Inappropriate Medication Use in the Elderly – A Modern Epidemic

Two Pharmacoepidemiological Observational Studies among Elderly Living at Home and in Nursing Homes and a Three-Round Delphi Consensus Process for the Development of the NORGEP-NH Explicit Criteria for Potentially Inappropriate Medication Use in Elderly Nursing Home Residents

Gunhild Alvik Nyborg
Thesis for PhD (Philosophiae Doctor)
Department of General Practice
Institute of Health and Society
University of Oslo

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“Medical science has made such tremendous progress

that there is hardly a healthy human left.”

Aldous Huxley

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2 SUMMARY OF THESIS IN ENGLISH

Background

Pharmacotherapy plays a large role in modern medicine and especially among the elderly polypharmacy is now common. Due to physiological changes of old age, elderly are at higher risk of side effects and interactions from medication.

Some substances, or combinations of substances, are more harmful to the elderly than others. These should be avoided whenever possible, due to their high risk of negative side effects. This has led to the development in different countries of lists of explicit criteria for potentially inappropriate medication use, including the Norwegian NORGEP criteria for potentially inappropriate medication use in the home-dwelling elderly, published in 2008. However, the extent of the problem of potentially inappropriate medication (PIM) use in Norwegian elders and their predictors was largely unexplored at the outset of this thesis.

Objectives

The aim of this thesis was to study the magnitude of the problem of potentially inappropriate medication use in the elderly, both home-dwelling and nursing home residents. Additionally to develop a tool to estimate potentially inappropriate medication use in elderly in nursing homes for use in both research, clinical decision making and quality control for medication use in nursing homes, and to test this tool in a nursing home population.

Methods

Through a national, cross-sectional observational study using data from the Norwegian Prescription Database and the NORGEP criteria, the prevalence of potentially inappropriate medication use in home-dwelling elderly ≥ 70 years and predictors were analysed. The data set included all prescriptions (except in-ward prescriptions) in the year of 2008, to 445.900 individuals (88.3% of the Norwegian population in this age group), altogether 11,491,065 prescriptions from 24,540 prescribers (Article 1).

The Norwegian General Practice – Nursing Home (NORGEP-NH) criteria were developed via survey software through a three-round Delphi consensus process with 80 participants; specialists in geriatrics or clinical pharmacology, physicians in nursing

homes and experienced pharmacists. These criteria are a further development of the NORGEP criteria especially designed for the nursing home sector (Article 2).

The NORGEP-NH criteria were then employed on a data set of 881 nursing home residents from 30 nursing homes in the county of Vestfold, Norway, in an observational, cross-sectional study of prevalence and factors associated with potentially inappropriate medication use in the nursing home setting (Article 3). Data were obtained from an interventional trial (IntraVenous treatment In Infections In Vestfold, the "3iV-study") on the effect of implementing intravenous treatment in nursing homes.

Main findings

We found that 34.8% of the Norwegian home-dwelling elderly ≥ 70 years were prescribed at least one PIM in 2008, 59.9% of these representing psychotropic drugs. Among the twenty percent who received more than ten medications over the year, two-thirds received a minimum of one PIM. Females had a higher risk for being exposed to PIMs than men (odds ratio 1.60, 99% C.I. 1.58-1.64) (Article 1).

The Norwegian General Practice – Nursing Home (NORGEP-NH) criteria, a list of 34 explicit criteria for potentially inappropriate medication use in nursing homes, were developed through a three-round Delphi consensus process. The final list consisted of 27 criteria proposed by the authors and 7 criteria based on suggestions from the panel. The degree of consensus increased for each round (Article 2).

According to the NORGEP-NH Single Substance (part A) and Combination (part B) criteria, 43.8% of the included nursing home residents received at least one PIM as a regular medication. When including the Deprescribing criteria (part C), and also drugs taken as needed, the prevalence of nursing home residents receiving medication that needs special surveillance was 92.7%. 69.7% of participants were prescribed at least one psychotropic drug on a regular basis. Females were more likely to be exposed to PIMs than males (odds ratio 1.60, p=0.007) (Article 3).

