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Use of prescription drugs in the older adult population – a nationwide pharmacoepidemiological study

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Abstract

Aim

Multi-morbidity and polypharmacy are common among older people. It is essential to provide a better understanding of the complexity of prescription drug use among older adults to optimise rational pharmacotherapy. Population-based utilisation data in this age group is limited. Using the Danish nationwide health registries, we aimed to characterise drug use among Danish individuals ≥60 years.

Methods

This is a descriptive population-based study assessing drug prescription patterns in 2015 in the full Danish population aged ≥60 years. The use of specific therapeutic subgroups and chemical subgroups and its dependence on age were described using descriptive statistics. Profiles of drug combination patterns were evaluated using latent class analysis.

Results

We included 1,424,775 residents (median age 70 years, 53% women). Of all the older adults, 89% filled at least one prescription during 2015. The median number of drug groups used was five per person. The most used single drug groups were anilides (34%), statins (33%), and platelet aggregation inhibitors (24%). Eighteen drug profiles with different drug combination patterns were identified. One drug profile with expected use of zero drugs and 11 drug profiles expected to receive more than five different therapeutic subgroup drugs were identified.

Conclusion

The use of drugs is extensive both at the population level and increasing with age at an individual level. Separating the population into different homogenous groups related to drug use resulted in 18 different drug profiles of which 11 drug profiles received on average more than five different therapeutic subgroup drugs.

What is already known about this subject

- The use of prescription drugs is common in older people
- The use of many drugs simultaneously increases the risk of adverse drug events and drug-drug interactions

What this study adds

- A better and updated understanding of the real-life utilisation of prescription drugs among older adults ≥60 years
- An understanding of how drugs tend to compound
- Drug profiles with clinical recognisable medication profiles for the entire older population

Introduction

The use of prescription drugs is widespread in older people[1,2], and the number of drugs used is increasing with age [3–6]. This is prompted by an increasing prevalence of multi-morbidity and hospitalisations by age supplemented by a higher number of specialists who treat single diseases[7–9]. Strict adherence to guidelines for each of the chronic conditions may complicate older persons' pharmacotherapy and may be associated with adverse drug events[10]. Furthermore, the use of many drugs simultaneously increases the risk of adverse drug events and drug-drug interactions[11,12]. Due to age-related changes in pharmacokinetics and pharmacodynamics, older people are at very high risk of such complications[1,5,11,13]. To this end, up to 30% of hospital admissions in older patients are related to adverse drug events[14–16]. Thus, pharmacotherapy in the older adults is very complicated, and the vast variety of drugs and drug combinations effect on the pharmacokinetics and pharmacodynamics and makes it a difficult phenomenon to analyse.

A better and updated understanding of the real-life utilisation of prescription drugs is needed, and further research is required to deepen our understanding of how drugs tend to compound and interact. In addition, identifying common drug profiles, i.e. which drugs are used together, to identify long-term risk drug profiles may enable health care policies, clinicians, and research fellows to optimise a rational pharmacotherapy, prescribing and deprescribing patterns among older adults. However, the population-based utilisation data in this age group is limited, and data are rather old. Therefore, we aimed to provide a detailed study of drug use and how it changes with age to identify different homogeneous drug profiles among older adults aged 60 years and older.

Methods

We performed a nationwide cross-sectional drug utilisation study in the older adult Danish population.

Data sources

Denmark has a public tax-financed health care system, which provides free and equal access to primary medical care, hospitals, and home care services for all people. Patient co-payments are required for prescription drugs. A central authority (the Reimbursement Committee) decides whether a particular drug is reimbursable. Some prescription drugs, e.g. benzodiazepines are not reimbursed[17]. Virtually all medical care in Denmark is furnished by the public health authorities, whereby the data resources allow accurate population-based studies, covering all inhabitants of Denmark.

We used data from five Danish nationwide registries; the National Prescription Registry, the Danish Education Registry, the Registry for Migration, the Danish Registry of Causes of Death, and the Civil Registration System. The National Prescription Registry contains full information on all prescription drugs dispensed at Danish community pharmacies including prescriptions for nursing home residents[17]. Prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC) classification system[18]. Drugs used during hospitalisation are not recorded in the register. The Danish Education Register contains information on ongoing and completed education[19]. The Register for Migration contains the date of both immigration and emigration[20]. The Danish Register of Causes of Death contains data on all deaths among people dying in Denmark[21]. The Civil Registration System contains various information including sex, date of birth, and updated information on vital status[22]. All Danish residents are recorded in the registries with a uniquely personal and permanent identification number that makes it possible to crosslink individual-level data across the different registries.

Study population

We included all Danish residents aged≥60 years on January 1 2016. Residents who migrated during 2015 were excluded to ensure full follow-up data on all subjects.

Study variables

Study drugs

We retrieved information on all redeemed prescriptions in 2015. The drugs were categorised according to ATC-codes into the anatomical main group (1st level), therapeutic subgroup (2nd level), and chemical subgroup (4th level)[18]. ATC Level 1, 2, and 4 are referred to as main drug group, therapeutic subgroup drug, and drug class, respectively. We defined drug users as individuals who had redeemed at least one prescription of a drug class or main drug group in 2015. In the latent class analysis (LCA), we disregarded the main drug group: anti-infectives for systemic use.

Sociodemographic factors

The marital status was categorised according to status on January 1 ,2016, as: married, widowed, divorced or single, whereas education was categorised according to the highest attained educational level at January 1 2016: short (7-10 years), medium (11-13 years) or long (≥14 years).

2.4 Analyses

First, we described baseline characteristics, i.e. sex, marital status, and education of the study population. To investigate simultaneous drug use, we measured the proportion of users of 0, 1-2, 3-4, 5-9, or 10+ different drug classes in 2015 stratified by age groups. Second, we determined the ten most frequently used drugs classes stratified by age groups. Third, we reported the number of redeemed drug classes among all residents as mean, median, interquartile range, minimum, and maximum, stratified by 1-year age categories. Finally, we identified the number of residents who filled at least one prescription of a main drug group in 2015. These analyses were stratified by 1-year age categories.

