

Temporal trends over two decades in the use of anticholinergic drugs among older community-dwelling people in Helsinki, Finland

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Tausta

Tietoisuus lääkkeiden antikolinergisistä haittavaikutuksista on lisääntynyt viimeisten vuosikymmenien aikana. Tunnettuja sivuvaikutuksia ovat suun ja silmien kuivuminen, virtsaumpi, ummetus, fyysisen ja kognitiivisen toimintakyvyn heikentyminen sekä kaatumisriskin lisääntyminen. Näitä haittoja aiheuttavat muun muassa monet psykoosilääkkeet, masennuslääkkeet ja opioidit. Haittavaikutukset koskevat erityisesti ikääntyneitä, yli 65-vuotiaita, henkilöitä. Samaan aikaan markkinoille on tullut uusia lääkkeitä, jotka ovat korvanneet vanhoja ja joista monella kyseisiä haittoja on vähemmän. Useiden lääkkeiden kohdalla niiden antikolinergisiä sivuvaikutuksia ei kuitenkaan varmuudella tiedetä. Muutoksista ja tunnetuista haitoista huolimatta tutkimustieto antikolinergisten lääkkeiden käytön muutoksista ja käytetyistä lääkkeistä erityisesti kotona asuvilla ikääntyneillä on vähäistä, vaikka tämä ikäryhmä kasvaa kiihtyvällä vauhdilla. Tämän tutkimuksen

tavoitteena oli selvittää Helsingissä kotona asuvien 75-95-vuotiaiden antikolinergisten lääkkeiden käyttöä ja muutosta vuosina 1999-2019 sekä käytettyjä lääkeluokkia ja niiden muutoksia.

Menetelmät

Tutkimus on osa Helsingin Vanhustutkimusta ja se sisälsi satunnaisotannalla valittuja 75-vuotiaita ja vanhempia kotona asuvia helsinkiläisiä. Vuosina 1999, 2009 ja 2019 tutkittaville lähetettiin postitse kirjekysely, jossa selvitettiin heidän taustatietoja, toimintakykyä, terveydentilaa ja käyttämiään lääkkeitä. Kyselyiden tulokset vietiin sähköiseen tietojärjestelmään ja lääkkeet ryhmiteltiin niiden ATC-koodien mukaan. Lääkkeiden antikolinerginen luokittelu tehtiin Duranin listan mukaan, joka uudehkona listana soveltui hyvin aineistoomme. Duranin lista ottaa huomioon myös lääkkeiden antikolinergisen vahvuuden ja ilmoittaa vahvuuksien summana tutkittavan antikolinergisen kuorman. Antikolinergisten lääkkeiden käytön yleisyys ja kuorma sekä käytetyt lääkeluokat eri vuosina määritettiin tilastollisin menetelmin. Tämän lisäksi käytön yleisyys ja kuorma tutkittiin erikseen 75-80-vuotiaiden ja 85-vuotiaiden ja sitä vanhempien ikäryhmissä.

Tulokset

Vuosina 1999-2019 sekä antikolinergisten lääkkeiden käytön yleisyys että kuorma vähenivät. 75-80-vuotiaiden ja 85-vuotiaiden ja vanhempien ikäryhmien välillä ei ollut merkitsevää eroa. Käytetyistä lääkeluokista vanhojen psykoosilääkkeiden, bentsodiatsepiinien, hypnoottien, virtsan karkailuun käytettävien lääkkeiden sekä astman ja keuhkohtaumataudin hoitoon käytettyjen lääkkeiden käyttö väheni, kun taas uusien psykoosilääkkeiden, masennuslääkkeiden, vahvojen opioidien ja antihistamiinien käyttö lisääntyi. Erityisesti lisääntyi masennuslääkkeeksi luokiteltavan mirtatsapiinin käyttö.

Pohdinta

Antikolinergisten lääkkeiden käytön ja kuorman väheneminen ovat tervetulleita muutoksia. Nämä muutokset ovat linjassa kansainvälisen tutkimustiedon kanssa, vaikka tutkimustieto onkin vähäistä. Käytetyissä lääkeluokissa havaittiin odotetusti vanhojen psykoosilääkkeiden korvautumista uudemmilla sekä vanhojen virtsan karkailuun käytettyjen lääkkeiden käytön vähenemistä. Näiden lisäksi havaittiin mirtatsapiinin voimakkaasti lisääntynyt käyttö bentsodiatsepiinien ja hypnoottien käytön laskiessa. Viime vuosikymmeninä lääkäreitä on valistettu viimeksi mainittujen lääkkeiden sedatiivisista haittavaikutuksista, ja mirtatsapiinin voimakkaasti lisääntynyt käyttö voi johtua sen lisääntyneestä käytöstä unilääkkeenä mahdollisesti näitä lääkkeitä korvaten. Uutta tutkimustietoa ja lääkäreiden koulutusta tarvitaan jatkuvasti mirtatsapiinin ja muiden uusien lääkkeiden käytöstä ja todellisista haittavaikutuksista erityisesti ikääntyneiden keskuudessa. Näin voidaan vähentää

lääkkeistä aiheutuvia haittavaikutuksia tässä voimakkaasti kasvavassa ja haavoittuvassa kansanosassa.

