Optimization of drug treatment in older people exposed to polypharmacy

“One size does not fit all”

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My interest in drug optimization for older people started several years ago, in my very first job as a physician in a nursing home. Many patients were admitted to the nursing home with functional decline, accompanied by family members who assumed that permanent institutional care was the only way forward. However, a few of these patients improved dramatically after having their drug regimens adjusted and could actually move home. This convinced me that critical reconsideration of long medication lists is extremely important and have the potential to improve many older peoples’ lives.

I have been privileged to be involved in this project from the very beginning. My main supervisor Torgeir Bruun Wyller and I started to share thoughts on how to design a polypharmacy trial already back in 2011. Many years have passed, in part because this study was quite work-demanding to plan and conduct, but I have learned so much.

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Even, Nella and Lilli the puppy: You are the best little family 😊.

The photos included in the thesis are of my father. He died late 2020 and did not see me finish this work, so I thought he deserved to be part of it.
<table>
<thead>
<tr>
<th>ABBREVIATIONS</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin-converting enzyme</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse drug event</td>
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<tr>
<td>ADL</td>
<td>Activities of daily living</td>
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<td>ADR</td>
<td>Adverse drug reaction</td>
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<td>AOU</td>
<td>Assessment of Underutilization</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
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<tr>
<td>CDR-SOB</td>
<td>Clinical Dementia Rating Scale Sum of Boxes</td>
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<td>CDSS</td>
<td>Clinical decision support system</td>
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<tr>
<td>CNS</td>
<td>Central nervous system</td>
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<tr>
<td>COS</td>
<td>Core outcome set</td>
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<tr>
<td>CPIC</td>
<td>The Clinical Pharmacogenetics Implementation Consortium</td>
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<td>CYP</td>
<td>Cytochrome P450</td>
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<tr>
<td>DDD</td>
<td>Defined daily dose</td>
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<tr>
<td>DPWG</td>
<td>The Dutch Pharmacogenetics Working Group</td>
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<tr>
<td>DRP</td>
<td>Drug-related problem</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency department</td>
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<tr>
<td>ES</td>
<td>Eva Skovlund</td>
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<tr>
<td>FDT</td>
<td>Five Digits Test</td>
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<tr>
<td>FIM</td>
<td>Functional Independence Measure</td>
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<tr>
<td>FP</td>
<td>Family physician</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>HRQoL</td>
<td>Health-related quality of life</td>
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<tr>
<td>IM</td>
<td>Intermediate metabolizer</td>
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<tr>
<td>IQCODE</td>
<td>Informant Questionnaire on Cognitive Decline in the Elderly</td>
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<tr>
<td>MAI</td>
<td>Medication Appropriateness Index</td>
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<tr>
<td>MDD</td>
<td>Multidose drug dispensing</td>
</tr>
<tr>
<td>MNA-SF</td>
<td>Mini Nutritional Assessment Short Form</td>
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<td>NM</td>
<td>Normal metabolizer</td>
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<tr>
<td>NORGEP</td>
<td>Norwegian General Practice Criteria</td>
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<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drug</td>
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<tr>
<td>PIM</td>
<td>Potentially inappropriate medication</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<td>---------</td>
<td>------------------------------------</td>
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<tr>
<td>PIP</td>
<td>Potentially inappropriate prescribing</td>
</tr>
<tr>
<td>PM</td>
<td>Poor metabolizer</td>
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<tr>
<td>PPO</td>
<td>Potential prescribing omission</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RR</td>
<td>Rita Romskaug</td>
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<tr>
<td>RSS</td>
<td>Relative Stress Scale</td>
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<tr>
<td>SPPB</td>
<td>Short Physical Performance Battery</td>
</tr>
<tr>
<td>START</td>
<td>Screening Tool to Alert doctors to the Right Treatment</td>
</tr>
<tr>
<td>STOPP</td>
<td>Screening Tool of Older Person’s Prescriptions</td>
</tr>
<tr>
<td>TBW</td>
<td>Torgeir Bruun Wyller</td>
</tr>
<tr>
<td>UM</td>
<td>Ultrarapid metabolizer</td>
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SUMMARY

Background
Older people are prescribed an increasing number of medications, and although many drugs may have good clinical indications individually, polypharmacy is associated with adverse health outcomes. Especially among multimorbid and frail older people, the trade-off between benefit and harm can be challenging to assess, and there is a need for strategies that can guide clinicians on how to provide the benefits of drug treatment but at the same time avoid negative consequences. Several trials aimed at improving drug therapy for older people have succeeded in improving drug-related outcomes, but an effect on surrogate outcomes does not necessarily mean that the patient has really benefited from the intervention. Systematic reviews conclude that drug review interventions so far have had minimal effect on patient-related outcomes and no effect on health-related quality of life (HRQoL), and that further studies are warranted.

Pharmacogenetics has received much attention as a tool to achieve more personalized drug treatment, and because frail and multimorbid older people have reduced ability to compensate for altered drug exposure resulting from pharmacogenetic variations, they may in particular benefit from such measures. Cytochrome P-450 (CYP) 2D6 is one of the most important enzymatic systems involved in drug metabolism that also shows extensive genetic heterogeneity. However, little knowledge exist on the clinical relevance of pharmacogenetic testing in this population.

Aims
The main objective of this thesis was to evaluate the effect of a thorough clinical drug review upon HRQoL and other patient-related outcomes in older, home-dwelling patients exposed to polypharmacy. To ensure comprehensive and clinically relevant drug reviews with a high probability of being implemented, we wanted the intervention to include a clinical geriatric assessment as well as direct collaboration between the geriatrician and the patients’ family physician (FP).

Additional aims were 1) to explore if we could identify predictors for a positive effect of the intervention, and 2) to explore the relevance of pharmacogenetic variations among the study participants.
**Methods**

From March 2015 to March 2017, 174 patients (mean age 83 years, 67.8% women) in 70 clusters were included in a cluster randomized controlled trial (RCT). The patients were randomized to either usual care, or to an intervention consisting of 1) geriatric assessment including a medical history, systematic screening for current problems, clinical examination, relevant supplementary tests, as well as a detailed review of each drug in use, 2) a meeting between the geriatrician and FP, with discussion of all drugs and establishing a collaborative plan for adjustments and follow-up, and 3) clinical follow-up by the geriatrician or FP, as agreed on.

The primary outcome was HRQoL, measured by the 15D instrument. Secondary outcomes included drug appropriateness, physical and cognitive functioning, caregiver burden, orthostatic blood pressure, falls, hospital admissions, use of home nursing service, admission to permanent institutional care, and mortality. Follow-up was after 16 and 24 weeks.

We also carried out supplementary post-hoc analyses, 1) to assess whether baseline patient characteristics or specific drug changes following the intervention were associated with change in HRQoL at follow-up, and 2) to examine prescribed dosages of CYP2D6 substrates in relation to genotype as well as the impact of CYP2D6 genotype on blood pressure and heart rate.

**Results**

Our main finding was that the intervention resulted in positive effects on HRQoL. Mean 15D scores deteriorated in both groups, but at a slower pace in the intervention group, and the estimated between-group difference was clinically relevant and statistically significant. Most secondary outcomes on physical and cognitive function were also in favor of the intervention, although not all reached statistical significance. There were more drug changes in the intervention group compared to the control group, and medication appropriateness improved following the intervention. We found no effect on the other secondary outcome measures.

Post-hoc analyses indicated that the patients with more inappropriate drug use at baseline benefited most from the intervention, but it was difficult to draw any certain conclusions on whether treatment adjustments within specific drug classes were more
important than others. We also found that dosing of CYP2D6 substrates was not adjusted according to genotype predicted CYP2D6 metabolism. Patients with reduced or absent CYP2D6 metabolism had significantly higher prevalence of orthostatic hypotension than those with normal metabolism, which could reflect a higher exposure of CYP2D6 substrates exhibiting hemodynamic effects in the former subgroup.

**Conclusion**

The study indicates that clinical geriatric assessments and drug reviews carried out in collaboration with the patients’ FP have the potential to improve HRQoL among older patients exposed to polypharmacy, and may also have positive effects on physical and cognitive functioning. Individualized dose adjustments supported by pharmacogenetic tests can potentially further optimize drug use in selected patients and may prevent adverse drug reactions (ADRs) in this vulnerable population. An individual approach, targeting the complexity of each patient’s drug regimen, is most likely the key of optimizing drug therapy for older people.
Sammendrag

Bakgrunn
Legemiddelbruken hos eldre er stadig økende, og selv om mange medisiner er til god nytte, så vet vi at polyfarmasi også er forbundet med negative helseeffekter. Spesielt hos skrøpelige eldre med mange sykdommer må man som lege ofte gjøre vanskelige avveiningar mellom fordeler og ulemper knyttet til behandlingen, og det er behov for mer kunnskap om hvordan man kan håndtere dette på best mulig måte. Det har blitt gjennomført mange studier av forskjellige tiltak for å forbedre medisinbruken hos eldre, og flere av disse har hatt effekt på legemiddeleffektmål. Effekt på slike surrogatendepunkt er imidlertid ikke ensbetydende med at pasienten har hatt reell nytte av intervensionen. Systematiske oversiktsartikler konkluderer med at det foreløpig ikke er evi dens for at legemiddelgjennomganger har noen betydningsfull effekt på pasientrelaterte effektmål, og det poengteres at det er stort behov for flere studier.

Farmakogenetikk har fått en del oppmerksomhet de senere årene som et verktøy for å oppnå mer personstiltpasset legemiddelbehandling. Skrøpelige eldre har redusert evne til å kompensere for den endrede legemiddeleksponeringen som kan følge av farmakogenetiske variasjoner, og er derfor en pasientgruppe som kan tenkes å ha særlig nytte av slike tiltak. CYP2D6 er et av de viktigste genetiske heterogene enzymene som er invol vert i legemiddelmetabolisme, og er derfor spesielt interessant. Det finnes imidlertid lite kunnskap om nytten av farmakogenetisk testing i denne populasjonen.

Formål
Hovedformålet med avhandlingen var å vurdere om en grundig legemiddelgjennomgang hos skrøpelige, eldre hjemmeboende pasienter med høyt medisinforbruk kunne ha positiv effekt på helselivskvalitet og andre pasientrelaterte endepunkt. For å sikre klinisk relevante legemiddelvurderinger med høy sannsynlighet for å bli gjennomført, inkluderte intervensionen en klinisk geriatriisk vurdering, og også direkte samarbeid mellom geriateren og pasientenes fastlege.

Øvrige formål var 1) å se om vi kunne identifisere prediktorer for en positiv effekt av intervensionen, og 2) å undersøke relevansen av farmakogenetiske variasjoner hos studiedeltakerne.
**Metode**

I perioden mars 2015 til mars 2017 ble 174 pasienter ( gjennomsnittlig alder 83 år, 67,8% kvinner) i 70 klynger inkludert i en klyngerandomisert, kontrollert studie. Pasientene ble randomisert til enten vanlig oppfølging hos fastlege eller en intervensjon som bestod av 1) en geriatrisk vurdering som inkluderte sykehistorie, systematisk kartlegging av aktuelle problemer, klinisk undersøkelse, supplerende undersøkelser og en kritisk vurdering av alle legemidler i bruk, 2) et møte mellom geriateren og fastlegen hvor de to legene diskuterte legemiddellisten og ble enige om en plan for medis injusteringer og videre oppfølging, og 3) klinisk oppfølging enten av geriater eller fastlege, ettersom hva som ble vurdert mest hensiktsmessig.

Hovedeffektmålet i studien var helselatert livskvalitet målt med instrumentet 15D. Som sekundære endepunkt valgte vi blant annet fysisk og kognitiv funksjon, kvalitet på legemiddelbehandlingen, pårørendebelastning, ortostatisk blodtrykk, fall, bruk av hjemmesykepleie, sykehusinnleggelser, hvorvidt pasientene fikk tildelt fast sykehjemsplass og mortalitet. Oppfølgings tidspunktene var etter 16 og 24 uker.

Vi gjorde også supplerende post-hoc analyser hvor vi 1) undersøkte i hvilken grad pasientkarakteristika før intervensjonen eller konkrete legemiddelendringer som følge av intervensjonen var assosiert med endringer i helselatert livskvalitet, og 2) undersøkte doseringen av CYP2D6 substrater i relasjon til genotype, samt betydningen av CYP2D6 genotype for pasientenes blodtrykk og puls.

**Resultater**

Hovedfunnet var at intervensjonen førte til positive effekter på helselatert livskvalitet. Gjennomsnittlig 15D-skrar forverret seg i begge gruppene, men i mindre grad i intervensjonsgruppen, og forskjellen mellom gruppene var både klinisk relevant og statistisk signifikant. De fleste sekundære endepunktene som målte fysisk og kognitiv funksjon tydet også på en positiv effekt av intervensjonen, selv om ikke alle oppnådde statistisk signifikans. Pasientene i intervensjonsgruppen fikk gjennomført flere legemiddelendringer enn kontrollgruppen, og kvaliteten på legemiddelbruken bedret seg som følge av intervensjonen. Det var ingen effekt på de øvrige sekundære endepunktene.
Post-hoc-analysene tydet på at pasientene med mest uhensiktsmessig legemiddelbruk ved inklusjonstidspunktet hadde best nytte av intervensjonen, men det var vanskelig å trekke noen sikre konklusjoner rundt hvorvidt justeringer i enkelte legemiddelklasser var viktigere enn andre. Vi fant også at doseringen med CYP2D6-substrater ikke ble justert i forhold til genetisk predikert CYP2D6-metabolisme. Pasienter med redusert eller fraværende CYP2D6-metabolisme hadde signifikant høyere forekomst av ortostatisk hypotensjon enn de med normal metabolisme, noe som kan skyldes en høyere eksponering for CYP2D6-substrater.

**Konklusjon**

Studien indikerer at en klinisk geriatrisk vurdering og legemiddelgjennomgang utført i samarbeid med pasientens fastlege har potensiale til å forbedre helselivskvalitet hos eldre pasienter som bruker mange medisiner, og også kan ha effekt på fysisk og kognitiv funksjon. Individuelle dosejusteringer støttet av farmakogenetiske tester kan optimalisere legemiddelbruken ytterligere hos utvalgte pasienter, og kan tenkes å forebygge bivirkninger i denne sårbare pasientgruppen. En individualisert tilnærming, hvor man tar høyde for kompleksiteten hos hver enkelt pasient og revurderer alle legemidler kritisk, er trolig nøkkelen til å optimalisere legemiddelbehandlingen hos eldre pasienter.
LIST OF PUBLICATIONS

I. Cooperation Between Geriatricians and General Practitioners for Improved Pharmacotherapy in Home-Dwelling Elderly People Receiving Polypharmacy – The COOP Study: Study Protocol for a Cluster Randomised Controlled Trial

II. Effect of Clinical Geriatric Assessments and Collaborative Medication Reviews by Geriatrician and Family Physician for Improving Health-Related Quality of Life in Home-Dwelling Older Patients Receiving Polypharmacy: A Cluster Randomized Clinical Trial

III. Factors Associated with Health-Related Quality of Life After a Comprehensive Drug Review Intervention in Older People Exposed to Polypharmacy

IV. Prescribed Doses of CYP2D6-Metabolized Drugs and Hemodynamic Responses in Relation to CYP2D6 Genotype Among Older Patients Exposed to Polypharmacy
1. BACKGROUND

1.1 Drug therapy in older people

Over the last decades, modern medicine and the development of drugs have contributed both to increased life expectancy and reduced morbidity for people living in developed countries. Unfortunately, there are also many possible negative health effects related to drug use (1). Especially among older people, the trade-off between benefit and harm can be challenging to assess, and it has been raised an international focus on the need for strategies to optimize drug treatment for this patient group (2).

The following sections will describe important reasons why drug use often gets more complicated with increasing age, give an overview over the extent of drug use among older people, as well as introduce the term polypharmacy and some of its implications.

1.1.1 Changes in pharmacokinetics and pharmacodynamics

With advancing age, several naturally occurring physiological changes can influence the tolerance for drugs (3), but the progress of aging shows great variability between individuals and older people are therefore very heterogeneous (4). Age-related changes concerning drug pharmacokinetics have largely been studied in those younger than 80 years, so it is also important to bear in mind that knowledge is scarce for the oldest age groups (5).

Pharmacokinetics describes how a drug is processed by the body after administration, and the four primary processes are absorption, distribution, metabolism and excretion. Figure 1 illustrates some important age-related pharmacokinetic changes.

Absorption of drugs taken orally can be affected by for example age-related decrease in the production of gastric acid, delayed gastric emptying or decreased gut motility, but generally there is no evidence that aging itself leads to clinically important reduced absorption of drugs, neither orally or from other extravascular sites (4, 6, 7).

Figure 1. Age-related pharmacokinetic changes
**Distribution** refers to how a drug is distributed throughout the body after entering the systemic circulation. The most important age-related changes relate to older people having a relative reduction in total body water and lean body mass, and an increased proportion of body fat, which alter the volume of distribution for many drugs. Fat-soluble drugs (e.g. diazepam) will have a greater volume of distribution and accumulate in fat tissue, leading to increased half-life and prolonged effect compared to what is seen in younger people. Highly water-soluble drugs (e.g. digoxin) will in contrast have smaller volumes of distribution, which can result in higher plasma concentrations (4, 7).

**Metabolism** involves transformation of biologically active substances into metabolites that can be excreted from the body, but also synthesis of active drugs from prodrugs. The liver is a major site for these reactions, and both liver size and hepatic blood flow decreases with age. Such changes can lead to reduced metabolism, especially phase I reactions where enzymes from the CYP family are commonly involved, but the overall clinical significance of this remains uncertain (4, 5, 7).

**Excretion** concerns removal of drugs or metabolites from the organism, and the kidneys play a key role in this process. The glomerular filtration rate (GFR) undergoes progressive reduction with age, although with great variation between individuals. Reduced GFR affects the clearance of water-soluble drugs, e.g., diuretics, metformin, angiotensin-converting enzyme (ACE) inhibitors and sotalol (5, 7). Drugs with narrow therapeutic index (e.g. digoxin, amino-glycosides) can quickly accumulate under such circumstances and lead to severe ADRs, and must be used with caution (7).

**Pharmacodynamics** is often described as “how the body responds to a drug” (4), and two physiological changes are illustrated in Figure 2. Age-related pharmacodynamic changes are challenging to investigate, but have been found to be relevant especially for cardiovascular drugs and drugs acting on the central nervous system (CNS) (7-9). Alterations in homeostatic mechanisms can make older people less able to compensate for various drug effects,
resulting in ADRs at a lower drug exposure than their younger counterparts. An example is the age-associated decreased baroreceptor sensitivity, which increases the risk of orthostatic hypotension, instability and falls from drugs that affect blood pressure (9, 10). For drugs acting on the CNS, elderly are especially vulnerable to negative effects of antipsychotics and benzodiazepines. The underlying mechanisms are largely unknown, but could involve alterations in neurotransmitters, or be related to decreased integrity of the blood-brain-barrier in older age (8, 10).

**1.1.2 The impact of multimorbidity**

Although many people live longer, with good health, the prevalence of multimorbidity, defined as having two or more long-term health conditions, increases with age as illustrated in Figure 3 (11-13).

![Figure 3. Number of chronic disorders by age group. Barnett et al, 2012 (11). Reprinted with permission from The Lancet.](image)

Long-term health conditions include physical and mental health conditions, but also conditions like learning disability and sensory impairment, symptom complexes such as frailty or chronic pain, and alcohol and substance misuse (13). The most important risk factor for multimorbidity is advancing age, but associations have also been seen with female sex, having had a high number of previous illnesses, and low socioeconomically status (11, 14).
Older people living with multimorbidity are generally at risk of functional decline, poor quality of life and high health care utilization (11, 12, 14). A problem directly related to drug use is that common conditions like impaired vision and hearing, swallowing difficulties or reduced motor or cognitive functioning can result in problems with administration or intake of medicines (7).

In addition, many health conditions can influence pharmacokinetics and pharmacodynamics, leading to even more unpredictable drug responses than those resulting solely from the age-related changes previously discussed (Figure 4). For example, in a patient with congestive heart failure, oedema in the intestinal wall can lead to reduced absorption of drugs, and a patient with diabetes can have more severely impaired kidney function than what is attributed to aging itself. Dementia has been associated with an increased permeability of the blood-brain barrier and impaired function of P-glycoprotein, a protein involved in removal of substances (e.g. drugs or metabolites) from the brain. A likely result is increased access of medicines in the brain, leading to an elevated risk of ADRs (4, 7). Frailty, a state of increased vulnerability due to decreased physiologic reserve caused by the accumulation of aging processes across multiple organ systems (15), has been associated with physiological changes such as reduced hepatic and renal drug clearance, as well as with a generally increased risk of ADRs that can be due both to pharmacokinetic and pharmacodynamic changes (4, 16). These are just a few examples of conditions that potentially influence the effects of drugs. Geriatric patients often have several concurrent long-term health conditions, and the overall impact on drug responses can become very complex.

Multimorbidity also gives rise to more precautions and contraindications because a drug given to treat one condition can be harmful or even contraindicated for another (drug-disease interactions). An example is the use of anticholinergic drugs for urinary incontinence. This can be well tolerated in a cognitively intact person, but in the presence of dementia, with reduced central cholinergic activity, such a drug could provoke further cognitive impairment or delirium (17).
1.1.3 Participation in drug trials

Although they respond differently to drugs than their younger counterparts, older people have been underrepresented in clinical drug trials for decades, especially in the presence of multimorbidity, frailty, and use of multiple drugs (17-19). As a result, there is poor evidence for the efficacy and safety of many drugs used by the geriatric population. Difficulties in recruiting older people to clinical trials, ethical considerations regarding exposure of multimorbid patients to experimental therapies, as well as methodological challenges concerning standardization, increased variability in outcomes and need of larger sample sizes probably all contribute to this shortcoming (17, 19).

Pharmaceutical drug trials often use outcomes such as survival or time to event. This can indeed apply also to older people, but outcomes like activities of daily living (ADL), physical or cognitive functioning and HRQoL are important to assess when investigating drug effects in geriatric populations (19, 20). A study by Fried et al, examining older people’s health outcome priorities, found that most rated “maintaining independence” as the most important health outcome, pain and/or symptom relief as second, and staying alive as least important (21).

RCTs are considered the highest level of evidence in the development of clinical treatment guidelines (18, 22). Because older patients rarely are included in these RCTs, and because guidelines mainly focus on one specific disease and do not take multimorbidity into account, they are often of limited use when clinicians are facing dilemmas on how to treat their older patients in real life (18, 22, 23).

1.1.4 Organization of health care systems

A focus on individual diseases also dominates the education of physicians and the way specialist health services are organized. For those with only one disease, being seen by a specialist in that field can be favorable. However, for patients with multiple health conditions, being seen by various specialists can result in suboptimal and fragmented care. Different specialists tend to focus on optimizing treatment for conditions related to the organ system in which they have specialized, and they may have an inadequate overview over risks and benefits associated with the patients’ total drug use (11, 24).
Multimorbid patients benefit from a generalist perspective. Geriatricians have a key role in providing this in hospitals, but most patients are mainly followed in primary care. FPs are generalists too, and often have the additional advantage of following their patients over a long period of time. Their experience and competence in dealing with complex older patients is, however, variable. In addition, primary care is not sufficiently established worldwide (11). Even in Norway, traditionally equipped with a strong primary health care system, there are currently major challenges in keeping and recruiting FPs. An increasing workload on the FPs, as well as a growing number of patients without a FP, threaten the complex patients’ need for close and personalized follow-up.

1.1.5 Drug consumption in the aging population
The world’s population is aging, mostly due to increased life expectancy and reduced fertility, and it is estimated that the global proportion of people 65 years or older will rise from 9.3% in 2020 to 16.0% in 2050 (25). In Norway, using the same commonly accepted cut-off of 65 years of age, it is estimated that the proportion of older people will increase from 18% in 2020 to 30% in 2070 (26). Figure 5 illustrates the expected development in number of people belonging to the three oldest age groups in Norway.

![Figure 5](image_url)

**Figure 5.** Number of older people in three age groups, registered 2000-2020 and projected 2021-2060 in three alternatives. Reprinted with permission from Statistics Norway.
Drug consumption increases with age, and the number of drugs used by the elderly population has gradually increased over time (27-29). In Britain, the number of older people using five drugs or more increased from 12.2% to 49.6% over the last two decades (30). In Scotland, the proportion of older people using ten drugs or more increased from 4.9% in 1995 to 17.2% in 2010 (31). The same trend is seen both in Norway and other Scandinavian countries (32-35). In a recent study including 45,593 Norwegian home-dwelling patients receiving their medicines by multidose drug dispensing, the mean number of drugs in use was 8.2 and as many as 33% of the patients used 10 or more medicines (36). A report from The Norwegian Prescription Database utilizing data up to as recent as 2017 shows no sign of declining drug use, and the steadily increasing proportion of older, home-dwelling drug users being dispensed as many as ≥ 15 different medications is illustrated in Figure 6 (33).

