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ORIGINAL RESEARCH ARTICLE

Development and Pilot Testing of an Algorithm-Based Approach to Anticholinergic Deprescribing in Older Patients

Tanja Wehran[1,2,3] · Annette Eidam[3] · David Czock[1] · Jürgen Kopitz[4] · Konstanze Plaschke[5] · Margarete Mattern[6] · Walter Emil Haefeli[1,2] · Jürgen Martin Bauer[3,7] · Hanna Marita Seidling[1,2]

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Abstract

Background Adverse anticholinergic drug reactions are common, yet evidence on how to reduce exposure to anticholinergic activity and reliably measure successful deprescribing is still scant. This study proposes an algorithm-based approach to evaluate and reduce anticholinergic load, and reports the results of its pilot testing.

Methods Based on published evidence and expert opinion, a list of 85 anticholinergic drugs and 21 algorithms for reducing anticholinergic load, e.g., by recommending alternative drugs with lower risk, were developed. An accompanying test battery was assembled by focusing on instruments that sensitively reflect anticholinergic load and may be sensitive to depict changes (Neuropsychological Assessment Battery to measure memory and attention, validated assessments for constipation, urinary symptoms, and xerostomia, as well as blood biomarkers). The approach was pilot-tested in a geriatric rehabilitation unit, with clinician feedback as the primary outcome and characterization of anticholinergic symptoms as the secondary outcome. The intervention was delivered by a pharmacist and a clinical pharmacologist who used the algorithms to generate personalized recommendation letters.

Results We included a total of 20 patients, 13 with anticholinergic drugs and 7 without. Recommendations were made for 22 drugs in nine patients from the intervention group, of which seven letters (78%) were considered helpful and 8/22 (36%) anticholinergic drugs were discontinued, reducing anticholinergic load in seven patients. In contrast to patients without drug change, memory assessment in patients with reduced anticholinergic load improved significantly after 2 weeks (6 ± 3 vs. -1 ± 6 points).

Conclusions The approach was well received by the participating physicians and might support standardized anticholinergic deprescribing.

1 Introduction

In geriatric medicine, anticholinergic adverse drug reactions have increasingly become the focus of many interventions designed to assess or improve prescribing quality. Although anticholinergic drugs are useful in specific indications, their negative effects on patient outcomes are clinically relevant in many cases. As an example, drugs with anticholinergic adverse effects are associated with xerostomia, falls, confusion, and delirium [1]. In one observational study, a higher cumulative dosage of anticholinergic drugs was associated with a more than 50% increase in the long-term occurrence of dementia [2].

Therefore, deprescribing anticholinergic drugs might reduce dementia-associated symptoms and may even reduce the risk of dementia. With the aim of improving cognitive function, some intervention studies have been conducted in patients taking anticholinergics [3], but with ambiguous results. Reducing a patient's anticholinergic load by 20% (as defined by the Anticholinergic Cognitive Burden Scale) could significantly improve dementia-related symptoms [4]. However, the real benefit resulting from the (complete) reduction of anticholinergic load remains unclear, as previous studies have either discontinued only single agents [5] or failed to show a significant improvement in cognitive outcomes [6].

While many deprescribing approaches have been tested, several strategies seem particularly promising. For instance, the intervention must be tailored to identify patients at risk, i.e., patients with a high anticholinergic load whose overall

Tanja Wehran and Annette Eidam contributed equally to this work.

Extended author information available on the last page of the article

Key Points

Based on previous evidence, we developed a list including 85 anticholinergic drugs, 21 algorithms for anticholinergic deprescribing, and a test battery to assess anticholinergic symptoms.

Uptake of personalized deprescribing recommendations in the pilot study was high and anticholinergic load could be reduced in 7/11 participants.

The results of this exploratory study indicate that our comprehensive approach for anticholinergic deprescribing is feasible and could offer a new strategy to potentially reduce anticholinergic load and adverse anticholinergic effects in older adults.

condition is not yet so irreversibly impaired that they can no longer benefit from a reduction in anticholinergic load. This assumption is underlined by a previous study that revealed a correlation of increasing anticholinergic load with cognitive impairment in patients without dementia but not in patients with dementia [7]. Second, appropriate alternative drugs with no or fewer central anticholinergic effects should be proposed. Simply identifying anticholinergic drugs may not lead to meaningful clinical consequences in patients with a perceived need for a specific drug and because of difficulties to identify a suitable alternative drug. A third aspect refers to the applied tests for the measurement of relevant endpoints. Such tests should be adequate to detect improvements in cognitive function after deprescribing. In one intervention study, improvement of the cognitive subscale of the Alzheimer's Disease Assessment Scale was observed 10 days after stopping the anticholinergic agent biperiden [5]. Fourth, such studies can fail for several reasons. For example, in one pilot study, patients did not agree with a medication change and some general practitioners refused to prescribe non-anticholinergic alternatives because they did not want to change the prescription of a specialist [8]. Hence, in deprescribing studies, intervention fidelity should be fostered by a practice-oriented, personalized approach that is well received by the treating physicians.