Avainsanat

Drugs with anticholinergic properties, Duran's list, community-dwelling older people, temporal trends



Temporal Trends Over Two Decades in the Use of Anticholinergic Drugs Among Older Community-Dwelling People in Helsinki, Finland

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Abstract

Background Knowledge of the adverse effects of drugs with anticholinergic properties (DAPs) has increased in recent decades. However, research on the temporal trends of the clinical use of DAPs is still sparse.

Objectives The aim of this study was to investigate the temporal trends of DAP use over two decades in the older community-dwelling population and to explore the medication classes contributing to the use of DAPs.

Methods The study involved random samples of ≥ 75 -year-old community-dwelling Helsinki citizens in 1999, 2009, and 2019 from the Helsinki Ageing Study. A postal questionnaire inquired about their health, functioning, and medications. The medications were categorized as DAPs according to Duran's list. In addition, we grouped DAPs into various medication groups.

Results The prevalence and burden of DAPs on Duran's list showed a decreasing trend over the years. In 1999 the prevalence was 20% and the burden 0.35, in 2009 they were 22% and 0.35, respectively, and in 2019 they were 16% and 0.23, respectively. There were no differences in how the 75- and 80-year-olds used DAPs compared with those aged 85 years and older. The proportion of typical antipsychotics, benzodiazepines, hypnotics, urinary antispasmodics, and asthma/chronic obstructive pulmonary disease medications decreased, whereas the proportion of atypical antipsychotics, antidepressants, strong opioids, and antihistamines increased. In particular the use of mirtazapine increased—to 3.9% in 2019. In 2019 the three most prevalent groups of DAPs were antidepressants (7.4%), opioids (2.7%), and antihistamines (2.4%).

Conclusions The decrease in the use of DAPs on Duran's list is a welcome change. Although the use of old, strong DAPs has decreased, new DAPs have simultaneously emerged. Physicians need continuous education in prescribing DAPs and more recent information on the use and effects of DAPs is needed in order to decrease their exposure among the rapidly growing older population.

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Key Points

The prevalence and burden of drugs with anticholinergic properties (DAPs) according to Duran's list decreased among community-dwelling older people from 1999 to 2019.

The typical antipsychotics seem to be replaced by atypical antipsychotics.

Benzodiazepines and hypnotics seem to be replaced by mirtazapine.

1 Introduction

International criteria have warned about the use of drugs with anticholinergic properties (DAPs) especially among older people [1]. Adverse effects of these drugs include dry mouth, dry eyes, constipation, urinary retention, poor physical function, cognitive decline, dizziness and falls [2–5]. Older people in particular are vulnerable to these side effects. Despite these well-known adverse effects and the availability of newer and safer alternative drugs, DAPs are still commonly used. In studies, their prevalence has varied greatly depending on the study population, criteria used, and context [6–9].

Evidence of the adverse effects of DAPs has increased over the decades along with expanding research into potentially inappropriate medications (PIMs) [1]. Therefore, the use of DAPs should have decreased in clinical practice over the years among community-dwelling older people if the prescribing physicians followed up the latest evidence [1]. In a register-based French study using the extended Duran's list [10] the prevalence of DAPs decreased from 45.6% in 2006 to 33.2% in 2015 [11]. A similar trend applied for an American study that included 35 potentially high-risk DAPs and prescription data for physician visits [12]. In that study the prevalence rate decreased from 6.1% in 2006–2007 to 4.7% in 2014–2015. However, the prevalence of DAPs increased from 20.7% in 1995 to 23.7% in 2010 in a Scottish study [9] using the modified Anticholinergic Risk Scale (ARS) [2]. The study data covered all prescriptions dispensed by community pharmacists [9]. Furthermore, the use of DAPs according to the Anticholinergic Cognitive Burden scale [13] similarly increased from 49.6% in 1990–1993 to 64.3% in 2008–2011 in an English study [14]. The study data were retrieved from prescription data of physician visits [14]. All studies involved 65-year-old and older mainly

community-dwelling people. A recent Finnish study on long-term care facilities suggested that according to the ARS [2] the users of DAPs increased in assisted living facilities over a 10-year period (41% in 2007 and 54% in 2017), whereas in nursing homes the use remained stable (52% in 2003 and 2017) [15]. Thus, the prevalence rates vary greatly depending on the study population, the criteria used, and how the medication data are collected.

