A cross-sectional study

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ABSTRACT

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Background: With advancing age the brain becomes more sensitive to centrally acting drugs thus increasing the risk of cognitive side-effects. The Swedish National Board of Health and Welfare developed indicators to measure and follow quality in older people's drug therapy, one being “Potentially Inappropriate Medications risking Cognitive impairment (PIMcogn)”. Associations between anticholinergics and cognitive impairment are described, especially in persons with Alzheimer's disease or Lewy Body Dementia/Parkinson's disease dementia, due to degenerated cholinergic pathways.

Objectives: To examine the prevalence of PIMcogn and if it differed between nursing home residents with and without a dementia diagnosis and between residents with different dementia aetiologies.

Methods: Descriptive cross-sectional study, based on residents ≥ 65 years in nursing home dementia units in Malmö, Sweden, in 2012–2013 (N = 574).

Results: The study population consisted of 76% women, the mean age was 86 years and a dementia diagnosis was registered in 92%. A total of 74% were prescribed at least one PIMcogn. Benzodiazepines were prevalent in 59%, opioids in 27%, antipsychotics in 20% and anticholinergics in 13%. Opioids used regularly and antiepileptics were more common in residents without a dementia diagnosis. The lowest proportion of anticholinergics was seen in the oldest age group, 11.0%. There was no difference seen in anticholinergics between dementia types with considerable cholinergic deficit and other dementia diagnoses.

Conclusions: Treatment with at least one PIMcogn was common. Usage of benzodiazepines and antipsychotics was, despite the knowledge of alarming side-effects, high. An awareness of the inappropriateness in prescribing anticholinergics to the oldest old seems to be apparent, but not to persons with cholinergic deficit.

1. Introduction

As the body ages, both pharmacokinetic, especially renal, and pharmacodynamic changes occur. The brain becomes more sensitive to drugs with central effects, which increases the risk of cognitive side effects, varying from mild cognitive impairment to confusion and dementia-like conditions. Inappropriate prescription of drugs implies that the risks connected with the drug exceed the benefits. The Swedish National Board of Health and Welfare has defined national indicators to measure and follow the quality of older people's drug treatments. Good quality means that the indicators are followed on a population basis and that drugs with a high risk of side effects are avoided. The indicators are primarily applied towards persons older than 75 years of age. One of the indicators is "Potentially Inappropriate Medications risking Cognitive impairment (PIMcogn)", such as drugs...
with anticholinergic effects, benzodiazepine derivatives, antipsychotics and opioids (Table 1).  

Internationally, different criteria are used to describe drugs that in older people may be considered inappropriate, for example Beer’s criteria and the Drug Burden Index. Beer’s criteria were the first criteria developed; the criteria were updated in 2019 and contain lists of PIMs. The Drug Burden Index (DBI) is a tool to measure the cumulative exposure to anticholinergic and sedative medications in elderly individuals. The indicators developed by the Swedish National Board of Health and Welfare are based on the international criteria and adjusted to the medications used in Sweden.  

A Swedish study described low quality in prescribing of drugs to residents in nursing homes (NH) or specific dementia unit NH. Trends indicating that the prevalence of PIMs in NH residents is increasing have previously been reported, however, a recent study described a modest decrease of PIMs in NH residents. A continued alertness about prescribing of PIMs to older people with dementia is considered highly important. It is therefore valuable to examine the prevalence PIMs that may cause cognitive impairment in NH dementia units.  

This study’s objective was to examine the quality of drug treatment in older people living in NH dementia units, according to the Swedish quality indicators, considering the drugs’ potential cognitive impairment and with a special focus on anticholinergics. The primary aim was to examine the prevalence of PIMcogn and the secondary aim was to find out if the prescription of PIMcogn differed between residents with and without a registered dementia diagnosis and between residents with different dementia diagnoses.  

2. Methods  

2.1. Design  

A descriptive cross-sectional study was conducted, based on data from residents in NH dementia units.  

2.2. Setting and participants  

Inclusion criteria were the following: residents aged 65 or more, living in NH dementia units in Malmö, the third-largest city in Sweden with approximately 340,000 inhabitants. Trends indicating that the prevalence of PIMs in NH residents is increasing have previously been reported, however, a recent study described a modest decrease of PIMs in NH residents. A continued alertness about prescribing of PIMs to older people with dementia is considered highly important. It is therefore valuable to examine the prevalence PIMs that may cause cognitive impairment in NH dementia units.  