Conclusions

The extent of potentially inappropriate medication use among Norwegian elderly is substantial among both men and women, both among home-dwelling and nursing home residents. The use of multiple psychotropic drugs is highly prevalent, especially so in the nursing homes. Elderly females are at higher risk than are their male counterparts, for

both PIMs and the use of multiple concurrent psychotropic drugs. The task of prescribing to elderly people, especially to the frail residents of the nursing homes, is complex. The work in this thesis has shown that prescribing to the elderly also has a high-risk profile. This reality must be reflected in educational efforts towards doctors and other medical staff and in organizational efforts regarding home care and nursing home resources.

3 SUMMARY OF THESIS IN NORWEGIAN

Bakgrunn

Farmakoterapi spiller en viktig rolle i moderne medisin, og spesielt blant eldre er polyfarmasi blitt vanlig forekommende. På grunn av fysiologiske aldersforandringer har eldre høyere risiko for å oppleve bivirkninger og interaksjoner av medisiner.

Noen medikamenter, eller kombinasjoner av slike, er mer risikable for de eldre enn andre. Disse bør unngås så langt som mulig, på grunn av deres høye risiko for negative bivirkninger. På bakgrunn av dette har man i flere land etter hvert utviklet lister med eksplisitte kriterier for potensielt uheldig legemiddelbruk hos eldre, inkludert de norske NORGEP-kriteriene beregnet på hjemmeboende eldre, som ble publisert i 2008.

Omfanget av uheldig legemiddelbruk hos eldre i Norge, og hvilke faktorer som kan henge sammen med denne, var i stor grad ubesvart ved innledningen til arbeidet med denne avhandlingen.

Formål

Formålet med dette arbeidet har vært å forsøke å belyse omfanget av potensielt uheldig legemiddelbruk hos eldre i Norge i dag, både hos hjemmeboende og i sykehjem. I tillegg ønsket vi å utvikle en liste med eksplisitte kriterier for potensielt uheldig legemiddelbruk spesielt beregnet på eldre sykehjemsbeboere. Vi ønsket også å teste relevansen av disse nye kriteriene på en sykehjemspopulasjon.

Metode

Gjennom en nasjonal tverrsnittsundersøkelse med data fra Reseptregisteret og ved hjelp av NORGEP-kriteriene analyserte vi prevalensen av, og prediktorer for, potensielt uheldig legemiddelbruk hos hjemmeboende eldre ≥ 70 år. Datasettet inkluderte alle forskrivninger (bortsett fra forskrivninger innenfor institusjoner) for hele 2008, til 445.900 individer (88.3% av den norske befolkningen i denne aldersgruppen), til sammen 11.491.065 forskrivninger fra 24.540 forskrivere (Artikkel 1).

Norwegian General Practice – Nursing Home kriteriene, NORGEP-NH-kriteriene, ble utviklet via web-basert survey software i en tre-runders Delphi konsensusprosess med 80 deltakere. Deltakerne var sykehjemsleger eller spesialister i geriatri eller klinisk

farmakologi. I tillegg deltok noen spesielt kvalifiserte farmasøyter. NORGEP-NH-kriteriene er en videreutvikling av NORGEP-kriteriene, spesielt beregnet for sykehjemssektoren (Artikkel 2).

NORGEP-NH-kriteriene ble så benyttet på et datasett fra 881 sykehjemsbeboere fra 30 sykehjem i Vestfold, i en tverrsnittsstudie som så på prevalensen av og faktorer forbundet med potensielt uheldig legemiddelbruk i sykehjem (Artikkel 3). Data ble innhentet fra en intervensjonsstudie, IntraVenøs behandling Ved Infeksjoner I Vestfold (3iV-studien), som så på effekten av innføring av intravenøs behandling i sykehjem.

Hovedfunn

Vi fant at 34.8% av alle norske hjemmeboende eldre ≥ 70 år i løpet av 2008 fikk forskrevet minst ett legemiddel som etter NORGEP-kriteriene karakteriseres som potensielt uheldig i denne aldersgruppen. 59.9% av disse var psykotrope medikamenter. 20% fikk forskrevet mer enn ti ulike medikamenter i løpet av året, og blant disse fikk 2/3 minst ett potensielt uheldig legemiddel. Kvinner hadde høyere risiko for å få forskrevet medikamenter i denne gruppen enn menn (odds ratio 1.60, 99% K.I. 1.58-1.64) (Artikkel 1).

