add the scores for all the drugs on the side of the page.

Score	Medicines	Patients score
1.	Alimemazine, Alverine, Alprazolam, Aripiprazole, Asenapine, Atenolol, Bupropion, Captopril, Cetirizine, Chlorthalidone, Cimetidine, Clidinium, Clorazepate, Codeine, Colchicine, Desloratadine, Diazepam, Digoxin, Dipyridamole, Disopyramide, Fentanyl, Furosemide, Fluvoxamine, Haloperidol, Hydralazine, Hydrocortisone, Ioperidone, Isosorbide, Levocetirizine, Loperamide, Metoprolol, Morphine, Nifedipine, Paliperidone, Prednisone, Quinidine, Ranitidine, Risperidone, Theophylline, Trazodone, Triamterene, Venlafaxine, Warfarin	
2.	Amantadine, Belladonna, Carbamazepine, Cyclobenzaprine, Cyproheptadine, Loxapine, Meperidine, Methotrimeprazine, Molindone, Nefopam, Oxcarbazepine, Pimozide	
3.	Amitriptyline, Amoxapine, Atropine, Benzotropine, Brompheniramine, Carbinoxamine, Chlorpheniramine, Chlorpromazine, Clemastine, Clomipramine, Clozapine, Darifenacin, Desipramine, Dicyclomine, Dimenhydrinate, Diphenhydramine, Doxepin, Doxylamine, Fesoterodine, Flavoxate, Hydroxyzine, Hyoscyamine, Imipramine, Meclizine, Methocarbamol, Nortriptyline, Olanzapine, Orphenadrine, Oxybutynin, Paroxetine, Perphenazine, Promethazine, Propantheline, Propiverine, Quetiapine, Scopolamine, Solifenacin, Thioridazine, Tolterodine, Trifluoperazine, Trihexyphenidyl, Trimipramine	Total:

If the patient has anticholinergic burden go to step 3 below. Note the ACB tool is not an exhaustive list of drugs with anticholinergic properties and should be used as a guide. Step 3 may be relevant where the drug isn't listed on the tool but others in its class are.

Figure A 3. An Anticholinergic burden scale calculation table for the draft ABDeS tool

Step 3 is the core medication review section. For each medication class, step 3 includes examples of common drugs in that class listed at the start of the section. The lists are based on medications in the ACB scale, and thus, are not a comprehensive list of all drugs within each class. Figures A4 and A5 show screenshots of the medication review component in step 3 for the drug class "Anticholinergic drugs for Urinary Incontinence".

For each drug class, pharmacists are prompted to:

1. Use a checklist to identify situations where deprescribing may be appropriate based on indication, effectiveness, interactions, adverse effects, adherence, and other considerations.
2. Review suggestions for safer pharmacological and non-pharmacological alternatives if the checklist indicates deprescribing may be suitable.
3. Refer to the provided taper guide recommendations, when appropriate, to safely discontinue or reduce doses of medications.
4. Involve patients in shared decision-making around potential deprescribing or tapering of medications.
5. Document the deprescribing rationale and patient preferences.

This structured process provides pharmacists with the resources and prompts needed to take action to reduce inappropriate anticholinergic medications. It aims to address barriers like 'lack of confidence' and 'lack of tools' identified in the BCW/COM-B analysis (Table 16). There were minor modifications to the sections on "Anticholinergic drugs for Urinary Incontinence" and "Opioids for non-cancer pain." However, the medication review content for the remaining classes was identical between the draft and final tool. For conciseness, the full draft ABDeS medication review sections are not reproduced here, as they closely resemble those presented in the final tool documentation in Appendix 5."

Anticholinergic drugs for Urinary Incontinence

³Oxybutynin, ³Tolterodine, ³Fesoterodine, ³Flavoxate,
³Darifenacin, ³Solifenacin, ³Propiverine

Check list

- Specify the indication for each medication
- Check the need for the drug (e.g. is patient wearing a catheter or incontinence pad). If unsure, consider a treatment break to assess effectiveness
- Does medication interact with the patient's condition or other drugs (drug-drug, drug-disease interaction)
- Is there presence of dual therapy for the same or different indications e.g. imipramine* and oxybutynin
- Is medication likely to cause more harm than benefit.
- Is the patient willing to be deprescribed
(Involve patient, family members and carers in decision making where appropriate)

Deprescribing triggers

- Dementia (risk of worsening confusion)(1, 2)
- Confusion (delirium may resolve after stopping)(7-9)
- Catheter (not needed)
- Continued use despite lack of improvement in symptoms (risk of adverse effect)
- Recent fall (possible risk of falls)(58, 59)
- Dual therapy (increased risk of adverse effects)
- Patients on anticholinesterase inhibitors e.g. donepezil, rivastigmine and glutamine (risk of worsening cognitive impairment)
- Chronic glaucoma, chronic constipation, and chronic prostatism (risk of worsening these conditions) (2)
- Other possible triggers no valid or current indication, drug- drug/drug-disease interaction, high anticholinergic burden, dual therapy, off label use, presence or high risk of serious adverse effects, and poor adherence

Figure A 4. Step 3 checklist and deprescribing triggers for the draft ABDeS tool

Anticholinergic drugs for Urinary Incontinence (continued)

Pharmaceutical alternatives

Switch if appropriate

•Mirabegron is an option for treating overactive bladder if treatment with an anticholinergic is contraindicated, ineffective, or if patient has unacceptable side effect (41). Mirabegron is contraindicated in severe uncontrolled hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)

Consider switching formulation if patient doesn't want to stop

•Modified release oxybutynin** (less adverse effect profile)

Non pharmacological alternatives (39)

Absorbent products

•Absorbent products, hand-held urinals and toileting aids (• as a coping strategy pending definitive treatment • as an adjunct to ongoing therapy • as long-term management options only after exploring other treatments • in severe cognitive or mobility impairment that may prevent other treatments)

Physical therapy

•Physiotherapist supervised pelvic floor muscle training (at least 3 months' duration as first-line treatment to women with stress or mixed urinary incontinence)
•Bladder training lasting (at least 6 weeks as first-line treatment to women with urgency or mixed urinary incontinence)

Lifestyle advice

•Recommend a trial of caffeine reduction
•Advise patients who have a BMI greater than 30 kg/m² to lose weight
•Advise a light modification of their fluid intake

After selecting an option

•Record deprescribing rationale (see additional deprescribing rationales if needed) and patient preference

•Communicate recommendation to prescriber or treatment team (to get feedback on the proposed medication changes and facilitate medication updates). Written or verbal communication should include; medication, intention, rationale, recommendation plan (e.g. dose change and follow up) and patient agreement

*Imipramine is not recommended to treat urinary incontinence due to adverse effect (39)

**Immediate release oxybutynin not recommended in frail older women at risk of sudden deterioration in their physical or mental health
Drug1= ACB 1; Drug2 = ACB 2; Drug3=ACB 3

Figure A 5. Pharmacological and non-pharmacological alternatives for draft ABDeS tool

Stage 4: Refining the draft Abdes tool

In total, ten pharmacists (5 from the interviews and five additional pharmacists) provided feedback and suggestions on how to improve the draft ABDeS tool. Responses were summarized into themes, described below.

Ease of use

A recurring theme among pharmacists was that the tool was easy to use, navigate and understand. This was reported by 9 of 10 pharmacists that provided feedback. They particularly welcomed the flow chart design and the concise nature of recommendations.

"It is clear and easy to follow, which is useful and practical, I liked how it is done in a stepwise way, and the pointers for deprescribing were clear" N2 (5 yrs qualified; GP; prescriber)

Usefulness

Pharmacists reflected on how useful the tool might be in community, noting that it was limited by most MUR's being targeted to medications without anticholinergic properties.

"With regards to MUR's people are focused on targeted medicines in 70% of patients, and unfortunately a lot of medicines on the list doesn't fall under targeted" T4 (5 yrs qualified; community)

However, a place for the tool was identified with non-target MUR's

"It's a really good tool to use in a GP practice and hospital setting. In terms of its use in community pharmacy, I think it would be quite useful in non-targeted MURs" Z2 (5 yrs qualified; community)

Another pharmacist mentioned that the tool would fit well into normal practice

"In practice, you would generally ask yourself these questions if there is no benefit, like these are questions I would ask and would be brought up during ward rounds"

and team meetings. I feel like the tool is appropriate and kind of fits into daily practice" A1 (4 yrs qualified; hospital)

ACB score cut off

Initially, no anticholinergic score cut-off point was added to the tool; this was so that pharmacist could evaluate a patient regardless of their anticholinergic score. The rationale behind this was that adverse outcomes had been reported in patients with scores below 3. However, the exclusion of a cut-off score was not acceptable to pharmacists. They agreed that due to the busy nature of clinical practice, patients needed to be prioritised, and a cut-off score was a meaningful way to do this.

"For Step 2, where you calculate the Anticholinergic Burden, is there a threshold of a score for when deprescribing should happen, e.g. if patients have a score of 3+ their prescriber needs to consider deprescribing?" Z2 (5 yrs qualified; community)

The draft tool was modified to include a cut-off score.

Recommendations that needed to be excluded

While reflecting on their practice, a pharmacist thought an opioid deprescribing trigger made little sense even though it was a STOP criterion.

"In the deprescribing triggers for opioids, I wasn't too sure of the practicality of it being used regularly without a laxative as a deprescribing marker" TA1 (10 yrs qualified; hospital/community)

After a discussion with other pharmacists, it was agreed that the recommendation should be excluded.

Communication exercise

Pharmacists thought that there was a need to improve the communication guide for pharmacists.

"There is little patient-centred material helping explain to patients why we look at it and the risks" Sa7 (9 yrs qualified; care home)

After further discussion, pharmacists that indicated they were willing to participate in the communication task (n=5) wrote out talking points to be included in the tool. This section titled 'Pharmacists communication guide' was included as the last section of the ABDeS tool.

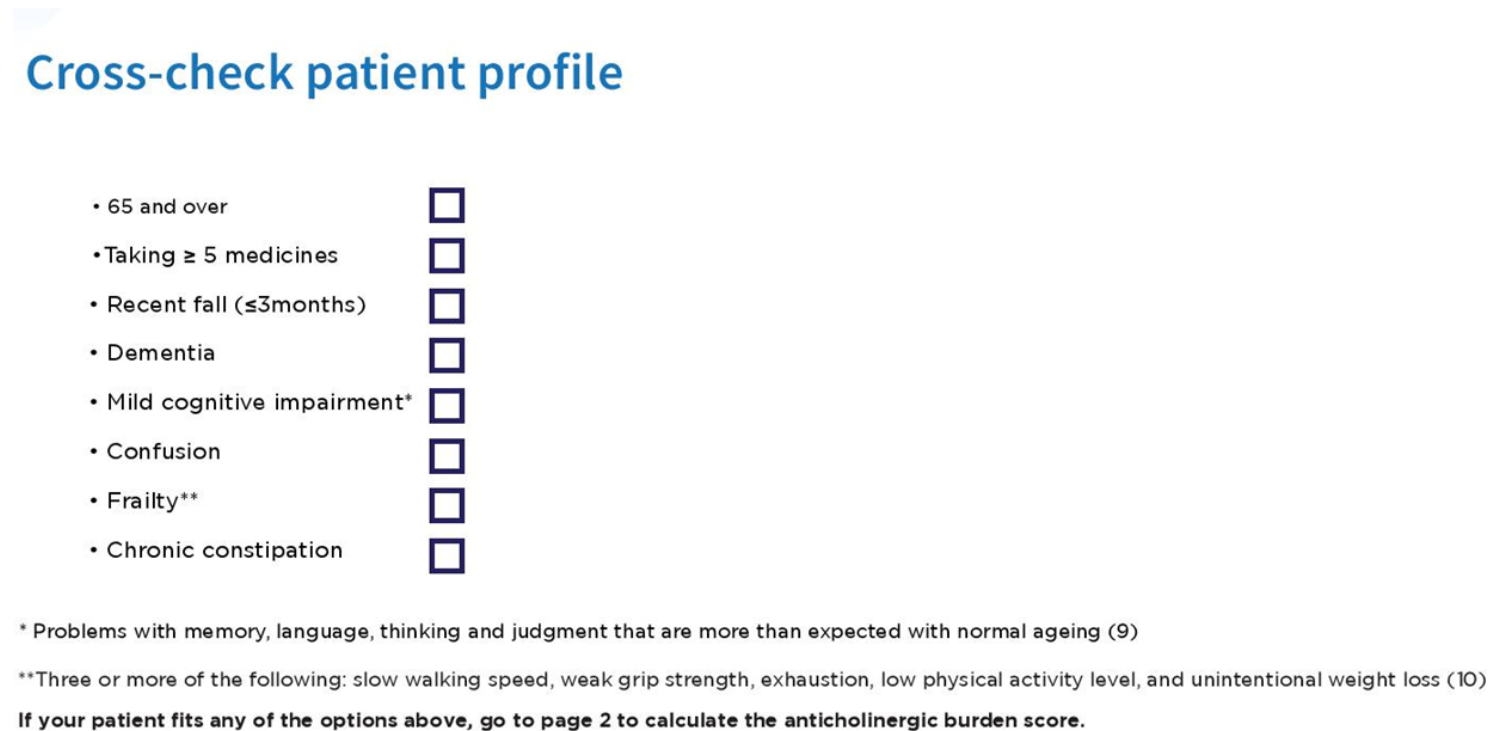
Others

Other feedback from pharmacists included adding a link to an online calculator to save time, adding check boxes, rephrasing and editing some areas of the tool, and adding an alternative drug. Where more clarification was needed, the amended tool was returned to the pharmacist for additional comments.

Changes made to the draft ABDeS tool following pharmacists' feedback are shown in the section below:

The ABDeS tool

Step 1: This section was modified to present all the risk factors under one heading to improve clarity and to include checkboxes. Figure A6 shows a screenshot of step 1 of the ABDeS tool.



Cross-check patient profile

- 65 and over ☐
- Taking ≥ 5 medicines ☐
- Recent fall (≤ 3 months) ☐
- Dementia ☐
- Mild cognitive impairment* ☐
- Confusion ☐
- Frailty** ☐
- Chronic constipation ☐

* Problems with memory, language, thinking and judgment that are more than expected with normal ageing (9)

**Three or more of the following: slow walking speed, weak grip strength, exhaustion, low physical activity level, and unintentional weight loss (10)

If your patient fits any of the options above, go to page 2 to calculate the anticholinergic burden score.

Figure A 6. Screenshot of step 1 of the ABDeS tool

Step 2: An ACB score cutoff of ≥ 3 was added, and a link to an online calculator (Figure A7). The online calculator combines the ACB scale and the German Anticholinergic Burden score (266, 267). Pharmacists might find it helpful when using the tool on an electronic device (e.g., computer) or when calculating anticholinergic burden for drugs not in the ACB scale.

