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ANTICHOLINERGIC BURDEN AND MOST COMMON ANTICHOLINERGIC-ACTING MEDICINES IN OLDER GENERAL PRACTICE PATIENTS

ANTIHOLINERGIČNO BREME IN NAJPOGOSTEJŠA ANTIHOLINERGIČNA ZDRAVILA PRI STAREJŠIH OBISKOVALCIH AMBULANTE DRUŽINSKE MEDICINE

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ABSTRACT

Introduction: Anticholinergic burden in older adults has been correlated with cognitive decline, delirium, dizziness and confusion, falls and hospitalisations. Nevertheless, anticholinergic-acting medications remain commonly prescribed in up to a third of older adults in primary care population. Our aim was to study the anticholinergic burden in older adults in Slovenian ambulatory setting and explore the most commonly involved medications which could be avoided by the physicians.

Methods: A cross-sectional study was conducted in 30 general practices in Slovenia as part of a larger trial. Data on prescribed medications were collected for randomly chosen adults of over 65 years of age visiting general practice, who were taking at least one regularly prescribed medication. Anticholinergic burden was calculated using Duran's scale and Drug Burden Index.

Results: Altogether, 622 patients were included, 356 (57.2%) female, average age of 77.2 (±6.2), with an average of 5.6 medications. At least one anticholinergic medication was present in 78 (12.5 %) patients. More than half (N=41, 52.6%) of anticholinergic prescriptions were psychotropic medications. Most common individual medications were diazepam (N=10, 1.6%), quetiapine (N=9, 1.4%) and ranitidine (N=8, 1.3%).

Conclusions: Though the prevalence of anticholinergic medications was low compared to international research, the most commonly registered anticholinergic prescriptions were medications that should be avoided according to guidelines of elderly prescriptions. It would be probably clinically feasible to further decrease the anticholinergic burden of older adults in Slovenian primary care setting by avoiding or replacing these medications with safer alternatives.

Keywords:
anticholinergic burden, aged, general practice, inappropriate prescribing

IZVLEČEK

Uvod: *Večje antiholinergično breme pri starejših odraslih je povezano s kognitivnim upadom, delirijem, zmedenostjo, padci in hospitalizacijami. Kljub temu ima predpisane antiholinergike skoraj tretjina starostnikov na primarnem nivoju. Želeli smo raziskati antiholinergično breme pri starostnikih v ambulantah družinske medicine v Sloveniji in najpogostejša zdravila z antiholinergičnim delovanjem, ki bi se jim zdravniki pri predpisovanju lahko izognili.*

Metode: *V presečni raziskavi smo v 30 ambulantah družinske medicine zbrali podatke o predpisanih zdravilih za naključno izbrane starostnike nad 65 let, ki so na dan raziskave zaradi kateregakoli razloga obiskali ambulanto in ki so kot redno terapijo jemali vsaj eno zdravilo. Antiholinergično breme smo izračunali s pomočjo Duranove lestvice in lestvice Drug Burden Index.*

Rezultati: *V raziskavo je bilo vključenih skupno 622 bolnikov, od tega 356 (57,2 %) žensk. Povprečna starost je bila 77,2 (± 6,2) leta, bolniki pa so jemali povprečno 5,6 zdravila. Vsaj eno antiholinergično zdravilo je jemalo 78 (12,5 %) bolnikov. Več kot polovica (N = 41, 52,6 %) vseh predpisnih zdravil z antiholinergičnimi učinki je bila psihotropnih. Med posameznimi zdravili so bili najpogosteje predpisani diazepam (N = 10, 1,6 %), kvetiapin (N = 9, 1,4 %) in ranitidin (N = 8, 1,3 %).*

Zaključki: *Prevalenca predpisovanja antiholinergičnih zdravil je bila nizka v primerjavi z mednarodnimi raziskavami, vendar pa so bila antiholinergična zdravila med najpogosteje predpisanimi zdravili, ki jih smernice o predpisovanju zdravil pri starostnikih odsvetujejo. Verjetno bi bilo mogoče še dodatno zmanjšati antiholinergično breme pri starostnikih na primarnem nivoju v Sloveniji s tem, da bi se tem zdravilom izognili ali jih zamenjali z varnejšimi alternativami.*

Ključne besede:
antiholinergično breme, starostniki, ambulante družinske medicine, neprimerno predpisovanje zdravil

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1 INTRODUCTION

Many older adults suffer from multiple chronic diseases and are commonly prescribed with several medicines for multiple different conditions. This may lead to prescribing of multiple medicines with an anticholinergic burden, both when anticholinergics are prescribed for their anticholinergic effect, as well as for medicines which can cause anticholinergic side effects due to anticholinergic properties but are not strictly classified as anticholinergics (1).