NORGEP-NH-kriteriene, en liste på 34 eksplisitte kriterier for potensielt uheldig legemiddelbruk hos eldre i sykehjem, ble utviklet gjennom en tre-runders Delphi konsensus-prosess. Den endelige listen besto av 27 kriterier som var foreslått av forfatterne samt 7 kriterier foreslått av panelet i runde 1. Graden av konsensus økte for hver runde (Artikkel 2).

I henhold til NORGEP-NH-kriteriene del A (enkeltmedikamenter som bør unngås) og del B (kombinasjon av medikamenter som bør unngås), fikk 43,8% av deltakerne i studien av sykehjemsbeboere i Vestfold minst ett potensielt uheldig legemiddel som fast forskrivning. Når vi også inkluderte kriterienes del C (medikamenter der man bør vurdere om det er mulig å seponere), og medikamenter forskrevet til bruk ved behov, var prevalensen av forskrivning av medisiner som trenger spesiell overvåkning 92.7%. 69.7% av deltakerne i studien fikk minst ett psykotropt legemiddel som fast forskrivning. Kvinner hadde høyere sannsynlighet for å få potensielt uheldige legemidler enn menn (odds ratio 1.60, p=0.007) (Artikkel 3).

Konklusjoner

Potensielt uheldig legemiddelbruk blant eldre i Norge i dag er omfattende blant både menn og kvinner, både hos hjemmeboende og hos sykehjemsbeboere. Samtidig bruk av flere psykotrope legemidler er vanlig, spesielt i sykehjem. Eldre kvinner har høyere risiko enn menn for både å få forskrevet slike potensielt uheldige legemidler, og for å få forskrevet flere psykotrope medisiner samtidig. Å forskrive legemidler til eldre, og spesielt til skrøpelige eldre i sykehjem, er en komplisert oppgave. Arbeidet med denne avhandlingen har vist at forskrivning til de eldre har en høy risikoprofil. Denne virkeligheten må reflekteres i videreutdanning av helsepersonell og i organiseringen av helsetjenester for både hjemmeboende eldre og for beboere i sykehjem.

4 PREFACE

One of the most memorable lectures I can recall from my time as a medical student at the University of Oslo was a lecture in Geriatrics by late professor Knut Laake. The lecture was on polypharmacy, a relatively new concept at the time. He told a story about an old woman who had been hospitalized at his ward. She was in a very poor clinical state and had a meagre prognosis. After thorough considerations, they discontinued all her medications – a substantial list of drugs taken on a daily basis. In the days that followed, the old woman became gradually more awake and alert, started eating and drinking herself and ended up being discharged – in many respects as a new person. His message to us was; Drugs can do harm. Sometimes less is more. Be brave.

Later, as a practicing physician, I found little research and no guidelines to lean on in my struggle to avoid over-medication in my older patients. It often came down to a “gut feeling”. Indeed, in this, you had to be brave.

I spent my first years working as an independent doctor after finishing my internship in Finnmark, Norway’s northernmost county, as a general practitioner and nursing home doctor. In such a remote area in an arctic climate, resources regarding health professionals were scarce. Working in the nursing home, my impression was of a somewhat random prescription practice. More than anything else, prescriptions for each patient seemed to be dependent on which doctor had seen the patient last. There seemed to be a lack of continuity and consistency.

Later, working as a nursing home doctor in Bærum, a rich community close to Oslo, I did notice a contrast to the more random practices of remote Finnmark. Nevertheless, there still seemed to be a lack of homogenous standards when it came to prescription practices. Each patient’s medical treatment still seemed to rely greatly on the subjective opinion of the individual prescribing physician. Later, I observed the same pattern working in a nursing home in the city of Moss in Østfold, one of the southernmost counties in Norway and historically more of a working class community. Alongside this, I also worked as a general practitioner in the same municipalities and in the city of Oslo. Everywhere there were seemingly random differences in the chosen pharmacological treatment for older patients, corresponding to the lack of general guidelines. The quality of prescribing in many instances was below optimal. (The same tendency for individual variation in prescription practices was later demonstrated in the USA (Chen et al. 2010).)

The problem of inappropriate medication use in the elderly is a topic frequently encountered in everyday settings. It seems every other person has an elder dear to them who has been “drugged” by too much and/or the wrong type of medication, or who has experienced serious side effects through drug interaction.