STEP 02

To calculate the patient's anticholinergic burden from the Anticholinergic cognitive burden (ACB) scale below, find the drug's ACB score from the relevant column and add the scores for all the drugs on the side of the page (11). Alternatively use this online calculator [here](#)

Score	Medicines	Patients score
1	Alimemazine, Alverine, Alprazolam, Aripiprazole, Asenapine, Atenolol, Bupropion, Captopril, Cetirizine, Chlorthalidone, Cimetidine, Clidinium, Clorazepate, Codeine, Colchicine, Desloratadine, Diazepam, Digoxin, Dipyrindamole, Disopyramide, Fentanyl, Furosemide, Fluvoxamine, Haloperidol, Hydralazine, Hydrocortisone, Iloperidone, Isosorbide, Levocetirizine, Loperamide, Metoprolol, Morphine, Nifedipine, Paliperidone, Prednisone, Quinidine, Ranitidine, Risperidone, Theophylline, Trazodone, Triamterene, Venlafaxine, and Warfarin	
2	Amantadine, Belladonna, Carbamazepine, Cyclobenzaprine, Cyproheptadine, Loxapine, Meperidine, Methotrimeprazine, Molindone, Nefopam, Oxcarbazepine, and Pimozide	
3	Amitriptyline, Amoxapine, Atropine, Benztropine, Brompheniramine, Carbinoxamine, Chlorpheniramine, Chlorpromazine, Clemastine, Clomipramine, Clozapine, Darifenacin, Desipramine, Dicyclomine, Dimenhydrinate, Diphenhydramine, Doxepin, Doxylamine, Fesoterodine, Flavoxate, Hydroxyzine, Hyoscyamine, Imipramine, Meclizine, Methocarbamol, Nortriptyline, Olanzapine, Orphenadrine, Oxybutynin, Paroxetine, Perphenazine, Promethazine, Propantheline, Propiverine, Quetiapine, Scopolamine, Solifenacin, Thioridazine, Tolterodine, Trifluoperazine, Trihexyphenidyl, and Trimipramine	
		Total:

If the patient has an anticholinergic burden of ≥ 3 , go to step 3 below. Note the ACB tool is not an exhaustive list of drugs with anticholinergic properties and should be used as a guide. Step 3 may be relevant where the drug is not listed on the tool, but others in its class are.

Figure A 7. Screenshot of step 2 of the ABDeS tool. Red circles highlight changes made

Step 3: Checkboxes were added to sections titled "checklists", and a wording change was made to a deprescribing trigger to improve correctness (for urinary incontinence drugs). The words were changed from "not needed" to "potentially not needed" (Figure A8).

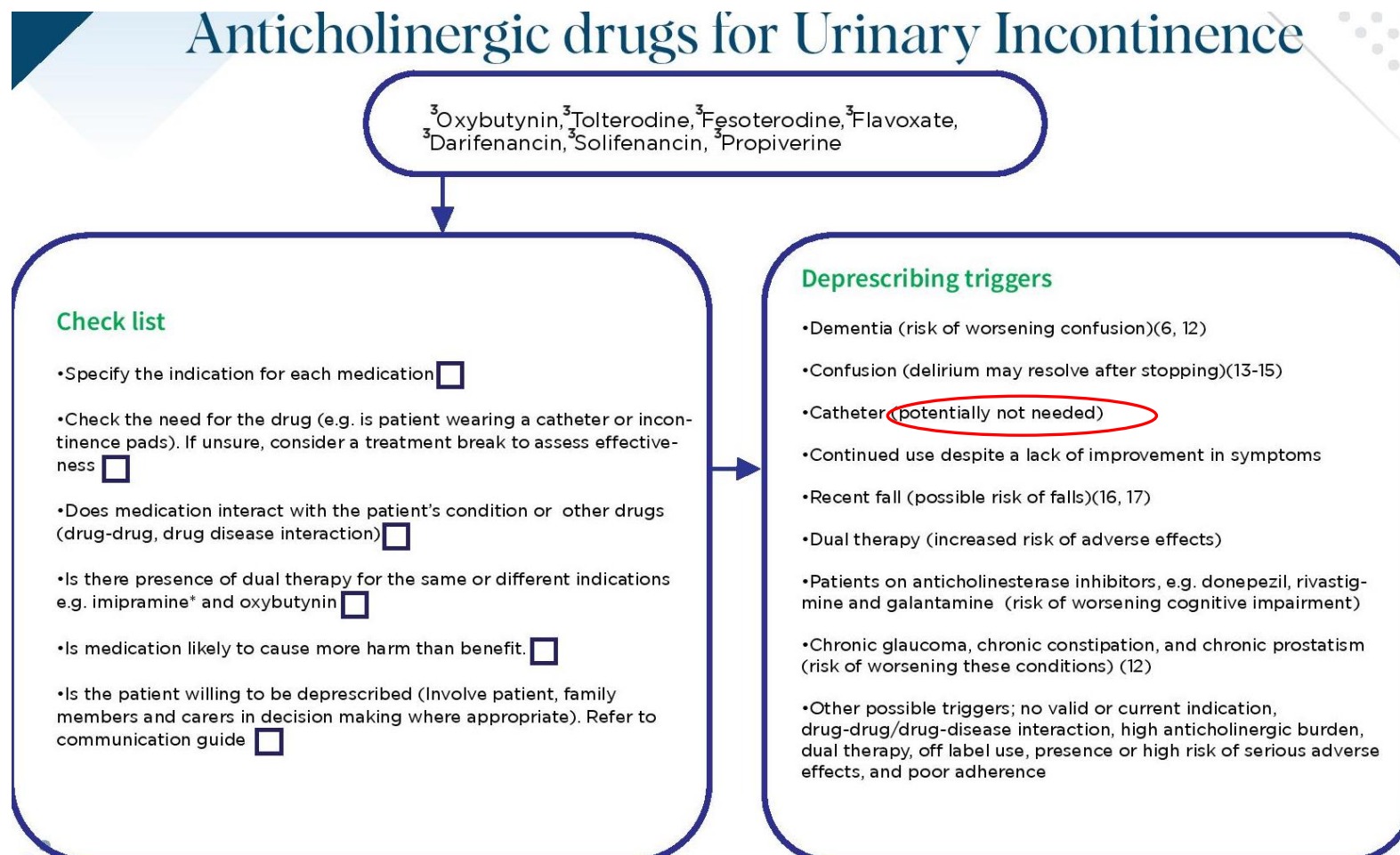


Figure A 8. Screenshot of Step 3 checklist and deprescribing triggers for the ABDeS tool. Red circles highlight changes made

An alternative recommendation was added (for urinary incontinence drugs) to step 3

Anticholinergic drugs for Urinary Incontinence (continued)

Pharmacological alternatives

Switch if appropriate

•Mirabegron is an option for treating overactive bladder if treatment with an anticholinergic is contraindicated, ineffective, or if a patient has unacceptable side effects (18). Mirabegron is contraindicated in severe uncontrolled hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)

•Trospium (decreased ability to cross the blood-brain barrier) (19)

Consider switching formulation if a stop isn't possible

•Modified release oxybutynin** (less adverse effect profile)

Non pharmacological alternatives (4)

Absorbent products

•Absorbent products, hand-held urinals and toileting aids (• as a coping strategy pending definitive treatment • as an adjunct to ongoing therapy • as long-term management options only after explor-

After selecting an option

•Record deprescribing rationale (see additional deprescribing rationales if needed) and patient preference ☐

•Communicate recommendation to prescriber or treatment team (to get feedback on the proposed medication changes and facilitate medication updates) . Written or verbal communication should include; medication, intention, rationale, recommendation plan (e.g. dose change and follow up) and details on patient agreement ☐

Figure A 9. Screenshot of Step 3 pharmacological and non-pharmacological alternatives for ABDeS tool. Red circle highlights change made

One opioid trigger in step 3 was removed. Figure A10 is a screenshot of step 3 of the draft ABDeS tool showing the deleted deprescribing trigger. See the ABDeS tool in Appendix 5 for the updated section.

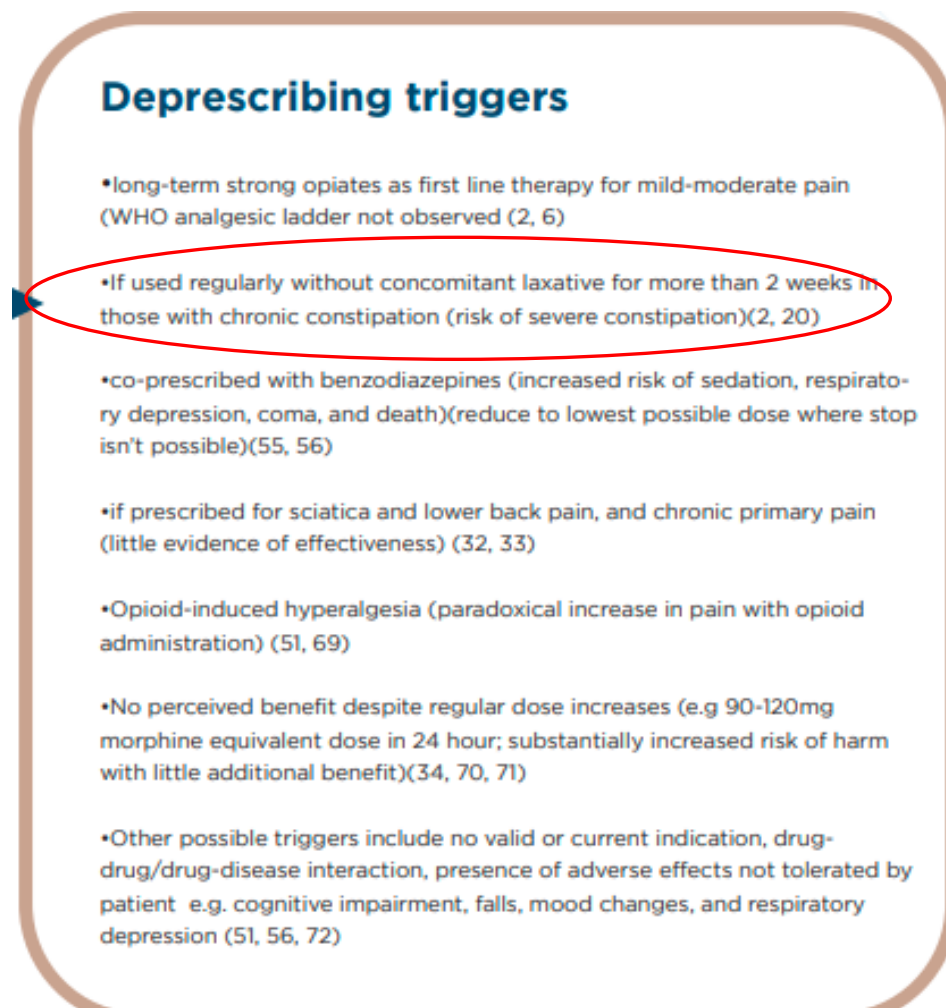


Figure A 10. Screenshot of Step 3 deprescribing triggers for opioids for non-cancer pain in draft tool. Red circles highlights deleted deprescribing trigger

The final section of Step 3 is a pharmacist communication guide, developed by pharmacists during the refinement process. This guide expands on the initial prompts for record keeping and prescriber communication by providing guidance on discussing deprescribing with patients.

During field testing, pharmacists felt a communication guide was needed to facilitate planned discussions with patients when recommending reducing or stopping medications. Therefore, the "After selecting an option" section was expanded into a more robust guide on what to say to patients about deprescribing. Figure A11 shows a screenshot the communication guide incorporated into Step 3 of the final ABDeS tool.



Figure A 11. Screenshot of pharmacists' communication guide in ABDeS tool

Summary of changes made

Key revisions to the draft ABDeS tool included:

- Adding a communication guide to facilitate patient discussions
- Incorporating a calculator link for simplified scoring
- Consolidating Step 1 risk categories under one heading
- Removing an opioid deprescribing trigger
- Adding an anticholinergic score cutoff
- Including an alternative medication recommendation
- Editing wording for clarity

Stage 5: Specifying the implementation strategy

Proctor's prerequisites to precisely specifying implementation strategies (e.g. naming and defining it) were used in the present study and described below (92).

What is the name of the strategy (name it)?

The implementation strategy employed in the present study is named following the ERIC taxonomy to ensure alignment with established implementation research terminology. The strategies adopted are:

- 1) Develop educational materials
- 2) Distribute educational materials
- 3) Tailor strategies (253).

What is the conceptual definition of the implementation strategy (define it)?

The purpose of this definition is to give the reader a general sense of what the strategy involves. The conceptual definition of 'develop educational materials' is to "*develop and format manuals, toolkits, and other supporting materials in ways that make it easier for stakeholders to learn about the innovation and for clinicians to learn how to deliver the clinical innovation*" (253). This strategy was applied to the present study by developing decision support for pharmacists (253).

Distribute educational materials is defined as distributing "educational materials (including guidelines, manuals, and toolkits) in person, by mail, or electronically". This describes how the tool will be delivered to pharmacists. Finally, tailor strategies were defined as tailoring "the implementation strategies to address barriers and leverage facilitators that were identified through earlier data collection (253). This described the process employed in the present study. The tool was designed to address the barriers highlighted in the interviews.

In addition to making the tool quick and easy to use to address time barriers, discreet components of the tool that address identified barriers and promote enabling factors include: 1) providing evidence-based guidance (BCT; credible source), 2) providing information on the consequence of increased anticholinergic burden in older adults (BCT; Information about health consequences), 3) providing guidance on what to say to

prescribers and patients so that communication can be planned (BCT: action planning), and 4) introducing a checklist of things to consider to cue deprescribing (BCT; prompts/clues). The way these components are linked to intervention function, BCTs and the COM-B analysis are summarised in appendix 4, table 25.

Who will use the tool (actor)?

Pharmacists working in hospitals, community settings (including GP surgeries), and care homes

What will need to be done (action)?

Pharmacists will use the ABDeS tool to identify patients at risk of anticholinergic burden, calculate anticholinergic scores, and conduct medication reviews to deprescribe/switch medications. Specific actions include:

- Screening patients using the checklist
- Calculating anticholinergic burden scores
- Reviewing medications and making deprescribing decisions
- Involving patients in shared decision making.
- Documenting rationale for changes

How should pharmacist choose to whom to apply the tool?

The targets were groups of patients judged by pharmacists to be more at risk of adverse outcomes. They are older adults aged 65 and over and/or with polypharmacy (defined as five or more medicines in the present study), and/or with cognitive impairment or dementia, and/or recent falls, and/or confusion, and/or chronic constipation, and/or frailty (three or more of the following: slow walking speed, weak grip strength, exhaustion, low physical activity level, and unintentional weight loss) (268).

When, where and how frequently will pharmacists use the tool?

The tool will be used by pharmacists in hospital, community (including GP surgeries) and care homes. The tool will be used when new medicines are started, during routine medication reviews (e.g. daily for newly admitted patient reviews in hospital), or during intervention reviews (e.g. when a patient complains of an adverse effect or when a pharmacist spots an issue with medication). The tool will be used as an additional resource during reviews, either as a digital link or in a printed format presented to pharmacists.

The tool will be implemented with as few disruptions as possible to standard clinical workflow. This will be achieved by telling pharmacists to tailor the tool to suit their practice. For example, the pharmacist will be asked to schedule reviews to their anticipated normal workflow (e.g. hospital pharmacist using the tool for routine reviews of each patient admitted). Before beginning the trial, the pharmacist will be asked to consider what they foresee as problematic in implementing the tools in the context of their work environment and how these issues could be mitigated.

How the outcome will be evaluated?

The initial evaluation will focus on whether the tool was acceptable and usable and the extent to which anticholinergic burden was reduced in older adults. The outcome will be evaluated using qualitative and quantitative methods.

Discussion

This chapter describes the development of the ABDeS clinical decision support tool to reduce anticholinergic burden in older adults using the Behavior Change Wheel framework informed by pharmacist interviews.