![Figure 6. Proportion of home-dwelling drug users in Norway who were dispensed ≥ 15 drugs (ATC 5th level codes) in 2004-2017 in the age groups 0-64 and ≥ 65 years by gender. Berg et al, 2018 (33). Reprinted with permission from The Norwegian Prescription Database.](image)

1.1.6 Polypharmacy

The term “polypharmacy” is commonly used when describing use of multiple medications, and most people can understand the general meaning of this. There is, however, no consensus of a more precise definition. This can be problematic in research because of difficulties in assessing for example the prevalence, consequences and management of polypharmacy (37-39). A review by Masnoon et al identified 138 different definitions of polypharmacy and associated terms (37). Of these, 80.4% were numerical
definitions, and the most common was “the use of five or more medications”. Associated terms like “excessive polypharmacy” and “hyperpolypharmacy” were often used for people taking 10 or more medications. Arguing that the specific number of drugs is less relevant, another approach is to rather define appropriate or rational polypharmacy versus inappropriate or problematic polypharmacy (37, 40).

**Negative effects of polypharmacy**

Despite different definitions being used, polypharmacy has nevertheless been associated with several negative clinical outcomes. The most important associations discussed in three recent reviews (1, 27, 29) are listed in Table 1. Some of the outcomes are directly related to drug use (e.g. the risk of drug-drug interactions), while others (e.g. mortality) are broader and more likely to be influenced by other health-related factors, thus making it difficult to establish causal relationships (1, 29).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug-related problems</strong></td>
<td>Polypharmacy is a risk factor for drug-drug and drug-disease interactions, ADRs, the use of potentially inappropriate medications, undertreatment and decreased adherence (29). Conflicting evidence for an association with ADRs (1).</td>
</tr>
<tr>
<td>Frailty</td>
<td>Support for an association between polypharmacy and frailty, but difficult to establish causal relationships due to confounding (1, 29).</td>
</tr>
<tr>
<td>Falls</td>
<td>Polypharmacy is associated with falls in several studies, but it is suggested that this mainly is related to specific fall-inducing drugs (29). Conflicting evidence for association with falls (1, 27).</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>Support for an association between polypharmacy and reduced cognitive function (27, 29). Conflicting evidence for an association with cognitive impairment (1).</td>
</tr>
<tr>
<td>Physical function</td>
<td>Many studies have found negative associations between polypharmacy and different measures of physical function, but it is difficult to establish causal relationships due to confounding (27, 29).</td>
</tr>
<tr>
<td>HRQoL</td>
<td>No evidence for an association between polypharmacy and HRQoL (29).</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>Support for an association between polypharmacy and hospital admissions (1, 27, 29).</td>
</tr>
<tr>
<td>Mortality</td>
<td>Several studies have found associations between polypharmacy and mortality, but it is difficult to establish causal relationships due to confounding (1, 29).</td>
</tr>
</tbody>
</table>

*Abbreviations: ADR = Adverse drug reaction. HRQoL = Health-related quality of life.*
What are the mechanisms behind the increasing drug consumption?

There has been a change towards a more proactive approach to pharmacological disease prevention and treatment of older people over the last decades, accompanied by increasing availability of effective medicines for various conditions. In general, this is both positive and highly appropriate, and contributes to the increased life expectancy we experience in the Western world (30, 41). An important reason why older people are prescribed many drugs relates to the increasing prevalence of multimorbidity with age. Clinical treatment guidelines are continuously being developed, and because they most often give recommendations based on what is appropriate for single medical conditions, multimorbid people will inevitably have indications for numerous drugs (1, 22, 41).

Treatment recommendations are usually only incorporated into guidelines if substantial evidence for the efficiency of a certain treatment exists. This favors implementation of pharmacological approaches, as it is less complicated to perform high quality drug trials than trials evaluating non-pharmacological interventions. Pharmaceutical companies of course also have an economical motivation for developing drugs and have considerable resources to spend on trials as well as marketing, something that rarely applies to non-pharmacological alternatives.

At the physician level, it may often be easier to prescribe a new drug than to carry out non-pharmacological approaches, which in part can be due to expectations from the patient (41, 42). The risk of excessive drug use has been found to increase with the number of prescribers, and although FPs are responsible for most repeat prescriptions, several drugs on a long medication list have often been initiated by different hospital specialists (32). FPs are supposed to have the role of a “controlling agent” and regularly review their patients’ medications, but have varying competence on assessing polypharmacy in older, multimorbid patients. Along with limited possibilities to discuss complex drug regimens with relevant hospital specialists, and mostly a very tight time schedule, it may often be easier to continue medications rather than going through a process of reconsidering their appropriateness (41, 43, 44).
1.2 Balancing benefits and harms

Optimization of drug treatment in older people is much about balancing benefits and harms. Our patients should be offered medications with an anticipated positive effect. The challenge is to assess the patients’ overall clinical situation and total drug use, and to adjust treatment accordingly, to avoid negative consequences. This chapter will give an overview over important drug-related problems (DRPs) in older people, and further introduce different initiatives and measures that can serve as elements of a drug optimization strategy.

1.2.1 Important drug-related problems in older people

There is no consensus on a definition of the theoretical concept of DRPs (45), but it can be explained as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” (46). This text will not give a systematic description of all possible DRPs but focus on those considered especially important, namely adverse drug reactions, drug interactions, inappropriate drugs, overprescribing, underprescribing, and adherence.

Adverse drug reactions

The terms medication error, adverse drug reaction (ADR) and adverse drug event (ADE) are commonly used when describing negative effects of drug use, and Table 2 summarizes their proposed definitions as well as an ADR classification system (47-49).

Table 2. Proposed definitions of medication error, adverse drug reaction and adverse drug event.

<table>
<thead>
<tr>
<th>Term</th>
<th>Proposed definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication error</td>
<td>“Any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer.” (47)</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>“A noxious, undesired, or unintended response to a therapeutic agent, which may be expected or unexpected, and may occur at dosages used for the prophylaxis, diagnosis, or therapy of disease, or for modifying physiological factors.” (49)</td>
</tr>
<tr>
<td></td>
<td>Type A: Augmented (often dose related and predictable)</td>
</tr>
<tr>
<td></td>
<td>Type B: Bizarre (not predictable, mostly not dose related)</td>
</tr>
<tr>
<td></td>
<td>Type C: Chronic (related to cumulative dose)</td>
</tr>
<tr>
<td></td>
<td>Type D: Delayed (appear after many years of treatment)</td>
</tr>
<tr>
<td></td>
<td>Type E: End of use (occur after drug withdrawal)</td>
</tr>
<tr>
<td></td>
<td>Type F: Unexpected failure of therapy (often dose related or caused by interactions)</td>
</tr>
<tr>
<td>Adverse drug event</td>
<td>“An injury resulting from the use of a drug” (e.g. ADRs, overdoses, dose reductions and discontinuations), which may sometimes result from medication errors. (47)</td>
</tr>
</tbody>
</table>
As previously discussed, age-related pharmacokinetic and pharmacodynamic changes, multimorbidity and polypharmacy contribute to variable drug responses and increased susceptibility to ADRs (Figure 7). The risk of experiencing negative effects of drug therapy is especially high in the presence of frailty (50), and it has also been shown that older women are more vulnerable to drug-related harm than older men (41).

**Figure 7.** Physiological changes, multimorbidity and polypharmacy increase the risk of ADRs

ADRs can range from mild symptoms to severe and life-threatening events. It is estimated that up to 10% of hospital admissions in older people are caused by ADRs, and the most common classes of drugs involved are non-steroidal anti-inflammatory drugs (NSAIDs), beta blockers, antibiotics, oral anticoagulants, antiplatelets, diuretics, digoxin, antihypertensives, opioids, and antidiabetics (51, 52). Most ADRs in older people are Type A reactions that are attributable to a drug’s known pharmacological effect, like hypoglycemia due to antidiabetics or bradycardia due to beta blockers, and many drug-related hospital admissions could have been prevented if the patients were monitored more closely (51-54).
Less dramatic ADRs can also have a pronounced impact on health, function and quality of life, but unfortunately, many such reactions are unspecific and difficult to identify. They can present as common symptoms like dizziness, falls, confusion, obstipation or reduced appetite, and can be perceived simply as related to aging – or a new disease (50). Such symptoms may thus be neglected and not further investigated, but there is also a risk of prescribing cascades, where new drugs are initiated to treat symptoms that in fact are ADRs (55). In the context of polypharmacy, ADRs can be caused by combinations of drugs rather than one specific drug, thus making it difficult to disentangle the problem. This can be due to CYP interactions (see later), but is probably more often related to additive effects when using several drugs with the same predictable ADR (e.g. constipation) (49, 56). It is also important to bear in mind that although a drug regimen has been well tolerated for decades, the physiological changes that come with increasing age, as well as new comorbidities, can suddenly provoke the manifestation of ADRs. New symptoms should therefore always be considered as possible ADRs, and physicians must be highly alert to these issues when caring for older people (50).

**Drug interactions**

*Pharmacokinetic drug-drug interactions* appear if one drug affects absorption, distribution, metabolism or excretion of another drug, thereby leading to alterations in serum concentration and/or clinical response (57). The CYP system is a common site for such interactions, and the risk of interactions increases with the number of drugs in use (31, 58, 59).

*Pharmacodynamic drug-drug interactions* occur if the pharmacological activity of two or more drugs result in amplification or decrease in clinical response (57). Such interactions are especially relevant in older people because physiological changes related to aging and disease reduce their ability to compensate for additive effects, e.g. by the use of multiple drugs affecting blood pressure.

Other drug interactions include drug-disease interactions (mentioned in chapter 1.1.2), as well as interactions between drugs and food, alcohol or herbal products (57).
Inappropriate choice of drug

If a patient is prescribed a drug that is not the most effective alternative to treat a certain medical condition, or if the drug is not effective at all, that is an inappropriate choice of drug (60). In older people, inappropriateness also often refers to specific drugs, combinations of drugs, or combinations of drugs and diseases that are considered especially risky. Potentially inappropriate prescribing (PIP) is a term that encompasses both potentially inappropriate medications (PIMs) and potential prescribing omissions (PPOs) (61). PIMs are drugs with well-known risks that potentially outweigh their benefits. It is, however, important to notice the word potentially, as the presence of PIMs (and PPOs) indicates an anticipated increased risk of experiencing negative effects of a current drug regimen, not that such negative consequences actually are present. Several tools for identifying PIP have been developed; this is further discussed in chapter 1.2.2.

Overprescribing

Overprescribing is defined as “the prescription of a drug that is clinically not indicated” (62), and includes the use of multiple drugs in cases where one drug could have been sufficient, as well as drugs given to treat ADRs (60). Overprescribing is frequent, but it is often challenging to decide whether a medication is (still) indicated (44).

Symptomatic drug therapy, medications prescribed to relieve unpleasant symptoms, are sometimes used for several years without being reconsidered (43). Examples of such drugs include analgesics, antidepressants, antihistamines, and proton pump inhibitors. Symptomatic drugs can be highly beneficial if they are effective, also among very old and frail patients (63). It can, however, often be difficult to know if the medications provide any benefit. Reconsiderations can be done by gradual dose reductions and/or drug withdrawals, but it is important to reintroduce the drug if the patient experiences worsening of symptoms. Generally, it is wise to establish a plan for when and how to reconsider such drugs already when they are prescribed the first time.

Drugs prescribed to prevent future illness, preventive drug therapy, often constitute a substantial part of older patients’ drug regimens (63). Examples of such drugs are antithrombotics, bisphosphonates, antihypertensives, and statins. Drugs used for primary or secondary prevention can also be beneficial for many older patients. However, with increasing frailty and reduced life expectancy, the goals of care may
change, and the relevance of preventive drug therapy should be reconsidered as illustrated in Figure 8 (63, 64).

![Figure 8. Reconsideration of preventive drug therapy](image)

**Underprescribing**

Underprescribing can simply be defined as “the omission of a drug that is needed”, given that there is no valid reason for not prescribing it (65). This is the case if a medical condition is left untreated or needs an additional drug to be adequately controlled (e.g. atrial fibrillation with rapid ventricular response, where a drug for rate control is not prescribed). Underprescribing also includes the failure of providing prophylactic treatment when indicated (e.g. to prevent osteoporosis) (60).

Underprescribing is found to be prevalent, especially for cardiovascular and musculo-skeletal diseases, and has been associated with negative consequences like increased risk of cardiovascular events, hospital admissions and death (65). Polypharmacy and multimorbidity actually increase the risk of underprescribing, possibly because clinicians are more reluctant to initiate new drugs in fear of provoking ADRs when the
patient already uses many drugs (66). Prevalence studies have found underprescribing to be most frequent among patients with dementia and frailty, and especially among those living in long-term care facilities (65), but as previously discussed: The choice of not prescribing otherwise indicated drugs can be well justified when taking the patient’s total situation into consideration. It is nevertheless important to remember that older patients can benefit from additional drugs, even in the context of polypharmacy.

**Adherence**

Adherence is described as “to which extent a person’s way of taking drugs corresponds with recommendations from a healthcare provider” (67), and complex drug regimens are associated with poor adherence in older people (68, 69). There are several possible reasons to non-adherence, either intentional or unintentional, which include practical problems with administration, failure to understand the instructions, forgetting to take drugs, economic reasons, or that the patient do not want to use the drug (60, 67). Non-adherence is frequent, with estimated prevalence ranging from 25-75% in older people, and has been associated both with negative clinical outcomes and increased number of hospital admissions (67).

Multidose drug dispensing (MDD), where patients are provided drugs in disposable bags which are labelled with the date and time for intake, have become widespread especially in Scandinavian countries and in the Netherlands (70). In Norway, MDD is in particular used by community-dwelling elderly who have their drugs delivered by the home nursing service, and by nursing homes (36). MDD has been found to increase drug adherence compared with manually dispensed drugs, despite lower cognitive function in patients receiving MDD (70). However, because the MDD prescriptions in Norway still are paper-based and need to be faxed to a pharmacy, physicians find it time consuming to carry out drug changes. Despite improved adherence, it has therefore been raised concerns to whether MDD lead to fewer drug adjustments and less appropriate drug use (36, 71, 72).
1.2.2 Initiatives and measures to optimize drug treatment

Along with increased recognition of the challenges related to drug treatment, several international and national initiatives have emerged over the later years. In 2017, the World Health Organization raised global awareness about the potential negative effects of drug therapy by identifying “Medication Without Harm” as their third international Global Patient Safety Challenge (2). They reaffirmed these objectives by selecting “Medication Safety” at the theme for the World Patient Safety Day 2022, which will take place 17 September 2022 (73).

Funded by the European Union’s Health Programme, The SIMPATHY Project (Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly) was created as a collaboration between eight European countries, with an aim of raising awareness about polypharmacy and to facilitate identification and implementation of the best way of managing polypharmacy across the European Union (74). Another imitative, IGRIMUP (The International Group for Reducing Inappropriate Medication Use & Polypharmacy), is represented by researchers from 32 countries and published their position statement and recommendations for action in 2018 (75). OPPEN (Optimizing Geriatric Pharmacotherapy through Pharmacoepidemiology Network) is an example of another initiative that recently published consensus principles for clinical practice, research, and education (76).

The above-mentioned initiatives discuss various measures that can be implemented in a process of improving drug therapy, and this has also been a research focus for several years. In the following, this chapter will describe important strategies developed with an aim of optimizing drug treatment for older people.

Tools to identify potentially inappropriate prescribing

Numerous tools for identifying PIMs and PPOs have been developed, and they are frequently used both as part of interventions and as outcome measures in drug optimization studies (61, 77). Such screening tools are used when trying to distinguish between “appropriate” and “inappropriate” polypharmacy and can potentially be helpful in identifying drugs that should be prioritized for reconsideration.
Most of the tools are *explicit*, meaning that they are criterion-based and typically include lists of drugs that should be avoided in certain (or all) situations, and can be applied with little or no clinical judgement. They are usually quite rigid, and do not consider the patients’ individual differences and complexity. Other tools are *implicit*, meaning that they are judgement-based and demand the user to apply clinical assessments and take the total drug use into account. Some tools even combine these two approaches and include both explicit and implicit criteria (61, 78).

Some of the most widely used implicit tools are the Medication Appropriateness Index (MAI) (79) and Assessment of Underutilization (AOU) (80), which we included as secondary outcomes and thus describe in Chapter 3.1.

Explicit tools are more often adopted than implicit tools, as they are quicker to complete and can be performed by personnel without comprehensive clinical knowledge (81). A recent review identified as many as 58 different tools (82). However, they have limited overlap, and are to varying degrees validated in terms of clinical relevance (77, 82). Some of the most well-known explicit tools are the Beers criteria (83, 84), Screening Tool to Alert doctors to the Right Treatment (START) (85), Screening Tool of Older Person’s Prescriptions (STOPP) (86), Drug Burden Index (87), and Anticholinergic Risk Scale (88). In Norway, the Norwegian General Practice Criteria (NORGEP) (89) and a variant developed especially for nursing homes (NORGEP-NH) (90) are also commonly used.

Examples of drug classes frequently reported by explicit screening tools are NSAIDs, benzodiazepines, tricyclic antidepressants, proton pump inhibitors, antihistamines, and antipsychotics (82, 91). However, the different tools do not always agree on their recommendations. Schiavo et al found that 31 of 58 tools proposed therapeutic alternatives to PIMs on their lists, but 69% of these proposed alternatives were in fact identified as PIMs by other screening tools (82).

When it comes to external validation, the most extensively studied explicit tools are STOPP/START, the Beers criteria, Drug Burden Index and Anticholinergic Risk Scale, which all have been associated with functional decline, falls, hospital admissions and mortality (77). Other reviews have also found associations between PIPs in general and ADRs, ADEs, emergency department (ED) visits and HRQoL (61, 92).
The prevalence of PIPs among older people is high, with two meta-analyses reporting pooled estimates at 33% in primary care and 43% in nursing homes (81, 93). However, the appropriateness of most drugs depends on the patients’ clinical context, and for multimorbid older people, it is often necessary with more comprehensive assessments (64, 77). Screening tools can nevertheless have an important role in alerting health care professionals to drugs that should be reconsidered (78).

**Medication reconciliations**

Medication reconciliation has been described as “a process that aims to create the most accurate list of medications at all transition points, with the goal of providing the correct medications to the patient” (94). Updated and accurate medication lists is a prerequisite before carrying out drug reviews or other drug optimization procedures and is by common sense important to ensure in all clinical settings. Medication reconciliations have been shown to reduce potentially harmful medication errors, but when implemented as the only measure, they are not convincingly effective in improving clinical outcomes (94, 95).

**Drug reviews**

There is no consensus on what a drug (or medication) review actually is, but the NICE guideline on medicines optimization has defined it as “a structured, critical examination of a person’s medicines with the objective of reaching an agreement with the person about treatment, optimizing the impact of medicines, minimizing the number of medication-related problems and reducing waste” (96). However, both in clinical and academic settings, the term “drug review” has been used to describe quite diverse procedures – ranging from superficial checkups aimed at identifying the presence of PIMs, to comprehensive assessments including clinical examination of the patient (97). It has been suggested to divide the different approaches into three types of drug reviews, as shown in Figure 9, which can be a useful distinction (97).
Drug reviews are usually performed by pharmacists, physicians, or multidisciplinary teams, and can take place for instance in hospitals, nursing homes or in the community (95, 97). They can be carried out in acute situations, or regularly to reconsider the appropriateness of chronic drug use (95). It is important to consider both the content of the drug review and the provider of the procedure when evaluating the relevance and effect of such interventions, among other things because pharmacists and physicians have different qualifications when it comes to reconsidering older patients’ drug treatment. For example, a pharmacist might have the best in-depth knowledge on specific pharmacological aspects, while a physician might have more knowledge about the medical conditions – as well as an ability to perform clinical examinations.

Clinical drug reviews are time-consuming to carry out, especially when including clinical assessments, but they result in a thorough evaluation of the patients’ drug regimen where also individual differences are considered. Proposed elements to include in such reviews are illustrated in Figure 10 (95, 97-99). Prescribing tools can support the process, but it is underscored that a clinical drug review goes beyond the detection of PIMs and should result in more extensive recommendations (95).
Figure 10. Proposed elements to include in a clinical drug review

Comprehensive geriatric assessment, a multidimensional assessment of a patient's health status across somatic, psychosocial, and functional domains, is a clinical method of great value when assessing frailty and making decisions on older peoples’ future treatment (100), and can be useful to include in the drug review process (101).
Deprescribing

Deprescribing has been defined as “the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient’s care goals, current level of functioning, life expectancy, values, and preferences” (43), and Scott et al have suggested a five-step protocol to facilitate deprescribing processes (Table 3).

**Table 3. Five-step protocol to deprescribing. Adapted from Scott et al, 2015(43).**

<table>
<thead>
<tr>
<th>Key Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Ascertain all drugs the patient is currently taking and the reasons for each one</td>
</tr>
<tr>
<td>2.</td>
<td>Consider overall risk of drug-induced harm in individual patients in determining the required intensity of deprescribing intervention</td>
</tr>
<tr>
<td>3.</td>
<td>Assess each drug for its eligibility to be discontinued:</td>
</tr>
<tr>
<td></td>
<td>- No valid indication</td>
</tr>
<tr>
<td></td>
<td>- Part of a prescribing cascade</td>
</tr>
<tr>
<td></td>
<td>- Actual or potential harm of a drug clearly outweighs any potential benefit</td>
</tr>
<tr>
<td></td>
<td>- Disease and/or symptom control drug is ineffective, or symptoms have completely resolved</td>
</tr>
<tr>
<td></td>
<td>- Preventive drug is unlikely to confer any patient-important benefit over remaining lifespan</td>
</tr>
<tr>
<td></td>
<td>- Drugs are imposing unacceptable treatment burden</td>
</tr>
<tr>
<td>4.</td>
<td>Prioritize drugs for discontinuation</td>
</tr>
<tr>
<td>5.</td>
<td>Implement and monitor drug discontinuation regimen</td>
</tr>
</tbody>
</table>

As can be seen, the deprescribing process shares many features with clinical drug reviews, but with a more explicitly stated goal of reducing drug use. A criticism has been that this focus leads to failure in considering inappropriate prescribing in its entirety, since underprescribing is also a common problem (66).

Clinical decision support systems

Computer software can potentially guide clinicians both when prescribing and reconsidering drugs. A systematic review found that clinical decision support systems (CDSS) can reduce PIP in hospitals, but that their effect on patient-related outcomes are uncertain (102). A recent large-scale RCT (The SENATOR trial) where a CDSS based on the STOPP/START criteria was introduced in hospital had no effect on ADRs, and the implementation of CDSS-generated advice was very low (15%) among attending physicians (103). A reason for low implementation was found to be that the system frequently produced recommendations of low clinical relevance in the context of serious acute illness (104).
1.2.3 Pharmacogenetics

As previously described, many factors affect the variability in drug responses among geriatric patients, including age-related physiological changes, comorbidities, reduced organ function, and drug-drug interactions. In addition, all people have genetic variations in drug-metabolizing enzymes and drug transporters that can significantly impact drug response. Some of the most well-known genetic polymorphic enzymes are from the cytochrome P450 (CYP) family (105). These enzymes assist in phase I reactions in the liver, converting lipophilic drugs to water-soluble products that can be more readily excreted, but also have a function in converting certain pharmacologically inactive prodrugs into their pharmacologically active form (e.g. the conversion of codeine to morphine) (105). It is estimated that approximately 70-80% of all drugs are metabolized by CYP enzymes, with the polymorphic enzymes CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5 being among the most important (106).

The association of pharmacogenetic variations with clinical and adverse effects of drug treatment has received increasing interest over the later years (107). Within the CYP-family, inherited genetic polymorphisms especially in CYP2C9, CYP2C19, CYP2D6 and CYP3A5 are found to greatly impact pharmacokinetics of drugs metabolized by these enzymes (108). Several variant alleles for the different CYP enzymes are identified, and their functional status can range from no function to increased function. Based on the combination of alleles, CYP phenotypes are divided in poor metabolizers (PMs), normal metabolizers (NMs), intermediate metabolizers (IMs) and ultrarapid metabolizers (UMs) (108).

Pharmacogenetic analyses, determining a patient’s phenotype for the various CYP enzymes, can be useful when individualizing and optimizing drug treatment, and much research has been undertaken in this field over the later years. The Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) have developed several genotype-based prescribing recommendations that can be applied. Focus has, however, most been on single drug-gene or disease-gene pairs, and little knowledge exist on the clinical relevance of pharmacogenetics in more complex situations (109). Because of their reduced ability to compensate for altered drug exposure resulting from pharmacogenetic variations, frail and multimorbid older people may in particular benefit from such measures.
1.3 Previous drug optimization trials

Systematic reviews conclude that there is no evidence of improvements on clinical outcomes by any of the different drug optimization strategies that previously have been carried out, but there is some evidence of an effect on drug-related outcomes (e.g. medication appropriateness) (110-119). The systematic reviews have assessed various measures including complex medication therapy management interventions by clinical pharmacists, medication reconciliation, prescription reviews (mostly utilizing explicit or implicit tools), clinical drug reviews, interventions based on CDSS’, academic detailing, and educational interventions. In addition, several deprescribing trials have emerged over the later years. Deprescribing strategies have in general been found to be safe, with a potential to reduce inappropriate prescribing, but evidence for clinical effects are lacking also here (120-125).

