Drug use and drug-related problems in nursing homes: prevalence, changes following medication review and variation between institutions

Drug use and medication review in nursing homes in Oslo

Thesis for the degree philosophiae doctor (ph.d.) at the University of Oslo

Amura Francesca Gladhaug

Department of General Practice

Institute of Health and Society

University of Oslo

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2 SUMMARY

Background

Nursing home (NH) residents are characterized by old age, multimorbidity, polypharmacy and a high prevalence of dementia. The common use of potentially inappropriate medications increases the risk for drug-related problems (DRPs), such as adverse drug reactions, sometimes with serious consequences. In Norway, the national prescription database does not include individual drug prescription data for persons living in NHs. Such data must therefore be collected from the institutions, e.g. as part of a research project. Although NH residents are considered more multimorbid and frail than their peers living at home, little is known about drug utilization of older people living at home as compared with their peers residing in NHs. Little has been published about the drug use at NHs in Oslo, even though the municipality has the largest NH population in Norway. Previous medication review (MR) studies, predominately from other regions in Norway, have shown variation between NHs in drug use, but little is known about the reasons for the variation. Knowledge about variation in DRPs between NHs is scarce. Whether the increased attention towards more appropriate drug treatment in NHs during the last decade has led to more uniform drug use needs to be investigated in larger studies. MRs are recommended interventions for identifying and resolving DRPs in NHs, but to which extent they reduce inappropriate medication use needs to be researched further.

This present thesis has focused on the drug utilization in NHs in Oslo investigating the:
- DRPs and changes in drug utilization after MRs in NHs (*article I*)
- variation between NHs in drug use and in DRPs (*article II*)
- differences between the drug use of older NH residents and their peers living at home (*article III*).

Methods and materials

This thesis consists of three cross-sectional studies. The drug use data in NHs was generated by 2,465 MRs performed at 41 NHs in Oslo during 2011 - 2014. The drug use data of Oslo residents ≥ 70 years old living at home in 2012 (n = 48,944) was retrieved from the Norwegian Prescription Database.

The MRs were performed according to a standardized procedure by multidisciplinary teams consisting of a pharmacist, NH physician and NH nurse. The pharmacists identified potential

DRPs by using the explicit criteria STOPP/START, the NORGEP criteria and the Norwegian drug–drug interaction database. The potential DRPs were discussed during MR meetings, taken into account the clinical information about the patients. Thereafter the teams agreed upon the DRPs and the interventions to resolve them.

Article I: The use of regular and pro re nata (prn) drugs was compared before and after the MRs in 2,465 long-term NH patients and the DRPs and interventions to solve them were described. Factors associated with DRPs and with change in the number of drugs after MR were explored by regression analysis.

Article II: The variation between 41 NHs in the use of regular drugs and in the DRPs was described. The NH quartiles with highest and lowest mean drugs per patient were compared in terms of drug use and DRPs. Relationships between drug use and DRPs and factors associated with DRPs at the respective NH were explored by using the Pearson's correlation coefficient and regression analysis.

Article III: the drug use of older people (≥ 70 years) living in a NH or in their own homes in Oslo during 2012 was described and compared by gender and by age.

Main findings

Article I: Following the MRs an average of 2.6 DRPs per patient were identified, 2.0 for regular and 0.6 for prn drugs. The use of unnecessary drugs (43.5%), excess dosing (12.5%) and lack of monitoring of the drug use (11%) were the most frequent DRPs. Opioids and psychotropic drugs were most commonly involved in all DRPs. Being a woman was associated with an 11% increased risk of DRPs. DPRs were not associated with the age of the NH residents. The most frequent change in drug use was to stop using the drug (42.4%) and almost half of the discontinued drugs (47.6%) were drugs for prn use. The need to monitor the drug use (22.7%) and to adjust, mainly decrease, the dosages (17.8%) involved almost exclusively drugs for regular use (96.0%). The mean number of drugs per patient decreased by 9.3% ($p < 0.01$) after the MR, from 6.8 to 6.3 for regular drugs and from 3.0 to 2.6 for prn drugs. For regular drugs, the reduction was significant for diuretics (4.7%), antidepressants (3.9%), hypnotics/sedatives (3.7%), antithrombotic agents (2.7%), antacid drugs (2.1%) and antipsychotics (1.8%). For prn drugs, the reduction was significant for opioids (11.2%), anxiolytics (7.1%), hypnotics/sedatives (5.8%), metoclopramide (3.5%), nonsteroidal anti-inflammatory drugs (NSAIDs) (2.9%), expectorants (2.7%) and antipsychotics (1.5%).

Article II: There was a large variation between the NHs in mean numbers of regular drugs per patient (from 4.8 to 9.3) and in mean DRPs per patient (from 0.5 to 3.4). The proportion of patients within each NH using psychotropic and analgesic drugs varied substantially between different institutions: antipsychotics from 3% to 50%, benzodiazepines from 24% to 99%, antidepressants from 9% to 75%, antidementia drugs from no use to 42%, opioids from no use to 65% and paracetamol from 16% to 74%. Using more drugs (IRR 95% CI: 1.07) and the use of opioids (IRR: 1.07), antipsychotics (IRR: 1.20), benzodiazepines (IRR: 1.08) and antidepressants (IRR: 1.18) were associated with more DRPs at the respective NHs. The quartiles of NHs with highest and lowest mean number of drugs per patient (7.7 vs. 5.7, $p < 0.001$) had comparable mean number of DRPs per patient (2.2 vs. 1.8, $p = 0.2$).

Article III: NH patients were more likely than their peers living at home to use antidementia drugs (Relative risk, RR = 5.7), antipsychotics (RR = 4.0), paracetamol (RR = 4.0), anxiolytics (RR = 3.0), antidepressants (RR = 2.8), dopaminergic drugs (RR = 2.7), antiepileptic drugs (RR = 2.4), loop diuretics (RR = 2.3), cardiac nitrates (RR = 2.1) or opioids (RR = 2.0). On the other hand, the NH residents were less likely to use statins (RR = 0.2), NSAIDs (RR = 0.3), osteoporosis drugs (RR = 0.3), thiazide diuretics (RR = 0.4), calcium channel blockers (RR = 0.5) or renin–angiotensin inhibitors (RR = 0.5). Both populations had only minor differences in drug use by gender and a trend towards less drug use with increasing age ($p < 0.01$). In each setting, ten drugs/therapeutic groups were identified which we consider to be in particular need for critical rethinking during future educational interventions or MRs.

Conclusions

The use of psychotropic and analgesic drugs was high and varied substantially between different NHs. The prevalence of DRPs also varied largely between the NHs, suggesting different prescription cultures at the institutions. The use of unnecessary drugs and excessive dosing were common, suggesting overtreatment. The use of more drugs, opioids and psychotropic drugs was associated with an increased risk for DRPs at the respective NHs. No difference was found in DRPs between the NH-groups with highest vs. lowest drug use. The MRs resulted in overall less drug use due to withdrawal of drugs, especially opioids and psychotropic drugs, and due to lowering of drug dosages.

Drug use by older people differs according to care level, and so do areas in need for quality improvement and further research.

3 NORSK SAMMENDRAG AV AVHANDLINGEN

Bakgrunn

Sykehjemsbeboere karakteriseres av høy alder, multimorbiditet, et høyt forbruk av legemidler og økt risiko for legemiddelinteraksjoner og bivirkninger. En stor andel har i tillegg kognitiv svikt som gjør det vanskelig å kommunisere om (bi)virkninger av legemidler. En stor andel av de som bor på norske sykehjem eksponeres for uhensiktsmessig medisinering og legemiddelrelaterte problemer som eksempelvis legemiddelbivirkninger, noen ganger med alvorlige konsekvenser. Fordi Reseptregisteret ikke omfatter sykehjemsbeboere, må deres legemiddelbruk hentes ut fra hver enkelt institusjon, for eksempel som del av et forskningsprosjekt. Man antar at sykehjemsbeboere er sykere enn hjemmeboende eldre, men det finnes lite kunnskap om eventuelle forskjeller i legemiddelbruken mellom sykehjemsbeboere og hjemmeboende eldre. Lite er kjent om legemiddelbruken på sykehjem i Oslo, på tross av at kommunen har den største sykehjemspopulasjonen i Norge. Tidligere studier av legemiddelgjennomgang på sykehjem, hovedsakelig fra andre deler av landet, har vist til dels stor variasjon i legemiddelbruken mellom sykehjemmene, men lite er kjent om årsakene til denne. Kunnskap om variasjon i legemiddelrelaterte problemer mellom sykehjemmene er veldig begrenset. Det er behov for nye og større studier for å undersøke om økt fokus på mer hensiktsmessig medisinering i sykehjem de siste årene har bedret kvaliteten og ført til mindre forskjeller i legemiddelbruken og legemiddelrelaterte problemer mellom sykehjemmene. Legemiddelgjennomgang er anbefalt metode for å heve kvaliteten av legemiddelbehandling i sykehjem. I hvilken grad legemiddelgjennomganger egentlig fører til mer hensiktsmessig legemiddelbruk er imidlertid fortsatt et åpent spørsmål. Det er derfor nødvendig med ytterligere forskning på dette området.

Denne avhandlingen beskriver legemiddelbruken på sykehjemmene i Oslo, med fokus på:

▪ legemiddelrelaterte problemer og endringer i legemiddelbruken etter legemiddelgjennomgang på sykehjemmene (*artikkel I*)

▪ variasjonen blant sykehjemmene i legemiddelbruken og i legemiddelrelaterte problemer (*artikkel II*)

▪ forskjeller mellom legemiddelbruken blant eldre Osloborgere som bor på sykehjem eller hjemme (*artikkel III*)

Metoder og materiale

Avhandlingen består av tre tverrsnittsstudier. Legemiddeldataene for sykehjemsbeboerne ble generert av 2465 legemiddelgjennomganger ved 41 sykehjem som har deltatt i et kvalitetssikringsprosjekt i perioden 2011-2014 i Oslo kommune. Legemiddeldataene for 48 944 eldre Oslo borgere som bodde hjemme i 2012, ble innhentet fra det nasjonale Reseptregisteret.

Legemiddelgjennomgangene ble gjennomført tverrfaglig av farmasøyt, sykehjemslege og sykepleier. Farmasøyten gjennomgikk medisinlisten og identifiserte potensielle legemiddelrelaterte problemer ved bruk av eksplisitte kriterier for uhensiktsmessig legemiddelbruk (STOPP/START og NORGEP) og den norske interaksjonsdatabasen. De identifiserte legemiddelrelaterte problemer og klinisk informasjon om den enkelte sykehjemspasient ble diskutert i de tverrfaglige team, og man ble enige om reelle legemiddelrelaterte problemer og om endringer i legemiddelbehandlingen.

Artikkel I: Bruken av faste og ved behov legemidler ble sammenlignet før og etter legemiddelgjennomgang på 2465 langtids sykehjemsbeboere. Legemiddelrelaterte problemer som ble identifisert ved legemiddelgjennomgang, og endringer i medisineringen ble beskrevet. Faktorer assosiert med legemiddelrelaterte problemer og med endringer i medisinering ble testet ved regresjonsanalyse.

Artikkel II: Variasjonen i bruken av faste legemidler og i legemiddelrelaterte problemer blant 41 sykehjem ble beskrevet. Kvartilene med sykehjem med høyest og lavest antall legemidler per pasient per sykehjem ble sammenlignet i forhold til legemiddelbruk og legemiddelrelaterte problemer. Assosiasjoner mellom legemidler og legemiddelrelaterte problemer, samt faktorer assosiert med legemiddelrelaterte problemer ved det respektive sykehjemmet, ble testet ved Pearson's korrelasjonskoeffisient og regresjonsanalyse.

Artikkel III: Legemiddelbruken av Osloborgere ≥ 70 år gamle boende på sykehjem eller hjemme i 2012 ble beskrevet og sammenlignet etter kjønn og aldersgrupper.

Resultater

Artikkel I: Ved legemiddelgjennomgang ble identifisert gjennomsnittlig 2,6 reelle legemiddelrelaterte problemer per pasient, 2,0 for faste legemidler og 0,6 for legemidler ved behov. De hyppigste legemiddelrelaterte problemer var bruken av unødvendig legemiddel (43,5%), bruken av for høy dose (12,5%) og behov for monitorering av legemiddelbruken (11,0%). Opioider og psykofarmaka var hyppigst involvert i alle legemiddelrelaterte problemer. Kvinner hadde 11% høyere risiko for legemiddelrelaterte problemer enn menn,

mens alder var ikke assosiert med risiko for legemiddelrelaterte problemer. Den hyppigste endringen i legemiddelbruken var å seponere unødvendige legemidler (42,4%) og nesten halvparten av disse var legemidler ved behov (47,6%). Monitorering av legemiddelbruken (22,7%) og reduksjon av legemiddeldosen (17,8%) involverte hovedsakelig faste legemidler (96,0%). Antall legemidler per pasient ble redusert med 9,3% ($p < 0.01$) etter legemiddelgjennomgang fra i gjennomsnitt 6,8 til 6,3 for faste legemidler og fra 3,0 til 2,6 for legemidler ved behov. For faste legemidler var reduksjonen signifikant for diuretika (4,7%), antidepressiva (3,9%), hypnotika/sedativa (3,7%), antitrombotika (2,7%), protonpumpehemmere (2,1%) og antipsykotika (1,8%). For legemidler ved behov var reduksjonen signifikant for opioider (11,2%), anxiolytika (7,1%), hypnotika/sedativa (5,8%), metoklopramid (3,5%), NSAIDs (2, 9%), mukolytika (2,7%) og antipsykotika (1,5%).
Artikkel II: Vi fant en stor variasjon blant sykehjemmene i gjennomsnittlig antall faste legemidler per pasient (fra 4,8 til 9,3) og i legemiddelrelaterte problemer per pasient (fra 0,5 til 3,4). Andel av pasienter som brukte psykofarmaka og analgetika varierte mye mellom sykehjemmene: antipsykotika fra 3% til 50 %, benzodiazepiner fra 24% til 99%, antidepressiva fra 9% til 75%, midler mot demens fra ingen bruk til 42%, opioider fra ingen bruk til 65% og paracetamol fra 16% til 74%. Det var ingen forskjell i gjennomsnittlig legemiddelrelaterte problemer per pasient (2,2 vs. 1,8, $p = 0,2$) mellom kvartilene av sykehjem med henholdsvis høyest og lavest gjennomsnittlig antall legemidler per pasient (7,7 vs. 5,7, $p < 0.001$). Bruken av flere legemidler (IRR 95 % CI: 1,07), opioider (IRR: 1,07), antipsykotika (IRR: 1,20), benzodiazepiner (IRR: 1,08) eller antidepressiva (IRR: 1,18) var assosiert med en høyere risiko for legemiddelrelaterte problemer ved det enkelte sykehjem.
Artikkel III: Sammenlignet med eldre hjemmeboende, brukte sykehjemsbeboerne oftere midler mot demens (relativ risk, RR = 5,7), antipsykotika (RR = 4,0), paracetamol (RR = 4,0), anxiolytika (RR = 3,0), antidepressiva (RR = 2,8), dopaminerge midler (RR = 2,7), antiepileptika (RR = 2,4), slyngediuretika (RR = 2,3), nitrater (RR = 2,1) og opioider (RR = 2,0). På den annen side brukte sykehjemsbeboerne færre statiner (RR = 0,2), NSAIDs (RR = 0,3), bisfosfonater (RR = 0,3), tiazider (RR = 0,4), kalsium antagonister (RR = 0,5) og midler med virkning på renin-angiotensin systemet (RR = 0,5). Begge populasjonene viste små forskjeller i legemiddelbruken etter kjønn, og en trend mot mindre bruk ved økende alder ($p < 0,01$). I hver av populasjonene har vi identifisert ti legemiddelgrupper vi mener bør være i fokus for fremtidige kvalitetsforbedringstiltak.

Konklusjoner

Legemiddelbruken på sykehjem var høy, og spesielt bruken av psykofarmaka og analgetika varierte mye mellom sykehjemmene. Omfanget av legemiddelrelaterte problemer varierte mye mellom sykehjemmene, muligens som tegn på forskjellig forskrivningspraksis ved sykehjemmene. De hyppigste legemiddelrelaterte problemer gjaldt overbehandling, enten ved bruk av unødvendige legemidler eller bruk av for høye doser. Det var ingen forskjeller i forekomsten av legemiddelrelaterte problemer mellom sykehjem med høyest versus lavest legemiddelbruk, til tross for at bruk av flere legemidler, opioider, antipsykotika, benzodiazepiner eller antidepressiva var assosiert med økt risiko for legemiddelrelaterte problemer ved de respektive sykehjemmene.

Som følge av seponering av spesielt psykofarmaka og opioider, og redusert legemiddeldosering ble bruken av legemidler redusert etter legemiddelgjennomgangene.

Legemiddelbruken hos eldre er svært forskjellig mellom de som bor i eget hjem og de som bor i sykehjem. Forskrivningsområdene med behov for kvalitetsforbedring og forskning vil derfor også være ulik i de to settingene.

4 PREFACE

My motivation for pursuing a ph.d. endeavor so late in my professional life is rooted in my genuine interest in research; from the first article and presentation while I was a medical student, to working with international clinical trials for many years at Nycomed Imaging/GE Healthcare Norway. I returned to clinical work in 2007 and since then, I hold full-time nursing home physician positions at three nursing homes in Oslo. I often experience that prescribing the "correct" medication to nursing home patients is challenging, mainly because of limited evidence on effects and safety of medicines in multimorbid old olds with short life expectancies. Quite often, decisions are difficult and may lead to plenty of concerns, like when you consider if an unsteady patient with atrial fibrillation should continue or should stop anticoagulant treatment after the last fall accident. Therefore, I was highly committed when "my" nursing home volunteered to participate in a project to improve the medication use at the nuring homes in Oslo (the medication review project). We enrolled all bed units at our institution so almost all of our patients underwent a medication review. I have seen the medication review as an opportunity for a systematic team assessment with potentials to improve the pharmacotherapy for our patients. Another incitement was the ongoing discussion on polypharmacy in nursing homes. In my opinion, the number of drugs in itself does not define safe medication use or not. I was also curious if my colleagues might have different prescription cultures. Later, I was given the opportunity to use datasets generated by this project in the planning of my thesis.

This ph.d. is a public-sector ph.d. (offentlig-sektor ph.d.) anchored at the Institute for Health and Society at the University of Oslo. My employer, the Nursing Home Agency in Oslo municipality, co-applied and partly financed my grant from the Norwegian Research Council. The motivation for the Agency was, as stated in the grant application, to establish own clinical research activities in the municipality focusing on geriatric and nursing home medicine issues that can be translated into interventions leading to improved medical care at the nursing homes.

This thesis contributes with new data on the drug utilization in a large nursing home population that has so far not been studied in detail. I hope that this thesis will contribute to improved procedures for drug utilization at the nursing homes and to further research on the pharmacotherapy of this vulnerable population. I am eager to apply the skills acquired during the ph.d. work and I'm looking forward to continuing research activities in nursing homes.

5 LIST OF PUBLICATIONS

Article I:

Fog AF, Kvalvaag G, Engedal K, Straand J. Drug-related problems and changes in drug utilization after medication reviews in nursing homes in Oslo, Norway. Scand J Prim Health Care. 2017;35:329–35. doi: 10.1080/02813432.2017.1397246

Article II:

Fog AF, Mdala I, Engedal K, Straand J. Variation between nursing homes in drug use and in drug-related problems. BMC Geriatr. 2020;20:336. doi: 10.1186/s12877-020-01745-y

Article III:

Fog AF, Straand J, Engedal K, Blix HS. Drug use differs by care level. A cross-sectional comparison between older people living at home or in a nursing home in Oslo, Norway. BMC Geriatr. 2019;19(1):49. doi: 10.1186/s12877-019-1064-8

6 LIST OF ABBREVIATIONS

ATC: Anatomical Therapeutic Chemical

BPSD: Behavioural and Psychological Symptoms in Dementia

CI: Confidence interval

DRP: Drug-related problem

IRR: Incidence rate ratio

MR: Medication review

NH: Nursing home

NH Agency: Nursing Home Agency

NORGEP: The Norwegian General Practice criteria

NORGEP-NH: The Norwegian General Practice – Nursing Home criteria

NorPD: Norwegian Prescription Database

NSAIDs: Nonsteroidal anti-inflammatory drugs

PCNE: Pharmaceutical Care Network Europe

PIM: Potentially inappropriate medication

prn: pro re nata (as needed)

RR: Relative risk

RU: Regular bed unit

SCU: Special care unit for patients with dementia

STOPP/START criteria: Screening Tool of Older People's Prescriptions and Screening Tool to Alert to Right Treatment criteria

7 BACKGROUND

7.1 General background

Older people

In developed countries, more and more people live long lives, increasing the share of older people in the population, especially of those 80 years and older, which changes the shape of the population pyramids. In the absence of a better cut-off measure, in most developed countries a chronological age of 65 years and above is accepted as a definition of an "elderly" or old person (1). Due to inter-individual variability in the aging process, health, disease and disability, older people are indeed a heterogeneous group, ranging from fit people living autonomous lives in the community, to frail and dependent nursing home (NH) residents. With the aging of the population, substantially more people of today are living with multimorbidity (2;3), dementia (4) and frailty (5). Despite the prevalence of these conditions, older people today live longer with less functional limitations or disabilities than equally olds in earlier generations (6;7). Most evidence for people aged < 85 years suggests postponement of limitations and disabilities, whereas for people aged ≥ 85 years, the situation is less clear (7).

Direct extrapolation of drugs' efficacy or safety to older people should be made with caution because the effects and safety of drugs in general are documented for younger adults with less comorbidities. Especially people older than 80 years of age have been under-enrolled in clinical trials (8). Older people are a "special population" as compared to younger adults due to their higher prevalence of multimorbidity, age-related changes in pharmacokinetics and pharmacodynamics and an increased risk for adverse drug reactions (8;9).

Multimorbidity

The most common chronic diseases in older people include cardiovascular disease, diabetes, osteoarthritis, cancer and dementia (3;10). The prevalence of older people with two or more chronic diseases (multimorbidity) is above 60% and among persons aged ≥ 85 years it is above 80% (11). Multimorbidity is commonly associated with functional decline (12), frailty (13), worse health outcomes, more complex clinical management and increased health care costs (3;14). Therefore, dealing with multimorbidity needs a person-centered rather than a disease-oriented approach (11;15). Although clinical guidelines discuss the older population, only a handful of them adequately address issues related to older patients with multimorbidities (16). A literature survey of trials from 11 Cochrane Reviews for four chronic

diseases (diabetes, heart failure, chronic obstructive pulmonary disease and stroke) showed that comorbidities receive little attention in trials treating chronic disorders, and that there is a need to better assess the effects of comorbidities on treatment outcomes (17). Due to multiple management regimens, comorbidity has a potential to generate a range of significant patient safety challenges, including use of contraindicated or potentially inappropriate drugs, adverse drug reactions and drug interactions. Age-related structural and physiological changes, like reduced renal and hepatic clearance, increased volume of distribution for lipid soluble drugs and altered sensitivity to several therapeutic drug groups, further increase the risk for adverse drug reactions. Thus, careful monitoring of the response to drugs and dose adjustments are required (9).