In this report, we describe a novel approach to reduce the patients' anticholinergic load and report the design and results of a deprescribing pilot study. The aim of the pilot study was to assess the feasibility of the newly developed approach and test how the recommendations to anticholinergic deprescribing were valued by the attending physicians. As secondary endpoints, we evaluated changes in the anticholinergic load and patients' anticholinergic symptoms.

2 Methods

The intervention was designed for older patients with no or only mild cognitive deficits and without acute medical deterioration or manifest dementia who were cared for in a setting such as a rehabilitation unit that allowed close and continuous monitoring of clinical changes.

2.1 Intervention Development

2.1.1 Development of an Anticholinergic Drug List

A prerequisite for effective anticholinergic deprescribing is to identify patients with potentially high anticholinergic load. Therefore, we defined a list of anticholinergic drugs based on the compilation by Durán and co-workers, which summarizes drugs contained in already available lists [9]. This list was successfully used in previous studies to define drugs with varying anticholinergic activity [10–12]. In these earlier studies, the list by Durán et al. was extended to include anticholinergic drugs with national approval taken by older cohorts. At the start of the study, no list tailored to the German drug market was available. Hence, in our adapted version, drugs not available on the German drug market were removed and compounds of the same Anatomical Therapeutic Chemical (ATC) class available on the German drug market were added if they also had anticholinergic activity. Included drugs had to be systemically active and have anticholinergic activity as determined by evaluation of the drug's mode of action (binding to muscarinic receptors), in vitro data (serum anticholinergic activity [SAA]), and/or reported typical anticholinergic (adverse) effects. Therefore, a non-systematic literature search in the PubMed database was conducted using the drug name or drug class and Medical Subject Headings (cholinergic antagonists, muscarinic antagonists, drug-related side effects, and adverse reactions) as well as free-text (e.g., anticholinergic, anticholinergic drugs). Our list was designed to be particularly sensitive to identify patients at risk of adverse cognitive effects of anticholinergic drugs. Therefore, drugs were rated as strong anticholinergics if they exerted a strong anticholinergic activity and were also able to cross the blood–brain barrier. The ability to penetrate the blood–brain barrier was verified using the database of Doniger and co-workers [13] or (implicitly) using the respective summary of product characteristics (indicating central nervous system adverse effects such as delirium or confusion). Weak anticholinergic drugs were defined as having a weak anticholinergic activity according to the list of Durán et al. or a strong anticholinergic activity without passing the blood–brain barrier.

The decision on whether or not to include drugs in the final list of anticholinergics was discussed with experts of

the respective indication (one psychiatrist, one pain expert, one urologist, one general practitioner, one internist, and two pharmacists). In case of discrepancies in the assessment, an independent research group with expertise in the field of assessing anticholinergic load [14] was consulted to discuss the selection before the final decision was made.

The final anticholinergic drug list included 85 drugs, of which 39 substances had strong and 46 drugs had weak anticholinergic effects (Table 1, Online Resource Fig. 2).

2.1.2 Development of Algorithms to Reduce the Anticholinergic Load

Core elements of the intervention were algorithms with deprescribing strategies (discontinuation, dose reduction, or change to an alternative drug) developed for all indications for which the listed anticholinergic drugs were commonly used. The same expert panel that was consulted in the development of the list of anticholinergic drugs was also involved in the development of the algorithms. The experts helped define the most common indication of each anticholinergic drug and possible alternatives. All algorithms were designed to have a similar structure. First, the algorithm recommended deprescribing of the anticholinergic drug. For drugs with known risk of dependency (e.g., benzodiazepines), or to avoid withdrawal symptoms (e.g., tricyclic antidepressants), a tapering scheme was provided. If treatment could not be stopped according to the physician's opinion, alternatives considered suitable for the respective indication, but with fewer anticholinergic effects, were recommended. For each alternative, additional information was provided (monitoring recommendations, interaction warnings, or dosage recommendations based on the patient's individual renal function). In the absence of adequate alternatives, a dosage reduction was considered (Online Resource Fig. 1).

A total of 21 algorithms were developed and therapeutic alternatives were defined for 12/21 indications (abdominal pain, agitation, allergy, anxiety disorder, depression, diarrhea, general pain, insomnia, muscular tension, nausea, urinary incontinence, and vertigo/dizziness). For the nine other indications, no algorithms could be developed because no adequate drugs with no or less anticholinergic activity could be identified (applies to chronic obstructive pulmonary disease and axillary hyperhidrosis), the treatments are complex and very individual and not appropriate to be changed in our study setting (rehabilitation unit) but should rather be modified only during a specialist consultation over a longer period of time (applies to bipolar disorder, epilepsy, Parkinson's disease, and schizophrenia), or because the anticholinergic drug is typically only used for short-term treatment (applies to dry cough, mydriasis (diagnostic use), and gastrointestinal ulcer).