Inclusion criteria were the following: residents aged 65 or more, living in NH dementia units in Malmö, the third-largest city in Sweden with approximately 340,000 inhabitants from different ethnic groups, during the period from January 2012 until March 2013. The cut off age was set to 65, although the indicators from The Swedish National Board of Health and Welfare are primarily applied towards persons older than 75 years of age, since NH residents are extra vulnerable/biologically aged. Exclusion criteria were residents in end of life (terminal palliative care), residents without a current medication list and residents with missing data regarding their personal identity number. Mean number of residents per NH unit was fifteen.  

2.3. Collection of data variables  

This study was part of a larger ongoing project at Lund University, Malmö, Sweden, approved by the Regional Ethical Review Board in Lund (registration numbers 2011/514 and 2012/597). Data were collected from all of Malmö’s NH dementia units (n = 40). The outcomes for the main project were the prevalence of dementia with Lewy body symptoms, the usage of psychotropics in older people with clinical signs of LBD and the survival among older people with two or more signs of LBD. From that project, data regarding age, gender, dementia diagnoses and medication lists collected from the Swedish national medication dispensing system were used. Multi-dose drug dispensing means that patients get their drugs machine dispensed into one unit for each dose occasion and packed in disposable bags.  

In south Sweden, electronic medical records (EMRs) are separate for inpatient and primary care. The previously collected data concerning dementia diagnoses only included diagnoses from the hospital EMRs. Dementia is, in Sweden, commonly diagnosed in primary health care and for the residents without registered dementia diagnoses in the hospital EMRs, we therefore also collected diagnosis data from the primary health care. In a few cases however, there was no diagnostic data available from primary care in the county systems if the patient was only cared for by a private care provider.  

The system containing primary health care diagnoses was searched for the period of January 2011 to March 2013, for the following International Classification of Diseases (ICD-10) coded dementia diagnoses: F00 (Dementia in Alzheimer’s disease), F01 (Vascular dementia), F02 (Dementia in other diseases classified elsewhere), F03 (Unspecified dementia), F04 (Organic amnestic syndrome, not induced by alcohol and other psychoactive substances), F10.7A (Residual and late-onset psychotic disorder, including alcoholic dementia N08), G30 (Alzheimer’s disease), G31 (Other degenerative diseases of nervous system, not elsewhere classified including G31.8A, Lewy body dementia). Having a registered dementia diagnosis may indicate that a proper investigation has been performed prior to the diagnosis. This means the chance is greater for an accurate diagnosis based on aetiology for the cognitive decline. Knowing the aetiology might increase the awareness to high-risk medications.  

Quality of treatment was defined as the prevalence of PIMcogn in accordance with the Swedish quality indicators, defined by the National Board of Health and Welfare.  

The medication lists were reviewed and PIMcogn were identified by Anatomical Therapeutic Chemical (ATC) Classification System (Table 1). Propiomazine (N05CM06), used to treat insomnia, was added to the list of drugs with anticholinergic effects, as it is considered having anticholinergic properties, however only registered in Sweden and therefore missing in internationally used anticholinergic scales. Notably, mirabegron (G04BD12), does not have anticholinergic effects and was therefore not included among other drugs for urine incontinence.  

3. Theory/calculations  

Previous international studies reported an association between anticholinergic drugs and cognitive decline and some studies even found an increased risk of developing dementia with high and prolonged use of anticholinergics. A review concluded that the damaging effect of anticholinergics is higher in more cognitively impaired individuals. In persons with Alzheimer’s disease (AD) and Lewy body dementia (LBD)/Parkinson’s disease dementia (PDD) the risk is considerable because of deficits in cholinergic neurotransmission, already reducing the cognitive capacity.
Anticholinergic burden is a concept to summarize anticholinergic effects of different drugs, as each anticholinergic drug may increase the risk of cognitive impairment. Considering this, we aimed to determine how common treatment with several anticholinergic drugs was and further examined this with respect to number of anticholinergic drugs and divided into subgroups. The subgroups were drugs for urinary frequency and incontinence, and one of either hydroxyzine, promethazine or alimemazine, as being commonly used as sedatives in Swedish NHs, according to clinical experience.

The pharmacological treatment for neuropsychiatric (NP) symptoms includes hypnotics/sedatives, anxiolytics, antipsychotics and antidepressants. In combining different psychotropic medications, the clinician must very cautiously avoid harmful interactions. Large studies on antipsychotics, especially conventional medications, have shown an association between their use and increased mortality in older people, especially those with dementia. Some studies have reported significant improvements in NP symptoms with atypical antipsychotics and rational use may improve the quality of life and functional status of elderly patients with NP diseases. However, these drugs are still often misused and there is a lack of knowledge on the risks of atypical antipsychotics in community-dwelling elderly patients.