Polypharmacy

Without a consensus definition, most definitions of polypharmacy are numerical, e.g. more than four or five and of more than nine or ten concomitant drugs (polypharmacy and excessive polypharmacy, respectively). However, the clinical relevance of using a numerical cut-off has never been validated (18). A European study across eight countries concluded that 49.7% of 4,023 NH residents experienced polypharmacy and 24.3% experienced excessive polypharmacy (19). The concomitant use of multiple psychotropic drug classes (psychotropic polypharmacy) is also prevalent, especially in people with dementia and living in NHs (20). Polypharmacy is associated with increased risk for drug-drug and drug-disease interactions (21;22) and for adverse drug reactions like delirium (23), impaired balance and falls (24) and constipation (25). Polypharmacy is also associated with increased risk for "prescribing cascades". That is when an adverse drug reaction is misinterpreted as a new medical condition, leading to prescription of additional drugs that may lead to a new adverse reaction that may lead to further prescription of drugs (26). A numerical definition is easy to use, in particular in retrospective pharmacoepidemiological database-studies in which inappropriateness would be otherwise very difficult to define. However, polypharmacy defined numerically can be misused normatively, implying that using five or more drugs in itself may reflect poor quality of care and pose a safety risk. Polypharmacy may very well be appropriate in the presence of multimorbidity. Therefore, an alternative definition of polypharmacy that changes the focus from "many" to "too many" is welcomed. The term inappropriate polypharmacy is thus defined as the use of more drugs that are clinically appropriate in the context of a patient's total morbidity (27). This shift is important because polypharmacy has paradoxically also been found to represent an increased risk for

underprescribing in older people (28). Hence, different definitions of polypharmacy are needed.

Inappropriate prescribing

Inappropriate prescription is defined as a drug prescription that is not in accordance with the clinical indication or the recommended dosage or duration of treatment (29). It encompasses underprescribing (no therapy given for a valid indication), overprescribing (the prescription of a medication that is clinically not indicated) and misprescribing (incorrect prescription for a given indication) (30). By means of expert consensus, several drugs and drug groups are considered potentially inappropriate medications (PIMs) for older people, and should therefore be avoided whenever possible. PIMs can be defined as *"medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative exists"* (31). The use of PIMs has been found to be common in NHs (32).

Several explicit criteria listing PIMs have been developed based on published reviews and expert opinions and they have been validated by consensus. Explicit criteria are used as rigid standards to measure pharmacological appropriateness of medication use, without addressing individual clinical differences between patients, or the complexity and appropriateness of the entire medication regimens (33). These criterion-based tools are drug- and/or disease-oriented and can be applied with little or no patient information. However, they are important educational tools that highlight medications for which risks of use more often exceed benefits in older adults, and situations in which potentially appropriate medications should be considered for use (33). As new drugs and safety evidence emerge, such criteria need to be updated to ensure their relevance. The most widely used explicit criteria for inappropriate medication use in older adults are the Beers criteria (31), latest updated in 2019 (34) and the Screening Tool of Older People's Prescriptions/Screening Tool to Alert to Right Treatment (STOPP/START) (35), updated in 2015 (36). The STOPP/START criteria consist of 65 potentially inappropriate drugs and 22 drugs to consider for people ≥ 65 years old (35) and they appear to be more sensitive than the Beers criteria in identifying PIMs in older people (37). A recent systematic review (38) found that the application of the STOPP criteria reduced the PIM rates in all the reviewed studies, whereas the application of the STOPP/START criteria could reduce falls, delirium episodes, shorten hospital length-of-stay and reduce primary and emergency care visits. However, none of the reviewed studies could demonstrate effects on quality of life or on mortality (38).

Explicit criteria need to be adapted to the country's specific guidelines and availability of approved medications. Partly based on the Beers criteria, several explicit criteria have been developed across the world, e.g in Canada (39), France (40), Australia (41), Germany (42), Italy (43) and Austria (44). The Norwegian general practice criteria (NORGEP-criteria) developed in 2009 consist of 36 explicit criteria including 21 single drugs and 15 drug-drug combinations, consistent with the national drug formulary and targeting ≥ 70 year olds seen in the primary care (45). In 2015, they were tailored for older people living in NHs (NORGEP-NH criteria) (46).

Minimizing inappropriate prescriptions may reduce negative clinical outcomes like adverse drug reactions, hospital admissions and even death (30;33). The Norwegian Knowledge Center for the Health Services published a systematic review of scientific publications on measures to reduce PIMs in NHs (47). Based on 18 randomized studies it was concluded that educational outreach, on-site education and medication reviews (MRs) may reduce PIMs in NHs, but the evidence for these conclusions was based on studies with rather low scientific quality. The report further recommended that better and larger studies should be conducted to determine whether such measures might affect patient-related health outcomes. Other more recent studies found that educational outreach changed the prescribing behaviours of general practitioners, especially for older people (48;49).

Medication appropriateness can also be assessed using implicit criteria, based on clinical judgment and validated using the patients' medical records. Implicit criteria assess the entire medication regimen and are not country specific, but it is time consuming to apply them and they depend on user's expertise in geriatric pharmacotherapy. The most used implicit criteria were developed in US in 1992; the Medication Appropriateness Index (29;50) consisting of ten questions to assess medication appropriateness of each drug in use, and the Lipton's criteria that evaluates each drug in the patient's regimen in seven categories of potential drug-therapy problems (51). Finally, a combination of explicit and implicit criteria is found in the Inappropriate Medication Use and Prescribing Indicators Tool developed in Australia (41).

Medication reviews (MRs)

Using explicit criteria, several procedures for medication reviews (MRs) were developed aiming to improve the quality of pharmacotherapy by identification and discontinuing useless or harmful medications, adjusting daily doses, initiating beneficial medicines or ensuring more appropriate monitoring of long-term conditions and medicines (47;52). An official Pharmaceutical Care Network Europe (PCNE) definition from 2016 states that *Medication*

review is a structured evaluation of a patient's medicines with the aim of optimizing medicines use and improving health outcomes. This entails detecting drug related problems and recommending interventions (53). This definition was accepted by 35 countries during a consensus process in 2018 (54).

MRs can be targeted at moments of transitions between health care services (i.e. discharge from hospital, admission to a NH), polypharmacy, the initiation of a new treatment or when the patient takes medications posing a risk for drug-related problems (DRPs), like anticoagulants, diuretics or NSAIDs. The MR procedures may differ by setting (hospital, primary care), if performed during or after drug dispensing (prospective/retrospective), the level of professional collaboration between physician, pharmacist, nurse and patient) and by the comprehensiveness of the documentation (55;56). Based on the comprehensiveness of the procedure, there are three types of MRs (table 1).

Table 1: Types and characteristics of medication reviews, modified from Clyne (55)

Characterisitics	**Type I prescription review**	**Type II adherence and compliance review**	**Type III clinical medication review**
Purpose	Prescription technical issues	Patient's medicine taking behaviour	Drug use in the context of clinical conditions
Review's focus	Medicines	Medicine use	Medicines and conditions
Patient's involvement	No	Yes	Yes
Clinical data available	Sometimes	Sometimes	Always

Community pharmacist-led MRs are available as part of the primary care services in several countries like US (57), UK (55) and Finland (56). However, there is evidence that without clinical information, pharmacists may overestimate potential DRPs using STOPP criteria and underestimate them using START criteria (58).

An online survey in 2010 reported that 16 out of 25 European countries had in place procedures for MRs, however, they varied in terms of who is eligible for MR, access to patient information, patient interview, documentation of the MR and competence requirements for pharmacists (59). Overall, type III MRs were seldom (6/25 countries) and targeted patients at risk for DRPs. In this survey, Norway reported type II local procedures with patient interview and access to prescription information. In the Norwegian guideline on how to conduct MRs issued in 2012 and updated in 2015, MRs performed in multidisciplinary

teams of pharmacists, physicians, nurses are recommended in all settings and such collaboration is especially suitable in NHs (60).

A prerequisite for any type of MR is to perform medication reconciliation, by comparing the medication list to those in the patient record or medication orders, to ensure that the medication list is complete and accurate, including all current medications, dosage, frequency and route of administration. Medication reconciliation is especially important for older people with polypharmacy and frequent transitions in care between hospital- and primary health care, as well as in NHs. Although studies suggest that medication reconciliation alone probably does not reduce post-discharge hospital utilization (61) or consistently improve patient outcomes (62), incorrect recording of drugs in use may lead to unintended discontinuation of drugs or failures to detect DRPs.

Drug related problems (DRPs)

DRPs are defined according to the PCNE as "*an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes"* (63). A potential problem means a condition that may cause drug-related morbidity if no action is undertaken; an actual problem is manifested with signs and symptoms. Other interchangeable or overlapping terms include drug-therapy problem, medication-related problem and medication error. Since the first standardized DRP classification system was developed in US in 1990 (64), several definitions and classifications have been developed in different countries, however without reaching a consensus on a universal definition or on a system for how to categorize the problems and their causes (65). A literature review on 268 studies that have reported DRPs using a DRP classification system, found that the most used systems were that of Cipolle (66) and Strand/Hepler (67). In the NH setting, the vast majority of studies choose to modify the system (65). The variability between classification systems makes comparisons between studies difficult. A summary of the DRP classification systems that are most frequently used in clinical trials in a NH-setting is provided in table 2.

Table 2: Drug-related problems classification systems frequently used in clinical studies, adapted from van Mil (68) and Basger (65)

Classification system	Main DRP categories*	Explicit definitions	Hierarchical system	Classification of causes	Validation published	Classification of interventions
Cipolle (66)	7	Yes	No	No	Yes	Yes
Hepler-Strand (67)	8	Yes	No	No	No	Yes
PCNE (63)	6	Yes	Yes	Yes	Yes	Yes
Westerlund (69)	13	Yes	No	Integrated	Yes	Yes
Norwegian (70)	6	Yes	Yes	Yes	Yes	Yes

*Cipolle classification: Need for additional drug therapy; Unnecessary drug therapy: Wrong drug; Dose too low; Dose too high; Adverse drug reaction; Inappropriate adherence
*Hepler-Straand classification: Untreated indications; Improper drug selection; Subtherapeutic dosage; Failure to receive drugs; Over dosage; Adverse reactions; Drug interactions; Drug use without indication
*Pharmaceutical Care Network Europe PCNE classification v 5 : Adverse drug event; Drug choice problem; Dosing problem; Drug use problem; Interactions; Other
*Westerlund classification: Uncertainty about aim of drug; Drug duplication; Drug-drug interaction; Contraindication; Therapy failure; Adverse effect
*Norwegian classification: Drug choice; Dosing; Adverse drug reaction; Interaction; Drug use; Other

The PCNE constructed a classification system in 1999 and since then, the system has been adapted regularly, most recently in 2020 (71). This classification is intended for use in research into the nature, prevalence and incidence of DRPs. It has an open hierarchical structure where higher levels are broadly defined and lower levels are more specific. It has unambiguous definitions for each DRP category and it can be adapted and expanded with subcategories according to need, setting and access to clinical information. The internal validation has been assessed based on case descriptions.

The Norwegian classification system (70) was developed based on the PCNE system v.5 (63) by means of a modified Delphi technique using clinical experience and consensus between physicians and pharmacists from various clinical and scientific positions. A panel of physicians and pharmacists has validated the clinical relevance of the system by using case reports, with an average agreement rate for the DRP category of 70%. The classification is intended for research and practice in primary healthcare, NHs, hospitals and pharmacies. The DRPs are divided into six main categories and 12 subcategories, listed in an order consistent with drug therapy evaluation in clinical practice. The system includes undertreatment under the category “need for additional drug”, although this problem is not associated with one

drug, but a presumption of adherence to clinical guidelines. A detailed presentation of the categories is presented in table 3.

Table 3: The Norwegian classification system for drug-related problems, from Ruths (70)

DRP category	**Definition**
1. Drug choice 1a Need for additional drug	One or more drugs are missing according to established national/international guidelines. Deviations from guidelines that are based on the patient's individual treatment goals and risk factors are not considered to be DRPs
1b Unnecessary drug	A drug that is seen as unnecessary if the indication is no longer present, with lack of discontinuation or double prescription of two or more drugs from the same therapeutic group
1c Inappropriate drug choice	Not given reason for deviation from concordance between drug and diagnosis/indication or absolute/relative contraindication because of for example age or comorbidity. Deviations that are based on the patient's individual treatment goal and risk factors are not considered to be DRPs.
2 Dosing 2a Too high dose 2b Too low dose 2c Sub-optimal dosing scheme 2d Sub-optimal formulation	Suboptimal dosing (including dosing time and formulation) according to established national/international guidelines. Deviations that are based on the patient's individual treatment goal and risk factors are not considered to be DRPs.
3 Adverse drug reaction	Any noxious, unintended, and undesired effect of a drug, which occurs at doses in humans for prophylaxis, diagnosis, or therapy (WHO)
4. Interaction	An interaction is occurring when the effect of a drug is changed by the presence of another drug, food, drink or some environmental chemical agent. Drug combinations with intended overall effect are not considered to be DRPs.
5. Drug use 5a Drugs administered by health personnel 5b Drugs administered by the patient	Patients' real drug use deviate from the doctor's prescription with respect to type of drug, dose or scheme. It is a prerequisite that prescriptions are based on a common understanding (concordance) between prescriber and patient (exception: patient with dementia, emergency situation, etc.) Problems with logistics are not considered to be DRPs.
6. Other 6a Need for/lack of monitoring of effect and toxicity of drugs	Monitoring with respect to effect and toxicity of drugs is not done or does not adhere to guidelines
6b Lack of or unclear documentation of the drug chart/prescription	
6c Other	In general therapy discussions that include several problems and do not belong in any other category

Nursing homes in Norway

NHs are important institutions for housing and care of frail older people who are unable to live in own homes any longer. By law, the municipalities must provide NH services for their inhabitants. Like in many other countries, NHs provide care at a level between hospitals and home based care. NHs are financed by municipalities with block grants from the state and

taxes paid by their inhabitants. All NHs receive a fixed amount based on the number of short- and long-term beds; the NHs can decide how to spend the fixed payment and how to organize the care. The NHs do not receive direct payment from their residents, the residents pay 85% of their pension to the state. The vast majority of the NHs are managed by municipalities (public NHs), but management may also be outsourced to private foundations (private non-profit NHs) or companies (private for-profit NHs).

The NH coverage is high, corresponding to approximately 15% of the population ≥ 80 years old, comparable to that in Denmark and Sweden (13% and 16%, respectively). In 2019, the Norwegian NH sector comprised approximately 1000 NHs with 39,466 beds, of which 32,105 were for long-term stay (72). The size of the NHs varies from relatively few beds, especially in rural areas, to large NHs with over 200 beds, the average size being about 50 beds. NHs usually have long-term beds for permanent residence and a few short-term beds for rehabilitation, but there are also NHs with exclusively long- or short-term beds.

The NHs provide care for both physically disabled and psychogeriatric patients. Admission to NH is based on needs, regardless of income and the admission criteria are rather uniform. NHs are institutions for treatment, but also a home-like place for permanent residence with single rooms with on-suite bathroom. The majority of long-term residents are women, the mean age is around 85 years, almost 80% have dementia (73) and the vast majority use many drugs due to multimorbidity (74). The average residence time is around two years and almost half of all deaths in Norway occur in NHs (75). People with behavioral and psychological symptoms (BPSD) are often cared for at special care bed units for people with dementia (SCU); compared to the regular bed units (RU), the SCUs are typically smaller and have a higher staff/resident ratio. Medical treatment is mostly provided by general practitioners working part-time in the NHs, but larger NHs in urban settings like Oslo, have employed full-time working NH physicians. The proposed standard of care by the Norwegian Medical Association was 90 long-term care NH residents per full time physician in 2012, but the coverage varies because the Health Authorities have not defined explicit minimum standards for NH-staffing. Further, the level of staffing with nurses varies across the NHs and at present, NHs do not employ in-house pharmacists.

7.2 Drug utilization areas in need for further knowledge

Strict adherence to therapy guidelines may expose NH residents to polypharmacy (19;22;76) and to inappropriate polypharmacy (77) and hence to an increased risk of drug–drug interactions (22) and adverse drug reactions (78). The presence of dementia adds further to this risk due to impaired ability to communicate drug effects. In Norway, the mean number of regular drugs per NH resident has increased during the last decades, from five in 2003 (79) to seven in 2007 (80) and eight in 2010 (76). Few studies report on the use of drugs used as needed (pro re nata, prn drugs), but a mean of three to four prn drugs per patient has been reported (76;81). Concerns regarding the quality of prn drugs administration in NHs have been put forward (82). A cross-sectional study of 513 long-term patients at seven NHs in Bergen addressed comorbidity correlations, especially in respect to cognitive impairment (81). In that study, the mean number of drugs per patient was 6.1 for regular drugs and 3.8 for prn drugs. Patients with cognitive impairment were prescribed significantly fewer regular drugs (5.7. vs. 7.1 drugs) and fewer cardiovascular drugs than cognitive intact patients.

Except for antipsychotics that now seems to decline (83), the prescribing of psychotropic drugs (84;85) and opioids (86) has increased during the last decades, about one in five residents using more than one psychotropic drug at the same time (83), in most cases as inappropriate long-term treatment for BPSD (87). A secondary data analysis of six cross sectional studies conducted between 1997 and 2009 reported prevalence of psychotropic drug use among 7,661 patients ≥ 65 years old from 336 Norwegian NHs (85). The study confirmed that the use of psychotropic drugs in NHs had increased considerably, especially due to the frequent use of antidepressant drugs. Predictors for psychotropic drug use were female gender (except for antipsychotics), age less than 80 years, and residency in SCU for patients with dementia (except for hypnotics). Although an increased prevalence rate of depression in old age has been reported in Norway (88), this alone cannot explain the extended use of antidepressants in NH settings. Staff distress (89) and pressure from nursing staff to calm down challenging behaviour is probably contributing to this increase (90).
The use of antidepressants in older people was linked to falls, hyponatremia and stroke/transient ischemic attacks (91). Antidepressants were shown to have poor effect in NH residents with dementia (92;93) and tapering down dosage and deprescribing is generally well tolerated (94). In the national guideline, antidepressants are recommended for treating BPSD only when non-pharmacological interventions alone had no effect (95).

The widespread long-term use of antipsychotic drugs, benzodiazepines and antidepressants for treating BPSD in NH patients is largely considered inappropriate and their use is associated with increased risk for adverse drug reactions like delirium (23), impaired balance and falls (24), stroke (96) and premature death (97).

One particular challenge for the NH-sector is the substantial variations in drug utilization patterns seen between otherwise comparable institutions with comparable patient populations. A study including 1,552 patients at 23 NHs in Bergen conducted in 1997 (79) showed especially large variations in the proportion of residents using antipsychotics (from 0% to 61%) and antidepressants (from 10% to 63%). Being in the oldest age group predicted less psychotropic drug use, while neither patients' gender, size of institution, or level of qualified nurse staffing were associated with the use of psychotropic drugs. Another study showed that patients were more likely to receive antidepressants if living in NHs with relatively more physician time (98). In a cross-sectional study of 513 long-term patients at seven NHs in Bergen, significant differences between NHs were shown for utilization of antipsychotics and antidepressants (81). Adding defined daily doses within each drug class increased the differences between institutions, indicating that institutions with high prevalence of use also used higher dosages. The authors concluded that the reasons for variation might also include skills and attitudes among the staff, since neither patients' age nor gender, or the level of staffing influenced the variation (81). Substantial variations in the use of antipsychotics between otherwise similar institutions have also been reported from other countries (99;100).

Systematic reviews on interventions to optimize prescribing for older people (52;101) concluded that MRs may identify and resolve DRPs, however with lack of evidence on effects of patient-related outcomes like adverse drug events, hospital admissions or mortality.

In the NH setting, MRs are recommended for improving quality and follow-up of drug therapy by disclosing needs for continued use or for better balancing risks with potential benefits (32). MRs involving collaboration between physicians, pharmacists and nurses has been used in NH settings in several countries and such collaboration is recommended in the Norwegian national guideline (60).

In Norwegian studies, PIMs and DRPs have been identified using explicit criteria for pharmacological inappropriateness (35;45;46) and drug-drug interaction database (102). DRPs are defined according to PCNE (63) and they are classified according to a national consensus classification system applicable for primary care, hospitals, NHs and pharmacies published in 2007 (70). Several studies have shown that a large proportion of NH residents are exposed to

DRPs (76;79;85;103-105). In two of these studies, a proportion of 77% and 88% of the patients experienced DRPs (mean 2.5 DRP per patient), with “lack of indication” being the most common DRP (76;104). Another study with MR by a pharmacist reported 3.5 DRPs per patient, with “unnecessary drug” and “monitoring required” being the most frequent DRPs (76).

In the absence of a common used procedure for performing MRs and for identifying PIMs, in combination with a lack of universal classification system for DRPs, comparing studies investigating DRPs is not straightforward. A selection of studies with MRs carried out by multidisciplinary teams is presented in table 4.

Table 4: Multidisciplinary medication review studies investigating drug-related problems in nursing homes

Study, year/ country/ (reference)	Patients (NHs)	Mean drugs/ patient	MR procedure	Mean DRP/patient (mean DRPs/NH)	Most common DRPs	Changes after MRs
Ruths, 2003/ Norway (79)	1354 (23)	5.0	Panel of 3 physicians and 1 pharmacist	1.8	Risk of adverse drug reaction Choice of drug	NR
Finkers, 2007/ The Netherlands (106)	91 (5)	> 9	Pharmacist Physician	3.5	Unclear indication Need for review	Mean reduction of drugs/patient from 13.5 to 12.7 ($p < 0.001$)
Kersten, 2009/ Norway (103)	48 (2)	8.0	Pharmacist Panel of 2 physicians	4.0 (3.0 – 5.5)[1]	Unnecessary drug Monitoring required	NR
Halvorsen, 2010/ Norway (76)	142 (3)	8.1 (3.4)[3]	Pharmacist Physician Nurse	3.5 (5.1)[2]	Unnecessary drug Monitoring required	Mean reduction of 1.5 regular drugs/patient ($p < 0.01$)
Davidsson, 2011/ Norway (104)	93 (1)	7.5	Pharmacist Physician Nurse	2.5	No clear indication Inappropriate drug choice	Mean reduction of drugs/patient from 7.4 to 6.8 ($p < 0.01$)
Brulhart, 2011/ Switzerland (107)	329 (10)	12.8	Pharmacist Physician Nurse	3.7	Unnecessary drug Too high dose	803 treatment adaptations - 373 drugs stopped - 197 dosages changed
Tverborgvik, 2012/ Norway (105)	224 (4)	10.5	Pharmacist Physician Nurse	2.0 (1.6 – 2.4)[1]	Unnecessary drug Inappropriate drug	10.7% mean reduction of drugs/NH ($p < 0.001$)
Devik, 2018/ Norway (108)	61 (5)	8.0	Pharmacist Physician Nurse	3.7	Unnecessary drug Need for additional drug	72% of interventions were accepted by the physician
Lenander, 2018/ Sweden (109)	1508 (25)	8.5 (2.8)[3]	Pharmacist Physician Nurse	2.2	Unnecessary drug Too high dose	Less patients used antipsychotics, anticholinergics, benzodiazepines and tramadol ($p < 0.001$)
Halvorsen, 2019/ Norway (110)	151 (4)	8.0 (3.7)[3]	Pharmacist Physician Nurse	4.6[2] (2.7 – 5.6)[1]	Unnecessary drug Too high dose	63% of interventions were accepted by the physician

[1] Range between the NHs; [2] DRPs identified by the pharmacist alone; [3] pro re nata drugs; NR not reported

Little was known about the variation in DRPs between NHs when this thesis was in planning. The mean DRPs per patient per NH varied between 3.0 and 5.0 in one study (103) and between 1.6 and 2.4 in another study (105). The NH with more physician resources used less drugs per patient and had less DRPs (103). However, due to the small number of patients, the

external validity of these studies is limited. During the work with this thesis, another study found a mean number of DRPs per patient from 2.7 to 5.6 between four rural NHs (110).