2.1.3 Development of an Anticholinergic Outcome Assessment Battery

For identifying the most appropriate outcome assessment battery to capture both peripheral and central adverse anticholinergic effects in this pilot study, a non-systematic literature search was performed and its results were evaluated by an expert panel including pharmacists, clinical pharmacologists, geriatricians, psychiatrists, and a psychologist. The experts agreed on the instruments to be used by discussion.

The selected outcome assessment battery comprised the following tests to assess patient-related symptoms: (1) the Neuropsychological Assessment Battery to measure memory and attention [15]; (2) three validated questionnaires referring to constipation [16], urinary symptoms [17], and xerostomia [18]; (3) one practical test for measuring xerostomia [19]; and (4) measured SAA [20] and whole blood activities of butyrylcholinesterase and acetylcholinesterase [21] as biomarkers. Online Resource Table 1 gives a detailed description of these different subtests within the outcome assessment battery and their methodology.

In contrast to a large number of available tests, such as the Consortium to Establish a Registry for Alzheimer's Disease-Plus [22], the Nürnberger Alters-Inventar [23], the Alzheimer's Disease Assessment Scale-Cognitive [24], the Montreal Cognitive Assessment [25], the Mini-Mental State Examination-2 (MMSE-2) [26], and the Syndrom-Kurztest [27], the Neuropsychological Assessment Battery [15] was the only cognitive test that fulfilled all criteria considered relevant for this deprescribing study, i.e. it was suitable for the analysis of different aspects of cognitive impairment (especially attention and memory), it offered an age-standardized interpretation of the test results, validated parallel versions were available, which allowed a repetition of the tests already after approximately 2 weeks, it was well established in the field of geriatric medicine, and it was available in German.

2.2 Pilot Testing

2.2.1 Setting and Study Population

The new approach was piloted in a monocenter controlled non-randomized study conducted at the geriatric rehabilitation unit of Agaplesion Bethanien Hospital Heidelberg in Germany. Inpatients were invited to participate if they were aged 65 years and older and were able to perform the outcome assessment battery. Therefore, a minimum of 24 points in the German version of the MMSE [28] was required. Exclusion criteria were diagnosed dementia, delirium and stroke (during the last 4 weeks), as indicated in the patient record. To assess the potential effects of medication

Table 1 Drugs considered as strong ($n = 39$) or weak ($n = 46$) anticholinergic drugs

Pharmacological group	Individual compound		
Drugs with strong anticholinergic activity			
Antidepressants	Amitriptyline	Imipramine	Nortriptyline
	Clomipramine	Maprotiline	Trimipramine
	Doxepin		
Antipsychotics	Chlorprothixene	Levomepromazine	Perazine
	Clozapine	Loxapine	Thioridazine
Drugs for Parkinson's disease	Biperiden	Procyclidine	Trihexyphenidyl
	Bornaprine		
Urological spasmolytics	Darifenacin	Oxybutynin	Solifenacin
	Fesoterodine	Propiverine	Tolterodine
Antihistamines	Chlorphenamine	Dimetindene	Hydroxyzine
	Clemastine	Diphenhydramine	Promethazine
	Cyproheptadine	Doxylamine	Triprolidine
	Dimenhydrinate		
Muscle relaxants	Orphenadrine	Pridinol	
Others	Atropine	Scopolamine	Tropicamide
	Cyclopentolate		
Drugs with weak anticholinergic activity			
Antidepressants	Mianserin	Opipramol	Paroxetine
Antipsychotics	Flupentixol	Perphenazine	Quetiapine
	Fluphenazine	Pimozide	Sulpiride
	Fluspirilene	Prothipendyl	Zuclopenthixol
	Olanzapine		
Drugs for Parkinson's disease	Amantadine	Budipine	
Urological spasmolytics	Flavoxate	Trospium	
Opioids[a] for pain treatment	Buprenorphine	Meptazinol	Pethidine
	Dihydrocodeine	Methadone	Piritramide
	Fentanyl	Morphine	Tapentadol
	Hydromorphone	Nalbuphine	Tramadol
	Levomethadone	Oxycodone	
Benzodiazepines	Diazepam	Temazepam	
Drugs for chronic obstructive pulmonary disease	Aclidinium	Ipratropium	Umeclidinium
	Glycopyrronium	Tiotropium	
Gastrointestinal drugs	Butylscopolamine	Pirenzepine	Ranitidine[b]
Anticonvulsants	Carbamazepine	Oxcarbazepine	
Others	Codeine[a]	Loperamide[a]	Methanthelinium

[a]Weak anticholinergic effects are suspected but remain unclear (probably class effect via inhibition of acetylcholine release; see [46–48])

[b]Approval of ranitidine was suspended by the European Medicines Agency in April 2020

changes, patients who were taking at least one drug with strong anticholinergic activity ('patients with anticholinergic load') were allocated to the intervention group, and patients who were not taking any anticholinergic medication ('patients with no anticholinergic load') were assigned to the control group. Patients with only weak anticholinergic drugs according to our list were not included in this pilot study to predominantly focus on patients more likely impaired by adverse anticholinergic effects in comparison with an unaffected control group.