Finally, we identified drug profiles using LCA. LCA is a method designed to identify subgroups of residents who show similar patterns of behaviour, e.g. drug use[23]. LCA classifies individuals into mutually exclusive latent classes and assumes that given the latent class membership the use of drugs is independent; thus, we used the LCA to identify different drug patterns in the general older adult population. Each class identified in the LCA will thus have similar drug patterns and therefore have the same drug profile. To reduced computer running time we selected five random samples of our population, each with 50,000 residents. For the same reason, we chose drugs at therapeutic subgroup level instead of drug classes. To avoid too few observation, the drugs were identified as the 95% most used drugs in 2015. Thus, the LCA was based on drugs from 28 therapeutic subgroups. Moreover, this made it possible to investigate the consistency of the drug profiles identified in five random samples. The number of drug profiles was estimated in an iterative process starting with a model with a two LCA class solution and continuing up to 20 LCA classes for each of the five datasets. To measure the relative fit of the models, which refers to the adequacy of one model's representation of data compared with that of another model, we used the Bayesian Information Criterion (BIC)[24]. This was used together with substantive interpretability and clinical judgment to determine the number of drug profiles for each of the five datasets[25]. Afterwards, the optimal number of drug profiles and parameter estimates were compared for the five datasets, and the final number of drug profiles was decided. The entropy-based pseudo-R^2 measure can summarise the association between the drug profiles. The values 0.36, 0.65, and 0.90 represent low-, medium-, and high-separation conditions, respectively[26]. Posterior probabilities for drug profile membership were calculated for all residents in the cohort using the average parameter estimates from the five datasets. All residents were assigned to a specific drug profile based on modal assignment (the drug profile with the highest posterior probability). The distribution of sex and the

median for age were performed for each drug profile. To account for local maxima of the likelihood function for LCA we initially used 450 randomly generated starting values. If the best likelihood were not replicated, then the number of starting values was increased.

Ethics and reporting

The study was approved by the Scientific Board of Statistics Denmark and the Danish Data Protection Agency (ref. 00003115). An approval from an ethics committee is not required for registry-based studies in Denmark. No identifiable patient data could be retrieved. The study was conducted by following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations[27].

Results

Drug use

We identified 1,424,775 residents aged ≥60 years in Denmark in 2015. The female proportion was 53%. The median age of the population was 70 years (interquartile range (IQR) 65-77, range 60 to 110) without differences across sex (70 years for men and 71 years for women). The most used single drug classes measured by the number of unique users were anilides (34%), statins (33%), platelet aggregation inhibitors (24%), proton pump inhibitors (21%), and calcium channel blockers (20%). (Table 1).

Of all the older adults, 89% filled at least one prescription during 2015. The median number of unique drug classes filled was five per person (IQR, 2-8), similar for men and women (four drug classes (IQR, 2-8) and five drug classes (IQR, 2-9), respectively). We observed a trend toward an increasing number of prescribed drug classes by age. However, with a levelling off around age 90 (Figure 1).

Cardiovascular drugs were the most used main drug group (1≥ prescription filled by 62% of all residents), followed by drugs related to the nervous system (48%), alimentary tract and metabolism (38%), anti-infectives for systemic use (35%), and blood and blood-forming organs (34%). This was largely consistent across age (Figure 2), although with a tendency towards a slightly increased proportion of drugs related to blood and blood-forming organs was observed whereas the proportion of drugs related to the genitourinary system and sex hormones decreased slowly by age.

Drug profiles

By using the drugs from the 28 covering 95% of all drug groups used in 2015, we fitted up to a 20 LCA class model. Looking at model fit, the BIC was lowest in the model with 19-drug profiles for four datasets and in the model with 18 drug profiles for one dataset. When comparing the therapeutic subgroup drug probabilities within each drug profile among the five different datasets for the 19-drug profile models, two of the 19-drug profiles were very differently estimated, showing no consistency among the datasets in how to identify them. However, for the 18-drug profile model, the results were similar (Appendix 1). Since no consistent pattern was obtained in the 19-drug profile model, and with a clinical judgment by a clinical difference in the drug profiles we used the 18-drug profile model as our final model. Moreover, the mean entropy-based pseudo-R^2 measure was in our study 0.67 (range: 0.66-0.68), placing the separation of the 18 drug profiles as medium-separation conditions.

Table 2 shows the conditional probabilities of the 28 therapeutic subgroup drugs in the 18 identified drug profiles and the relationship between age and sex for each drug profile. Multiple drug use was in this study defined as receiving drugs from five or more different therapeutic subgroup drugs. Multiple drug use was observed in 11 drug profiles (drug profile 1 to 11). Two of these drug profiles had a considerable overlap (drug profile 1 and 4). Thus, one drug profile (drug profile 1) consisted of high probabilities for all 28 therapeutic subgroup drugs and was characterised by the highest expected numbers of therapeutic subgroup drugs whereas the other drug profile (drug profile 4) had a high probability of receiving all therapeutic subgroup except for mineral supplements and diuretics. The second highest number of expected therapeutic subgroup drugs was observed in combination with the highest median age, and the highest proportion of females. The probability of receiving a drug for both the cardiovascular system, alimentary tract and metabolism, and for the blood and blood-forming organs were characterised for drug profile 1-7. An expected number of different therapeutic subgroup drugs under five were characterised for drug profile 12-18. The highest proportion of males was found in drug profile 12. Similar, drug profile 16 was characterised by low probability of receiving drugs except for hypertensive drugs. Drug profile 18 was the largest. It had a prevalence of 21% and consisted of those with a probability of zero or very close to zero for receiving any drug from the different included therapeutic subgroup drugs. The median age for residents in drug profile 18 was the lowest among the 18 drug profiles at 67 years old, and the sex ratio was also almost 1:1. Thus, the most prevalent drug profiles characterised by expected multiple drug use were drug profile 1-6 (11.2-7.6 expected therapeutic subgroup drugs) and had a total prevalence of 19%. To characterise the different therapeutic subgroup drugs used in LCA we have listed the three most frequent drug classes at the 28 different therapeutic subgroup drugs in Appendix 2.