The chapter begins by discussing how an inductive approach identified additional themes beyond predefined domains, revealing perspectives on the pharmacists' role. This will be followed by a discussion of the development process of the ABDeS tool using the BCW framework, from mapping barriers and facilitators to refinement using user feedback. Finally, the implementation strategy development is described.

Identifying themes and additional contextual information

A recent systematic review was done to investigate how studies that employed the TDF in health care professionals (HCP's) or public samples can be optimised. The authors reported that of the 38 studies included, only ten allowed flexibility in data analysis, with an even smaller sample (n=5) reporting overarching inductive themes that were subsequently mapped to TDF (241). The authors recommended a flexible application of the TDF to avoid missing additional context by restricting data analysis. Therefore, an inductive approach to identifying themes was used in the present study to uncover additional contextual information and prevent 'forcing the data into a mould'.

The results from this exercise showed that while participants acknowledged the importance of pharmacists in deprescribing, some pharmacists also thought doctors could take on more responsibility. For example, not starting the drugs where alternatives with lower burden are available or deciding on a stop date for the medication. Previous studies have reported differing views on pharmacists' role in deprescribing, with some pharmacists feeling uncertain about where the final responsibility for avoiding or stopping potentially inappropriate medications in older adults lies (269, 270).

Another finding was how pharmacists viewed opportunities to deprescribe. While some pharmacists took a 'post side effect' view of anticholinergic burden (deprescribing as a response to reported adverse effect), others advocated a proactive approach. This (post side effect view) was also seen in Chapter 2, where pharmacists stopped the most drugs with high ACB scores in patients with dementia. Similarly, a previous study reported that geriatricians and pharmacists agreed that current practice is reactive to adverse outcomes

rather than proactive in avoiding harm (271). This finding may be because pharmacists are trained to deprescribe as a response to side effects, drug interactions or contraindications. However, the case of older adults presents a new 'frontier' where drugs may neither be contraindicated nor have interactions. Nevertheless, they can be inappropriate in older adults, especially where a safer alternative exists, requiring pharmacists to think beyond responding to adverse outcomes to deprescribing proactively to reduce the risk of adverse outcomes in this population.

Barriers and facilitators to deprescribing medicines with anticholinergic properties

Another important finding was the barriers pharmacists perceived to reducing anticholinergic burden in practice. The most recurrent being a lack of confidence, relating to fear about the consequences of stopping the medication, and lack of knowledge and tools available to help with decision making. Also, communication with other HCP's was limited by a lack of confidence. If medications are to be deprescribed, then recommendations will have to be communicated to other HCP's. This finding highlighted the importance of developing a decision support tool. Lack of confidence has also been identified in previous studies. For example, In a previous study to develop a hospital deprescribing framework, pharmacists identified a lack of confidence in decision-making as a barrier to deprescribing in older adults (271). Similarly, another study reported a lack of confidence with less experienced pharmacists (269).

These barriers are not limited to pharmacists alone, as other clinicians continue to find it difficult to deprescribe. Notably, in previous studies involving doctors, a challenge to deprescribing, especially for junior doctors, was not knowing what should be discontinued or actions to take once inappropriate prescribing is identified (271-273). Also, in a systematic review on deprescribing barriers in GP surgeries, the lack of decision-making systems, tools, and resources was identified as barriers to deprescribing (274). Furthermore, applying existing guidelines to older adults was criticised for not including recommendations for deprescribing, being based on trials involving younger patients and being heavily reliant on expert knowledge (274, 275).

Mapping barriers and facilitators to the behavioural change wheel

Unlike other behaviour change theories like the Theory of Planned Behaviour and the Transtheoretical Model, the BCW is a comprehensive framework that integrates the COM-B and accounts for psychological factors, environmental factors, and determinants of automatic and reflective processes (276). The use of the behavioural change wheel combined with the Theory Domains Framework made available an array of options that allowed for a systematic approach to developing the ABDeS tool.

Key behaviour domains that needed changing in pharmacists were identified, including physiological capability (knowledge), reflective motivation (belief about capabilities and consequence), and physical opportunity (environmental context and resources/tools, time). Similarly, a study to characterise geriatrician and pharmacist barriers and enablers to deprescribing identified similar TDF domains, including beliefs about consequences, environmental context and resources (271). Furthermore, in another study on community pharmacist's views regarding challenges in reducing inappropriate medication, the authors identified TDF domains such as beliefs about capabilities, environmental context, resources, and knowledge(269). Like the present study, pharmacists criticized guidelines for highlighting which drugs were inappropriate but without guidance on managing them (269).

Behavioural change techniques such as action planning, information on health consequences, credible source and restructuring the physical environment have been reported to have some effectiveness in deprescribing interventions (264). Thus, deprescribing medicines with anticholinergic burden is likely to be facilitated by the combination of BCTs identified in the present study. Accordingly, in the present study, mapping identified barriers and enablers to intervention functions, and BCTs led to the ABDeS tool's development. Further strengthening the study results, feedback was sort from interviewed pharmacists and additional pharmacists, resulting in key changes to the final format version of the resource as described above. The inclusion of additional pharmacists was to bring in a "fresh perspective". Notably, the feedback was similar from both groups of pharmacists.

Despite the little is more approach advocated by the BCW developers, it was necessary to target the seven behaviours because of how interrelated they were. For example, identifying patients with higher risk could cue a check on medication appropriateness and stopping or switching a drug.

The anticholinergic burden decision support (ABDeS) tool

The iterative and collaborative development process ensured that the tool was developed to suit pharmacists' needs and allowed for acceptability and practicability to be evaluated before future implementation. Based on the analysis of the qualitative interview, it was evident that for the tool to be acceptable, it would need to save time and be easy to use. The resultant tool is a 3 step anticholinergic burden decision support (ABDeS) that includes; 1) a checklist to identify patients who are at increased risk of anticholinergic burden; 2) an anticholinergic burden calculation table and guide; 3) A medication review section (Appendix 5).

The ABDeS tool was developed for five classes of drugs identified as a concern in the present study and Chapter 3. They are TCA's, anticholinergics for urinary incontinence, opioids, benzodiazepines, and antipsychotics. These classes of drugs were also prioritised by healthcare professionals, including nurses, pharmacists, and doctors, in a previous study to identify medication classes where deprescribing guidelines for use in older adults are a priority (277).

Feedback from pharmacists resulted in alteration of wording and arrangement identified as confusing, modification of prescribing triggers, the inclusion of a medicine, inclusion of a threshold ACB score and a communication guide developed by pharmacists. Furthermore, pharmacists reported that the decision support would be beneficial to their practice, concise yet detailed, and easy to use.

Implementation strategies

Implementation strategies are described as 'the how' of interventions. They are approaches and techniques that improve innovation adoption, implementation, and sustainability (278). Different implementation strategies have been described, including discrete, multifaceted and blended strategies. Discrete strategies involve a single action or process (e.g. an educational meeting). Multifaceted strategies involve two or more discrete strategies (e.g. an education meeting in addition to technical assistance), and blended strategies involve multiple discrete strategies interwoven to address various levels of barriers and branded as an implementation intervention (279).

Intervention designers are encouraged to start considering implementation strategies during the intervention development process to encourage effective integration into practice. The BCW analysis allowed tailoring the tool to pharmacist's preferences and specifying some aspects of implementation, such as who will use the tool. However, there was a need to further specify the implementation strategy beyond what was available using the BCW framework. Therefore, the implementation strategy was specified in stage 5 of the tool's development process. This involved establishing who will use the tool, when they will use it, whom they will use it on, where and how frequently they will use it, and what they will do. In addition, the implementation strategies were named and defined.

Implementation strategies have been criticised for being poorly defined and described using inconsistent wording, limiting replication in research and clinical practice. This inconsistency also limits the development of an evidence base (e.g. meta-analysis). To solve this problem, proctor developed prerequisites for specifying implementation strategies, including naming it, defining it, specifying who is expected to enact the strategy, their actions, setting the strategy will be enacted in, expected outcome, dose, and temporality (92).

In addition, the ERIC taxonomy was also developed to help name and define strategies. The framework comprises 73 discrete implementation strategies evaluated in a modified Delphi process, each given a name and definition (253). This work sought to build on the earlier findings by Powell et al. that classified 68 discrete strategies according to 8 domains after a comprehensive review of the literature (279). The present study employed the ERIC and Proctor specifications to specify the implementation strategy. The present study specified three discrete implementation strategies named by the ERIC taxonomy as; 1) Develop educational materials; 2, Distribute educational materials; and 3) Tailor strategies (253)

When developing clinical decision support, ensuring it can be integrated into the user's workflow is critical for adoption and impact. This is especially true when targeting complex older patients, as pharmacists describe high workloads and time limitations as barriers. The ABDeS tool was intentionally designed to align with pharmacists' existing practices based on their input during interviews, which emphasized the need for a quick, uncomplicated format. The tool also incorporated factors that improve the usability of tools. These considerations shaped the design of the tool to include features such as:

- A concise checklist format focusing on key actions to simplify use and save time
- A calculator link and scoring table to minimise time spent on ACB calculations
- Actionable recommendations rather than assessments to avoid workflow disruptions
- The tool automatically provides decision support rather than requiring the user to undertake additional tasks

It is envisaged that the tool will be used in various clinical settings (e.g., hospital and community) and during natural workflow events like when reviewing new medicines, during routine medication reviews, or intervention reviews as an additional resource (e.g. digital link or printed resource). Making the ABDeS tool available digitally or as a printed handout provides flexibility to accommodate different practice settings and mobility needs. For example, a hospital pharmacist can access the digital tool at a workstation or print a pocket version for ward rounds.

Feedback from pharmacists indicated that the ABDeS tool was easy to use and fit well into their practice in its current format. However, optimising integration and ensuring sustainability may require adapting the ABDeS tool for enhanced digital capabilities. For example, integrating the tool with existing pharmacy IT infrastructure could further facilitate use at the point of care. Automated scoring and alerts when opening patient profiles could also increase use by flagging high risk cases unobtrusively.

While digitizing the ABDeS tool could improve functionality, any upgrades should ideally take a user-centred design approach, to ensure enhanced adoption while limiting additional challenges. Simply integrating the tool into a digital format could potentially introduce unintended challenges like increased time spent on learning a new digital interface, errors in digital components, disruption of familiar paper-based workflows, manual data entry, and alert fatigue (280). Therefore, when exploring optimising the Abdes tool for digital environments, it will be important to consider these potential issues.

Implications

It should be noted that reducing ACB in older people is a complex clinical challenge and is not limited to changing pharmacist behaviour alone. Other issues such as addressing GP barriers to deprescribing and patient resistance to change may need to be addressed to reduce anticholinergic burden.

Therefore, a combination of interventions may be required. This study could have been designed to target all stakeholders. However, Introducing small, sustainable changes and building on those over time have been advocated to improve the effectiveness of interventions (229). If the present tool is effective in a future study, it could be combined with other interventions to reduce anticholinergic burden in older adults.

In addition, the development process established a good foundation for future implementation of the ABDeS tool to reduce inappropriate anticholinergic prescribing in its current format. However, Involving pharmacists in further efforts to adapt the tool for integration into existing pharmacy computer systems and tailoring the implementation protocol may enhance usability and adoption and lead to improved clinical outcomes across different contexts.

Strength and limitations

A strength of the study was the use of a theoretical approach that was systematic, giving transparency to the development process. Another strength was that stakeholders involvement allowed the tool to be tailored to their preferences through an iterative process. Besides, one of the criticisms of member checking is that participants might agree with everything the researcher suggests for fear of offending. In the present study, participants often expressed disagreements indicating they felt at ease. Furthermore, using the BCW allowed identifying behavioural change techniques to incorporate into the tool (e.g. prompts/cues) that would otherwise have not been considered.

Despite the many advantages of using the BCW, some challenges were identified. For example, the BCW process relies on researchers to make subjective judgements based on the context of the study. This could mean that another researcher presented with the same data may reach a different conclusion. Therefore, to improve trustworthiness, investigator triangulation and member checks were used at different points in the process. In addition, the reason for rejecting various options was described.

Another limitation of the present study was its small sample size. However, participants were sampled from various settings across the UK, including the east midlands, west midlands, London, south-east and south-west, possibly improving the transferability of the results. Furthermore, this study provided an in-depth description of the research process to enable an analysis of transferability by the reader (281).

Conclusion

Despite evidence that anticholinergic burden in older adults is linked to increased risk of adverse events, older adults with a high prevalence of falls, dementia and delirium are prescribed a wide variety of medicines with anticholinergic properties. This study aimed to assist pharmacists in making deprescribing recommendations by simplifying the decision-making process to reduce anticholinergic burden in this population

The objectives of this study were;

1. To develop a clinical decision-making tool to identify and reduce anticholinergic burden in older adults
2. To specify the implementation strategy for the tool

This is the first study to use the COM-B Model/TDF/BCW to develop a decision support tool to promote consideration for anticholinergic burden among pharmacists. The current study described how the ABDeS tool was developed and the evidence and theory used to inform the development process.

The ABDeS tool includes 1) a checklist to identify patients at increased risk of anticholinergic burden, 2) an anticholinergic burden calculation table and guide, and 3) A medication review section. Feedback from participating pharmacists resulted in changes to the final format version of the ABDeS tool. Future feasibility testing is required to assess the feasibility of use in clinical practice before future effectiveness testing.

Chapter 5: Conclusion

Chapter 1 highlighted how improved socio-economic development meant that people were living longer but not necessarily healthier. It provided a definition for anticholinergic burden and the contribution of non-traditional anticholinergics to this score. Because many of these medications are not seen as anticholinergics, HCP's may overlook their contribution to anticholinergic burden. The chapter made the case that anticholinergic burden had important health implications in older adults, particularly on a reduced standard of living, increased disability, burden on the health care system and additional costs. In this chapter, the inconsistent evidence of the relationship between cognitive impairment, mortality and anticholinergic burden were highlighted. Therefore, a systematic review and meta-analysis of prospective studies that allow temporality to be established were proposed as a method to strengthen and provide clarity to this relationship.

The chapter also highlighted the high rate of prescribing medicines with anticholinergic properties in clinical practice despite available guidance. Improving the appropriateness of prescribed medicines was proposed to improve drug safety and reduce adverse effects in the older population. The chapter also describes how this thesis aligned closely with the MRC framework in combination with amendments by Bleijenberg et al., In developing an intervention to reduce anticholinergic burden in older adults. In particular, this thesis identified and defined the problem using In-depth interviews with pharmacists as well as literature, employed the behavioural change wheel as the theoretical framework, determined the needs of stakeholders by identification of facilitators and barriers to reducing anticholinergic burden, examined current practice in a UK hospital, modelled process and outcomes by iteratively improving the tool, and used the BCW in combination with the Proctor specification that allowed implementation to be further specified, all leading to intervention design.

The overall aim of this thesis was to develop an intervention to reduce anticholinergic burden in older adults. The objectives were:

1. Evaluate the strength of the association between anticholinergic burden and cognitive impairment/mortality
2. Evaluate normal practice regarding anticholinergic burden in frail hospitalised patients

3. Describe the co-development of a clinical decision-making tool that takes into account identified barriers

The first step in the process was to conduct a systematic review and meta-analysis of prospective cohort studies on the association between anticholinergic burden and cognitive impairment/mortality. The process and findings are described in Chapter 2. The review identified 19 studies, including ten on cognitive function, eight on mortality, and one on both mortality and cognitive impairment. The review provided important information for answering the following questions; (i) (what is the strength of the association between anticholinergic burden, cognitive impairment, and mortality), (ii) (what are the differences between measures of anticholinergic burden that have been used to predict the risk of mortality and cognitive impairment in prospective cohort studies), (iii) (what are the measures of anticholinergic burden that are associated with the greatest risk of adverse outcomes), and (iv) (what measures of cognition are most likely to detect cognitive impairment due to increased anticholinergic burden in prospective cohort studies). A key finding in Chapter 2 was the moderate evidence of a temporal relationship between anticholinergic burden and cognitive impairment. This, in addition to some evidence of a dose-response in the expected direction, justified further research into developing an intervention to reduce anticholinergic burden in clinical practice.