2.2.2 Delivery of the Intervention and Study Design

The entire study flow is depicted in Fig. 1. The patients' medication list was taken from the patient file, and in case of uncertainty (e.g., with regard to completeness), verified by consultation with their primary care physician or specialist. The anticholinergic outcome assessment battery was collected at baseline. A member of the study group administered the subtests, whereas the blood sample (SAA, esterases) was collected as an additional sample during a routine laboratory assessment by a member of the hospital staff.

The algorithms to reduce the anticholinergic load were used to generate personalized recommendation letters for

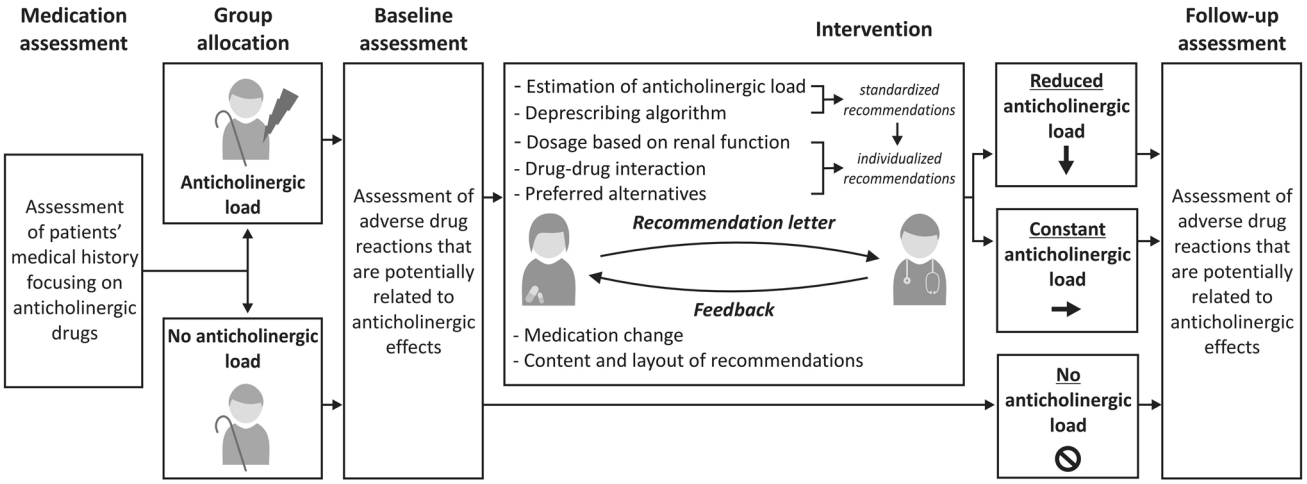

Fig. 1 Study procedure

the attending physicians of the participants in the intervention group. The recommendation letters were prepared in a standardized, quality assured (i.e., dual control) way by a clinical pharmacist and a clinical pharmacologist. These letters adapted the standardized algorithms to the individual patient's medical history by addressing the following questions (Online Resource Fig. 1).

1. If an anticholinergic drug is stopped, does the remaining medication have to be adapted (for example due to a drug–drug interaction that is not relevant anymore)? If yes, please adapt the (dose of the) co-medication.
2. If an alternative drug is needed, has the alternative drug been previously used unsuccessfully in the patient's history (non-responder)? If yes, please consider more appropriate alternatives.
3. If an alternative drug is needed, are there any new drug–drug interactions expected to occur with the patient's co-medication? If yes, please consider other alternatives or adapt the (dose of the) co-medication.
4. If a dose reduction is needed, is a suitable dosage form available on the market to achieve this dose? Please consider adequate dosage forms or evaluate further alternatives.

If needed for any individualization of the recommendation letter, the actual estimated glomerular filtration rate and other appropriate laboratory values (e.g., plasma sodium) were extracted from data routinely collected in the rehabilitation unit. The recommendation letter was also supplemented with information on the results of the anticholinergic outcome assessment battery, which reported the patient's conditions as well as comorbidities that could be exacerbated by anticholinergics (e.g., Sjögren's syndrome associated with xerostomia).

Each letter reported its information in three different presentation formats (flowchart, table, and plain text) to determine the attending physicians' preferences for a particular report format. During the patient's rehabilitative stay, the attending physicians had the following options: stopping the drug without an alternative drug, replacing the drug with a recommended alternative or another alternative, or maintaining the medication regimen unchanged. No incentives were used to promote any choice.