Over time, I pondered: Was what I had observed representative of a general problem? If so, what was the magnitude of this problem? To what extent did this actually affect the well-being of those subject to this practice? Moreover, could anything be done in order to improve the situation?

Eventually, I presented these thoughts to Professor Jørund Straand at the Department of General Practice. Straand had already many years of research in this field behind him, and with the help of him and my main supervisor Mette Brekke, we found the research questions for this thesis.

While this thesis was under way, it was my opinion from my part time work at an Oslo hospital rehabilitation unit for elderly people, that an increased focus on inappropriate prescribing to the elderly might have some effect on prescription practice. Due to intensified efforts by health professionals, and research nationally and internationally, there seemed to be an increasing awareness among Norwegian doctors towards the problem. However, there is still a long way to go, as I will show later in this thesis.

This thesis is my humble contribution to the existing knowledge in the field.

Since this thesis was handed in, Article 3 has been published in BMC Geriatrics. Here is the full reference for the published article:

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5 LIST OF PUBLICATIONS

Paper 1

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Paper 3

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6 LIST OF ABBREVIATIONS

3iV-study: IntraVenøs behandling Ved Infeksjoner I Vestfold (IntraVenous treatment In Infections In Vestfold)
ADE: Adverse Drug Event
ADL: Activities of Daily Living
ADR: Adverse Drug Reaction
ATC: The WHO Anatomical Therapeutical and Chemical Classification System
BPSD: Behavioural and Psychological Symptoms of Dementia
CAM: Confusion Assessment Method
CI: Confidence interval
DDD: Defined daily dose
ICC: Intra-cluster Correlation Coefficient
IQR: Interquartile Range
MS: Mean Score
NFKF: Norwegian Society of Clinical Pharmacology
NGF: Norwegian Geriatrics Society
NH: Nursing Home
NNH: Number needed to harm
NNT: Number needed to treat
NORGEP: The Norwegian General Practice criteria
NORGEP-NH: The Norwegian General Practice - Nursing Home criteria
NorPD: The Norwegian Prescription Database
NSD: The Norwegian Social Sciences Data Services
OR: Odds ratio
PIP: Potentially Inappropriate Prescription
PIM: Potentially Inappropriate Medication
PPO: Potential Prescribing Omission
RCT: Randomized controlled trial
RR: Risk ratio
SD: Standard Deviation
SQL: Structured Query Language

Pharmacological:
ACE-inhibitors: Angiotensin-converting enzyme inhibitors
ARB: Angiotensin receptor blockers
AT2-antagonists: Angiotensin II receptor antagonists
Coxibs: Cyclooxygenase-2-selective inhibitors
NSAIDs: Non-steroid anti-inflammatory drugs
SRNIs: selective norepinephrine reuptake inhibitors
SSRIs: Selective serotonin re-uptake inhibitors
TCAs: Tricyclic antidepressants

In this thesis, the term “external criteria” will mean, “external criteria for potentially inappropriate medication use in the elderly” – unless stated otherwise in the text.

7 BACKGROUND

'The idea is to die young, as late as possible.'

- Ashley Montagu

A hundred years ago, or even fifty, practically no one was using any medication on a regular basis. Then the pharmacological era began, and one discovery took the other. In 1923, Frederick Banting received the Nobel Prize for the discovery of insulin, sharing credits with his assistant Charles Best. The same year the first vaccine was developed, against diphtheria, and in 1928, Alexander Fleming discovered penicillin. Sulfa was first taken into use in 1935. In the 40'ies researchers managed to isolate cortisone, and in the 50'ies some of the first new psychiatric substances, among them chlorpromazine, saw daylight. After this, the scientific field of pharmacology has developed exponentially, opening up a whole range of new possibilities within medical treatment, and an increasing number of medications have hit the market. We have seen the average life span steadily increase, quality of life (QoL) in the last years of life likewise.