3.1. Statistical methods

PIMcogn were classified as dichotomous variables and descriptive statistics were used. The prevalence of PIMcogn was also compared between residents with and without a registered dementia diagnosis, using Pearson’s chi-squared test or Fisher’s exact test.

The NH residents were divided into age groups (65–74, 75–84 and 85–105 years). Persons aged 85 years or older are often referred to as the “oldest old” and hence were defined as one age group. Opioids, benzodiazepines and anticholinergics were further divided into subgroups, by “regular treatment” and “any treatment” (i.e. regular and as needed treatment as documented in the EMRs and the medication dispensing system, without knowledge of how frequent the drugs were used if documented “as needed”).

Further, we analyzed the prevalence of anticholinergic drug use in the group of NH residents with either AD or LBD/PDD and if it differed from the prevalence in residents with other dementia types. Missing data on dementia diagnosis (n = 6) was handled by performing these comparison analyses only for residents where diagnosis data was registered in the county systems.

SPSS version 26.0 was used for calculations. The level of statistical significance was set at p < 0.05.

4. Results

A total of 574 residents living in NH dementia units were included, and 437 (76.1%) of them were women. The mean age was 86.0 (± 7.0) years, with a range from 65 to 105 years. A dementia diagnosis was registered for 523 residents (92.1%, n = 568, missing data on dementia diagnosis in six residents). Of those, 23.5% had AD, 4.0% had LBD/PDD, 23.3% had vascular dementia and 31.5% had unspecified dementia.

In total, 73.9% of the residents were treated with drugs from at least one of the groups of PIMcogn. Treatment with drugs from one of the groups was seen in 33.1%, whereas 40.8% were treated with drugs from two or more of the groups (Table 2). There was no significant difference between groups of different age ranges regarding number of PIMcogn groups (p = 0.100).

Table 3 shows that 58.9% of the residents were treated with benzodiazepine derivatives whereof half of them on regular treatment. Oxazepam was the predominant prevalent benzodiazepine. Opioids were used in 26.7% of the residents and regularly in 17.9%. Treatment with antipsychotics was prevalent in 19.7%. The proportions of residents treated with any kind of PIMcogn are shown in Table 2.

Treatment with opioids, antiepileptics and anticholinergics tended to be more common among the residents without a registered dementia-diagnosis, but only significant considering the treatment with opioids regularly (p = 0.046) and antiepileptics (p = 0.029) (Table 3).

In total, 61.7% of the NH residents were in the oldest group, 85–105 years. There was a significant difference regarding anticholinergic drugs between the age groups, with the lowest proportion in the oldest group (p-value 0.002). The proportions of antipsychotics and benzodiazepine derivatives in the different age groups are presented in Table 4.
of all residents were prescribed at least one anticholinergic drug. Treatment with hydroxyzine, promethazine or alimemazine represented 58.7% of the anticholinergic drug use. Treatment with drugs for urinary frequency and incontinence was found in four residents. There was no significant difference (p-value = 0.390) in anticholinergic drug use between the group of residents with AD or LBD/PDD and the group of residents with other types of dementia, i.e. vascular dementia, dementia NOS or unknown type of dementia (Table 6).

5. Discussion

5.1. Key results

This descriptive cross-sectional study, based on data from residents in NH dementia units in Malmö, showed that three out of four residents were treated with drugs from at least one of the group of drugs of PIMcogn. Furthermore, it showed that the prevalence of treatment with benzodiazepines was 59% (whereof half were treated on a regular basis), with opioids 27%, with antipsychotics 20% and with anticholinergics 13%. The lowest proportion of anticholinergics was seen in the oldest group of residents (85–105 years). There was no significant difference in use of anticholinergics in residents with AD or LBD/PDD, i.e. the patients with the greatest cholinergic deficits, compared to residents with other dementia diagnoses.

5.2. Findings in relation to existing literature

In this study population PIMcogn were frequently used, which confirms previous national findings on residents in NHs or NH dementia units. In the neighboring countries Finland and Norway a high prevalence of PIMs similarly was found for residents in NHs (35–70%) and in Switzerland eight out of ten NH residents received at least one PIM. International systematic reviews reported a prevalence of PIMs in persons with cognitive impairment ranging from 20% to 50% and of 43% in older people living in NHs. The prevalence above is varying, probably partly due to different criteria for inappropriate drugs used internationally. This study focused on PIMcogn, which is not completely consistent with other criteria used, such as Beers criteria or DBI, and therefore the results are not directly comparable.