Discussion

In this cross-sectional nationwide drug utilisation study, we investigated prescribing patterns and drug combination profiles in older adults in Denmark in 2015. Our study showed that extensive drug use among older adults was very common. Older people aged ≥60 years, redeemed drugs from five (median) different drug classes at the pharmacy each year. The number of redeemed drugs increased by age from a median level at 4 for persons between 60 and 69 years old to a median level at 8 for older people aged ≥80 years. However, the distribution of drugs from main groups was almost stable across age groups. Further, we identified 18 different drug profiles; one drug profile with a low probability of receiving any drugs, which included 21 % of the population ≥60, and 11 drug profiles, which on average received drugs from more than five different therapeutic subgroups.

Our study investigated current drug use among older adults in Denmark and showed that drug consumption is well within the range of previous studies. Previous studies were, however, primarily based on selected populations and fairly old data sets. To our knowledge, no other studies have included the entire Danish population ≥60 years. A Swedish study showed that older adults (≥65) used an average of 4.6 different drugs (ATC level 5)[28] whereas, a Danish study found that the median number of drugs among residents ≥60 years was 5 (IQR: 2-9) (ATC level 5)[29]. We confirmed the findings from Linjakumpu et al.[3] that the number of drugs increased by age. However, the increase in the number of redeemed drug classes seems larger in our study. One reason for this might be the larger population and the general increase in drug consumption. Similar to our findings, Lagerin et al.[30] reported that the number of drugs at ATC level 3 stabilised at the age of 85-90. This stabilisation of the drug use can be expected because the increased life expectancy in the older population has raised the prevalence of multi-morbidity[31], and the number of drugs was highly correlated with the number of chronic conditions[28]. The impact of evidence-based clinical guidelines for the treatment of the specific disease may also contribute to the observed increase in drug use[32]. This can be explained by the fact that each guideline has several recommended drugs and the majority of older people are multimorbid.

We found that cardiovascular drugs were the most commonly used main drug group, which is in accordance with previous findings. Barat et al. found that the two most common prescription drugs among 75-years-old community-dwelling residents were cardiovascular drugs (25%) and central nervous system drugs (23%)[33]. In a Swedish study among older adults ≥ 78 years of age, cardiovascular drugs were also the most frequently used drugs followed by nervous system drugs, and alimentary tract metabolism drugs[32]. Similar results were found by Wastesson et al.[34]. We further found that the

distribution of main drug groups was stable over age, which indicates that the drug patterns do not change significantly with age and suggest that drugs may not be discontinued in late life.

A complex drug burden is potentially harmful to the patients and difficult to manage[10,35]. The drug burden is often measured by the number of different drugs used but ignoring the complexity of the drug profiles. To our knowledge, LCA has never been performed in a large, national population, and with therapeutic subgroup drugs as outcomes. In previous studies, LCA has been used to define, e.g., subtypes of drug abuse in a Swedish cohort (n=192,501)[36] and to identify patterns of drug use associated with lower serum sodium concentration in older hospitalised patients (n=101)[37]. In both studies, the drugs were selected to fit a selected patient group, and the analysis included only a limited number of drugs or drug classes, whereas only three and six different drug profiles were identified. In this study 18-drug profiles, i.e. clinical recognisable medication patterns were identified. For example, drug profile 13 is characterised by a high probability of receiving drugs for diabetes, agents acting on the renin-angiotensin system, and lipid-modifying agents. In general, the drug profiles demonstrated very complex therapeutic profiles and reflecting the high level of multimorbidity. However, the drug profiles should be explored more thoroughly to fit the clinical practice, e.g. to risk-stratified patients in a hospital or a general practice. When identifying drug profiles, LCA is considered highly suitable because the drug groups differ qualitatively from each other. Also, we found similar drug profiles for the five randomly selected samples which indicates that the 18 drug profiles are very stable. The drug profiles allow us to study drug use and drug combinations in a new way. By using the drug profiles, it is possible to identify in which of the drug profiles a given drug is used, and thereby restrict studies of adverse effects to individuals with different drug combination profiles. Real word evidence in different drug profiles makes the result more usable in clinical practice. We believe that the new method is important also when studying drug channelling bias in more sufficient ways, and when studying polypharmacy more comprehensively.

Strengths and limitations

Our study is the first study investigating drug profiles in a large population using LCA. The use of LCA in an unselected population enables a nuanced identification and description of drug profiles. More in-depth knowledge of the drug patterns is desired, e.g. studying drug profiles at drug class level instead of at therapeutic subgroup level. This was, however, not possible in this study due to the lack of computer power. In future studies, drug profiles have the potential to be evaluated on drug class level, to achieve knowledge on among other drug safety, interactions, adverse drug events,

maybe by investigating individuals with a specific drug profile. Another strength of this study is that data were obtained from nationwide registers containing high-quality data. This ensures complete coverage and eliminates the risk of selection bias.

A limitation of this study is that certain drugs can be purchased over the counter in Denmark and drug, therefore, can be slightly underestimated. Olesen et al.[38] found that 28 percent of the patients aged 65 years or more used non-prescription drugs. Indeed, the majority are prescription drugs, especially with respect to the most potent drugs and those with the greatest potential of interactions. Another potential limitation is that we had no information on drug adherence among older adults. Though we know the older adults have filled the prescription, we do not know whether the older adults have taken the drug. At the same time, we eliminate primary non-adherence, which is a strength. We required at least one prescription for all drugs in the analyses, though we did not know if the older adults were compliant to the given drug. Due to the excessive computer running time, we were further compelled to reduce the population to five random samples of 50,000 individuals each. We assume a sample of 50,000 individuals as a large population, and that the results would not be different compared with the final population.