Commonly reported peripheral side effects of anticholinergic medicines include dry mouth, dry eyes, constipation, urinary retention, blurred vision and increased heart rate, while central effects range from dizziness, sedation, confusion and delirium (1-3). Multiple studies reported the association between anticholinergic effect on cognitive function (1, 3-5), increased risk of delirium (3), dizziness and confusion (6), but also falls (1, 3, 6), hospitalisations (1, 7), and physical function (1, 5, 8), especially in vulnerable populations such as old (1) or patients with Parkinson disease (9).

Older adults are more at risk for anticholinergic side effects than young people because of increased permeability of the blood-brain barrier, decreased drug metabolism and elimination and age-related deficit in central cholinergic transmission (2). Several instruments have been developed and validated to determine the anticholinergic burden, among others are Anticholinergic Risk Scale (ARS) (6), Anticholinergic Drug Scale (ADS) (10), Anticholinergic Cognitive Burden Scale (ACB) (11) and Drug Burden Index (DBI) (12). However, there is a poor agreement between different anticholinergic scales in terms of medicines included and the results are, therefore, difficult to compare (13, 14). Several studies, using different instruments, found the prevalence of exposure to anticholinergic medicines between 9% to 55.9% (5, 14, 15). A comparison of scales in several studies showed that instruments differed in sensitivity and specificity because of their differences in identification criteria for anticholinergics. Despite this, most scores were associated with adverse clinical outcomes of interest (5, 14). The strongest predictor was DBI – Anticholinergic Component (ACH) Score (14).

Recently, Duran et al., used the existing anticholinergic risk scales to develop a list of anticholinergic medicines that occur in most scales and have confirmed anticholinergic properties as an attempt to standardise measurement of anticholinergic drug burden (16).

In most European countries, general practitioners prescribe the majority of medicines patients receive, and have a comprehensive overview of medical therapy of their patients, which contributes to a high-quality care, measured by process-quality indicators (17, 18). However, there have been few studies about the quality of prescription in older adults, in general practice in Slovenia.

Our aim was to explore anticholinergic burden in older general practice patients in Slovenia and determine the most commonly used medicines and prescribing patterns contributing towards anticholinergic burden.

2 METHODS

2.1 Design and Setting

A cross-sectional study was conducted in 30 Slovenian general practices spread throughout the country. All statistical regions except Pomurje were represented. The study was a sub-part of the main trial that has been described elsewhere (19).

2.2 Study Population

Study population consisted of 622 older general practice patients. Participating physicians selected one working day in advance and recruited all eligible patients who visited their practice on that day. If they recruited less than 20 patients, they could select another day until they recruited 20 to 30 patients. The eligible patients who were over 65 years of age, were receiving at least one prescribed medicine in regular therapy and were cognitively able to answer questionnaires and give informed consent to the study. Patients with life expectancy of less than 1 year (in terminal stages of diseases) were excluded. One of the patient withdrew consent after initially participating in the study and was not included in the analysis.

2.3 Data Collection

Patients, who fulfilled inclusion criteria and signed informed consent, filled out a questionnaire on demographic and other health data. For the purposes of the main trial, a computer application was developed into which participating physicians entered enrolled patients' medicines.

As a basis for measuring anticholinergic burden, we used the list of anticholinergic medicines created by Duran et al., which is a uniform list of anticholinergic medicines for which either agreement on anticholinergic properties exists, or a reputed reference source confirms the anticholinergic properties. The list consists of 100 medicines which are further divided into low-potency anticholinergics and high-potency anticholinergics and assigned score 1 (low-potency) or 2 (high potency). Duran's scale was developed from seven previously-used instruments as an attempt to standardise the list of anticholinergic medicines, in response to poor agreement between different published scales (16). Further, we calculated DBI-ACH score based on medicines contained

in Duran's scale. DBI-ACH measures the exposure to anticholinergic medicines and considers the daily dosage of medicine (12).