Thus, there are still relatively few studies exploring temporal trends in the use of DAPs among community-dwelling older people. Furthermore, many of these studies examine two time points and do not cover recent years. The aim of this study was to investigate the temporal trends over two decades in the use of anticholinergic medication, the prevalence of their use as well as their burden, among older community-dwelling people in Helsinki, Finland, by comparing the cohorts of 1999, 2009, and 2019. Another objective was to find out which medication classes contribute to the use of DAPs and how this has developed over the years.

2 Methods

This study is part of the Helsinki Ageing Study, which is a longitudinal cohort study investigating the health and well-being of the community-dwelling older population in Helsinki [16]. Since 1989 the postal questionnaires have been repeated every 10 years to different random samples of older people aged 75, 80, 85, 90, and 95 years living in Helsinki. The current study examines questionnaire data from the 1999, 2009, and 2019 samples, which we call cohorts. Random samples were retrieved from the Finnish Population Information System and the questionnaire was resent to those who did not answer the first time. The approximate response rates were based on estimates of how many survey recipients were living in permanent institutional care, were deceased, or had moved away between the retrieval of the random sample data and the mailing of the questionnaires. We included only community-living older adults and excluded all those living in permanent institutional care.

The Helsinki Ageing Study received ethical permission from Helsinki University Hospital. The study was conducted according to the guidelines of the Declaration of Helsinki.

The postal questionnaire included the same questions at each time point. The items included demographic information, health and diseases, medications, and ability to function. Demographic variables such as age and sex were retrieved from the population register. Respondents were asked about their marital status (married or cohabiting/single/divorced or separated/widowed) and in the statistical analysis were categorized as widowed and others. Education

was inquired about and was divided into two categories: less than 8 years or 8 years or more.

Respondents were also asked about their diseases. They were asked about 19 common chronic diseases or conditions (e.g., having diabetes, arthrosis, Alzheimer's disease) and in the 20th question they could add all the other diseases that were not specifically asked. This was used to construct participants' Charlson comorbidity index, which takes into account the number and seriousness of diseases [17]. Respondents were also asked about how they felt about their health condition, and in the analysis self-reported health was categorized as good (response options healthy or quite healthy) or poor (quite unhealthy, unhealthy). In addition, participants were asked whether they needed daily help from another person (yes/no). The responders answered the questionnaire themselves or with the help of their proxy, which was also inquired about in the questionnaire.

The respondents gave a list of their regular prescribed drugs. We carried out some random verifications on the lists with medical records and found that the lists given by the patients matched. We grouped the medications as DAPs according to Duran's list [10]. Duran's list was developed by creating a uniform list of clinically relevant anticholinergic drugs according to a systematic review of previous anticholinergic risk scales. As a result, it contains 100 DAPs that are ranked by their anticholinergic potency as either low (score 1) or high (score 2). The final score is the sum of these potencies, which also defines the variable anticholinergic burden [10]. The DAP medications were coded according to the Anatomical Therapeutic Chemical (ATC) classification system [18].

In the analysis, we studied the prevalence of all DAPs as well as the mean anticholinergic burden in various cohorts. The cohorts were also explored according to age groups. The groups were 75- and 80-year-olds and 85 years and older. The prevalence and the burden were studied separately in these age groups in various cohorts. The proportions of various drug classes of DAPs among all participants according to the ATC codes were calculated and compared between the cohorts. In addition, we calculated the proportions of various drug classes of DAPs among users of DAPs in each year cohort.

2.1 Statistical Methods

The descriptive statistics were presented as means with standard deviations or as counts with percentages. The linearity across the three cohorts was evaluated using the Cochran–Armitage test (chi-square test for trend), logistic models, and analysis of variance with an appropriate contrast (orthogonal).

The relationships between age and cohorts with regard to users of Duran's list and burden were evaluated using

generalized linear models (e.g., analysis of covariance and logistic models) with an appropriate distribution and link function. In these analyses we have further divided the age groups into 75- and 80-year-olds as well as 85 years and older. Models were adjusted for sex and Charlson comorbidity index. In the case of violation of the assumptions (e.g., non-normality) for continuous variables, a bootstrap-type method or Monte Carlo *p*-values (small number of observations) for categorical variables were used. Normal distributions were evaluated graphically and with the Shapiro-Wilk *W* test. In all analyses *p* values < 0.05 were considered significant. Stata 17.0 (StataCorp LP, College Station, TX, USA) was used for the analysis.