In conclusion, we found that the use of drugs is extensive both at the population level and at the individual level and that it is increasing with age. Cardiovascular drugs, analgesics and psychotropic drugs were the most prevalent drug classes. Eighteen different drug profiles were identified, 11 drug profiles reflecting probable drug combination profiles among users of multiple drug use. The identified drug profiles described clinical recognisable medication patterns. The drug profiles have the potential to be used in future studies investigating high-risk prescriptions patterns. Studies of the older adult population with diverging drug profiles may provide useful information to prevent drug-related problems and optimise drug treatment. For instance, with more research into risk patterns, we can produce risk profiles that will provide a better understanding of which patients benefit most from medication review. Furthermore, these risk profiles may also benefit the patients when a new medication is added to the treatment for a more rational drug prescribing.

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Author Contributions

Christensen, Juul-Larsen, Petersen have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Christensen, Pottegård, Petersen. Acquisition, analysis, or interpretation of data: Christensen, Pottegård, Petersen. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Christensen, Petersen. Administrative, technical, or material support: Petersen. Study supervision: Kaae, Andersen, Pottegård, Petersen.

Conflict of Interest Disclosures

There are no competing interests to declare.

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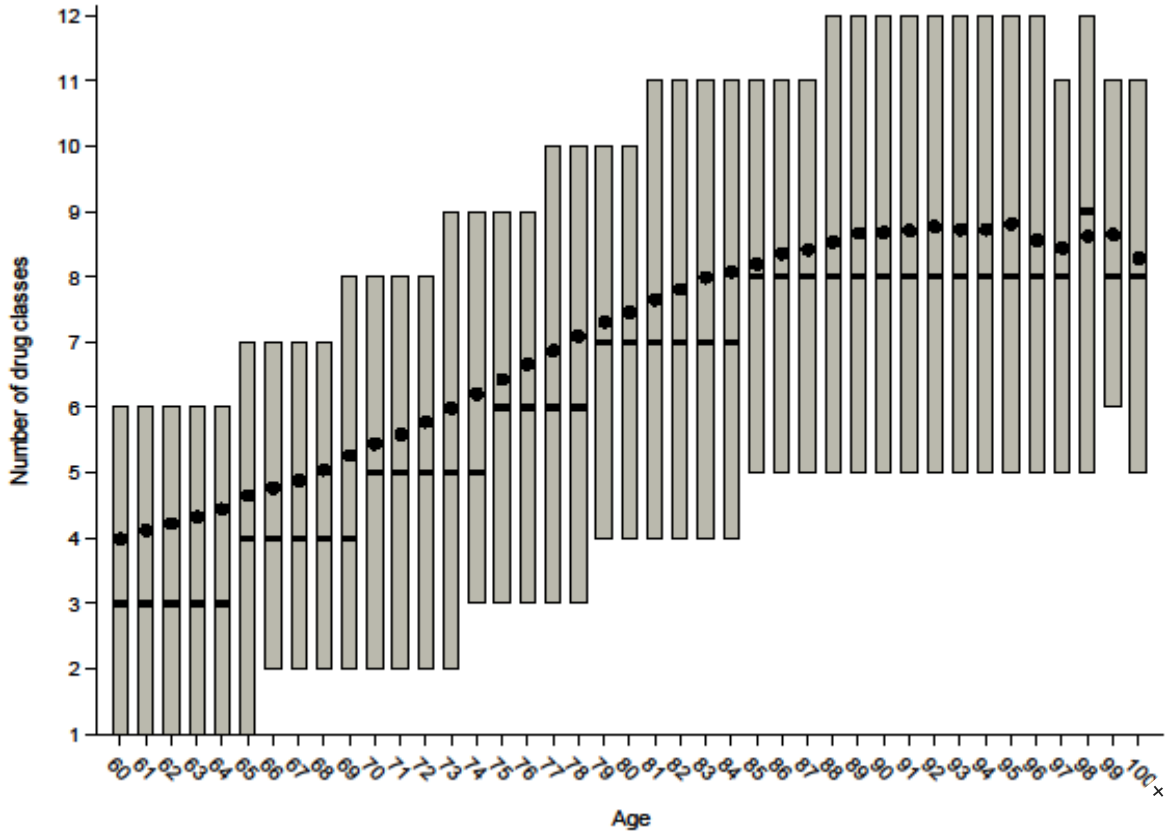

Figure 1: Number of unique drug classes depicted as a function of age.
Boxes represent the interquartile range with the median score shown as a horizontal line and the means represented as circles.