In Norway, people older than 67 years represent about 15% of the population but use 45% of all prescription drugs (111), the vast majority prescribed by general practitioners. Direct comparisons of morbidity between older persons living in NHs and at home are lacking, but cognitive impairment, BPSD, Parkinson's disease and stroke are all more prevalent in NH residents than among people living in the community (10). In 2008, a national survey reported that one in three people ≥ 70 years living at home were exposed to PIMs and that one in five were issued more than ten different drugs (112). In 2011, another cross-sectional study of 11,254 patients aged ≥ 65 years using multi-dose dispensed drugs, reported significant differences between drug use in NHs compared with elderly people receiving home nursing services, with more use of psychotropic drugs in NHs (113). Due to differences in morbidity and life expectancy, it is likely that the drug use differs by care level, for example with more symptomatic and palliative approach in the NH setting.

To conclude, this review of previous studies in Norwegian NHs has identified several areas in need for further knowledge:

• The drug use in NHs, in particular psychotropic and opioid drugs has been a topic of research during the last years and knowing the prevalence of drug use is important for both research and clinical practice. As long as NorPD does not cover the NH-sector, residents' drug use data must therefore be collected from the institutions, e.g. as part of a research project. In particular it is needed more data from Oslo because, although the municipality has the largest NH-sector in the country, just a few small studies have investigated the drug use at the NHs in Oslo. There is also a need to know more about the prn drug use in NHs because these drugs add to the medication burden of the patients and consequently might pose a safety risk.

• MR studies substantiate that DRPs are common in NHs, however, there is limited knowledge about changes in drug use following MRs. The development of new clinical guidelines and an increased awareness on PIMs and safety issues in old age support the continuous need for more MR studies and more knowledge about DRPs.

• The variation in drug use between NHs should be investigated further because little is known about the variation in DRPs between NHs and factors associated with it. One should expect that the focus during the last years on a more appropriate medication in the NH-setting

might have reduced the variation in drug use. To the best of our knowledge, we have not found any studies investigating the variation in the drug use and in the DRPs among NHs with comparable physician and qualified nurse staffing.

• NH residents are regarded to be frailer than home-dwelling older people, but whether they are treated differently with pharmaceuticals than their peers living at home remains to be substantiated.

8 AIMS

The aim of this thesis was to investigate the drug use at NHs in Oslo municipality, and more specifically:

1) Describe the DRPs identified by multidisciplinary MRs and the interventions carried out to resolve them. Compare the drug use before and after MR and explore predictors for the observed changes in drug use (*article I*).

2) Describe the variation between the NHs in their drug use, particularly psychotropic drugs and analgesics. Describe the variation in DRPs between the NHs and explore the associations between the drug use and the DRPs at the respective NHs (*article II*).

3) Compare the drug use in older people living at home and in a NH and identify the most pronounced differences in drug use, aiming also to identify areas of concern as well as in need for quality improvement of the drug use in the two settings (*article III*).

9 METHODS AND MATERIALS

This thesis consists of three cross-sectional studies based on drug use data generated by a Medication Review Project (NH population) and drug use data retrieved from the NorPD (Home population).

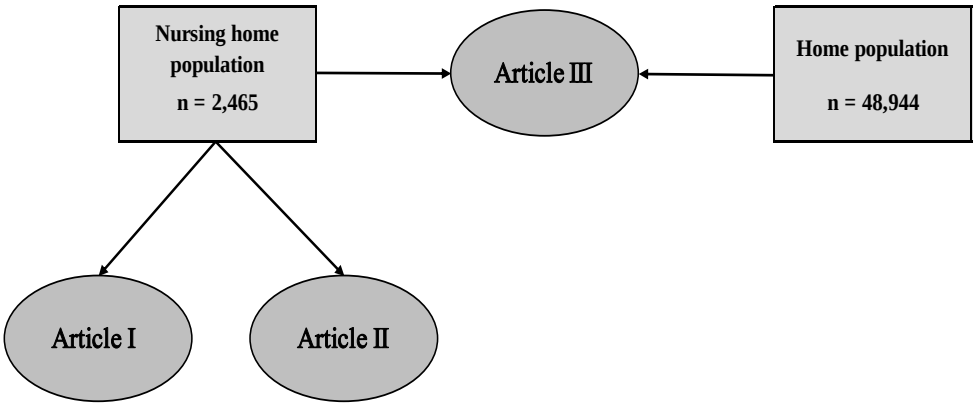

Figure 1: Overview on data materials

The Medication Review Project

The Medication Review Project (MR Project) was performed by the Nursing Home Agency (NH Agency) in Oslo municipality at 41 NHs in Oslo during 2011 to 2014. Among other tasks, the NH Agency assists the NHs in processes related to quality improvement and professional development. The MR Project aimed to improve the quality of drug use in the NHs of the municipality, in line with a national campaign on safe drug utilization in NHs (74).

Although NHs in Oslo are heterogeneous with regard to size, type of services (long-term or short-term care), bed units (RU and SCU) and management (public and private), they have fairly comparable staff time and employ full-time physicians, not part-time general practitioners as in many other places in Norway. Most NHs are using the electronic patient record system Gerica (114), a system that does not support prescription tools or drug interaction databases (102), thus the NH physician must validate their own prescriptions without the help of electronically alert systems integrated with the electronic patient record system.

All NHs with long-term care residents in Oslo municipality (n = 51) were invited to participate in the project. The NHs that volunteered to participate (n = 41) selected one, several or all the bed units in their institution to perform MRs. The participating bed units were either RU or SCU with long-term care beds. The NH Agency performed MRs in two rounds, respectively between November 2011 - November 2012 and August 2013 - February 2014. In total 30 NHs participated in the first round and 24 NHs in the second. Thirteen of the NHs participated in both rounds, however with different bed units and patients than in the first round.

It was aimed that all patients from the selected bed units should undergo MR. Except for those terminally ill (those receiving end-of-life palliative treatment), all patients and their next of kin received information about the project in written, including that the data collected during the project could later be used for research purposes.

In total 2,625 long-term care patients were asked to participate in the project. Eighteen patients refused and 142 scheduled MRs were not performed because the patient either died (n = 32), became terminally ill (n = 33), moved to another institution (n = 18), or for some other logistical reasons (n = 59). Thus 2,465 patients (on average 60 patients per NH, range from19 to 136 patients) had their medication use reviewed by a multidisciplinary team, 1,489 patients in the first round and 976 patients in the second round (Figure 2).

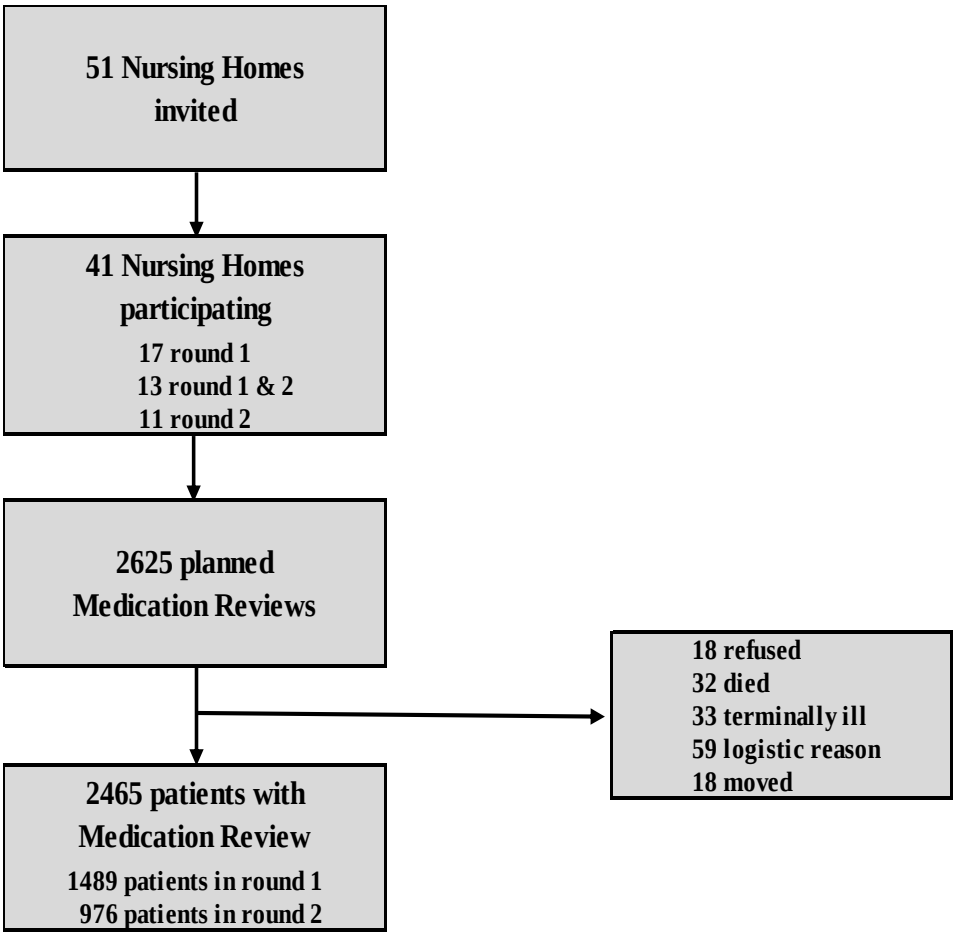

Figure 2: Recruitment to the Medication Review Project

The MRs consisted of a structured evaluation of each patient's drug use. A multidisciplinary panel made up by an externally hired clinical pharmacist, the NH physician and the nurse responsible for the patient conducted the MRs. Altogether five pharmacists from a pharmacy chain (Apotek1) were involved in the MRs, each with responsibility for several hundred MRs. Training sessions were held for the involved physicians, nurses and pharmacists before project start. The MR procedure was standardized in line with the national guideline for MRs (60).

The MR procedure

The NHs provided to the study pharmacists the patients' medication charts, which contained all the current drugs administered on a regular or prn schedule. Information that could identify the patient was removed from the charts, the patient being identified by a study number. The charts contained information about gender, age (in years), type of bed unit (RU or SCU) and the NH (identified by a number). The pharmacist documented the drugs according to the

Anatomical Therapeutic Chemical (ATC) classification system (115) and by the administration mode (regular or prn).

The pharmacist systematically reviewed the information from the patients medication charts and identified DRPs by using the explicit criteria for pharmacological inappropriateness STOPP/START (35) and the NORGEP-criteria (45), and the drug-drug interaction database (102). The DRPs were defined according to the PCNE: "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes" (63).

The pharmacist presented the identified DRPs for the NH physician and the nurse at face-to-face MR meetings held at the respective NHs. The meetings lasted about two hours and about eight patients had their medication use reviewed at each meeting.

The panel discussed each patient's medication use and the potential DRPs identified by the pharmacist, aiming at consensus on measures to improve the patient's medication use. The physician and nurse provided supplementary clinical (e.g. diagnosis, lab-tests) and functional information about the patient from the patient's medical record. The DRPs could be accepted or rejected, and in case of disagreement, the physician held the final decision.

The accepted DRPs were classified according to the Norwegian classification system (70). Six DRP categories were applied: 1) Drug choice problem (with subcategories 1a) need for additional drug, 1b) unnecessary drug, 1c) inappropriate drug choice); 2) Dosing problem (with subcategories 2a) too high, 2b) too low, 2c) sub-optimal dosing scheme, 2d) sub-optimal formulation); 3) Adverse drug reactions; 4) Interactions; 5) Inappropriate drug use (with subcategories 5a) administered by health personnel, 5b) administered by patient) and 6) Other (with subcategories 6a) monitoring required, 6b) unclear documentation, 6c) not classified).

The panel agreed upon interventions to resolve the DRPs. The interventions were classified as follows: stop the drug, drug switch (the discontinued drug is replaced by a new drug), start new drug, adjust the drug dose, monitor the drug use and other measures (70).

At the end of the meeting, the pharmacist documented the DRPs and the interventions agreed upon by the panel. The potential DRPs identified by the pharmacist alone that were rejected by the physician were not recorded. After the meeting, the NH physician implemented the changes to the medication list that were accepted by the patient/next of kin. The pharmacist documented whether the interventions were implemented or not.

Organizing of the data files

A database in SPSS was created with data on all the patients with MR (n = 2,465). Drugs were categorized according to the ATC classification system (116). All listed drug items without ATC codes (like nutritional supplements, multivitamins, omega-3 products, cranberry products) were excluded.

A drug–drug interaction was recorded as one DRP.

A new file with the drug use after MR was created by adding or removing drugs according to the interventions implemented after the MR (*article I*).

Drug use data from the Norwegian Prescription Database (NorPD)

The drug use of people living at home was retrieved from the NorPD. The NorPD is a pseudonymous registry including information about all prescription drugs dispensed at pharmacies in Norway and covers all people living in the country, except those living in long-term care institutions such as NHs.

The age threshold of ≥ 70 years was defined in line with the explicit NORGEP criteria.

Cross-sectional NorPD data were extracted on all prescription drugs purchased during the year 2012 by persons ≥ 70 years living in Oslo municipality (n = 48,944 people). Drug data in terms of defined daily dose were not retrieved due to lack of corresponding drug use data in the NHs. The following variables were recorded in the data set: the person's gender, age group (70 - 79 years, 80 - 89 years and ≥ 90 years) and the drugs in use by ATC-code.

Statistical analyses

The independent variables used in the three articles are listed in the table below.

Table 5: Overview of the independent variables

Variables	Article I	Article II	Article III
Gender	X	X	X
Age	X	X	X
Nursing home		X	
Total drugs at baseline	X		
Regular drugs at baseline	X	X	
Prn drugs at baseline	X		
Total drugs after MR	X		
Regular drugs after MR	X		
Prn drugs after MR	X		
Drug-related problems (DRP)	X	X	
Intervention to resolve DRPs	X		
User of drug (baseline)		X[1]	X[2]

Drugs as counts and drug name (ATC-code); [1]defined as using that particular drug on a regularschedule; [2]defined as using that particular drug on a regular and/or prn schedule

In *article II*, explanatory variables comprised of the size of the NHs, defined as the number of beds for long-term care (otherwise the NHs were comparable) and the pharmacist involved in the MR.

In *article III*, the drug prevalence rate in the population living at home was defined as the proportion of people who received at least one supply of a drug in 2012. Drugs for chronic and stable use are dispensed at pharmacies in quantities corresponding to about three months' use, therefore, prevalence rates were calculated based on purchase data for both three and twelve months. Because the prevalence rates were almost identical, the annual drug prevalence rates were used for the statistical analyses for reasons of feasibility.

The drug prevalence rate for the NH population was defined as the proportion of patients who used the drug in question at the time of the MR.

The same drug issued both regularly and prn to the same person was defined as one prescription; this approach fits better to the data available from the general outpatient population and it is commonly used in pharmacoepidemiological studies based on registry data (116).

In all three articles, data were presented using descriptive analyses; continuous variables were described using means with standard deviations (SDs) and the categorical variables using frequencies and percentages.

Differences between proportions (percentages) where established from the two-sample test of proportions and presented with 95% confidence intervals (CIs) (*article I*).

We used relative risks (RRs) with 95% CIs to estimate the likelihood of using the drug groups in the NHs compared to the likelihood of using them in the homes (*article III*). Associations between numerical variables were determined using the Pearson's correlation coefficient "r" (*article II*). The chi-square test for trend in proportions was used to assess the presence of a linear trend across levels of a factor variable (*article III*). Count data related to drug use and to DRPs were analyzed in terms of incidence rate ratios (IRR) with 95% CIs, using a Poisson regression model with random effects (RE) at NHs and adjusted for age and gender (*article I* and *article II*).

In *article II*, the NHs were grouped into four quartiles, based on their mean number of drugs per patient, the upper quartile comprising NHs with highest numbers. When a NH was allocated to a particular quartile, data from all patients in that institution were allocated to that quartile. The upper and lower quartiles were compared using independent samples t-test and presented with 95% CI.

For all analyses, the significance level was set at $\alpha \leq 0.05$. Analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY) and Stata SE (Stata Corp LP, College Station, TX).

Table 6: Overview on study design, data materials and statistics

Article/Title/ Design	**Data materials**	**Variables / statistical analyses**
I. Drug-related problems and changes in drug utilization after medication reviews in nursing homes in Oslo, Norway Cross-sectional before/after study	2,465 long-term NH[1] patients at 41 NHs	- Drug use and DRPs[2]/ descriptive analyses - Changes in drug use after MR[3]/ two-sample test of proportions with 95% CI[4] - Factors associated with DRPs and with change in the number of drugs after MR/ Poisson regression model with IRR[5] with 95% CI
II. Variation between nursing homes in drug use and in drug-related problems Cross-sectional, clustered at NH level	41 NHs with 2,465 long-term NH patients	-Variation in drug use and in DRPs/ descriptive analyses at NH level - Differences in DRPs and in use of particular drug groups between NHs with highest and lowest mean number of drugs per patient/ independent samples t-test with 95 % CI and p-value - Relationships between drug use and DRPs at the NH-level/ Pearson's correlation coefficient "r" - Factors associated with DRPs at the NHs/ Poisson regression model with IRR with 95% CI
III. Drug use differs by care level. A cross-sectional comparison between older people living at home or in a nursing home in Oslo, Norway Cross-sectional	2,313 people ≥ 70 years old living in NH 48,944 people ≥ 70 years old living at home	- Drug prevalence rates/ descriptive analyses - Differences in drug prevalence rates between the two populations and by gender and by age groups/ relative risk (RR) with 95% CI - Associations between drug prevalence rates and age groups/ chi-square test for trend in proportions

[1] NH (nursing home); [2] DRPs (drug-related problems); [3] MR (medication review); [4] CI (confidence interval); [5]IRR (incidence rate ratio);

10 ETHICS AND DATA SECURITY

After reviewing the research study protocol, the Regional Committee in Medical Research Ethics in South-East Norway (reference no. 2015/786) and the Norwegian Centre for Research Data (reference no. 2015/43659) concluded that their approvals were not needed.

The database is stored on the server of the University of Oslo and all data are anonymous.

The NH Agency submitted the Medication Review Project to the Regional Committee in Medical Research Ethics in South-East Norway in 2011. The committee concluded that it was a quality improvement project and therefore neither committee clearance nor informed consent procedure were required (2011/1989). However, all patients and their next of kin were informed in written about the project, including that the data generated by the project will later be used for research. Patients, who refused (themselves or their next of kin) to participate, were not included in the project.

11 FUNDING

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12 SYNOPSIS OF THE ARTICLES

12.1 Article I

Drug-related problems and changes in drug utilization after medication reviews in nursing homes in Oslo, Norway

Objectives: To describe the DRPs identified during MRs and the changes in drug utilization after the MRs, and to explore factors associated with the observed changes.

Methods: Observational before-after study of 2,465 long-term care patients at 41 NHs in Oslo. Multidisciplinary teams (pharmacist, NH physician and NH nurse) agreed upon the DRPs and interventions to resolve them. Changes in drug use after MR were analyzed using the two-sample test of proportions with 95% CI; factors associated with DRPs and with changes in drug use were tested by logistic regression.

Results: The mean age of the 2,465 patients was 85.9 years, 74.2% of the patients were women; women were older than men were (mean 86.9 and 82.8 years, respectively).
The MRs identified 6,158 DRPs, an average of 2.6 DRPs per patient, 2.0 for regular and 0.6 for prn drugs. Of these patients, 17.3% had no DRPs. The remaining 82.7% of the patients had on average 3.0 DRPs per patient. Use of unnecessary drugs (43.5%), excess dosing (12.5%) and monitoring of drug use required (11%) were the most frequent DRPs. Being a woman was associated with an 11% increased risk of DRPs, but not age.

Of the 6,283 interventions to change the drug therapy, 42.4% were to discontinue the drug, almost half (47.6%) being prn drugs. Need for closer monitoring of the drug use (22.7%) and dosage adjustments (17.8%) involved almost exclusively drugs for regular use (96%).

The mean number of drugs decreased after the MR from 6.8 to 6.3 ($p < 0.001$) for regular drugs and from 3.0 to 2.6 ($p < 0.001$) for prn drugs. Patients with DRPs experienced a decrease of 1.1 drugs after MR (0.5 for regular and 0.6 for prn drugs). No associations were found between the change in the number of drugs (regular or prn) and the patients' age or gender. The reduction was significant for the regular use of diuretics (4.7%), antidepressants (3.9%), hypnotics/sedatives (3.7%), antithrombotic agents (2.7%), antacid drugs (2.1%) and antipsychotics (1.8%). For prn use, the reduction was significant for opioids (11.2%),

anxiolytics (7.1%), hypnotics/sedatives (5.8%), metoclopramide (3.5%), NSAIDs (2.9%), expectorants (2.7%) and antipsychotics (1.5%).

Conclusions: The MRs resulted in overall less drug use due to discontinuation of drugs, especially psychotropic and opioid drugs and to lowering the drug dosages. MRs lead to a closer follow-up to optimize the potential benefits of the drug use. Future research on MRs should include patient-related clinical outcomes.

Addendum: The table below was not included in *article I* for reasons of space. It summarizes the most frequent DRPs associated with the use of psychotropic, analgesic and cardiovascular drugs.

Table 7: The three drug-related problems most frequently associated with the use of psychotropic drugs, analgesics and cardiovascular drugs

Drugs			**Three most frequently DRP categories related to the drug classes listed**								
Therapeutic group	N	Nprn	No. 1	n	n (prn)	No. 2	n	n (prn)	No. 3	N	n (prn)
Hypnotics /sedatives	515	185	Unnecessary drug	296	160	Dosing too high	92	9	Inappropriate drug choice	43	7
Opioids[1]	509	323	Unnecessary drug	249	226	Inappropriate drug choice	80	49	Drug-drug interaction	50	21
Antidepressants	456		Drug-drug interaction	124		Unnecessary drug	115		Monitoring required	43	
Anxiolytics	403	244	Unnecessary drug	213	164	Inappropriate drug choice	56	32	Dosing too high	50	22
Paracetamol	354	146	Dosing too high	108	36	Unnecessary drug	104	59	Additional drug	103	25
Diuretics	308	22	Unnecessary drug	152	20	Dosing too high	65		Inappropriate drug choice	43	
Antithrombotic agents[2]	262		Unnecessary drug	81		Drug-drug interaction	66		Dosing too high	33	
Antipsychotics	228	40	Unnecessary drug	66	30	Monitoring required	52	2	Adverse drug reaction	28	
Beta-blockers	190		Drug-drug interaction	48		Unnecessary drug	28		Dosing too high	28	
Heart therapy[3]	150	32	Unnecessary drug	46	25	Monitoring required	36		Dosing too high	20	
Renin-angiotensin	125		Monitoring required	46		Unnecessary drug	16		Drug-drug interaction	15	
Antidementia drugs	114		Monitoring required	48		Unnecessary drug	38		Dosing too high	6	

N = the total number of drugs involved in the problem listed, both regular and prn drugs; Nprn = the share within the therapeutic group comprised by prn drugs involved in the problem listed; n = number of DRPs; n(prn) = the share within the DRP category associated with prn drugs; [1]ATC-N02A comprising weak opioids (codeine, tramadol) and strong opioids; [2]ATC- B01A (mainly warfarin, acetylsalicylic acid and heparin); [3] ATC-C01A (digitalis) and ATC-C01D (nitrates).