The application checked entered medicines against medicines on Duran's list of anticholinergic scale and calculated the burden score for every patient by adding together the assigned scores for each medicine from the list. Patients with a score of at least 2 were considered to have a high anticholinergic burden.

Basic patient data was described by standard descriptive methods. All data were entered into Microsoft Excel 2007 and transferred and analysed with IBM SPSS Version 24.0 (SPSS Inc., Chicago, IL, USA).

3 RESULTS

Data was collected for 622 patients from 30 different general practices from all regions in Slovenia, while 15 patients (2.4%) refused to participate in the study. Characteristics of the population are presented in Table 1.

Table 1. Descriptive statistics.

Characteristic	
Gender N (%)	
• Male	266 (42.8%)
• Female	356 (57.2%)
Average age in years (±SD)	77.2 (±6.2)
• Range (years)	65-101
Number of prescribed medicines N (±SD)	5.6 (±2.9)
Presence of polypharmacy (5 or more medicines)	374 (60.1%)

At least one medicine with anticholinergic properties was present in 78 patients (12.5%). Anticholinergic burden by score is presented in Table 2.

Table 2. Anticholinergic burden in patients with anticholinergic medicines (N=78).

Anticholinergic burden (score)	N (%) of patients with anticholinergic medicines
1	54 (69.2%)
2	19 (24.4%)
3	4 (5.1%)
4	1 (1.3%)

DBI was calculated for all patients receiving anticholinergic medicines. 10 patients had DBI≥1, while the rest had DBI between 0.11 and 0.94. Patients with DBI<1 had an anticholinergic burden score of 1 or 2, while patients with DBI≥1 had an anticholinergic burden score between 2 to 4. The highest DBI score was 1.83, in the patient with anticholinergic burden score of 4.

Of the 100 medicines on the list, only 24 medicines occurred in our population. They are shown in Table 3.

Table 3. List of anticholinergic medicines in patients with an anticholinergic burden.

Medicine (ATC code)	N (%) of patients with anticholinergic burden N=78	% of all enrolled patients N=622	Anticholinergic burden
Psychotropic medicines (N)	41 (52.6%)	6.6%	
Diazepam (N05BA01)	10 (12.8%)	1.6%	1
Quetiapine (N05AH04)	9 (11.5%)	1.4%	1
Paroxetine (N06AB05)	7 (9.0%)	1.1%	1
Amitriptilyne (N06AA09)	6 (7.7%)	1.0%	2
Mirtazapine (N06AX11)	4 (5.1%)	0.6%	1
Citalopram (N06AB04)	4 (5.1%)	0.6%	1
Fentanyl (N02AB03)	2 (2.6%)	0.3%	1
Olanzapine (N05AH03)	2 (2.6%)	0.3%	1
Carbamazepine (N03AF01)	2 (2.6%)	0.3%	1
Fluoxetine (N06AB03)	2 (2.6%)	0.3%	1
Risperidone (N05AX08)	2 (2.6%)	0.3%	1
Promazine (N05AA03)	1 (1.3%)	0.2%	1
Clozapine (N05AH02)	1 (1.3%)	0.2%	2
Lithim (N05AN01)	1 (1.3%)	0.2%	1
Trazodone (N06AX05)	1 (1.3%)	0.2%	1
Alimentary tract and metabolism medicines (A)	11 (14.1%)	1.8%	
Ranitidine (A02BA02)	8 (10.3%)	1.3%	1
Domperidone (A03FA03)	3 (3.8%)	0.5%	1
Respiratory system and allergy medicines (R)	11 (14.1%)	1.8%	
Loratadine (R06AX13)	4 (5.1%)	0.6%	1
Cetirizine (R06AE07)	3 (3.8%)	0.5%	1
Fexofenadine (R06AX26)	2 (2.6%)	0.3%	1
Theophylline (R03DA04)	2 (2.6%)	0.3%	1
Musculo-skeletal system medicines (M)	6 (7.7%)	1.0%	
Tizanidine (M03BX02)	6 (7.7.%)	1.0%	2
Genitourinary system medicines (G)	5 (6.4%)	0.8%	
Darifenacin (G04BD10)	3 (3.8%)	0.5%	2
Tolterodine (G04BD07)	2 (2.6%)	0.3%	2
Cardiovascular system medicines (C)	1 (1.3%)	0.2%	
Disopyramide (C01BA03)	1 (1.3%)	0.2%	1

The patient who scored 4 (DBI 1.83) was taking mirtazapine (score 1), darifenacin (score 2), and promazine (score 1) concurrently. Of ATC categories, most commonly prescribed medicines were psychotropic medicines, representing 12 medicines from 21 occurring in our population, and occurring in more than half of the patients that had at least one anticholinergic-acting medicine prescribed.

