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A nationwide register-based study

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Abstract

Background: the number of centenarians increases rapidly. Yet, little is known about their health and use of medications.

Objective: to investigate pharmacological drug use in community-dwelling and institutionalized centenarians compared to nonagenarians and octogenarians.

Methods: we analysed data on dispensed drugs for centenarians (n=1,672), nonagenarians (n=76,584) and octogenarians (n=383,878) from the Swedish Prescribed Drug Register, record-linked to the Swedish Social Services Register. Multivariate logistic regression analysis was used to analyse whether age was associated with use of drugs, after adjustment for sex, living situation and co-morbidity.

Results: in the adjusted analysis, centenarians were more likely to use analgesics, hypnotics/sedatives and anxiolytics, but less likely to use antidepressants than nonagenarians and octogenarians. Moreover, centenarians were more likely to use high-ceiling diuretics, but less likely to use beta-blockers and ACE-inhibitors.

Conclusions: centenarians high use of analgesics, hypnotics/sedatives and anxiolytics either reflects a palliative approach to drug treatment in centenarians or that pain and mental health problems increase into extreme old age. Also, centenarians do not seem to be prescribed cardiovascular drug therapy according to guidelines to the same extent as nonagenarians and octogenarians. Whether this reflects an age or cohort effect should be evaluated in longitudinal studies.
Drug use in centenarians in Sweden – A nationwide register-based study

Introduction

The world has seen dramatic reductions in old age mortality [1]. Life expectancy has increased and the number of centenarians has doubled or more in most developed countries during the last ten years [2]. It has been estimated that if life expectancy continues to rise at the same rate as during the last 160 years, about 50 percent of people born in the beginning of this century will live to see their 100th birthday [3]. Thus, extremely old people should be regularly included in epidemiological studies, and not only in highly specialised centenarian studies, which often focus on centenarians as healthy survivors [4-6]. On the contrary, centenarians are not necessarily healthy when they reach one hundred years [7]. Rather, morbidity and mortality have been postponed into extreme old age [8-10].

Drug therapy in old age is complicated by multiple diseases, organ failure and cognitive impairment. Older people are therefore more sensitive to drugs and at the same time they use more drugs than younger age groups. Taken together, elderly people have the greatest risk of adverse drug reactions [11]. In contrast to the common notion that drug use increases with higher age, previous studies have indicated that drug use is lower in centenarians than in nonagenarians [6, 12, 13]. However, research on drug use in centenarians is scarce and often based on small and selected samples without comparisons to other age groups [7, 14-16]. Thus, we used nationwide register data to investigate drug use in both community-dwelling and institutionalised centenarians compared to nonagenarians and octogenarians. To our knowledge, this study is the largest investigation of drug use in centenarians published so far.
Drug use in centenarians in Sweden – A nationwide register-based study

Methods

Study population

The Swedish Prescribed Drug Register is one of the largest pharmacoepidemiological databases in the world. Data is collected at Swedish pharmacies and then transferred to the National Board of Health and Welfare. The register contains individual-based information on all prescribed dispensed drugs in Sweden (about nine million inhabitants). Over-the-counter drugs, drugs used in hospitals or drugs supplied from drug storerooms are not covered in the register. Variables include detailed data on dispensed drugs, age, sex, personal identification number and place of residence [17].

We focused on individuals born 1908 or earlier, who were dispensed a prescribed drug between 1 July and 30 September 2008 (n=1 672). This population of centenarians corresponded to 94% (1 672/1 775) of the total population aged 100 years and older in Sweden on 30 September 2008 according to Statistics Sweden’s census data. For age-related comparisons of drug use, we also included people born 1909-1928 (n=460 462).