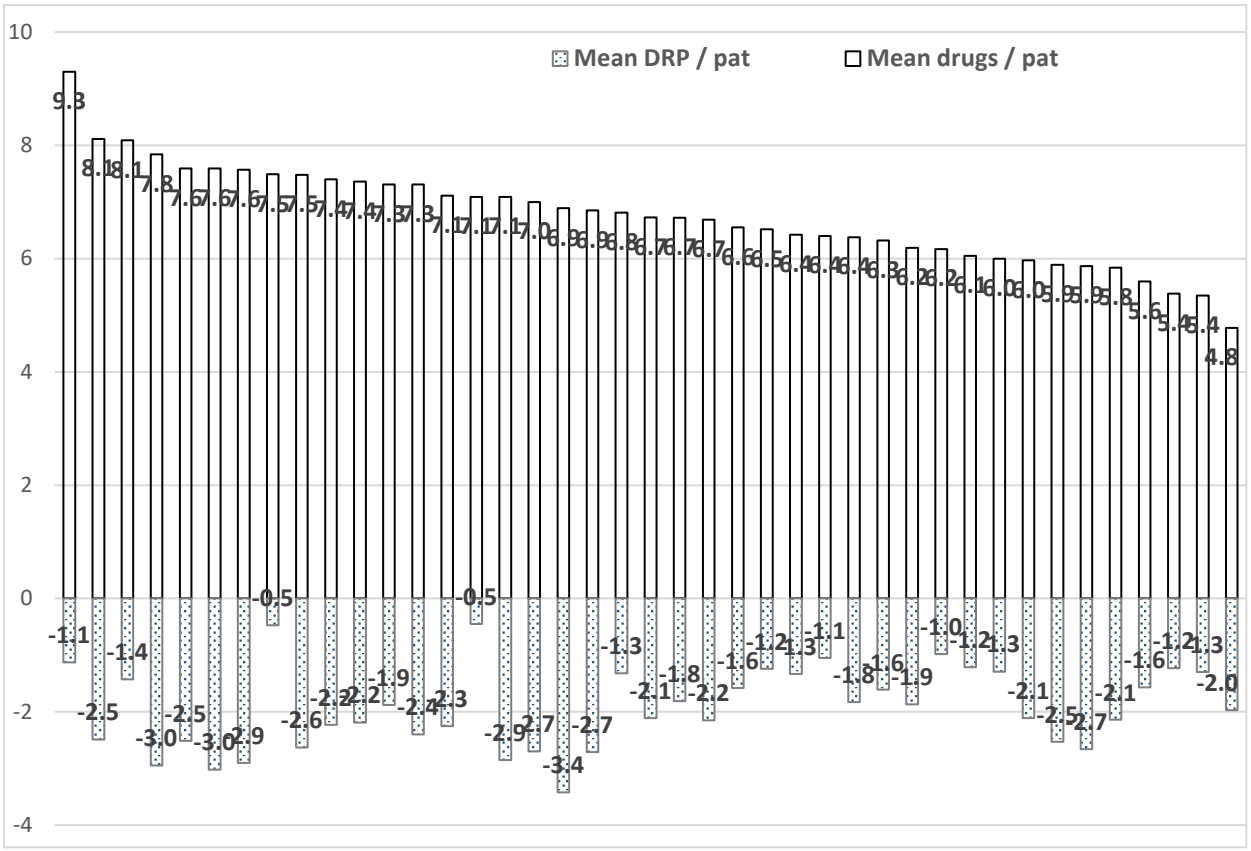
12.2 Article II

Variation between nursing homes in drug use and in drug-related problems

Objectives: To analyze variations in drug use and DRPs between different NHs.

Methods: Cross-sectional medication review study including 2465 long-term care residents at 41 NHs in Oslo. Regular drug use was retrieved from the patients' medical records. DRPs were identified by using STOPP/START and NORGEP criteria and a drug-drug interactions database. NHs were grouped in quartiles based on average levels of drug use. The upper and lower quartiles were compared using independent samples t-test and associations between drug use and DRPs were tested by logistic regression.

Results: Patients' mean age was 85.9 years, 74.2% were women. Mean numbers of regular drugs per patient was 6.8 and varied between NHs from 4.8 to 9.3. The proportion of patients within each NH using psychotropic or analgesic drugs varied largely: antipsychotics from 3% to 50%, benzodiazepines from 24% to 99%, antidepressants from 9% to 75%, antidementia drugs from no use to 42%, opioids from no use to 65% and paracetamol from 16% to 74%. NHs using more drugs also used more opioids ($r = 0.7$) and more benzodiazepines ($r = 0.4$). Mean DRPs per patient was 2.0 and varied between NHs from 0.5 to 3.4 (Figure 3).



Each bar represents one NH with their respective mean number of drugs per patient (upper part of each bar) and mean number of DRPs per patient (lower part of each bar below the zero line).

Figure 3: Variation between nursing homes in drug use and in drug-related problems

The use of unnecessary drugs was associated with excessive dosing (r = 0.8), inappropriate drug choice (r = 0.5) and need for additional drug (r = 0.4) at the respective NHs.
The quartiles of NHs with highest and lowest mean number of drugs per patient (7.7 vs. 5.7, p < 0.001) had comparable mean number of DRPs per patient (2.2 vs. 1.8, p = 0.2).
Using more drugs or being a woman were associated with a 7% and 9% increase in DRPs, respectively. The use of antipsychotics, antidepressants, benzodiazepines and opioids were associated with an increased risk for DRPs at the respective NHs of 20%, 18%, 8% and 7%, respectively.

Conclusions: The use of psychotropic and analgesic drugs was high and varied substantially between different NHs, suggesting different drug prescription cultures at several institutions. There was no difference in DRPs between the group of NHs with highest and lowest drug use, although using more drugs, opioids and psychotropic drugs was associated with an increased risk for DRPs at the respective NHs.

12.3 Article III

Drug use differs by care level. A cross-sectional comparison between older people living at home or in a nursing home in Oslo, Norway.

Objectives: To identify areas of concern and in need for quality improvement in the drug use of people aged ≥ 70 years living at home or in a NH.

Methods: Cross-sectional observational study from Oslo, Norway. Information about drug use by people living at home in 2012 was retrieved from the NorPD. Drug use in NHs was recorded by MRs performed during November 2011- February 2014. Prevalence rates and relative risk (RR) with 95% CI were compared between uses of therapeutic groups with prevalence rates of ≥ 5%. Drug use was compared for the total population and by gender and age group.

Results: Older people (both genders; $n = 2{,}313$) in NHs were more likely than people living at home ($n = 48{,}944$) to use antidementia drugs (RR = 5.7), antipsychotics (RR = 4.0), paracetamol (RR = 4.0), anxiolytics (RR = 3.0), antidepressants (RR = 2.8), dopaminergic drugs (RR = 2.7), antiepileptic drugs (RR = 2.4), loop diuretics (RR = 2.3), cardiac nitrates (RR = 2.1) or opioids (RR = 2.0).

By contrast, people living in a NH were less commonly prescribed statins (RR = 0.2), NSAIDs (RR = 0.3), osteoporosis drugs (RR = 0.3), thiazide diuretics (RR = 0.4), calcium channel blockers (RR = 0.5) or renin–angiotensin inhibitors (RR = 0.5). Each of the populations had only minor differences in drug use by gender and a trend towards less drug use with increasing age ($p < 0.01$).

Ten drugs in both settings were identified to be in particular need for critical rethinking during future educational interventions or MRs (table 8).

Table 8: Drugs in need for critical rethinking

Drug	Nursing home	Home
Antidementia drugs	Severe dementia: overuse?	Mild dementia: underuse?
Antipsychotic drugs	BPSD[1]: Too much, too long? Deprescribing should be tried	(little use)
Antidepressants	Overuse: Poor effect in people with dementia. Consider tapering down dosage and deprescribing	Possible overuse: Consider tapering down dosage and deprescribing
Anxiolytics Hypnotics/sedatives	Overuse	Probable overuse
Opioids[2]	Overuse	Probable overuse
Clomethiazole	Overuse: should be avoided whenever possible for reasons of safety	(almost no use at all)
NSAIDs	(little use)	Overuse – try paracetamol instead
Osteoporosis drugs	Possible underuse?	Possible underuse?
Statins	(little use)	Possible overuse (oldest age group?)
Drugs for peptic ulcer	Possible overuse	Possible overuse

[1] Behavioral and psychiatric symptoms in dementia; [2]Opioids comprise minor and major opioids

Conclusions: Drug use by older people differs according to care level, and so do areas probably in need for quality improvement and further research. In NH residents, this relates to a probable overuse of psychotropic drugs and opioids. Among older people living at home, the probable overuse of NSAIDs and a possible underuse of cholinesterase inhibitors and osteoporosis drugs should be addressed.

13 GENERAL DISCUSSION

13.1 Methodological considerations

This thesis has some methodological limitations because the research protocol was prepared after the quality improvement project that generated the MR data was completed:

▪ The lack of sample size calculation and of a control group was mitigated by using a cross-sectional observational design in all three studies.

▪ The recruitment of NHs and of the bed units may possibly have been subjected to selection bias. It was not documented the NHs' reasons to accept or to decline the invitation to participate, neither the process to recruit the bed units at the respective NHs. Further, there were no minimum requirements for how many MRs that should be performed at each NH. However, this possible bias was mitigated by the high number of MRs performed and because a vast majority of the invited NHs participated in the project.

▪ After the MRs were completed in November 2012, it was decided to continue the project and perform a second round with MRs. In this second round, participants were eleven new NHs and thirteen NHs that had participated in the first round. However, the latter now with new bed units and therefore with new patients. In this research, all patients with MR were treated as one cohort where one single MR generated cross-sectional data for each subject. Due to the large number of patients, we consider that the results had not been affected if some few patients by chance had two MRs because they had moved to another NH or to another bed unit during the project period.

▪ The DRPs identified alone by the pharmacist were not documented, neither the physicians' reasons for rejecting some DRPs. Without documenting the DRPs identified by the pharmacist alone, it was not possible to determine the acceptance rate of the DRPs at the NHs. A Norwegian study reported that NH physicians rejected one third of all DRPs identified by the pharmacist in a multidisciplinary MR team (76), whereas in a study from Spain, the physician rejected slightly more than one in eight STOPP recommendations to discontinue drugs and two thirds of the START recommendations (117). It is therefore possible that different acceptance rates have influenced the variation in DRPs found between the NHs (*article II*).

The internal and external validity of our findings

Article I and article II: We consider that the internal validity is high because the vast majority of the invited NHs participated in the project and they provided complete datasets. Furthermore, the MRs were performed in a reliable way at all sites, ensured by training the staff before the MRs and using the same standardized tools (35;45;102) and classification system during the reviews (70). Each of the five pharmacists participated in several hundred MRs at many different NHs, which also contributed to the use of similar procedures at all sites.

In general, the use of explicit criteria for PIMs might be questioned, as they do not address individual differences or the appropriateness of the entire medication (33). This was compensated for through face-to-face discussions on the entire medication list for each patient and taking into consideration clinical data on functioning, lab-tests and other clinical information about the patient. We therefore consider that the explicit criteria to identify DRPs was appropriate for the NH population at the time the MRs were performed and this thesis was in preparation. The results are representative for the NH population in Oslo municipality because 82% of the NHs and 61% of all long-term care patients in the municipality participated in the MRs. Further, the patient-mix across the participating NHs is quite similar and the NHs are quite comparable with respect to staffing. Using the same DRP classification system as in other Norwegian studies and because the NH-sector in Norway is quite uniform, our findings are representative at national level. The multidisciplinary MR procedure and the international drug classification system contribute to the external validity of our results in comparable NH-settings in other countries.

Article III: In this drug utilization study, the drug use was investigated in terms of prescription prevalence rates. The home population was one cohort without differentiating between robust and frail home-dwelling older people. The drug prevalence rates for those living at home differed only marginally between data captured over three vs. twelve months, thus being comparable with the point prevalence data for those living in NHs. We consider that our data are representative for each of the populations and that they have an acceptable validity for identifying the most significant differences in drug use patterns between older people living in the two settings. Because we included large populations in both settings, we regard our results to be representative for comparable health care settings.

13.2 Discussion of results

13.2.1 Drug utilization at NHs

Number of drugs

We found an average of 6.8 regular drugs per patient, whereas previous studies from Bergen reported 5.0 (79) and 6.1 regular drugs per patient (81); the higher number of drugs in our study possibly reflects a general tendency of higher drug use at NHs during the last decades, probably among others, due to an increased use of psychotropic drugs (85). Other MR studies performed in Oslo and Bergen around the same time as our study reported 7.5 (104), 8.0 (103), 8.1 (76) and 10.5 (105) regular drugs per patient, whereas recent studies from other regions (108;110) reported an average of 8.0 drugs per patient. The somewhat higher drug use in these studies might reflect prescription or organizational differences at the NHs, or that the relatively few NH included in these studies were, by chance, HNs with higher prescription rates. MR studies from Switzerland (107) and Sweden (109) reported means of 12.8 and 8.5 drugs per patient, whereas a large European study on drug utilization at NHs found a mean of 8.0 drugs per patient with a large variation between the participating countries (19). Although there are possible different prescription traditions between the countries, e.g. lower overall drug use in Norwegian NHs as compared to Swedish NHs (118), our findings are in general consistent with literature. The mean number of regular drugs per patient varied largely between the NHs, from 4.8 to 9.3 (*article II*), probably explained by differences in the proportion of patients at SCUs who tend to be younger and less multimorbid and by different prescribing traditions among physicians. Other Norwegian studies found, among less institutions, variation in drug use from 7.0 to 9.5 (103) and from 6.0 to 9.3 regular drugs per patient (110), that is consistent with our findings.

Psychotropic drugs

Unfortunately, we just have point prevalence data without information on dosage and duration of treatment or what drug combinations were used to treat BPSD. Nevertheless, we conclude that regular use of psychotropic drugs were probably overused in the total NH population (*article I*) and especially at some NHs (*article II*), both before and after the MR, possibly reflecting the patients' need for continued treatment or perhaps more importantly, reluctance among physicians and nursing staff to discontinue the drugs (90).

The considerable variation between the NHs in the proportion of patients using psychotropic drugs on a regular schedule (*article II*), is generally consistent with those reported by other Norwegian NH studies (81;98), as well as with studies from Europe (99), US (100;119) and

Canada (120). We do not know the reasons for this variation, but one explanation may be that local prescription habits (119) for calming down noisy patients also reflect a need for relieving staff pressure (90). A previous study with comparable NHs located in Western Norway and staffed with general practitioners, also reported great variations in psychotropic drug use between the NHs that hardly could be explained by quantitative differences between the institutions (98). Another study found that NHs with high prevalence rates also tended to use higher dosages (81). This is of concern because these drugs may have many and serious side effects in particular in frail old people with dementia (97).The probable psychotropic overuse in NH residents represent an important challenge for future quality improvement measures, emphasizing the need for continuous training of both NH physicians and nurses in geriatric pharmacotherapy.

Antipsychotics administered on a regular schedule were used by 18.3% of the patients (*article I*), which is less than figures reported in previous Norwegian studies where almost one in four (23.0 – 24.4%) residents used an antipsychotic drug (81;98) and more in line with a more recent study (83) where the prevalence was about one in five (19.9%). The lower prevalence of antipsychotic drug use seen in more recent studies, ours included, may possibly reflect an increased concern about their modest efficacy in reducing aggression and psychosis (97;121) and poor safety in older people, with increased risk for all-cause mortality, stroke and extrapyramidal symptoms (96;122;123). However, the use of antipsychotic drugs varied substantially between different NHs in Oslo, from 3.0% to 50.0% (*article II*). Others have also reported large variations in the antipsychotic use ranging from 10% to 61% (98) and from 14% to 36% (81). Somewhat more use may be justified by more patients at SCUs, however, not to the extent as reported here. Even if we did not have access to data on duration of treatment, we suggest that most regular users of antipsychotics were long-term users. Tapering down and deprescribing unnecessary antipsychotic drugs can safely be done in most patients without worsening of symptoms (121;124), including in long-term users (125). Initiatives for more restrictive prescribing were shown to reduce antipsychotic use by 40% (from 23.9% to 14.3%) in NHs in US (126). The high prescription rates of antipsychotics reflect inappropriate prescription practices in need of educational interventions for quality improvement.

Antidepressants were used by 37.5% of the patients (*article I*), whereas other Norwegian studies found rates ranging from 31.0 to 50.9% (81;83;98;104). The unacceptable variation from 9.1% to 75.0% between the NHs in Oslo is even larger than variations previously

reported from Bergen in 2012 from 22% to 56% (81) and in 2001 from 10% to 61% (98). It is unlikely that the large observed variation between how antidepressants are used in different NHs reflect corresponding variations between patients. It is more likely that the variation has something to do with the attitudes, beliefs or knowledge among the health professionals working at the institution. There is no clear evidence for the efficacy of antidepressants in people with dementia and depressive symptoms (92;127) and the probable overuse of antidepressants calls for initiatives to avoid unnecessary long-term use, like more non-pharmaceutical treatment, systematic use of tests like the Cornell-test (128;129) and routines for trying to taper down and discontinue antidepressants at regular intervals (94).

We found that 11.6% of the patients used *cholinesterase inhibitors* and *memantine*, whereas others have reported slightly higer rates of 12.7% and 13.7% (81;83). The variation between the NHs in our study was very large, from no use at all to 41.7%, a much larger variation than that found by Krüger, from 7.0% to 26% (81). Here may be several reasons for the differences that should be addressed in future research.

Respectively 32.6% and 21.4% of the patients regularly used *hypnotics/sedatives* or *anxiolytics* (*article I*). The overall benzodiazepine use varied largely between the NHs ranging from 23.7% to 98.6% (*article II*). Compared to our study, two older Norwegian studies found lower use of hypnotics/sedatives and anxiolytics, respectively 14% and 15% in the study by Ruths (98) and 19.3% and 22.0% in the study by Kruger (81), consistent with the trend of increased use of benzodiazepines in NHs during the last years (85). A recent study by Gulla (83) found quite similar results with ours with 30.5% of the patients using hypnotics/sedatives and 23.9% using anxiolytics (83). Although we do not know the duration of the treatment or what benzodiazepines dosages were used, the high use of benzodiazepines at the NHs (*article I*) and at some NHs in particular (*article II*), is an issue of concern. Available data, although limited, do not support the routine use of benzodiazepines for the treatment of BPSD (130) and their use is associated with sedation and falls (131).

Analgesic drugs

We found that 34.3% of the patients used *opioids* (*article I*), with a variation between NHs from no use at all to 65.2% (*article II*) whereas Krüger found a prevalence of 14.6% and a variation from 4% to 31% (81). The differences may be related to including minor opioids in our findings, but also due to a more general trend of higher opioid use in NHs during the last decades in Norway (86) and other countries (132;133). Thus, an increase in opioid use may reflect improved recognition and treatment of pain (132) as chronic pain may be

communicated in terms of BPSD (73) and may be undertreated in patients with dementia (134). However, initiatives are needed to monitor opioid-related adverse reactions like sedation, falls and respiratory depression, especially when used concurrently with benzodiazepines. We cannot explain why opioids were not used at all at one NH. A possible explanation may be physician's reluctance to prescribe opioids. *Paracetamol* was used by 44.5% of the patients (*article I*), whereas other studies found comparable or higher rates of 40.2% and 70.2% (81;110). The variation in paracetamol use between the NHs was from 15.8% to 73.9% and it is possible that paracetamol was underused at some NHs. The very low use of NSAIDs is consistent with the national trend in the NH-setting (86).

Other drugs

Numerous other therapeutic drug groups were used by a high proportion of NH patients, e.g. cardiovascular drugs, anti-anemia drugs, antacid drugs (mainly proton pump inhibitors), drugs used in hypothyroidism, drugs for osteoporosis, drugs for chronic obstructive pulmonary disease, diabetes and glaucoma (*article I*), reflecting the high disease burden in NH residents. Compared with the drug use of their peers living at home (*article III*), we found a higher risk for using psychotropic drugs in NHs, which is consistent with the higher rate of people with dementia and BPSD in that setting. Perhaps due to higher rate of disability and shorter life expectancy, NH patients tend to use a more symptomatic than prophylactic treatment for cardiovascular disease, such as cardiac nitrates and diuretics. The palliative approach in NH setting may also explain higher use of opioids and paracetamol and a corresponding low use of NSAIDs that, although efficient in reliving musculoskeletal pain and inflammation, have a poor safety in old age, including side effects like life threatening bleedings (135) and cardiovascular events (136). However, the large variation between the NHs (*article II*) and the significant decrease in the number of drugs per patient after the MRs (*article I*), support that there is a potential for further reducing the drug utilization, especially at NHs with high prescription levels.

13.2.2 Medication review to reduce drug related problems

In *article I* we found a mean of 2.0 DRPs per patient for problems associated with the use of regular drugs. Other Norwegian studies with similar MR procedures reported means of 2.0 (105), 2.5 (104), 3.5 (76), 3.7 (108), 4.0 (103) and 4.6 (110), whereas studies from Sweden, The Netherlands and Switzerland reported means of 2.2 (109), 3.5 (106) and 3.7 (107). One study using implicit criteria found 1.8 DRPs per patient (98). The lower prevalence of DRPs in our study compared with most other studies can be explained by the fact that we only recorded DRPs agreed upon by the team, not all problems suggested by the pharmacist alone. Regional differences in patient-mix and NHs might also play a role here, the most recent studies (108;110) being performed in the middle and northen part of Norway at smaller mostly rural NHs. It may be speculated that full-time working NH physicians might also be part of a possible explanation here. In spite of lower DRPs rates, the distribution of the problems was comparable to those reported in other studies, with most problems associated with unnecessary use of drugs, excess dosing or inadequate monitoring of the drug therapy. Almost all the recommended interventions to resolve the DRPs were implemented, in line with other studies using multidisciplinary MRs (76;107).

The average number of regular drugs used per patient decreased after the MR (*article I*). However, the intervention did not change the patterns of drug use in the NH population, hence the same drug groups being used most frequently before and after the MR. The use of all drug groups showed a downward tendency after the MR, except for drugs for thyroid therapy that remained unchanged. However, the reduction was significant only for few drug groups, such as antipsychotics, hypnotics/sedatives, antidepressants, diuretics, antithrombotic agents and antacid drugs (mainly PPI).

The MRs reduced the average prn drugs per patient, the largest decrease being found for opioids and anxiolytics, probably because of their overuse for BPSD (90). In another study, two thirds of the prn medication was never administered to the patients during the 15 weeks follow-up (137). This suggests that the prn medication should be included in the regular MRs, to reflect the actual needs of the patient.

Underprescribing was less common, just 7.4% of all DRPs. Most new drugs issued after the MRs were iron supplements, B12-vitamin or folic acid for anemia, paracetamol for pain and calcium and vitamin D for osteoporosis (*article I*). The MR method in itself might contribute

to less focus on the identification of unmet medical needs. Physicians may also have a higher threshold for adding a new drug to a person already taking many. Polypharmacy may therefore paradoxically represent a risk factor for underprescribing (28).

Potential adverse drug reactions comprised only 4.7% of the DRPs, however, mainly involving drugs with safety hazards like hypnotics/sedatives, anxiolytics and antipsychotics. Also potential drug-drug interactions were rare (4.4%), possibly because the physician mainly accepted clinically relevant interactions; the very low use of NSAIDs may also have contributed here.

Finally, we can conclude that drugs administered regularly for BPSD dominated the DRP categories that led to drug discontinuation or a re-evaluation of the rationale for continued drug treatment. We do not know if the implemented changes remained stable over time, but this should be expected based on other studies that found that 88% of the changes were maintained after three months (104).

Variation in DRP

The variation between NHs regarding the mean number of DRPs per resident per NH (from 0.5 to 3.4) was large, up to seven-fold, although the NHs were otherwise comparable: publicly funded, administered by the same agency, with the same type of bed units, staffed according to county standard and providing care for comparable patient-mix (*article II*). For comparison, the mean DRPs per patient per NH was higher but varied less in other Norwegian studies, from 1.6 to 2.4 (105), from 2.7 to 5.6 (110) and from 3.0 to 5.5 (103). In one of these studies, performed at two NHs located in Oslo, the higher rate for DRPs was found at the NH with less physician time (103).