3 Results

For the analysis there were 2,598 participants in 1999, 1,637 in 2009, and 1,810 in 2019, and the approximate response rates were 80%, 73%, and 74%, respectively. The proportion of the oldest-olds increased over time. The proportion of women, those widowed, and those with low education decreased over time. The Charlson comorbidity index decreased and the proportion of those with good self-rated health increased. However, the number of regularly used medications increased (mean 3.2 in 1999, 4.8 in 2009, and 4.9 in 2019) as did the proportion of those using five medications or more (29% in 1999, 47% in 2009, and 49% in 2019). The mean number of psychotropics increased in the later cohorts over time. The prevalence of those using anticholinergic medication according to Duran's list decreased over the years as did the anticholinergic burden. In 1999 the prevalence was 20% and the burden 0.35, in 2009 they were 22% and 0.35 (respectively), and in 2019 they were 16% and 0.23 (respectively). The results of the participants' basic demographics and medications are shown in Table 1.

When the cohorts were further divided according to their age into 75- and 80-year-olds and 85 years and older, there was a significant decrease over the years in the prevalence of those using anticholinergic medication in the whole cohorts for 1999, 2009, and 2019 ($p = 0.005$) but no difference between the age groups ($p = 0.24$), and there was no interaction ($p = 0.66$) (adjusted for sex and Charlson comorbidity index) (Fig. 1, left-hand side). The same applies to anticholinergic burden according to Duran's list. In both age groups, there was a significant decrease between the whole cohorts in the burden of DAPs ($p < 0.001$) but no difference between the age groups ($p = 0.82$), and there was no interaction ($p = 0.73$) (adjusted for sex and Charlson comorbidity index) (Fig. 1, right-hand side).

Table 1 Characteristics of the participants in the cohorts by year

	1999	2009	2019	<i>p</i> for linearity
Participants	2594	1583	1653	
Demographics, <i>n</i> (%)				
Women	1847 (71)	1089 (69)	1065 (64)	< 0.001
Age, years				< 0.001
75	734 (28)	386 (24)	411 (25)	
80	714 (28)	378 (24)	401 (24)	
85	643 (25)	349 (22)	366 (22)	
90 and 95	503 (19)	470 (30)	475 (29)	
Widowed	1175 (47)	658 (42)	580 (35)	< 0.001
Education < 8 years	1335 (54)	578 (37)	394 (24)	< 0.001
Health and functioning				
Charlson, ^a mean (SD)	2.1 (1.9)	2.0 (1.8)	1.7 (1.6)	< 0.001
Self-rated health good, <i>n</i> (%)	1896 (77)	1150 (74)	1329 (82)	< 0.001
Needs daily help, <i>n</i> (%)	434 (17)	340 (22)	285 (17)	0.51
Medications				
Regularly used drugs, mean (SD)	3.2 (2.8)	4.8 (3.6)	4.9 (3.6)	< 0.001
Use of ≥5 medications, <i>n</i> (%)	764 (29)	747 (47)	802 (49)	< 0.001
Psychotropics, mean (SD)	0.3 (0.7)	0.5 (0.8)	0.4 (0.8)	< 0.001
Users of DAPs according to Duran's list, <i>n</i> (%)	519 (20)	349 (22)	266 (16)	< 0.001
Burden of DAPs according to Duran's list among the cohort, mean (SD)	0.35 (0.82)	0.35 (0.78)	0.23 (0.60)	< 0.001

DAP drug with anticholinergic properties, SD standard deviation

^aCharlson et al. [17]

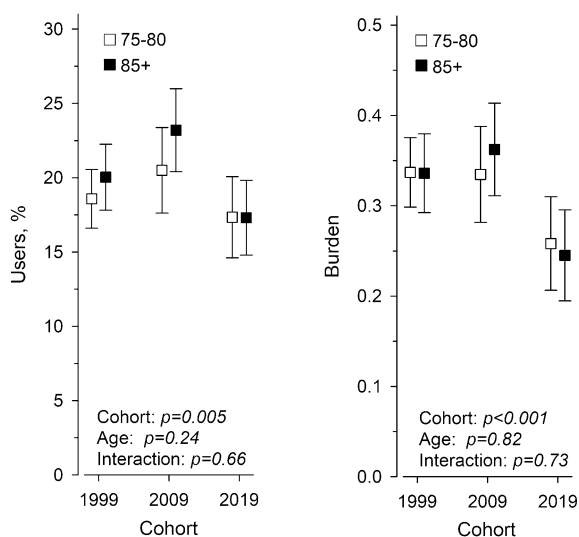


Fig. 1 The left panel of the figure shows the users of anticholinergic medications according to Duran's list and divided according to year cohorts and age groups. The right panel shows the mean anticholinergic burden of anticholinergic medications according to Duran's list divided according to year cohorts and age groups. Whiskers show 95% confidence intervals. All analyses are adjusted for sex and Charlson comorbidity index [17]