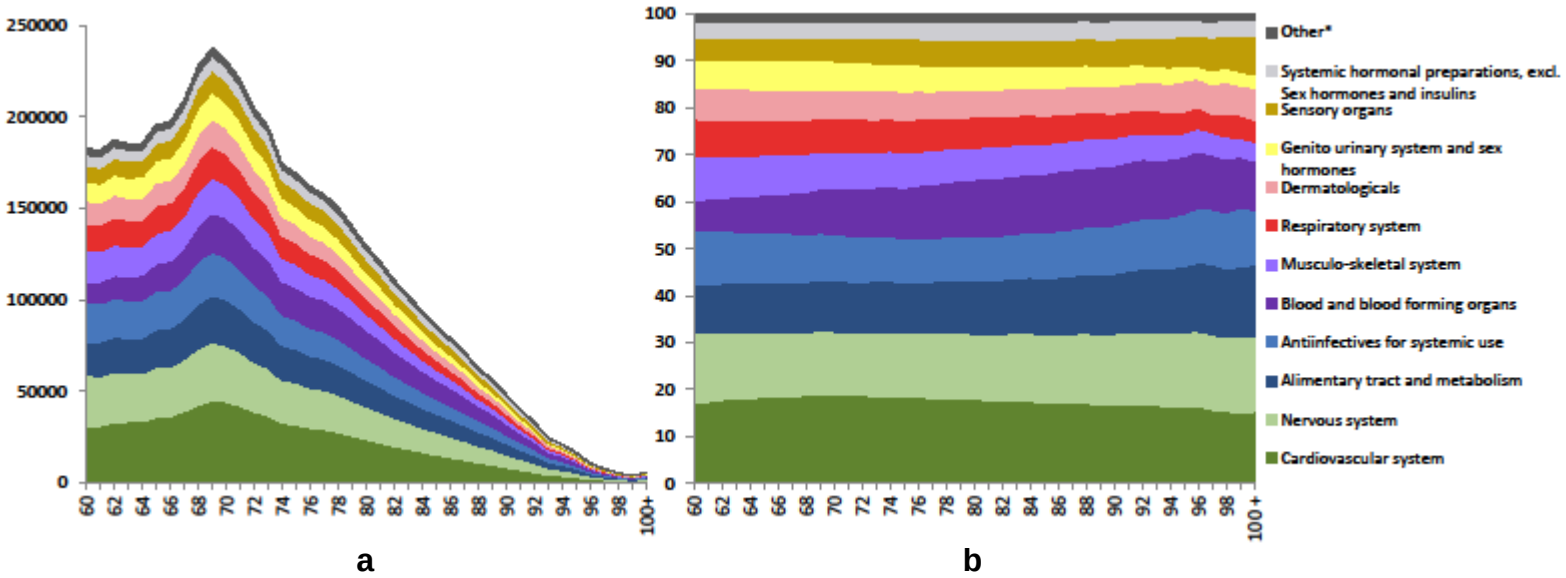

Figure 2 Parts a-b: Overall distribution of drugs used.

2A: Number of main drug groups stratified by age. 2B: Percentage of main drug groups stratified by age.

1 **Table 1. Demographic and drug characteristics.**

Characteristic	Total No. (%)	Age groups (year) 60-69 No. (%)	70-79 No. (%)	80+ No (%)
	1424775	688623 (48.3)	490295 (34.4)	245857 (17.3)
Sociodemographic characteristics				
Female sex	759255 (53.3)	348609 (50.6)	258311 (52.7)	152335 (62.0)
Marital status				
Married[a]	842138 (59.1)	456828 (66.3)	300875 (61.4)	84435 (34.3)
Widowed	274533 (19.3)	48189 (7.0)	96843 (19.75)	129501 (52.7)
Divorced	201153 (14.1)	112102 (16.3)	68038 (13.9)	21013 (8.6)
Single	106951 (7.5)	71504 (10.4)	24539 (5.0)	10908 (4.4)
Highest achieved education[b]				
Short (7-10 years)	498173 (36.0)	185095 (27.4)	186750 (39.2)	126328 (54.9)
Medium (11–12 years)	551070 (39.9)	294205 (43.6)	188201 (39.5)	68664 (29.8)
Long (≥13 years)	333118 (24.1)	195837 (29.0)	102088 (21.4)	35193 (15.3)
Medication				
Median number drug classes (IQR[c])	5 (2-8)	4 (1-7)	5 (3-9)	8 (4-11)
Number of simultaneously used drugs classes				
0	155,692 (10.9)	105,130 (15.3)	40,986 (8.4)	9,576 (3.9)
1-2	253,138 (17.8)	157,282 (22.8)	76,033 (15.5)	19,823 (8.1)
3-4	264,930 (18.6)	141,372 (20.5)	90,590 (18.5)	32,968 (13.4)
5-9	477,536 (33.5)	201,525 (29.3)	178,395 (36.4)	97,616 (39.7)
10+	273,479 (19.2)	83,314 (12.1)	104,291 (21.3)	85,874 (34.9)
10 most frequent drugs classes				
Anilids ((N02BE)	483,772 (34.0)	184,981 (26.9)	173,338 (35.4)	125,453 (51.0)
HMG CoA reductase inhibitors (C10AA)	466,062 (32.7)	190,265 (27.6)	189,804 (38.7)	85,993 (35.0)
Platelet aggregation inhibitors excl. heparin (B01AC)	337,985 (23.7)	109,735 (15.9)	134,318 (27.4)	93,932 (38.2)
Proton pump inhibitors (A02BC)	295,668 (20.8)	120,132 (17.4)	108,428 (22.1)	67,108 (27.3)
Dihydropyridine derivatives (C08CA)	285,250 (20.0)	107,662 (15.6)	110,412 (22.5)	67,176 (27.3)
Beta blocking agents, selective (C07AB)	241,009 (16.9)	82,228 (11.9)	94,658 (19.3)	64,123 (26.1)
Propionic acid derivatives (M01AE)	229,475 (16.1)	120,989 (17.6)	78,864 (16.1)	29,622 (12.0)
ACE inhibitors, plain (C09AA)	206,732 (14.5)	80,935 (11.8)	79,301 (16.2)	46,496 (18.9)
Beta-lactamase sensitive penicillins (J01CE)	199,701 (14.0)	94,581 (13.7)	67,817 (13.8)	37,303 (15.2)
Thiazides and potassium in combination (C03AB)	185,262 (13.0)	65,308 (9.5)	71,188 (14.5)	48,766 (19.8)

2 [a] Includes registered partnership
3 [b] Missing: 42,414 people
4 [c] IQR= interquartile range

Table 1: The conditional probabilities of the 28 therapeutic subgroup drugs in the 18 identified drug profiles.