Secondly, to inform the intervention development work, current practice regarding anticholinergic burden in a UK hospital needed to be evaluated in detail in Chapter 3. Hospitalised frail older adults provided an ideal population because of their increased susceptibility to adverse effects combined with an environment that provided valuable opportunity to review all patients medications, make changes and monitor the short-term effect of these changes. The study highlighted considerable scope for further reduction in anticholinergic burden leading to the next step in the process: developing a decision support tool for pharmacists.

Chapter 4 started the intervention development process by identifying barriers and facilitators to recommending deprescribing from pharmacists' interviews. These barriers and facilitators were mapped to the BCW framework for analysis. After analysis, the areas that needed to change were physiological capability (knowledge), reflective motivation (belief about capabilities and consequence), and physical opportunity (environmental context and resources/tools, time). Thus, the BCTs; action planning (e.g. through providing guidance on what to say to prescribers and patients to facilitate planned communication), information on health consequences (e.g. through providing information on the consequence of increased anticholinergic burden in older adults), credible source

(e.g. through providing evidence-based guidance), and prompts/clues (e.g. through introducing a checklist of things to consider with the purpose of cueing deprescribing) were selected to be incorporated into the tool.

The results from the BCW analysis led to the development of a 3-step anticholinergic decision support tool (ABDeS). The tool was designed to guide pharmacists through decision making for five classes of drugs identified in Chapter 3. The first step was a checklist to identify patients at increased risk of anticholinergic burden. The second step was an anticholinergic burden calculation table and guide, and the third step was the medication review section. The tool was refined through an iterative process.

Practical Implications

The population of older adults with multimorbidity and polypharmacy continues to grow, and this presents an ever-increasing challenge to healthcare systems. In addition, preventable adverse outcomes of medication present an additional burden to already stretched health care resources. Reducing the use of drugs with anticholinergic properties in older adults could improve the quality of life of these adults and result in large savings for the NHS from a reduction in falls, cognitive impairment, hospitalisation, and disability.

Community-dwelling older adults with polypharmacy and anticholinergic burden are likely to regularly visit the community pharmacy to collect their prescription medications, presenting an opportunity for pharmacists to review medicines and reduce anticholinergic burden in a setting that boasts long term relationships with the patients. However, it merits noting that medicines use reviews which provided an incentive for pharmacists to conduct interventions, and periodic reviews are being phased out presently and will stop by the end of 2021 (282). This incentive was especially important in encouraging community pharmacists to take time out of their busy schedules to perform medication reviews. The MUR will be replaced by a new structured medication review carried out by pharmacists working within primary care networks (PCNs) as part of a new GP contract arrangement (282, 283). While this is a welcome development, the largest number of pharmacists are employed within community pharmacies. This means that community pharmacists could potentially have a significant impact on reducing anticholinergic burden. Also, the nature of repeat dispensing means that some patients may not visit the GP for up to 6 months. Within this time, the patient would more likely go to the community pharmacy when collecting prescription medications, for other minor ailments or general complaints (e.g. to report an adverse effect), providing opportunities for a medication

review by pharmacists. The stop of MUR's could reduce the number of pharmacists doing reviews and thus, reduce the opportunities to identify and reduce anticholinergic burden in community pharmacy.

Primary care networks (PCNs) of local GP practices and community teams cover populations of between 30,000 and 50,000 people across England and were established in July 2019 to integrate community-based multidisciplinary teams, including GP's, pharmacists, nurses, and geriatricians (283). NHS England expects pharmacists role within a PCN to involve the management of chronic conditions, withdrawing medications no longer needed, clinical medication reviews to proactively manage complex polypharmacy, especially in frail older adults, people with multiple co-morbidities, people in care homes, and those with learning disabilities and autism (284). Involving pharmacists within these teams is likely to provide additional benefits to patient safety (285). It merits noting that these pharmacists will either be prescribers or prescribers in training (282). Meaning that a lot of them will actively deprescribe drugs (286). This presents an opportunity for the tool to be used to reduce anticholinergic burden. However, a PCN is able to recruit one pharmacist per 30,000 patients, meaning that a single pharmacist is likely to be spread thin across multiple member GP surgeries, impacting the opportunities to reduce anticholinergic burden.

Educational implications

For junior pharmacists to perform new roles within the PCN, additional training is needed to imbibe new skills (283, 284). This presents an opportunity for anticholinergic burden materials, including the ABDeS tool, to be added to the education curriculum. In general, educators in clinical pharmacy could consider developing curricula in the area of deprescribing medicines with anticholinergic properties in older adults, incorporating the present tool to guide deprescribing.

Recommendations for future work

This thesis provides evidence to inform future research that aims to reduce the anticholinergic burden in older adults. Based on the thesis findings, it is suggested that future research should begin with a study to evaluate the usability, acceptability, sustainability, and effectiveness of the ABDeS deprescribing tool in reducing anticholinergic burden of older adults in various clinical settings. A mixed-method approach that involves semi-structured interviews and thematic analysis is suggested to gain an in-depth understanding of pharmacists' perceptions of the usability, acceptability, and sustainability of the ABDeS tool. Furthermore, effectiveness can be evaluated in multiple parallel groups using one-way Analysis of Variance (ANOVA) and Pearson's correlation for parametric data or Kruskal Wallis and Spearman's correlation for non-parametric data with the level of statistical significance set at $\alpha = 0.05$.

It is also suggested that future research should also focus on additional areas outlined below 1) Evaluating the effectiveness of the tool in improving clinical patient outcomes, 2) Evaluating the impact of upgrading the pharmacy curriculum to include anticholinergic burden, 3) Addressing GP barriers to reducing anticholinergic burden and 4) Strategies to improve collaboration and communication between pharmacists and other healthcare professionals in routine clinical practice

Conclusion

An important novel aspect of this thesis was developing the tool using the BCW analysis of the barriers and facilitators identified during the interviews in Chapter 4. Previous interventions were not theory-based and did not involve interviews with pharmacists. Thus, the needs of these pharmacists were not enquired or met. The attitudes and opinions of pharmacists on barriers to considering anticholinergic burden are important if appropriate, safe, and meaningful deprescribing is to be achieved. Another novel aspect of this thesis was evaluating the rationale for pharmacists stopping medications in Chapter 2. Previous studies on anticholinergic burden have not reported on the rationale for pharmacist deprescribing.

The overall aim of this thesis was to develop an intervention to reduce anticholinergic burden in older adults. The findings in this thesis also demonstrated that high anticholinergic burden in older adults is a prevalent problem. The pharmacist was identified as a useful but underexploited resource to reduce anticholinergic burden from a supportive

or direct role in deprescribing. The findings presented in this thesis clarify the relationship between anticholinergic burden and mortality/cognitive impairment, an understanding of the current practice regarding anticholinergic burden in a UK hospital, and the barriers and facilitators to pharmacists reducing anticholinergic burden in practice. Given the complexity of barriers to deprescribing (e.g., GP barriers, patient barriers, and pharmacist barriers), deprescribing interventions are likely to require a multifaceted approach. The insights gained from this thesis provide directions for future research into reducing anticholinergic burden in older adults.

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Appendix 1: Systematic Review Supplementary Data, Data Extraction, and Study Selection Checklist

Data extraction template for full articles

Article identification	Reviewer:
	Year:
	Author:
	Country:
Methods	Duration:
	Study design:
	Sample size:
Participants	Population description:
	Settings and/or locations:
	Age:
	Sex:
	Race/Ethnicity:
Statistical methods:	
Outcome measures:	
Results/effect size:	Any results
	Anticholinergic scale, significant and non-significant longitudinal association (+/-):
	Cognitive tool, significant, and non-significant longitudinal association (+/-):
Adjustment for confounders:	

Exposure to anticholinergic burden at baseline and follow-up:

Study selection checklist

Title. First author, Year
 Longitudinal (observation or intervention) study (yes/no)
 Anticholinergic scale use (yes/no)
 Presence of a measure of outcome (cognition)
 Assess exposure to anticholinergic drugs at baseline and follow-up
 Include (yes (1) /no (0)
 Notes

Table 17. Comparison between scales

Drugs with an ACB score of 1	MARANTE	CRAS	ABC	ARS	ADS	AAS
Alimemazine			2			
Alverine			2			
Alprazolam		1	3		1	

Brompheniramine					3	
Cimetidine	1			2	2	
Clorazepate			3		1	
Codeine	1	1	2		1	
Colchicine			3			
Digoxin			3		1	1
Disopyramide					2	
Furosemide			3		1	1
Fluvoxamine					1	2
Loperamide	1	1		2	1	
Ranitidine	1	2		1	2	2
Theophylline	1		2		1	2
Diazepam	1					
Fentanyl	1					
Cetirizine	1					
Haloperidol	1					
Morphine	1					
Risperidone	1					
Trazodone	1					
Drugs with an ACB score of 2	MARANTE	CRAS	ABC	ARS	ADS	AAS
Amantadine	1			2	1	
Belladonna		3	3			
Carbamazepine	1	1			2	
Cyclobenzaprine		1		2	2	
Cyproheptadine				3	2	
Drugs with an ACB score of 3	MARANTE	CRAS	ABC	ARS	ADS	AAS
Benztropine				3	3	4
Clozapine	2			2	3	4

Doxepin	2	3			3	4
Nortriptyline	2	3		2	3	3
Olanzapine	1	3		2	1	3
Orphenadrine			3		3	4
Paroxetine	1	2		1	1	3
Perphenazine		2		3	1	
Propantheline		2			3	
Quetiapine	1	2		1		2
Scopolamine		3		3	3	4
Thioridazine		3		3	1	
Tolterodine	2	3	3		3	4
Trifluoperazine			3		3	4
Trihexyphenidyl	2	3	3		3	4
Amitriptyline	2					
Clomipramine	2					
Diphenhydramine	2					
Hydroxyzine	2					
Imipramine	2					
Oxybutynin	2					
Promethazine	2					
Trimipramine			3		3	4

Table 18. Sensitivity analysis of pooled estimates for moderate-high burden associated with mortality

Analysis Number	Studies excluded in the meta-analysis	Pooled hazard ratio (95% CI)	P-value for the effect	I ² parameter, %	χ ² (P-value)
1.	None Lattanzio(1) 2018 included	1.86 [1.39, 2.49]	<0.0001	71%	17.3(0.004)

2.	Lattanzio(1) 2018	1.94 [1.35, 2.77]	<0.0003	77%	17.02(0.002)
3.	Corsonello 2018	1.72 [1.29, 2.29]	<0.0002	69%	12.93(0.01)
4.	Lattanzio(1) 2018 and Corsonello 2018	1.76 [1.22, 2.53]	<0.003	77%	12.90 (0.003)
5.	Jamsen and Lattanzio(1) 2018	1.79 [1.21, 2.66]	<0.003	78%	13.52(0.04)
6.	Kumpula and Lattanzio	2.34 [1.56, 3.51]	<0.0003	67%	9.20(0.03)
7.	Myint 2015 and Lattanzio(1) 2018	2.18 [1.16, 4.12]	<0.02	82	17(0.0007)
8.	Wauters and Lattanzio(1) 2018	1.82 [1.23, 2.69]	<0.003	79%	14.63(0.002)
9.	Including Lattanzio, Myint and Wauters	1.70 [1.44, 2.01]	<0.00001	14%	2.33(0.31)
10.	Including Corsonello Myint and Wauters	2.25 [1.38, 3.69]	<0.001	68%	6.19(0.05)
11.	Excluding Jamsen, kumpula, Lattanzio, and Wauters (ACB scale)	2.15 [1.10, 4.19]	<0.02	75%	4(0.05)

Table 19. Sensitivity analysis of pooled estimates for low burden associated with mortality

Analysis Number	Studies excluded in meta-analysis	Hazard ratio (95% CI)	P-value for the effect	I ² parameter, %	χ ² (P-value)
1.	None	1.28 [1.18, 1.39]	<0.00001	0	0.76(0.86)
2.	Lattanzio(1) 2018	1.29 [1.19, 1.39]	<0.00001	0	0.66(0.72)
3.	Corsonello 2018	1.28 [1.18, 1.38]	<0.00001	0	0.10(0.95)
4.	Lattanzio(1) 2018 and Myint 2015	1.53 [0.90, 2.59]	<0.11	0	0.23(0.63)
5.	Myint 2015	1.33 [0.94, 1.88]	<0.11	0	0.72(0.70)
6.	Wauters 2017 (ACB scales only)	1.28 [1.18, 1.39]	<0.00001	0	0.76(0.68)

7.	Lattanzio(1) and Wauters (ACB scales only)	1.29 [1.19, 1.39]	<0.00001	0	0.66(0.42)
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Table 20. Anticholinergic burden classification for meta-analysis

Study 1	Hazard ratio	Low ACB= 1 DBI less than 0.5	Moderate to high Acb 2 and over DBI 0.5 and over	Data not used	Low - Moderate ACB 1-2 DBI >0 and ≤1	High anticholinerg ic burden (3 and over) or DBI over 1	Controlled for	Decision
Myint	1.00	ACB score of 1 1.28 (1.18-1.39)	ACB 2-3 1.65 (1.49- 1.82)	ACB 3 1.83 (1.53-2.20)			Age, sex, class, education, and physical activity	Include
kumpula	1.00	nil	ARS score ≥3 1.05 (0.75- 1.46)	ARS 1-2 1.08 (0.84-1.41)			Age, sex, nutrition	Include
Jamsen	1.00	DBI not specified	2.75(1.60– 4.75).	N/A			Age, dementia	include
Corsonello	1.00	ACB score 1: HR 1.70 (0.86–3.63)	ACB score 2: HR 3.32 (1.67– 6.60)	ACB score 3: HR 3.31 (1.45–7.56) ACB score 4: HR 4.16 (1.46–11.5) ACB score 5: HR 6.38 (1.41–28.9)			Age and gender	include
Lattanzio 1	1.00	ACB score 1: HR 1.19 (0.75–1.90)	ACB score ≥ 2: HR 1.69 (1.09– 2.65)	N/A			Age, sex,	Partially Include (for sensitivity analysis). Similar cohort to Corsonello
Wauters	1.00	MARANTE 0.5–1.5 : 1.31 (0.57–3.02)	MARANTE scale ≥ 2: HR 2.77 (1.43–5.38)	N/A			number of medications taken at baseline and with the level of multi-morbidity	Include

Lattanzio 2	1.00	Independent group ACB score of 1= 0.92 (0.45–1.89) dependent group 1.50 (0.81–2.73)	Independent ACB score ≥ 2: HR 1.06 (0.50– 2.34) Dependent 2.25 95% confidence (CI) 1.22–4.1	All data			Age, sex,	Exclude exact cohort included
Daupinot		nil	nil	N/A	DBI category not specified.	DBI category not specified	No control	Exclude. DBI category was not specified, and the study did not control for any co- founders.
Fox								Exclude (odds ratio not appropriate for analysis)