The physicians in the rehabilitation unit were informed about the study and were required to give their own written informed consent to have their feedback on the recommendation letter evaluated. The recommendation letter was provided to the attending physician in the rehabilitation unit by a personal contact, in our case a clinical pharmacist.

In order to assess short-term effects, the anticholinergic outcome assessment battery was repeated 2 weeks after the baseline assessment. If the anticholinergic medication or its dose was changed based on the recommendation letter, the follow-up assessment was conducted 2 weeks after the regimen change rather than 2 weeks after the baseline assessment. If the patient was discharged earlier than 2 weeks after the medication change, the follow-up assessment could be conducted at the patient's home. For all outcome calculations, the intraindividual difference between baseline and follow-up assessment was used, with positive values indicating an improvement over time and negative values indicating deterioration.

2.2.3 Outcomes

The primary outcome of the feasibility study was the clinician's feedback on the recommendation letter, while secondary outcomes were the characterization of anticholinergic

symptoms during the course of the study and the feasibility of the deprescribing strategies.

2.2.4 Data Analysis and Statistical Methods

After the intervention, the group of patients with anticholinergic load was divided into patients whose anticholinergic load could be reduced (at least one anticholinergic drug was discontinued or substituted, or the dose was reduced) and patients whose anticholinergic load could not be changed. No matching or stratification was made due to the expected small sample size. The physicians' responses to the recommendation letter were evaluated based on their written feedback, and the number of accepted recommendations was counted.

To characterize the study cohort, means with standard deviations were reported for continuous patient data, and absolute numbers with percentage proportions for categorical data. Differences between patient groups were calculated with a double-sided *t*-test for independent groups (for continuous data) and a Chi-square test (exact Fisher's test) for the evaluation of categorical data. Endpoints were based on the intraindividual difference between the baseline and the follow-up assessment of each patient and only evaluated in patients participating in both assessments (per protocol analysis). Missing values were not imputed because of the small sample size. Pearson correlations between cognitive outcomes and measured SAA (see the Online Resource) were calculated to assess their relationship. All calculations were made using IBM SPSS Statistics version 22 (IBM Corporation, Armonk, NY, USA). A p value < 0.05 was considered statistically significant.

2.2.5 Sample Size

Because this was an exploratory feasibility study, no sample size calculation was made a priori. We deliberately planned to consecutively recruit patients until at least 20 patients with at least one drug with strong anticholinergic activity had been enrolled in whom the study intervention resulted in a complete discontinuation of all anticholinergic drugs.

3 Results

Between May 2017 and May 2018, a total of 20 patients were recruited (Fig. 2). Four participants, two in the intervention group and two in the control group, were lost to follow-up before the baseline assessment (e.g., because they were discharged, transferred to acute care, or discontinued the anticholinergic drug) (see Fig. 2) and were excluded from the final analyses. Eleven participants in the final study sample used strong anticholinergic drugs. The control group included the remaining five participants without anticholinergic load.

Table 2 lists the characteristics of the final study population. Strong anticholinergic drugs used by the patients included amitriptyline, biperiden, clozapine, dimenhydrinate, doxepin, fesoterodine, and solifenacin.

3.1 Proposed and Implemented Medication Changes

Recommendation letters proposing medication changes to reduce the anticholinergic load were issued for 9/11 patients in the intervention group (Table 3). No recommendation letters were issued for two patients because specialist evaluation was deemed necessary to modify treatment (Online Resource Table 2). Of the 22 anticholinergic drugs used by the 11 patients in the intervention group, seven strong anticholinergic drugs and one weak anticholinergic drug were either reduced or replaced by the attending physicians, leaving 7 participants in the intervention group (63.6 %) with a reduced anticholinergic load (Fig. 2). The attending physicians modified the treatment for six strong anticholinergic drugs as recommended (Table 3), while one strong anticholinergic drug (clozapine) (Online Resource Table 2) was discontinued independent of the recommendation letter after reassessment of the indication.

3.2 Feedback from the Treating Clinicians on the Intervention

The treating physicians ($n = 6$) provided their written feedback on all nine recommendation letters (Table 3). The majority of the recommendation letters were found to be helpful ($n = 7$, 77.8 %). The most common reason for rejecting the proposed medication changes (40%) was patient refusal to change their medication. Flowcharts ($n = 5$) or tables ($n = 4$) were the preferred layout formats in the recommendation letter (Table 3).