There were changes in the use of various anticholinergic medication classes between the cohorts. The proportion of those prescribed any antipsychotic remained quite stable, while the proportion of typical antipsychotics decreased significantly ($p < 0.001$) and atypical antipsychotics increased ($p < 0.001$). At the same time, the proportion of benzodiazepines, hypnotics, antiepileptics, urinary antispasmodics, asthma/COPD (chronic obstructive pulmonary disease) medications, ranitidine, and antiemetics decreased. There was practically no use of lithium, antiparkinsonian drugs, hydroxyzine, muscle relaxants, belladonna, gastrointestinal antispasmodics, loperamide, and disopyramide at any time point. The proportion of antidepressants increased, in particular mirtazapine ($p < 0.001$). The same applies to the use of antihistamines. The overall use of opioids did not change over time but the use of strong opioids increased modestly ($p = 0.014$). In 2019 the most used DAP classes were antidepressants (7%), opioids (3%), and antihistamines (2%). The results of the use of anticholinergic medications on Duran's list among all participants are shown in Table 2.

The proportions of various drug classes among the users of DAPs on Duran's list were also calculated. The results are shown in Table 3.

Table 2 Use of drugs with anticholinergic properties on Duran's list by medication class in each cohort year among all study participants each year

	1999	2009	2019	<i>p</i> for linearity
Participants	2594	1,583	1,653	
Medication class (ATC code), ^a <i>n</i> (%)				
Antipsychotics	40 (1.5)	34 (2.1)	30 (1.8)	0.42
Typical antipsychotics (N05AA01, N05AA02, N05AC02, N05AD01, N05AF04)	37 (1.4)	5 (0.3)	1 (0.1)	
Atypical antipsychotics (N05AH02, N05AH03, N05AH04, N05AX08)	3 (0.1)	30 (1.9)	29 (1.8)	
Antidepressants	158 (6.1)	153 (9.7)	123 (7.4)	0.037
Tricyclics (N06AA04, N06AA06, N06AA09, N06AA10, N06AA12)	60 (2.3)	37 (2.3)	30 (1.8)	
SSRIs (N06AB03, N06AB04, N06AB05)	88 (3.4)	86 (5.4)	39 (2.4)	
Mirtazapine (N06AX11)	17 (0.7)	42 (2.7)	65 (3.9)	
Benzodiazepines (N05BA01, N05BA02)	68 (2.6)	33 (2.1)	12 (0.7)	< 0.001
Hypnotics (N05CD05, N05CD07)	126 (4.9)	63 (4.0)	30 (1.8)	< 0.001
Lithium (N05AN01)	2 (0.1)	2 (0.1)	0 (0.0)	0.42
Antiepileptics (N03AE01, N03AF01, N03AF02)	27 (1.0)	9 (0.6)	8 (0.5)	0.032
Opioids	66 (2.5)	64 (4.0)	45 (2.7)	0.51
Weak opioids (N02AC04, N02AX02, R05DA04)	62 (2.4)	55 (3.5)	33 (2.0)	
Strong opioids (N02AA01, N02AA05, N02AB03, N07BC02)	5 (0.2)	9 (0.6)	12 (0.7)	
Antiparkinsonian drugs (N04BX02, N04BA03)	0 (0.0)	3 (0.2)	0 (0.0)	0.74
Urinary antispasmodics (G04BD04, G04BD07)	38 (1.5)	27 (1.7)	6 (0.4)	0.003
Muscle relaxants (M03BC01, M03BX01, M03BX02)	13 (0.5)	5 (0.3)	5 (0.3)	0.29
Antihistamines (R06AE05, R06AE07, R06AX13, R06AX26)	24 (0.9)	19 (1.2)	40 (2.4)	< 0.001
Hydroxyzine (N05BB01)	6 (0.2)	2 (0.1)	1 (0.1)	0.16
Belladonna (A03B)	1 (0.0)	0 (0.0)	0 (0.0)	0.32
Asthma/COPD ^b medications (R01BA02, R03BB01, R03DA04)	95 (3.7)	24 (1.5)	10 (0.6)	< 0.001
Gastrointestinal drugs				
Gastrointestinal antispasmodics (A03BA03)	1 (0.0)	0 (0.0)	0 (0.0)	0.32
Ranitidine (A02BA02)	23 (0.9)	5 (0.3)	2 (0.1)	< 0.001
Antiemetics (N05AB04)	16 (0.6)	3 (0.2)	1 (0.1)	0.002
Loperamide (A07DA03)	0 (0.0)	5 (0.3)	4 (0.2)	0.030
Cardiovascular medicines				
Disopyramide (C01BA03)	9 (0.3)	2 (0.1)	0 (0.0)	0.009

n = number of users of the medication or medication class each year, % = percentage of users of the medication or medication class of all participants each year