We also closely examined the prescription of most common medicines on our list. Prescribing doses and regimens are shown in Table 4.

Table 4. Dosing regimen for some of the most common anticholinergic medicines.

Medicine	Dose and frequency	N of cases
Diazepam	2mg daily	2
	5 mg daily	2
	5mg once to three times weekly	5
	5 mg twice monthly	1
Quetiapine	25 mg once daily	7
	100 mg once daily	1
	400 mg once daily	1
Ranitidine	150 mg once daily	8
	300 mg once daily	1
Amitriptyline	25 mg once daily	4
	25 mg two to three times daily	2

4 DISCUSSION

In our study, the prevalence of elderly general practice visitors taking anticholinergic medicines was low (12.5%). Most patients were taking only one medicine with low-potency anticholinergic effect. The most common were psychotropic medicines. Study population included patients from all parts of Slovenia apart from Pomurje and could, therefore, represent Slovenian population of older general practice visitors with chronic diseases.

A study in a cohort of community-dwelling older men showed the prevalence of exposure to anticholinergic medicine use between 13% and 39% using different instruments, while Salahudeen et al., found the prevalence of 22.8% to 55.9% depending on the scale which was used (14, 15), and Mayer et al., found prevalence of 9% to 31% in a cohort of general practice patients older than 50 years (5). Given these findings, the prevalence of anticholinergic medicines in our study was comparatively low. One of the reasons may be the instrument we used, which has been shown to have relatively high specificity in comparison to other scales (5). In addition, the elderly people participating in our study may have received different medicines, especially psychotropic ones, in comparison with a nursing home or hospitalised population.

Presence of anticholinergic medicines in elderly people is considered potentially inappropriate and may, therefore, be considered as one of the indicators of quality prescription. Additionally, one of the indicators could be the proportion of patients with a higher anticholinergic burden, which in our study was below 4% of all observed patients for anticholinergic burden score, and even lower when the daily dosage of medicines was considered (only 1.6% patients had DBI 1 or higher). Comparing these numbers with other research is unfortunately difficult because of the poor agreement of various anticholinergic scales among themselves, which is about how great a burden individual medicine presents. Currently, there is no standard determining of still acceptable level of presence of anticholinergic medicines, such as in the case of prescribing of antibiotics (20), which makes it hard to judge how the prevalence of anticholinergics relates to the quality of care.

Despite the low prevalence, it is worrying that not only are the psychotropic medicines still the most common anticholinergic medicines present in the study population, but that the most commonly prescribed medicines are medicines that are inadvisable in elderly people according to several different sets of prescribing criteria (21, 22). This is especially important because multimorbid elderly people, who are already exposed to polypharmacy, are more likely to suffer from psychiatric disorders, like depression, anxiety or sleep disorders (23-25). Diazepam, a long-acting benzodiazepine, was present in 1.6% of patients in our study. In majority of the cases, the physicians prescribed it to be taken several times per week, not every day. However, due to a longer half-time in elderly people, this may not suffice to avoid adverse effects since the effects can linger to the next day even when taken a night before (26). In the second place was quetiapine, which raises concerns because of its common off-label use (27). It is often used for the treatment of insomnia in elderly, though evidence for such use is scarce (28) and there are concerns about adverse effects (29). Indeed, in all but two cases in our study, quetiapine was prescribed in a low dose of 25mg daily, which likely indicates just such a use. Similar concerns have been raised about other atypical antipsychotics on our list (30). Both quetiapine and risperidone are among the most commonly-used antipsychotics in Slovenia (31). In the third place, present in 1.1% of general practice patients, was paroxetine, which could be replaced by another SSRI inhibitor with weaker anticholinergic properties. Similarly, amitriptyline is not only inadvisable in elderly people, but was, in our study, also used in low doses probably ineffective for treatment of depression. Interestingly, all but one prescriptions of amitriptyline in our study were prescribed by just one physician.