1.3.1 Drug review interventions

When looking at drug review interventions in particular, the conclusions are the same as above: Drug reviews have been found to have effect on drug-related outcomes, but there is minimal evidence for an effect on clinical outcomes, and no evidence for an effect on HRQoL (126-132). When combined with other interventions, like patient education, professional education or transitional care, Dautzenberg et al (133) found that drug reviews may be associated with a lower risk of hospital readmissions compared to usual care, but mostly there are no such associations reported in the systematic reviews.

I will describe a systematic review by Huiskes et al (131) more in detail because it focused on drug reviews as an isolated short-term intervention, thus being especially relevant for this thesis. Only 7 of 31 studies (134-140) in Huiskes’ review concerned an intervention aimed at older people that involved a physician, at the same time reporting patient-related outcomes. In two of the studies (134, 135), physician input was by a clinical pharmacologist who took part in discussions after assessments performed by a clinical pharmacist, and the physician did not have direct contact with the patients. Recommendations following drug reviews were presented written to attending physicians, and generally had low implementation rates. The authors did not provide information on actual drug changes, and found no effect on patient-related outcomes.
In two studies, physicians performed prescription reviews for the detection of PIP, also without direct contact between physician and patient. In the study by Olsson et al (136), results of prescription reviews were sent to FPs, but only 8 out of 99 reviews resulted in action. There were no changes in drug use, and no effect on HRQoL. The study by Gallagher et al (137) had implementation rates of >90% and found improvements in drug appropriateness, but no effect on health care use, mortality, or falls. A study by Michalek et al (138) carried out drug reviews using a tool combining explicit and implicit criteria. The authors concluded that drug appropriateness improved and the number of falls were reduced during admittance in a geriatric rehabilitation ward with an average follow-up time of 20 days, but they found no effect on ADL.

In a study by Williams et al (139), prescription reviews were first done by a pharmacist followed by multidisciplinary drug reviews where a physician was present, but neither in this study the physician was directly involved in evaluating the patient. The authors found no effect on physical or cognitive functioning, depression, anxiety or HRQoL. Implementation rate of recommendations was suboptimal due to patient resistance towards reduction of psychoactive drugs, and the actual drug changes were considered “minor”. In addition, patients were described as fit and healthy, which could have led to a ceiling effect, and a follow-up of only 6 weeks might be too short to show an effect. Advice on drug changes were presented directly to the patients by the researchers, and although the FP had approved the recommendations, the authors conclude that FPs should be directly involved in the intervention as to facilitate implementation.

A study by Pope et al (140) was the only included in Huiskes’ review in which patients were directly assessed by a physician. Here, clinical geriatric assessments were followed by multidisciplinary prescription reviews. The study found significant reductions in the number of drugs used by the intervention group (mean -0.6) compared to the control group (mean 0.4), but no effect on hospital admissions, mortality, cognitive functioning, or ADL. The population in this study were residents in a continuing care hospital, described as especially sick and dependent, and the patient selection could thus have made it more challenging to achieve clinical improvements.

The other studies in Huiskes’ review (141-146) focusing especially at older people and reporting patient-related outcomes were pharmacist-led drug review interventions where
either written recommendations were sent to the patients’ FP or actively discussed with the FPs, but none of them found any effect on clinical outcomes.

On the following pages, Table 4 lists drug review interventions among older people that have included patient-related outcomes. The studies were identified through screening of the most relevant systematic reviews on the topic (112, 113, 115-117, 126-131, 133). In addition, a PubMed search was performed on April 27, 2022, to identify recently published trials not included in the systematic reviews. The search was limited to RCTs published in English during the last five years, and was performed using the terms “drug review” or “medication review” (title/abstract). This resulted in 89 studies that were screened for relevance.

Selection criteria for studies included in Table 4:
- Randomized controlled trial
- Patients ≥65 years of age
- Reporting patient-related outcome measures
- Published 2002 or later

Excluded: Studies targeted at patients with specific diseases only (e.g., diabetes, patients in hemodialysis), studies performed in nursing homes, interventions implementing education of health personnel or completely automated CDSS-algorithms, trials focused exclusively on deprescribing, interventions combining very diverse other measures in addition to drug reviews (e.g. optimalization of nutritional status in addition to drug review).
<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Setting/participants</th>
<th>n</th>
<th>Intervention</th>
<th>Outcomes/period</th>
<th>Results/comments</th>
</tr>
</thead>
</table>
| Kornholt 2022 (147) | Geriatric outpatient clinic. Referred patients using ≥9 drugs. | 408 | 1) Usual geriatric care + additional consultation with pharmacologist focusing on clinical drug reviews, cooperating with attending physician and FP, or 2) usual care. | 1. HRQoL (EQ-5D) at 4 months  
2. HRQoL at 13 months, falls, hospital admissions, mortality  
Follow-up at 4+13 months | Positive effect on HRQoL and mortality at 4 months, not significant at 13 months. No effect on hospital admissions or falls. More drug changes in IG (mean -2.0 drugs) compared to CG (-0.6). |
| Curtin 2020 (148) | Hospital. Age ≥75 using ≥5 drugs. Frail and in need of nursing home at discharge. | 130 | 1) Deprescribing guided by explicit tool (STOPP/Frail); research physician made drug withdrawal plan directly presented to attending physician who chose to implement or not, or 2) usual care. | 1. Mean change in number of drugs  
2. Hospital admissions, falls, HRQoL (QALIDEM + ICECAP-O) and mortality  
Follow-up at 3 months | Significantly more drug changes in IG (mean -2.6 drugs) compared to CG (-0.4) at 3 months. No effect on other outcomes. |
| Michalek 2014 (138) | Hospital. Patients admitted to a geriatric rehabilitation ward. Age >70 using ≥3 drugs. | 114 | 1) Drug review by physician according to FORTA list, or 2) usual care. | 1. Change in drug appropriateness from admittance to discharge  
2. ADL function at discharge, falls  
Follow-up until discharge (mean 20 days) | Significant improvement in drug appropriateness and less falls recorded in IG during hospital stay. No effect on ADL. |
| Olsson 2012 (136) | Primary care. Patients recently discharged from hospital. Age ≥75 using ≥5 drugs. | 150 | 1) Prescription review by study physician (focused on PIMs, DDIs and medication errors/discrepancies btw drug lists) sent to FP, 2) prescription review sent to FP + drug record sent to patient, or 3) usual care. | 1. HRQoL (EQ-5D, EQ-VAS)  
2. Prescription quality  
Follow-up at 6+12 months | No effect on HRQoL. No change in drug use or drug-risk indicators. Of 99 prescription reviews sent to FPs, only 8 resulted in actions. |
| Gallagher 2011 (137) | Hospital. Patients admitted to a general medicine ward. Age ≥65, no drug limit. | 400 | 1) Prescription review by research physician using START/STOPP, discussed with attending physician who could chose to accept advice or not, or 2) usual care. | 1. MAI/AOU at discharge and 6 months.  
2. Length of hospital stay, readmissions, number of FP visits, falls, mortality  
Follow-up at 6 months | Improvement in MAI and AOU at discharge and after 6 months. No effect on other outcomes. A total of 183 recommendations in 111 patients, >90% accepted by attending physicians. |
| Pope 2011 (140) | Residential continuing care hospital. All admitted patients were eligible. | 225 | 1) Clinical assessment by geriatrician + prescription review by multidisciplinary panel (assisted by prescription tools), with advice sent to attending physician (FP), or 2) usual care (FP). | 1. Number of drugs, drug costs  
2. Hospital admissions, mortality, ADL, and cognitive function  
Follow-up at 6 months | Significant reduction in number of drugs in IG (mean -0.6) compared to CG (mean 0.4). No effect on other outcomes. Drug changes recommended in 93% of patients; 80% implemented. |
### Multidisciplinary team-led interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Intervention Details</th>
<th>Outcomes</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blum 2021 (OPERAM)</strong></td>
<td>Hospital. Multi-morbid patients aged ≥70 using ≥5 drugs.</td>
<td>1) Structured drug optimization by physician and pharmacist using combination of implicit assessments and a CDSS based on START/STOPP, or 2) usual care.</td>
<td>1. First drug-related hospital admission 2. Mortality, falls, EQ-5D, ADL, pain/discomfort, drug compliance</td>
<td>No effect on any outcomes except for HRQoL, which was better in IG at 12 months. No between-group difference in number of drugs. At 2 months, at least one recommendation implemented in 62%.</td>
</tr>
<tr>
<td><strong>Mahlknecht 2021</strong></td>
<td>Primary care. 43 FPs with patients aged ≥75 using ≥8 drugs.</td>
<td>1) Prescription review by three experts (internal medicine, clinical pharmacology, evidence-based medicine) presented as written advice on discontinuation sent to FP, or 2) usual care.</td>
<td>1. Hospitalization/death 2. Number of drugs, hospitalization, falls, mortality, HRQoL (EQ-5D + EQ-VAS), affective status, cognitive function</td>
<td>Reduction of falls in IG. No effect on any of the other outcomes. Implementation rate 24%. No between-group difference in drug changes or drug use.</td>
</tr>
<tr>
<td><strong>Lisby 2018 (135)</strong></td>
<td>Hospital. Non-elective patients admitted to an orthopedic ward. Age ≥65 using ≥4 drugs.</td>
<td>1) Drug review (clinical pharmacist collected information, talked to patient &amp; discussed with clinical pharmacologist) presented as written advice to attending physician, or 2) usual care.</td>
<td>1. Time to first unplanned contact with physician after discharge 2. Length of hospital stay, mortality, readmissions, ED visits, HRQoL</td>
<td>Effect on numbers and time to first ED visit in favor of IG, but also almost significant (p=0.05) difference disfavoring IG on primary outcome. No effect on other outcomes. Implementation rate 18%. No information on drug use at follow-up.</td>
</tr>
<tr>
<td><strong>Lisby 2010 (134)</strong></td>
<td>Hospital. Patients admitted to internal medicine ward. Age ≥70 using ≥1 drug.</td>
<td>1) Drug review (clinical pharmacist collected information, talked to patient &amp; discussed with clinical pharmacologist) presented as written advice to attending physician, or 2) usual care.</td>
<td>1. Length of hospital stay 2. Readmissions, ED visits, mortality, HRQoL (EQ-5D)</td>
<td>No effect on any outcomes. Implementation rate &lt;50%. No information on drug use at follow-up.</td>
</tr>
<tr>
<td><strong>Williams 2004 (139)</strong></td>
<td>Community. Age ≥65 using ≥5 drugs, ≥2 “problematic” drugs. Recruited by advertising etc.</td>
<td>1) Prescription review by pharmacist (MAI, DDIs) followed by interdisciplinary team drug review (physician, nurse, pharmacist); result discussed with patient and FP, but advice given directly to patient from the team, or 2) usual care.</td>
<td>1. Physical functioning (Timed Manual Performance Test, Physical Performance Test, Functional Reach Assessment) 2. Cognitive functioning (Wechsler/Randt) 3. Depression, anxiety, Rand 36-item Health Survey, symptom review</td>
<td>No effect on any outcomes. Mean reduction of -1.5 drugs in IG and -0.1 in CG. Withdrawal was advised for an average of 4.5 drugs, but patients were resistant (this applied to psychoactive drugs in particular, and the changes carried out were judged as “minor” by the authors).</td>
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</tr>
<tr>
<td><strong>Hospital. Age ≥65, no drug limit.</strong></td>
<td><strong>2644</strong></td>
<td><strong>1403</strong></td>
<td><strong>600</strong></td>
<td><strong>629</strong></td>
</tr>
<tr>
<td>1) Clinical drug review (pharmacist in collaboration with ward physician), 2) same as 1 + post discharge follow-up by phone, or 3) usual care.</td>
<td>1. Unplanned visits to hospital/ED 2. Drug-related admissions, visits with FP, mortality ++ Follow up at 12 months</td>
<td>1. Number of uncontrolled health problems 2. Number of drugs, DRPs Follow up at 6 months</td>
<td>1. Drug-related readmission 2. Mortality, all readmissions, other health care utilization Follow up at 30+180 days</td>
<td>1. HRQoL (EQ-5D-5L + EQ-VAS), number of health problems 2. Number of drugs, drug changes, severity of VAS scores, healthcare consumption Follow up at 3+6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Follow-up 6 months. Reduction in number of uncontrolled health problems in IG. 1676 suggestions to solve DRPs, 58% accepted.</td>
<td></td>
<td>Improved EQ-VAS and reduced number of health problems with impact on daily life in IG. No effect on EQ-5D-5L or total number of health problems. Mean 1.7 drugs added in IG and 1.4 in CG, mean 1.5 drugs stopped in IG and 1.0 in CG.</td>
</tr>
<tr>
<td>Reference</td>
<td>Setting</td>
<td>Population</td>
<td>Intervention</td>
<td>Outcomes</td>
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</tbody>
</table>
| Campins 2017       | Primary care. Age ≥70 using ≥8 drugs. | 503 1) Clinical drug review (good Palliative-Geriatric Practice algorithm + START) followed by discussion with FP, who agreed with patient on implementation, or 2) usual care. | 1. Drug appropriateness  
2. Hospital admissions, mortality, EQ-SD, adherence, primary care, and ED consultation rate ++  
Follow-up at 3+6+12 months | Significantly lower number of prescriptions + more dose adjustments, discontinuations, and substitutions in IG than CG. No effect on other outcomes. |
| Gustafsson 2017    | Hospital. Age ≥65 and cognitive impairment or dementia. | 429 1) Drug reconciliation, clinical drug review and participation in ward rounds, discussing advice with attending physician, or 2) usual care. | 1. Risk of drug-related readmission  
2. All-cause readmission  
Follow-up 180 days | ≥1 DRP in 66% patients, 82% of advice implemented. No effect in primary analyses, but reduced risk of drug-related readmissions in a subgroup without heart failure. |
| Van der Linden 2017 | Hospital. Patients admitted to acute geriatric wards. | 172 1) Clinical drug review including explicit criteria (RASP), recommendations reported actively to attending physicians, or 2) usual care. | 1. Composite of drug discontinuation + dose reductions at discharge  
2. PIMs, drug changes, delirium (in-hospital)  
3. Falls, ED visits, EQ-SD, mortality  
Follow-up at 3 months | 18% more drugs reduced in dose or discontinued in IG, and also more drugs started + reduction of PIMs. Improved HRQoL in IG. No effect on other outcomes. |
| Basger 2015        | Hospital. Age ≥65 using ≥5 drugs. | 183 1) Discharge medication counselling and clinical drug review, recommendations sent to FP, or 2) usual care. | 1. Change in drug appropriateness, HRQoL, number and causes of DRPs identified, implementation rates  
Follow-up at 3 months | No effect on any of the outcomes. FPs implemented 42% of advice. |
| Briggs 2015        | Emergency department. Age ≥70 using ≥5 drugs. | 1021 1) Clinical drug review by an experienced hospital pharmacist within the ED, or 2) usual care. | 1. Hospital admissions, length of stay, admission to an aged care facility, FP acceptance of advice  
Follow-up at 4 months | Fewer admissions in IG. No effect on other outcomes. FPs implemented 49% of advice. |
| Lenander 2014      | Primary care. Age ≥65 using ≥5 drugs. | 209 1) Patient-centered clinical drug review with advice to patients and (written) to FPs, or 2) usual care. | 1. DRPs, number of drugs  
2. Health care utilization, self-rated health (one question)  
Follow-up at 12 months | Significant decrease in DRPs and number of drugs in IG (-0.7) compared to CG (-0.1). No effect on health care utilization. Self-rated health in favor of IG. |
| Touchette 2012     | Ambulatory care. Age ≥65 using ≥6 drugs, at risk for DRPs. | 637 1) Pharmaceutical care including clinical drug review with 2-page clinical synopsis of patient’s medical history, lab values and current medication regimen, issues resolved through patient education and written advice to FPs, 2) same as 1 but without clinical information, or 3) usual care. | 1. Potential ADEs  
2. Health care utilization (visits at ED, hospital, FP), best possible medication history obtained from patients  
Follow-up at 3+6 months | No difference in potential ADEs or health care utilization. DRPs declined in both intervention groups over time. Fewer drug discrepancies in IG 1.55% of advice implemented. |
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Characteristics</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bryant 2011</td>
<td>Community pharmacies</td>
<td>Age ≥ 65 using ≥ 5 drugs.</td>
<td>1) Clinical drug review discussed with FP, follow-up by pharmacist at 3, 6 and 12 months, or 2) usual care.</td>
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<td></td>
<td></td>
<td></td>
<td>1. HRQoL (SF-36), MAI</td>
<td>Improved MAI but no effect on HRQoL. 46% of recommendations were implemented. Significantly more drug changes in IG, but most were not advised by the pharmacists.</td>
</tr>
<tr>
<td>Hellström 2011</td>
<td>Hospital</td>
<td>Age ≥ 65 using ≥ 1 drug.</td>
<td>1) Drug reconciliation + prescription review, discussed with attending personnel, or 2) usual care.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1. Change in appropriateness (MAI) to discharge</td>
<td>Improved MAI scores and fewer drug-related readmissions in IG.</td>
</tr>
<tr>
<td>Gillespie 2009</td>
<td>Hospital</td>
<td>Age ≥ 80, no drug limit.</td>
<td>1) Drug reconciliation, clinical drug review discussing DRPs with attending physician, patient education, phone call after 2 months, or 2) usual care.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1. Hospital visits (total and drug-related)</td>
<td>No difference between groups in number of patients readmitted or total number of readmissions, but fewer drug-related readmissions and ED visits in IG.</td>
</tr>
<tr>
<td>Weber 2008</td>
<td>Primary care. Age ≥ 70 using ≥ 4 drugs, ≥ 1 psychoactive drug</td>
<td>1) Prescription review by pharmacist or geriatrician, electronic message with advice sent to FP, or 2) usual care.</td>
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<tr>
<td></td>
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<td></td>
<td>1. Number of falls</td>
<td>Trend of decreased use of psychoactive drugs in IG. Non-significant reduction of falls in IG.</td>
</tr>
<tr>
<td>Lenaghan 2007</td>
<td>Primary care. Age ≥ 80 using ≥ 4 drugs and ≥ 1 drug-related risk factor</td>
<td>1) Clinical drug review, patient education, advice discussed with FP, or 2) usual care.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1. Hospital admissions</td>
<td>Reduction in prescribed drugs in IG (-0.3) compared to CG (0.6). No difference on other outcomes.</td>
</tr>
<tr>
<td>Spinewine 2007</td>
<td>Hospital. Admitted to geriatric ward, age ≥ 70. No drug limit.</td>
<td>1) Pharmaceutical care (including drug review) in addition to usual geriatric care, or 2) usual geriatric care.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1. Prescription quality (MAI, Beers, ACOVE)</td>
<td>Significant improvement in prescription quality at discharge, no difference after 3 months. No effect on other outcomes.</td>
</tr>
<tr>
<td>Holland 2005</td>
<td>Primary care. Recently discharged from hospital, age ≥ 80 using ≥ 2 drugs.</td>
<td>1) Home-visit evaluating adherence, drug review reporting possible ADRs or interactions to FP; repeated after 6-8 weeks, or 2) usual care.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1. Readmissions</td>
<td>Increased number of readmissions in IG. No difference on other outcomes.</td>
</tr>
<tr>
<td>Graffen 2004</td>
<td>Community. Age ≥ 65 using ≥ 5 drugs.</td>
<td>1) Drug review, recommendations discussed with FP, or 2) usual care.</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1. HRQoL (SF-36)</td>
<td>Of 687 advices on drug changes, FP implemented 243. No effect on hospital admissions. Effect only on sub-items of SF-32 in IG.</td>
</tr>
<tr>
<td>Study</td>
<td>Setting</td>
<td>Sample Size</td>
<td>Intervention</td>
<td>Follow-up</td>
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<tr>
<td>Lim 2004</td>
<td>Geriatric outpatient clinic. Patients using ≥3 drugs.</td>
<td>126</td>
<td>1) Patient counselling, clinical drug review, recommendations discussed with FP, or 2) usual care.</td>
<td>Follow-up at 2 months</td>
</tr>
<tr>
<td>Sellors 2003</td>
<td>Primary care. 48 FPs with patients aged ≥65 using ≥5 drugs.</td>
<td>889</td>
<td>1) Clinical drug review with written recommendations sent to FPs, or 2) usual care.</td>
<td>Follow-up at 5 months</td>
</tr>
<tr>
<td>Zermansky 2001</td>
<td>Primary care. Age ≥65 using ≥1 drug.</td>
<td>1188</td>
<td>1) Clinical drug review with a pharmacist that either implemented changes or discussed with FP, or 2) usual care.</td>
<td>Follow-up at 12 months</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACOVE = Assessing Care of Vulnerable Elders. ADE = Adverse drug event. ADL = Activities of daily living. ADR = Adverse drug reaction. AOU = Assessment of Underutilization. CDSS = Clinical decision support system. CG = Control group. DDI = Drug-drug interaction. DRP = Drug related problem. ED = Emergency department. FP = Family physician. FORTA = Fit for the aged. HRQoL = Health-related quality of life. IG = Intervention group. MAI = Medication Appropriateness Index. PIM = Potentially inappropriate medication. START = Screening Tool to Alert doctors to the Right Treatment. STOPP = Screening Tool of Older Person’s Prescriptions.
1.3.2 Outcome measures in polypharmacy trials

Numerous trials aimed at optimizing drug treatment for older people have been carried out in various settings like hospitals, nursing homes, outpatient clinics and primary care. However, due to substantial differences both in study design, content of different interventions and choice of outcome measures, it has been difficult to draw conclusions on the most promising approaches (113, 115, 168).

Many trials have used drug-related surrogate outcomes like the number of drugs in use or the number of potentially inappropriate medications in use (169). We have seen that different variants of drug reviews, which is the most relevant type of intervention for this thesis, have been found to improve such measures, but this does not necessarily mean that the patients have really benefited from the intervention (77, 114, 131). Patient-related outcomes beyond hospital admissions and mortality have to a very limited degree been included in previous trials (113, 118, 130, 131).

To overcome the challenge of heterogeneous outcomes, and to ensure that elements perceived as important for older patients themselves are measured, two core outcome sets (COS) for polypharmacy trials have been developed. Beuscart et al developed a COS for drug reviews in multimorbid older patients with polypharmacy (20), while Rankin et al focused at trials that aimed at improving the appropriateness of polypharmacy in older people in primary care (170). The development of both core outcome sets involved Delphi surveys where researchers, health care professionals and older people were represented, and all previously used outcomes in relevant trials were identified through systematic searches. Beuscart et al also performed a qualitative study with older people and their caregivers to potentially identify new outcomes perceived as important for the patients. There was a clear consensus on including HRQoL in the COS, while frequently used outcomes related to all-cause healthcare use and mortality were considered not to be essential. Rankin et al list as many as 16 outcomes; the seven highest-ranking being serious ADRs, medication appropriateness, falls, medication regimen complexity, HRQoL, mortality and medication side effects. Table 5 present the included outcomes in both core outcome sets.
Table 5. Two core outcome sets for polypharmacy trials

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Beuscart et al, 2018</th>
<th>Rankin et al, 2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive functioning</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>●</td>
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<tr>
<td>Pain relief</td>
<td>●</td>
<td></td>
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<tr>
<td>Patient perception of treatment burden</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Falls</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Serious adverse drug reactions</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>All cause hospital admissions</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Drug-related hospital admissions</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Patients’ knowledge</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Drug-related outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication adherence</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Medication appropriateness</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Clinically significant drug interactions</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Number of drugs prescribed</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Medication overuse</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Medication underuse</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Therapeutic duplication</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Medication regimen complexity</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Medication side effects</td>
<td>●</td>
<td></td>
</tr>
<tr>
<td>Prescribing errors</td>
<td>●</td>
<td></td>
</tr>
</tbody>
</table>

1.3.3 Pharmacogenetic interventions among older people

A recent systematic review by O'Shea et al (109) identified 12 studies evaluating different pharmacogenetic interventions in patients with multimorbidity or polypharmacy. Most of the studies involved medication management by pharmacists that resulted in advice being presented to the patients’ FP, and the genetic testing mainly involved CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5 and VKORC1. Due to heterogeneity in study design and variable quality of the included studies, the authors found limited evidence on the efficacy of pharmacogenetic interventions to improve clinical outcomes. However, a high proportion of genetic variations that could impact prescribing was observed, and a general finding was that physicians had a higher acceptance rate for advice on DRPs if the recommendation involved pharmacogenetics.

Only three of the included studies were RCTs, all considered to be at high risk of bias, and only one reported clinical outcomes. In this pilot study by Elliot et al (171), patients
with a mean age of 76, using or initiating treatment with drugs known to have drug-gene interactions, were randomized to pharmacist management either with or without pharmacogenetic profiling. The authors conclude that the intervention had a statistically significant positive effect on readmissions and number of ED visits after 60 days. No effect was observed on other clinical outcomes like pain, anxiety, depression, ADL functioning, or falls.

Two other reviews were published in 2021. Meaddough et al (172) explored the impact of pharmacogenetic testing on clinical outcomes in patients exposed to polypharmacy, while Inventor et al (173) examined the evidence specifically among older people. Both reviews conclude with potential clinical benefits, but also state that evidence is limited due to few high-quality studies.