3.3 Changes of Outcomes Measured with the Test Battery

Follow-up data were available for 14 patients: six patients with reduced anticholinergic load (anticholinergic drugs were discontinued or substituted), three patients with unchanged anticholinergic load (unchanged anticholinergic medication), and five control patients without anticholinergic

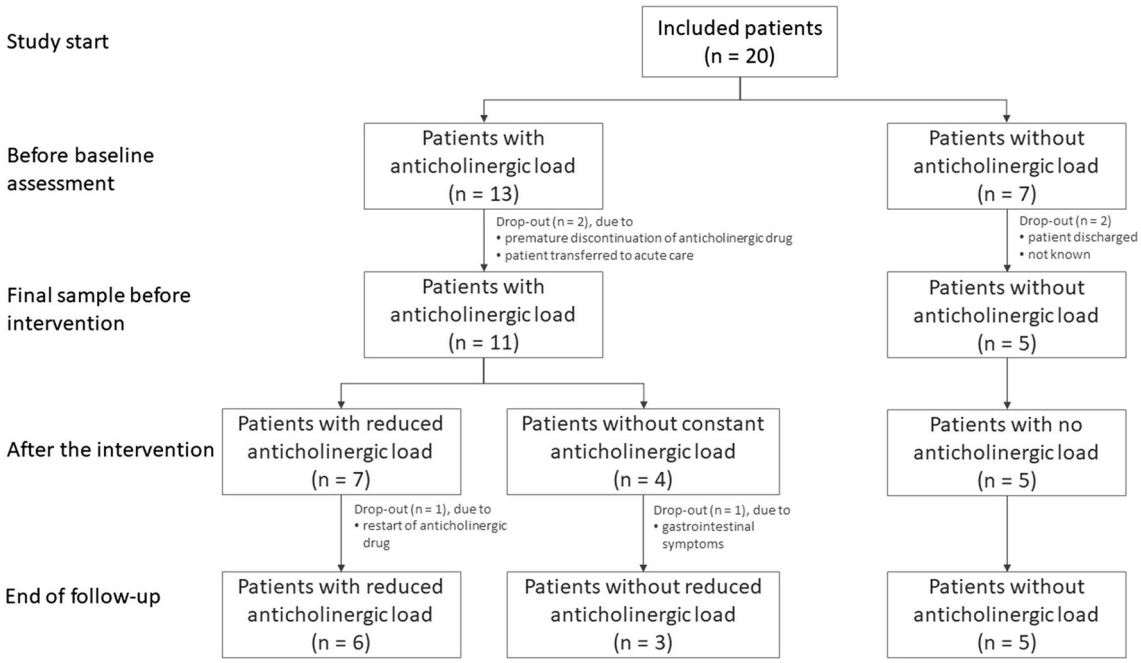

Fig. 2 Consort diagram depicting patient flow during the pilot test

load (Fig. 2). There was a significant improvement on the Neuropsychological Assessment Battery memory test between baseline and follow-up assessment in patients with reduced anticholinergic load compared with patients with unchanged medication (6 ± 3 vs. -1 ± 6 points) (Online Resource Table 3). In addition, the Neuropsychological Assessment Battery memory score correlated significantly with changes in measured SAA (difference between baseline and follow-up assessment based on all participants; Pearson $r^2 = 0.36$, $p = 0.03$) (Online Resource Fig. 3). There were no differences between groups in the other tests assessing cognitive and peripheral adverse effects or biomarkers (Online Resource Table 3).

4 Discussion

Anticholinergic load and cognitive impairment have been linked in many association studies [29–31] but interventions to reduce anticholinergic load and resulting in cognitive improvement have been rarely reported [32]. This could be due to several reasons: The study was difficult to implement [30], physicians refused to adopt the proposed modifications [8], the *complete* elimination of anticholinergics proved to be barely feasible [6, 32, 33], patients with advanced dementia were enrolled in whom cognitive impairment may not be reversible [6, 33], and the instruments used to measure cognitive performance may not have been sensitive enough to detect subtle improvements in cognition [33, 34]. Therefore, future proof-of-principle studies should (1) enroll patients with cognitive impairment that is likely to be at least partly reversible; (2) suggest individualized therapy changes that are easy to follow; (3) communicate the recommendations to the treating physician in a format that makes them easy to understand and implement; (4) monitor the effect of the intervention with feasible and sensitive instruments; and (5) use study designs that avoid excessive dropout rates.

In this work, a simple and standardizable approach considering these key principles was developed and pilot-tested. The approach was well accepted by the treating physicians and indeed resulted in treatment changes. In doing so, the approach combines intervention elements that have been shown to be successful in previous deprescribing studies (e.g., providing personalized recommendations rather than standard recommendations [34], or having clinical pharmacists or clinical pharmacologists provide recommendations instead of an electronic system [35]). Our intervention relied on a team-based approach in which responsibility for conducting the medication review and determining the patient's anticholinergic load was assigned to a clinical pharmacist, while overall responsibility for deprescribing remained with the treating physician. Healthcare professionals have previously indicated a preference for such an interdisciplinary cooperation in deprescribing anticholinergics [36], which successfully reduced the anticholinergic load caused by urinary antimuscarinics in a recent study [37].