Profile	P[a]	1	2	3	4	5	6	7	8
Profile size, No (%)		42,743 (3)	28,496 (2)	56,991 (4)	56,991 (4)	42,743 (3)	42,743 (3)	71,239 (5)	42,743 (3)
Age, median (IQR)	70 (62-77)	78 (71-84)	81 (72-89)	78 (71-84)	75 (69-82)	75 (68-82)	71 (66-77)	72 (68-78)	73 (66-81)
Sex, female (%)	53.3	62.5	72.7	48.7	49.7	61.1	68.6	36.1	74.9
Expected number of therapeutic subgroup drugs		11.2	8.3	8.1	7.6	7.6	7.2	6.7	6.7
Therapeutic subgroup drug									
A02: Drugs for acid related disorders	22%	**72%**	**60%**	**30%**	**49%**	**45%**	**43%**	20%	**62%**
A06: Drugs for constipation	5%	**29%**	**43%**	**6%**	**12%**	**22%**	2%	1%	**25%**
A10: Drugs used in diabetes	11%	**34%**	5%	**20%**	**16%**	**28%**	11%	**55%**	2%
A12: Mineral supplement	10%	**63%**	**74%**	**59%**	0%	**16%**	8%	**18%**	2%
B01: Antithrombotic agents	30%	**90%**	**43%**	**99%**	**100%**	**62%**	28%	**77%**	17%
B03: Antianemic preparations	6%	**25%**	**22%**	**9%**	**13%**	**17%**	5%	**11%**	**14%**
C01: Cardiac Therapy	6%	**38%**	**12%**	**46%**	**33%**	3%	3%	**8%**	2%
C03: Diuretics	23%	**91%**	**91%**	**96%**	12%	**36%**	**37%**	**48%**	18%
C07: Beta blocking agents	20%	**59%**	22%	**81%**	**55%**	**25%**	21%	**55%**	10%
C08: Calcium channels blockers	21%	**41%**	**24%**	**33%**	**33%**	**39%**	**32%**	**62%**	12%
C09: Agents acting on the renin-angiotensin system	36%	**60%**	27%	**66%**	**47%**	**62%**	**59%**	**96%**	20%
C10: Lipid modifying agents	33%	**76%**	15%	**64%**	**73%**	**73%**	**45%**	**91%**	16%
D07: Topical dermatological Corticosteroids	13%	**26%**	**22%**	15%	**21%**	**16%**	**35%**	13%	**23%**
G03: Sex hormones and modulators of the genital system	10%	**17%**	**14%**	6%	**13%**	10%	**26%**	3%	**26%**
G04: Urologicals	10%	**16%**	11%	**13%**	**18%**	**14%**	12%	**14%**	11%
H02: Corticosteroids for system use	6%	**27%**	**19%**	**8%**	**12%**	0%	**19%**	2%	**17%**
H03: Thyroid therapy	6%	**14%**	**12%**	**10%**	**8%**	**11%**	**10%**	5%	**11%**
M01: Antiinflammatory and antirheumatic products	19%	**25%**	23%	10%	**24%**	19%	**32%**	11%	**46%**
M05: Drugs for treatment of bone diseases	6%	**16%**	**19%**	6%	**11%**	**8%**	**8%**	1%	**16%**
N02: Analgesics	38%	**94%**	**89%**	**53%**	**76%**	**73%**	**63%**	31%	**97%**
N03: Antiepileptics	5%	**20%**	**17%**	3%	**10%**	**20%**	4%	3%	**23%**
N04: Anti-parkinson drugs	2%	**6%**	**6%**	1%	**3%**	**7%**	2%	0%	**7%**
N05: Psycholeptics	15%	**45%**	**42%**	16%	**30%**	**46%**	**28%**	6%	**55%**
N06: Psychoanaleptics	13%	**40%**	**44%**	11%	**22%**	**61%**	15%	8%	**48%**
R01: Nasal preparations	6%	**11%**	5%	4%	**9%**	2%	**41%**	3%	**13%**
R03: Drugs for obstructive airways diseases	13%	**41%**	**29%**	**19%**	**22%**	**13%**	**43%**	7%	**25%**
R06: Antihistamines for systemic use	6%	**17%**	**12%**	4%	**11%**	6%	**43%**	3%	**19%**
S01: Ophthalmologicals	17%	**31%**	**29%**	18%	**26%**	**23%**	**48%**	17%	**31%**

Profile	9	10	11	12	13	14	15	16	17	18
Profile size, N (%)	71239 (5)	28,496 (2)	71,239 (5)	113,982 (8)	56,991 (4)	1,245 (0.1)	128,230 (9)	156,725 (11)	99,734 (7)	299,203 (21)
Age, median (IQR)	71 (66-77)	74 (68-81)	74 (68-82)	72 (68-79)	70 (65-75)	69 (64-75)	68 (64-74)	70 (65-75)	69 (64-74)	67 (63-72)
Sex, female (%)	55.1	69.2	75.3	34.7	39.0	63.8	60.8	50.2	62.7	49.0
Expected number of therapeutic Subgroup drugs	6.4	5.2	5.1	4.3	4.2	3.3	3.0	2.9	2.8	0.5
Therapeutic subgroup drug										
A02: Drugs for acid related disorders	**41%**	**33%**	18%	13%	14%	17%	25%	10%	18%	3%
A06: Drugs for constipation	4%	5%	2%	0%	1%	**7%**	3%	0%	1%	0%
A10: Drugs used in diabetes	**18%**	4%	7%	3%	**56%**	2%	1%	3%	1%	1%
A12: Mineral supplement	7%	7%	**41%**	1%	0%	0%	0%	4%	0%	0%
B01: Antithrombotic agents	35%	30%	24%	**97%**	34%	10%	3%	7%	4%	1%
B03: Antianemic preparations	6%	**16%**	6%	3%	**8%**	7%	4%	2%	4%	1%
C01: Cardiac Therapy	1%	1%	1%	**13%**	0%	1%	0%	1%	1%	0%
C03: Diuretics	**32%**	20%	**100%**	12%	8%	6%	5%	21%	4%	1%
C07: Beta blocking agents	23%	10%	**30%**	**47%**	4%	8%	3%	17%	2%	1%
C08: Calcium channels blockers	**43%**	23%	**33%**	25%	21%	8%	4%	**43%**	4%	1%
C09: Agents acting on the renin-angiotensin system	**72%**	33%	43%	42%	**69%**	14%	11%	**68%**	10%	4%
C10: Lipid modifying agents	**55%**	28%	31%	**66%**	**85%**	16%	7%	28%	11%	4%
D07: Topical dermatological Corticosteroids	14%	8%	15%	10%	10%	12%	11%	10%	**22%**	5%
G03: Sex hormones and modulators of the genital system	12%	11%	**14%**	4%	4%	**15%**	**13%**	7%	**19%**	5%
G04: Urologicals	**14%**	7%	4%	**14%**	**14%**	7%	9%	10%	10%	4%
H02: Corticosteroids for system use	6%	**52%**	4%	2%	2%	1%	5%	1%	**10%**	0%
H03: Thyroid therapy	6%	**10%**	**12%**	4%	6%	**9%**	4%	4%	7%	2%
M01: Antiinflammatory and antirheumatic products	**71%**	18%	16%	7%	14%	8%	**58%**	9%	10%	4%
M05: Drugs for treatment of bone diseases	4%	**43%**	7%	3%	2%	7%	6%	3%	**8%**	2%
N02: Analgesics	**100%**	**60%**	42%	20%	22%	35%	**78%**	13%	17%	3%
N03: Antiepileptics	**7%**	3%	2%	2%	1%	**11%**	3%	1%	1%	0%
N04: Anti-parkinson drugs	2%	2%	1%	1%	1%	**5%**	1%	0%	0%	0%
N05: Psycholeptics	18%	14%	12%	5%	5%	**46%**	10%	5%	9%	1%
N06: Psychoanaleptics	9%	15%	8%	5%	7%	**45%**	5%	4%	5%	1%
R01: Nasal preparations	5%	0%	2%	4%	3%	2%	4%	3%	**23%**	1%
R03: Drugs for obstructive airways diseases	11%	**44%**	12%	7%	7%	7%	9%	6%	**26%**	2%
R06: Antihistamines for systemic use	5%	0%	4%	2%	3%	3%	3%	2%	**18%**	0%
S01: Ophthalmologicals	16%	19%	18%	13%	14%	16%	12%	12%	**30%**	7%