1.3.4 Knowledge gaps
Since previous studies mostly have failed to find significant associations between drug review interventions and patient-related outcomes, and because the studies including patient-related outcomes to a large degree only have used outcomes related to health care utilization, there is a need of trials evaluating also other patient-related outcomes, as outlined in the two described core outcome sets for polypharmacy trials (113, 118, 130, 131).

Few studies include clinical evaluations by a physician, and many trials have utilized prescription reviews without directly involving the patient at all. Feedback after drug reviews have often been limited to written recommendations to attending physicians or FPs, and implementation rates of advice in these settings have often been suboptimal. The FP is responsible for repeat prescriptions and long lasting follow up of the patients, and thus have a large impact on their drug regimens. Based on previous studies, it seems important to involve physicians with medical responsibility more directly in the interventions to ensure relevant recommendations with a higher probability of being implemented. Especially little evidence has been found on the effect of collaborative approaches between geriatricians and primary health care physicians, and the relevance of pharmacogenetics has to a very little degree been studied in old, multimorbid patients.
2. RESEARCH AIMS

Based on the identified knowledge gaps, we wanted to design a RCT with an intervention where older, home-dwelling patients exposed to polypharmacy received a thorough review of their drug regimens, and to evaluate the intervention by use of patient-related outcome measures. To ensure comprehensive and clinically relevant drug reviews with a high probability of being implemented, we wanted the intervention to include clinical geriatric assessment as well as direct collaboration between the geriatrician and the patients’ FP.

The overall goal of the intervention was to individualize and optimize drug treatment across all drug classes. As pharmacogenetics has received much attention as a tool to achieve personalized drug treatment, but to a very little degree has been studied in older, multimorbid people, we also wanted to explore the relevance of pharmacogenetic variations among the participants.

The specific aims of each paper were:

I. To investigate whether clinical geriatric assessments and collaborative drug reviews carried out by a geriatrician in cooperation with the patient’s FP could have positive effects on HRQoL and other patient-relevant outcomes in home-dwelling older patients receiving polypharmacy (Paper I and II)

II. To examine potential associations between baseline patient characteristics as well as drug changes following the intervention and change in HRQoL at follow-up (Paper III)

III. To examine the prescribed dosages of CYP2D6 substrates in relation to genotype in the participants and to assess the impact of CYP2D6 genotype on blood pressure and heart rate (Paper IV)
3. MATERIAL AND METHODS

*Paper III and IV are based on data collected as part of the RCT. Chapter 3.1 will first describe material and methods for the RCT, while chapter 3.2 and 3.3 focus on relevant details that apply to paper III and IV, respectively.*

3.1 Paper I-II

We carried out a cluster randomized, single-blind, controlled trial with follow-up after 16 and 24 weeks. The inclusion period ranged from March 2015 to March 2017.

3.1.1 Participants

Assuming that cooperation with primary health care physicians is of great importance when the goal is to optimize drug treatment for home-dwelling people, we wanted to involve FPs to participate in collaborative drug reviews for their older patients. We used a cluster randomized design where the inclusion process started out with recruitment of FPs, followed by identification of suitable patients from their lists. We also established contact with the local home nursing service in order to cooperate both in the process of recruiting patients and assessing some of the outcomes.

Recruitment of FPs

FPs from the counties of Akershus and Oslo, Norway, were eligible to participate with patients from their lists. The study physician (RR) attended either common FP meetings within each municipality or meetings at individual FP offices to inform about the study and recruit physicians. If such meetings were not possible, the FPs received written information about the study, followed by a phone call to clarify if they were interested. We did not have the capacity to enroll all FPs in the selected areas, and FPs within a reasonable driving distance were prioritized. The Norwegian Directorate of Health was requested to approve participation in the study as an educational activity, and the FPs earned two educational credits per patient included and followed through the study.

Patient inclusion and exclusion criteria

We expected that our intervention would be of most potential benefit for the oldest patients with the most pronounced polypharmacy and chose the inclusion and exclusion criteria listed in Table 6.
Table 6. Patient inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Listed with one of the participating FPs</td>
<td>Expected to become permanently institutionalized within six months</td>
</tr>
<tr>
<td>Home-dwelling</td>
<td>Life expectancy judged to be six months or less</td>
</tr>
<tr>
<td>Medications administered by the home nursing service</td>
<td>Moderate/severe dementia (i.e., Clinical Dementia Rating scale score &gt; 1) and contact</td>
</tr>
<tr>
<td>Age 70 years or more</td>
<td>with the closest proxy less than once every second week</td>
</tr>
<tr>
<td>Use of at least seven different systemic medications</td>
<td>Not speaking or understanding Norwegian</td>
</tr>
<tr>
<td>Use of at least seven different systemic medications</td>
<td>The FP does not want the patient to participate</td>
</tr>
<tr>
<td>Use of at least seven different systemic medications</td>
<td>(in case of important reasons not covered by the other exclusion criteria)</td>
</tr>
<tr>
<td>taken regularly (preparations for inhalation, vitamin</td>
<td></td>
</tr>
<tr>
<td>supplements and laxatives are included, but not topical</td>
<td></td>
</tr>
<tr>
<td>drugs like eye drops and ointments)</td>
<td></td>
</tr>
<tr>
<td>Signed informed consent given by the patient or his/her</td>
<td></td>
</tr>
<tr>
<td>closest proxy</td>
<td></td>
</tr>
</tbody>
</table>

**Screening and recruitment of patients**

Most home-dwelling patients with medications administered by the home nursing service have their medications prepared by multidose packaging systems. Drug lists for patients listed with participating FPs were obtained from the pharmacy delivering MDDs and screened, either by the home nursing service or by FP office staff, to identify patients fulfilling the inclusion criteria. Drug lists for patients with manually dispensed drugs were screened by the home nursing service. Eligibility was considered by the FP, based on the exclusion criteria. Patients eligible for participation were contacted by the home nursing service or the FP’s office, explaining the study, and asking whether the researchers might contact them. If this was accepted, the patients received a home visit from the research assistant, who gave supplementary information and obtained an informed consent if the patient wanted to participate.

**3.1.2 Trial procedures**

**Randomization and blinding**

Cluster randomization at the physician level was performed to avoid between-group contamination. To avoid large variations in cluster sizes, each FP participated with a maximum of five patients, and stratification was performed based on the number of contributing patients (1-2 versus 3-5). Randomization was computer-generated and carried out in blocks of unknown and variable size. A statistician not otherwise involved in trial procedures (ES) prepared the allocation sequence. The research assistant, who provided all assessments, was blinded with respect to allocation.
**Intervention**

Our intervention consisted of three main parts: clinical geriatric assessment of the patients combined with a thorough review of their medications; a targeted meeting between the geriatrician and the FPs; and clinical follow-up.

**Geriatric assessment and drug review**

As soon as possible after randomization, the patients received a home visit by a physician trained in geriatric medicine (RR), supervised by a senior consultant (TBW). In advance, the geriatrician obtained necessary information on the patient’s medical history and actual medication from hospital records, the FP’s electronic patient record, the home nursing service, and other relevant sources. The geriatrician carried out a medical history and a physical examination, both with focus on conditions most relevant for the patient’s total medication use. Relevant blood analyses and other supplementary tests were ordered if not already available. The geriatric work-up was aimed at evaluating whether current medications were indicated, whether the relevant conditions were satisfactorily compensated, whether the dosages were appropriate, whether the patient had symptoms of adverse drug reactions, and whether drug-drug interactions or drug-disease interactions were present or likely to occur. For more details on the clinical assessments, see eFigure 1 and 2 in the Supplementary content of Paper II.

**Meeting between the geriatrician and FP**

The main purpose of this meeting was to combine the competence and knowledge of the geriatrician with that of the FP. The geriatrician summarized the findings from the geriatric assessment and drug review, and the two physicians discussed the patient’s drug list systematically. The geriatrician could suggest changes in the drug regimen, but the FP retained the medical responsibility for the patient and was in charge of all medication changes. Approximately 15 minutes were spent discussing each patient.

**Clinical follow-up**

Depending on medication changes that had been done, the two physicians arranged the necessary follow-up within the project period. The follow-up could consist of a clinical evaluation, further drug adjustments, blood tests etc., and could be carried out by the FP, the geriatrician or through telephone contact with the patient, the relative or the home nursing service, depending on the circumstances.
Control group
The control group received usual care from their FP, who was offered our assistance in performing drug reviews after the study period was completed.

Data collection
Background information on diagnoses and comorbidity were obtained from the FP’s electronic patient records. The patients received three home visits from the research assistant: at baseline, 16 and 24 weeks (+2 weeks). All assessments directly involving the patient were performed at these visits. Proxy information was collected through phone calls and/or questionnaires sent by mail if the proxy was not present at the research assistant’s home visit.

3.1.3 Baseline characteristics and outcome measures
Baseline characteristics
Demographics, diagnoses and background variables regarding cognitive functioning, comorbidities and nutritional status were assessed at baseline, as listed in Table 7. The pharmacogenetic tests were used as part of the drug review in the intervention group but analyzed retrospectively in the control group.

Table 7. Baseline assessments

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics, diagnoses</td>
<td>Obtained from interview with patient/proxy and electronic patient record.</td>
</tr>
<tr>
<td>Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE-SF)</td>
<td>Proxy-based scale developed to identify cognitive decline, assessing change in cognitive function over a period of 10 years (174). Consist of 16 items rated from 1 to 5, where a mean score is calculated from the sub items. Higher scores indicate more cognitive impairment.</td>
</tr>
<tr>
<td>Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB)</td>
<td>Proxy-based scale developed to assess the severity of dementia (175, 176). The scale consists of six items which are rated from 0 to 3, adding up to a sum score (“sum of boxes”) ranging from 0 to 18. Higher scores indicate more cognitive impairment.</td>
</tr>
<tr>
<td>Cumulative Illness Rating Scale (CIRS)</td>
<td>Developed to assess the degree of comorbidity (177). The scale assesses 14 organ systems, rating comorbidity in each on a scale ranging from 0 to 4, adding up to a sum score ranging from 0 to 56. Higher scores indicate more severe comorbidity.</td>
</tr>
<tr>
<td>Mini Nutritional Assessment Short Form (MNA-SF)</td>
<td>Screening tool developed to assess nutritional status (178, 179). The scale consists of six questions concerning different aspects relevant for the risk of malnutrition, adding up to a sum score ranging from 0 to 14. Higher scores indicate better nutritional status.</td>
</tr>
<tr>
<td>Pharmacogenetic tests</td>
<td>CYP2C19, CYP2C9 and CYP2D6 analyzed for all patients.</td>
</tr>
</tbody>
</table>
Primary outcome measure

With an aim of improving drug treatment across a broad spectrum of drug classes within a heterogeneous group of patients, the challenge was to find a primary outcome measure with a potential of capturing this diversity. We chose HRQoL, hypothesizing that most improvements in the drug treatment of older patients, such as better pain relief, better symptom control in heart failure, less iatrogenic dehydration or less sedation, could have the potential to improve HRQoL.

15D is a generic, 15-dimensional instrument concerning different aspects of HRQoL that has been used in similar geriatric interventions (180, 181). The dimensions are mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity. Each dimension is rated on an ordinal scale with five levels, and the respondent chooses the level best describing his/her present health status. Single index scores are calculated by population-based utility weights, and range from 0 to 1, with higher scores indicating better HRQoL (182). A change in single index score of ± 0.015 or more is considered clinically important, and a change of more than 0.035 in the positive direction represents “much better HRQoL” (183). The questionnaire can be found attached in the Appendix.

Because the included patients were old and often not familiar with self-administration of questionnaires, 15D was administered by interview. Usually, the questionnaire is filled in by the individual whom it concerns, but it can also be answered by proxy raters. If the patient had moderate or severe dementia (i.e., CDR-SOB > 1), or the research assistant considered that they did not understand the questions, the interview was carried out with the closest proxy. To ensure that the proxy had updated knowledge on the patient’s state of health, these ratings were only used if the patient and the proxy had regular contact (at least once every second week). To account for patients that might lose their ability to respond to 15D during the follow-up period, the questionnaire was administered to the closest proxy for all patients. The same source (patient or proxy) for the 15D score was used at all assessment points for each patient.
**Secondary outcome measures**

Secondary outcome measures are listed in Table 8 and further explained in the following text. All assessments were performed by the research assistant if not otherwise stated.

**Table 8. Secondary outcome measures with timetable**

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Baseline</th>
<th>16 weeks</th>
<th>24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Physical Performance Battery</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Gait speed</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Grip strength</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span forward and backward</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Trail making test A + B</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Five Digits Test</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>Assessments of drug use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current drug use and changes in pharmacotherapy</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Medication Appropriateness Index</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Assessment of Underutilization</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td><strong>Other assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Falls</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Orthostatic blood pressure</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Relative Stress Scale</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Functional Independence Measure</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Number of days in own home</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Admission to permanent institutional care</td>
<td></td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Use of home nursing service (hours per week)</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>

To explore the possible effects of the intervention on various aspects of older peoples’ health and functioning, several secondary outcomes were included. The tests assessing physical functioning were generally chosen because they were feasible to perform in a home environment, have a low ceiling effect and good sensitivity to change, and because we assumed that most of the participants would be able to complete them. As for cognitive functioning, we presumed that attention, processing speed and executive functioning were most likely to be influenced by changes in drug regimens, as these functions are easily affected by for example sedation or general fatigue.

**Short Physical Performance Battery (SPPB):** Developed to assess physical function by measuring standing balance, gait speed and ability to rise from a chair (184). Sum scores range from 0 to 12, with higher scores indicating better physical performance.
**Gait speed:** Assessed by using a 4-meter-long track, starting from a still, standing position, with the possibility of walking a few meters after completion (185, 186).

**Grip strength:** Assessed using a Kern MAP 80K1 dynamometer, with three attempts on each hand. The patients were positioned on a chair with a 90-degree angle in knees and elbows, the arm close to the truncus, and a neutral position of the wrist. They were not allowed to support neither hands nor arms. The highest value of all six attempts was used in the analyses, measured in kilograms (187, 188).

**Digit span:** Developed to assess different aspects of working memory (189). Forward digit span assesses in particular attention, passive storage and retrieval, while backward digit span assess storage, active procession and retrieval and is more dependent on working memory. Results were reported as the maximum digit span completed.

**Trail Making Test A and B:** Developed to assess processing speed, attention and executive function, and measured by the number of seconds used to complete the tests (190).

**Five Digits Test (FDT):** Developed to assess mental processing speed and the ability to direct and switch attentional control (191). FDT consists of four conditions: reading, counting, inhibiting, and shifting. For all conditions, the time spent on completing the test and the number of uncorrected mistakes were registered. Because of the large number of secondary outcomes, we chose to focus solely on time when reporting the results.

**Drug use and changes in pharmacotherapy:** Updated drug lists were obtained at all assessment points. The research assistant checked if drugs were taken as prescribed by asking the patient and the home nursing service if there had been any discrepancies. Multi-dose packages were also inspected to see if their content matched the drug lists. Nonprescription drugs and pro re nata (PRN) drugs taken regularly were counted as “regular drugs”, but PRN drugs taken only occasionally were not. Drugs were registered according to the Anatomical Therapeutic Chemical (ATC) classification system (192).

**Medication Appropriateness Index (MAI):** Developed to assess drug therapy appropriateness (79). Each drug in use was evaluated by ten criteria concerning the drugs’ appropriateness and, by the application of weights, given a summated MAI score per
drug ranging from 0 to 18 (193). Weighted MAI scores per patient were calculated by summat ing scores for each drug in use, where higher scores represent less appropriate drug use. The MAI was assessed by a clinical pharmacist blinded for group allocation. Assessments were based on anonymized patient summaries, including information from the FP’s electronic patient record on important events during follow-up.

Assessment of Underutilization of Drugs (AOU): Developed to assess underprescribing (80). Scores represent the number of omissions of drugs that should have been prescribed. Assessments were done by a clinical pharmacist as described for the MAI.

Falls: Registered in calendars handed out to patients or caregivers. The number of falls was assessed at each follow-up visit.

Orthostatic blood pressure: Blood pressure was assessed using a validated, automated blood pressure monitor (UA-767 Plus 30, A&D Medical, San Jose, CA, USA). An appropriate cuff size was ensured for each patient. Supine blood pressure and pulse rate were measured twice, after a minimum of five minutes of rest, and the mean value was used for the analyses. The patient then stood up, and measurements were repeated after one minute. Orthostatic hypotension was defined as a fall in SBP of at least 20 mmHg or a fall in DBP of at least 10 mmHg after 1 minute in standing position.

Weight: Measured using the same, portable weight machine for all assessments.

Relative stress scale (RSS): Developed to evaluate the degree of carer burden, and assessed by interview of the closest relative (194). Sum scores range from 0 to 60, with higher scores representing a higher burden of care.

Functional Independence Measure (FIM): Developed to assess physical and cognitive disability (195). The scale consists of 18 items that are rated from 1 to 7 based on the level of assistance required to perform activities of daily living. Thirteen of the items are physical domains based on the Barthel Index, and five are cognition items. Sum scores range from 18 to 126, with higher scores indicating more independence.

Hospital admissions and admissions to permanent institutional care: The research assistant asked the patients, their closest proxy, and the home nursing service about
admissions to hospital, nursing home or other institutions. The FP’s electronic patient record for the follow-up period was also checked for notes on hospital admissions.

**Use of home nursing service:** Information on the current use of home nursing service was given by the home nursing service at each follow-up visit.

**Mortality:** Information on mortality was provided by the FP or home nursing service, verified by assessing the Norwegian National Population Register.

### 3.1.4 Statistics

A statistical analysis plan was published online (http://tbwyller.no/COOP_SAP.pdf) before analyses were initiated, and analyses of the primary outcome were performed by a senior statistician (ES) blinded to group allocation. All analyses were performed with SPSS, version 25.0.0.1 (IBM) or Stata, version 15 (StataCorp).

We planned to include a total of 200 patients, with 100 in each randomization group. This was expected to give > 80% power to detect a difference of 0.035 in 15D score after 16 weeks, at a two-sided significance level of 5%.

The primary analysis was done as a modified intention-to-treat analysis, as outcome data were missing for a few patients. We used an analysis of covariance (ANCOVA) model, with 15D score at 16 weeks as the dependent variable, randomization group as the fixed factor, and cluster size and baseline 15D score as covariates. A clustered sandwich estimator of the standard error with FP as the cluster was applied. Missing data were imputed by multiple imputation.

Secondary analyses included adjustment for covariates that in beforehand were expected to be prognostic of the outcome, i.e., age, sex, CIRS, CDR-SOB and the use of home nursing service. If their introduction to the model changed the effect estimate for the randomization variable with ≥ 10%, they were introduced in a final model including all variables with an effect of this size. We also carried out a linear mixed model analysis, adjusting for cluster size, applying an unstructured covariance matrix, and using a clustered sandwich estimator to estimate standard errors (SE). Multiple additional sensitivity analyses were also performed.
Responder analyses classified all patients with an improvement of at least 0.015 in 15D score as responders. These analyses were performed by logistic regression, adjusted for cluster size and covariates as described above, using the clustered sandwich estimator to estimate SE.

Secondary outcomes with repeated measurements were analyzed by linear mixed model as described above, while outcomes measured only once were analyzed by multiple linear regression or logistic regression, as appropriate.

More details on power calculations, imputation procedures and the various statistical analyses can be found in the Supplementary content of Paper II.
3.2 Paper III

Since our intervention was extensive and time-consuming we wanted to explore if it was possible to identify predictors for having a positive effect, as this could potentially be helpful in tailoring future drug reviews towards the patients most likely to benefit, as well as provide guidance on which drugs to prioritize for optimization.

In this post hoc analysis, we therefore investigated if any baseline patient characteristics or specific drug changes following the intervention were associated with change in HRQoL at follow-up.

3.2.1 Participants

All patients from the RCT completing follow-up at week 16 were included in the analysis examining baseline characteristics. The analysis exploring drug changes during the intervention and follow-up period was restricted to the intervention group.

3.2.2 Included variables and outcome measures

The included baseline variables were age, sex, CIRS, MNA-SF, CDR-SOB, FIM, MAI, AOU, SPPB, gait speed, grip strength, Digit Span Forward and Backward, Trail Making Test A, use of home nursing service, orthostatic hypotension, and drug use. Drug changes during intervention and follow-up were assessed by examining the total number of drug changes, number of withdrawals/reduced dosages, number of new drugs/increased dosages, any change in prescription quality as assessed by change in MAI score, and drug changes within the different ATC groups. The outcome measure was HRQoL as assessed by 15D. We also included a case from the intervention group to illustrate the complexity of the evaluations that were carried out.

3.2.3 Statistics

Associations between baseline characteristics and change in 15D score were explored by interaction analysis. Results were reported as means with standard deviations and an interaction \( p \) value indicating whether the difference between the intervention and the control group depended on the interaction variable. The explanatory variables were dichotomized. When possible, sensitivity analyses with continuous scale-values were also performed. For events during intervention and follow-up, we used linear regression
with change in 15D from baseline to week 16 as dependent variable. Results were reported as unstandardized coefficients (B), their 95% confidence intervals (CIs) and a p value. B represents the predicted difference in 15D change per increased unit in the explanatory variable, where a positive value denotes improved HRQoL. Analyses were performed using SPSS, version 26 (IBM).
3.3 Paper IV

This post hoc analysis was in part motivated by our experiences with pharmacogenetic testing during the intervention. We had an impression that especially among patients using metoprolol, which is a drug extensively metabolized by CYP2D6, many were found to have CYP2D6-metabolizer phenotypes indicating reduced or absent metabolism. Some of these patients were still prescribed high dosages of metoprolol, and we were curious to see if this might be associated with an increased risk of adverse effects.

Pharmacogenetic testing is rarely used in clinical practice, and it may be argued that knowledge of genotype is of limited relevance, since physicians nevertheless will adjust dosages according to the clinical response. It is, however, uncertain if the underlying genotypes are actually reflected by the prescribed dosages when physicians are unaware of the patients’ ability to metabolize CYP2D6 substrate drugs.

In this cross-sectional study utilizing baseline data from the RCT, we therefore examined the prescribed dosages of CYP2D6 substrates in relation to genotype, and assessed the impact of CYP2D6 genotype on blood pressure and pulse rate.

3.3.1 Participants

All patients included in the RCT with available CYP2D6 genotype were included in the present study and categorized into CYP2D6 metabolizer subgroups based on genotype. Details on phenotype classification are found in Paper IV.

3.3.2 Included variables and outcome measures

In order to compare daily dosages across a variety of CYP2D6-metabolized drugs, prescribed dosages for all substrates were calculated as the percent of a daily defined dose (DDD). The average percent of DDD was calculated for each patient for comparisons between CYP2D6 metabolizer subgroups.

The analyses exploring impact of CYP2D6 genotype on hemodynamic variables assessed systolic and diastolic blood pressure, change in systolic blood pressure after one minute in standing position, pulse rate, and the presence of orthostatic hypotension and bradycardia.
3.3.3 Statistics

In the study population, only two ultrarapid metabolizers (UMs) used a CYP2D6 substrate, and this phenotype subgroup was therefore excluded from the analyses. The other patients were divided into two metabolizer subgroups for comparison, normal metabolizers (NMs) versus intermediate and poor metabolizers (IMs/PMs) merged into one group.

Since several non CYP2D6-drugs can affect blood pressure and pulse rate, the use of drugs from relevant ATC drug classes were assessed between the genotype subgroups (see Paper IV for details). We also registered co-administration of CYP2D6 inhibitors.

For non-normally distributed variables, the Mann-Whitney $U$ test was used to test for differences between the CYP2D6 metabolizer subgroups. For normally distributed variables, comparisons were performed using the independent samples $t$-test. Categorical variables were assessed by Pearson’s chi-square test or Fischer’s exact test, as appropriate. In the case of statistically significant findings by univariate analysis, multivariate logistic regression was performed to account for potential confounders.

All analyses were performed with SPSS, version 25.0.0.1 (IBM).
4. SUMMARY OF RESULTS

*Paper I is a study protocol and does not contain any results. The following sections summarize the results of paper II-IV.*

4.1 Paper II

**Effect of Clinical Geriatric Assessments and Collaborative Medication Reviews by Geriatrician and Family Physician for Improving Health-Related Quality of Life in Home-Dwelling Older Patients Receiving Polypharmacy: A Cluster Randomized Clinical Trial.**

174 patients (mean age 83 years, 68% women) in 70 clusters underwent randomization (87 intervention, 87 control), and 158 (90.8%) completed the trial. A flowchart of the participants in the study is embedded in Paper II.

Mean (SD) 15D score at baseline was 0.708 (0.121) in the intervention group and 0.714 (0.113) in the control group. At week 16, mean (SD) 15D score was 0.698 (0.164) in the intervention group and 0.655 (0.184) in the control group, with an estimated between-group difference of 0.045 (95% CI, 0.004 to 0.086; \( p = 0.033 \)). At week 24, the mean (SD) 15D score was 0.675 (0.186) in the intervention group and 0.620 (0.216) in the control group, with an estimated between-group difference of 0.052 (95% CI, -0.002 to 0.105; \( p = 0.06 \)). The development of 15D scores is illustrated in Figure 11.