However, no drug with effect is without potential side effects. Today, polypharmacy is an increasingly common occurrence, especially among the elderly, being more prone to comorbidities. Onder et al found polypharmacy defined as 5‑9 drugs in 49.7% of European nursing home residents and excessive polypharmacy defined as ≥10 drugs in 24.3% of residents (Onder et al. 2012). Adverse drug reactions (ADRs) have become an addition to the disease panorama over the last decades: an American meta-analysis from 1998 found an incidence of altogether 7% for serious (6.7%) or fatal (0.3%) adverse side effects of drugs among all hospitalizations (Lazarou et al. 1998). In Norway, a study found that 18.2% of all deaths in a department of internal medicine was related to ADRs, and elderly and people with multiple comorbidities were especially at risk (Ebbesen et al. 2001).

7.1 On the increased risk associated with medication use in the elderly

"Every drug is a triangle with three faces, representing

the healing it can bring, the hazards it can inflict,

and the economic impact of each" - Jerry Avorn

Due to physiological changes that happen as we age, elderly people are at higher risk of experiencing negative side effects from the use of medications or interactions between them (Wehling 2013). You could say that elderly people have a smaller spare tank – they use a larger proportion of their organs' capacity under normal circumstances, than do their younger counterparts. Thus, the ingestion of medications that impose strain on organs like the kidneys, or on cognitive capacity, is more likely to result in noticeable side effects. Sight and hearing may be impaired, motor function likewise, leading to a situation where a marginal deterioration of balance may have potentially serious consequences. The percentage of fat in the body relative to fluids increases with age, affecting how drugs are distributed and metabolized. These altered pharmacodynamic and pharmacokinetic factors all add to the complexity of medication use in the elderly.

Nonetheless, the scientific norm has been for people exceeding a certain age, and people with comorbidities, to be excluded from drug trials. This is understandable if you wish to standardize test conditions, but it means that many trials have never tested the drug in question on the population that will most likely be the consumers of the drug. We extrapolate results from drug trials performed on younger, healthier populations onto the multi-morbid, frail elderly. There is thus little evidence on the efficacy and safety of medication use among the very old, much less when they are taking many drugs at the same time. We obviously need more trials that target the elderly population, but statistically, it is impossible to perform RCTs that cover all possible combinations of comorbidities and polypharmacy that we see in clinical practice.

How would for instance numbers needed to treat (NNT) and numbers needed to harm (NNH) look if trials on ACE-inhibitors and AT2-antagonists were performed on an elderly population in a real life setting, where marginally functioning kidneys and concomitantly taking metformin for diabetes is relatively common? This is a kind of setting that is

relevant when the number of drugs given to elderly on a regular basis approaches ten, as we see these days (Fulton et al. 2005, Onder et al. 2012).

7.2 Risk of bias in drug trial reporting

To add insult to injury, pharmaceutical companies have financial incentives towards increasing drug consumption (Avorn 2005). This may lead to a risk of bias in the reporting of drug trials. Trials have been comparing non-equivalent doses, or comparing new substances to placebo. A Cochrane review of 48 cross-sectional studies, cohort studies, systematic reviews and meta-analyses, with a median number of included studies per paper of 137, found that trials sponsored by the pharmaceutical industry on average reported more positive results than non-industry sponsored trials (RR for better effect 1.32, RR for less harm 1.87, RR for more positive conclusion 1.31) (Lundh et al. 2012). An article in JAMA examining honorary and ghost authorships in peer-review medical journals found that 44% of the examined articles in Lancet were partly written by ghost writers (Flanagin et al. 1998). Research bias or misconduct has unfortunately been exposed repeatedly (Seife 2015). These circumstances may have added to the tendency that when new drugs are introduced they are often not replacing the old, but added to them, increasing the risk of polypharmacy and increasing the complexity of the prescribers' assessments.

7.3 Polypharmacy, medication underuse, and deprescribing

Thus, many factors have contributed to the trend of increasing the number of medications in use, some wanted, and some unwanted. The result is extra burden in the form of ADRs and interactions, reduced QoL, and large economic cost to society.

One of the risks of polypharmacy is the increased rate of medication errors. When the number of medications is high, there is an increased risk that health personnel will lose track of the patient's medication in present use (Rognstad et al. 2004), and compliance may fall. This situation can lead to a sense of insecurity, which in itself can reduce QoL. You risk introducing new medications to treat symptoms that are in fact side effects from the old. One question of interest is whether the total number of medications given to elderly people today is high enough for us to have reached a tipping point, in which controlled discontinuation of drugs will improve the situation, at least in the very old. There is some evidence for this; an Israeli controlled study to combat polypharmacy

(Garfinkel et al. 2007) found intervention group mortality, referral rates, and drug cost to fall significantly.