Appendix 2: Chapter 3's Supplementary Data

Table 21. Classes of medicines with anticholinergic properties

Drug class	Drug Name	Admission	Discharge
Psychotropic drugs			
Tricyclic antidepressant	Amitriptyline***	11	7
Benzodiazepine	Diazepam*	3	3
Antipsychotics	Olanzapine***	1	1
	Aripiprazole*	1	1
SNRI	Venlafaxine*	1	1
Antiparkinsonian	Amantadine**	1	1
Anticonvulsant	Carbamazepine**	3	2
	Oxycarbazepine**	0	1
Antidepressant	Trazodone*	4	3
	Total	25	20
Incontinence drugs			
Antimuscarinics	Tolterodine***	4	1
	Solifenacin***	3	2
	Oxybutynin***	2	1
	Total	9	4
Blood pressure/ Cardiac drugs			
Loop diuretic	Furosemide*	27	22
Nitrate	Isosorbide*	8	9
Beta-blocker	Atenolol*	5	5
	Metoprolol*	3	3
Cardiac glycoside	Digoxin*	7	4
Calcium-channel blockers	Nifedipine*	3	3
Vasodilator	Hydralazine*	1	1
	Total	54	47
Pain relief			
Opioids	Codeine*	17	21
	Morphine*	2	7
	Fentanyl*	2	2
	Total	21	30
Others			
Vitamin k antagonist	Warfarin*	14	13

Antihistamine (H1 & H2)	Ranitidine*	8	11
	Cetirizine*	1	1
Corticosteroid	Prednisolone*	5	5
	Hydrocortisone*	1	1
Xanthine	Theophylline*	1	1
Antipropulsive	Loperamide*	4	4
Anti-gout agent	Colchicine*	0	1
	Total	34	37

Table 22. Additional opportunities to deprescribe

Medication of the patients on admission	Additional drugs with the patient are discharged with	Drugs stopped during admission	Comment/scope for improvement
Furosemide*, peptac, ranitidine *, doxazosin, bisoprolol, felodipine, colecalciferol, ISMN*, losartan. Co-codamol*, GTN, simvastatin, aspirin	0	Losartan, aspirin and peptac	The patient has an ACB score of 4—alternatives to ranitidine; lansoprazole, or omeprazole (no anticholinergic burden) (51). Aspirin stopped; this might preclude the need for ranitidine
Colecalciferol, folic acid, atorvastatin, furosemide*, alendronic, phosphate Sandos, apixaban, prednisolone*	Colestyramine and loperamide*	0	ACB score of 3. Dependent ankle Oedema with no sign of heart failure? compression hosiery recommended (STOPP/START) (225)
Rosuvastatin, bisoprolol, lactulose, diazepam*, GTN, sertraline, lansoprazole, warfarin*, paracetamol, furosemide*, zopiclone	Codeine*, Colecalciferol, Adcal d3	Furosemide* Lactulose, zopiclone, sertraline, and lansoprazole	ACB score of 3. Diazepam, codeine combination. MHRA warning, risk of death. Codeine started in the hospital. Non –pharmacological alternatives should be considered for diazepam (287)
Salbutamol, beclomethasone/formoterol, prednisolone*, carbocisteine, lansoprazole, furosemide*, citalopram, lorazepam, simvastatin, morphine*, paracetamol, aspirin, and tiotropium	0	0	ACB score of 3. Benzodiazepine, opioid combination. MHRA warning, risk of death. Non –pharmacological alternatives should be trailed for benzo. Therapy duplication? Is there a need for benzodiazepine? Patient on Citalopram. Citalopram is licensed for panic disorders. Alternatively, escitalopram is licensed for Generalised anxiety disorder (NICE Clinical guideline [CG113]) (288).
Levothyroxine, atenolol*, docusate, codeine*, paracetamol, apixaban, clobetasone ointment, ISMN gel	Aspirin and clopidogrel, liquid paraffin, ranitidine*	0	ACB score increased to 3. Review ranitidine at the start of therapy. Alternative gastro-protective agent lansoprazole (does not interact with new citalopram or new drug clopidogrel like omeprazole and esomeprazole) with lower burden (289)
Adcal, amlodipine, simvastatin, omeprazole, donepezil, citalopram, E45, paracetamol	Ranitidine*, docusate, Gaviscon and lactulose	Omeprazole	Anticholinesterase inhibitor and anticholinergic burden. Review ranitidine at the start of therapy. An alternative gastroprotective agent with a lower burden is lansoprazole (which does not interact with citalopram like omeprazole)(289). Consider after a drug holiday from PPI's

Senna tabs, lansoprazole , adcal d3, donepezil, docusate, sertraline, rivaroxaban, and paracetamol	Morphine*, fentanyl*, glycerine, and macrogol	Docusate	Anticholinesterase inhibitor and anticholinergic burden. Preferable to give one strong opioid than combine these, e.g. combine dose in morphine. Fentanyl patches are contraindicated in opioid-naïve patients (MHRA warning) (290). Rapid escalation worrying. Recommend that pharmacist review medication at the start.
Citalopram, folic acid , tamsulosin , ranitidine* , levothyroxine, macrogol, memantine, paracetamol, clopidogrel, dermol, diprobase	0	0	Anticholinesterase inhibitor and anticholinergic. Possible alternatives to ranitidine antacids (short term use) or PPI (lansoprazole and pantoprazole no interaction with citalopram and clopidogrel) (289)
Memantine,	Furosemide*, bisoprolol, and loperamide*,	0	Anticholinesterase inhibitor and anticholinergic. Review need for loperamide. Consider recommending an assessment of the underlying cause of diarrhoea , oral rehydration therapy and lifestyle advice (NICE Clinical knowledge Summary: diarrhoea) (291).
Fostair, tiotropium inhaler, salbutamol inhaler, furosemide*, isosorbide mono*, atenolol*, levetiracetam, topiramate, atorvastatin, solifenacin***, mirtazapine 15, GTN, and macrogol	0	0	ACB score of 6 on discharge. Discussion with the patient on stopping solifenacin. Review need: high anticholinergic burden and potentially inappropriate in older adults (27, 51).
Folic acid, lansoprazole, furosemide*	Morphine*	0	Ankle oedema with no sign of heart failure? Compression hosiery is recommended instead of furosemide (STOPP/START) (225). Review new medication. WHO pain ladder not followed
Ferrous fumarate, alfacalcidol,	Furosemide* and sandocal	0	Review new medication. Ankle oedema with no sign of heart failure. Compression hosiery is recommended instead of furosemide (STOPP/START) (225).
Terbutaline, salbutamol, Symbicort, atorvastatin, lisinopril, levothyroxine, furosemide*, oxybutynin***, topiramate, rivaroxaban,	0	Salbutamol	ACB score of 4 on discharge. Discussion with the patient on stopping oxybutynin. Review need: high anticholinergic burden and potentially inappropriate in older adults (27, 51).
Gtn, metoprolol*, ranitidine*, pravastatin, doxazosin, ISMN*, ramipril, paracetamol, cetraben, Fexofenadine	Clopidogrel and apixaban	0	ACB 3 on discharge. Review need for ranitidine. Alternatives like antacids and lansoprazole with no anticholinergic burden should be considered (51)

Naproxen, candesartan, amlodipine, prednisolone*, lamotrigine, carbamazepine**, alendronic acid, cetirizine*, codeine*, fentanyl patch*, Aspirin, pro cal-neutral	Oxcarbazepine**, macrogol, phenytoin, clonazepam, enoxaparin, lidocaine, morphine*, paracetamol, ranitidine*, Diazepam*, vitamin b and c	Alendronic acid , amlodipine, aspirin, candesartan, cetirizine*, codeine*, fentanyl*, lamotrigine, and carbamazepine**	ACB 6 on discharge. Benzo and opioid prescribed together. Risk of death and other adverse effects (287). Non – pharmacological alternatives should be considered for diazepam.
Simvastatin, atenolol*, amitriptyline***, allopurinol, carbamazepine**, gabapentin, folic acid, doxazosin, clopidogrel	Clotrimazole cream	0	ACB 6 on discharge from hospital. Review need to combine amitriptyline, gabapentin and carbamazepine. Recommend stop of carbamazepine if for neuropathic pain (292)
Metform, galantamine, trazodone*, furosemide*, atorvastatin, Beclomethasone spray	Cetraben, dermol, mometasone ointment	Beclomethasone spray	Anticholinesterase inhibitor and anticholinergic. Review need for furosemide. Ankle oedema with no sign of heart failure? Compression hosiery is recommended instead of furosemide (STOPP/START) (225)
furosemide*, metformin, losartan, amlodipine	colectal and adcal	losartan and amlodipine	Ankle oedema with no sign of heart failure? Compression hosiery is recommended instead of furosemide (STOPP/START) (225)

Appendix 3: Patient Information, Consent Form, and Interview Guide

Participant Information Sheet

Title of Study: The development of a clinical decision-making tool to reduce anticholinergic burden in older adults

Name of Chief Investigator: Adam Gordon

Local Researcher: Grace Ojo

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. Talk to others about the study if you wish. Ask us if there is anything that is not clear.

What is the purpose of the study?

Anticholinergic medicines are commonly used for a variety of medical conditions. However, many other drugs not recognized as anticholinergics also possess anticholinergic properties. When multiple drugs are prescribed, the anticholinergic effect of these drugs can add up. The sum of these anticholinergic effects (the anticholinergic burden) has been reported to be associated with adverse reactions such as cognitive impairment, falls, physical impairment, and mortality. Consequently, about 25% of the overall population and 50% of the older population could be at risk of these adverse outcomes.

Despite guidance on avoiding the use of anticholinergics in older adults, little consideration is given to anticholinergic burden as these medicines are still commonly prescribed, even in frail older populations with a high prevalence of falls, impaired physical function, dementia, and delirium.

The purpose of this study is to develop a clinical decision-making tool that addresses the challenges and barriers to decision-making and provides information to pharmacists on anticholinergic burden that could simplify an otherwise complex process and lead to a change in practice.

Why have I been invited?

You are being invited to take part in the development of the decision tool because you are a pharmacist. Pharmacists play an important role in medication management by routinely performing medicines reviews on older adults. Improved pharmacist consideration for anticholinergic burden during medication reviews can lead to a reduction in anticholinergic burden.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. This would not affect your legal rights.

What will happen to me if I take part?

If you take part:

Step 1; an initial interview date will be set at your location of preference. In the interview, we will discuss barriers to consideration of anticholinergic burden in practice identification of at-risk patients, decision-making practices, challenges that might occur during the process and perception of what the tool should include. The interview should last 30-45 minutes.

Step 2; A decision-making tool will be made after the interview and will be presented to you. You will be expected to use it to report suggestions for improvement and usability concerns to the researcher. Another interview may be scheduled to discuss these issues depending on your preference.

Expenses and payments

Participants will not be paid to participate in the study. Travel expenses will be offered for costs incurred as a result of participation.

What are the possible disadvantages and risks of taking part?

Participating in the research is not anticipated to cause you any disadvantages or discomfort. The potential physical and/or psychological harm or distress will be the same as any experienced in everyday life

What are the possible benefits of taking part?

We cannot promise the study will help you, but the information we get from this study may help to improve the consideration of anticholinergic burden among pharmacists and reduce potential adverse events.

What happens when the research study stops?

By the end of the research, it is expected that a decision-making tool will have been developed. You will be provided with a summary of the results of this study. Should the research stop earlier than planned, we will tell you and explain why.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers, who will do their best to answer your questions. The researchers' contact details are given at the end of this information sheet.

Will my taking part in the study be kept confidential?

We will follow the ethical and legal practices, and all information about you will be handled in confidence.

If you join the study, we will use the information collected from you during the course of the research. This information will be kept strictly confidential, stored in a secure and locked office and on a password-protected database at the University of Nottingham. Under UK Data Protection laws, the University is the Data Controller (legally responsible for the data security), and the Chief Investigator of this study (named above) is the Data Custodian (manages access to the data). This means we are responsible for looking after your information and using it properly. Your rights to access, change or move your information are limited as we need to manage your information in specific ways to comply with certain laws and for the research to be reliable and accurate. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can read our privacy notice and find out more about how we use your information at <https://www.nottingham.ac.uk/utilities/privacy.aspx>

The data collected for the study will be looked at and stored by authorised persons from the University of Nottingham who are organising the research. They may also be looked at by authorised people from regulatory organisations to check that the study is being carried out correctly. All will have a duty of confidentiality to you as a research participant, and we will do our best to meet this duty.

Your contact information will be kept by the University of Nottingham for two years after the end of the study so that we are able to contact you about the findings of the study and possible follow-up studies (unless you advise us that you do not wish to be contacted). This information will be kept separately from the research data collected, and only those who need it will have access to it. All other data (research data) will be kept securely for seven years. After this time, your data will be disposed of securely. During this time, all precautions will be taken by all those involved to maintain your confidentiality; only members of the research team given permission by the data custodian will have access to your personal data.

In accordance with the University of Nottingham's, the Government's, and our funders' policies, we may share our research data with researchers in other universities and organisations, including those in other countries, for research in health and social care. Sharing research data is important to allow peer scrutiny, re-use (and therefore avoiding duplication of research) and to understand the bigger picture in particular areas of research. Data sharing in this way is usually anonymised (so that you could not be identified), but if we need to share identifiable information, we will seek your consent for this and ensure it is secure. You will be made aware, then, if the data is to be shared with countries whose data protection laws differ from those of the UK and how we will protect your confidentiality.

What will happen if I do not want to carry on with the study?

Your participation is voluntary, and you are free to withdraw at any time, without giving any reason, and without your legal rights being affected. If you withdraw, we will no longer collect any information about you or from you, but we will keep the information about you that we have already obtained as we are not allowed to tamper with study records, and this information may have already been used in some analyses and may still be used in

the final study analyses. To safeguard your rights, we will use the minimum personally-identifiable information possible.

What will happen to the results of the research study?

The results of the study will be included as part of a PhD thesis, and we will also aim to publish it in a peer-reviewed journal and present it at appropriate academic conferences.

Who is organising and funding the research?

This research is being organised by the University of Nottingham and is being funded by the division of Rehabilitation and Ageing

Who has reviewed the study?

All research in healthcare is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the Faculty of Medicine and Health Sciences Research Ethics Committee.

Further information and contact details

CONSENT FORM

Title of Study: The development of a clinical decision-making tool to reduce anticholinergic burden in older adults

Name of Researcher: Grace Ojo

Name of Participant:

Please initial box

1. I confirm that I have read and understood the information sheet version number 1 dated () for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. I understand that should I withdraw, then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐
3. I understand that relevant sections of the data collected during the study may be looked at by authorised individuals from the University of Nottingham, the research group, and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐
4. I understand that the interview will be recorded and that anonymous direct quotes from the interview may be used in the study reports. ☐
5. I understand that the information collected about me will be used to support Other research in the future and may be shared anonymously with other researchers. ☐
6. I agree to take part in the above study. ☐

Name of Participant

Date

Signature

Name of Person taking consent

Date

Signature

Interview guide

The questions asked will fit broadly into the categories outlined below:

Information Sheet and Consent Form: Confirm that the participant has read and understood the Participant Information Sheet. Provide the opportunity for the participant to ask any further questions about the interview.