Information from the three month period about when the prescription was filled, the amount of drug and the prescribed dosage was used to calculate the duration of drug exposure to obtain a list of concurrently used drugs on the last day of the study period. Thus, drug use was evaluated for each individual on the arbitrarily chosen date of 30 September 2008. In Sweden, the maximum quantity of drugs prescribed is for 90-days supply [18, 19]. When prescribed dosage was incomplete or missing (8.7%), we based our calculations of drug exposure on defined daily doses (DDDs). The DDD is the assumed average dose per day for a drug used for its main indication in adults [20]. For each drug, the mean prescribed daily dose (PDD) [20] for regular use was calculated. In the few cases where the PDD could not be calculated, we assumed 0.9 DDDs for regularly used drugs (based on calculations of the total mean value for regularly used drugs among the elderly in the study population). For drugs prescribed as
Drug use in centenarians in Sweden – A nationwide register-based study

needed, 0.45 DDDs (50% of 0.9) was employed. For dermatological and eye preparations, 1
DDD was assumed [19]. If a person was dispensed the same drug in different doses during the
study period, this was counted as one dispensed drug.

The study population derived from the Swedish Prescribed Drug Register was record-linked
by personal identification number to the Swedish Social Services Register to obtain
information about living situation (i.e. community-dwelling or institution) on 30 June 2008.

The Swedish Social Services Register has national coverage of individual-based information
about social services financed by Swedish municipalities, including institutional care for
people aged 65 years and older. In Sweden, only a negligible amount of institutional care for
older people falls outside the municipal system and very few persons receive long term care in
hospitals.

Measurements

The dispensed drugs were classified according to the Anatomical Therapeutic and Chemical
classification system (ATC), as recommended by the World Health Organization [20].

Age was categorized into three groups: 80-89 (octogenarians; reference group), 90-99
(nonagenarians) and ≥100 years (centenarians). Living situation was defined as community-
dwelling (own home) or institution (e.g. nursing home, sheltered accommodation). Number of
other drugs, used as a proxy for overall co-morbidity [21], consisted of the number of filled
prescriptions other than the drugs under study.

Statistical analysis

The most commonly dispensed drug classes in centenarians were compared to nonagenarians
and octogenarians. We used both univariate and multivariate logistic regression analysis to
investigate whether age was related to use of these drugs. In the univariate (unadjusted)
analyses, only age was entered as explanatory variable, without adjustment for other
variables. In the multivariate (adjusted) analyses, adjustment was made for sex, living
Drug use in centenarians in Sweden – A nationwide register-based study

situation and number of other drugs. The results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs). SPSS for Windows (SPSS, Version 17, Chicago, IL, USA) was used for the analyses.

**Role of the funding source**

This work was supported financially by the Swedish Council for Working Life and Social Research [2007-1947] and the Swedish Research Council [2007-5870].

The sponsor of the study had no role in the design, execution, analysis or interpretation of data, or writing of the study.
Drug use in centenarians in Sweden – A nationwide register-based study

Results

On average, centenarians were 101 years old and used 5.1 drugs per person, nonagenarians were 92 years old and used 5.7 drugs and octogenarians were 84 years and used 5.3 drugs. Table 1 shows that institutionalized used on average more drugs than community-dwelling persons, although this difference was smaller for centenarians. The majority of the study participants were women and the proportion of women increased with age (octogenarians: 62%; nonagenarians: 72%; and centenarians: 84% women). The proportion of institutionalized people also increased with age (octogenarians: 11%; nonagenarians: 34%; and centenarians: 59% in institutions) and women lived in institutions to a greater extent than men in all three age groups.

Table 2 shows 16 of the most commonly dispensed drugs classes among centenarians compared to nonagenarians and octogenarians stratified by living situation. Institutionalized individuals had a higher prevalence of use of most drug classes compared to their community-dwelling counterparts. However, this difference was in general less pronounced in centenarians.

The most frequently used drug class in centenarians was high-ceiling diuretics, which was less common in nonagenarians and octogenarians. However, other types of cardiovascular drugs (i.e. antithrombotic agents, beta blockers and ACE inhibitors) were less common in centenarians compared to nonagenarians and octogenarians.