In a systematic review of clinical trials of withdrawal of medication in patient populations ≥65 years, adverse effects from medication withdrawal were not frequently encountered (Iyer et al. 2008). They found withdrawal of psychotropic medications to be associated with a reduction in falls and improved cognition. Withdrawal of antihypertensives was not associated with increase in mortality.

In considering the cessation of drugs, questions include whether the indication is strong enough, whether the upsides overrule the downsides, and whether the existing evidence can be applied in the relevant case. One study from Israel (Garfinkel et al. 2010) suggests that some elderly may have their QoL improved by the cessation of medication following a specific algorithm – the Good Palliative – Geriatric Practice (GP-GP) Algorithm. The algorithm was tested in a prospective cohort study where the intervention was to stop as many medications of non-vital importance as possible. After withdrawal of 58% of all medications, only 2% had to be reinstated due to recurrence of symptoms, and 88% of patients reported global improvement of own perceived health. No significant episodes or deaths could be ascribed to the discontinuation of drugs during the mean follow-up of 19 months.

The term deprescribing was recently introduced as a new term, defined as “cessation of long-term therapy, supervised by a clinician” (Alldred 2014). Polypharmacy trends demand that strategies like these are prioritized in clinical practice.

However, medication underuse has also been shown to be an important problem in the elderly. An American study using the Beers criteria found that patients using less than eight medications were more likely to be missing a potentially beneficial drug, than to be taking medication considered inappropriate (Steinman et al. 2006). Polypharmacy is a concept that has both positive and negative aspects; it depends on the appropriateness of the prescriptions rather than the amount (Viktil K 2008).

However, polypharmacy raises problems of its own. As J. Aronson states in an editorial in British Journal of General Practice: “For example, if a patient takes eight medicines, each of which carries an independent 5% chance of an adverse drug reaction, the overall risk of an adverse reaction is 34%, and there are 28 potential drug–drug interactions, taking only pairs of drugs into account” (Aronson 2006). Thus, even with

appropriate medication use, there are many risks to consider and Aronson's argument adds to the importance of keeping inappropriate prescribing at a minimum.

7.4 The concept of Appropriateness

Appropriateness is defined in the Oxford English Dictionary as "special fitness, suitability, or applicability". In the health sector, the appropriateness of a diagnostic test or any medical treatment has most often been defined from a cost-benefit perspective: If the potential benefits exceed the potential risks, the measure is deemed appropriate. Conversely, inappropriateness implies that the risks outweigh the benefits. In geriatric pharmacology, the term "potentially inappropriate medication use" has traditionally been employed to describe situations where the risks associated with the use of the substance potentially may outweigh the benefits of the medication use (Beers 1992), or a situation where pharmacotherapy does not meet the established medical standards. This risk-benefit definition is also used in this thesis.

The appropriateness of medication use can be assessed using indicators of prescribing quality. These can be explicit; drug specific or diagnosis specific, or they can be implicit, person-specific, based on clinical judgment. Earlier, most reviews of medication use in elderly were performed with implicit criteria, the Medication Appropriateness Index (MAI) being frequently used (Hanlon et al. 1992). Such reviews can only be performed by experts with the right experience and knowledge, and access to clinical information, and they will be hard to replicate due to the subjective nature of the assessment (low reliability) (Dimitrow et al. 2011, Kaufmann et al. 2014).

Explicit criteria have become more common in later years. These criteria are drug specific and can be employed by people without specialist knowledge in a field, and can be applied on medication lists or drug register data. This may be appealing for healthcare providers and researchers as they only require data on the drug treatment. These criteria are more rigid, and do not incorporate individual considerations, such as the severity of different comorbidities and earlier experiences with side effects. Explicit criteria need to be updated regularly and are specific to each country or market and its pharmacological prescribing traditions.