ATC Anatomical Therapeutic Chemical, COPD chronic obstructive pulmonary disease, SSRI selective serotonin reuptake inhibitors

^aWorld Health Organization ATC code (https://www.whocc.no/atc_ddd_index/) [18]

4 Discussion

Comparing the community-dwelling cohorts of older people aged 75+ years from 1999, 2009, and 2019, the proportion of people using DAPs according to Duran's list decreased significantly. The same applies to the mean burden of DAPs. There was a similar decline in both the 75- and 80-year-olds as well as in those aged 85 years and older, and there was no difference in the prevalence or burden of DAPs between the age groups. The profile of various drug classes of DAPs changed remarkably. The typical antipsychotics were substituted by the atypical antipsychotics. The proportion of antidepressants increased, which was explained by the

increased use of mirtazapine. Benzodiazepines and hypnotics became less frequently used. In most drug classes of DAPs on Duran's list, the use was very low or nonexistent throughout the time period.

Comparing the use and burden of DAPs between various studies is challenging. This is due to differing criteria for defining DAPs, the study population (community-dwelling vs. institutionalized), and the method used for collecting the medication data. In an Australian study comparing four different criteria, the prevalence of DAPs varied from 13 to 39% in 2015 in community-dwelling older men [8]. There are a few studies using Duran's list that investigated community-dwelling older people in 2010–2017 [11, 19, 20].

Table 3 Proportions of used anticholinergic medications on Duran's drugs with anticholinergic properties (DAPs) list among the users of DAPs on Duran's list according to each year

	1999	2009	2019	<i>p</i> for linearity
Users of anticholinergic medications on Duran's list	519	349	266	
Medication class (ATC code), ^a <i>n</i> (%)	1999 <i>N</i> = 519	2009 <i>N</i> = 349	2019 <i>N</i> = 266	
Antipsychotics, <i>n</i> (%)	40 (8)	34 (10)	30 (11)	0.090
Old neuroleptics, typical antipsychotics (N05AA01, N05AA02, N05AC02, N05AD01, N05AF04), <i>n</i> (%)	37 (7)	5 (1)	1 (0)	
Atypical antipsychotics (N05AH02, N05AH03, N05AH04, N05AX08), <i>n</i> (%)	3 (1)	30 (9)	29 (11)	
Antidepressants, <i>n</i> (%)	158 (30)	153 (44)	123 (46)	< 0.001
Tricyclics (N06AA04, N06AA06, N06AA09, N06AA10, N06AA12), <i>n</i> (%)	60 (12)	37 (11)	30 (11)	
SSRIs (N06AB03, N06AB04, N06AB05), <i>n</i> (%)	88 (17)	86 (25)	39 (15)	
Mirtazapine (N06AX11), <i>n</i> (%)	17 (3)	42 (12)	65 (24)	
Benzodiazepines (N05BA01, N05BA02), <i>n</i> (%)	66 (13)	33 (9)	12 (5)	< 0.001
Hypnotics (N05CD05, N05CD07), <i>n</i> (%)	125 (24)	63 (18)	30 (11)	< 0.001
Lithium (N05AN01), <i>n</i> (%)	2 (0)	2 (1)	0 (0)	0.49
Antiepileptics (N03AE01, N03AF01, N03AF02), <i>n</i> (%)	27 (5)	9 (3)	8 (3)	0.078
Opioids, <i>n</i> (%)	66 (13)	64 (18)	45 (17)	0.064
Weak opioids (N02AC04, N02AX02, R05DA04), <i>n</i> (%)	62 (12)	55 (16)	33 (12)	
Strong opioids (N02AA01, N02AA05, N02AB03, N07BC02), <i>n</i> (%)	5 (1)	9 (3)	12 (5)	
Antiparkinsonian drugs (N04BX02, N04BA03), <i>n</i> (%)	0 (0)	3 (1)	0 (0)	
Urinary antispasmodics (G04BD04, G04BD07), <i>n</i> (%)	38 (7)	27 (8)	6 (2)	0.014
Muscle relaxants (M03BC01, M03BX01, M03BX02), <i>n</i> (%)	13 (3)	5 (1)	5 (2)	0.45
Antihistamines (R06AE05, R06AE07, R06AX13, R06AX26), <i>n</i> (%)	24 (5)	19 (5)	40 (15)	< 0.001
Hydroxyzine (N05BB01), <i>n</i> (%)	6 (1)	2 (1)	1 (0)	0.21
Belladonna (A03B), <i>n</i> (%)	1 (0)	0 (0)	0 (0)	
Asthma/COPD medications (R01BA02, R03BB01, R03DA04), <i>n</i> (%)	95 (18)	24 (7)	10 (4)	< 0.001
Gastrointestinal drugs				
Gastrointestinal antispasmodics (A03BA03), <i>n</i> (%)	1 (0)	0 (0)	0 (0)	
Ranitidine (A02BA02), <i>n</i> (%)	23 (4)	5 (1)	2 (1)	< 0.001
Antiemetics (N05AB04), <i>n</i> (%)	16 (3)	3 (1)	1 (0)	0.003
Loperamide (A07DA03), <i>n</i> (%)	0 (0)	5 (1)	4 (2)	0.012
Cardiovascular medicines				
Disopyramide (C01BA03), <i>n</i> (%)	9 (2)	2 (1)	0 (0)	0.022