The second most commonly used drug class among centenarians was minor analgesics, which were twice as common in centenarians as in octogenarians. In addition, opioids were more frequently used by centenarians than nonagenarians and octogenarians. Hence, centenarians had an overall higher use of analgesics than both nonagenarians and octogenarians.

Centenarians also had a high use of hypnotics/sedatives, antidepressants, anxiolytics and laxatives.
Drug use in centenarians in Sweden – A nationwide register-based study

The gender differences in drug use in centenarians were generally small and similar to that of octogenarians and nonagenarians. The largest difference was found for antidepressants, which were used by one in five of the female and one in ten of the male centenarians. We further explored the association between age and the most commonly used drugs in logistic regression analyses (Table 3). The results showed that centenarians were more likely to use analgesics (minor analgesics and opioids), hypnotic/sedatives, anxiolytics and laxatives than nonagenarians and octogenarians in both the unadjusted and adjusted analysis. Centenarians were also more likely to use antidepressants than octogenarians in the unadjusted analysis. However, the association was reversed in the adjusted analysis. Further, centenarians were more likely to use high-ceiling diuretics, but less likely to use antithrombotic agents, beta blockers and ACE inhibitors compared to nonagenarians and octogenarians.
Drug use in centenarians in Sweden – A nationwide register-based study

Discussion

Our large nationwide study of drug use in old age shows that centenarians use on average a similar number of drugs as octogenarians. Also, institutionalization increased markedly with age [22]. This indeed raises the question whether centenarians really have less health problems than younger elderly people [5, 6].

Further, centenarians used more analgesics (i.e. opioids and minor analgesics) than nonagenarians and octogenarians. Use of analgesics has been associated with institutionalization [23, 24] and more centenarians than octogenarians and nonagenarians lived in institutions. Therefore, it was surprising to find that centenarians had a higher probability of use of analgesics also after adjustment for living situation. Research about pain in centenarians has given conflicting results; there are findings of both a decreased frequency of pain [25] and comparable levels of pain in centenarians and younger elderly [26]. Our finding of higher use of analgesics in centenarians could reflect an actual increased level of pain in extreme old age or a palliative approach to pain treatment in centenarians.

Centenarians’ high use of laxatives might also reflect palliative care and side effects of opioids [27].

In a study of non-institutionalized Finns, centenarians had a lower use of psychotropic drugs than younger elderly people [13]. Conversely, in our study, centenarians used more anxiolytics, hypnotics/sedatives and antidepressants than octogenarians. However, after adjustment for sex, living situation and co-morbidity, centenarians were more likely to use hypnotics/sedatives and anxiolytics, but less likely to use antidepressants than nonagenarians and octogenarians. As with analgesics, our finding of centenarians’ higher use of hypnotics/sedatives and anxiolytics does not support the notion that centenarians are healthier than younger elderly people.
Drug use in centenarians in Sweden – A nationwide register-based study

There was a negative association between centenarians and use of antidepressants in the adjusted analysis. However, previous research has revealed that depressive symptoms are more common in centenarians than octogenarians [28]. Depression in extreme old age may be difficult to detect, particularly in patients with dementia. Instead of melancholy, the depression may be expressed as agitation and confusion [29]. This might lead to treatment with anxiolytics and hypnotics/sedatives instead of antidepressants in depressed centenarians. The cardiovascular drug use also differed between the three age groups. The most commonly used drug class in centenarians was high-ceiling diuretics, which was only half as commonly used by octogenarians. A high use of diuretics has also been reported in Finnish centenarians [14]. Octogenarians and nonagenarians in our study were more likely to use antithrombotic agents, beta blockers and ACE inhibitors than centenarians. Hence, centenarians do not seem to be prescribed cardiovascular drug therapy according to guidelines to the same extent as nonagenarians and octogenarians [14, 30]. Use of older types of drugs in centenarians either reflects a cohort or an age effect. That is, drug therapy initiated in younger ages is likely to be continued into old age. Alternatively, physicians might be hesitant to introduce new drugs to very old patients and, consequently, prescriptions for ‘old’ drugs may be routinely renewed (particularly in the institutional setting).