When we compared the group of NHs with highest vs. lowest mean number of drugs per patient, we found no difference in the prevalence of DRPs (*article II*). Although the somewhat limited number of NHs in the quartiles might challenge this finding, the descriptive analysis (figure 3) shows that some NHs in the quartile with highest levels of drug use also had very low levels of DRPs. One should therefore be cautious to use the average number of drugs per patient as a measure for prescription quality at the respective NH. The strong correlations found between need for additional drug, use of unnecessary drug, excessive dosing and inappropriate drug choice, suggest that prescription quality is multifaceted and hence, in case it is suboptimal, e.g. high rate of DRPs, this will affect several areas of drug prescribing practice. In *article II*, the large differences in DRP levels between otherwise comparable NHs might also to some extent be explained by NH physicians' different acceptance rates

regarding suggested DRPs. Because we did not record the proposed DRPs, only the accepted ones, we are not able to explore this further. Although the DRP system is a practical tool to sort out different categories of problems, it is not known if their use in fact lead to better patient-related outcomes than MR procedures undertaken without using DRPs. This should be investigated in future research.

14 CONCLUSIONS

The use of psychotropic and analgesic drugs was high in the NHs and the regular use of these drugs varied largely between the different NHs. These drugs were most commonly involved in all types of DRPs and in interventions on the patients' medication use. Although the MRs reduced the regular use of antipsychotics, hypnotics/sedatives and antidepressants, their use was still high after the MRs. Our data do not permit us to conclude if this high use reflects patients' need for continued treatment or a reluctance among the staff to discontinue them. However, their use in NHs needs critical rethinking due to their poor effect and safety in older people with dementia.

The most frequent DRPs were use of unnecessary drugs and too high dosing, hence the MRs reduced the overall drug utilization by withdrawal of regular and prn drugs and by lowering the dosing of regular drugs. The third most frequent DRP was a requirement to monitor the effect and safety of the drug, thus the MRs probably ensured a more appropriate monitoring of long-term medicine use. Because the vast majority of the interventions to resolve DRPs were accepted by the patients/next of kin, we consider that the MRs contributed to a more appropriate medication for the benefit of the patients. We also believe that the MRs had an educational effect on the NH staff involved in the reviews, leading to more awareness on balancing efficacy and safety issues, which is needed for safer drug use at NHs.

The current low evidence for the effect of MRs on clinical outcomes does not change our view that MRs are recommended tools to improve medication appropriateness in NHs. We support that standardized MRs should be part of the regular clinical follow up of the NH residents, at least annually, but preferably every six months due to the short life expectancy of most residents

The large variation in drug use and DRPs between otherwise comparable NHs, along with a significant decrease in drug use after MRs suggest a potential for further reducing the drug utilization, especially at NHs with high prescription levels. We therefore support educational outreach and other interventions to increase the skills of the NH staff in geriatric pharmacology to improve medication appropriateness.

While we have reliable drug use data for older people living at home, we still lack a similar registry for people living in NHs. The large differences in drug use between older people

living in a NH or at home show that these two settings are completely different worlds when it comes to pharmacoepidemiology. Thus, it is urgently needed to include the drug use of the NH residents in the national prescription registry NorPD.

15 CLINICAL IMPLICATIONS AND FUTURE RESEARCH

The translation of knowledge into clinical practice at the NHs in Oslo was initiated by discussing the DRPs and the changes in drug use after MRs (*article I*) at a meeting with NH physicians held by the NH Agency in 2018. Among future interventions was identified the need to systematically record the clinical indication for each drug prescription on the medication lists.

The results from this thesis, supplemented with clinical feedback from the NH physicians should be used by the NH Agency to critically evaluate and improve the procedures for MRs in the municipality. Such improved procedures might be of interest also for others in the NH-sector. There is a need to organize regular educational meetings for the NH physicians highlighting different therapeutic challenges as disclosed during MRs, with discussions on experiences, challenges and initiatives for further improving the procedure.

The large variation in drug use between different NHs needs to be debated with the NH physicians, with the aim to find out how we could avoid unacceptable variations, and how to determine if a variation is due to a particular patient-mix at a particular NH – or not. Such initiative would give a better foundation for comparisons between the NHs than the annual drug purchase statistics, and it may lead to identifying areas in need for improvement across the NHs or at particular NHs. Further, it will also be a good start for identifying topics for courses in geriatric pharmacotherapy for the NH physicians.

Future research

It is urgently needed to investigate patient-related outcomes related to interventions following the MRs, primarily quality of life outcomes due to the short life expectancy of the NH residents. Further, one could explore the validity of the DRP concept related to patient outcomes.

The unexpected large variation in the use of regular drugs between the NHs should be investigated further. Such study might find out if variations are unacceptable and if so, suggest interventions to reduce them. NHs with unexpected high drug/PIM use might be in need for educational outreach interventions and perhaps comprehensive collaborative MRs. The NHs in Oslo now systematically perform MRs by physician and nurse for each patient at admission and thereafter every six months. It is therefore to be hoped that these efforts may have improved the all over drug use quality. This may possibly also have led to less variation between different NHs in how they treat comparable patients.

At present, the NHs in Oslo are using multidose dispensed drugs. One should investigate whether the pharmacy supplying multidose dispensed drugs has a database with the NH users and if their personal number identifies the users in the database. If this is the case, efforts should be undertaken to make that database available for research in collaboration with the NH Agency. If this is feasible, assessment of the drug use at the NHs using multidose dispensed drugs will be much easier and it could be done regularly to monitor the changes in drug use patterns and the variations between institutions.

We substantiated a large difference in the pharmacotherapy of older people by care setting, with more use of PIMs and a palliative approach in NHs. In my experience, new residents commonly present polypharmacy, including concomitant use of psychotropic drugs at admission. It would be of interest to follow up longitudinally the residents' drug use based on the MRs performed at admission and thereafter every six months. Because such MRs are already part of routine care at the NHs in Oslo, research may be part of routine care and hence feasible.

Finally, inappropriate medication use in NHs represents a serious challenge for the quality of care of older people. However, research on drug utilization among NH residents in Norway suffers from lack of registry data for people living in NHs. Including the NH residents into the NorPD would therefore represent a huge step forward. This would enable monitoring and evaluating the drug utilization in NHs at national, regional and local levels - both cross-sectional and longitudinally. Since the NorPD is no longer pseudo-anonymous, this will make record linkage with other data sources much easier based on the eleven-digit person number.

I hope that this thesis will contribute to research activities initiated by among others, the NH Agency in Oslo, to improve procedures for drug utilization at NHs and the pharmacotherapy of older people.

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RESEARCH ARTICLE

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Drug-related problems and changes in drug utilization after medication reviews in nursing homes in Oslo, Norway

Amura Francesca Fog[a,b], Gunnar Kvalvaag[a], Knut Engedal[c] and Jørund Straand[b]

[a]Nursing Home Agency, Oslo, Norway; [b]Department of General Practice, Institute of Health and Society, University of Oslo, Oslo, Norway; [c]Norwegian National Advisory Unit for Aging and Health, Vestfold County Hospital HF, Toensberg and Oslo University Hospital, Oslo, Norway

ABSTRACT

Objective: We describe the drug-related problems (DRPs) identified during medication reviews (MRs) and the changes in drug utilization after MRs at nursing homes in Oslo, Norway. We explored predictors for the observed changes.
Design: Observational before-after study.
Setting: Forty-one nursing homes.
Intervention: MRs performed by multidisciplinary teams during November 2011 to February 2014.
Subjects: In all, 2465 long-term care patients.
Main outcome measures: DRPs identified by explicit criteria (STOPP/START and NORGEP) and drug–drug interaction database; interventions to resolve DRPs; drug use changes after MR.
Results: A total of 6158 DRPs were identified, an average of 2.6 DRPs/patient, 2.0 for regular and 0.6 for pro re nata (prn) drugs. Of these patients, 17.3% had no DRPs. The remaining 82.7% of the patients had on average 3.0 DRPs/patient. Use of unnecessary drugs (43.5%), excess dosing (12.5%) and lack of monitoring of the drug use (11%) were the most frequent DRPs. Opioids and psychotropic drugs were involved in 34.4% of all DRPs. The mean number of drugs decreased after the MR from 6.8 to 6.3 for regular drugs and from 3.0 to 2.6 for prn drugs. Patients with DRPs experienced a decrease of 1.1 drugs after MR (0.5 for regular and 0.6 for prn drugs). The reduction was most pronounced for the regular use of antipsychotics, antidepressants, hypnotics/sedatives, diuretics, antithrombotic agents, antacid drugs; and for prn use of anxiolytics, opioids, hypnotics/sedatives, metoclopramide and NSAIDs.
Conclusion: The medication review resulted in less drug use, especially opioids and psychotropic drugs.

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Drug-related problems; medication review; nursing home; elderly; discontinuation

Introduction

In Norway, the nursing home (NH) sector comprising 42,000 beds provide care for both physically disabled and psychogeriatric patients. About 80% of NH patients are cognitively impaired and most have at least one significant neuropsychiatric symptom [1,2]. A typical NH patient is an old (mean age, 86 years) and frail female with short life expectancy [3]. Because of multiple comorbidities, they use around eight drugs on a regular basis [1,4,5] and have thus an increased risk of drug–drug interactions [4] and adverse drug reactions [6]. Frailty, cognitive impairment [3] and age-related changes in pharmacokinetics and pharmacodynamics add further to these risks [7].

A drug-related problem (DRP) is 'an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes' [8]. Previous Norwegian studies using different tools for identifying drug–drug interactions [9] and potentially inappropriate prescriptions for the elderly [10,11] have reported that NH patients are frequently exposed to DRPs [1,12,13].

In the NH setting, medication reviews (MRs) are recommended for improving the quality and the follow-up of the drug therapy by substantiating needs for continued use or for better balancing risks with potential benefits [14,15]. However, although MRs may identify and resolve DRPs, there is a lack of evidence about their effects on 'hard' patient outcomes such as adverse drug events, hospital admissions or death [15]. MRs involving collaboration between physicians, pharmacists and nurses have been used in NH settings in several

CONTACT Amura Francesca Fog a.f.fog@medisin.uio.no Department of General Practice, Institute of Health and Society, University of Oslo, Postbox 1130 Blinderen, N-0318 Oslo, Norway

countries [1,13,16–18] and such collaboration is recommended in the Norwegian national guideline [14].

The aims of this study were to describe the DRPs identified at multidisciplinary MRs and the interventions that were carried out to resolve them, as well as changes in drug use that followed the MRs. We explored some predictors for the observed changes.

Methods

Patients

Of the 51 NHs in Oslo with long-term care patients ($n = 4020$), 41 accepted to participate in a MR project involving one or more units in their institutions. The project took place between November 2011 and February 2014. Except for those terminally ill, all patients (next of kin for patients with dementia) at the participating units were asked to participate in the MR project ($n = 2625$ patients). Eighteen refused and 142 scheduled MRs were not performed because the patient either died ($n = 32$), became terminally ill ($n = 33$), moved to another institution ($n = 18$), or for some other logistical reasons ($n = 59$). Therefore, a total of 2465 patients (on average 60 patients/NH, range 19–136) had their medication use reviewed by a multidisciplinary team.

Medication reviews

The MRs were conducted as a structured evaluation of each patient's drug use by the NH physician and a registered nurse employed at the unit in collaboration with an externally hired clinical pharmacist. Training sessions were held for the involved physicians, nurses and pharmacists before project start.

From the patient's anonymized medication lists, the pharmacist identified potential DRPs using explicit criteria for pharmacological inappropriateness listed in the STOPP/START criteria [10] and the Norwegian general practice (NORGEP) criteria for assessing potentially inappropriate prescribing to older persons [11] together with the drug–drug interaction database DRUID [9]. At the MR meeting, the physician provided supplementary clinical information from the patient's medical record. The medication and the possible DRPs were discussed aiming at consensus on measures to improve the patient's medication use. In case of disagreement, the physician held the final decision. DRPs and interventions on the drug use were classified according to a consensus-based classification system [8] (see Box 1). Medication lists for about eight patients were reviewed at each meeting that lasted about two hours. The interventions accepted by the patient (next of kin for patients with dementia) were thereafter implemented.

Box 1. Classification of DRPs [8]:

1. Drug choice problem, with subcategories: 1(a) need for additional drug, 1(b) unnecessary drug, 1(c) inappropriate drug choice;
2. Dosing problem, with subcategories: 2(a) too high, 2(b) too low, 2(c) suboptimal dosing scheme, 2(d) suboptimal formulation;
3. Adverse drug reactions;
4. Interactions;
5. Inappropriate drug use, with subcategories 5(a) administered by health personnel, 5(b) administered by patient;
6. Other, with subcategories: 6(a) monitoring of drug use required, 6(b) unclear documentation, 6(c) not classified.

Classification of interventions to resolve DRPs:

1. Stop the drug
2. Drug switch
3. Start new drug
4. Adjust the drug dose
5. Monitor the drug use
6. Other measures

Data retrieval for the present study

The following variables were recorded in our data set: NH identification number, patient's age and gender, patient's drugs in use before and after the MR (drug name, regular or prn use), DRPs (category linked to the drug involved) and interventions implemented (category linked to the drug involved).

Drugs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system [19]. Drug items without ATC codes (e.g. nutritional supplements, multivitamins) were not included. A drug–drug interaction was recorded as only one DRP.

Statistics

Descriptive statistical analyses were performed using IBM SPSS Statistics v.24 (IBM Corp., Armonk, NY). We explored whether DRPs or the change in the number of drugs after the MR were associated with the patients' age or gender using a Poisson regression model with NH random effects (RE) in Stata SE 14 (Stata Corp LP, College Station, TX). The model was fitted to the individual data of each patient with MR ($n = 2465$), grouped at the level of the NHs ($n = 41$) and further adjusted for drug counts at baseline. Model estimates in terms of incidence rate ratios (IRR)

Table 1. Baseline characteristics of the long-term care patients participating in the medication review project.

Variables	All patients	Age <80 years	Age 80–89 years	Age ≥90 years
Patients with MR, *n* (%)	2465 (100)	463 (18.8)	1023 (41.5)	979 (39.7)
Gender, *n* (%)				
Female	1828 (74.2)	274 (59.2)	752 (73.5)	802 (81.9)
Male	630 (25.6)	188 (40.6)	267 (26.1)	175 (17.9)
Number of drugs, *n* (%)				
Regular drugs	16,634 (69.3)	3324 (68.3)	6960 (70.7)	6350 (68.3)
Prn drugs	7369 (30.7)	1540 (31.7)	2881 (29.3)	2948 (31.7)
Total drugs	24,003 (100)	4864 (100)	9841 (100)	9298 (100)
Mean drugs/patient(±SD)				
Regular drugs	6.8 ± 3.3	7.2 ± 3.6	6.8 ± 3.3	6.5 ± 3.1
Prn drugs	3.0 ± 2.1	3.3 ± 2.3	2.8 ± 2.0	3.0 ± 2.2
Total drugs	9.8 ± 4.4	10.5 ± 4.7	9.6 ± 4.3	9.5 ± 4.3

Missing gender data (7 patients).
The mean numbers of drugs by gender were similar: 6.8 for regular drugs and 3.0 for prn drugs.

Table 2. Categories of drug-related problems and the three drugs (therapeutic groups) most commonly involved in the problem listed.

Drug-related problems (*n* = 6158)		The three drugs most commonly involved in the drug-related problems listed					
Problem	*n* (%)	No. 1	*n* of drugs	No. 2	*n* of drugs	No. 3	*n* of drugs
Unnecessary drug	2680 (43.5)	Hypnotics/sedatives	296	Opioids[b]	249	Anxiolytics	213
Excess dosing	770 (12.5)	Paracetamol	108	Antacid drugs	103	Hypnotics/sedatives	92
Monitoring of drug use required	680 (11.0)	Antidepressants	103	Antidementia drugs	48	Renin–angiotensin system	46
Inappropriate drug choice	503 (8.2)	Opioids	80	Anxiolytics	56	Hypnotics/sedatives	43
Need for additional drug	453 (7.4)	Anti-anaemia drugs[a]	130	B-complex vitamins	62	Paracetamol	43
Adverse drug reaction	287 (4.7)	Hypnotics/sedatives	37	Anxiolytics	32	Antipsychotics	28
Drug–drug interactions	271 (4.4)	Antidepressants	124	Antithrombotic agents	66	Opioids	50
Under-dosing	169 (2.7)	Paracetamol	27	Opioids	26	Thyroid therapy	23
Suboptimal dosing/formulation	141 (2.4)	Beta-blockers	21	Paracetamol	18	Hypnotics/sedatives	6
Other	127 (2.0)	Anti-thrombotic agents[d]	17	Opioids	7	Anxiolytics	7
Inappropriate drug use	77 (1.2)	Paracetamol	12	COPD drugs[c]	9	Opioids	4

[a]iron supplements, B_{12} vitamin and folate.
[b]ATC-N02A comprising weak opioids (codeine, tramadol) and strong opioids.
[c]Chronic obstructive pulmonary disease drugs comprising adrenergic/anti-cholinergic drugs (systemic or inhalation use) and glucocorticoids (inhalation use).
[d]ATC-B01A (mainly warfarin, acetylsalicylic acid and heparin).

and their 95% confidence intervals for numbers of DRPs and drugs after MR were calculated for both genders and different age groups (≥90 years as reference group). The significance level was set at $\alpha = 0.05$.

Ethics

After reviewing the research study protocol, the Regional Committee in Medical Research Ethics in South-East Norway (reference no. 2015/786) and the Norwegian Centre for Research Data (reference no. 2015/43659) concluded that their approvals were not needed.

Results

The mean age of the 2465 patients was 85.9 years (range 36–108) and women were older than men (mean 86.9 and 82.8 years, respectively). Patients' baseline characteristics are presented in Table 1.

In total, the MR identified 6158 DRPs, an average of 2.6 DRPs/patient (range 0–14), 2.0 for regular and 0.6 for prn drugs. In total, 17.3% of the patients had no DRP at the MR. The 82.7% of the patients with DRPs had an average of 3.0 DRPs/patient, 2.3 for regular and 0.7 for prn drugs. Female gender (IRR with 95% CI: 1.11 [1.04–1.17]) was associated with an increased risk of DRPs, but not age.

The DRPs and the drugs most commonly related to them are listed in Table 2. Overall, 6409 drugs were involved in the DRPs (75.2% regular drugs and 24.8% prn drugs). Drugs used prn were most commonly involved in the DRP categories unnecessary drug use (43%), inappropriate drug choice (25%) and excess dosing (11%) and they most commonly consisted of opioids (20.7%), anxiolytics (15.6%) and hypnotics/sedatives (11.8%).

The 6158 DRPs led to 6283 interventions to change the drug therapy, including 125 drug–drug interactions that led to changes in the use of both drugs (Table 3). Of the 2662 discontinued drugs, 47.6% were drugs for prn use, most commonly opioids (20.6%), anxiolytics (14.5%) and hypnotics/sedatives (12.9%). Dosage adjustments and needs for closer monitoring the drug use involved almost exclusively drugs for regular use (96%). The proposed changes in drug therapy were implemented, except for 31 that were

Table 3. Interventions to resolve drug-related problems (DRPs) and the three drugs (therapeutic groups) most commonly involved in changes to the drug therapy regimens.

Interventions to resolve DRPs ($n = 6283$)		The three drugs most commonly involved in the interventions listed					
Intervention	*n* (%)	No. 1	*n* of drugs	No. 2	*n* of drugs	No. 3	*n* of drugs
Stop drug	2662 (42.4)	Opioids[a]	293	Hypnotics/sedatives	242	Anxiolytics	217
Monitor drug use	1455 (22.7)	Antidepressants	182	Antithrombotic agents[b]	112	Hypnotics/sedatives	84
Dose adjustment	1141 (17.8)	Hypnotics/sedatives	131	Paracetamol	128	Antacid drugs[c]	112
Drug switch	438 (6.8)	Opioids	68	Hypnotics/sedatives	41	Diuretics	32
Start new drug	436 (6.8)	Anti-anaemia drugs[d]	124	B-complex vitamins	62	Paracetamol	41
Other	151 (2.4)	Paracetamol	17	Beta-blockers	13	Hypnotics/sedatives	8

[a]ATC-N02A comprising weak opioids (codeine, tramadol) and strong opioids.
[b]ATC-B01A (mainly warfarin, acetylsalicylic acid and heparin).
[c]Mainly proton pump inhibitors.
[d]Iron supplements, B_{12} vitamin and folate.

declined by the patient (next of kin for patients with dementia).

After the MR, the total number of drugs used by all patients went down by 9.3% (from 24,003 to 21,777 drugs; $p < .01$). The mean number of drugs per patient went down from 9.8 to 8.9 ($p < .001$) and the decrease was significant ($p < .001$) for both regular (from 6.8 to 6.3) and prn drugs (from 3.0 to 2.6). For the 82.7% of the patients who had any DRPs, the average decrease in the number of drugs was 1.1 (0.5 for regular and 0.6 for prn drugs). No associations were found between the change in the number of drugs (regular or prn) and the patients' age or gender. The changes in the drug use following the MRs are presented for regular and prn drugs in Tables 4 and 5, respectively. Individual drugs for regular use, which were most commonly discontinued after the MR, were zopiclone (from 23.4% to 20.4%, $p < .01$) and furosemide (from 14.7% to 11.8%, $p < .001$). The prn drugs most often discontinued were oxazepam (from 37.5% to 32.8%, $p < .001$), zopiclone (from 15.6% to 12.9%, $p < .01$), metoclopramide (from 12.5% to 9%, $p < .001$), and clomethiazole (from 7.1% to 4.8%, $p < .001$).

Discussion

To our knowledge, this is the first study to report the effect of multidisciplinary MRs at NHs in terms of DRPs and drug use changes related to both regular and prn drugs.

We found on average 2.6 DRPs/patient (3.0 for patients with DRPs) and that regular drugs contributed to 77% of all DRPs. Psychotropic drugs and opioids were most commonly involved in all types of DRPs and the subsequent interventions. The use of all therapeutic drug groups went down after MR, except for thyroid therapy. In the 82.7% of the patients with DRPs, the number of drugs was reduced with on average 1.1 drugs; most discontinued medications comprised opioids and psychotropic drugs, which should be used with caution in frail elderly.

Our study has some limitations that warrant consideration. We have analysed data from a pragmatic project without random patient selection or a control group for comparison. However, we consider the validity of the results to be reasonable high because 82% of all NHs included 61% of all long-term care patients in the municipality, and because terminal illness was the only exclusion criterion. Furthermore, the patients' age and sex distribution correspond well with that of the total NH population in the city and country [4,12,13,20–22]. Similar MR procedures at the various sites were ensured through training of the MR teams, standardized tools and classification systems [8–11] and because each pharmacist participated in several hundred MRs. The use of the NORGEP criteria [11] may be questioned because they were not developed in particular for nursing home settings and because more recent criteria tailored for the nursing home setting, the NORGEP-NH criteria [23] are now available. However, the NORGEP-NH criteria had not been published when this study started and it was the STOPP-START and NORGEP criteria that were included in in the national guideline for MRs in nursing homes [14].

Although direct comparison with other studies is challenged by differences in MR procedures or drugs targeted, the distribution of the DRPs is comparable to other studies [1,13,16], with problems most frequently associated with unnecessary drug use, excess dosing or inadequate monitoring/follow-up of the drug therapy. The lower prevalence of DRPs as compared to other Norwegian studies reporting 2.5–3.5 DRPs/patient [1,12,13], might be related to more staffing with full-time rather than part-time physicians in Oslo and an increased focus in recent years on safer prescribing practice for the elderly. The average number of drug used per patient before the MR compares well or is slightly lower than in other studies reporting 6.1–9.8 regular [1,4,5,13,16,20,24,25] and 2.8–3.8 prn

Table 4. The proportion of patients using regular drugs before and after the medication review and reductions in drug use after the medication review.