Medicines review

- How often do you do medicines reviews
- Are you familiar with anticholinergic burden (describe it)
- How do you identify patients for medication reviews on
- Identification of patients with a higher risk of having an increased anticholinergic burden (e.g. Describe the ways in which patients with a higher risk of adverse events from anticholinergic burden can be identified? (who needs to identify them, and when do they need to be identified/opportunities to identify them)
- Medicines review process/ what should be considered
- The process of decision making (e.g. what is the decision-making process after patient identification and/or what is considered before making a decision to recommend deprescribing). do you use an ACB tool
- Barriers and challenges to reducing anticholinergic burden in older adults
- What needs to be done differently, when and where does it need to be done and how often
- Producing a tool to achieve a change in behaviour (e.g. what elements do you think the tool should possess to make it effective and usable/ What would you most like to see in a tool that will make your job easier)

Other topics to be explored in the categories outlined above include the barriers to identifying these patients, activities that could lead to a reduced burden, and information needs of health care professionals, information sources, non-pharmacological, and pharmacological alternatives

Appendix 4: Chapter 4's Supplementary Data

Table 23. Reasons for rejecting intervention functions.

COM-B component (TDF context)	Relevant Intervention function options (definition)	Does intervention functions meet the APEASE criteria (Affordability, practicability, Effectiveness/cost-effectiveness, acceptability, Side effects/safety, and equity) in the context of improving pharmacist's consideration for anticholinergic burden during medication reviews
Physiological capability (knowledge)	Education (increasing knowledge or understanding)	Not affordable in this context. Not practicable because there is not enough time to take pharmacists out of the ward or a busy community pharmacy for an educational programme
Reflective motivation (belief about capabilities and consequences)	Persuasion (using communication to induce positive or negative feelings and stimulate action, e.g., encouraging improved consideration for anticholinergic burden by providing easy and quick-to-use decision support)	Yes
	Modelling (providing an example for pharmacists to imitate)	Not practicable to deliver in this context due to limited resources and practicability issues around trying to get pharmacists out of their daily workflow to watch another pharmacist make interventions to reduce anticholinergic burden.
	Enablement (improving means and reducing barriers to encourage behaviour change, e.g., education to reduce knowledge barriers to promote consideration for anticholinergic burden)	Yes
	Education (increasing knowledge or understanding)	Not affordable in this context. Not practicable because there is not enough time to take pharmacists out of the ward or a busy community pharmacy for an educational programme
Physical opportunity (resources/tools, time)	Training (Imparting skills)	Not practicable due to time constraints on pharmacists
	Restriction (using rules to reduce the opportunity to engage in competing behaviours to promote target behaviour)	Not practicable in this context as there are no options to restrict.
	Environmental restructuring (changing the physical or social context, e.g., providing cues and prompts)	Yes
	Enablement (improving means and reducing barriers to encourage behaviour change, e.g., decision support to reduce time and resource barriers to promote consideration for anticholinergic burden)	Yes
Intervention functions selected: Persuasion, enablement, and environmental restructuring		

Table 24. APEASE criteria for BCTs. Why were they excluded

Intervention functions	Individual behaviour change techniques*	Is the BCT relevant, or does it meet the APEASE criteria (affordability, practicability, effectiveness/cost-effectiveness, acceptability, side effects/safety, equity) in the context of improving pharmacist's consideration for anticholinergic burden during medication reviews
Persuasion	- Credible source - Information about social and environmental consequences - Information about health consequences - Feedback on behaviour/on outcome(s) of the behaviour	- Yes - Not relevant in this context - Yes - Not practicable in this context. Beyond the scope of the present study to conduct a trial to assess the outcome of behaviour Unlikely to motivate pharmacists unless there was an associated reward or a threat of punishment for failing to consider anticholinergic medication reviews.
Environmental restructuring	- Adding objects to the environment - Prompts/cues - Restructuring the physical environment - Restructuring of the social environment	- Not relevant in this context - Yes - Yes - Not relevant in this context
Enablement	- Social support (unspecified) - Social support (practical) - Goal setting (behaviour) - Goal setting (outcome) - Adding objects to the environment - Problem-solving - Action planning - Self-monitoring of behaviour - Restructuring the physical environment - Review behaviour goal(s) - Review outcome goal(s)	- Not relevant in this context - Not practicable - Not practicable. Interventions are made on a case-by-case basis depending on medication appropriateness. Setting goals may be difficult to operationalize - Not practicable in this context. - Not relevant in this context - Not relevant in this context. Pharmacists are unlikely to have the time or interest in formulating and developing the change strategy themselves - Yes - Not practicable - Yes - Not practicable - Not affordable or practical
Frequently used BCTs selected	Information about health consequences Prompts/cues Credible source Restructuring the physical environment Action planning	

*commonly used BCTs

The selected BCTs were mapped to the COM-B components and presented below:

Table 25. Selected BCTs mapped to the COM-B components and delivery strategy

Com-B and TDF components served by intervention functions	Intervention function	Behaviour change techniques	Delivery strategy
Reflective motivation (belief about capabilities and consequences)	Persuasion	Credible source Information about health consequences	Providing evidence-based guidance Provide information on the consequence of increased anticholinergic burden in older adults
	Enablement	Restructuring the physical environment Action planning	Decision support to reduce time and resource barriers to promote consideration for anticholinergic burden Decision support will also provide guidance on what to say to prescribers and patients so that communication can be planned. What to do before, during and after a review so that actions, including communication between pharmacist and patient, and prescriber, could be planned
Physical opportunity (resources/tools, time)	Environmental restructuring	Prompts/cues Restructuring the physical environment	Provide prompt and cues of what to do and when to do it in a decision support tool. Introduce a stimulus with the purpose of cueing medication review, which would be used at the time of performance of medication review, such as a checklist of things to consider. It could be written or computerised. Decision support to reduce time and resource barriers to promote consideration for anticholinergic burden
	Enablement	Restructuring the physical environment Action planning	As above As above

Table 26. AGREE GRS results for guidelines, guidance and consensus documents

Study	Domain 1	Domain 2	Domain 3	Domain 4	Comments
NICE guideline NG97* (223)	7	4	7	7	Organised, but recommendations are not always easy to find.
Cleare 2015* (293)	7	5	7	7	Organised, but recommendations are not always easy to find
Nice guideline [CG90] * (294)	7	5	7	7	Organised, but recommendations are not always easy to find
Clive 2011** (295)	5	7	3	6	Involved stakeholders but limited evidence of systematic development. Organised and easy to find recommendations. Limited reproducibility
Katzman 2014* (296)	7	6	7	6	Organised, systematic process with easy-to-find recommendations
Pottie 2018* (297)	7	6	7	7	Involved relevant stakeholders, including pharmacists. Systematic and easy to use
Scottish Polypharmacy Guidance 2018** (28)	5	5	5	5	Evidence not developed systematically. Involved appropriate stakeholders. Limited reproducibility
NICE guideline CG161* (298)	7	6	7	7	Organised well
Lise 2018* (299)	7	6	7	7	Involved appropriate stakeholders, including a pharmacist. Clinically sound
Nice draft guideline*. (300)	7	4	7	7	Recommendations were difficult to find
NICE guideline [NG59]* (301)	7	6	7	7	Organised and brief
Veterans affairs guideline 2017* (302)	7	4	7	7	Organised but bulky recommendations are not easy to find.
Nice guideline [NG123]* (303)	6	4	7	7	Organised but bulky. Recommendations are not always easy to find.
Nice guideline [TA290]* (304)	7	6	7	7	Easy to find recommendations
Guidance for opioid reduction in primary care 2017**.(305)	3	5	4	4	Minimal description of stakeholders. Very few references to verify evidence. Very little information on the way the guide was developed

Emyr 2014** (306)	3	7	4	5	Easy to find recommendations. Possibly Involved relevant stakeholders. Listed pharmacists
Nice clinical knowledge summary**: 2020 (307)	6	6	5	7	The guide was developed by relevant stakeholders. Easy to find recommendations. Needed more information on cross tapering
Nice guidelines [CG113] * (288)	7	6	7	7	Stepped, so easier to follow.
British Pain Society. 2012** (308)	7	4	7	6	Involved stakeholders. Bulky guide and recommendations were not easy to find.
STOPP /START 2008*** (309)	7	6	5	7	Involved stakeholders. Ok to follow. Doubtful how reproducible the Delphi process is.

*Guideline **Guidance document ***Consensus document

Table 27. Member checking exercise

Domain	Sa7 (9 yrs qualified; care home)	S4(6 yrs qualified; community)	T4 (5 yrs qualified; community)	LB8 (10 yrs qualified; care home)
1. Potential target behaviours	<i>Yes, Is routine reviews, specifically medication reviews?</i>	<i>I agree</i>	<i>I find the statement fair. I do think you need to highlight that some actions may mainly be done by hospital pharmacists or those that work in a GP practice. Also, in regards to medicine reviews, patients who are on anticholinergic medications are not classified as high-risk patients when conducting MUR in the community, so they may be missed if we don't update the high-risk MUR criteria</i>	<i>Fair</i>
2. Prioritising behaviour based on likely impact	<i>Yes, it appears fair and considered.</i>	<i>Fair (very detailed breakdown)</i>	<i>Yes, I find it fair. The 'triggering routine review' may not work in community but could be suggested in the hospital</i>	<i>Fair</i>
3. Specifying behaviour	<i>I disagree with using over 65 as the criteria to trigger interactions. I believe looking at overall frailty and polypharmacy may be more appropriate than picking a particular age.</i>	<i>Fair</i>	<i>Fair. In regards to the 'Identifying patients with high anticholinergic burden during medicines reviews (scoring ACB),' I believe you should also consider pharmacy technicians in the hospital and community setting, as well as dispensers in the community. Since they have also had training on medication, they can be utilised to identify and make the pharmacist aware</i>	<i>I wonder if it's appropriate to state 'whom' as the pharmacist only for all the behaviours. Consider whether some behaviours should be broader and include healthcare professionals undertaking medication review (not just pharmacists) – for example, 2-6).</i>
BT1. Identifying patients with high anticholinergic burden during medicines reviews (scoring anticholinergic burden)	<i>Agree - need to be national/local agreed guidance as medication inclusion of various tools currently available can vary.</i>	<i>Fair</i>	<i>I agree</i>	<i>Fair</i>
Bt2. Checking that medication with anticholinergic properties are appropriate	<i>Yes, online tools that flag it would be beneficial</i>	<i>Fair</i>	<i>I agree</i>	<i>Fair, although this is also potentially influenced by the response to task 3 and 'whom' doing the behaviour. If broader, physical opportunity (time) improved</i>

BT3. Behaviour Target 3: Stopping drugs that unnecessarily contribute to anticholinergic burden during	<i>Fair - training and confidence are very important in this area.</i>	<i>Fair</i>	<i>I agree</i>	<i>Fair</i>
Bt4. Switching to an alternative with a lower anticholinergic burden during medication reviews	<i>Agree - it would be good to have a recognised patient-friendly leaflet that explained the risks simply of a high ACB so that they could go away and think about things/</i>	<i>Fair</i>	<i>I agree</i>	<i>Fair</i>
Bt5 Tapering dose with the aim to stop	<i>This is fair</i>	<i>Fair</i>	<i>I agree</i>	<i>Fair</i>
BT6. Revising in light of any adverse outcomes.	<i>Yes, and having the resources, e.g. leaflets as mentioned above, to support you going through it with the patient.</i>	<i>Fair</i>	<i>I agree</i>	<i>Fair</i>
BT7. Communicating to all relevant professional	<i>Also, ensure that a clear system is in place to facilitate communication. For example, in GP, regular debriefs can be especially beneficial to facilitate this kind of intervention.</i>	<i>Fair</i>	<i>I agree</i>	<i>Fair</i>

Appendix 5: Additional Information and ABDeS tool

Table 28 Summary of data sources

Data collection stage	Data source within ICM	Description	How the source was used	Advantage	Disadvantage
1 st data collection	Clinical record section	This contained the patient's clinical information. The tab listed all patient's medications, including those started temporarily in hospital (e.g. enoxaparin), those admitted on, stopped temporarily, and permanently. Each medication was marked "admitted on", "discharged with", or left without a note (e.g. enoxaparin). The tab included when they were administered and who administered it.	The source was used to record medicines on admission and discharge. It also was helpful in collecting the total number of medicines used by patients. In addition, the age of the patient was recorded from this tab	It contains valuable information on the day-to-day medication regimen of patients	It did not always give an accurate picture. For example, patients went home with some medications that were not denoted "discharged with". Therefore, It did not provide a clear picture of what patients were discharged with or what was temporarily or permanently stopped. It also did not say who stopped what.
1 st and 2 nd data collection	Medicines management checklist	This comprised summary information on co-morbidities, advice from the pharmacist on medicines, and pharmacist notes.	Used to identify medication stopped by a pharmacist, check for the pharmacist's rationale for stopping the medication and identify patients with dementia	A great resource for additional information	It did not contain all the required information and had to be supplemented with information elsewhere
2 nd Data collection	discharge summary	The discharge summary contained information on what medicines patients were discharged on, what medications were stopped, what drugs were started, and who stopped what during hospital stay.	Used in 2 nd round of data collection to identify what was stopped and started and who stopped what.	A great resource for additional information	A discharge summary was not found in 5 cases; therefore, data from other sources alone were extracted, 2 of the missing discharge summaries were justified because the patients had died
2 nd Data collection	Comprehensive geriatric assessment	Documentation that summarises the patient's assessment. The source contained a medication review section that also summarises interventions made by pharmacists	Used to cross-check information from discharge summary and clinical record tab	A great resource for additional information	It did not contain all the required information and had to be supplemented with information elsewhere

Table 29 Raw data and individual changes of prescribed medication during hospitalization

Characteristics Name	level	frequency	%	
Age,	72	2	1.9	
	73	1	0.9	
	75	2	1.9	
	76	7	6.5	
	78	1	0.9	
	79	4	3.7	
	Total	17	15.8	
	80	4	3.7	
	81	5	4.6	
	82	7	6.5	
	83	7	6.5	
	84	5	4.6	
	85	5	4.6	
	86	4	3.7	
	87	8	7.4	
	88	5	4.6	
	89	9	8.3	
	Total	59	54.5	
	90	4	3.7	
	91	7	6.5	
	92	7	6.5	
	93	5	4.6	
	94	1	0.9	
	95	1	0.9	
	96	2	1.9	
	97	3	2.8	

	98	2	1.9	
	Total	32	29.7	
	Level	Frequency	%	Total number of medicines
Number of medicines prescribed on admission	1	4	3.7	4
	2	3	2.8	6
	3	6	5.6	18
	4	8	7.4	32
	5	5	4.6	25
	6	10	9.3	60
	7	7	6.5	49
	8	13	12	104
	9	10	9.1	90
	10	13	12	130
	11	12	11.1	132
	12	2	1.9	24
	13	7	6.5	91
	14	1	0.9	14
	15	2	1.9	30
	17	2	1.9	34
	18	3	2.8	54
	Total	108	100	897
	Level	Frequency	%	Total number of medicines
Number of medicines prescribed on discharge	1	1	0.9	1
	2	3	2.8	6
	3	2	1.9	6
	4	7	6.5	28
	5	9	8.3	45

	6	6	5.6	36
	7	7	6.5	49
	8	15	13.9	120
	9	16	14.8	144
	10	13	12	130
	11	8	7.4	88
	12	3	2.8	36
	13	8	7.4	104
	14	1	0.9	14
	15	4	3.7	60
	16	1	0.9	16
	18	1	0.9	18
	19	3	2.8	57
	Total	108	100	958