Female centenarians used only slightly more drugs than their male counterparts and the differences in individual drug use were generally small. This might suggest that gender differences in drug use [31] level off in very old age. Also, institutionalization was a determinant of drug use, although less so for centenarians than for octogenarians and nonagenarians.

The cross-sectional design of our study does not allow us to draw conclusions regarding causality and we cannot differentiate between cohort and age effects. The Swedish Prescribed Drug Register does not include information about over-the-counter drugs, drugs used in
Drug use in centenarians in Sweden – A nationwide register-based study

hospitals or drugs supplied from drug storerooms, which leads to an underestimation of drug use in the institutional setting. Further, data on dispensed drugs may not adequately reflect what is actually consumed.

Moreover, our method is built on an assumption that all current drugs were dispensed during the observed three month period, due to the fact that drugs are prescribed for use during at the most 90 days in Sweden. Therefore, we might have disregarded drugs that were dispensed before the three month period and used at a slower rate than intended. At the same time, we might have included drugs that were dispensed during the three month period but discontinued prematurely. Also, drug sales have been reported to be lower during the summer [32], which could lead to a general underestimation of drug use in our study. In addition, our method is based on interpretations of the dispensed drugs’ dosages as written by the prescribers, as well as assumptions about DDDs when information about dosage was incomplete or missing [18, 19].

The Swedish Prescribed Drug Register does not include information about the underlying indications or diagnoses for prescription of drugs. Thus, we cannot determine if certain health conditions were under or over treated. We also lacked data on general health status, although we did control for a proxy for overall co-morbidity (i.e. number of other drugs).

In conclusion, our large nationwide study suggests that the level of drug use in centenarians is comparable to that of octogenarians. Centenarians are more likely to use analgesics, hypnotics/sedatives and anxiolytics than nonagenarians and octogenarians. This may indicate pain and mental health problems in extreme old age. Further research of health status in relation to drug use is needed, to evaluate whether our findings reflect a palliative approach to drug treatment in centenarians.
Drug use in centenarians in Sweden – A nationwide register-based study

Also, centenarians do not seem to be prescribed cardiovascular drug therapy according to guidelines to the same extent as nonagenarians and octogenarians. Whether this reflects an age or cohort effect should be investigated in longitudinal studies.

Conflicts of interest

None

Ethics committee approval

This study was approved by the ethical board in Stockholm (Dnr 2009/477-31/3) and we only analysed non-identifiable data.
Drug use in centenarians in Sweden – A nationwide register-based study

References

Drug use in centenarians in Sweden – A nationwide register-based study


Drug use in centenarians in Sweden – A nationwide register-based study


Table 1. Characteristics of the octogenarians, nonagenarians and centenarians stratified by living situation, 2008

<table>
<thead>
<tr>
<th></th>
<th>Octogenarians (n=383 878)</th>
<th>Nonagenarians (n=76 584)</th>
<th>Centenarians (n= 1 672)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Community-dwelling (n=340 048)</td>
<td>Institution (n=43 830)</td>
<td>Community-dwelling (n=50 903)</td>
</tr>
<tr>
<td>Mean age (years ± SD)</td>
<td>83.8 ± 2.7</td>
<td>85.1 ± 2.7</td>
<td>92.2 ± 2.2</td>
</tr>
<tr>
<td>Median age (interquartile range)</td>
<td>83 (81-86)</td>
<td>85 (83-87)</td>
<td>92 (90-93)</td>
</tr>
<tr>
<td>Sex % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>91.2 (133 467)</td>
<td>8.8 (12 946)</td>
<td>73.8 (15 594)</td>
</tr>
<tr>
<td>Women</td>
<td>87.0 (206 581)</td>
<td>13.0 (30 884)</td>
<td>63.7 (35 309)</td>
</tr>
<tr>
<td>Median number of dispensed drugs (interquartile range)</td>
<td>4 (2-7)</td>
<td>7 (5-10)</td>
<td>5 (3-7)</td>
</tr>
</tbody>
</table>
Table 2. Dispensed drug classes in relation to age and living situation, 2008. Values are % (n)