Table 5 shows drugs with significant anticholinergic effect where 13.1% of all residents were prescribed at least one anticholinergic drug. Treatment with hydroxyzine, promethazine or alimemazine represented 58.7% of the anticholinergic drug use. Treatment with drugs for urinary frequency and incontinence was found in four residents. There was no significant difference (p-value = 0.390) in anticholinergic drug use between the group of residents with AD or LBD/PDD and the group of residents with other types of dementia, i.e. vascular dementia, dementia NOS or unknown type of dementia (Table 6).

Compared to the current results of almost 60% being treated with benzodiazepines, the prevalence in similar populations in Sweden was previously found to be 12% (though only long-acting) and in Australia 17% (short- and long-acting). In designing this study, long-acting benzodiazepines were not separated from short-acting, in accordance with the list of PIMcogn. Long-acting benzodiazepines should, in general, be avoided, but short-acting are sometimes used in short periods to treat insomnia, anxiety and behavioral and psychological symptoms of dementia (BPSD). However, benzodiazepine use in elderly is associated with an increased risk of sedation, cognitive impairment, delirium, falls and fractures and even when only taking regular treatment in consideration, the prevalence in this study was alarmingly high. Non-pharmacological options should always be the first choice in soothing anxiousness and may replace high-risk pharmaceutical treatment when appropriate. Decision-makers should therefore plan for educational measures and staff training allowing optimal caregiving and nursing. This study is based on data from 2012 to 2013 and statistics on use of benzodiazepines show a decreasing trend in persons aged 65 and above, both nationally and in the south of Sweden, although the use is higher in the south of Sweden. The reason for the latter is unknown. There might be differences in staffing levels in NHs in different parts of Sweden, in therapeutic traditions, or in ethnicity, with potentially higher expectation on pharmacological solutions in medical situations. Initiatives have been taken regionally to diminish the use of benzodiazepines.

The use of opioids in this study population confirms previous studies from NHs with dementia units. Opioids were more prevalent in residents without a dementia diagnosis, which is in line with previous research. This might be explained by NH residents with dementia being undertreated for their pain, or a prescriber awareness of opioids’ potential effects on cognition, resulting in alternative and more appropriate analgesic choices, pharmacological or non-pharmacological.

Antipsychotics were used in 20% of NH residents, which is consistent with previous reports from NHs (6–38%). One study reported NH residents with dementia twice as likely to be prescribed antipsychotics. Another study found that approved indications for treatment were often missing (defined as psychotic condition, other disease with psychotic symptoms and dementia with BPSD such as severe aggressiveness). However, rational use of atypical antipsychotics may improve the quality of life and functional status of patients with NP diseases.

Table 6 shows drugs with significant anticholinergic effect in nursing home residents with different types of dementia.

| Kind of anticholinergic treatment | Dementia-diagnosis | No dementia-diagnosis | P-value |
|----------------------------------|--------------------|-----------------------|---------|
| All treatment, regularly and as needed, n (%) | n = 523 | n = 45 | 0.304 |
| Drugs for urinary frequency and incontinence, n (%) | 2 (0.4) | 1 (2.2) | 0.767 |
| Hydroxyzine/Promethazine/Alimemazine, n (%) | 39 (7.5) | 4 (8.9) | 0.63 |

1 Alzheimer’s disease or Lewy body dementia/Parkinson’s disease dementia.
2 Other types of dementia, i.e. vascular dementia, dementia NOS or unknown type of dementia.
3 ATC-code G04BD excl. G04BD12 (mirabegron).
4 Treatment with one of these drugs.
Persons with dementia have a greater risk of cognitive decline, cerebrovascular events and mortality when treated with antipsychotics. Effects on behavioral symptoms of BPSD are modest and other alternatives are preferable. Hence, antipsychotics should be prescribed only after having tried other non-pharmacological or pharmacological options and then in short periods with scheduled evaluations. Clinicians should keep in mind that no guidelines can address the complexities of an individual patient.

The assessment of anticholinergic drug use is based on the Swedish indicators from the Swedish National Board of Health and Welfare, which includes only drugs with a marked anticholinergic effect. The anticholinergic burden has not been examined. Other instruments used to identify anticholinergics, for example Beers criteria, DBI and different ACB-scales include drugs with varying anticholinergic effects. Compared to the current prevalence of 13%, previous studies on NH residents with dementia report anticholinergics with marked effect in 19% in Sweden and 11%–37% in the United States. Similar results as in this study showing a lower proportion of anticholinergics in the oldest age group, were earlier described. This might indicate an awareness of the inappropriateness in using anticholinergics in the oldest old.