The ABDeS Tool

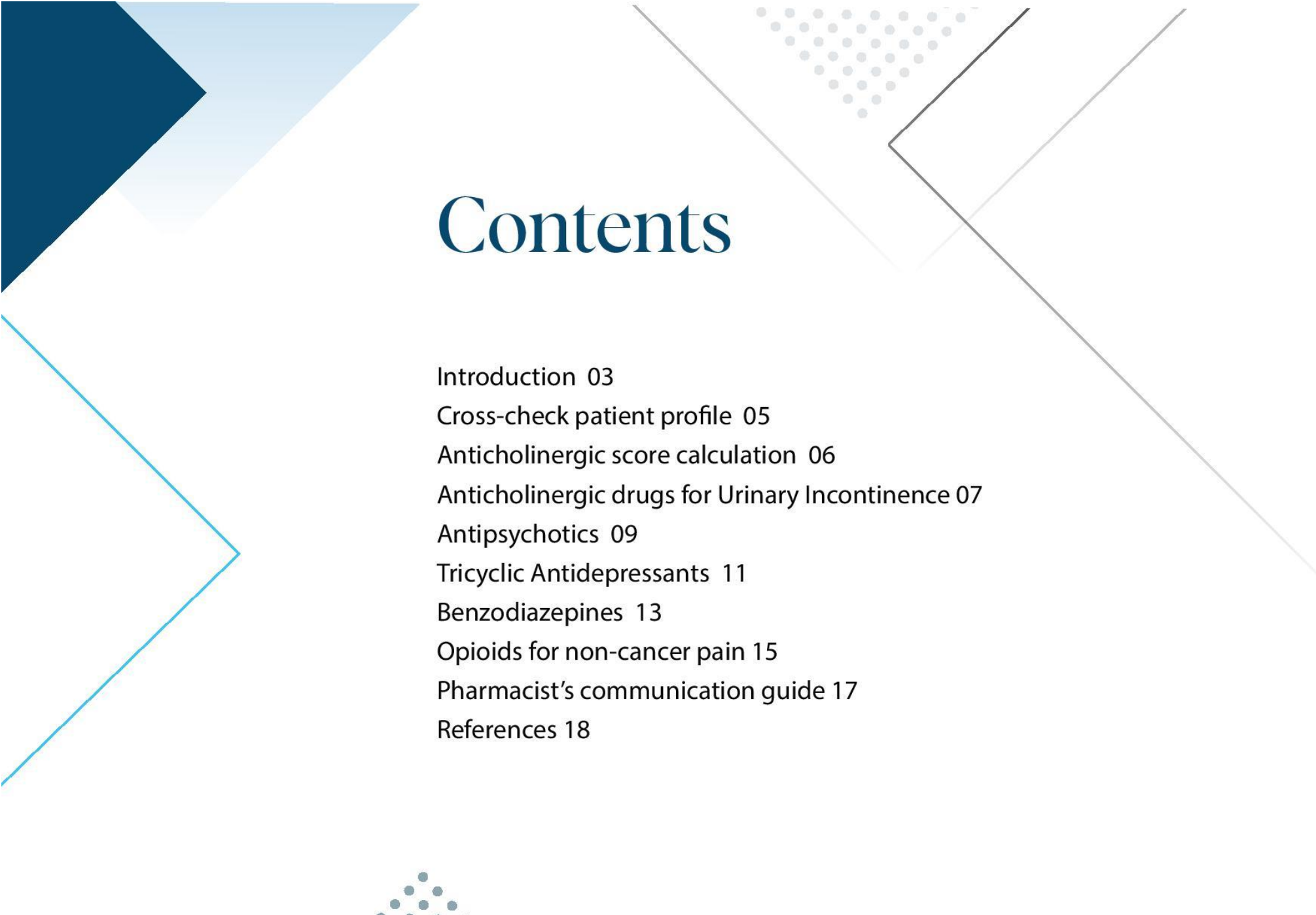


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The (3 step) Anticholinergic Burden Decision Support tool





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Introduction

Older adults may be more vulnerable to medicines' adverse effects because of important pharmacodynamic and pharmacokinetic changes that often accompany the natural ageing process. Anticholinergic medicines are commonly used for a variety of medical conditions. However, many other drugs not recognised as anticholinergics also possess anticholinergic properties. When multiple drugs are prescribed, the anticholinergic effect of these drugs can add up. The sum of these anticholinergic effects (the anticholinergic burden) has been reported to be associated with adverse reactions such as cognitive impairment, falls, physical impairment, and mortality (1, 2). Consequently, about 25% of the overall population and 50% of the older population could be at risk of these adverse outcomes (3).

Some current recommendations on reviewing anticholinergics

- **NICE guidance on the management of urinary incontinence in women (NICE NG123)** recommends that coexisting conditions (e.g. poor bladder emptying, cognitive impairment or dementia), current use of other medicines that affect total anticholinergic load and risk of adverse effects, including cognitive impairment should be considered when prescribing anticholinergic medicines to treat overactive bladder (4).
- **NICE guidance on falls in older people (CG161)** recommends that people who have had a fall or are at increased risk of falling should have their medication reviewed as part of a multifactorial risk assessment. It recommends that psychotropic medications (e.g. neuroleptics, sedatives and antidepressants) should be reviewed and if possible discontinued, reducing an older adults risk of falling (5)
- **NICE guidance on dementia (NG97)** recommends that people with suspected dementia are referred to a specialist dementia diagnostic service once reversible causes of cognitive decline have been investigated. These include delirium, depression, sensory impairment [such as sight or hearing loss], or cognitive impairment from medicines associated with anticholinergic burden. Also, It recommends considering minimising the use of medicines associated with increased anticholinergic burden, and where possible to look for alternatives during medication reviews (6)



• **The 2015 American Geriatric Society Beers Criteria For Potentially Inappropriate medication use in older patients** strongly recommends that the use of anticholinergic drugs including; medicines for urinary incontinence (e.g., oxybutynin and tolterodine), and skeletal muscle relaxants (e.g., methocarbamol and orphenadrine) be avoided in older adults (7).

• **The Scottish polypharmacy guidance 2018**, highlights anticholinergic medicines as a class of poorly tolerated drug in older adults(8).

The purpose of this tool is to provide decision support to assist pharmacists in making deprescribing recommendations around medicines with anticholinergic properties. The tool also supports verbal or written communication between pharmacists, patients, and other health care professionals. This tool consists of 3 steps, including:

Step 1; identifying patients at higher risk of anticholinergic burden adverse effects

Step 2; calculating a patient's Anticholinergic burden score

Step 3; reviewing the medication to identify opportunities to deprescribe

Health care professionals should exercise their clinical judgement in using this tool and tailor it to individual patients.



STEP 01

Cross-check patient profile

- 65 and over ☐
- Taking ≥ 5 medicines ☐
- Recent fall (≤ 3 months) ☐
- Dementia ☐
- Mild cognitive impairment* ☐
- Confusion ☐
- Frailty** ☐
- Chronic constipation ☐

* Problems with memory, language, thinking and judgment that are more than expected with normal ageing (9)

**Three or more of the following: slow walking speed, weak grip strength, exhaustion, low physical activity level, and unintentional weight loss (10)

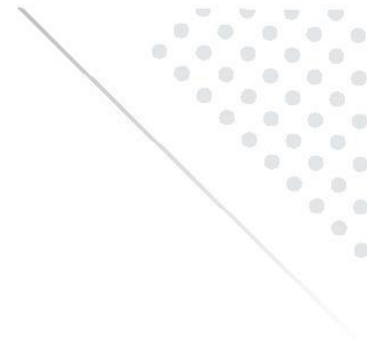
If your patient fits any of the options above, go to page 2 to calculate the anticholinergic burden score.

STEP 02

To calculate the patient's anticholinergic burden from the Anticholinergic cognitive burden (ACB) scale below, find the drug's ACB score from the relevant column and add the scores for all the drugs on the side of the page (11). Alternatively use [this online calculator](#)

Score	Medicines	Patients score
1	Alimemazine, Alverine, Alprazolam, Aripiprazole, Asenapine, Atenolol, Bupropion, Captopril, Cetirizine, Chlorthalidone, Cimetidine, Clidinium, Clorazepate, Codeine, Colchicine, Desloratadine, Diazepam, Digoxin, Dipyrindamole, Disopyramide, Fentanyl, Furosemide, Fluvoxamine, Haloperidol, Hydralazine, Hydrocortisone, iloperidone, Isosorbide, Levocetirizine, Loperamide, Metoprolol, Morphine, Nifedipine, Paliperidone, Prednisone, Quinidine, Ranitidine, Risperidone, Theophylline, Trazodone, Triamterene, Venlafaxine, and Warfarin	
2	Amantadine, Belladonna, Carbamazepine, Cyclobenzaprine, Cyproheptadine, Loxapine, Meperidine, Methotrimeprazine, Molindone, Nefopam, Oxcarbazepine, and Pimozide	
3	Amitriptyline, Amoxapine, Atropine, Benztropine, Brompheniramine, Carbinoxamine, Chlorpheniramine, Chlorpromazine, Clemastine, Clomipramine, Clozapine, Darifenacin, Desipramine, Dicyclomine, Dimenhydrinate, Diphenhydramine, Doxepin, Doxylamine, Fesoterodine, Flavoxate, Hydroxyzine, Hyoscyamine, Imipramine, Meclizine, Methocarbamol, Nortriptyline, Olanzapine, Orphenadrine, Oxybutynin, Paroxetine, Perphenazine, Promethazine, Propantheline, Propiverine, Quetiapine, Scopolamine, Solifenacin, Thioridazine, Tolterodine, Trifluoperazine, Trihexyphenidyl, and Trimipramine	Total:

If the patient has an anticholinergic burden of ≥ 3 , go to step 3 below. Note the ACB tool is not an exhaustive list of drugs with anticholinergic properties and should be used as a guide. Step 3 may be relevant where the drug is not listed on the tool, but others in its class are.



STEP 03

Reviewing the medication



Anticholinergic drugs for Urinary Incontinence

³Oxybutynin, ³Tolterodine, ³Fesoterodine, ³Flavoxate,
³Darifenacin, ³Solifenacin, ³Propiverine

Check list

- Specify the indication for each medication ☐
- Check the need for the drug (e.g. is patient wearing a catheter or incontinence pads). If unsure, consider a treatment break to assess effectiveness ☐
- Does medication interact with the patient's condition or other drugs (drug-drug, drug disease interaction) ☐
- Is there presence of dual therapy for the same or different indications e.g. imipramine* and oxybutynin ☐
- Is medication likely to cause more harm than benefit. ☐
- Is the patient willing to be deprescribed (Involve patient, family members and carers in decision making where appropriate). Refer to communication guide ☐

Deprescribing triggers

- Dementia (risk of worsening confusion)(6, 12)
- Confusion (delirium may resolve after stopping)(13-15)
- Catheter (potentially not needed)
- Continued use despite a lack of improvement in symptoms
- Recent fall (possible risk of falls)(16, 17)
- Dual therapy (increased risk of adverse effects)
- Patients on anticholinesterase inhibitors, e.g. donepezil, rivastigmine and galantamine (risk of worsening cognitive impairment)
- Chronic glaucoma, chronic constipation, and chronic prostatism (risk of worsening these conditions) (12)
- Other possible triggers; no valid or current indication, drug-drug/drug-disease interaction, high anticholinergic burden, dual therapy, off label use, presence or high risk of serious adverse effects, and poor adherence

Anticholinergic drugs for Urinary Incontinence (continued)

Pharmacological alternatives

Switch if appropriate

- Mirabegron is an option for treating overactive bladder if treatment with an anticholinergic is contraindicated, ineffective, or if a patient has unacceptable side effects (18). Mirabegron is contraindicated in severe uncontrolled hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg)

- Trosipium (decreased ability to cross the blood-brain barrier) (19)

Consider switching formulation if a stop isn't possible

- Modified release oxybutynin** (less adverse effect profile)

Non pharmacological alternatives (4)

Absorbent products

- Absorbent products, hand-held urinals and toileting aids (• as a coping strategy pending definitive treatment • as an adjunct to ongoing therapy • as long-term management options only after exploring other treatments • in severe cognitive or mobility impairment that may prevent other treatments)

Physical therapy

- Physiotherapist supervised pelvic floor muscle training (at least 3 months' duration as first-line treatment to women with stress or mixed urinary incontinence)
- Bladder training lasting (at least 6 weeks as first-line treatment to women with urgency or mixed urinary incontinence)

Lifestyle advice

- Recommend a trial of caffeine reduction
- Advise patients who have a BMI greater than 30 kg/m² to lose weight
- Advise a light modification of their fluid intake

After selecting an option

- Record deprescribing rationale (see additional deprescribing rationales if needed) and patient preference ☐

- Communicate recommendation to prescriber or treatment team (to get feedback on the proposed medication changes and facilitate medication updates) . Written or verbal communication should include; medication, Intention, rationale, recommendation plan (e.g. dose change and follow up) and details on patient agreement ☐

*Imipramine is not recommended to treat urinary incontinence due to adverse effect (4)

**Immediate release oxybutynin not recommended in frail older women at risk of a sudden deterioration in their physical or mental health

¹Drug= ACB 1; ²Drug = ACB 2; ³Drug =ACB 3

Antipsychotics

First generation;³Chlorpromazine,³Perphenazine,³Trifluoperazine,²Loxapine,²Pimozide,¹Haloperidol

Second generation;³Olanzapine,³Quetiapine,³Clozapine,¹Aripiprazole,¹Asenapine,¹Paliperidone,¹Risperidone

Check list

- Specify the indication for each medication ☐
- Check for the original diagnoses (These recommendations do not apply to patients with co-morbid mental illness, e.g. schizophrenia, persistent delusional disorder, psychotic depression, and bipolar affective disorder. Consult specialist for advice before any attempt to deprescribe)(8) ☐
- Check the need for the drug (Is it effective?) ☐
- Check for the duration of treatment ☐
- Does it interact with the patient's condition or other drugs (drug-drug, drug-disease interaction)? ☐
- Is there a presence of dual therapy for the same or different indications ☐
- Is medication likely to cause more harm than benefit ☐
- Is the patient willing to be deprescribed (Involve patient, family members and carers in decision making where appropriate)? Refer to communication guide ☐

Deprescribing triggers

- No clear benefit (6)
- Recent falls (increased risk of gait abnormality) (12, 20)
- if inappropriate use (e.g. to used treat mild to moderate psychotic symptoms (21)
- If on antipsychotic for behavioural symptoms of dementia (BPSD) for more than 3 months with stable symptoms (limited benefit with increased risk of mortality, cerebrovascular and other adverse events) (8, 20, 22)
- Other possible triggers; no valid or current indication, drug-drug/drug-disease interaction, high anticholinergic burden, dual therapy, off label use, presence or high risk of serious adverse effects, and poor adherence

Antipsychotics(continued)

Taper guide

Gradual withdrawal recommended to avoid withdrawal symptoms* and relapse. Initially a 25-50% reduction in total daily dose and monitor for one to two weeks . If the withdrawal is tolerated, then reduce dose by a further 25% or stop if the present dose is the recommended starting dose. If reduction at 25% or 50% isn't tolerated, reduce taper rate (e.g. 10%) (8, 22, 23).

Starting dose; risperidone = 0.5mg, Olanzapine = 2.5mg, Quetiapine, = 50mg, and Aripiprazole= 5mg

Pharmacological alternatives (lower anticholinergic burden)

- Risperidone (licensed for BPSD) and Aripiprazole

Non pharmacological alternatives (6, 23-25)

Tailored interventions e.g.