Table 2 Characteristics of study participants with (reduced, unchanged) or without anticholinergic burden

Characteristic	Patients with anticholinergic load			Control group with no anticholinergic load
	Patients with anticholinergic load (in total)	Subgroup 1: patients with reduced anticholinergic load after intervention	Subgroup 2: patients with constant anticholinergic load after intervention	
No. of patients	11[a]	7[a]	4[a]	5
Mean age, years (±SD)	81 (5)	80 (3)	83 (8)	84 (11)
Sex				
Female [*n* (%)]	10 (91)	6 (86)	4 (100)	3 (60)
Male [*n* (%)]	1 (9)	1 (14)	0 (0)	2 (40)
Median MMSE (range)	26 (25–30)	26 (25–30)	27 (25–30)	29 (24–30)
Anticholinergic drugs: (the following columns list the number of patients with the respective drug)				
Amitriptyline	1		1	
Biperiden	1		1	
Clozapine	1	1		
Diazepam[b]	1	1		
Dimenhydrinate	2	2		
Doxepin	4	2	2	
Fesoterodine	1	1		
Hydromorphone[b]	1	1		
Oxycodone[b]	4	3	1	
Quetiapine[b]	1	1		
Solifenacin	1	1		
Tapentadol[b]	1	1		
Tioptropium[b]	2	2		
Trospium[b]	1		1	

MMSE Mini-Mental State Examination, *SD* standard deviation

[a]Exclusion of one patient with reduced anticholinergic load and one patient with unchanged anticholinergic load after baseline assessment. There were no significant differences in any of the listed characteristics between the three groups ($p > 0.05$). For six participants (drop-outs), no baseline or follow-up data were assessed, therefore only their anticholinergic medication is shown in this table

[b]Weak anticholinergic drug

In addition to these established strategies, our approach includes several patient-centered monitoring parameters that are novel in the context of deprescribing studies of anticholinergic drugs. For instance, most earlier studies only calculated the patients' anticholinergic load according to their medication and independent of relevant patient characteristics such as age and (pre-existing) cognitive impairment (e.g., Gnjidic et al. [8]). In our study, we summarized patient comorbidities that can deteriorate under treatment with anticholinergic drugs and considered the patient's baseline condition by measuring the *intraindividual* change between baseline and follow-up (instead of comparing absolute values between groups of patients). Therefore, not only the team-based delivery of the intervention but also the inclusion of personalized information tailored to the individual patient may have contributed to the treating physicians' appreciation of the recommendation letter and their reliance on it in making further clinical decisions. In the qualitative feedback, they particularly valued the additional information on potential drug interactions and monitoring advices, which may explain the high adoption rate compared with a previous study that only suggested alternative drugs without any further information [33]. Moreover, previous qualitative research indicates that general practitioners and specialists may assign responsibility to each other for deprescribing anticholinergics, which could represent a barrier to reduce the anticholinergic load of affected patients [38]. Therefore, our approach of issuing only recommendations for indications in which specialists are not highly needed may also have contributed to the satisfactory uptake of the intervention in a rehabilitation setting.

In our exploratory study, patients whose anticholinergic load was successfully reduced showed significantly better scores on the Neuropsychological Assessments Battery memory test. This finding supports our approach of both carefully selecting assessments to measure cognitive performance and targeting a population without advanced cognitive impairment for anticholinergic deprescribing, and furthers the idea of tackling anticholinergic deprescribing

Table 3 Implemented interventions and feedback from the attending physicians on the suggested recommendations

Patient	Anticholinergic drug	Intervention	Chosen alternative drug	Reasons for not implementing change					Recommendation		Information text[a]		Preferred layout		
				Wrong indication	Patient refused change	Change not reasonable	GP unavailable for further information	Other (free text)	Helpful	Not helpful	Helpful	Not helpful	Flowchart	Table	Text
1	Dimenhydrinate	↓	None						x		x		x		
2	Dimenhydrinate	↓	Granisetron	x[b]						x	x		x		
3	Doxepin	↓	None						x		x			x	
4	Doxepin	↓	Mirtazapine						x		x			x	
5	Fesoterodine	↓	Trospium[c]						x		x		x		
6	Solifenacin	↓	Trospium[c]						x		x			x	
	Diazepam[c]	=						x[d]	x		x			x	
	Quetiapine[c]	=							x		x			x	
7	Amitriptyline	=			x					x	x			x	x
8	Doxepin	=			x				x		x		x		
9	Doxepin	=					x		x		x		x		

↓ indicates stopped, = indicates no change, *x* indicates appropriate, *GP* general practitioner

[a]The information text included notes, for example, on drug–drug interactions with the patient's co-medication and on how to monitor therapeutic alternatives

[b]The corresponding recommendation letter proposed alternatives for the indication vertigo/dizziness; however, it was later found that the patient suffered from nausea

[c]Weak anticholinergic co-medication

[d]Drug was not stopped and no alternative drug was chosen due to known benzodiazepine abuse/possible withdrawal symptoms

as a measure to prevent rather than to reverse dementia [39]. Yet, given the small sample size, our study offers a promising signal that needs to be confirmed in a well-powered, controlled, prospective trial.