<table>
<thead>
<tr>
<th>ATC-code</th>
<th>Drug class</th>
<th>Octogenarians (n=383 878)</th>
<th>Nonagenarians (n=76 584)</th>
<th>Centenarians (n= 1 672)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Community-dwelling (n=340 048)</td>
<td>Institution (n=43 830)</td>
<td>Community-dwelling (n=50 903)</td>
<td>Institution (n=25 681)</td>
</tr>
<tr>
<td>C03C</td>
<td>High-ceiling diuretics</td>
<td>21.6 (73 379)</td>
<td>38.0 (16 664)</td>
<td>34.7 (17 659)</td>
</tr>
<tr>
<td>N02B</td>
<td>Minor analgesics</td>
<td>16.2 (55 187)</td>
<td>46.9 (20 567)</td>
<td>22.8 (11 603)</td>
</tr>
<tr>
<td>B01A</td>
<td>Antithrombotic agents</td>
<td>46.3 (157 450)</td>
<td>50.8 (22 277)</td>
<td>48.1 (24 503)</td>
</tr>
<tr>
<td>N05C</td>
<td>Hypnotics/sedatives</td>
<td>19.6 (66 640)</td>
<td>33.2 (14 567)</td>
<td>25.8 (13 143)</td>
</tr>
<tr>
<td>A06A</td>
<td>Laxatives</td>
<td>8.6 (29 329)</td>
<td>33.9 (14 863)</td>
<td>13.5 (6 888)</td>
</tr>
<tr>
<td>B03B</td>
<td>Vitamin B12 and folic acid</td>
<td>17.0 (57 697)</td>
<td>30.4 (13 319)</td>
<td>24.0 (12 237)</td>
</tr>
<tr>
<td>N06A</td>
<td>Antidepressants</td>
<td>12.1 (41 054)</td>
<td>46.7 (20 452)</td>
<td>12.4 (6 327)</td>
</tr>
<tr>
<td>C07A</td>
<td>Beta blocking agents</td>
<td>38.1 (129 612)</td>
<td>30.3 (13 282)</td>
<td>34.0 (17 326)</td>
</tr>
<tr>
<td>A02B</td>
<td>Drugs for peptic ulcer and gastro-oesophageal reflux</td>
<td>14.4 (48 970)</td>
<td>24.5 (10 721)</td>
<td>15.4 (7 829)</td>
</tr>
<tr>
<td>N05B</td>
<td>Anxiolytics</td>
<td>7.1 (24 254)</td>
<td>24.2 (10 588)</td>
<td>8.8 (4 480)</td>
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<tr>
<td>D02A</td>
<td>Emollients and protectives</td>
<td>5.7 (19 378)</td>
<td>14.1 (6 166)</td>
<td>8.1 (4 134)</td>
</tr>
<tr>
<td>N02A</td>
<td>Opioids</td>
<td>8.2 (27 771)</td>
<td>18.0 (7 903)</td>
<td>9.8 (4 967)</td>
</tr>
<tr>
<td>C01D</td>
<td>Nitrates</td>
<td>10.7 (36 239)</td>
<td>10.3 (4 496)</td>
<td>14.8 (7 523)</td>
</tr>
<tr>
<td>A11E</td>
<td>Vitamin B-complex, incl. combinations</td>
<td>5.9 (20 213)</td>
<td>11.6 (5 078)</td>
<td>9.0 (4 569)</td>
</tr>
<tr>
<td>C03D</td>
<td>Potassium-sparing diuretics</td>
<td>6.1 (20 603)</td>
<td>8.7 (3 818)</td>
<td>8.9 (4 511)</td>
</tr>
<tr>
<td>C09A</td>
<td>ACE inhibitors</td>
<td>18.0 (61 203)</td>
<td>15.7 (6 900)</td>
<td>14.9 (7 574)</td>
</tr>
</tbody>
</table>
### Table 3. Logistic regression for dispensed drug classes in relation to age, 2008