![Figure 11](image-url). Mean 15D scores at baseline, week 16, and week 24 by randomization group. Reprinted with permission from JAMA Internal Medicine.
Secondary analyses adjusting for dementia severity, as well as the linear mixed model analyses, reached statistical significance both at week 16 and 24, and all additional sensitivity analyses gave similar results (see eTable 5 in the Supplementary content of Paper II). The proportion of responders was higher in the intervention group compared with the control group at week 16 (adjusted odds ratio, 3.32; 95% CI, 1.47 to 7.46; \( p=0.004 \)) and week 24 (adjusted odds ratio, 2.74; 95% CI, 1.13-6.65; \( p=0.03 \)).

Changes in gait speed, grip strength, Digit Span, Trail Making Test A and B, and FDT were in favor of the intervention group, although only grip strength at week 16, Digit Span Forward at week 24 and Trail Making Test A at week 16 reached statistical significance. Medication appropriateness (MAI and AOU) improved in the intervention group compared with the control group both at week 16 and 24. There were no statistically significant between-group differences regarding other secondary outcomes. Three patients died in the intervention group and seven in the control group (odds ratio (OR) 0.36; 95% CI 0.08 to 1.58).

As illustrated in Figure 12, the intervention group experienced more drug changes than the control group. From baseline to week 16, a mean of 2.7 drugs were withdrawn and 1.3 new drugs started for patients in the intervention group, while patients in the control group had a mean of 0.7 drug withdrawals and 0.6 new drugs started.

![Figure 12. Number of drug changes from baseline to week 16 by randomization group](image)
4.2 Paper III

Factors Associated with Health-Related Quality of Life after a Comprehensive Drug Review Intervention in Older People Exposed to Polypharmacy

Complete data sets were available for 163 patients, 84 in the intervention group and 79 in the control group.

Patients in the intervention group with a baseline MAI score ≥ 14 improved their 15D scores at week 16, while this was not seen for those with MAI scores < 14 or for the control group (interaction $p=0.04$). However, repeating the analysis with explanatory variables entered as continuous data, no statistically significant associations were found (interaction $p=0.7$).

Increased treatment intensity with paracetamol during follow-up was associated with a decline in 15D score from baseline to week 16 [$B \, -0.098 \, (95\% \, CI, \, -0.149 \, to \, -0.047; \, p<0.001)$], while deprescribing of opioids was associated with improved 15D score [$B \, 0.072 \, (95\% \, CI \, 0.018 \, to \, 0.126; \, p=0.01)$]. An increased treatment intensity with mineral supplements was also associated with improved 15D score [$B \, 0.059 \, (95\% \, CI, \, 0.005 \, to \, 0.112; \, p=0.03)$], while deprescribing of urological drugs was associated with reduced 15D score [$B \, -0.054 \, (95\% \, CI, \, -0.099 \, to \, -0.008; \, p=0.02)$].

Besides this, we found few associations. The article presents a case illustrating the complexity of the measures and the difficulty in identifying single characteristics predicting intervention response.
4.3 Paper IV  
Prescribed Doses of CYP2D6-Metabolized Drugs and Hemodynamic Responses in Relation to CYP2D6 Genotype Among Older Patients Exposed to Polypharmacy

CYP2D6 genotype was available for a total of 173 patients, and the genotype-predicted phenotype subgroups comprised 3 UMs (1.7%), 79 NMs (45.7%), 75 IMs (43.4%) and 16 PMs (9.2%).

The use of CYP2D6 inhibitors did not differ between metabolizer subgroups. Only weak CYP2D6 inhibitors were in use, and drug-drug-genotype interactions and phenoconversion were considered unlikely due to the limited inhibitory potency of these agents. The genotype-predicted CYP2D6-metabolizing phenotype was thus not adjusted for by any co-medications.

A total of 19 CYP2D6 substrates were in use, including three prodrugs, and metoprolol and tamsulosin were the two most frequently used CYP2D6 substrate drugs. The mean harmonized dosage of CYP2D6-metabolized drugs was 58% of DDD for NMs, 59% of DDD for IMs, and 63% of DDD for PMs. There was no statistically significant difference in drug dosages between NMs and IMs/PMs, neither for active CYP2D6 substrates (p=0.76) or for prodrugs (p=0.74).

As for the hemodynamic variables, there was no statistically significant difference between NMs and IMs/PMs in systolic blood pressure (p=0.79), diastolic blood pressure (p=0.58), or pulse rate (p=0.34). Systolic blood pressure dropped in all groups after one minute in standing position, but there was no statistically significant difference between groups (p=0.15).

Orthostatic hypotension was present in 24% of NMs, 44% of IMs and 50% of PMs. When comparing NMs and merged IMs/PMs, this difference was statistically significant (p=0.03). All patients with orthostatism used at least one non-CYP2D6 drug that could potentially increase the occurrence of orthostatism, but the mean number of such drugs did not differ between genotype subgroups. We also examined this by logistic regression and found that the difference between IMs/PMs and NMs was unaffected both by the number of such drugs and comorbidity (adjusted odds ratio 2.6; 95% CI 1.1-6.3; p=0.04).
5. DISCUSSION

5.1 Interpretation of main results

Our main finding was that clinical assessments and drug reviews carried out by a geriatrician in collaboration with the patients’ FPs resulted in positive effects on HRQoL. Mean 15D scores decreased in both groups, but at a slower pace in the intervention group, and the estimated between-group difference was well above the threshold of 0.035 which is considered to represent a substantial difference in HRQoL (183). The responder analyses indicated that a higher proportion of patients in the intervention group experienced clinically significant improvements in 15D scores compared with the control group. We therefore regard the results to be clinically relevant.

Medication appropriateness improved following the intervention, but there was virtually no change in the control group. Prescription tools were not an important feature of our study, but we considered it relevant to include a standardized measure on drug appropriateness for evaluation of the drug changes that were carried out. Thus, according to the clinical pharmacist that made these judgement-based assessments, our drug reviews resulted in improved pharmacotherapy.

Most secondary outcomes on physical and cognitive function were in favor of the intervention. Although not all reached statistical significance, this nevertheless indicate that optimization of older patients’ drug regimens can yield positive effects beyond the subjective experience of improved HRQoL. However, there were no statistically significant effects regarding ADL functioning, falls, hospital admissions, mortality, orthostatic blood pressure, carer burden, or use of formal care resources. For these outcomes, other aspects of the patient’s health and social situation might be of greater importance.

The patients with more inappropriate drug use at baseline seemed to benefit most from the intervention, but it was difficult to draw any certain conclusions on whether treatment adjustments within some drug classes were more important than others. The individualized approach of the intervention, targeting the complexity of each patient’s drug regimen, was most likely the main contributing reason for clinical response.
We also found that dosing of CYP2D6 substrates was not adjusted according to genotype predicted CYP2D6 metabolism, and that patients with reduced or absent CYP2D6 metabolism had significantly higher prevalence of orthostatic hypotension than those with normal metabolism. This could reflect a higher exposure of CYP2D6 substrates exhibiting hemodynamic effects (e.g. metoprolol, tamsulosin) in the former subgroup, and may indicate that individualized dose adjustments supported by pharmacogenetic tests have the potential to prevent ADEs in this vulnerable population.

5.2 Why was our intervention effective?

Geriatric interventions are often of a complex type, in part because older patients are highly heterogeneous, but also because the general focus in geriatric medicine is on multimorbidity and geriatric syndromes rather than single diseases (196). The degree of flexibility of the actual intervention is also relevant, as the standardization of complex interventions often is focused more on the underlying process and function of the intervention than on the exact components that are provided for each participant (197). Complex interventions can thus be challenging to reproduce and implement in real world conditions. Because of the pragmatic nature of our intervention, as well as the almost infinite combinations of health conditions, drugs and other factors possibly affecting patient outcomes, there is no simple answer to why our intervention turned out to be effective. The following text will, however, discuss this in relation to important components of the RCT.

5.2.1 Choice of intervention

A basic methodological choice was the design of the intervention, where clinical assessments of the patients by a geriatrician were combined with comprehensive drug reviews that took both previous medical history, present clinical situation as well as patient preferences into account.

As previously stated, most systematic reviews assessing drug reviews as an isolated intervention conclude that there is no evidence of an effect on patient-related outcomes, and when looking closer at the included studies in these reviews, there is a paucity of studies utilizing clinical assessments and drug reviews by a physician. In fact, the only
study identified that resembles ours is a RCT by Kornholt et al, published February 2022 (147). In that study, patients using ≥9 drugs that were referred to a geriatric outpatient clinic were randomized either to receive usual geriatric care or usual geriatric care and an additional consultation focusing on reviewing drugs, aligning treatment with the patient’s wishes, and ensuring cross-sectoral communication. The physician providing the additional consultation was a clinical pharmacologist, but the drug regimens were discussed both with the usual-care geriatrician as well as the patients’ FP. The clinical drug review consisted of a thorough examination of the patient’s drug regimen to assess risk/benefit profiles of all prescribed drugs, as well as assessing potential drug-drug interactions and inappropriate medications. A total of 408 patients were included, and at follow-up after 4 months there was a statistically significant between-group difference in HRQoL (EQ-5D-5L index score) and mortality rates in favor of the intervention group. There were more drug changes in the intervention group (1180) compared to the control group (456), mostly discontinuations, but also reduced dosages, new prescriptions, and increased dosages. This resulted in statistically significant reduced numbers of drugs in the intervention group (-2.0) compared to the control group (-0.6).

In our opinion, true optimization of complex drug regimens can only be achieved if the patient is involved in the evaluation, if clinical information is available, and if all drugs are thoroughly reviewed. Interventions that only use prescription tools are less likely to capture the complexity of multimorbid, geriatric patients, and thus less likely to provide health benefits (56). The knowledge of PIMs is important, but otherwise well indicated drugs can also lead to a negative health impact. A review examining drug-related hospital admissions in older people state that a focus on PIMs could make the rest of the medication list appear safe, while in fact other drugs also often cause ADRs (51), and the majority of DRPs identified during a drug review intervention was found not to be associated with explicit prescribing criteria (198). Steinman et al also conclude that drugs-to-avoid criteria have limited power to differentiate between patients with and without real prescribing problems (199).

Thus, the study by Kornholt et al and our RCT complement each other and indicate that positive clinical effects can be achieved from drug reviews, if the intervention is clinically oriented and sufficiently comprehensive.
Cooperation between health care systems

Another important part of our intervention was the involvement of FPs, and we believe that this collaboration improved the quality of the drug reviews that were carried out. While geriatricians are trained in the evaluation of complex health conditions and polypharmacy, they often have limited information about previous medical history and limited possibility to follow the patient over time, elements that are typical strengths in the follow-up by FPs. Geriatricians and FPs therefore have complementary strengths for managing complex drug regimens in frail elderly patients. Most of the participating FPs knew their patients well and contributed with important knowledge in the discussions on medication changes. The FPs were generally grateful to have the possibility to collaborate with a colleague about their patients, as many had limited experience in performing structured evaluations of such complex pharmacotherapy. Time constraints were also a frequent complaint, and the FPs reported that they often could not prioritize to be as thorough in their own drug evaluations as desired.

Although the geriatrician could suggest changes in the drug regimen, the FP retained the medical responsibility for the patient and was in charge of all drug adjustments. Thus, the collaboration between the two physicians was important to reach a common understanding, achieve implementation of medication changes, and to ensure relevant follow-up of the patients.

Kornholt et al also involved FPs directly in the discussions on drug treatment, while several other drug review interventions utilizing written recommendations sent to FPs and/or attending physicians experienced low implementation rates of their advice on drug adjustments (134-136). Systematic reviews confirm that written feedback on drug reviews in the absence of other forms of communication have limited effect (97), and a study directly comparing written recommendations and case-conferences concluded that case-conferences with FPs lead to significantly more drug changes (200).

We therefore believe that the close cooperation between the study physician and the patients’ FPs was an important reason for the positive result of the study.
5.2.2 Patient selection
We assumed that our intervention would be most relevant for the oldest and most frail patients, with relatively pronounced polypharmacy, and decided that only patients using seven or more drugs should be included. This is a somewhat higher cut-off than many other studies have used, while Kornholt et al narrowed the inclusion criteria even more and set the limit at ≥ 9 drugs. It has been shown that the risk of negative health effects of drug use increase with the number of drugs in use (27), but the choice of ≥ 7 drugs was, however, a pragmatic choice reflecting a compromise between including patients with a high probability of DRPs but at the same time ensuring steady patient flow. On average, the included patients used 10 different drugs each, and we believe that this pronounced polypharmacy increased the probability of positive effects of the intervention. It could be argued that patients using specific high-risk drugs would be even more likely to benefit from a drug review, but following the previous argumentation that non-PIM drugs might actually to a larger degree contribute to prescribing problems (198, 199), we decided not to include such limitations.

We did not use a clinical measure of frailty as an inclusion criteria but reasoned that by including only patients that had their drugs delivered by the home nursing service, we would approach the most frail population of older home-dwelling people, since well-functioning and healthy persons seldom receive home nursing service. Since frailty has been found to increase the risk of ADRs (50), a focus on performing drug reviews in these vulnerable patients can be assumed to be rational.

Our patients were clinically relatively stable, and the FPs rarely had any particular concern on their drug use in beforehand of the study. It is possible that our intervention could have been even more powerful in a population with for example subacute functional decline, or if we focused solely on patients where the FP had major concerns about their drug use. On the other hand, such patients could have more competing health conditions that could affect outcomes, thus making it less likely to achieve clinical improvement. It is, however, interesting to see that even in our participants, where the FPs in general were not very concerned about their drug regimens, numerous drug adjustments leading to positive effects on patient-related outcomes were still possible to implement.
Since the intervention was extensive and time-consuming, we were curious to see if any subgroups of patients were more likely to achieve improvement in HRQoL than others, as this could help tailoring similar drug reviews towards the patients most likely to benefit. Paper III therefore explored baseline characteristics of the included patients, but we found no such associations neither with age, sex, comorbidity, nutritional status, ADL functioning, dementia, physical functioning, nor total number of drugs in use. This might indicate that within this already selected group of patients, all had an equal potential of improvements in HRQoL. However, it must be noted that our sample size was limited, and the power to detect weak associations was low.

The results suggested that the patients with most inappropriate drug use at baseline had best effect of the intervention. This seems reasonable, as more inappropriate drug use, as evaluated by judgement-based implicit criteria, could be expected to give more ADRs and thus more potential benefit of a drug optimization intervention. However, our measure of inappropriateness (MAI) was based on a thorough evaluation of drug regimens in relation to clinical information and is probably too extensive to be used as a screening tool to identify patients prioritized for drug reviews.

5.2.3 Implemented drug changes
We have not reported the acceptance rate of recommended drug changes following the intervention. The main reason for this is that many of the recommendations were dependent on the patients’ clinical development after one (or a few) initial drug changes, thus making it difficult to perform consistent calculations on what was really recommended. For example, if a patient using three medications with antihypertensive indication was found to be hypotensive, we often suggested to first withdraw one of the medications. The FP should then monitor the effect on blood pressure levels and continue withdrawal of one drug at a time until acceptable measurements were achieved.

Although not formally investigated, we have an impression that some of the FPs did not pursue such stepwise procedures sufficiently. This could of course be because the FP was satisfied with the achieved change, or because the recommendations were considered irrelevant, but it could also be due to time constraints and that further drug adjustments simply were not prioritized. Most follow-up after the initial collaborative drug review was performed by the FPs, but the geriatrician revisited three patients that
were especially complex and in need of repeated, comprehensive assessments while drug adjustments were carried out. An additional follow-up by the geriatrician in all patients could have been useful and potentially improved outcomes, but this was not feasible within the limits of the trial.

From baseline to week 16, the intervention group experienced significantly more drug changes than the control group. The intervention group had on average 2.7 drug withdrawals, 1.0 dose reductions and 1.3 new drugs started, while the control group had an average of 0.7 drug withdrawals, 0.2 dose reductions and 0.6 new drugs started. As described in Paper II, most changes were from four ATC groups: The cardiovascular system (ATC group C); alimentary tract and metabolism (ATC group A); nervous system (ATC group N); and blood and blood-forming organs (ATC group B). Many previous drug review trials have achieved only minor drug changes or have failed to report details on the actual drug changes that were carried out, but an intervention where many drug adjustments are implemented is more likely to affect clinical outcomes.

The net effect of the implemented drug changes was reduced treatment intensity, which reflects the previous discussed problem with overprescribing in older people. Many drugs lacked a clear indication, and it was frequently discovered that symptomatic drug therapies had never been reconsidered in terms of efficacy. For many of the patients, preventive drug therapies for various conditions were also found not to be indicated, or no longer relevant. However, it is important to highlight that the intervention also led to many new prescriptions, including both symptomatic and preventive drug therapies. Our goal was not deprescribing per se, even if that approach can be of high value. Optimized pharmacotherapy will sometimes involve initiation of new drugs, even in the context of polypharmacy, and we believe that individualized drug reviews should take this into account. The improvements in MAI scores for the intervention group reflects relevant drug withdrawals and dose adjustments, but the improvements in AOU indicate that underprescribing was indeed also addressed.

In Paper III, we tried to disentangle if specific drug changes in the intervention group were associated with change in HRQoL. We found some associations, for example between increased treatment intensity with non-opioid analgesics (e.g. paracetamol) and reduced HRQoL, as well as improved HRQoL associated with deprescribing of opioids. These finding could be explained by ADRs of paracetamol and opioids. Another
explanation could be “confounding by indication”, e.g. that the patients prescribed paracetamol experienced advancing disease or new health events leading to a need for analgesia, but at the same time resulting in reduced HRQoL. For the opioid users, pain could have resolved independently of drug use, and this could be the reason both for improved HRQoL and withdrawal of opioids. In addition, we found an association between reduced HRQoL and deprescribing of urological drugs that may indicate a worsening of urological symptoms exceeding any benefit of reduced ADRs of these drugs, as well as an association between increased treatment intensity with minerals and improved HRQoL that might reflect that these patients had symptomatic low levels of e.g. magnesium or potassium.

However, the most striking result in Paper III was the lack of associations, and because we carried out multiple significance tests implying a considerable risk of type 1 errors, the reported associations must be interpreted with caution. The patients came with numerous combinations of health conditions and medications, and many were subject to simultaneous drug adjustments in different drug categories. This complexity is difficult to disentangle with statistical methods, as illustrated in Paper III by a case from the intervention group. Thus, again: We believe that an individualized approach to each patient, with a careful and critical evaluation of all drugs, is the key to truly improved drug therapy for older people.

5.2.4 Choice of primary outcome measure
Since surrogate outcomes do not necessarily translate into real benefit for the patient, it was important for us to include patient-related outcome measures. Many previous drug optimization interventions have focused on health care use and mortality (20), but systematic reviews have not found evidence of positive effects on these outcomes (114). It has been proposed that drug review interventions are not powerful enough to give an effect, as older people have many competing risks of being admitted to hospital and to die (131). In our study, the intervention group experienced more hospital admissions than the control group, although the difference was not statistically significant. By first look, this could be regarded as solely negative, but because our intervention included thorough clinical examinations, some patients were referred to hospital due to serious health conditions discovered through the geriatric work up. Thus, some of the admissions were actually a positive consequence of the intervention. To rely on the use
of health care resources as the primary outcome measure may therefore not be the most relevant choice (201). As for mortality, three patients died in the intervention group and seven in the control group in our study, but these between-group differences were not statistically significant. Many studies, including ours, are not adequately powered to detect differences in mortality.

To capture patient-relevant changes following various drug adjustments, we initially discussed to use a composite primary outcome combining measures of physical and cognitive functioning. However, there is broad evidence of an association between various chronic health conditions and Patient Rated Outcome Measures (PROMs) like HRQoL, and such measures can thus serve as a common metric for evaluating the influence of multiple health conditions and their treatment (202). We therefore ended up with choosing HRQoL as our primary outcome measure, hypothesizing that most improvements in the total drug regimen of older patients have the potential to improve HRQoL. The 15D instrument is internationally less well-known than other assessment tools for evaluating HRQoL, like for example EQ-5D or SF-36. In our opinion, 15D assesses more dimensions that we experience as important for the wellbeing of older people, and we believe that several of the 15 dimensions can be associated with common ADRs, or clinical effects caused by suboptimal drug treatment. Before initiating the study, we piloted the instrument and found it to be responsive to change in symptom burden following drug adjustments.

The 15D instrument was originally validated in a large Finnish population, and a set of utility weights elicited from this population is used in an additive aggregation formula to generate the 15D score (203). It can be argued that the use of a Finnish valuation algorithm was suboptimal to use in a Norwegian population. Norwegian utility weights were under development when we initiated the study, but this work was completed too late for us to implement (204). However, this is a general problem of such instruments, as samples can show great variations depending on for example socioeconomical, demographic or cultural characteristics of the participants, leading to within-country variations that can be even larger than between-country variations (205). As Finland is a Scandinavian country in many aspects quite similar to Norway, we believe that the use of Finnish valuation algorithms was adequate. The fact that we studied older patients exposed to polypharmacy, while the utility weights were developed in a younger
population, might be of greater concern. The valuation algorithms are based on healthy peoples’ beliefs and valuations of hypothetical health conditions, which may not be valid for the patients’ that actually live with these conditions (206). However, as also the two before-mentioned core outcome sets on polypharmacy trials recommend the use of HRQoL in such trials, we believe that our choice of 15D was adequate.

Proxy rating of the 15D questionnaire is generally accepted as valid (203) and has been successfully used in previous studies (207). We emphasized for the proxy raters that we expected them to score the instrument as they thought the patients themselves would have done. We cannot, however, rule out a possible bias when using proxy raters. A recent study indicates that proxy ratings on different measures of HRQoL consistently differ from ratings given by patients (208). However, our primary outcome is the development of HRQoL over time, and the same source for the 15D score was used at all assessment points. This can be expected to reduce the impact of a potential bias in the proxy scores. Only 13 of the 15D questionnaires were filled in by proxy raters in the intervention group, and 6 in the control group.

5.3 Other methodological considerations

5.3.1 Secondary outcome measures

Physical functioning
We were in general satisfied with our choice of assessments on physical function, but the participants’ baseline scores on SPPB were lower than anticipated, which could have led to a floor effect. Results on gait speed were missing in 12 participants due to amputations and paresis, but the test was otherwise well accepted. Grip strength was satisfactory performed in all patients.

Cognitive functioning
The cognitive tests were mostly well accepted by the participants, but we experienced many missing responses on the Trail Making Tests and Five Digits Test due to impaired vision. Trail Making Test B turned out to be cognitively demanding, with only 40 patients able to complete the test. Thus, due to a high number of imputed values, these results are difficult to interpret.
**Medication appropriateness**

The choice of MAI and AOU was based on the fact that these are implicit measures, where each drug is critically evaluated based on the patient’s clinical situation, and thus can be regarded as more comprehensive and relevant than explicit criteria. Their assessments were, however, dependent on the judgement and experience of one clinical pharmacist. We initially also recruited a professor in geriatrics for assessment of these measures, with a plan of having the two assessors reach consensus on their evaluations. The geriatrician, however, withdrew from participation, and we were not able to find a new physician willing to do this job. Assessments of MAI and AOU were time-consuming; the clinical pharmacist reported to use 30-60 minutes on each assessment. Although MAI and AOU thus give a comprehensive and judgement-based evaluation of drug appropriateness, these measures are demanding to include as outcome measures.

**Falls**

Falls were recorded through calendars handed out to participants, where they (or their relatives, in case of cognitive impairment) were asked to fill in if any fall occurred. We initially planned to call once a month to collect data and remind the participants of filling out the calendars, but had to abandon this plan due to time constraints. Fall calendars were thus collected at 16 and 24 weeks, with the other outcome assessments, which may have led to poorer data quality and a risk of not registering all falls. We were nevertheless a bit disappointed that we did not find any effect on the number of falls, as this is known to be a frequent ADR from e.g. psychotropic drugs and antihypertensives.

**5.3.2 Multidisciplinarity**

Clinical pharmacists have had a major role in previous drug review trials. We discussed whether a clinical pharmacist should be a part of the intervention, collaborating with the geriatrician. However, including an additional profession in an already complex intervention would make it even more challenging to disentangle the relevance of the different components. Economic considerations were also in part a reason for not involving a clinical pharmacist.
5.3.3 Selection bias
Since it was voluntary to participate in the study, both for FPs and patients, it is reasonable to believe that our study is affected by selection bias. It was generally difficult to come in contact with FP practices, and it is possible that those accepting a visit to be informed about the study, and subsequently participating, were more interested in the challenges related to drug treatment in older people than those who did not want to participate. Thus, cooperation and implementation of advice might have been poorer if also less enthusiastic FPs had been recruited. On the other hand, if the participating FPs were more interested in geriatric pharmacotherapy than those not participating, the patients listed with the latter FPs could have had more inappropriate drug regimens with a higher potential for improvements following a drug review.

The patients willing to participate could also have been more positive towards drug adjustments than those who did not enter the study. However, patients not interested in participation might have had even more inappropriate drug regimens, especially regarding psychoactive drugs, as these patients often are afraid of drug withdrawals.