Consistent with previous findings, no significant difference in exposure for anticholinergics was found between residents with or without a dementia diagnosis. A Spanish study found dementia severity, to have a non-AD neurodegenerative dementia and to live in a NH being factors increasing the odds of being exposed to anticholinergic drugs. In Australia anticholinergics were more frequent in people with dementia, whereas a Finnish study described NH residents with dementia having a lower anticholinergic burden compared to residents without dementia. In this study the use of hydroxyzine, promethazine or alimemazine together represented six out of ten of the anticholinergic drug use. Drugs for urinary frequency and incontinence were found in only four residents (0.7%). This contrasts with American NH dementia units, where these drugs are the most commonly used anticholinergics. Attempts have earlier been made to switch anticholinergics to drugs with lower anticholinergic burden, with varying results in cognitive function and BPSD symptoms. There was no difference in anticholinergic drug use between residents with cholinergic deficit, i.e. AD or LBD/PDD, and other dementia types although the risk of harm is higher in dementia with cholinergic deficit.

In the south of Sweden, interdisciplinary medication reviews involving pharmacists are recommended for NH residents and seem to be a valuable method concerning reducing the number of PIMs and thereby improving the quality of pharmacotherapy. National and regional statistics show that use of PIMs has decreased the last years, but anticholinergics remain relatively stable regionally.

5.3. Policy implications

Quality of life must be considered highly important in NH residents and both pharmacological and non-pharmacological treatments should be optimized to achieve good effects and minimize harm. Drugs classified as PIM/PIMcogn might in individual cases be appropriate under surveillance and with age-adjusted doses. However, associations between exposure to an increasing number of PIMs and lower quality of life has been described. Using multiple categories of potentially harmful medications were related to poor health-related quality of life, poor psychological well-being and poor self-rated health. Decision-makers should therefore plan for staffing levels allowing optimal caregiving and nursing. More time for the responsible physician allocated on NHs and further education in geriatric pharmacotherapy for prescribers are other important measures.

5.4. Strengths and limitations

The cross-sectional design was a meaningful method to extract information on a large number of NH residents, in all NH dementia units in Malmö. The study design, however, comes with some limitations. Indications for the different treatments are not known, but the drug-specific quality indicators are population-based and so we can conclude that the quality on treatment with PIMcogn must be considered low. Further, we don’t know if treatments were temporary, if any evaluation on effect was planned or if drug reduction was ongoing. Doses have not been assessed. Anticholinergic burden was not assessed, since there is no validated scale for Swedish conditions yet. Dementia severity was not registered but was probably moderate to severe since our study participants were living in a NH dementia unit. Considering antipsychotics, there was no information on whether the residents had underlying psychiatric disorders in addition to dementia.

Since many NH residents are treated in primary health care, they might have more specific dementia diagnoses registered there. Diagnosis data from primary health care was only collected in the cases where no diagnosis was registered in hospital EMRs. This may affect our results on use of anticholinergics in different dementia diagnoses.

5.5. Future research

Several interventions aiming at decreasing prescriptions of PIMcogn in NHs can be thought of. Computer-assisted alerts might be further developed to warn the prescriber not only that the patient is old but has a diagnosis of dementia and so discourage from prescribing of PIMcogn. More time for the responsible physician allocated on NHs and repeatedly educational arrangements are possible interventions to be evaluated.

Further, a study designed in similarity to this one in the same settings could evaluate if any differences in PIMcogn prescription can be seen today compared to when the data of this study was collected. This would allow to assess if the ongoing attention on the subject has had impact on the prescription pattern.

6. Conclusions

Treatment with at least one drug potentially causing cognitive impairment was common in NH dementia units in Malmö during the study period. Usage of benzodiazepines and antipsychotics was, despite the knowledge of alarming side-effects, high.

An awareness of the inappropriateness in prescribing anticholinergics to the oldest old seems to be apparent, but not to persons with cholinergic deficit due to AD or LBD/PDD.

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Authors’ contributions

All authors contributed to the study conception and design. Data collection was performed by Iris Zahirovic. Material preparation and analysis were performed by Jenny Hansen Kristensson with support from Sara Modig. The first draft of the manuscript was written by Jenny Hansen Kristensson and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Informed consent forms were given to the head nurse at the 40 NHs, they thereafter collected oral informed consent from the residents and/or their family members. If the resident lacked the capacity to consent himself/herself because of fragility the family member and/or trustee made this decision together with the head nurse before being included in the study. The Regional Ethical Review Board in Lund approved the study (registration numbers 2011/514 and 2012/597).

Data availability statement

The anonymized datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.
Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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