<table>
<thead>
<tr>
<th>ATC-code</th>
<th>Drug class</th>
<th>Unadjusted analysis, OR (95% CI)</th>
<th>Adjusted analysis*, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Octogenarians</td>
<td>Nonagenarians</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n=383 878)</td>
<td>(n=76 584)</td>
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<tr>
<td></td>
<td></td>
<td>(n=383 878)</td>
<td>(n=76 584)</td>
</tr>
<tr>
<td>C03C</td>
<td>High-ceiling diuretics</td>
<td>Ref 2.01 (1.98-2.05)</td>
<td>2.55 (2.32-2.81)</td>
</tr>
<tr>
<td>N02B</td>
<td>Minor analgesics</td>
<td>Ref 1.87 (1.84-1.90)</td>
<td>2.61 (2.37-2.88)</td>
</tr>
<tr>
<td>B01A</td>
<td>Antithrombotic agents</td>
<td>Ref 1.04 (1.03-1.06)</td>
<td>0.65 (0.59-0.72)</td>
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<tr>
<td>N05C</td>
<td>Hypnotics/sedatives</td>
<td>Ref 1.50 (1.48-1.53)</td>
<td>1.83 (1.65-2.02)</td>
</tr>
<tr>
<td>A06A</td>
<td>Laxatives</td>
<td>Ref 1.98 (1.94-2.02)</td>
<td>3.21 (2.89-3.57)</td>
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<tr>
<td>B03B</td>
<td>Vitamin B12 and folic acid</td>
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<td>1.68 (1.51-1.87)</td>
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<td>N06A</td>
<td>Antidepressants</td>
<td>Ref 1.37 (1.34-1.39)</td>
<td>1.17 (1.03-1.32)</td>
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<tr>
<td>C07A</td>
<td>Beta blocking agents</td>
<td>Ref 0.77 (0.75-0.78)</td>
<td>0.36 (0.32-0.41)</td>
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<td>A02B</td>
<td>Drugs for peptic ulcer and gastro-oesophageal reflux</td>
<td>Ref 1.19 (1.17-1.21)</td>
<td>1.12 (0.98-1.27)</td>
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<td>N05B</td>
<td>Anxiolytics</td>
<td>Ref 1.58 (1.54-1.62)</td>
<td>2.04 (1.80-2.32)</td>
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<tr>
<td>D02A</td>
<td>Emollients and protectives</td>
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<td>2.39 (2.08-2.73)</td>
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<td>N02A</td>
<td>Opioids</td>
<td>Ref 1.40 (1.37-1.43)</td>
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</tr>
<tr>
<td>C01D</td>
<td>Nitrates</td>
<td>Ref 1.38 (1.35-1.41)</td>
<td>1.14 (0.98-1.32)</td>
</tr>
<tr>
<td>A11E</td>
<td>Vitamin B-complex, incl. combinations</td>
<td>Ref 1.55 (1.51-1.60)</td>
<td>1.64 (1.40-1.92)</td>
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<td>Potassium-sparing diuretics</td>
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<td>1.61 (1.37-1.89)</td>
</tr>
<tr>
<td>C09A</td>
<td>ACE inhibitors</td>
<td>Ref 0.76 (0.74-0.77)</td>
<td>0.37 (0.31-0.44)</td>
</tr>
</tbody>
</table>

*Adjusted for sex, living situation and number of other drugs