4.1 Limitations

Despite all its advantages, the suggested approach still has some limitations that are worth mentioning. First, this feasibility study only included 20 patients in total (and not 20 patients in the intervention group as planned because of difficulties with recruiting patients), and hence it is rather difficult to extrapolate the results to a larger population. Second, we could not assess whether the recorded symptoms are *actually* related to anticholinergic drugs because we did not allocate patients randomly to treatment and control groups. Furthermore, other drugs and circumstances could induce similar symptom changes and therefore many of these symptoms are not specific to an anticholinergic mechanism [40–45]. However, the improvement of (anticholinergic adverse) symptoms after deprescribing the anticholinergic drug seems to support such a causal relation. Third, we did not assess whether the results are sustainable, a question that has to be addressed in a (long-term) confirmatory study to make its results meaningful. Ideally, a review of the patient's medication after a few months should assess whether (in our setting) the general practitioner agrees with the medication changes carried out in the rehabilitation unit and maintains the modification (sustainability of the intervention). Concurrently, the pharmacodynamics of these changes should also then be assessed. Fourth, our approach did not comprise specific shared decision-making strategies, and we may not have sufficiently included the individual patients and their preferences in the actual deprescribing process. The patients' refusal to stop their anticholinergic medication was the main reason for not implementing the respective recommendations in this trial. Providing patient engagement was identified as a key point to consider in anticholinergic deprescribing trials in a recent study of stakeholder views [36], and including patient engagement in the suggested approach might further increase the uptake of the deprescribing recommendations. Fifth, we did not issue recommendations in cases where the deprescribing of anticholinergic drugs should only be handled by a specialist. Including specialist recommendations in our approach might help assess the benefits of deprescribing anticholinergic drugs across the different indications and reach an even larger group of patients.

5 Conclusion

This work describes both an intervention and a set of outcome measures to reduce the anticholinergic drug load in older patients in a standardized way while considering individual circumstances and conditions (personalized intervention). In this first small feasibility study with 20 patients, treating physicians valued the recommendations and when the anticholinergic load decreased, an improvement in memory function was also seen.

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Declarations

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Conflicts of interest Tanja Wehran, Annette Eidam, David Czock, Jürgen Kopitz, Konstanze Plaschke, Margarete Mattern, Walter Emil Haefeli, Jürgen Martin Bauer, and Hanna Marita Seidling filled in an International Committee of Medical Journal Editors (ICMJE) statement and declare that there are no conflicts of interest with regard to this work.

Availability of data Data is not publicly available because this potential use case was not included in the patient's and physician's informed consent forms. Patients (as well as physicians) agreed to the use of their data in the context of the study but were not informed and did not agree upon their data being publicly available. However, data are available in anonymized form upon reasonable request at klinische.pharmakologie@med.uni-heidelberg.de.

Ethics approval and trial registration The study was approved by the responsible Ethics Committee of the Medical Faculty of Heidelberg University (protocol # S-116/2017), registered in the German Clinical Trials Register (#DRKS00012346), and was planned and conducted in accordance with the current version of the Declaration of Helsinki.

Consent to participate All participants (physicians and patients) provided written informed consent.

Consent for publication Not applicable.

Code availability Not applicable.

Author contributions The authors contributed to this paper as follows. Study design: All authors. Development of the anticholinergic drug list, algorithms, and test battery: TW, WEH, DC, MM, HMS, AE, JMB.

Development of recommendations: TW, DC, HS. Data collection: TW, AE. Laboratory measurements: JK, KP. Data analysis: TW, AE, WEH, JMB, HMS. Review of the manuscript: All authors.

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Authors and Affiliations

Tanja Wehran[1,2,3] · Annette Eidam[3] · David Czock[1] · Jürgen Kopitz[4] · Konstanze Plaschke[5] · Margarete Mattern[6] · Walter Emil Haefeli[1,2] · Jürgen Martin Bauer[3,7] · Hanna Marita Seidling[1,2]

✉ Hanna Marita Seidling
hanna.seidling@med.uni-heidelberg.de

1 Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg University, Medical Faculty Heidelberg / Heidelberg University Hospital, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

2 Cooperation Unit Clinical Pharmacy, Heidelberg University, Im Neuenheimer Feld 410, 69120 Heidelberg, Germany

3 Center for Geriatric Medicine, Heidelberg University Hospital, Agaplesion Bethanien Hospital, Rohrbacher Straße 149, 69126 Heidelberg, Germany

4 Institute of Pathology, Heidelberg University, Im Neuenheimer Feld 224, 69120 Heidelberg, Germany

5 Department of Anaesthesiology, Heidelberg University Hospital, Im Neuenheimer Feld 420, 69120 Heidelberg, Germany

6 Department of General Psychiatry, Heidelberg University Hospital, Voßstraße 4, 69115 Heidelberg, Germany

7 Network Aging Research, Heidelberg University, Bergheimer Straße 20, 69115 Heidelberg, Germany