The medications are divided according to their medication class and year cohort

N = number of users of Duran's DAPs in each year; *n* = number of users of the medication or medication class each year; % = percentage of users of the medication or medication class of the users of DAPs on Duran's list in the respective year

ATC Anatomical Therapeutic Chemical, COPD chronic obstructive pulmonary disease, SSRI selective serotonin reuptake inhibitors

^aWorld Health Organization ATC code (https://www.whocc.no/atc_ddd_index/) [18]

The studies showing higher prevalence rates (from 32.1 to 33.2%) than ours include patients discharged from hospital [20] or a combined sample of community-dwelling and institutionalized older people with the extended Duran's list [11]. Our 2019 prevalence (16%) is more in line with a Slovenian study finding (12.5%) that included 65+ primary-care visitors who were receiving at least one regularly prescribed medication [19].

In our study, the prevalence of DAP users seemed to slightly increase from 20% in 1999 to 22% in 2009 and then

decrease to 16% in 2019. However, the statistically significant decrease is calculated over the whole time period. Our finding is in line with the French study, which suggested a decreasing trend from 2006 to 2015 in both the prevalence and the burden of mainly Duran's DAPs [11]. Our study is also in line with the three other studies exploring temporal trends of DAPs from 1990 to 2015 [9, 12, 14]. According to our study and these few studies exploring temporal trends among community-dwelling older people, it seems that the peak use of DAPs may have been in about 2010, albeit the

French study shows a slight continuous decrease over the years [9, 11, 12, 14]. This finding is also in line with the recent study exploring temporal trends in the use of DAPs in US nursing homes [21], whereas there are also contradictory findings [15]. However, with the exception of the French study [11], all of these other studies exploring temporal trends used different criteria for DAPs than our study [9, 11, 12, 14, 15, 21].

The burden of DAPs also decreased over time. This may be due to the changes in the proportion of DAP use in specific drug classes. The high-potency DAPs were either replaced by lower potency options (typical antipsychotics vs. atypical antipsychotics) or decreased significantly (urinary antispasmodics). In 2019 the most commonly used DAP classes were antidepressants (7.4% of all participants), opioids (2.7%), and antihistamines (2.4%). Comparing this with other studies is challenging due to the various criteria used and due to different groupings of DAPs. Many studies also lack information on the specific drug classes of DAPs.

The proportion of users of typical antipsychotic DAPs decreased, whereas the proportion of atypical antipsychotics increased. This is comforting since the atypical antipsychotics have fewer side effects than the typical antipsychotics, although they still include cardiovascular risks [22]. Compared with other studies using Duran's list, our finding of prevalence of antipsychotics in 2019 (1.8% of all participants) seems to be at about the same level [19] or lower [20] than in previous studies. Among antidepressant DAPs, the number of participants using selective serotonin reuptake inhibitors and tricyclics remained stable, while the proportion using mirtazapine increased significantly. The overall prevalence of the antidepressant mirtazapine in 2019 (3.9%) was higher than the prevalence of any other medication class. In line with Aalto et al.'s study, the increased use of mirtazapine is most likely due to its off-label low-dose use as a hypnotic [15]. The proportions of anticholinergic benzodiazepines and hypnotics were more than halved over two decades. Mirtazapine may have replaced other hypnotics in the last cohort.

The proportion of anticholinergic opioids remained stable, even though the use of strong opioids slightly increased. As we examined the use of regularly used medications, the use of opioids (in 2019 overall use 2.7%) seem to be still quite modest compared with other countries like France [11] and the USA [23], and we cannot talk about an opioid crisis in Finland [24]. However, our study may underestimate the use of opioids since the fairly widely used buprenorphine plaster is not included in Duran's list [10].