	All patients, $n = 2465$ % of patients using the drug		
Therapeutic group	Before MR	After MR	**Reduction (95% CI)[a]**
Laxatives	82.0	81.6	0.4
Antithrombotic agents	46.2	43.5	2.7 (−1.0–5.5)
Paracetamol	44.5	43.7	0.8
Antidepressants	37.2	33.3	3.9 (1.2–6.6)
Opioids	34.3	33.1	1.2
Hypnotics/sedatives	32.6	28.9	3.7 (1.1–6.3)
Diuretics	32.0	27.3	4.7 (2.2–7.2)
Anti-anaemia drugs	27.1	26.2	0.9
Beta-blockers	24.9	23.9	1.0
Anxiolytics	21.4	20.2	1.2
Antacid drugs	21.0	18.9	2.1 (−0.1–4.3)
Osteoporosis drugs	20.3	19.5	0.8
Thyroid therapy	20.2	20.2	–
COPD drugs	18.8	17.4	1.4
Antipsychotics	18.3	16.5	1.8 (−0.3–3.9)
Drugs for glaucoma	15.6	15.4	0.2
Antiepileptic drugs	12.4	12.4	–
Drugs used in diabetes	11.9	11.4	0.5
Digitalis and nitrates	11.9	10.8	1.1
Antidementia drugs	11.6	10.5	1.1
Antibiotics	9.8	9.1	0.7
Calcium blockers	8.6	7.5	1.1
Antihistamines	6.4	5.0	1.4
Lipid modifying agents	6.0	5.1	0.9
Oral corticosteroids	6.2	6.0	0.2
Anti-Parkinson drugs	5.4	5.2	0.2
Others	86.5	77.7	8.8 (6.4–11.2)
Total *n* of drugs	16,634	15,563	6.4 (2.2–4.4)

[a]The 95% confidence interval is shown only if significant.

Table 5. The proportion of patients using pro re nata drugs before and after the medication review and reductions in drug use after the medication review.

	All patients, $n = 2465$ % of patients using the drug		
Therapeutic group	Before MR	After MR	**Reduction (95% CI)[a]**
Paracetamol	49.0	48.0	1.0
Anxiolytics	48.1	41.0	7.1 (4.3–9.9)
Opioids	38.9	27.7	11.2 (8.6–13.8)
Laxatives	29.1	26.3	2.8 (0.3–5.3)
Hypnotics/sedatives	24.9	19.1	5.8 (3.5–8.1)
Expectorants	12.9	10.2	2.7 (0.9–4.5)
Nitrates	12.7	11.8	0.9
Metoclopramide	12.5	9.0	3.5 (1.8–5.2)
NSAIDs	6.8	3.9	2.9 (1.6–4.2)
Diuretics	5.7	5.1	0.6
Drugs used in diabetes	5.2	5.0	0.2
Antipsychotics	4.9	3.4	1.5 (0.4–2.6)
Others	48.0	42.2	5.8 (1.7–9.9)
Total *n* of drugs	7369	6214	15.3 (6.6–10.0)

[a]The 95% confidence interval is shown only if significant.

drugs [4,20]. The high drug utilization at NHs may also partly reflect that the drug regiments are based on guidelines developed for younger patients with less comorbidity and the lack of consensus on best practice for pharmacotherapy in the oldest old.

The higher use of opioids in our population as compared with findings in a previous Norwegian study [22] may be related to less use of NSAIDs and increased use for chronic pain. In NH patients with dementia, chronic pain is commonly communicated in terms of neuropsychiatric symptoms [2] and treatment of pain can reduce both agitation and other neuropsychiatric symptoms [26]. This may therefore also explain the more use of analgesics in our study.

Compared to other studies, we found a slightly higher use of hypnotics/sedatives [20,21], but less use of antidepressants [13,20,21] and antipsychotics [20,21] and a comparable use of anxiolytics [20,21]. Although reduced, their utilization was still high after the MR, possibly reflecting the patients' need for continued treatment or reluctance among physicians and nursing staff to discontinue the drugs [27]. Studies of withdrawing long-term use of antipsychotics [28] or anti-depressants [29] in Norwegian NHs have shown that in most cases, discontinuation does not result in more NPS or relapse of depression. We do not know of any studies on discontinuing anxiolytics in NH residents. However, based on their questionable therapeutic long-term effects on anxiety symptoms [30], we consider that these drugs probably are still overused in frail NH patients who are at particular risk of falls and fractures [6].

Based on the results of this study, we support that MRs should be part of the regular clinical follow up of NH residents [14].

Conclusions

The MR resulted in overall less drug use, most pronounced for psychotropic drugs and opioids, and in a closer follow-up to optimise the potential benefits of the drug use. Future research on MRs should include patient-related clinical outcomes.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Notes on contributors

Amura Francesca Fog, is a nursing home physician at the Nursing Home Agency in Oslo municipality and a phd candidate at the Department of General Practice, Institute of Health and Society, University of Oslo. She has contributed to conception and design of the work, the interpretation of the results and wrote the manuscript.

Gunnar Kvalvaag, formerly chief medical officer at the Nursing Home Agency in Oslo municipality, has contributed to conception of the work and also assisted in the interpretation of the results and revision of the manuscript.

Knut Engedal, professor at the Norwegian National Advisory Unit for Aging and Health, Vestfold County Hospital HF in Toensberg and Oslo University Hospital, has contributed to design of the work and also assisted in the interpretation of the results and revision of the manuscript.

Jørund Straand, is professor at the Department of General Practice, Institute of Health and Society, University of Oslo. He has contributed to conception and design of the work, the interpretation of the results and revision of the manuscript.

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RESEARCH ARTICLE Open Access

Variation between nursing homes in drug use and in drug-related problems

Amura Francesca Fog[1,2*], Ibrahimu Mdala[2], Knut Engedal[3] and Jørund Straand[2]

Abstract

Background: Residents at nursing homes (NHs) are at particular risk for drug related harm. Regular medication reviews using explicit criteria for pharmacological inappropriateness and classification of drug related problems (DRPs) have recently been introduced as measures to improve the quality of medication use and for making the treatment more uniform across different institutions. Knowledge about variation in DRPs between NHs is scarce. To explore if increased attention towards more appropriate drug treatment in NHs have led to more uniform treatment, we have analyzed variations between different nursing homes' drug use and DRPs.

Methods: Cross-sectional medication review study including 2465 long-term care residents at 41 NHs in Oslo, Norway. Regular drug use was retrieved from the patients' medical records. DRPs were identified by using STOPP/START and NORGEP criteria and a drug-drug interactions database. NHs were grouped in quartiles based on average levels of drug use. The upper and lower quartiles were compared using independent samples t-test and associations between drug use and DRPs were tested by logistic regression.

Results: Patients' mean age was 85.9 years, 74.2% were women.
Mean numbers of regular drugs per patient was 6.8 and varied between NHs from 4.8 to 9.3.
The proportion of patients within each NH using psychotropic and analgesic drugs varied largely: antipsychotics from three to 50%, benzodiazepines from 24 to 99%, antidepressants from nine to 75%, anti-dementia drugs from no use to 42%, opioids from no use to 65% and paracetamol from 16 to 74%.
Mean DRPs per patient was 2.0 and varied between NHs from 0.5 to 3.4.
The quartiles of NHs with highest and lowest mean drugs per patient (7.7 vs. 5.7, $p < 0.001$) had comparable mean number of DRPs per patient (2.2 vs. 1.8, $p = 0.2$). Using more drugs and the use of opioids, antipsychotics, benzodiazepines and antidepressants were associated with more DRPs.

Conclusions: The use of psychotropic and analgesic drugs was high and varied substantially between different NHs. Even if the use of more drugs, opioids and psychotropic drugs was associated with DRPs, no difference was found in DRPs between the NHs with highest vs. lowest drug use.

Keywords: Older people, Nursing homes, Medication review, Psychotropic drugs, Opioids, Drug related problems

* Correspondence: a.f.fog@medisin.uio.no
[1]Nursing Home Agency, Oslo Municipality, Norway
[2]General Practice Research Unit, Department of General Practice, Institute of Health and Society, University of Oslo, Postbox 1130 Blinderen, N-0318 Oslo, Norway
Full list of author information is available at the end of the article

Background

Residents in nursing homes (NHs) are often old and due to multimorbidity and frailty have short life expectancies and extensive needs for assistance for carrying out activities of daily living. Dementia and BPSD (Behavioural and Psychological Symptoms in Dementia) represent the most significant mental health challenges in the NH setting affecting respectively 80 and 72% of the residents [1]. Due to multiple diagnoses and symptoms, NH residents often use many drugs and in Norway during the last decades, the use of regular drugs has increased from about five to eight drugs per NH resident [2, 3]. The use of psychotropic drugs [4] and opioids [5] has increased, except for the prevalent use of antipsychotics that now seem to decline [6]. About one in five residents, uses more than one psychotropic drug at the same time [6], in most cases as long-term treatment for BPSD [7].

Due to age-related changes in pharmacokinetics and pharmacodynamics, frail and old people are at higher risk for drug related harms [8] and the presence of dementia ads further to this risk due to impaired ability to communicate drug effects. The widespread use of antipsychotic drugs, benzodiazepines and antidepressants for BPSD is largely inappropriate, because they are commonly used instead of recommended non-pharmacological interventions [9, 10], they have limited effects and their use is associated with an increased risk for adverse drug reactions like delirium, impaired balance and falls and stroke [11]. Substantial variations in drug use have previously been reported among residents in otherwise similar NHs with comparable patient populations [12–15], even if located in the same geographical area [13], and that institutions with high prevalence of drug use tend to use higher dosages [14], probably due to different prescription cultures and organizational factors at the institutions.

Potentially inappropriate medications (PIM), as defined by explicit criteria [16] are common in NHs [17]. In Norway, medication reviews (MRs) are now recommended for the identification of drug related problems (DRPs) among NH residents [18]. The Norwegian national guidelines on dementia also recommend that in NHs, MRs should be done at least once every year [9]. DRP, defined as "an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcome" [19], are identified by using explicit criteria for pharmacological inappropriateness and drug-drug interaction databases.

According to previous studies, DRPs are common in the NH-setting [2, 3, 13]. However, little is known about the variation in DRPs between comparable NHs and how this variation relates to corresponding variations in drug use [20].

Based on a cross sectional study in 41 NHs with 2465 residents [21], we aim to describe the variation between the NHs with respect to their drug use (in particular for psychotropic drugs and analgesics) and corresponding variation in DRPs, and to explore the associations between the two.

Methods

This is a clustered (by NH) cross-sectional study of the baseline data from a multidisciplinary MR project in 41 NHs (2465 long-term care patients) in Oslo, Norway, that took place during November 2011 and February 2014 [21].

The NHs were recruited by invitation. Of the 51 NHs in Oslo municipality with long-term patients ($n = 4020$), 41 NHs accepted to performed MRs at one, several or all the bed units in their institutions. All patients, and next of kin for patients with dementia at the participating bed units, were asked to participate in the study ($n = 2625$ patients) with the exception of those terminally ill. Eighteen patients refused and 142 scheduled MRs were not performed because the patient died ($n = 32$), became terminally ill ($n = 33$), moved to another NH ($n = 18$) or due to logistical reasons ($n = 59$) during the study period. In average 60 patients per NH (range 19–136 patients per NH) underwent MR. The MRs were conducted as a structured evaluation of each patient's entire drug use and the assessment of DRPs was standardized across the NHs. Training sessions were held for the involved physicians, nurses and pharmacists ($n = 5$) before project start.

At each NH, a multidisciplinary panel made up by the responsible physician and nurse from the NH together with an externally hired clinical pharmacist, performed MRs according to a standardized procedure in line with the national guideline for MRs [18]. Medication lists for about eight patients were reviewed at each meeting that lasted about 2 h. Prior to the MR meetings, and based on anonymized medication list, the pharmacist collected data on the drugs used and reviewed the medication charts to identify possible DRPs by using the explicit criteria for pharmacological inappropriateness STOPP/START [22] and the Norwegian NORGEP criteria targeting population 70 years and older seen in primary care [23], as well as the national drug-drug interaction database [24]. At the review meetings, the panel assessed the drug use and possible DRPs taken into consideration clinical information (e.g., diagnoses, lab-tests) from the patient's medical record. The panel then agreed upon and classified the DRPs according to a national consensus classification system [25]. Six DRP categories were applied: 1) Drug choice problem (with subcategories 1a) need for additional drug, 1b) unnecessary drug, 1c) inappropriate drug choice); 2) Dosing problem (with subcategories 2a) too high, 2b) too low, 2c) sub-optimal dosing scheme, 2d) sub-optimal formulation); 3) Adverse

drug reactions; 4) Interactions; 5) Inappropriate drug use (with subcategories 5a) administered by health personnel, 5b) administered by patient) and 6) Other (with subcategories 6a) monitoring required, 6b) unclear documentation, 6c) not classified). In case of disagreement, the physician held the final decision.

For each patient we retrieved the following variables from the baseline-data of the MR project: patient's age, gender, regularly used drugs (name, ATC-code [26], DRPs (category and drug involved), NH identification number, residency at regular (RU) or special care unit for dementia (SCU), and the pharmacist involved in the MR. We especially focussed on the use of psychotropic and analgesic drugs because their use, although largely considered potentially inappropriate [9, 10], has increased in NHs [4, 5] and because they are frequently involved in DRPs [3, 13, 14, 20, 21]. Psychotropic drugs comprise antipsychotics (ATC code: N05A), benzodiazepines (anxiolytics N05B and hypnotics/sedative N05C), antidepressants (N06A), and antidementia drugs (N06D). Analgesics comprise opioids (N02A) and paracetamol (N02B). For each NH we recorded the total number of beds for long-term care and the bed unit mix (RU, SCU or both). All NHs were publicly funded and had comparable staffing of physicians and qualified nurses in line with the county standard; all NHs were non-academic and did not have in-house pharmacists.

Statistical analyses

Depending on data distribution, numerical data were summarized using mean with standard deviation (SD) or median and range.

For each NH, we calculated the mean number of regular drugs per patient, the mean number of DRPs per patient, the proportion of patients using the targeted psychotropic and analgesic drugs and the proportion of patients exposed to any DRPs. We grouped the NHs into four quartiles, based on their mean number of drugs per patient, the upper quartile comprising those with highest numbers. When a NH was allocated in a particular quartile, data from all residents in that institution were allocated to the quartile. The NHs with highest levels (comprising the upper quartile) were compared to the NHs in the lowest quartile, and mean differences with 95% confidence intervals (CI) were calculated using independent t-test. Relationships between the drug use and the DRPs at the respective NHs were identified using Pearson's correlation coefficient (r). Counts of DRPs per patient were analyzed using a Poisson regression model with random effects clustered by NH and adjusted for gender and age. We obtained estimates of incidence rate ratios (IRR) from the Poisson regression model, which showed the relative change in counts in one category of a variable relative to the referent category. The analyses were performed using Stata SE 15 (Stata Corp LP, College Station, TX) and IBM SPSS Statistics v.24 (IBM Corp., Armonk, NY).

Results

The 41 NHs had in average 102 beds (range 32 to 185). Seven NHs had only RUs, three NHs had only SCUs and 31 NHs had both types of bed units.

Of the 2465 patients with MR, 1868 were residents living in RUs and 597 at SCUs. The mean age of the residents was 85.9 years (range 36–108 years). The age distribution was comparable across the NHs, except for two institutions especially designed for younger people with dementia (61.3 and 68.4 years, respectively). There were more women (74.2%), who on average were older than men (86.9 vs. 82.8 years). The gender distribution was comparable across the NHs. In total 16,634 drugs were used on a regular schedule, the mean proportion of drugs per patient was 6.8 ± 0.9 and the mean number of drugs per patient varied between the NHs from 4.8 to 9.3. Overall, the most commonly used drugs were for the 'nervous system' (2.2 drugs per patient, range of 1.4–3.1) and of these, 2.0 drugs per patient (range 1.3–2.7) were psychotropic and analgesic drugs. At the MR meetings, 4847 DRPs in 84.1% of the patients were identified. Psychotropic drugs and analgesics were involved in 33.9% of all DRPs (Table 1). The most frequent problems were use of unnecessary drug (31.9%), excess dosing (14.2%) and requirement to monitor the drug use (14.2%).

The mean number of drugs per patient and the mean number of DRPs per patient at each of the 41 NHs are presented in Fig. 1. (Fig. 1).

The proportion of patients within each NH using different psychotropic drugs varied substantially between the NHs: antipsychotics from 3.0 to 50.0%, benzodiazepines from 23.7 to 98.6%, antidepressants from 9.1 to 75.0%, and antidementia drugs from none to 41.7%. For opioids and paracetamol, the variation in use ranged from respectively no use to 65.2% and from 15.8 to 73.9%. (Table 2) NHs using more drugs also used more opioids (Pearson correlation coefficient $r = 0.682$) and benzodiazepines ($r = 0.411$). Regardless of the total drug use, associations were found between the use of antidepressants and antidementia drugs ($r = 0.451$), opioids and benzodiazepines ($r = 0.434$), opioids and paracetamol ($r = 0.358$), opioids and antidementia drugs ($r = -0.315$) and between antidementia drugs and antipsychotics ($r = 0.432$).

Between the NHs, the mean DRPs per patient varied substantially, from 0.5 to 3.5. The use of unnecessary drugs was associated with excessive dosing (Pearson correlation coefficient $r = 0.801$), inappropriate drug choice

Table 1 The drug groups commonly involved in drug-related problems in the total cohort (2465 patients at 41 nursing homes)

Drug-related problems (DRPs)		Drugs		The drug groups commonly involved in the drug-related problems listed			
Categories of DRPs	*n* (%)	ATC-N drugs[a] *n* (%)	All other drugs *n* (%)	No. 1	*n* of drugs	No. 2	*n* of drugs
Need for additional drug (1a)	372 (7.7)	50 (13.4)	322 (86.6)	B vitamins[b]	155	Iron supplements	39
Unnecessary drug (1b)	1544 (31.9)	474 (30.7)	1070 (69.3)	Benzodiazepines[c]	185	Antidepressants	121
Inappropriate drug choice (1c)	382 (7.9)	131 (34.3)	251 (65.7)	Benzodiazepines	60	Opioids[d]	31
Excess dosing (2a)	688 (14.2)	291 (42.3)	397 (57.7)	Benzodiazepines	110	Proton pump inhibitors	103
Under-dosing (2b)	160 (3.3)	71 (44.4)	89 (55.6)	Opioids	23	Thyroid therapy	23
Adverse drug reaction (3)	276 (5.7)	134 (48.6)	142 (51.4)	Benzodiazepines	63	Antipsychotics	28
Drug–drug interactions[e] (4)	419 (8.6)	207 (49.4)	212 (50.6)	Antidepressants	115	Antithrombotic agents[f]	55
Monitoring of drug use required (6a)	687 (14.2)	329 (47.9)	358 (52.1)	Antidepressants	105	Antipsychotics	50
Other[g]	364 (6.5)	88 (24.2)	276 (75.8)	Beta-blockers	33	Paracetamol	25
DRPs (total)	4847 (100)	1775 (36.6%)	3072 (63.4%)	Benzodiazepines	489	Antidepressants	456

[a]Psychotropic drugs and analgesics *n* = 1642 (92.5% of all ATC-N drugs)
[b]B12 vitamin, folate and B-complex vitamins
[c]Benzodiazepines comprising anxiolytics (N05B) and hypnotics/sedatives (N05C)
[d]Weak opioids (codeine, tramadol) and strong opioids (N02A)
[e]One drug–drug interaction was recorded as two problems
[f]Mainly warfarin, acetylsalicylic acid and heparin (ATC-B01A)
[g]The remaining DRP categories

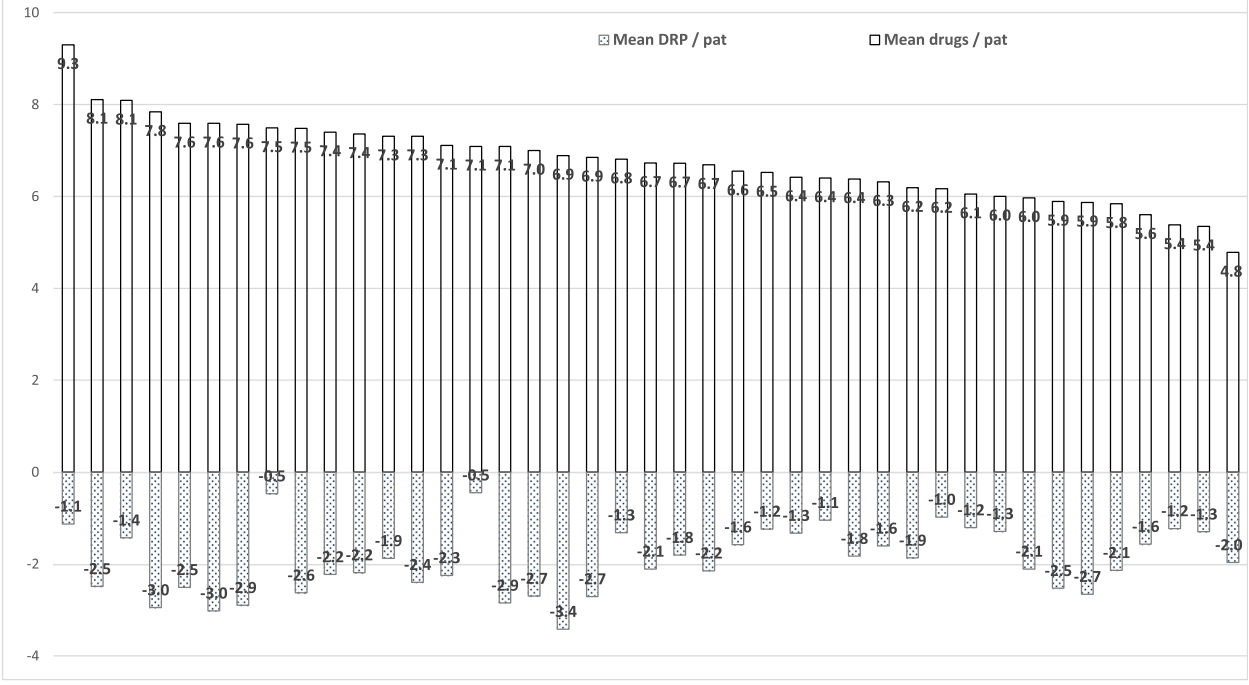

Fig. 1 Variation in the number of drugs and of drug-related problems per patient at the 41 nursing homes . Each bar represents one NH with their respective mean drugs per patient (above) and mean DRPs per patient (below the zero line, respectively). The NHs are listed in the same order as in Table 2

Table 2 Variation in the proportion of patients using psychotropic and analgesic drugs at the 41 nursing homes

Nursing Home	Patients *n*	Antipsychotics %	Benzodiazepines %	Antidepressants %	Antidementia %	Opioids %	Paracetamol %
1	30	23	67	47	7	53	37
2	57	39	98	42	11	51	32
3	23	9	65	57	0	65	74
4	19	37	37	16	5	26	16
5	61	13	39	38	8	30	38
6	49	12	33	53	18	35	73
7	92	21	63	29	13	46	45
8	88	14	78	45	9	61	45
9	88	13	48	30	10	31	51
10	60	30	67	35	15	38	40
11	64	13	64	36	6	50	73
12	72	19	49	50	22	33	49
13	85	18	56	51	7	49	55
14	73	21	63	27	7	51	27
15	94	10	83	28	3	48	66
16	34	12	59	26	9	26	44
17	80	43	84	34	15	31	46
18	136	21	52	39	18	32	44
19	55	4	51	9	0	36	35
20	68	15	59	47	10	26	44
21	66	14	41	29	21	27	41
22	72	18	42	42	14	47	44
23	59	3	53	42	14	39	47
24	38	11	61	32	5	32	45
25	42	31	36	50	12	26	33
26	48	23	29	71	42	19	46
27	78	17	77	36	12	28	44
28	63	13	41	24	10	29	62
29	41	17	46	59	12	27	54
30	52	33	40	50	0	15	54
31	65	11	26	25	14	29	40
32	38	21	24	45	11	37	26
33	24	50	71	75	33	0	21
34	38	21	24	26	3	21	32
35	19	5	53	37	11	21	42
36	53	42	72	28	36	23	34
37	73	12	55	25	8	36	32
38	81	10	42	25	7	23	43
39	61	21	43	28	8	30	34
40	63	16	38	41	2	16	32
41	63	11	37	24	2	14	44

($r = 0.490$) and need for additional drug ($r = 0.399$) at the respective NHs.