Apart from psychotropic medicines, most commonly occurring in our study were medicines from ATC group A, chiefly ranitidine, and antihistaminic medicines from ATC group R. It is likely ranitidine could be replaced by a proton-pump inhibiting medicine either continuously or even as needed (32). In a similar vein, there are

antihistaminic medicines available that are not listed as having anticholinergic properties and could be exchanged for antihistaminic present on our list, thus decreasing the calculated anticholinergic burden.

Finally, less than 1% of our patients regularly received antimuscarinic medicine from ATC group G, which are commonly used to treat symptoms of urinary incontinence. Evidence does not encourage the use of these medicines in elderly, as the benefit is limited and there is concern about the side effects of medicines (33). In an Australian study, bladder instability was the most common problem that led to the prescription of a high potency anticholinergic medicine (34). In Slovenia, insurance rules demand that the first prescription of these medicines comes from urologists or gynaecologists, which may have contributed to decreased availability and therefore, lower prescription of these medicines (35).

It is likely that at least some of the anticholinergic medicines were prescribed by clinical specialists attending to the patients, for example, most atypical antipsychotics and bladder antimuscarinic medicines. In that case, general practitioners might be unwilling to change the prescription against a clinical specialist recommendation despite being aware of the possible anticholinergic side effects. However, in context of patient-oriented care, general practitioner should together with patient, weigh risks and benefits of medicines contributing towards anticholinergic burden and decide on continuing or discontinuing recommended medicines.

Altogether, we estimate that the majority of implicated medicines could probably be replaced by medicines with similar effect or from the same or similar class that is not present on Duran's anticholinergic list. This means that despite the low prevalence of anticholinergic medicines on our population, quality of prescribing in our cohort of general practice patients in regard to medicines with anticholinergic properties could be improved. However, as a caution, though anticholinergic medicines have been shown to correlate with a number of poor outcomes in elderly (falls, delirium, cognitive impairment, physical function, constipation, confusion and so on), the evidence for benefit in discontinuing anticholinergics is, as yet, scarce (36). In practice, as always, in addition to awareness of an anticholinergic burden of a particular patient's prescriptions and possibility of anticholinergic side effects, all physicians caring for older patients should use clinical judgment and trade-off of risks and benefits to guide prescribing and deprescribing in older adults.

There are some limitations to our study. We used Duran's scale, which does not consider the doses of anticholinergic medicines. The advantage of Duran's scale is the precise specification of included medicines, including ATC code. Because of this standardisation, it has been used several times since its development (5, 37). The scale has been found to have a high specificity and to have a good correlation with a cognitive and functional decline and falls in observed population (5). Of the 100 medicines on Duran's list, however, 37 are not registered in Slovenia and could not be prescribed (33), which may have contributed to the low result. We excluded patients with severe dementia who were unable to answer the questionnaire and terminally ill patients with life expectancy of less than 1 year. Both might be the reason for the underestimation of anticholinergic burden since anticholinergic medicines are often used in these conditions. We only included older adults with at least one regularly taken medicine, so perfectly healthy elderly people who might lead to a decrease of prevalence of an anticholinergic burden were not in the study population. We did not consider the over-the-counter medicines that the patients could buy themselves; however, few medicines with anticholinergic properties are available over-the-counter in Slovenia, and as the national insurance covers medicines for a great majority of patients, the proportion of medicines bought over the counter that could influence our results is likely very small.

5 CONCLUSION

Although prevalence of anticholinergic medicines in our population was low, the examination of individual medicines indicates that it would be possible to decrease it further. The majority of anticholinergic burden was contributed by psychotropic medicines, several of which are inadvisable in elderly people and could be replaced by other medicines. Most common and likely to be possible medicines to avoid or replace by other medicines were diazepam, quetiapine, ranitidine, paroxetine and amitriptyline. General practitioners should avoid prescribing these medicines, particularly when a patient is already taking another medicine with possible anticholinergic effect and should be aware of the possibility of anticholinergic side effects in older people taking anticholinergic medicines when these cannot be avoided.

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CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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ETHICAL APPROVAL

The study was reviewed and approved by Slovenian National Ethics Committee.

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