[a]=probability of receiving the therapeutic subgroup drug in general

Bold: 25% Increase of the overall probability. The colored boxes: Increase of at least 10 percent points over the overall probability. Different colors represent different main groups

Appendix 1:

Supplement to: Use of prescription drugs in the older adult population – a nationwide pharmacoepidemiological study. Christensen LD*, Reilev M, Juul-Larsen HG, Jørgensen LM, Kaae S, Andersen O, Pottegård A, Petersen J. *Corresponding author: Clinical Research Center, Copenhagen University Hospital Hvidovre, Denmark, Kettegaard Allé 30, 2650 Hvidovre, Denmark. E-mail: Line.due.christensen@regionh.dk or linedue@gmail.com, phone: (+45) 38623350

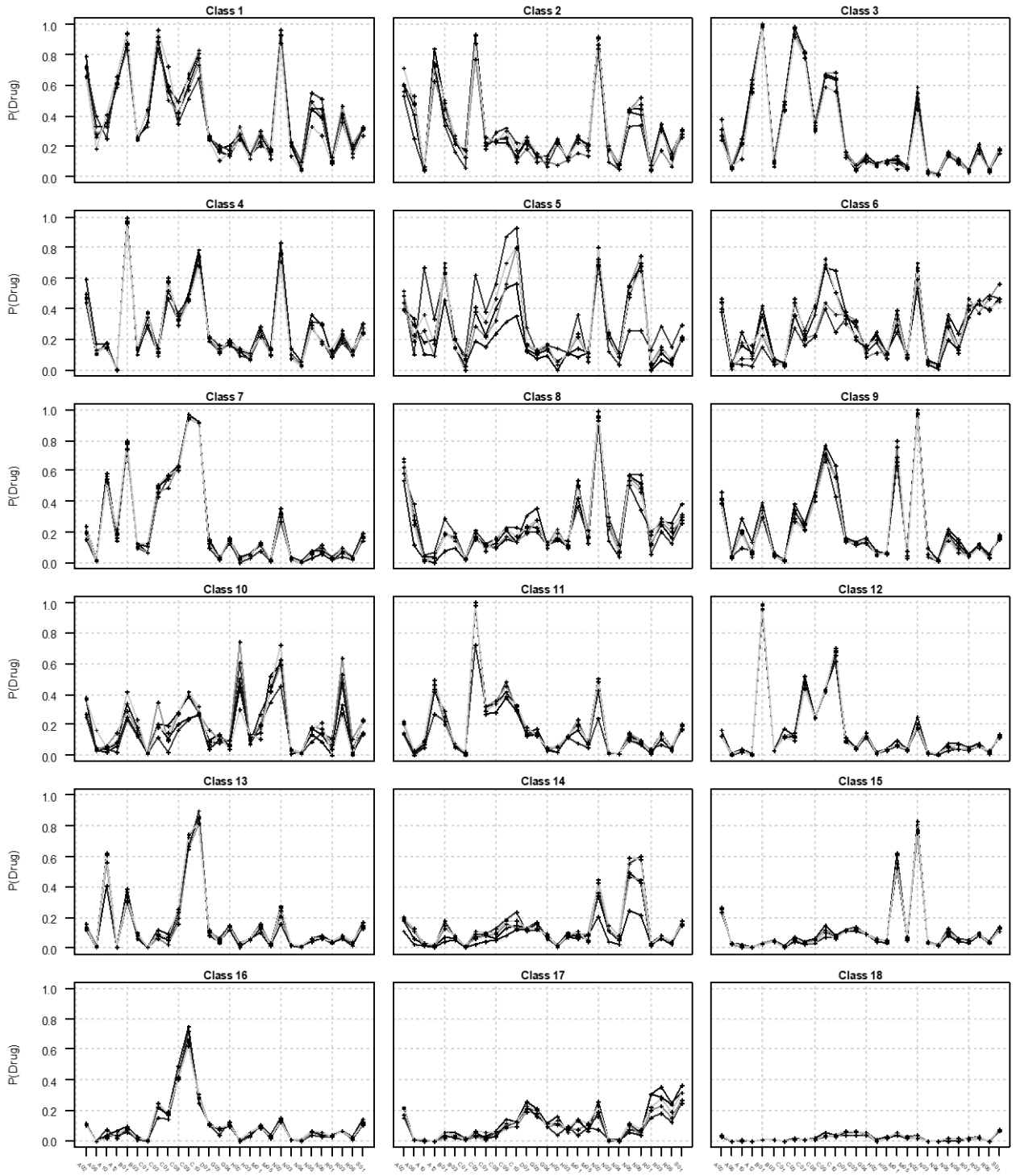

Figure 3. 18 drug profile model. Five datasets with 50,000 individuals for each class.