The NHs with highest levels of mean drugs per patient (10 NHs, comprising the upper quartile) used more opioid drugs than the NHs with lowest levels of mean drugs/patient (10 NHs, comprising the lower quartile), whereas there were no significant differences in the prevalence of DRPs, except for drug-to-drug interactions. (Table 3).

In the total cohort clustered by NH, using more drugs or being a woman were associated with a 7% [IRR 95% CI: 1.07 (1.06, 1.08), $p < 0.001$] and a 9% [IRR: 1.09 (1.0, 1.2), $p = 0.007$] increase in DRPs, respectively. The use of opioids [IRR: 1.07 (1.0, 1.1) $p = 0.01$], antipsychotics [IRR: 1.20 (1.1, 1.3) $p < 0.001$], benzodiazepines [IRR: 1.08 (1.0, 1.1) $p = 0.007$] and antidepressants [IRR: 1.18 (1.1, 1.2) $p < 0.001$] were associated with an increased risk for DRPs at the respective NHs. Residing at SCU was associated with less DRPs [IRR: 0.85 (0.8, 0.9) $p < 0.001$], whereas age, size of NH or the participating pharmacist (out of in total five) involved in the MRs were not associated with the frequency of DRPs at the NHs.

Discussion

We found considerable variation in the drug use among the NHs, in terms of number of drugs used on regular basis. This was in particular pronounced for the use of analgesics and psychotropic drugs where the variation was extremely large. We believe that this variation reflect local therapeutic subcultures involving inappropriate drug use. Our findings here represent an important challenge for future quality improvement measures, especially because the psychotropic drugs include risk for many and serious side effects in frail old people with dementia [11]. However, our results are generally consistent with those reported elsewhere for long-term care

Table 3 Variation between the 41 nursing homes in drug use and drug-related problems and the differences between the quartile of nursing homes using highest and lowest number of drugs

Variables	All NHs (***n*** = 41) Mean (range)	Differences between the NHs using highest (***n*** = 10) and lowest (***n*** = 10) number of drugs			
		Mean Q_4	Mean Q_1	Diff (95%CI)[a]	*P*-value
Drug use					
Drugs/patient	6.8 (4.8–9.3)	7.7	5.7	2.0 (1.6, 2.6)	< 0.001
Proportion of patients using:					
≥ 9 drugs	34.2 (15.9–52.2)	44.2	22.0	22.2 (18.5, 25.9)	< 0.001
Opioids	33.1 (0.0–65.2)	42.1	22.0	20.1 (8.7, 31.4)	0.002
Paracetamol	43.5 (15.8–73.9)	44.7	34.0	10.6 (−1.5, 22.7)	0.08
Antipsychotics	19.1 (3.0–50.0)	20.3	20.9	- 0.6 (−12.3, 11.0)	0.9
Benzodiazepines	52.8 (23.7–98.6)	57.8	45.7	12.1 (−4.9, 29.1)	0.2
Antidepressants	37.8 (9.1–75.0)	38.2	35.3	2.8 (−10.2, 15.9)	0.6
Antidementia drugs	11.4 (0.0–41.7)	10.7	12.0	- 1.3 (−10.6, 8.1)	0.8
Drug-related problems (DRPs)					
Proportion of patients with DRPs	84.1 (31.8–100.0)	85.2	86.2	- 1.0 (−14.9, 12.8)	1.0
DRPs/patient	2.0 (0.5–3.4)	2.2	1.8	0.4 (−0.3, 1.0)	0.2
Categories of DRPs:					
- Unnecessary drug	0.6 (0.1–1.3)	0.6	0.6	0.0 (−0.2, 0.3)	1.0
- Excessive dosage	0.3 (0.1–0.6)	0.3	0.3	0.0 (−0.1, 0.2)	0.2
- Monitor use required	0.3 (0.0–0.7)	0.3	0.3	0.0 (−0.1, 0.2)	0.9
- Need for new drug	0.2 (0.0–0.4)	0.2	0.1	0.1 (−0.01, 0.1)	0.1
- Drug-drug interaction	0.2 (0.0–0.5)	0.2	0.1	0.1 (0.01, 0.2)	0.03
- Adverse drug reaction	0.1 (0.0–0.4)	0.2	0.1	0.1 (− 0.04, 0.2)	0.2
- Inappropriate drug	0.1 (0.1–0.5)	0.1	0.2	- 0.1 (−0.1, 0.1)	0.9
Demographics					
Mean age, years	85.9 (61.3–90.0)	84.6	84.5	0.1 (−6.4, 6.7)	1.0
Proportion of males	25.8 (13.6–47.4)	27.5	24.5	3.0 (−6.0, 12.0)	0.5

[a]The mean of the lower quartile (Q_4) was compared to the mean of the lower quartile (Q_1) using the Independent samples T test, with difference in means with 95% CI and *p*-value

home residents in Norway [12, 14], Europe [27], US [15, 28] and Canada [29].

Further, the study documented that the rates of DRPs varied up to seven-fold (from 0.5 to 3.4) between the NHs. To the best of our knowledge, only two medication review studies have previously reported variation in DPRs between NHs: one in two urban NHs, from 3.0 to 5.5 mean DRPs per patient [20] and another study in four rural NHs, from 2.7 to 5.6 mean DRPs per patient [30]. The mean of 2.0 DRPs per patient found in the total cohort is below those previously reported in Norway [2, 3, 13], probably because we reported DRPs agreed upon by the team, not all DRPs suggested by the pharmacist.

The associations between the uses of opioids, antipsychotics, benzodiazepines or antidepressants and increased risk of DRPs are consistent with the fact that so many of these drugs are commonly considered potentially inappropriate and should therefore be avoided whenever possible in frail olds. In our study, psychotropic and analgesic drugs were involved in just one third of the total DRPs, and it would be expected that by including also drugs for pro re nata use ("as needed"), this would probably have increased even more the contribution of psychotropic and analgesic drugs to the numbers of DRPs [21]. The correlation between the use of many drugs and more opioids and benzodiazepines at the respective NHs might reflect local prescription cultures [28], or simply a way to relieve staff pressure [31], as prescription of psychotropic drugs and painkillers in combination is not recommended to treat neither pain nor BPSD [9, 32].

We found no difference in the levels of DRPs between the NHs with highest and lowest drug use, although using more drugs was associated with DRPs. This unexpected finding might be due to our analytic strategy by grouping the NHs into quartiles, in addition to a large variation in the levels of DRPs within each group (e.g., three high-drug use NHs with low levels of DRPs and four low-drug use NHs with high levels of DRPs). The strong correlations found between need for additional drug, use of unnecessary drug, excessive dosing and inappropriate drug choice, suggest that prescription quality is multifaceted and hence, in case it is suboptimal, e.g. due to a high rate of DRPs, this will affect several areas of drug prescription practice.

The large difference in DRP levels found between otherwise comparable NHs most probably reflect different institutional prescription cultures, with higher prescription rates at NH-level irrespective of the patient's clinical indications [29] or different organizational initiatives for patient safety at the NH [33]. To improve the quality of drug use in the NH setting, staff should be educated in geriatric pharmacotherapy and on alternative non-pharmacological interventions [9, 10]. Other measures should include implementing educational programs on person-centred care [34] and multidisciplinary medication reviews [18], which may also include collaboration with a geriatrician [35].

Strengths and limitations

The strength of this close to practice study was the standardized procedure for MRs, with face-to-face meetings between pharmacist, physician and nurse, having access to patients' clinical information, and agreeing on actual DRPs for each patient.

It is an important limitation that we have only recorded the DRPs that were accepted by the physicians, without recording all the DRPs that were initially suggested by the pharmacists. Hence, we do not know how the physicians' acceptance rates varied between the different NHs and how appropriate their rejections were [30]. Some doctors may have experienced suggestions to change their treatment as a threat and criticism towards their own prescribing practice.

The explicit criteria used in this study were updated [16] and tailored for the NH-setting [36] after the study had started, however, we do not believe that using the updated criteria would have changed our results significantly. Instead, it may be questioned if the explicit criteria used were sensitive enough to detect over- and underprescription, or inappropriate medication among multimorbid, frail NH residents commonly exposed to extensive off-label pharmacological treatment for BPSD. Although DRPs, as identified in our study, might have limitations as quality indicators for drug prescription, the NHs with high levels of DRPs probably have proportionally larger potentials for quality improvement.

We believe that the sample of institutions and residents is representative for the long-term care NH-setting because the vast majority of the NHs in the municipality participated in the study. This is a cross-sectional study, and thus we are not able to draw conclusions about causal relationships for the variation. The NHs in Oslo are quite similar: They are publicly financed and administered by the same agency, are non-academic institutions operating in the same regulatory and clinical practice context. They are staffed with full-time nursing home physicians and registered nurses according to the country standard. None of them had an in-house pharmacist. The patient-mix is quite similar due to equal admission criteria. Grouping the NHs in quartiles might be challenged due to the somewhat limited number of NHs.

Conclusions

Drug use and DRPs varied substantially between comparable NHs. The use of psychotropic and analgesic

drugs was high and the unacceptable variation between NHs suggests different and inappropriate drug prescription cultures at several institutions. The use of unnecessary drugs and excessive dosing were common, suggesting overtreatment. There was no difference in DRPs between the group of NHs with highest and lowest drug use, although using more drugs, opioids and psychotropic drugs was associated with an increased risk for DRPs at the respective NHs. Future research on variation between NHs in drug use and DRPs should include variables that describe patient-level factors, such as degree of functional and cognitive impairment of the residents and organizational characteristics, such as leadership, staff number per resident, proportion of registered nurses and postgraduate training of the NH physicians in geriatric pharmacotherapy.

Abbreviations

ATC: Anatomical Therapeutic Chemical classification system;
BPSD: Behavioural and psychiatric symptoms of dementia; DRP: Drug-related problems; IRR: Incidence rate ratios with 95% confidence interval;
MR: Medication review; NH: Nursing home; r: Pearson's correlation coefficient;
RU: Regular unit; SCU: Special care unit for dementia

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Authors' contributions

AFF, JS, KE and IM were involved in the study design and contributed to writing the manuscript. AFF retrieved the data and IM together with AFF analysed the data. AFF drafted the manuscript. All authors read and approved the final draft of the manuscript.

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Availability of data and materials

All data generated or analysed during this study are included in this published article. The datasets used and/or analysed during the current study are available form the corresponding author on reasonable request.

Ethics approval and consent to participate

According to the Norwegian act on medical and health research, no formal ethical approval was needed for the present study. Formal consent was not required because data is anonymous. The study protocol of the medication review project at the nursing homes, which generated the data used here, was presented to the Regional Committee in Medical Research Ethics in South-East Norway (reference no. 2015/786) and the Norwegian Centre for Research Data (reference no. 43659). Both bodies concluded that their formal approval was not needed.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Nursing Home Agency, Oslo Municipality, Norway. [2]General Practice Research Unit, Department of General Practice, Institute of Health and Society, University of Oslo, Postbox 1130 Blinderen, N-0318 Oslo, Norway. [3]Norwegian National Advisory Unit for Aging and Health, Vestfold County Hospital HF, Toensberg and Oslo University Hospital, Oslo, Norway.

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RESEARCH ARTICLE Open Access

Drug use differs by care level. A cross-sectional comparison between older people living at home or in a nursing home in Oslo, Norway

Amura Francesca Fog[1,2*], Jørund Straand[2], Knut Engedal[3] and Hege Salvesen Blix[4]

Abstract

Background: Drug consumption increases with age, but there are few comparisons of drug use between old people living at home or in a nursing home. To identify areas of concern as well as in need for quality improvement in the two settings, we compared drug use among people aged ≥70 years living at home or in a nursing home.

Methods: Cross-sectional observational study from Oslo, Norway. Information about drug use by people living at home in 2012 was retrieved from the Norwegian Prescription Database. Drug use in nursing homes was recorded within a comprehensive medication review during November 2011–February 2014. Prevalence rates and relative risk (RR) with 95% confidence intervals were compared between uses of therapeutic groups with prevalence rates of ≥5%. Drug use was compared for the total population and by gender and age group.

Results: Older people (both genders) in nursing homes ($n = 2313$) were more likely than people living at home ($n = 48{,}944$) to use antidementia drugs (RR = 5.7), antipsychotics (RR = 4.0), paracetamol (RR = 4.0), anxiolytics (RR = 3.0), antidepressants (RR = 2.8), dopaminergic drugs (RR = 2.7), antiepileptic drugs (RR = 2.4), loop diuretics (RR = 2.3), cardiac nitrates (RR = 2.1) or opioids (RR = 2.0). By contrast, people living in a nursing home were less commonly prescribed statins (RR = 0.2), nonsteroidal antiinflammatory drugs (NSAIDs) (RR = 0.3), osteoporosis drugs (RR = 0.3), thiazide diuretics (RR = 0.4), calcium channel blockers (RR = 0.5) or renin–angiotensin inhibitors (RR = 0.5). Each of the populations had only minor differences in drug use by gender and a trend towards less drug use with increasing age ($p < 0.01$).

Conclusions: Drug use by older people differs according to care level, and so do areas probably in need for quality improvement and further research. In nursing home residents, this relates to a probable overuse of psychotropic drugs and opioids. Among older people living at home, the probable overuse of NSAIDs and a possible underuse of cholinesterase inhibitors and osteoporosis drugs should be addressed.

Keywords: Older people, Community, Nursing homes, Drug use, Prevalence, Prescription database, Dementia, Cardiovascular drugs, Opioids, Psychotropic drugs

* Correspondence: a.f.fog@medisin.uio.no; http://www.med.uio.no/helsam
[1]Nursing Home Agency, Oslo Municipality, Oslo, Norway
[2]General Practice Research Unit, Department of General Practice, Institute of Health and Society, University of Oslo, Postbox 1130 Blinderen, N-0318 Oslo, Norway
Full list of author information is available at the end of the article

Background

With the aging of populations, substantially more people are living with multi-morbidity [1, 2], dementia [3] or frailty [4]. Despite the prevalence of these conditions, older people today live longer with fewer functional limitations and disabilities than equally olds in earlier generations [5]. In Norway, it is a national priority to support people living in their own homes as long as possible. Based on individual needs and regardless of income, the municipality is responsible for providing either home-based nursing services or long-term care in a nursing home.

Direct comparisons of morbidity between older persons living at home and in nursing homes are lacking, but cognitive impairment, neuropsychiatric symptoms, Parkinson's disease and stroke are all more prevalent in nursing home residents than among those living in the community [6]. In Norway, almost half of all deaths take place in nursing homes [7].

Older people use more drugs than any other group, although the scientific evidence for drug efficacy and safety is limited, particularly for those older than 80 years. In Norway, people older than 67 years represent about 15% of the population but use 45% of all prescription drugs [8], the vast majority prescribed by general practitioners.

Because of differences in morbidity and life expectancy between older people living at home or in a nursing home, it is likely that the drug use differs by care level, for example with more symptomatic and palliative approach in the nursing home setting. It has been reported that nursing home residents use more psychotropic drugs and fewer cardiovascular drugs than their age-matched peers living in the community [9–11]. Clinical guidelines rarely take the clinical setting, or a patient's multi-morbidity or limited life expectancy into consideration. Strict adherence to guidelines may therefore also contribute to inappropriate polypharmacy in older people [12]. Due to the differences in morbidity, disability and drug use between older people residing in nursing homes or at home, measures to improve drug prescription practice for older people needs to be tailored for the care-level setting in question. For planning of future quality improvement studies to fit with the clinical setting, it is therefore relevant to analyse both differences and similarities in drug use between older people in these two settings. This may ensure that the most important problems in each setting will be addressed. Describing drug use patterns for older people residing in the two settings may identify areas of concern as well as in need for quality improvement, and it may guide the focus for further research into the field.

In this study we have described the drug use in older people living at home or in a nursing home to identify the most pronounced differences in drug use, aiming also to identify areas of concern as well as in need for quality improvement of the drug use in the two settings.

Methods

We collected information about the drug use of people aged 70 years old or older who were living at home or in a nursing home in the Oslo municipality, Norway from two sources.

Drug use for people living at home in 2012 ($n = 48{,}944$ people) was retrieved from the Norwegian Prescription Database (NorPD). The NorPD contains information about all prescription drugs dispensed at pharmacies in Norway and covers all people living in the country, except those living in long-term care institutions such as nursing homes [8].

The drug use data for people living in a nursing home were retrieved from the database of a medication review project performed at 41 of 51 nursing homes in Oslo municipality during November 2011–February 2014 [13]. The 41 nursing homes were representative of nursing homes in the municipality. From that project's baseline data (i.e., before the medication review), we retrieved information about the drug use of the long-term nursing home residents ≥70 years old ($n = 2313$) [13].

For both populations, the collected datasets included information about the drug names and the person's gender and age group (70–79 years, 80–89 years and ≥ 90 years).

Drugs were categorized according to the Anatomical Therapeutic Chemical (ATC) classification system [14].

Statistical analyses

The drug use prevalence rate in the population living at home was defined as the number of people who received at least one supply of a drug in 2012. In Norway, drugs for chronic and stable use may be prescribed for 1 year's use, however dispensed at pharmacies in quantities corresponding to about 3 months' use. Therefore, we calculated drug prevalence rates based on purchase data for both 3 months and 12 months. Because the prevalence rates were almost identical, we have used the annual drug prevalence rates for the statistical analyses for reasons of feasibility.

The drug use prevalence rate in the nursing home population was defined as the number of people who used the drug in question at the time of the medication review. We defined the same drug issued both regularly and as needed (pro re nata, prn) to the same person living in a nursing home as one prescription. This approach fits better to the data available from the general outpatient population and it is often used in

Table 1 Demographic characteristics of old people living at home and in a nursing home

Demographic characteristics	H (n = 48,944)	NH (*n* = 2313)
Women, n (%)	29,326 (59.9)	1752 (76.0)
Age 70–79 years, n (%)	27,299 (55.8)	311 (13.4)
Age 80–89 years, n (%)	17,645 (36.0)	1023 (44.3)
Age 90+ years, n (%)	4000 (8.2)	979 (42.3)

H (home population), NH (nursing home population). Gender information was missing for seven NH residents

pharmaco-epidemiological studies based on registry data [15].

The drug use in the two populations was compared in STATA SE 14 (Stata Corp LP, College Station, TX) using the relative risk (RR) with 95% confidence interval (95% CI) and the population living at home as the reference group. The analyses were performed also by gender and by age group. Associations between drug use and age group were determined using the chi-squared test for trend in proportions or Cochran–Armitage test for trend [16]. The level of significance was set at 0.05. We report statistical significance with RR (95% CI). We interpreted

Table 2 Drug use in older people living in a nursing home versus those living at home

Drug therapeutic group (ATC-3th level)[a]	Drug use prevalence (%)		Relative Risk (RR)	
	H (n = 48,944)	NH (*n* = 2313)	95% CI	*p*-value
Opioids	22.7	46.3	2.0 (2.0, 2.1)	<0.01
Paracetamol	18.2	72.1	4.0 (3.9, 4.1)	<0.01
Antiepileptic drugs	4.0	9.5	2.4 (2.1, 2.7)	<0.01
Dopaminergic drugs	1.5	3.9	2.7 (2.2, 3.4)	<0.01
Antipsychotics	4.0	17.2	4.3 (3.9, 4.8)	<0.01
Anxiolytics	16.2	48.4	3.0 (2.9, 3.1)	<0.01
Hypnotics/sedatives	28.6	49.2	1.7 (1.7, 1.8)	<0.01
Antidepressants	11.2	31.6	2.8 (2.7, 1.8)	<0.01
Antidementia drugs	2.0	11.4	5.7 (5.0, 6.5)	<0.01
Cardiac glycosides	3.2	5.8	1.8 (1.5, 2.2)	<0.01
Cardiac nitrates	7.5	15.4	2.1 (1.9, 2.3)	<0.01
Loop diuretics	14.0	31.7	2.3 (2.1, 2.4)	<0.01
Other diuretics[b]	6.6	2.9	0.4 (0.3, 0.6)	<0.01
Beta-blockers	29.1	24.8	0.9 (0.8, 0.9)	<0.01
Calcium channel blockers	19.6	9.0	0.5 (0.4, 0.5)	<0.01
Renin–angiotensin drugs	41.1	18.6	0.5 (0.4, 0.5)	<0.01
Statins	35.0	5.7	0.2 (0.1, 0.2)	<0.01
Antithrombotic agents[c]	47.4	44.0	0.9 (0.9, 1.0)	<0.01
Inhalators[d]	17.8	18.3	1.0 (0.9, 1.1)	0.55
Corticosteroids, systemic	10.2	6.6	0.7 (0.6, 0.8)	<0.01
Antihistamines, systemic	11.6	8.2	0.7 (0.6, 0.8)	<0.01
Vitamin B_{12} and folic acid	6.5	13.6	2.1 (1.9, 2.4)	<0.01
Thyroid therapy	10.9	16.1	1.5 (1.4, 1.6)	<0.01
Peptic ulcer drugs[e]	17.2	21.4	1.3 (1.2, 1.4)	<0.01
Antidiabetics[f]	10.2	11.1	1.1 (1.0, 1.2)	0.15
Drugs for glaucoma	9.3	10.4	1.1 (1.0, 1.3)	0.08
Oestrogens	6.3	4.6	0.7 (0.6, 0.9)	<0.01
Benign prostate hypertrophy drugs	6.1	2.3	0.4 (0.3, 0.5)	<0.01
Osteoporosis drugs	6.5	2.1	0.3 (0.3, 0.4)	<0.01
NSAIDs	20.7	5.5	0.3 (0.2, 0.3)	<0.01

H (home population), NH (nursing home population). RR (relative risk with 95% confidence interval and p-value and the population living at home as the reference group)
[a]Drugs with prevalence rates ≥5% in at least one of the populations, except for dopaminergic drugs
[b]The vast majority were thiazides
[c]Mostly anti-platelet agents, such acetylsalicylic acid (36.2% vs. 31.2%) and warfarin (11.5% vs. 9.0%)
[d]Steroid, adrenergic and anticholinergic inhalators
[e]The vast majority were proton pump inhibitors
[f]Oral antidiabetic drugs RR = 2.4(2.0, 2.9) and insulin RR = 0.7(0.6, 0.9)

Table 3 Use of particular drugs in older people living in a nursing home or at home

Drugs (ATC-5th level)[a]	Drug use prevalence (%)		Relative Risk (RR)	
	H (n = 48,944)	NH (n = 2313)	95% CI	p-value
Morphine	0.3	4.5	13.7 (10.7, 17.4)	<0.01
Oxycodone	1.8	10.1	5.7 (4.9, 6.5)	<0.01
Fentanyl	0.5	6.2	12.4 (1.1, 15.2)	<0.01
Buprenorphine	1.1	11.9	10.7 (9.3, 12.3)	<0.01
Codeine analgesics	17.3	17.5	1.0 (0.9, 1.1)	0.75
Tramadol	6.8	12.5	1.8 (1.6, 2.1)	<0.01
Haloperidol	0.3	4.1	15.8 (12.1, 20.6)	<0.01
Clozapine, olanzapine, quetiapine	0.8	5.3	6.9 (5.6, 8.4)	<0.01
Risperidone	0.4	5.4	14.0 (11.2, 17.5)	<0.01
Oxazepam	7.7	41.7	5.5 (5.2, 5.8)	<0.01
Diazepam	8.1	8.6	1.1 (0.9, 1.2)	0.35
Zopiclone, zolpidem	27.3	39.8	1.5 (1.4, 1.5)	<0.01
Clomethiazole	0.1	8.5	68.8 (51.8, 91.4)	<0.01
Citalopram, escitalopram sertraline, paroxetine	6.4	19.7	3.1 (2.9, 3.4)	<0.01
Mianserin, mirtazapine, venlafaxine	4.6	14.8	3.2 (2.9 3.6)	<0.01
Donepezil, rivastigmine, galantamine	1.8	5.7	3.2 (2.7, 3.9)	<0.01
Memantine	0.4	5.7	15.0 (12.1, 18.7)	<0.01

H (home population), NH (nursing home population). RR (relative risk with 95% confidence interval and p-value and the population living at home as the reference group)
[a]Drugs with prevalence rates ≥4% in at least one of the populations

the findings on the assumption that differences reach clinical significance when the RR was ≤0.5 or ≥ 2.