In line with previous studies, the proportion of anticholinergic urinary antispasmodics (oxybutynin and tolterodine) decreased [12, 15, 21], which is a welcome and expected finding, as newer and safer drugs have emerged [25]. Interestingly, a major increase was seen in the use of

antihistamines on Duran's list in ≥ 75 -year-old community-dwelling people. The same temporal trend is suggested in the French study in which the fourth most used anticholinergic drug in 2015 was desloratadine [11]. Fortunately, the use of the old, sedating antihistamine hydroxyzine remained low. In other drug classes of DAPs, the use was very low or non-existent throughout the time period.

Overall, the changing prescription patterns on Duran's list suggest that physicians' prescriptions have moved towards more evidence-based medicine in prescribing anticholinergic medications. In Finland, there has been wide discussion about harm caused by DAPs or sedatives to older people. However, there are also some new harmful vogue trends such as using mirtazapine as a sleeping pill. The therapeutic arsenal has also changed and certain old and obsolete medications have been replaced with newer and less harmful medications. These include typical antipsychotics, urinary antispasmodics, old asthma and COPD medications, and ranitidine. When interpreting the results, we must remember that this study examined only the use of DAPs according to Duran's list, and some of the decreases we identified may have been replaced with DAPs that are not yet identified or with medications that have other side effects. However, Duran's list is quite comprehensive, including many medications commonly used among the older population in Finland (such as antidepressants, antihistamines, antipsychotics, benzodiazepines, hypnotics, and opioids), so some careful conclusions must be made.

There are several strengths to this study. The cohorts were large and the response rates were high. The samples also included very old people (90 and 95 years old). Therefore, the samples represent fairly well the Finnish urban community-dwelling population. The questionnaires included the same items covering two decades, allowing comparisons of medication use over two decades, which is a long period of time. The study is one of the few to explore temporal trends in the use of DAPs in community-dwelling older people. Furthermore, this is one of very few studies presenting and comparing various anticholinergic drug classes over time.

One of the major challenges lies in defining the anticholinergic medications itself. Choosing any of the anticholinergic criteria is always a trade-off, and there is no common agreement on which of the scales best describes the anticholinergic medications and should be used. In the analysis we did preliminary research on several criteria and we chose Duran's list, which is created by a systematic review of previous anticholinergic scales, and the scales included in it are based on expert opinion, measuring medications' serum anticholinergic activity, and a literature review. In our Finnish and community-dwelling older people context, Duran's list offered a meaningful list of DAPs that is not too wide nor too narrow. In addition, being 8 years old, it includes

some newer drugs than some earlier criteria, which are also commonly used. It also allowed a wider comparison of the medications used by older adults. Nevertheless, we do not know whether it is the best criteria to define DAPs, and the use and trends may differ according to different criteria. A consensus on the topic is needed in order to get the most reliable and comparable information on the topic.

Furthermore, the study population is restricted to Helsinki, Finland, and the medication prescribing reflects Finnish trends. Although the response rates were high enough, the non-responders might be those with a high number of comorbidities and, thus, also a high number of medications. Indeed, those over 90+ years were more often helped by their proxies when completing the questionnaire.

One limitation is that the medications were self-reported. However, at two time points (1999 and 2019) we made thorough assessments of participants and the medication lists could be verified by face-to-face assessments. Unfortunately, we do not have information on the actual doses of the medications that the older people were using. Finally, the study is cross-sectional so causalities cannot be identified.

5 Conclusion

The decrease in the prevalence and burden of DAPs on Duran's list is evident in the community-dwelling older people in Finland. The use of old, strong DAPs has decreased but new contributors to the use of DAPs have emerged. More studies are needed to explore the adverse effects of the newer DAPs as well as the changes in the prescription culture. Physicians need continuous education in prescribing DAPs.

Declarations

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Conflict of interest The authors have no conflicts of interest to declare.

Ethics approval The Helsinki Ageing Study received ethical permission from Helsinki University Hospital. The study was conducted according to guidelines of the Declaration of Helsinki.

Consent to participate The participants provided written consent in the questionnaire.

Consent for publication Not applicable.

Availability of data and material The data are available on request from the corresponding author.

Code availability Not available.

Authors' contributions Design/conduct of the study (M-OR, HR, HRÖ, RST, TES, KHP, ULA); acquisition of subjects and/or data (M-OR,

HJK, RST, TES, KHP, ULA); analysis and interpretation of data (M-OR, HJK, KHP, ULA); preparation of manuscript (M-OR, HR, HRÖ, HJK, RST, TES, KHP, ULA). All authors read and approved the final submitted manuscript, and agree to be accountable for the work.

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