Appendix 2:

Supplement to: Use of prescription drugs in the older adult population – a nationwide pharmacoepidemiological study. Christensen LD*, Reilev M, Juul-Larsen HG, Jørgensen LM, Kaae S, Andersen O, Pottegård A, Petersen J. *Corresponding author: Clinical Research Center, Copenhagen University Hospital Hvidovre, Denmark, Kettegaard Allé 30, 2650 Hvidovre, Denmark. E-mail: Line.due.christensen@regionh.dk or linedue@gmail.com, phone: (+45) 38623350

Table 3. Three most frequent drug classes in the 28 therapeutic subgroup drugs used for the Latent Class Analysis

Therapeutic subgroup drugs	Drug classes
A02: Drugs for acid related disorders	A02BC: proton pump inhibitors, A02AA: magnesium compounds, A02AD: combinations and complexes of aluminium, calcium and magnesium compounds
A06: Drugs for constipation	A06AD: Osmotically acting laxatives, A06AB: Contact laxatives, A06AG: Enemas
A10: Drugs used in diabetes	A10BA: Biguanides, A10BB: Sulfonylureas, A10AE: Insulins and analogues for injection, long-acting
A12: Mineral supplement	A12BA: Potassium, A12AA: Calcium, A12AX: Calcium, combinations with vitamin D and/or other drugs
B01: Antithrombotic agents	B01AC: Platelet aggregation inhibitors excl. heparin, B01AA: Vitamin K antagonists, B01AF: Direct factor Xa inhibitors
B03: Antianemic preparations	B03BA: Vitamin B12 (cyanocobalamin and analogues), B03BB: Folic acid and derivatives, B03AA: Iron bivalent, oral preparations
C01: Cardiac Therapy	C01DA: Organic nitrates, C01AA: Digitalis glycosides, C01BD: Antiarrhythmics, class III
C03: Diuretics	C03AB: Thiazides and potassium in combination, C03CA: Sulfonamides, plain, C03DA: Aldosterone antagonists
C07: Beta blocking agents	C07AB: Beta blocking agents, selective, C07AG: Alpha and beta blocking agents, C07AA: Beta blocking agents, non-selective
C08: Calcium channels blockers	C08CA: Dihydropyridine derivatives, C08DA: Phenylalkylamine derivatives, C08DB: Benzothiazepine derivatives
C09: Agents acting on the renin-angiotensin system	C09AA: ACE inhibitors, plain, C09CA: Angiotensin II antagonists, plain, C09DA: Angiotensin II antagonists and diuretics
C10: Lipid modifying agents	C10AA: HMG CoA reductase inhibitors, C10AX: Other lipid modifying agents, C10AB: Fibrates
D07: Topical dermatological Corticosteroids	D07AC: Corticosteroids, potent (group III), D07AB: Corticosteroids, moderately potent (group II), D07AD: Corticosteroids, very potent (group IV)
G03: Sex hormones and modulators of the genital system	G03CA: Natural and semisynthetic estrogens, plain, G03FA: Progestogens and estrogens, fixed combinations, G03FB: Progestogens and estrogens, sequential preparations
G04: Urologicals	G04BE: Drugs used in erectile dysfunction, G04CA: Alpha-adrenoreceptor antagonists, G04BD: Drugs for urinary frequency and incontinence
H02: Corticosteroids for system use[a]	H02AB: Glucocorticoids, H02AA: Mineralocorticoids
H03: Thyroid therapy	H03AA: Thyroid hormones, H03BB: Sulfur-containing imidazole derivatives, H03BA: Thiouracils
M01: Antiinflammatory and antirheumatic products	M01AE: Propionic acid derivatives, M01AB: Acetic acid derivatives and related substances, M01AX: Other antiinflammatory and antirheumatic agents, non-steroids
M05: Drugs for treatment of bone diseases	M05BA: Bisphosphonates, M05BX: Other drugs affecting bone structure and mineralization, M05BB: Bisphosphonates, combinations
N02: Analgesics	N02BE: Anilids, N02AX: Other opioids, N02AA: Natural opium alkaloids
N03: Antiepileptics	N03AX: Other antiepileptics, N03AF: Carboxamide derivatives, N03AG: Fatty acid derivatives
N04: Anti-parkinson drugs	N04BC: Dopamine agonists, N04BA: Dopa and dopa derivatives, N04BD: Monoamine oxidase B inhibitors
N05: Psycholeptics	N05CF: Benzodiazepine related drugs, N05BA: Benzodiazepine derivatives , N05AH: Diazepines, oxazepines, thiazepines and oxepines
N06: Psychoanaleptics	N06AA: Non-selective monoamine reuptake inhibitors, N06AB: Selective serotonin reuptake inhibitors, N06AX: Other antidepressants
R01: Nasal preparations	R01AD: Corticosteroids, R01AX: Other nasal preparations, R01AA: Sympathomimetics, plain
R03: Drugs for obstructive airways diseases	R03AC: Selective beta-2-adrenoreceptor agonists, R03AK: Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics, R03BB: Anticholinergics
R06: Antihistamines for systemic use	R06AX: Other antihistamines for systemic use, R06AE: Piperazine derivatives, R06AD: Phenothiazine derivatives
S01: Ophthalmologicals	S01AA: Antibiotics, S01XA: Other ophthalmologicals, S01CA: Corticosteroids and antiinfectives in combination

9 [a] Only two drug classes