7.5 Explicit criteria to assess medication use in elderly people

At the outset of this thesis, only a few lists of explicit criteria had been developed. The first set of explicit criteria regarding potentially inappropriate medication use in the elderly were the Beers' original U.S. criteria for nursing home residents (Beers et al. 1991). These criteria were updated in 1997 (Beers 1997) and 2003 (Fick et al. 2003), both times for a general, home-dwelling elderly population. The Irish STOPP (Screening Tool of Older People's Potentially Inappropriate Prescriptions)/START (Screening Tool to Alert doctors to Right Treatment) criteria were first published in 2008 (Gallagher et al. 2008). STOPP consisted of 65 criteria for potentially inappropriate medication use in the elderly, in the form of, for instance, "Avoid thiazide diuretic with history of gout". Thus, the use of the STOPP criteria is dependent on some clinical information. Likewise, START included 22 criteria for medication that should be started if not in use in elderly with different medical conditions, e.g. "Warfarin in the presence of chronic atrial fibrillation". A challenge for clinicians in a busy general practice may be the comprehensiveness of the criteria (Dalleur et al. 2014) - an argument with diminishing weight as computerized alert systems become more common.

The Norwegian NORGEP criteria (see Appendix 1) were developed for the Prescription Peer Academic Detailing (Rx-PAD) study (Rognstad et al. 2009). They consist of 21 single substances and 15 drug combinations to be avoided whenever possible in elderly patients. The list was developed especially with the clinical setting in mind and focuses on general principles.

In addition to these, the Canadian McLeod criteria (McLeod et al. 1997), an Australian (Basger et al. 2008) and a French set of criteria (Laroche et al. 2007), and a few more U.S. criteria were available at the time. Most of these were developed in Delphi-like consensus processes. In a systematic review, Dimitrow et al described criteria published up until 2010 (Dimitrow et al. 2011), and Chang et al have compared the different until then published criteria (Chang et al. 2010).

In the course of this thesis, the field has developed. Several new lists have been developed, among them the German PRISCUS criteria (Holt et al. 2010). The Beers criteria for home-dwelling elderly were updated in 2012 (American Geriatrics Society Beers Criteria Update Expert 2012) and 2015 (American Geriatrics Society Beers Criteria Update Expert 2015) and STOPP/START has also seen an update (O'Mahony et

al. 2015). A new systematic review found altogether 46 different sets of criteria published from 1991-2013 and categorized them according to target population and type of criteria (explicit/implicit/mixed) (Kaufmann et al. 2014).

The baseline study from the Rx-PAD (KTV) study that this work arose out of found that 18.4% of patients received one or more PIP from their GP (Brekke et al. 2008). The study used a precursor to the NORGEP criteria and did not include prescriptions from doctors other than the patients' regular GP. At the time of the outset of this thesis, the NORGEP criteria had not yet been published. The NORGEP criteria have since been used in studies of hospitalized subpopulations (Bakken et al. 2012, Kersten et al. 2015).

The different versions of explicit criteria have been employed in prevalence studies from many countries. A systematic review found the prevalence of inappropriate medication use in home-dwelling elderly to range from 11.5% to 62.5% (Guaraldo et al. 2011). Figures vary according to the explicit criteria in use and differences in research population. A common finding is a prevalence of PIMs in the range 25-35% (Blalock et al. 2005, Maio et al. 2006, Amann et al. 2012, Bradley et al. 2012, Bell et al. 2013).

7.6 Linking PIMs to unwanted outcomes

Although there is a known relationship between ADRs and end points like hospitalization and death (Ebbesen et al. 2001, Wester et al. 2008), there is so far not enough evidence as to what effect PIMs have on end points like QoL, ADRs/ADEs, falls, hospitalizations, morbidity, mortality, and economic costs.

Using data from an RCT, Lund et al found that PIMs according to the implicit criteria Medication Appropriateness Index (MAI) were predictive of ADEs, but they were not able to demonstrate such a relationship when analyzing data using the explicit set of Beers 2003 criteria. The authors ascribed this lack of significance to lack of power (Lund et al. 2010). Others have identified PIMs as measured by explicit criteria as one of the main risk factors for ADEs in older adults (Laroche et al. 2007, Hamilton et al. 2011). A study of the predictive validity of the Beers 2003 and 2012 vs. the STOPP criteria found that all criteria were modestly prognostic for ADEs, emergency department visits, and hospitalizations (Brown et al. 2016).