5.3.4 External validity
Our use of a complex, pragmatic, and not completely standardized intervention might be viewed as a limitation regarding replication. We provided a detailed description of the intervention in the Supplementary material of Paper II. However, in an intervention where each patient is individually assessed with the unique health conditions and medications that are present, the recommended medication changes are inevitably dependent on the competence of the physician performing the assessments. Because all interventions were carried out by one single physician, we do not know if other geriatricians would have achieved similar results.

5.3.5 Statistics
As for the RCT, our statistical analysis plan was published before unblinding of the data. We initially based the analysis on ANCOVA, but resulting from the review process of Paper II, also linear mixed model analyses and responder analyses were included. The Supplementary content of Paper II lists multiple other sensitivity analyses, that all lead to similar conclusions. Statistical considerations for Paper III and IV are covered in relation to the discussion of their results.
5.3.6 Practical considerations

The involvement of FPs was important, but recruitment was challenging and work-demanding, and the inclusion rate was slower than anticipated in periods. The major obstacle was to approach the FPs the first time and be invited to inform about the study, as most of them were positive and wanted to participate after receiving information. Recruitment was more efficient when the study physician was invited to give information at common FP meetings within each municipality.

We also experienced that follow-up assessments became work-demanding for the research assistant after some months of inclusion, as she had to combine inclusion of new patients, baseline registrations and follow-up assessments, and coordinate this so that all assessments were done at the appropriate time. Two follow-up assessments with only 8 weeks between them might not be of very high value, and if we could choose again, we would probably have chosen only one time point.

5.4 Implementation

A major objection to our intervention is probably that it is time-consuming. The clinical consultation lasted approximately one to one and a half hour per patient, and in addition 10-15 minutes were spent on discussing each drug regimen with the FP. In the study setting, patients were visited by the geriatrician at home, but this was a choice primarily motivated by making participation as easy as possible for the patients, as to facilitate recruitment. The reason for holding collaborative meetings at the FPs office was also motivated by making it easy and economically attractive for the FPs to participate, because they could use a tax for physical, multidisciplinary meetings. However, clinical examinations would probably be more efficiently carried through in a clinical outpatient clinic, with all facilities present. We also believe that the discussion with FPs could be done by phone or video conference, as the most important issue was to have a discussion and not only sending a written conclusion.

Since April 2021, we have piloted the intervention at the Geriatric outpatient clinic at Oslo University Hospital. Patients are referred by their FPs and meet at the outpatient clinic. They are first seen by a nurse who collects background information on social situation and ADL functioning, collects blood samples, performs an electrocardiogram,
and assesses orthostatic blood pressure, grip strength, nutritional status and cognitive screening tests. Patients are then seen by a geriatrician, carrying out a medical history focused on drug treatment, a clinical examination, as well as a critical review of their drug regimens. The FP is then invited (by an electronic message) to participate in a telephone-based discussion on potential drug adjustments. The outpatient visit last approximately 1.5-2 hours, depending on the complexity, but this is comparable to the time spent on other newly referred patients to the outpatient clinic.

### 5.5 Pharmacogenetics

We found no difference in the mean prescribed dosage of CYP2D6 substrates between the various CYP2D6 metabolizer subgroups. Since *CYP2D6* genotype is a major determinant of the exposure of the studied drugs, this may indicate that physicians’ clinical judgement is insufficient in optimizing dosages for older patients. This is supported by the significant differences in orthostatic hypotension between CYP2D6 metabolizer subgroups.

We found that all metabolizer subgroups were prescribed lower dosages of CYP2D6 substrate drugs than generally recommended, as indicated by the calculated percentage of DDD. This could reflect reduced drug tolerability in our participants, or precautious physicians. Other factors than variability in CYP2D6 metabolism may therefore be of similar or greater importance for dose requirements of the studied drugs. However, taking into account the therapeutic heterogeneity of the CYP2D6 substrates and the significant impact on risk of orthostatism, we consider it likely that older patients with reduced or absent CYP2D6 metabolism should receive lower doses of CYP2D6 substrates than those with normal metabolism.

The results may indicate that individualized dosing based on genotype has the potential of preventing ADRs in these vulnerable patients, but since the present study is based on a post-hoc analysis of a limited population size, the potential increased risk of ADRs in older CYP2D6 IMs/PMs should be further investigated prospectively in larger patient populations. It would also be of value to include other outcome measures that could be related to ADRs of relevant drugs, for example general fatigue and constipation, which is frequently associated with the use of metoprolol.
5.5.1 Methodological considerations
The most important weakness of the study is that relatively few patients were included, which reduces the statistical power of the comparisons. It would also be preferable to study IMs and PMs as separate subgroups, but the limited power did not allow for reasonable statistical comparisons of three CYP2D6 subgroups. In addition, we did not have sufficient data for all participants to include renal or hepatic impairment as covariates in the analyses, and it is possible that such adjustments could have affected the observed findings. A more refined classification or subgrouping of CYP2D6 genotype-predicted phenotypes has also been developed after the initiation of our study (209), which may improve the clinical interpretation of the possible association between CYP2D6 metabolism and treatment outcomes.

5.5.2 Could pharmacogenetic testing be useful in geriatric patients?
Three systematic reviews have concluded with potential benefits of pharmacogenetic testing among older, multimorbid patients, but evidence is limited, and we have only identified one RCT utilizing pharmacogenetic testing in older people and at the same time reporting clinical outcomes (171).

Although pharmacogenetic testing to some degree is being utilized, especially among psychiatric patients where dosing of psychoactive drugs often are affected by genetic variation, it is generally rarely used in clinical practice. There are several barriers to the implementation of pharmacogenetics, where considerations of cost-effectiveness, lack of knowledge among health professionals on how to interpret and apply the results, as well as a paucity of ways to integrate pharmacogenetic results into electronic health records are among the most important (109, 173, 210).

Thus, routine screening with pharmacogenetic test panels of all older patients with polypharmacy is probably not advisable, but for selected groups of patients using drugs with known gene-related variations in exposure, pharmacogenetic testing can be a useful supplement when optimizing drug therapy.
5.6 Ethical considerations

The participating FPs were given comprehensive information about the project and assessed the eligibility of their patients. Most FPs knew their patients well in beforehand, and knew if there were special concerns regarding physical, cognitive, or psychiatric problems suggesting that the patient should not participate.

Generally, we considered the risk of participating as minimal, as the intervention consisted of a presumably more thorough drug review than would else be carried out. However, we could not rule out that patients could experience for instance ADRs of newly prescribed drugs, or withdrawal reactions in the case of discontinuations. Some studies have found an increased risk of adverse effects following drug withdrawals, while others have found drug withdrawals and deprescribing in general to be safe and with a potential of improving health outcomes (125, 211). As our goal was optimized pharmacotherapy, we would nevertheless make careful assessments of benefits and harms of various drug adjustments before implementing any change to the drug regimens.

We believed that the intervention probably would be beneficial, raising an ethical concern regarding the control group. We therefore offered the FPs our assistance in performing drug reviews in the control group after completion of the study period. All FPs received a letter providing information on how to contact the study physician for such assistance after all their patients had completed follow-up, but none of them took advantage of this offer. We do not know if this was because they had no concern regarding their patients’ drug use and did not find it indicated to perform collaborative drug reviews, if it was related to time constraints, or other factors. One patient from the control group contacted the study personnel directly and expressed a wish of having performed a drug review, which was undertaken. When taking the positive result of the study into account, there might be an ethical concern related to the control group not receiving an intervention.

Inclusion of patients was based upon informed consent, and information was given both written and orally. Some patients were unable to give a valid consent due to dementia. Patients with dementia could be particularly vulnerable to suboptimal drug treatment and were regarded as important to include despite their cognitive difficulties. Patients
with dementia were therefore included based on informed consent from a close relative in combination with assent from the patient. If the patient was able to understand basic information about the study, we used a simplified consent form in combination with fully informed consent from a close relative.

The trial was approved by the Regional Committee for Medical and Health Research Ethics (reference number 2014/1488) and by the Data Protection Officer at Oslo University Hospital and was carried out in accordance with the 1964 Declaration of Helsinki and its later amendments. ClinicalTrials.gov Identifier: NCT02379455.
6. CONCLUSIONS

- Clinical geriatric assessments and drug reviews carried out in collaboration with the patients’ FP have the potential to improve HRQoL among older patients exposed to polypharmacy.
- Results indicate that drug optimization also can have a positive effect on physical and cognitive functioning.
- Patients with most inappropriate drug use may benefit the most of collaborative, clinical drug reviews.
- Individualized dose adjustments supported by pharmacogenetic tests may have a potential to prevent ADRs in this vulnerable population.
- An individual approach, targeting the complexity of each patient’s drug regimen, is most likely the key of optimizing drug therapy in older people.
7. SUGGESTIONS FOR FUTURE RESEARCH

The study has generated many interesting data that have not yet been analyzed. Of particular interest are:

- Changes in different subcategories of MAI, such as drugs with no clinical indication, clinically significant drug-drug or drug-disease interactions, and their associations with 15D scores
- Sub-items of the 15D instrument: which domains were improved and are there relevant associations with drug adjustments that were carried out?
- Prevalence of PIMs/PPOs as defined by explicit prescribing tools (e.g. START/STOPP) and to which extent they were associated with implemented drug changes
- Prevalence of drug-drug-gene interactions
- Analysis of which pharmacogenetic results that lead to recommendations of drug adjustments

On a larger scale, RCTs examining the clinical impact of pharmacogenetic testing among older people exposed to polypharmacy are warranted.

However, highest priority has further research to see if our results can be replicated in a similar intervention where another physician is responsible for the drug reviews, and where the intervention is more affordable within the frame of ordinary routines, and not dependent on a particularly interested FP. We have received funding to initiate a new study, this time recruiting older patients admitted to the acute municipal hospital, in Norwegian called “Kommunal akutt døgnenhet” (KAD), in Oslo. We plan to perform a RCT using a modified version of the intervention used in the present study. The main amendments in the new study are 1) that a KAD physician (supervised by a geriatrician) carries out the clinical assessment, the drug review and the dialogue with the FP as part of the regular clinical work, 2) that the dialogue is based on phone/video conference and not a physical meeting, and 3) that the individual patient will constitute the randomization unit and that his or her FP will automatically be offered a discussion about the drug use. If the FP for a patient in the intervention group declines, the patient is still in the intervention group. Thus, acceptability for the FPs to participate is now also part of the evaluation, improving external validity.
REFERENCES


APPENDIX

QUALITY OF LIFE QUESTIONNAIRE (15D©)
15D©/Harri Sintonen (www.15D-instrument.net)

Please read through all the alternative responses to each question before placing a cross (x) against the alternative which best describes your present health status. Continue through all 15 questions in this manner, giving only one answer to each.

QUESTION 1. MOBILITY
1 ( ) I am able to walk normally (without difficulty) indoors, outdoors and on stairs.
2 ( ) I am able to walk without difficulty indoors, but outdoors and/or on stairs I have slight difficulties.
3 ( ) I am able to walk without help indoors (with or without an appliance), but outdoors and/or on stairs only with considerable difficulty or with help from others.
4 ( ) I am able to walk indoors only with help from others.
5 ( ) I am completely bed-ridden and unable to move about.

QUESTION 2. VISION
1 ( ) I see normally, i.e. I can read newspapers and TV text without difficulty (with or without glasses).
2 ( ) I can read papers and/or TV text with slight difficulty (with or without glasses).
3 ( ) I can read papers and/or TV text with considerable difficulty (with or without glasses).
4 ( ) I cannot read papers or TV text either with glasses or without, but I can see enough to walk about without guidance.
5 ( ) I cannot see enough to walk about without a guide, i.e. I am almost or completely blind.

QUESTION 3. HEARING
1 ( ) I can hear normally, i.e. normal speech (with or without a hearing aid).
2 ( ) I hear normal speech with a little difficulty.
3 ( ) I hear normal speech with considerable difficulty; in conversation I need voices to be louder than normal.
4 ( ) I hear even loud voices poorly; I am almost deaf.
5 ( ) I am completely deaf.

QUESTION 4. BREATHING
1 ( ) I am able to breathe normally, i.e. with no shortness of breath or other breathing difficulty.
2 ( ) I have shortness of breath during heavy work or sports, or when walking briskly on flat ground or slightly uphill.
3 ( ) I have shortness of breath when walking on flat ground at the same speed as others my age.
4 ( ) I get shortness of breath even after light activity, e.g. washing or dressing myself.
5 ( ) I have breathing difficulties almost all the time, even when resting.

QUESTION 5. SLEEPING
1 ( ) I am able to sleep normally, i.e. I have no problems with sleeping.
2 ( ) I have slight problems with sleeping, e.g. difficulty in falling asleep, or sometimes waking at night.
3 ( ) I have moderate problems with sleeping, e.g. disturbed sleep, or feeling I have not slept enough.
4 ( ) I have great problems with sleeping, e.g. having to use sleeping pills often or routinely, or usually waking at night and/or too early in the morning.
5 ( ) I suffer severe sleeplessness, e.g. sleep is almost impossible even with full use of sleeping pills, or staying awake most of the night.

QUESTION 6. EATING
1 ( ) I am able to eat normally, i.e. with no help from others.
2 ( ) I am able to eat by myself with minor difficulty (e.g. slowly, clumsily, shakily, or with special appliances).
3 ( ) I need some help from another person in eating.
4 ( ) I am unable to eat by myself at all, so I must be fed by another person.
5 ( ) I am unable to eat at all, so I am fed either by tube or intravenously.
QUESTION 7. SPEECH
1 ( ) I am able to speak normally, i.e. clearly, audibly and fluently.
2 ( ) I have slight speech difficulties, e.g. occasional fumbling for words, mumbling, or changes of pitch.
3 ( ) I can make myself understood, but my speech is e.g. disjointed, faltering, stuttering or stammering.
4 ( ) Most people have great difficulty understanding my speech.
5 ( ) I can only make myself understood by gestures.

QUESTION 8. EXCRETION
1 ( ) My bladder and bowel work normally and without problems.
2 ( ) I have slight problems with my bladder and/or bowel function, e.g. difficulties with urination, or loose or hard bowels.
3 ( ) I have marked problems with my bladder and/or bowel function, e.g. occasional 'accidents', or severe constipation or diarrhea.
4 ( ) I have serious problems with my bladder and/or bowel function, e.g. routine 'accidents', or need of catheterization or enemas.
5 ( ) I have no control over my bladder and/or bowel function.

QUESTION 9. USUAL ACTIVITIES
1 ( ) I am able to perform my usual activities (e.g. employment, studying, housework, free time activities) without difficulty.
2 ( ) I am able to perform my usual activities slightly less effectively or with minor difficulty.
3 ( ) I am able to perform my usual activities much less effectively, with considerable difficulty, or not completely.
4 ( ) I can only manage a small proportion of my previously usual activities.
5 ( ) I am unable to manage any of my previously usual activities.

QUESTION 10. MENTAL FUNCTION
1 ( ) I am able to think clearly and logically, and my memory functions well
2 ( ) I have slight difficulties in thinking clearly and logically, or my memory sometimes fails me.
3 ( ) I have marked difficulties in thinking clearly and logically, or my memory is somewhat impaired.
4 ( ) I have great difficulties in thinking clearly and logically, or my memory is seriously impaired.
5 ( ) I am permanently confused and disoriented in place and time.

QUESTION 11. DISCOMFORT AND SYMPTOMS
1 ( ) I have no physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
2 ( ) I have mild physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
3 ( ) I have marked physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
4 ( ) I have severe physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.
5 ( ) I have unbearable physical discomfort or symptoms, e.g. pain, ache, nausea, itching etc.

QUESTION 12. DEPRESSION
1 ( ) I do not feel at all sad, melancholic or depressed.
2 ( ) I feel slightly sad, melancholic or depressed.
3 ( ) I feel moderately sad, melancholic or depressed.
4 ( ) I feel very sad, melancholic or depressed.
5 ( ) I feel extremely sad, melancholic or depressed.

QUESTION 13. DISTRESS
1 ( ) I do not feel at all anxious, stressed or nervous.
2 ( ) I feel slightly anxious, stressed or nervous.
3 ( ) I feel moderately anxious, stressed or nervous.
4 ( ) I feel very anxious, stressed or nervous.
5 ( ) I feel extremely anxious, stressed or nervous.
QUESTION 14. VITALITY
1 ( ) I feel healthy and energetic.
2 ( ) I feel slightly weary, tired or feeble.
3 ( ) I feel moderately weary, tired or feeble.
4 ( ) I feel very weary, tired or feeble, almost exhausted.
5 ( ) I feel extremely weary, tired or feeble, totally exhausted.

QUESTION 15. SEXUAL ACTIVITY
1 ( ) My state of health has no adverse effect on my sexual activity.
2 ( ) My state of health has a slight effect on my sexual activity.
3 ( ) My state of health has a considerable effect on my sexual activity.
4 ( ) My state of health makes sexual activity almost impossible.
5 ( ) My state of health makes sexual activity impossible.
PAPERS I-IV
Cooperation between geriatricians and general practitioners for improved pharmacotherapy in home-dwelling elderly people receiving polypharmacy – the COOP Study: study protocol for a cluster randomised controlled trial

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Abstract

Background: Polypharmacy and inappropriate drug use is associated with negative health outcomes among older people. Various interventions for improving drug treatment have been evaluated, but the majority of studies are limited by the use of surrogate outcomes or suboptimal design. Thus, the potential for clinically significant improvements from different interventions is still unclear. The main objective of this study is therefore to evaluate the effect upon patient-relevant endpoints of a cooperation between geriatricians and general practitioners on complex drug regimens in home-dwelling elderly people.

Methods: This is a cluster randomised, single-blind, controlled trial where general practitioners are invited to participate with patients from their lists. The patients must be 70 years or older, use at least seven different medications and have their medications administered by the home nursing service. We plan to recruit 200 patients, with randomisation at physician level. The intervention consists of three main parts: (1) clinical geriatric assessment of the patient, combined with a thorough review of their medications; (2) a meeting between the geriatrician and general practitioner, where the two physicians combine their competence and knowledge and discuss the drug list systematically; (3) clinical follow-up, depending on the medication changes that have been done. The study period is 24 weeks, and the patients are assessed at baseline, 16 and 24 weeks. The primary outcome measure is health-related quality of life according to the 15D instrument. Secondary outcome measures include physical and cognitive functioning, medication appropriateness, falls, carer burden, use of health services (hospital or nursing home admissions, use of home nursing services) and mortality.

Discussion: Our choice of patient-relevant outcome measures will hopefully provide new knowledge on the potential for clinical improvements after performing comprehensive medication reviews in home-dwelling elderly people receiving polypharmacy.

Trial registration: ClinicalTrials.gov, NCT02379455. Registered on 27 February 2015.

Keywords: Polypharmacy, Inappropriate drug use, Medication review, Geriatrics, Elderly, Home-dwelling

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Background
Polypharmacy
The drug consumption among older people has increased in the last decades [1] and polypharmacy is frequent [2]. It has been shown that 20% of Norwegians aged 70 plus are prescribed more than ten different drugs annually [3]. In a study of drug consumption among elderly (65 plus) users of home services in eight European countries, 51% used more than six and 22% used more than nine different drugs during a week [4].

A complex clinical situation involving multimorbidity may justify a high number of drugs, and a properly titrated polypharmacy can be beneficial for the individual patient. However, most therapeutic guidelines are based upon research carried out in patients with a limited number of co-morbid conditions. Accordingly, such guidelines may be of limited value in frail and multimorbid elderly patients [5, 6]. The more drugs an individual patient consumes, the more demanding is the trade-off between benefits and harms, and the more tightly should the clinical condition be monitored. Polypharmacy increases the risk of adverse drug reactions (ADR{s}), interactions and other drug-related problems (DRPs), and the risk increases almost linearly with the number of drugs used [7–9]. Several studies among older people indicate that inappropriate drug use is a major reason for poor health and impaired function [10–12], preventable hospital admissions [13–15], and even deaths [16]. A recent Norwegian study reported that of home-dwelling elderly (75 plus) emergency-admitted to hospital, almost 40% were prescribed at least one potentially inappropriate medication (PIM) [17]. DRPs are often caused by overmedication, choice of inappropriate drugs, or inadequate monitoring and follow-up [12]. Underuse of potentially beneficial drugs is probably also a significant problem in the elderly [18, 19].

Improving prescribing quality
Optimisation of pharmacotherapy should be based on a comprehensive assessment of all relevant medical conditions as well as the patient’s functional ability, resources and preferences. However, health services are often organised in a way that makes it difficult to attain a sufficiently good overview of the clinical situation to make good medication reviews in frail and multimorbid patients. Specialists in hospitals mainly see the patient during acute exacerbations of their chronic diseases, and will naturally focus upon drugs relevant for the acute illness – especially drugs relevant for the organ system in which they have specialised. On the other side, general practitioners (GPs) are responsible for the long-term follow-up and repeat prescriptions. Because most GPs attain limited experience in handling complex health states, they may be reluctant to change medications initiated by hospital specialists [20]. Geriatricians are trained in the management of complex health conditions and polypharmacy and have firm knowledge about age-related changes in physiology and pharmacology [21], but typically see patients over a short period of time, either in an acute geriatric ward or in the geriatric outpatient department. Thus, the geriatrician often has limited information about the patient’s medical history, and has a limited possibility to follow the patient over time, elements that are typical strengths in the follow-up made by the GP. Geriatricians and GPs therefore have complementary strengths for managing complex drug regimens in frail elderly patients, and a closer cooperation between these two specialities could be beneficial.

A majority of interventions for improving drug treatment among older people are evaluated by the use of surrogate outcomes such as frequency of DRPs [22], number of prescribed drugs [23], or prevalence of PIMs [24]. Many studies also suffer from suboptimal design, such as observational studies and interventional studies without a control group [25] or without randomisation [26]. A recent Cochrane review [27] concluded that interventions to improve drug therapy appear beneficial in terms of reducing inappropriate prescribing, but the clinical benefits of such reductions are unclear. Interventional studies of measures to facilitate better prescriptions, using a scientifically sound design and at the same time utilising patient-relevant outcomes as well as outcomes capturing the effect upon the families and the health care services, are so far very rare.

Study objectives
The aim of this study is to evaluate the effect of drug optimisation interventions resulting from a cooperation between geriatricians and GPs on clinically relevant outcome measures in home-dwelling elderly people using complex drug regimens.

Methods/design
Study design
This is a cluster randomised, single-blind, controlled trial with 24 weeks follow-up. GPs are recruited to participate in the study with patients from their lists. In order to avoid “contamination” between intervention and control patients, cluster randomisation on physician level instead of individual randomisation on patient level is performed. The outcomes are assessed at baseline and after 16 and 24 weeks. Patient flow is illustrated in Fig. 1. See Additional file 1 for the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist and Additional file 2 for the SPIRIT figure.

Recruitment of GPs
GPs from the counties of Akershus and Oslo, Norway, are invited to participate in the study. All GPs in these
areas are eligible for participation. The GPs receive written invitations, followed by a phone call to clarify if they are interested. When possible, information about the study is also given at GP meetings within each municipality.

**Study population**

We assume that the comprehensive clinical evaluation and medication review that we will test is most relevant for the oldest and most frail patients, with relatively pronounced polypharmacy. We have therefore chosen the following inclusion and exclusion criteria:

**Patient inclusion criteria**

- Listed with one of the participating GPs
- Home-dwelling
- Medications administered by the home nursing service
- Age 70 years or more
- Use of at least seven different systemic medications taken regularly (preparations for inhalation, vitamin supplements and laxatives are included, but not topical drugs like eye drops and ointments)
- Signed informed consent given by the patient or his/her closest proxy

**Patient exclusion criteria**

- Expected to become permanently institutionalised within 6 months
- Life expectancy judged to be 6 months or less
- Moderate/severe dementia (i.e., Clinical Dementia Rating Scale (CDR) score > 1) and contact with the closest proxy less than once every other week
- Not speaking or understanding Norwegian
- The GP does not want the particular patient to participate (in case of important reasons not covered by the other exclusion criteria)

**Screening and inclusion**

The majority of home-dwelling patients with medications administered by the home nursing service have
their medications prepared by multi-dose packaging systems delivered by a pharmacy. Medication lists from the pharmacy are screened by the home nursing service or by GP office staff to identify patients fulfilling the inclusion criteria. The GPs then consider the eligibility of their patients based on the defined exclusion criteria.

Patients eligible for participation are contacted by the home nursing service or the GP’s office, explaining the study and asking whether the researchers may contact them. If this is accepted, the patients receive a home visit from a research assistant who gives complementary oral and written information. Informed written consent is obtained from all participants or from their closest relative in cases where the patient is unable to give a valid consent due to reduced cognitive functioning.

Randomisation and blinding
In order to avoid large variation in cluster sizes, each GP can participate with a maximum of five patients. To assure as equal group sizes as possible, the GPs are stratified based on the number of contributing patients; 1–2 patients versus 3–5. Randomisation is computer-generated and carried out in blocks of unknown and variable size. The allocation sequence is prepared by a statistician not involved in recruitment, and is made available to the researchers in sealed, opaque envelopes. In order to minimise the risk of selection bias, randomisation takes place after inclusion of all patients within each cluster. The GPs are included sequentially according to the capacity in the project. The research assistant, who provides all the assessments, is blinded with respect to allocation. Given the nature of the intervention, it is not feasible to blind the patients, their relatives or the GPs. The effects of the intervention will be analysed blindly, i.e. with the two randomised groups denominated “A” and “B” but without knowledge regarding which group is the control and which the intervention group.