Results

People living in a nursing home (n = 2313) were generally older and were more often women than those living at home (n = 48,944) (Table 1).

Compared with people living at home (the reference group), people living in a nursing home more frequently used antidementia drugs [RR = 5.7)], antipsychotics (RR = 4.0), paracetamol (RR = 4.0), anxiolytics (RR = 3.0), antidepressants (RR = 2.8), dopaminergic drugs (RR = 2.7), antiepileptic drugs (RR = 2.4), loop diuretics (RR = 2.3), cardiac nitrates (RR = 2.1) or opioids (RR = 2.0) (Table 2).

By contrast, people living in a nursing home were less commonly issued statins (RR = 0.2), nonsteroidal antiinflammatory drugs (NSAIDs) (RR = 0.3), osteoporosis drugs (RR = 0.3), thiazide diuretics (RR = 0.4), calcium channel blockers (RR = 0.5) or renin–angiotensin drugs (RR = 0.5) (Table 2).

The RRs for use of opioids, antipsychotics, anxiolytics, hypnotic/sedatives, antidepressants and antidementia drugs in nursing home residents compared with those living at home are presented in Table 3. In particular clomethiazole (RR 68.8), haloperidol (RR = 15.8), memantine (RR = 15.0), risperidone (RR = 14.0), morphine (RR = 13.7), fentanyl (RR = 12.4) and buprenorphine (RR = 10.7) were indeed more often issued for nursing home residents than for older people living at home. Weak opioids were frequently used in both settings; the use of tramadol was higher in nursing homes (RR = 1.8), but the use of codeine-containing analgesics did not differ between populations (RR = 1.0).

Differences in drug use by gender are presented in Table 4. Except for opioids, the differences between home and nursing home populations in the use of drugs affecting the nervous system were larger for men than for women (home population as the reference group).

Differences in drug use by age group are presented in Table 5. With the exception of antiepileptic drugs and dopaminergic agents, a negative trend in the percentage of people using particular drugs with increasing age was observed for people living at home ($p <$ 0.01). For people living in a nursing home, a negative trend in the percentage of people using the drug with increasing age ($p <$ 0.01) was observed for paracetamol, antiepileptic drugs, dopaminergic agents, antipsychotics, anxiolytics, antidepressants, antidementia drugs, cardiac glycoside and nitrates, loop diuretics, statins and antidiabetics (Table 5).

Discussion

In this comprehensive comparison of the drug use among older people living at home or in nursing homes, we have reported data on drug groups and individual drugs not commonly reported by others [9–11, 17–19]. We found large differences in drug use by people aged 70 years and older according to their place of residence.

Table 4 Drug use in women and men living in a nursing home or at home

Drug groups	Women ($n = 31,078$)			Men ($n = 20,152$)			Women vs men	
	H	NH		H	NH		H	NH
	%	%	RR[a] (95% CI)	%	%	RR[a] (95% CI)	RR[b] (95% CI)	RR[b] (95% CI)
Opioids	25.7	48.6	2.3 (2.2, 2.4)	18.3	38.7	2.2 (2.0, 2.5)	1.2 (1.2, 1.2)	1.1 (1.1, 1.2)
Paracetamol	22.4	73.6	3.3 (3.2, 3.4)	12.0	67.7	5.9 (5.5, 6.3)	1.3 (1.3, 1.3)	1.1 (1.0, 1.2)
Antiepileptic drugs	4.1	8.5	2.1 (1.8, 2.5)	3.9	12.6	3.4 (2.7, 4.3)	1.0 (1.0, 1.1)	0.9 (0.8, 1.0)
Dopaminergic agents	1.2	3.2	2.6 (2.0, 3.4)	1.8	6.3	3.7 (2.7, 5.2)	0.8 (0.8, 1.0)	0.8 (0.7, 1.0)
Antipsychotics	4.7	17.1	3.7 (3.3, 4.1)	2.9	17.5	6.2 (5.1, 7.6)	1.2 (1.1, 1.2)	1.0 (0.9, 1.1)
Anxiolytics	20.1	49.2	2.5 (2.3, 2.6)	10.5	45.9	4.6 (4.1, 5.0)	1.3 (1.2, 1.3)	1.0 (1.0, 1.1)
Hypnotics/sedatives	34.3	49.1	1.4 (1.4, 1.5)	20.2	49.5	2.6 (2.3, 2.8)	1.3 (1.2, 1.3)	1.0 (1.0, 1.1)
Antidepressants	13.8	33.0	2.4 (2.2, 2.6)	7.3	27.7	3.9 (3.4, 4.5)	1.3 (1.2, 1.3)	1.1 (1.0, 1.1)
Antidementia drugs	2.2	10.8	5.0 (4.3, 5.8)	1.8	13.7	8.0 (6.4, 0.1)	1.1 (1.0, 1.1)	0.9 (0.9, 1.0)
Cardiac glycosides	3.2	5.7	1.8 (1.5, 2.2)	3.2	5.9	1.9 (1.4, 2.7)	1.0 (1.0, 1.0)	1.0 (0.9, 1.1)
Cardiac nitrates	7.1	15.8	2.2 (2.0, 2.5)	8.2	14.1	1.8 (1.5, 2.2)	0.9 (0.9, 1.0)	1.0 (1.0, 1.1)
Loop diuretics	14.7	32.2	2.2 (2.0, 2.4)	12.9	29.9	2.4 (2.1, 2.8)	1.1 (1.0, 1.1)	1.0 (1.0, 1.1)
Other diuretics	7.5	3.0	0.4 (0.3, 0.5)	5.3	2.3	0.5 (0.3, 0.8)	1.2 (1.1, 1.2)	1.1 (0.9, 1.2)
Beta-blockers	27.1	25.1	0.9 (0.9, 1.0)	32.1	23.6	0.8 (0.7, 0.9)	0.9 (0.9, 0.9)	1.0 (1.0, 1.1)
Calcium channel blockers	19.2	9.5	0.5 (0.4, 0.6)	20.1	7.6	0.4 (0.3, 0.5)	1.0 (0.9, 1.0)	1.1 (1.0, 1.1)
Renin–angiotensin	40.1	17.9	0.4 (0.4, 0.5)	42.6	20.7	0.5 (0.4, 0.6)	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)
Statins	31.8	4.7	0.1 (0.1, 0.2)	39.7	9.2	0.2 (0.2, 0.3)	0.9 (0.8, 0.9)	0.8 (0.7, 0.9)
Antithrombotic agents	42.7	42.0	1.0 (0.9, 1.0)	54.6	50.1	1.0 (0.9, 1.0)	0.8 (0.8, 0.8)	0.9 (0.9, 1.0)
Inhalators	18.6	17.8	1.0 (1.0, 1.1)	16.5	23.1	1.0 (1.0, 1.0)	1.1 (1.0, 1.1)	0.9 (0.9, 1.0)
Corticosteroids	11.1	6.3	0.6 (0.5, 0.7)	8.9	7.4	0.9 (0.6, 1.2)	1.1 (1.1, 1.1)	1.0 (0.9, 1.1)
Antihistamines	13.6	7.6	0.6 (0.5, 0.7)	8.7	9.9	1.2 (0.9, 1.5)	1.2 (0.2, 1.2)	0.9 (0.8, 1.0)
Drugs for peptic ulcer	18.2	21.7	1.2 (1.1, 1.3)	15.7	20.0	1.3 (1.1, 1.6)	1.1 (1.1, 1.1)	1.0 (1.0, 1.1)
Antidiabetics	8.5	8.6	1.0 (0.9, 1.2)	12.8	11.7	0.9 (0.7, 1.2)	0.8 (0.8, 0.8)	0.9 (0.8, 1.0)
Osteoporosis drugs	9.8	2.6	0.3 (0.2, 0.4)	1.4	0.7	0.5 (0.2, 1.4)	1.6 (1.6, 1.0)	1.2 (1.1, 1.3)
NSAIDs	22.7	5.6	0.6 (0.5, 0.7)	17.8	5.2	0.3 (0.2, 0.4)	1.1 (1.0, 1.1)	1.0 (0.9, 1.1)

H (home population), NH (nursing home population). RR (relative risk with 95% confidence interval)
Number of women (H = 29,326, NH = 1752) and men (H = 19,618, NH = 554)
[a]RR values calculated using the home population as the reference group
[b]RR values calculated using women as the reference group

Antidementia drugs were substantially more often used in those living in a nursing home, regardless of age or gender. This might be expected because about 80% of the nursing home residents are cognitively impaired [20], as compared with 18% of people aged 80 years and 41% of those older than 90 years living in the community [6]. However, the higher use of antidementia drugs by men than women in nursing homes (13.7% vs. 10.1%) should be investigated in further research. The use of cholinesterase inhibitors at home (1.8%) was lower than expected because these drugs are recommended palliative treatment for people with mild to moderate dementia [21, 22], most of whom are living at home. The very low use of memantine among those living at home is consistent with that the vast majority of people with severe dementia are being cared for in nursing homes.

Our observation that antipsychotics, antidepressants and anxiolytics were used more often in nursing homes is consistent with the findings of others [9–11, 18]. This probably reflects the high prevalence of significant behavioural and psychiatric symptoms of dementia (BPSD) [20] and obstacles for implementing non-pharmaceutical measures in the nursing home setting. The use of antipsychotics in nursing homes in our study was lower than in other studies [9, 11, 18, 19, 23, 24], perhaps explained by recent warnings against long term antipsychotic use because of severe side effects such as cognitive decline [25, 26], falls [27], stroke [28] and even death [29], as well as poor long-term effect on agitation [30]. We however still consider the overall use of psychotropic drugs in nursing homes to be too high because their efficacy in people with dementia is generally poor [31] and commonly harmful, and deprescribing is generally well tolerated [32, 33]. The prevalent use of clomethiazole in nursing home residents (8.5%) is surprising and it should be investigated further, given that this is a drug with a poor safety record that in general should be avoided in older people [34].

Table 5 Drug use in people living in a nursing home or at home by age groups

Drug groups	Age 70–79 years *n* = 27,610			Age 80–89 years *n* = 18,668			Age ≥ 90 years *n* = 4979			Chi-square test for trend in proportion	
	H	NH		H	NH		H	NH		*p*-value[a]	*p*-value[b]
	%	%	RR (95% CI)	%	%	RR (95% CI)	%	%	RR (95% CI)		
Opioids	20.4	51.0	2.5 (2.2, 2.8)	25.0	42.8	1.7 (1.6, 1.8)	28.4	48.5	1.7 (1.6, 1.9)	< 0.01	0.71
Paracetamol	14.0	68.3	4.9 (4.5, 5.3)	21.7	70.0	3.2 (3.1, 3.4)	31.6	75.5	2.4 (2.3, 2.6)	< 0.01	< 0.01
Antiepileptic drugs	3.9	20.8	5.4 (4.3, 6.8)	4.2	9.4	2.2 (1.8, 2.7)	3.5	6.0	1.7 (1.3, 2.4)	0.84	< 0.01
Dopaminergic agents	1.4	7.4	5.3 (3.5, 7.9)	1.6	4.7	2.9 (2.1, 3.8)	1.0	2.0	2.2 (1.3, 3.7)	0.48	< 0.01
Antipsychotics	3.8	25.0	6.7 (5.5, 8.2)	4.3	18.4	4.3 (3.7, 5.0)	4.4	13.5	3.1 (2.5, 3.8)	< 0.01	< 0.01
Anxiolytics	14.7	54.5	3.7 (3.3, 4.1)	17.8	49.6	2.8 (2.6, 3.0)	19.8	45.2	1.8 (1.6, 1.9)	< 0.01	< 0.01
Hypnotics/sedatives	24.0	48.1	2.0 (1.8, 2.3)	33.1	49.7	1.5 (1.4, 1.6)	41.0	49.0	1.2 (1.1, 1.3)	< 0.01	0.95
Antidepressants	10.1	39.7	4.0 (3.4, 4.6)	12.5	33.8	2.7 (2.5, 3.0)	13.3	26.8	2.0 (1.8, 2.3)	< 0.01	< 0.01
Antidementia drugs	1.1	13.5	12.4 (9.2, 16.8)	3.1	15.3	16.1 (14.1, 18.5)	3.4	6.7	2.0 (1.5, 2.6)	< 0.01	< 0.01
Cardiac glycosides	1.8	2.9	1.6 (0.9, 3.1)	4.6	5.0	1.1 (0.8, 1.4)	7.1	7.7	1.1 (0.8, 1.4)	< 0.01	< 0.01
Cardiac nitrates	5.1	9.9	1.0 (1.0, 1.0)	9.7	12.9	1.0 (1.0, 1.0)	14.6	19.8	0.9 (0.9, 1.0)	< 0.01	< 0.01
Loop diuretics	8.3	25.3	3.1 (2.5, 3.7)	18.4	27.9	1.5 (1.4, 1.7)	33.1	37.7	1.1 (1.0, 1.3)	< 0.01	< 0.01
Other diuretics	5.7	2.2	0.4 (0.2, 0.8)	7.8	2.4	0.3 (0.2, 0.5)	8.4	3.6	0.4 (0.3, 0.6)	< 0.01	0.12
Beta-blockers	25.3	21.2	0.8 (0.7, 1.0)	33.2	25.0	0.8 (0.7, 0.8)	37.6	25.8	0.7 (0.6, 0.8)	< 0.01	0.14
Calcium channel blockers	17.6	6.4	0.4 (0.2, 0.6)	21.9	9.9	0.5 (0.4, 0.5)	23.1	9.0	0.4 (0.3, 0.5)	< 0.01	0.42
Renin–angiotensin	40.1	20.8	0.5 (0.4, 0.6)	42.7	19.3	0.5 (0.4, 0.5)	40.6	17.0	0.4 (0.4, 0.5)	< 0.01	0.09
Statins	37.0	14.4	0.4 (0.3, 0.5)	35.2	5.9	0.2 (0.1, 0.2)	20.0	2.9	0.1 (0.1, 0.2)	< 0.01	< 0.01
Antithrombotic agents	41.7	39.4	0.9 (0.8, 1.1)	53.9	45.9	0.9 (0.8, 0.9)	58.5	43.5	0.7 (0.7, 0.8)	< 0.01	0.60
Inhalators	18.5	25.1	1.0 (1.0, 1.0)	17.9	20.8	1.0 (1.0, 1.0)	11.6	15.0	0.9 (0.9, 1.0)	< 0.01	< 0.01
Corticosteroids[3]	9.6	6.4	0.7 (0.4, 1.0)	11.4	8.1	0.7 (0.6, 0.9)	9.4	5.1	0.5 (0.4, 0.7)	< 0.01	0.08
Antihistamines[3]	12.7	9.3	0.7 (0.5, 1.0)	10.7	8.5	0.8 (0.6, 1.0)	8.8	7.6	0.9 (0.7, 1.1)	< 0.01	0.28
Drugs for peptic ulcer	15.8	24.7	1.6 (1.3, 1.9)	19.0	20.8	1.1 (1.0, 1.2)	18.7	20.9	1.1 (1.0, 1.3)	< 0.01	0.27
Antidiabetics	11.4	16.3	1.4 (1.1, 1.8)	9.2	10.3	1.1 (0.9, 1.4)	5.9	6.0	1.0 (0.8, 1.3)	< 0.01	< 0.01
Osteoporosis drugs	5.1	0.3	0.1 (0.0, 0.4)	8.2	3.0	0.4 (0.3, 0.5)	7.8	1.7	0.2 (0.1, 0.4)	< 0.01	0.70
NSAIDs	23.6	6.1	0.3 (0.2, 0.4)	18.1	5.2	0.3 (0.2, 0.4)	12.7	5.6	0.4 (0.3, 0.6)	< 0.01	0.93

H (home population), NH (nursing home population). RR (relative risk with 95% confidence interval and the population living at home as the reference group)
Number of people in each age group: 70–79 years (NH = 311; H = 27, 299), 80–89 years (NH = 1023; H = 17, 645) and ≥ 90 years (NH = 979; H = 4, 000)
[a]Chi-squared test for trend in proportion of drug usage at home
[b]Chi-squared test for trend in proportion of drug usage in nursing homes

Overall, there is generally poor evidence for the efficacy of antidepressants, including selective serotonin reuptake inhibitors, in people with dementia and BPSD [35]. That the use of antidepressants in nursing homes declined with residents' age has also been reported by others [18, 19]. A possible explanation for this may also be decreasing prevalence of depressive symptoms with increasing dementia severity [36].

Consistent with findings by others [10, 11, 19], more paracetamol and opioids were used by nursing home residents. This may partly reflect the lower use of NSAIDs for osteoarthritis in nursing home residents, but may also reflect empiric analgesic treatment in people with dementia of agitated behaviour presumed to be caused by pain [37]. That at least 20% of older people living at home use NSAIDs is a matter of concern, especially because their use might be even higher due to their possible purchase without prescription. NSAIDs are probably most commonly issued for degenerative pain without inflammation (a simple analgesic might thus be a safer option) and they pose an increased risk for gastrointestinal bleedings and adverse cardiovascular events [38]. That we in both settings found a more prevalent use of opioids than reported by others [10, 11, 18, 19] also warrants further investigation. Opioids used as part of end-of-life palliative treatment in nursing homes cannot explain this finding because palliative units were not included in the medication review.

The differences found for the uses of cardiovascular drugs between the two settings suggest that cardiovascular treatment may be more symptomatic and palliative in nursing homes than for their home-dwelling peers [10, 19, 39]. Because of the lower rate of disability and

Table 6 Older people residing in nursing homes or at home: ten drugs in particular need for critical rethinking during educational interventions or medication reviews

Drug	Nursing home	Home
Antidementia drugs	Severe dementia: overuse?	Mild dementia: underuse?
Antipsychotic drugs	BPSD[1]: Too much, too long? Deprescribing should be tried	(little use)
Antidepressants	Overuse: Poor effect in people with dementia, consider tapering down dosage and deprescribing	Possible overuse: Consider tapering down dosage and deprescribing
Anxiolytics Hypnotics/sedatives	Overuse	Probable overuse
Opioids	Overuse	Probable overuse
Clomethiazole	Overuse: should be avoided whenever possible for reasons of safety	(almost no use at all)
NSAIDs	(little use)	Overuse – try paracetamol instead
Osteoporosis drugs	Possible underuse?	Possible underuse?
Statins	(little use)	Possible overuse (oldest age group)?
Drugs for peptic ulcer	Possible overuse	Possible overuse

[1]Behavioral and psychiatric symptoms in dementia

longer life expectancy among home-dwelling older people relative to nursing home residents, the potential benefits for both primary and secondary cardiovascular prevention are larger for those living at home.

Deprescribing of prophylactic drug treatment in nursing home residents with short life expectancies may explain the lower use of both statins and osteoporosis drugs by nursing home residents. However, the use of osteoporosis drugs was lower than expected among home-dwelling women because osteoporosis, with its consequent risk of fractures, is a leading health hazard in old people in Norway [40].

Based on the study results and our own clinical experience, we have identified ten drugs in particular need for critical rethinking during future educational interventions or medication reviews in the two settings (Table 6).

Our study has some limitations. We compared the drug use of two populations that differ in terms of morbidity and frailty without recording clinical data (e.g. diagnoses, Charleston morbidity scores, in-home care service use). We assumed that institutionalization is a proxy for frailty and a high prevalence of dementia, and we have not differentiated between robust and frail older people living at home. Drug use was investigated in terms of the prevalence of use, but we did not have access to the prescribed daily dosages or how often drugs intended for prn actually were used. Despite these limitations, we consider that our data are representative for each of the populations and have acceptable validity for identifying the most significant differences in drug use patterns between older people residing in the two settings. The prevalence rates of drug use for those living at home differed only marginally between data captured over 3 or 12 months, thus being comparable with the point prevalence data for those living in nursing homes. We included drug use data from more than half of the nursing home population in Oslo and the entire population living at home in the municipality. The patient demographics and findings in our study are also consistent with our clinical experience and with data reported in other studies [9–11, 18, 19]. We believe that the large number of participating nursing homes and the large size of the home-dwelling population account for the external validity of our findings.

Conclusions

This study substantiates that older people living in a nursing home and at home represent two different pharmacologically realities. Further research should investigate when the changes in drug prescription occur in the process of institutionalization or if the two settings may have different therapeutic cultures that partly may explain their different prescription practices. In Norway, the inclusion of prescription data from nursing homes in the NorPD would enable monitoring their drug use over time and follow up on changes in drug use patterns.

Abbreviations

ATC: Anatomical Therapeutic Chemical classification system;
BPSD: behavioural and psychiatric symptoms of dementia; NorPD: Norwegian Prescription Database (NorPD); NSAIDs: nonsteroidal antiinflammatory drugs; RR: relative risk with 95% confidence interval

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Availability of data and materials
All data generated or analyzed during this study are included in this published article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The Norwegian Prescription Database (NorPD) contains data about all dispensed drugs in Norway and it is publically accessible on http://www.norpd.no/. Data from NorPD is intended for general scientific research purposes, statistical analysis and planning. No permissions were required to access the NorPD and to retrieve the study data.

Authors' contributions
AFF, JS, KE and HSB were involved in the study design and contributed to writing the manuscript. HSB and AFF retrieved the drug use data. AFF drafted the manuscript. All authors read and approved the final draft of the manuscript.

Ethics approval and consent to participate
According to the Norwegian act on medical and health research, no formal ethical approval was needed for the present study. Formal consent was not required because data is anonymous.
The study protocol of the medication review project at the nursing homes, which generated part of the data used here, was presented to the Regional Committee in Medical Research Ethics in South-East Norway (reference no. 2015/786) and the Norwegian Centre for Research Data (reference no. 43659). Both bodies concluded that their formal approval was not needed. The other part of the data used here was aggregated tabulated data retrieved from the Norwegian Prescription Database (NorPD). No permissions were required to access and retrieve the study data. The privacy of the individual is strictly protected and data is anonymous.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Author details
[1]Nursing Home Agency, Oslo Municipality, Oslo, Norway. [2]General Practice Research Unit, Department of General Practice, Institute of Health and Society, University of Oslo, Postbox 1130 Blinderen, N-0318 Oslo, Norway. [3]Norwegian National Advisory Unit for Aging and Health, Vestfold County Hospital HF, Toensberg and Oslo University Hospital, Oslo, Norway. [4]Department of Drug Statistics, Norwegian Public Institute of Health, Oslo, Norway.

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