- One on one conversations
- Gentle exercise
- Aromatherapy
- Therapeutic use of music or dancing
- Animal-assisted therapy
- Massage
- Multisensory stimulation
- Pleasant activities

After selecting an option

- Record deprescribing rationale (see additional deprescribing rationales if needed) and patient preference ☐
- Communicate recommendation to prescriber or treatment team (to get feedback on the proposed medication changes and facilitate medication updates). Written or verbal communication should include; medication, Intention, rationale, recommendation plan (e.g. dose change and follow up) and details on patient agreement ☐

*Withdrawal symptoms e.g. nausea and vomiting ,sweating and anxiety

¹Drug1= ACB 1;²Drug2 = ACB 2;³Drug3=ACB 3

Tricyclic Antidepressants

³Amitriptyline, ³Amoxapine, ³Clomipramine, ³Imipramine, ³Doxepin, ³Nortriptyline, ³Desipramine and ³Trimipramine

Checklist

- Specify the indication for each medication ☐
- Check the need and validity of the prescription drug, e.g. is it effective? ☐
- Does it interact with the patient's condition or other drugs (drug-drug, drug-disease interaction) ☐
- Duration of treatment ☐
- Is there presence of dual therapy for the same or different indications? (e.g. TCA for pain used in combination with other antidepressant) ☐
- Is medication likely to cause more harm than benefit. ☐
- Is the patient willing to be deprescribed or tapered (Involve patient, family members and carers in decision making where appropriate)? Refer to communication guide ☐

Deprescribing triggers

- Dementia (may cause worsening cognitive impairment) (6, 12, 26)
- Narrow-angle glaucoma, constipation, cardiac conduction abnormalities, prostatism, or prior history of urinary retention (risk of exacerbating these conditions) (risk of worsening these condition) (27-31)
- Recent Falls (or history of recurrent falls in the past year) (increased risk of falls and fractures) (32-34)
- The patient has been taking an antidepressant for the recommended period (6-12 months) or no active depression $\geq$ 6 months (8, 27)
- if initiated as first-line antidepressant treatment (higher risk of adverse effects than SSRI's and SNRI's) (27, 35)
- Other possible triggers include no valid or current indication, drug-drug/drug-disease interaction, high anticholinergic burden, dual therapy, off label use, presence or high risk of serious adverse effects, and poor adherence.

Taper guide (taper where possible to avoid withdrawal symptoms) (36)

Gradually by 25% of the daily dose every 1-4 weeks. Consider alternate day dosing to aid with weaning if dosage forms are limited. If withdrawal symptoms*occur, reduce the rate of taper. If the reason for deprescribing is due to serious adverse effects, recommend rapid discontinuation. Consider recommending reducing the dose in older adults where a stop isn't possible

Tricyclic Antidepressants (continued)

Pharmacological alternatives (lower anticholinergic burden)

These are a list of alternatives with little to no anticholinergic burden. Consider recommending a switch in the presence of troublesome side effect, inappropriate or invalid indication, and no treatment effect. Note that substitution with other sedative medicines may produce the same adverse effects and that less anticholinergic alternatives often have other concerns

SSRIs

- Safer choice in older adults (beware of the risk of falls risk and hyponatraemia; avoid paroxetine) (27)

- If switching from a TCA (except for clomipramine) to an SSRI (citalopram, escitalopram, or sertraline), gradually reduce TCA dose to 25–50 mg or half the usual dose. Start SSRI then slowly withdraw TCA over the next 5–7 days (37)

SNRI

- Venlafaxine (11), Duloxetine (8, 38)

- If switching from TCA (except clomipramine) to an SNRI cross-taper cautiously starting with low dose SNRI. e.g. reduce the dose of TCA by 25–50% weekly, while starting low dose SNRI and increasing gradually (37)

Other options

- Lofepramine (lower incidence of adverse effects compared to other TCA's) (27, 39, 40). Direct switch possible (37)
- Trazodone (sedating, but less pronounced anticholinergic effect)(8, 41). Cross-taper cautiously (37)

*Withdrawal symptoms include dizziness, nausea, paraesthesia, anxiety, diarrhoea, flu-like symptoms, and headache may occur within 5 days of stopping or reducing the TCA. • Symptoms are often self-limiting and rarely lasting for more than 1–2 weeks. However, occasionally they can be severe, particularly if the drug is stopped abruptly(43).

Non pharmacological alternatives (36, 42)

Mild to moderate major depression

- Self-help based on the principles of cognitive behavioural therapy (CBT) (including behavioural activation and problem-solving techniques)
- Computerised cognitive behavioural therapy (CCBT)
- Structured group physical activity programme.
- CBT, interpersonal therapy (IPT) or behavioural activation initial inadequate response to initial psychological interventions

Moderate to severe depression

- Antidepressant treatment + psychological intervention (CBT or IPT)

After selecting an option

- Record deprescribing rationale (see additional deprescribing rationales if needed) and patient preference ☐

- Communicate recommendation to prescriber or treatment team (to get feedback on the proposed medication changes and facilitate medication updates). Written or verbal communication should include; medication, Intention, rationale, recommendation plan (e.g. dose change and follow up) and details on patient agreement ☐

Benzodiazepines

¹Alprazolam, Diazepam

Check list

- Check for the original diagnoses and if these are stable. These recommendations do not apply to uncontrolled anxiety, untreated depression, and alcohol withdrawal (with these, the priority is to manage the condition first, before attempting drug withdrawal) (45) ☐
- Check the need and validity of the drug ☐
- Duration of use ☐
- Does it interact with the patient's condition or other drugs (drug-drug, drug-disease interaction, dual therapy) ☐
- Check if drug prescribed with an opioid ☐
- Is the patient willing to be deprescribed or tapered to the lowest possible dose (Involve patient, family members and carers in decision making where appropriate)? Refer to communication guide ☐
- Reassure patients that they can control how slow the taper goes (45) ☐
- Reassure them that the symptoms are usually mild ☐

Deprescribing triggers

- Where prescribed for insomnia on its own (If insomnia is severe, consider starting non-pharmacological treatments before the withdrawal of a benzodiazepine)(risk of adverse effect including cognitive impairment and falls) (44-46)
- Where medical problems for which drug was prescribed are controlled or stable (loss of efficacy over time with increased risk of adverse effect including falls, fractures, cognitive impairment and dependence) (45, 47)
- Benzodiazepines for ≥ 4 weeks (risk of prolonged sedation, cognitive impairment, falls and fractures). (12, 48, 49)
- Recent fall (last 3 months) (falls and fracture risk)(12, 50)
- If the patient is on an opioid (the combination may result in sedation, respiratory depression, coma and death) if there are no other appropriate alternatives, consider tapering to lowest effective dose (51)
- Other possible triggers; include no valid or current indication, drug-drug/drug-disease interaction, high anticholinergic burden, dual therapy, off label use, presence or high risk of serious adverse effects, and poor adherence

Taper guide (consider recommending taper to lower dose even where an eventual stop isn't possible)

- Decrease patient's dose by 25% (or alternative rate decided on) every 2 weeks and then a slower taper of 12.5% every 2 weeks near the end dose. If symptoms relapse or taper not going well, consider maintaining current dose for 1-2 weeks before attempting the next dose reduction (at a slower rate where possible)(44)
- Consider switching to diazepam or clonazepam for patients on short-acting potent benzodiazepines (e.g. alprazolam and lorazepam) for ease of formulation (45, 52). However, no evidence that switching reduces the incidence of withdrawal symptoms or improves cessation rates. Taper by no more than diazepam 5mg or clonazepam 0.25mg equivalent/week. Reduce taper rate when the dose is below 20mg of diazepam (e.g. 1-2 mg/week) (53)

Benzodiazepines(continued)

Non-pharmacological alternatives

Insomnia

- Cognitive behavioural therapy for insomnia (CBT-I) is more effective than pharmacological therapy to treat short-term and long-term insomnia in older adults (54, 55).
- Provide patient information on Good sleep hygiene (55)
- Consider recommending a sleep diary (for a minimum of 2 weeks) to help in identifying lifestyle factors that may impact insomnia(55)

Anxiety

- Low-intensity psychological interventions: individual non-facilitated or facilitated self-help materials and psychoeducational groups (56)
- High-intensity psychological intervention, e.g. CBT or progressive muscular relaxation applied relaxation (56)
- Psychological treatments in people living with mild to moderate dementia (6)

Panic disorders

- CBT (moderate to severe panic disorders) (56)
- Individual non-facilitated or facilitated self-help materials (mild-moderate panic disorder) (56)

Lifestyle advice

- General promotion of healthy behaviours as appropriate(e.g. good nutrition, exercise, good sleep hygiene, reduced caffeine and alcohol use)(56)

Inform patients (and caregivers) of withdrawal symptoms. Common withdrawal symptoms include rebound anxiety, insomnia, irritability, Sweating, Gastrointestinal symptoms, tremors, Dizziness and tinnitus (44, 45) . Reassure them that the symptoms are usually mild

¹Drug= ACB 1; ²Drug = ACB 2; ³Drug =ACB 3

Pharmacological alternatives (low anticholinergic burden)

- The effectiveness of non-pharmacological and pharmacological therapy is similar to the treatment of anxiety and related disorders in older adults (56, 57). Switching may also cause dizziness and falls.

Generalized anxiety disorder

- Escitalopram (caution in hyponatremia)(58)
- Duloxetine (caution in older adults) and venlafaxine* (58)
- Pregabalin (associated with falls, dizziness, gait abnormality, confusion and dependence issues)(58)

Panic disorders

- Citalopram and escitalopram (stop caution)(56)

Insomnia

Modified-release Melatonin (may cause drowsiness and falls) 2 mg once daily for up to 13 weeks(55). Not recommended in patients with Alzheimer's disease

After selecting an option

- Record deprescribing rationale (see additional deprescribing rationales if needed) and patient preference ☐
- Communicate recommendation to prescriber or treatment team (to get feedback on the proposed medication changes and facilitate medication updates). Written or verbal communication should include; medication, Intention, rationale, recommendation plan (e.g. dose change and follow up) and details on patient agreement ☐

Opioids for non-cancer pain

¹Fentanyl, Codeine and Morphine

Check list

- Specify the indication for each medication ☐
- Check the need for the drug (e.g. does the patient take it. If so are they fine without the medicine). Are opioids less effective for the condition (e.g. chronic lower back pain, fibromyalgia, widespread pain, and chronic primary pain*) ☐
- Co prescribed with benzodiazepine? (increasing the risk of sedation, respiratory depression, coma, and death (60) ☐
- Duration of treatment (little evidence of opioid effectiveness for long term use) ☐
- Does it interact with the patient's condition or other drugs (drug-drug, drug-disease interaction, dual therapy) ☐
- Does it require the involvement of specialist team, e.g. complex, severe pain, opioid dependence, withdrawal syndrome, psychiatric comorbidity (64) ☐
- Is the patient willing to be deprescribed (Involve patient, family members and carers in decision making where appropriate)? Refer to communication guide ☐

Deprescribing triggers

- long-term strong opiates as first-line therapy for mild-moderate pain (WHO analgesic ladder not observed (12, 59)
- Co-prescribed with benzodiazepines (increased risk of sedation, respiratory depression, coma, and death)(reduce to the lowest possible dose where a stop isn't possible)(60, 61)
- If prescribed for sciatica and lower back pain, and chronic primary pain (little evidence of effectiveness) (62, 63)
- Opioid-induced hyperalgesia (paradoxical increase in pain with opioid administration) (64, 65)
- No perceived benefit despite regular dose increases (e.g. 90-120mg morphine equivalent dose in 24 hours; substantially increased risk of harm with little additional benefit)(66-68)
- Other possible triggers include no valid or current indication, drug-drug/drug-disease interaction, presence of adverse effects not tolerated by patient, e.g. cognitive impairment, falls, mood changes, and respiratory depression (61, 64, 69)

Opioids for non-cancer pain(continued)

Taper guide (recommend taper to avoid withdrawal symptoms*)

Option 1; Maintain the modified-release (MR) dose initially, and wean down the immediate release when needed (PRN) doses.

Option 2; Wean down the MR dose first, and keep the PRN immediate release dose steady (70)

Taper by 5-20% of the daily dose every 4 weeks. Initiate rapid taper (e.g. 5-20% per week) if risks are too high to consider a gradual taper (64, 66)

Pharmacological alternatives (little to no anticholinergic burden)

- Where appropriate consider the use of simple analgesics, e.g. paracetamol
- NSAID for lower back pain (risk of potentially serious adverse events)

Non-pharmacological alternatives (can also complement analgesic use)

Interdisciplinary collaboration to provide psychological therapy

- Cognitive behavioural therapy acceptance and commitment therapy (ACT) and other non-drug techniques (e.g. supervised group exercise programmes, relaxation, massage, and heat therapy) (62, 63, 66, 71)
- Acupuncture in chronic primary pain** (63, 71, 72)

After selecting an option

- Record deprescribing rationale (see additional deprescribing rationales if needed) and patient preference ☐
- Communicate recommendation to prescriber or treatment team (to get feedback on the proposed medication changes and facilitate medication updates). Written or verbal communication should include; medication, Intention, rationale, recommendation plan (e.g. dose change and follow up) and details on patient agreement ☐

*Withdrawal symptoms may include nausea, vomiting, sweating, anxiety, craving, and insomnia. If no withdrawal symptoms continue to wean and stop, otherwise pause longer between changes (64)

**Chronic primary pain; defined as "pain that persists for longer than three months and is associated with significant emotional distress or functional disability and that cannot be explained by another chronic condition" (73).

¹Drug1= ACB 1;²Drug2 = ACB 2;³Drug3=ACB 3

Pharmacists' communication guide

Establishing the need for the medication.

- Do you know why you are on this medication
- Have the original complaint been resolved
- Do you think it's working
- Have you tried anything else and did it work

Bringing up stopping or tapering a drug

- You are experiencing these symptoms because you are on a combination of medications that increase the risk of these symptoms. Can I go through them with you, so we can decide which ones you can stop or reduce?
- I can see that you are on several medications that can increase your risk of memory problems and falls. Are you okay for me to go through them with you, to see which you can stop or reduce?
- Having reviewed your medicines, I can see that some of the combinations you are on can increase side effects like confusion and falls.

Switching

- There is an alternative to this medication; it comes with less risk of memory problems and will provide the same benefit.

Emphasising risk of continuing

- To reduce your risk of adverse events, it is important to reduce medications that increase your risk of cognitive impairment, falls, and fractures
- Even though you might not be experiencing any side effect now, with these medications, it can take some people years to see the memory effect

Highlighting risk vs benefit of continuing medication

- For example, Informing patients of the risk of continuing benzodiazepine may produce a desire to taper (74, 75). "This medicine may give you short term benefits, but it may also cause problems with your memory, and increase your risk of falls, fractures and motor vehicle accidents. It also loses its effectiveness with time as your body gets used to it
- Reducing or stopping opioids frequently improves function, quality of life and pain control. This may take some time, and your pain may briefly get worse. (76)

Reassuring patient

- We can try it for a few weeks to see how you get on and come back later to review it
- You may experience certain withdrawal effects, but they are usually mild and will go away as the body gets used to functioning without the drug.
- You can control the rate of your dose reduction if that's what you would prefer
- If you are not comfortable stopping the medicine, shall we try reducing your dose and seeing how you get on with that

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