Intervention
Our intervention consists of three main parts: clinical geriatric assessment of the patient combined with a thorough review of their medications; a targeted meeting between the geriatrician and the GP; and clinical follow-up.

Geriatric assessment and medication review
The patients receive a home visit by a physician trained in geriatric medicine (RR). In advance, the geriatrician obtains necessary information on the patient’s medical history and actual medication from hospital records, the GP’s electronic patient record, the home nursing service and other relevant sources. The geriatrician carries out a medical history from the patient (if necessary supplemented by a close relative) and a physical examination, both with focus on conditions most relevant for the patient’s total medication use. Relevant blood analyses and other supplementary tests are ordered if not already available (ECG, haematological tests, electrolytes, renal function, natriuretic peptides, thyroid function, nutritional indicators, serum concentration of relevant drugs, pharmacogenetic testing etc.). The geriatric work-up is aimed at evaluating whether current medications are indicated, whether the relevant conditions are satisfactorily compensated, whether the dosages are appropriate, whether the patient has symptoms of ADRs, and whether drug-drug interactions or drug-disease interactions are present or likely to occur. A drug interaction database [28], lists of anticholinergic drugs [29, 30], the STOPP/START criteria [31] and the NORGEP criteria [32] are also used. The geriatrician is provided with clinical supervision from a senior consultant in geriatric medicine (TBW).

Meeting between the geriatrician and GP
The main purpose of this meeting is to combine the competence and knowledge of the geriatrician with that of the GP. The geriatrician summarises the findings from the geriatric assessment and medication review, and the two physicians discuss the patient’s drug list systematically. The geriatrician may suggest changes in the drug regimen, but the GP retains the medical responsibility for the patient, and is in charge of all ordinations and medication changes.

Clinical follow-up
Depending on medication changes that have been done, the two physicians arrange the necessary follow-up within the project period. The follow-up can consist of a clinical evaluation, further drug adjustments, blood tests etc., and can be carried out by the GP the geriatrician or through telephone contact with the patient, the relative or the home nursing service, depending on the circumstances.

Control group
The control group receives “usual care” from their GPs during the study period, but the GPs in the control group are offered our assistance in performing medication reviews after the study period is completed.

Outcome measures
Follow-up occurs at 16 and 24 weeks (±2 weeks) after baseline registrations, in order to study the course of any change over time.

Primary outcome measure
The primary endpoint is change in health-related quality of life (HRQoL), measured by the 15D instrument (single index version) at 16 weeks. 15D is a generic, 15-dimensional instrument concerning different aspects of
HRQoL [33, 34] that has been used in similar geriatric interventions [35, 36]. The dimensions are mobility, vision, hearing, breathing, sleeping, eating, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity. Each dimension is rated on an ordinal scale with five levels, and the respondent chooses the level best describing his/her present health status. The 15D can be used both as a profile measure and as a single index. The single index, representing the overall HRQoL, varies between 0 (poorest HRQoL) and 1 (excellent HRQoL), and is calculated by using a set of population-based preference or utility weights [33, 37]. Usually, the 15D questionnaire is filled in by the individual whom it concerns, but it is also validated for proxy raters.

We hypothesise that most improvements in the total drug regimen of frail older patients, such as better pain control, better symptom control in heart failure, less parkinsonian side effects, less iatrogenic dehydration or less sedation, have the potential to improve HRQoL. Accordingly, in our opinion 15D is an appropriate outcome measure when the aim is to improve the total drug regimen in an individualised manner across a broad spectrum of drug classes within a heterogeneous group of older users of multiple drugs. The patients included in our study are old, and many are not familiar with self-administration of questionnaires of this kind. 15D is therefore administered by interview. This is done by the research assistant, blind to group allocation. If the patient has a moderate or severe dementia (CDR > 1), and/or the research assistant considers that they do not understand the questionnaire, the interview is carried out with the closest proxy. To account for patients who might lose their ability to respond to 15D during the follow-up period, and in order to compare the answers given by patients themselves and their proxies, we administer 15D to the closest proxy in all cases.

Secondary outcome measures

Secondary endpoints are on the patient, family and local community level.

1. Patient-related endpoints
   - 15D after 24 weeks
   - Short Physical Performance Battery (SPPB), a simple test of mobility that combines the results of walking speed, chair stand and balance tests [38]
   - Gait speed [39]
   - Hand grip strength (hand dynamometry)
   - Functional Independence Measure (FIM), a measure of physical and cognitive disability [40]
   - Trail Making Test A and B, measuring processing speed, focused and split attention, and executive functioning [41]
   - “Digit Span”, a digit repetition test of working memory, measuring attention [42]
   - Five Digits Test, measuring attention and executive functions [43]
   - Appropriateness of current prescribing as assessed by the Medication Appropriateness Index (MAI) [44] and the Assessment of Underutilization (AOU) [45]
   - Number of falls during the follow-up period
   - Orthostatic blood pressure
   - Weight
   - All changes in the pharmacotherapy taking place during the intervention and follow-up period
   - Mortality

2. Family-related endpoints
   - Carer burden according to the Relative Stress Scale (RSS) [46]

3. Endpoints related to the local community and use of health services
   - Hospital admissions (with reasons)
   - Number of days the patient has spent in his or her own home (in contrast to being in hospital, nursing home or other institutions)
   - Admission to permanent institutional care
   - Current use of home nursing service (hours per week)

Background variables

The outcomes are measured at baseline, in order to check and adjust for possible inequalities. In addition, the following descriptive variables are registered:

- Demographic data
- Diagnoses according to ICD-10
- Cumulative Illness Rating Scale (CIRS) [47]
- Clinical Dementia Rating Scale (CDR) [48]
- Course of cognitive symptoms during the last 10 years, according to the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) [49]
- Nutritional status, assessed by the Mini Nutritional Assessment Short Form (MNA-SF) [50]
- Current drug use

Data collection

Background information on diagnoses and comorbidity are obtained from the GP’s electronic patient records. The patient receives three home visits from the research assistant; at baseline, 16 and 24 weeks (±2 weeks). These visits take place where the patient is living at that moment; this might be the patient’s own home, a nursing facility or a rehabilitation institution. All assessments directly involving the patient are performed at these visits. Proxy information is collected through telephone calls and/or questionnaires sent by mail, if the proxy is
not present at the home visit. Updated drug lists are obtained at all assessment points. The MAI [44] and AOU [45] are assessed by clinical pharmacists and geriatricians not involved in the intervention. The use of home nursing service and admissions to hospital, nursing home or other institutions is registered. In case of hospital admissions, the discharge summary is obtained. See Table 1 for study assessment procedures and timetable.

Sample size, statistical power and statistical analysis
The primary endpoint 15D is on an interval scale, and is expected to be reasonably normally distributed. We will analyse this measure by ANCOVA, as recommended by Vickers and Altman [51]. Other outcome measures will be analysed by ANCOVA (continuous data) or logistic regression (categorical data) as appropriate. Non-normally distributed variables will be transformed in order to try to achieve a distribution that is more feasible for analysis. Robust estimation of standard errors will be used to handle within-cluster (physician) correlation. A detailed statistical analysis plan will be developed that will detail imputation processes for missing data etc.

The number of patients in the intervention group is planned to be approximately 100, and each GP can participate with 1–5 patients. This means that the number of GPs (clusters) will be 20–100 in the intervention group. A similar number of patients and GPs will be included in the control group.

It is difficult to make valid assumptions on the correlation between patients within each cluster. In order to estimate the power of the study, we have chosen to estimate power in a worst case (perfect correlation) and a best case (no correlation) scenario. The true correlation is expected to be much closer to the latter, as the potential for intervention will vary between the individual patients. Based on previous studies using 15D, the standard deviation of change over time is expected to be between 0.07 and 0.08 [35, 36, 52]. The minimum important change (MIC) for the change in 15D scores is ± 0.015 [53]. A change of more than 0.035 in the negative direction represents “much worse HRQoL,” and a change of more than 0.035 in the positive direction “much better HRQoL” [53]. Based on previous studies, in addition to a pilot study, we believe that our intervention is extensive enough to potentially improve the patients HRQoL to “much better” (>0.035). As can be seen from Table 2, the power to detect a difference of 0.035 will be in the range 59 to 94%, and most probably > 80%.

Discussion
Polypharmacy and inappropriate drug use constitute a major health risk for elderly patients. On the other side, comorbid conditions and bothersome symptoms may give good reasons to prescribe many drugs. The challenge is to personalise the polypharmacy and to find the best combination of drugs for each individual patient. For this purpose, thorough clinical evaluations and close monitoring of the patient’s condition is necessary.

When designing the COOP study, we emphasised examination of real-life scenarios. Our intention is to individualise the treatment, but at the same time to evaluate

Table 1 Study assessment procedures and timetable

<table>
<thead>
<tr>
<th>Assessments directly involving the patient</th>
<th>Baseline visit</th>
<th>16 weeks follow-up</th>
<th>24 weeks follow-up</th>
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<tr>
<td>Demographics, diagnoses, CIRS, MNA-SF</td>
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<td>Orthostatic blood pressure</td>
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<td>Weight</td>
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<tr>
<td>Assessments of drug use</td>
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<td>Current drug use and changes in pharmacotherapy</td>
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<td>MAI</td>
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<tr>
<td>AOU</td>
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<tr>
<td>Assessments based on observation and/or proxy information</td>
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<tr>
<td>FIM</td>
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<tr>
<td>CDR</td>
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<tr>
<td>Assessments based on information from a close relative</td>
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<td>RSS</td>
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<td>IQCODE</td>
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<tr>
<td>Administrative data</td>
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<tr>
<td>Hospital admissions (with reasons)</td>
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<tr>
<td>Number of days in own home</td>
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<tr>
<td>Admission to permanent institutional care</td>
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<tr>
<td>Use of home nursing service (hours per week)</td>
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<tr>
<td>Mortality</td>
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</table>

Abbreviations: CIRS Cumulative Illness Rating Scale, MNA-SF Mini Nutritional Assessment Short Form, SPPB Short Physical Performance Battery, MAI Medication Appropriateness Index, AOU Assessment of Underutilization, FIM Functional Independence Measure, CDR Clinical Dementia Rating Scale, RSS Relative Stress Scale, IQCODE Informant Questionnaire on Cognitive Decline in the Elderly.
Table 2 Estimation of power in different scenarios

<table>
<thead>
<tr>
<th>Δ</th>
<th>SD</th>
<th>r</th>
<th>Power %</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>59</td>
</tr>
<tr>
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<td>0</td>
<td>87</td>
</tr>
<tr>
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<td>0.07</td>
<td>1</td>
<td>71</td>
</tr>
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<td>0.07</td>
<td>0</td>
<td>94</td>
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<td>43</td>
</tr>
<tr>
<td>0.025</td>
<td>0.07</td>
<td>0</td>
<td>71</td>
</tr>
</tbody>
</table>

A change in 1SD HRQoL index score, SD standard deviation of change over time in 1SD score, R correlation between patients within each cluster

the intervention with stringent scientific methods. In our opinion, the project is innovative in improving cooperation between hospital specialists and the primary health care system and evaluating the effect with patient-related outcome measures.

A majority of previous interventions for improving drug treatment among older adults have been evaluated by the use of surrogate outcomes, such as the number of prescribed drugs [23] or prevalence of PIMs [54], but this does not necessarily indicate whether the patient has really benefited from the intervention. We have chosen patient-relevant outcome measures, and will hopefully be able to contribute with valuable knowledge about clinical effects of comprehensive medication reviews.

There are some limitations to the study. The participants will be old and multimorbid, and prone to experience new illnesses and clinical deterioration during the study period, regardless of the intervention. This might make the intervention less powerful. It is also possible that the GPs who choose to participate are particularly interested in drug treatment in the elderly, and therefore have more knowledge and awareness about this topic than GPs that do not participate. The participating patients might therefore be better followed up beforehand, making it less likely that the intervention will give any effects.

The patients and their relatives are not blinded. There is a risk that the research assistant might be unblinded, even if it is clearly explained to the participants that they should not reveal their group allocation. Nor are the GPs blinded, and the GPs in the control group may pay extra attention to the drug treatment for their patients during the study period, even if they are not provided with advice from the geriatrician.

Since our aim is to address the various comorbidities and clinical problems that are unique for each participating patient, the intervention is not completely standardised. Successful interventions for geriatric patients have often been of a complex type [55–57], whereas the implementation of one single measure will be less likely to give an effect. A major challenge when studying complex interventions is to describe the intervention with sufficient precision as to facilitate replication [57]. Our main strategy for this will be to compensate for the necessary degree of pragmatism in the interventional approach with a detailed description of the interventions that were in fact carried out, in particular changes in the drug regimens of the individual patients.

This is quite an extensive intervention, but if it is effective, we will argue that it can be carried out for those patients having the most complex polypharmacy – within the existing framework of a geriatric outpatient clinic.

Trial status
The first patient was included on 17 March 2015. The study is ongoing.

Additional files

Additional file 1: SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol. (PDF 58 kb)

Additional file 2: SPIRIT figure. (PDF 15 kb)

Abbreviations
AORs: Adverse drug reactions; AOU: Assessment of Underutilization; CDR: Clinical Dementia Rating Scale; CIRS: Cumulative Illness Rating Scale; DRPs: Drug-related problems; FIM: Functional Independence Measure; GP: General practitioner; HRQoL: Health-related quality of life; IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly; MAI: Medication Appropriateness Index; MIC: Minimal important change; MNA-SF: Mini Nutritional Assessment Short Form; PIM: Potentially inappropriate medications; RSS: Relative Stress Scale; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; SPPB: Short Physical Performance Battery

Acknowledgements
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Availability of data and materials
Not applicable.

Authors’ contribution
TBW and RR initiated the study, TBW, RR, EMA, JS, HK, ES and KHP contributed in design and planning of the study and have critically revised the manuscript. ES also provided statistical expertise, and has carried out the randomisation procedure and the sample size calculations. RR is responsible for the daily running of the study and collecting data, and wrote the manuscript. All authors have approved the final manuscript.

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

Consent for publication
Not applicable.

Ethics approval and consent to participate
The Regional Committee for Medical and Health Research Ethics (REK) has decided that the study is exempt from review in Norway, as it is considered as health service research (REK 2014/1488, 19 August 2014). The study is approved by the Data Protection Official at Oslo University Hospital (reference number 2014/15359), and is carried out in accordance with the Declaration of Helsinki.
The participating GPs are given comprehensive information about the study, and give written consent to participate. Inclusion of patients in the study is based upon informed consent, and information is given written as well as orally. Cognitive intact patients are included on the basis of written, informed consent. Some patients who otherwise fulfill the inclusion criteria may be unable to give a valid consent due to dementia or psychiatric disorders. We regard such patients to be particularly vulnerable to suboptimal pharmacotherapy, and thus particularly important to include in the study. We therefore include such patients based on informed consent from a close relative in combination with consent from the patient. If the patients are able to understand basic information about the project, we use a simplified consent form in combination with fully informed consent from a close relative.

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SHORT COMMUNICATION

Prescribed Doses of CYP2D6-Metabolized Drugs and Hemodynamic Responses in Relation to CYP2D6 Genotype Among Older Patients Exposed to Polypharmacy

Rita Romskaug1 · Torgeir Bruun Wyller1,2 · Jørund Straand3 · Hege Kersten4,5 · Espen Molden4,6

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Abstract

Background Many drugs with dose-dependent effects on hemodynamic variables are metabolized by cytochrome P450 2D6 (CYP2D6). The aim of this study was to compare prescribed dosages and hemodynamic responses of such drugs in relation to pharmacogenetic variability in CYP2D6 metabolism among patients aged ≥ 70 years exposed to polypharmacy.

Materials and Methods We included 173 patients with detailed information about drug use. The patients were retrospectively subjected to CYP2D6 genotyping, which comprised the most common variant alleles encoding reduced, absent, or increased CYP2D6 metabolism. In order to compare dosages across different CYP2D6-metabolized drugs, all prescribed daily doses were harmonized to the ‘percent of a daily defined dose’ (DDD). The mean harmonized DDD was compared between genotype-predicted normal metabolizers (NMs) and patients with reduced or absent CYP2D6 enzyme activity, defined as intermediate or poor metabolizers (IMs/PMs). Blood pressure, pulse, and patient proportions with orthostatism and bradycardia were also compared between genotype subgroups.

Results The genotype-predicted phenotype subgroups comprised 79 NMs (45.7%), 75 IMs (43.4%), and 16 PMs (9.2%). There were no differences in dosing of CYP2D6 substrates between NMs and IMs/PMs (p = 0.76). A higher proportion of CYP2D6 IMs/PMs experienced orthostatism (p = 0.03), while there were no significant subgroup differences for the other hemodynamic variables.

Conclusion In this real-life clinical setting of patients aged ≥ 70 years, dosing of CYP2D6 substrates were not adjusted according to genotype-predicted CYP2D6 metabolism. The increased occurrence of orthostatism in patients with reduced/absent CYP2D6 metabolism may indicate that individualized dosing based on genotype has the potential to prevent adverse effects in these vulnerable patients.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40266-020-00763-0) contains supplementary material, which is available to authorized users.

Key Points

Pharmacogenetic variation in CYP2D6 metabolism can affect clinical effects as well as adverse effects of many drugs.

We found that patients aged ≥ 70 years with reduced or absent CYP2D6 metabolism received equal doses of CYP2D6-metabolized drugs as patients with normal CYP2D6 metabolism, and had an increased occurrence of orthostatism.

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1 Introduction

Individual variability in drug response depends on many factors in addition to the prescribed dosage, in particular, age, gender, organ functions, polypharmacy, drug–drug interactions, and pharmacogenetics. In recent years, increasing attention has been paid to the impact of pharmacogenetic differences on clinical and adverse effects of drug treatment [1], and in particular the role of genetic polymorphisms in drug-metabolizing enzymes [2].

Cytochrome P450 2D6 (CYP2D6) is one of the most well studied genetic polymorphic enzymes involved in drug metabolism. CYP2D6-metabolizing phenotype is closely related to genotype, and patients are generally divided into the following four phenotype subgroups based on genotype: ‘poor metabolizers (PMs),’ ‘intermediate metabolizers (IMs),’ ‘normal metabolizers (NMs),’ and ‘ultrarapid metabolizers (UMs)’ [3]. Population frequencies of the various CYP2D6 phenotype subgroups differ between ethnic groups due to environmentally driven selection of ‘best-fit’ genotypes. In Caucasian populations, the proportion of PMs is higher than in other ethnic groups, while the proportion of UM is generally higher in southern versus northern world regions [4].

CYP2D6 is involved in the metabolism of about 25% of all clinically used drugs [5]. For drugs where CYP2D6-mediated metabolism is a major eliminating pathway, the systemic exposure (effective dose) is very dependent on CYP2D6 genotype [4]. The relative effective dose may differ up to tenfold across different CYP2D6 genotype subgroups. This implies a great potential for variability in therapeutic response for non-genotype-adjusted dosages [4]. For older people, where secondary eliminating pathways are often reduced (e.g., renal filtration or secretion), the genotype effect could be even more pronounced, making dosage adjustments critical in order to avoid overtreatment.

The usual situation is that PMs are at risk of over-exposure and side effects at standard dosages, but in UM the potential clinical outcome is the opposite. For psychotropic agents and β-blockers, for instance, increased risk of side effects has been reported in PMs and insufficient clinical response in UM [6, 7]. However, for some opioid analgesics being defined as prodrugs activated by CYP2D6 (e.g., codeine and tramadol), the potential clinical consequences are the opposite. In the case of codeine, PMs have been reported to obtain insufficient analgesia [8], while severe case reports have been published showing respiratory depression in UM due to increased CYP2D6-mediated bi-activation of codeine to morphine [9, 10].

Older people exposed to polypharmacy have a high risk of adverse drug reactions (ADRs) [11]. Many CYP2D6-metabolized drugs commonly used by older people exhibit hemodynamic effects, including cardiovascular and psychotropic drugs [4, 12]. It could be hypothesized that older IMs and PMs are at higher risk for ADRs, such as orthostatic hypotension or bradycardia, if dosages are not adequately adjusted. Genotyping is rarely used in clinical practice, and it may be argued that knowledge of the genotype is of limited relevance, since physicians will nevertheless adjust dosages according to the clinical response. It is, however, uncertain if the underlying genotypes are actually reflected by the prescribed dosages when physicians are unaware of the patients’ ability to metabolize CYP2D6 substrate drugs.

The aim of this study was therefore to examine the prescribed dosages of CYP2D6 substrates in relation to genotype in home-dwelling patients aged ≥ 70 years exposed to polypharmacy. Secondarily, we assessed the impact of CYP2D6 genotype on blood pressure and heart rate.

2 Methods

2.1 Study Population and Data Collection

Data were taken from baseline assessments of participants in a recently published cluster randomized clinical trial (RCT) investigating drug-related issues in elderly people receiving polypharmacy [13]. In accordance with the inclusion criteria of the RCT, the present observational study comprised home-dwelling patients aged ≥ 70 years, using at least seven daily medications administered by the home nursing service. The rationale for including these patients was based on the hypothesis that they would benefit most of the geriatric intervention studied in the RCT.

Measurements of blood pressure and pulse rate were carried out by a research assistant during a home visit, using a validated, automated blood pressure monitor (UA-767 Plus 30, A&D Medical, San Jose, CA, USA). Supine blood pressure and pulse rate were measured twice, after a minimum of 5 minutes’ rest, and the mean value was used for the analyses. The patient then stood up, and measurements were repeated after 1 min. Comorbidity was assessed by the Cumulative Illness Rating Scale (CIRS) [14], based on a retrospective review of the patients’ medical records. Dementia severity was assessed by the Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) [15, 16].

Inclusion of patients was based upon informed consent. Patients unable to give a valid consent due to dementia were included based on informed consent from a close relative, in combination with assent from the patient. The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Norway and by the Data Protection Official at Oslo University Hospital, and was carried out in accordance with the Declaration of Helsinki [17].
2.2 Identification of CYP2D Substrates

Medication charts were obtained from the patients' family physician (FP), and actual drug use was confirmed by patients and/or caregivers. Drugs were registered according to the Anatomical Therapeutic Chemical (ATC) classification system [18]. In order to define a major relevance of CYP2D6 in the metabolism of the various drugs used by the patients, descriptions of metabolic pathways available from the website http://www.pharmgkb.org were applied. We also reviewed summaries of product characteristics (SPCs) to obtain information about the relevance of CYP2D6 in the respective drugs’ metabolism. Co-administration of CYP2D6 inhibitors was also registered.

2.3 Genotyping and Phenotype Classification

Venous blood samples collected on tubes with ethylenediaminetetraacetic acid (EDTA) as anticoagulant were used for determination of CYP2D6 genotype, and the analyses were performed at the Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway. Briefly, extracted DNA samples were analysed for targeted CYP2D6 variant alleles known to encode absent, reduced, or increased CYP2D6 metabolism using Taqman-based real-time PCR assays. The CYP2D6 genotyping comprised the non-coding variants CYP2D6*3 (rs55742686), CYP2D6*4 (rs3892097), CYP2D6*5 (whole gene deletion), and CYP2D6*6 (rs5030655), the reduced-function variants CYP2D6*9 (rs5030656), CYP2D6*10 (rs1065852), and CYP2D6*41 (rs28371725), as well as copy number analysis to identify multiplication of functional alleles giving rise to ultrarapid metabolism.

The patients were categorized into CYP2D6 metabolizer subgroups based on genotype. PMs were defined as homozygous carriers of non-coding alleles (CYP2D6*3, *4, *5, and *6). IMs were defined as heterozygous carriers of non-coding alleles, homozygous carriers of reduced-function alleles (CYP2D6*9, *10, and *41), or carriers of genotypes with combined reduced-function and non-coding alleles. NMs were defined as homozygous carriers of two fully functional (wild-type) alleles (CYP2D6*1) or carriers of one reduced-function allele combined with a wild-type allele. UMs were defined as carriers of multiple (> 2) copies of alleles encoding normal metabolic activity. This categorization of CYP2D6 metabolizer subgroups for statistical analyses is in accordance with standard practice at the time when the study was conducted, while a modification of the phenotype classification was recently published by members of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group [19].

2.4 Outcome Measures

2.4.1 Dosages

Our first aim was to examine the prescribed dosages of CYP2D6-dependent drugs in relation to genotype. As defined by WHO, “the defined daily dose (DDD) is the assumed average maintenance dose per day for a drug used for its main indication in adults” [20]. In order to examine the prescribed daily dosages across a variety of drugs, prescribed dosages for all substrates were calculated as percent of DDD. The average percent of DDD was calculated for each patient for comparisons between CYP2D6 metabolizer subgroups. As differences in CYP2D6 metabolism will affect the response of drugs administered in pharmacologically active forms or prodrugs (e.g., codeine and tramadol) differently, separate comparisons were performed for these two situations.

2.4.2 Hemodynamic Variables

Our second aim was to examine the impact of CYP2D6 genotype on hemodynamic variables. The outcome measures used for these analyses were systolic (SBP) and diastolic blood pressure (DBP) measured in the supine position, change in SBP after 1 min in standing position, pulse rate, orthostatic hypotension, and bradycardia. Orthostatic hypotension was defined as a fall in SBP of at least 20 mmHg or a fall in DBP of at least 10 mmHg after 1 min in standing position, while bradycardia was defined as a pulse rate < 60/min.

2.5 Statistical Analyses

In the study population, UMs using a CYP2D6 substrate only comprised two patients, and this phenotype subgroup was therefore excluded from the statistical analyses. The patients were divided into two CYP2D6 metabolizer subgroups for outcome comparisons, NMs versus IMs and PMs merged into one group.

Since several non-CYP2D6 drugs can affect blood pressure, the use of such drugs from ATC group C01DA (nitrates), C02 (antihypertensives), C03 (diuretics), C07 (β-blocking agents), C08 (calcium channel blockers), C09 (agents acting on the renin-angiotensin system), G04CA (α-adrenoceptor antagonists), N02A (opioids), N03 (antiepileptics), N04 (anti-parkinson drugs), N05 (psycholeptics), and N06A (antidepressants) was compared between the CYP2D6 metabolizer subgroups. Likewise, to account for non-CYP2D6 drugs that could contribute to bradycardia, the use of such drugs from ATC group C01AA (digitalis glycosides), C01B (antiarrhythmics, class I and III), C07 (β-blocking agents), and C08D (selective calcium channel blockers with direct cardiac effects) were assessed between

△ Adis
the genotype subgroups. However, the prescribed DDDs of the non-CYP2D6 drugs were not reviewed, prohibiting quantification of the potential modulation effect of these agents on the hemodynamic variables between the two CYP2D6 metabolizer subgroups.

For non-normally distributed variables, the Mann-Whitney $U$ test was used to test for differences between the CYP2D6 metabolizer subgroups. For normally distributed variables, comparisons were performed using the independent samples t-test. Group differences for categorical variables were tested by Pearson’s chi-square test or Fischer’s exact test, as appropriate. In the case of statistically significant findings by univariate analysis, multivariate logistic regression was performed to account for potential confounders.

All statistical analyses were performed using IBM SPSS Statistics version 25.

3 Results

A blood sample for CYP2D6 genotyping was obtained from 173 Caucasian patients. The genotype-predicted phenotype subgroups comprised 3 UMs (1.7%), 79 NMs (45.7%), 75 IMs (43.4%), and 16 PMs (9.2%). Characteristics of the respective metabolizer subgroups are presented in Table 1. The use of CYP2D6 inhibitors did not differ between metabolizer subgroups. Only weak CYP2D6 inhibitors were in use (i.e., escitalopram, mirabegron, and amiodarone). Although the CYP2D6 inhibitors were all detected in the NM or IM subgroups, both with functional metabolism, drug–drug–genotype interactions and phenocconversion was considered as unlikely due the limited inhibitory potency of the mentioned agents. Thus, the genotype-predicted CYP2D6-metabolizing phenotype was not adjusted for by any co-medications.

3.1 Dosages of CYP2D6 Substrates in Relation to Genotype

In the included patient population, a total of 19 different CYP2D6 substrates were in use, including three prodrugs. Their mean prescribed daily dosages and the respective percentage of DDD are presented in the various genotype subgroups in Table 2. Metoprolol was by far the most frequently used CYP2D6 substrate drug, being prescribed to 76 (43.9%) of the patients (Table 2).

The mean harmonized dosage of CYP2D6-metabolized drugs administered in the pharmacologically active form was 58% of DDD for NMs, 59% of DDD for IMs, and 63% of DDD for PMs (Table 3). There was no statistically significant difference in drug dosages of active CYP2D6 substrates between NMs and IMs/PMs ($p = 0.76$).

For CYP2D6 prodrugs, the mean dosage was 49% of DDD for NMs, 43% of DDD for IMs, and 43% of DDD for PMs (Table 3). There was no statistically significant difference in dosages of the prodrugs between NMs and IMs/PMs ($p = 0.74$).

3.2 Hemodynamic Effects in Users of CYP2D6 Substrates in Relation to Genotype

Table 2 provides an overview of hemodynamic variables in users of CYP2D6 substrates, except from prodrugs, in the various genotype subgroups. There was no statistically significant difference between NMs and IMs/PMs in SBP ($p = 0.79$), DBP ($p = 0.58$), or pulse rate ($p = 0.34$) measured in the supine position. SBP dropped in all groups after 1 min in the standing position, but there was no statistically significant difference between groups ($p = 0.15$). Nine patients had no measurements of standing blood pressure, and could not be examined for orthostatic hypotension.

The patient proportions with orthostatic hypotension (OH) was significantly higher for merged IMs (OH 44%)/PMs (OH 50%) than for NMs (OH 24%), $p = 0.03$. All patients with valid measurements of orthostatic hypotension

<Table 1 Characteristics of participants in different CYP2D6 genotype subgroups>

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>UM ($n = 3$)</th>
<th>NM ($n = 79$)</th>
<th>IM ($n = 75$)</th>
<th>PM ($n = 16$)</th>
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<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>79.7 (9.0)</td>
<td>84.1 (7.8)</td>
<td>82.9 (7.0)</td>
<td>81.9 (6.5)</td>
</tr>
<tr>
<td>Female gender, $n$ (%)</td>
<td>3 (100)</td>
<td>55 (70)</td>
<td>48 (64)</td>
<td>11 (69)</td>
</tr>
<tr>
<td>Number of CYP2D6 substrate drugs in use, mean (SD)</td>
<td>1.3 (1.2)</td>
<td>0.9 (0.9)</td>
<td>1.0 (0.7)</td>
<td>0.9 (0.9)</td>
</tr>
<tr>
<td>Total number of drugs used regularly, mean (SD)</td>
<td>11.0 (2.7)</td>
<td>9.4 (2.6)</td>
<td>10.0 (2.8)</td>
<td>10.0 (2.8)</td>
</tr>
<tr>
<td>CIRS sum, mean (SD)</td>
<td>18.3 (2.1)</td>
<td>16.6 (4.6)</td>
<td>16.8 (4.0)</td>
<td>16.4 (4.0)</td>
</tr>
<tr>
<td>CDR sum of boxes, mean (SD)</td>
<td>5.0 (5.0)</td>
<td>2.4 (3.3)</td>
<td>2.0 (3.3)</td>
<td>2.8 (3.6)</td>
</tr>
</tbody>
</table>

CDR Clinical Dementia Rating Scale, CIRS Cumulative Illness Rating Scale, CYP2D6 cytochrome P450 2D6, IM intermediate metabolizer, NM normal metabolizer, PM poor metabolizer, SD standard deviation, UM ultrarapid metabolizer

Table 4 provides an overview of hemodynamic variables in users of CYP2D6 substrates, except from prodrugs, in the various genotype subgroups. There was no statistically significant difference between NMs and IMs/PMs in SBP ($p = 0.79$), DBP ($p = 0.58$), or pulse rate ($p = 0.34$) measured in the supine position. SBP dropped in all groups after 1 min in the standing position, but there was no statistically significant difference between groups ($p = 0.15$). Nine patients had no measurements of standing blood pressure, and could not be examined for orthostatic hypotension.

The patient proportions with orthostatic hypotension (OH) was significantly higher for merged IMs (OH 44%)/PMs (OH 50%) than for NMs (OH 24%), $p = 0.03$. All patients with valid measurements of orthostatic hypotension

triangle Adis
<table>
<thead>
<tr>
<th>CYP2D6 substrate</th>
<th>UM (n = 3)</th>
<th>NM (n = 79)</th>
<th>IM (n = 75)</th>
<th>PM (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Dose Mean (SD)</td>
<td>Average % of DDD</td>
<td>n</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>1</td>
<td>100.0 mg</td>
<td>67</td>
<td>34</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>5</td>
<td>0.4 mg (0.0)</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7</td>
<td>23.6 mg (8.0)</td>
<td>79</td>
<td>4</td>
</tr>
<tr>
<td>Oxycodone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>25.8 mg (36.7)</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Codeine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>90.0 mg</td>
<td>90</td>
<td>3</td>
</tr>
<tr>
<td>Tramadol&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>300.0 mg</td>
<td>100</td>
<td>7</td>
</tr>
<tr>
<td>Donepezil</td>
<td>1</td>
<td>1.00 mg</td>
<td>133</td>
<td>5</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>3</td>
<td>25.0 mg (0.0)</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>1</td>
<td>150.0 mg</td>
<td>150</td>
<td>2</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>2</td>
<td>6.0 mg (2.8)</td>
<td>150</td>
<td>2</td>
</tr>
<tr>
<td>Mianserin</td>
<td>1</td>
<td>30.0 mg</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>1</td>
<td>12.5 mg</td>
<td>33</td>
<td>2</td>
</tr>
<tr>
<td>Propranolol</td>
<td>3</td>
<td>46.7 mg (30.6)</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Amiodarone</td>
<td>1</td>
<td>100.0 mg</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1</td>
<td>1.0 mg</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>1</td>
<td>10.0 mg</td>
<td>67</td>
<td>1</td>
</tr>
<tr>
<td>Doxepin</td>
<td>1</td>
<td>20.0 mg</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Paroxetine</td>
<td>1</td>
<td>10.0 mg</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Tolterodine</td>
<td>1</td>
<td>4.0 mg</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Entire material (N = 173)

*CYP2D6* cytochrome P450 2D6, *DDD* defined daily dose, *IM* intermediate metabolizer, *NM* normal metabolizer, *PM* poor metabolizer, *SD* standard deviation, *UM* ultrarapid metabolizer

<sup>a</sup>Prodrug
used at least one non-CYP2D6 drug (range 1–8) that could potentially increase the occurrence of orthostatism, but the mean number of such drugs did not differ between the genotype subgroups \((p = 0.53)\). The observed higher occurrence of orthostatism for IMs/PMs was further examined by logistic regression, showing that the difference versus NMs was unaffected by total numbers of drug use and comorbidity \((\text{adjusted OR (OR)} 2.6, 95\% \text{ CI } 1.1–6.3; \quad p = 0.04)\) \([\text{Table S1 in the electronic supplementary material (ESM)}]\).

Data on renal and hepatic function were not systematically available for the included patients.

The calculated proportion of patients with bradycardia was also higher for IMs (29%) and PMs (33%) than for NMs (20%), but the association between metabolizer subgroup and bradycardia was not statistically significant \((p = 0.22)\). The mean number of non-CYP2D6 drugs potentially affecting pulse rate did not differ between the genotype subgroups \((p = 0.43)\).

Metoprolol was the most frequently used CYP2D6 substrate \((n = 76)\), which made it interesting to perform subgroup analyses for these patients (Table 5). There were no statistically significant differences between NMs and IMs/PMs for any of the hemodynamic variables in metoprolol-treated patients, but we observed a trend towards higher occurrence of orthostatic hypotension for IMs/PMs compared with NMs \((p = 0.07)\). As above, this finding was further examined by logistic regression (Table S2 in the ESM).

### Table 3

<table>
<thead>
<tr>
<th>CYP2D6 substrate</th>
<th>UM ((n = 2))</th>
<th>NM ((n = 50))</th>
<th>IM ((n = 59))</th>
<th>PM ((n = 10))</th>
<th>(p) value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment intensity for users of CYP2D6 (non-prodrugs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of non-CYP2D6 drugs potentially affecting pulse rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment intensity for users of CYP2D6 prodrugs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Hemodynamic variables for users of drugs inactivated by CYP2D6 ((N = 108)) by CYP2D6 genotype subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients using only CYP2D6 prodrugs are excluded</td>
</tr>
<tr>
<td>(<em>p</em> value is based on comparisons between two groups: NMs versus IMs/PMs (UMs excluded)</td>
</tr>
<tr>
<td>(^b) Comprising drugs from ATC groups C01DA, C02, C03, C07, C08, C09, G04CA, N02A, N03, N04, N05, and N06. Counts are included only for patients having valid measurements of orthostatism</td>
</tr>
<tr>
<td>(^c) Comprising drugs from ATC groups C01AA, C01B, C07, and C08D</td>
</tr>
<tr>
<td>(^d) Amiodarone, mirabegron, escitalopram</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supine SBP, mean (SD)</th>
<th>2 132 (4)</th>
<th>46 135 (22)</th>
<th>51 138 (22)</th>
<th>9 127 (15)</th>
<th>0.79</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine DBP, mean (SD)</td>
<td>2 85 (7)</td>
<td>46 74 (12)</td>
<td>51 72 (13)</td>
<td>9 75 (18)</td>
<td>0.58</td>
</tr>
<tr>
<td>Change in SBP after 1 min standing, mean (SD)</td>
<td>2 10 (5)</td>
<td>46 10 (12)</td>
<td>51 10 (13)</td>
<td>9 10 (18)</td>
<td>0.58</td>
</tr>
<tr>
<td>Orthostatic hypotension, (n) (%)</td>
<td>2 1 (50)</td>
<td>46 2 (40)</td>
<td>51 3 (50)</td>
<td>9 3 (50)</td>
<td>0.03</td>
</tr>
<tr>
<td>Pulse rate, mean (SD)</td>
<td>2 73 (9)</td>
<td>46 70 (12)</td>
<td>51 67 (13)</td>
<td>9 67 (17)</td>
<td>0.34</td>
</tr>
<tr>
<td>Bradycardia, (n) (%)</td>
<td>2 0 (0)</td>
<td>46 9 (20)</td>
<td>51 15 (29)</td>
<td>9 3 (33)</td>
<td>0.22</td>
</tr>
<tr>
<td>Number of non-CYP2D6 drugs potentially affecting the risk of orthostatism, (n) mean (SD)</td>
<td>2 5 (1.4)</td>
<td>46 3 (1.7)</td>
<td>51 4 (1.4)</td>
<td>9 3 (1.4)</td>
<td>0.53</td>
</tr>
<tr>
<td>Number of non-CYP2D6 drugs potentially affecting pulse rate, (n) mean (SD)</td>
<td>2 5 (0.7)</td>
<td>46 0.9 (0.5)</td>
<td>51 1.0 (0.6)</td>
<td>9 0.9 (0.6)</td>
<td>0.43</td>
</tr>
<tr>
<td>Co-administration of CYP2D6 inhibitors, (n) (%)(^d)</td>
<td>2 0 (0)</td>
<td>46 4 (9)</td>
<td>51 7 (14)</td>
<td>9 0 (0)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

\(\Delta\) Adis
Discussion

There was no difference in the mean prescribed dosage of CYP2D6 substrates between the various CYP2D6-metabolizer subgroups, either for drugs inactivated by CYP2D6 or those activated by CYP2D6 (prodrugs). As CYP2D6 genotype is known to be a major determinant of the exposure of the studied drugs, this may indicate that the physicians’ clinical judgement is insufficient when the aim is to optimize dosages for older patients and avoid ADRs. This is supported by the significant difference in orthostatism between CYP2D6 slow and normal metabolizers. It would have been favorable to study IMs and PMs as separate subgroups, but the limited power did not allow for reasonable statistical comparisons of three CYP2D6 subgroups. However, it was interesting to observe an increased occurrence of orthostatism by a stepwise reduction in CYP2D6 metabolizer phenotype, where 24% of NMs, 44% of IMs, and 50% of PMs had this symptom. As the present study is based on a post-hoc analysis of a limited population size, the potential increased risk of ADRs in older CYP2D6 IMs/PMs should be further investigated prospectively in larger patient populations.

The patients included in our study were aged 70 years or older, multimorbid, and exposed to extensive polypharmacy, and therefore especially vulnerable to ADRs [21]. The fact that all metabolizer subgroups were prescribed lower doses of CYP2D6 substrate drugs than generally recommended, as indicated by the calculated percentage of DDD, could reflect a reduced drug tolerability in the included patient population, or precautionary physicians. Other factors than variability in CYP2D6 metabolism may therefore be of similar or greater importance for dose requirements of the identified CYP2D6 substrates. However, taking into account the therapeutic heterogeneity of the CYP2D6 substrates and the significant impact on risk of orthostatism, we consider it likely that older patients with reduced or absent CYP2D6 metabolism should be dosed lower than those with normal metabolism. In line with this, use of CYP2D6 genotyping should be considered as a tool for optimized dosing in older patients receiving complex treatment with multiple drugs.

We have not found other studies evaluating the impact of CYP2D6 polymorphisms on treatment intensities across various CYP2D6 substrates, but prescribed dosages in relation to CYP2D6 genotype of single drugs has, to some extent, been investigated [22–27]. For example, in a large population-based cohort of elderly patients, Bijl et al. found significantly lower maintenance doses of antidepressants in PMs compared with NMs [22]. For metoprolol, which is extensively metabolized by CYP2D6, some studies have found that PMs were prescribed significantly lower doses than NMs [23–25], while others did not find such differences [26, 27].

Despite CYP2D6 PMs obtaining a fivefold higher exposure of metoprolol per dose, the reported findings of the impact of CYP2D6 genotype on hemodynamic variables and side effects are conflicting [28, 29]. While some studies have found associations between CYP2D6 genotype and clinical

---

**Table 5** Hemodynamic variables for users of metoprolol (N = 76) by CYP2D6 genotype subgroup

<table>
<thead>
<tr>
<th></th>
<th>UM (n = 1)</th>
<th>NM (n = 34)</th>
<th>IM (n = 34)</th>
<th>PM (n = 7)</th>
<th>p valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine SBP, mean (SD)</td>
<td>129 (16)</td>
<td>135 (23)</td>
<td>137 (23)</td>
<td>129 (16)</td>
<td>0.93</td>
</tr>
<tr>
<td>Supine DBP, mean (SD)</td>
<td>71 (19)</td>
<td>71 (19)</td>
<td>71 (19)</td>
<td>71 (19)</td>
<td>0.35</td>
</tr>
<tr>
<td>Change in SBP after 1 min standing, mean (SD)</td>
<td>32 (12)</td>
<td>34 (12)</td>
<td>31 (12)</td>
<td>34 (12)</td>
<td>0.17</td>
</tr>
<tr>
<td>Orthostatic hypotension, n (%)</td>
<td>6 (13)</td>
<td>7 (13)</td>
<td>6 (13)</td>
<td>7 (13)</td>
<td>0.42</td>
</tr>
<tr>
<td>Pulse rate, mean (SD)</td>
<td>66 (13)</td>
<td>73 (18)</td>
<td>73 (18)</td>
<td>73 (18)</td>
<td>0.42</td>
</tr>
<tr>
<td>Bradycardia, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

CYP2D6 cytochrome P450 2D6, DBP diastolic blood pressure, IM intermediate metabolizer, NM normal metabolizer, PM poor metabolizer, SBP systolic blood pressure, SD standard deviation, UM ultrarapid metabolizer

*The p-value is based on comparisons between two groups; NMs versus IMs/PMs (UMs excluded)

b Comprising drugs from ATC groups C01DA, C02, C03, C07, C08, C09, G04CA, N02A, N03, N04, N05, and N06
c Comprising drugs from ATC groups C01AA, C01B, C07, and C08D
d Amiodarone, mirabegron, escitalopram
effects [6, 23, 24, 30, 31], others have not [26, 32–34]. This may partly be explained by the fact that most studies were performed in a naturalistic setting without any controlled dosing protocol. In the present study, the metoprolol dosing was similar regardless of CYP2D6 genotype, with a non-significantly higher proportion of patients with orthostatism in CYP2D6 IMs/PMs versus NMs. Thus, in older CYP2D6 IMs/PMs, it seems rational to initiate metoprolol treatment with a lower dose than usually recommended.

There were relatively few patients using CYP2D6 substrates other than metoprolol with strong hemodynamic effects, such as tricyclic antidepressants (TCAs) [35]. We cannot rule out that patients with reduced or absent CYP2D6 metabolism have previously used more CYP2D6 substrates, but that ADRs caused these drugs to be stopped before the initiation of our study.

The most important weakness of our study is that relatively few patients were included, which reduces the statistical power of the comparisons. Further studies should therefore replicate our findings, preferably in larger populations of older patients. In addition, we did not have sufficient data for all participants to include renal or hepatic impairment as covariates in the analyses, and cannot rule out that this could have affected the observed findings. Another aspect is that more refined classification or subgrouping of CYP2D6 genotype-predicted phenotypes by the use of the functional allele enzyme activity scores, which is currently advised to be applied by the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG), may improve the clinical interpretation of the possible association between CYP2D6 metabolism and treatment outcomes. However, very limited clinical research is performed on the pharmacogenetic impact of drug effects and side effects in the increasing population of home-dwelling older patients. In this context, our findings are novel, and highlight the possible relevance of pharmacogenetic differences for drug response in older patients subjected to polypharmacy.

5 Conclusions

In a naturalistic clinical setting of older, home-dwelling patients, dosing of CYP2D6 substrates was not adjusted according to genotype-predicted CYP2D6 metabolism. The increased frequency of orthostatism in CYP2D6 IMs/PMs versus NMs may therefore reflect higher exposure of CYP2D6 substrates in the former subgroup, and in particular metoprolol, which was by far the most commonly used CYP2D6 substrate with hemodynamic effects. Further studies should therefore investigate if dose adjustments based on preemptive CYP2D6 genotyping can improve clinical outcomes and reduce side effects in older patients subjected to polypharmacy.

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Author Contributions RR had full access to all data in the study and is responsible for the data integrity and accuracy of the data analysis. Study concept and design: all authors. Acquisition of data: RR. Analysis and interpretation of data: all authors. Statistical analysis: RR. Preparation of the manuscript: RR. Critical revision of the manuscript for important intellectual content: all authors. Funding acquisition: TBW. Supervision: TBW, EM. All authors read and approved the final manuscript.

Compliance with Ethical Standards

All procedures were in accordance with the ethical standards of the institutional and national research committee (the Regional Committee for Medical and Health Research Ethics in Norway) and with the 1964 Helsinki declaration and its later amendments.

Funding The study was funded by the Research Council of Norway (Grant number 222033/LAB).

Conflict of interest RR, TBW, JS, HK, and EM declare that they have no conflict of interest.

Ethical approval The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Norway and by the Data Protection Official at Oslo University Hospital.

Data availability The datasets analyzed during the current study are not publicly available due to restrictions from the Norwegian Data Protection Officer, but are available from the corresponding author on reasonable request.

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Romskaug R. et al. Prescribed Doses of CYP2D6-Metabolized Drugs and Hemodynamic Responses in Relation to CYP2D6 Genotype Among Older Patients Exposed to Polypharmacy.

Drugs & Aging 2020

https://doi.org/10.1007/s40266-020-00763-0

Table S1. Risk factors for orthostatism, users of drugs inactivated by CYP2D6 (n=98)^a

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted models</th>
<th></th>
<th></th>
<th>Adjusted model</th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95 % CI</td>
<td>p value</td>
<td>OR</td>
<td>95 % CI</td>
<td>p value</td>
</tr>
<tr>
<td>CYP2D6 genotype subgroup IM/PM^b</td>
<td>2.6</td>
<td>1.1-6.3</td>
<td>0.04</td>
<td>2.6</td>
<td>1.1-6.3</td>
<td>0.04</td>
</tr>
<tr>
<td>Use of non-CYP2D6 drugs potentially affecting the risk of orthostatism^c</td>
<td>1.0</td>
<td>0.8-1.3</td>
<td>0.88</td>
<td>1.0</td>
<td>0.7-1.3</td>
<td>0.93</td>
</tr>
<tr>
<td>CIRS sumscore</td>
<td>1.0</td>
<td>0.9-1.1</td>
<td>0.61</td>
<td>1.0</td>
<td>0.9-1.2</td>
<td>0.59</td>
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</tbody>
</table>

^aPatients only using prodrugs and patients with no valid measurements of orthostatism are excluded
^bNM = reference group, UM excluded from analyses
^cNumber of drugs from ATC group C01DA, C02, C03, C07, C08, C09, G04CA, N02A, N03, N04, N05 and N06

Abbreviations: CI = Confidence interval, CIRS = Cumulative Illness Rating Scale, CYP2D6 = Cytochrome P450 2D6, IM = Intermediate metabolizer, NM = Normal metabolizer, OR = Odds ratio, PM = Poor metabolizer, UM = Ultrarapid metabolizer
Table S2. Risk factors for orthostatism, users of metoprolol (n=76)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unadjusted models</th>
<th>Adjusted model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95 % CI</td>
</tr>
<tr>
<td>CYP2D6 genotype subgroup IM/PM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.7</td>
<td>0.9-8.2</td>
</tr>
<tr>
<td>Use of non-CYP2D6 drugs potentially affecting the risk of orthostatism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.1</td>
<td>0.8-1.6</td>
</tr>
<tr>
<td>CIRS sum score</td>
<td>1.0</td>
<td>0.9-1.2</td>
</tr>
</tbody>
</table>

<sup>a</sup>NM = reference group, UM excluded from analyses
<sup>b</sup>Number of drugs from ATC group C01DA, C02, C03, C07, C08, C09, G04CA, N02A, N03, N04, N05 and N06

Abbreviations: CI = Confidence interval, CIRS = Cumulative Illness Rating Scale, CYP2D6 = Cytochrome P450 2D6, IM = Intermediate metabolizer, NM = Normal metabolizer, OR = Odds ratio, PM = Poor metabolizer, UM = Ultrarapid metabolizer