There is some evidence of an increased risk of falls with increasing PIMs (Stockl et al. 2010, Wilson et al. 2011). Some studies have shown no difference in end points like

hospitalization, hospital stay and mortality between populations with high and low drug burden/level of PIMs (Onder et al. 2005, Budnitz et al. 2007, Jano et al. 2007, Ishii et al. 2016), others have found increased hospitalization and mortality rates and reduced QoL with increasing drug burden (Klarin et al. 2005, Lau et al. 2005, Pitkala et al. 2014). Several studies have implied that PIMs have a high economic cost both to the individual and to society (Fu et al. 2007, Cahir et al. 2010, Stockl et al. 2010, Bradley et al. 2012, Chiatti et al. 2012, Hill-Taylor et al. 2013). Lau et al found increased OR for hospitalization and death in nursing home residents receiving PIMs compared to those without PIMs (Lau et al. 2005). However, other studies have found only limited evidence of these same correlations (Hill-Taylor et al. 2013).

The chosen tools used for analysis of PIMs and drug burden vary in these surveys, as do the end points, and the results sometimes vary according to the chosen criteria (Hamilton et al. 2011). In addition, differences in patient populations will make results less comparable.

There is still a need for more research in order to establish these relationships for the various explicit criteria.

7.7 Interventions to improve quality of prescribing in the elderly

The Rx-PAD study (Straand et al. 2006) tested the effects of a tailored educational intervention including an audit towards general practitioners. The intervention resulted in -0.5 (95% C.I. -0.6 to -0.4) PIPs per 100 prescriptions in the intervention group, but also to -0.3 (95% C.I. -0.4 to -0.2) PIPs per 100 prescriptions in the control group, possibly due to a Hawthorne effect (Rognstad et al. 2013).

A Cochrane review did not find statistically significant effects from pharmacist led medication reviews in home-dwelling elderly (Nkansah et al. 2010). There were no interventions in which the patient's physicians were given extra resources to invest in medication reviews in comparison with pharmacist-led reviews. Thus, this option has not been studied or compared to other forms of medication reviews. Another Cochrane review studying the effect of medication review by pharmacist or other health care professional in hospitalized adult patients found no evidence that medication reviews reduce hospitalization or mortality (Christensen et al. 2016), however, noting that follow-up was short; 30 days to 1 year. Yet another review has favoured pharmacogeriatric

education efforts towards prescribers, electronic prescribing, and the use of the STOPP tool (Lavan et al. 2016).

A Swedish study found patients receiving their medication through the automated multi-dose drug dispensing system to have poorer quality of drug treatment than patients receiving ordinary prescriptions, i.e. directly from their physician, also when corrected for gender, age, comorbidities, and residency (Sjoberg et al. 2011).

A Canadian RCT targeting physicians with the aim of reducing the number of potentially inappropriate prescriptions, using a team of 2 doctors, one nurse and one pharmacist to overlook the patients' medications and send suggestions by mail to the patients' GPs, did not get statistically significant results in reducing the amount of PIPs (Allard et al. 2001).

In the nursing home sector, the Norwegian Knowledge Centre for the Health Services summarized available RCTs in improving prescribing quality in nursing homes in 2009 (Forsetlund et al. 2011). Their conclusion was that although some studies did show an effect in reducing PIMs from pedagogic interventions towards health personnel and medication reviews conducted by pharmacists in an interdisciplinary setting, for most other interventions no significant effect was found, and the quality of the evidence was mostly considered low or very low.

Pitkala et al tested an intervention where nursing staff received two four-hour trainings regarding PIMs and found that the decreased rate of PIMs in the intervention wards was associated with a reduced hospitalization rate and better maintained QoL (Pitkala et al. 2014). Blozic et al. found in a nurse-led, interventional educational study from Switzerland that the prescription rate of PIMs decreased from 14.5% pre-intervention to 2.8% post-intervention (relative risk [RR] = 0.2; 95% CI 0.06, 0.5) according to the Beers 2003 criteria (Blozik et al. 2010). This is the lowest rate of PIMs recorded in NHs to this writer's knowledge. One reason for this may be that about half of the substances on the Beers list were not available in Switzerland and were excluded in the survey. In addition, for this study one had access to clinical information and could therefore exclude prescriptions that are not always considered inappropriate, but that will still be included in most surveys of PIPs where clinical information is lacking.

Having on-screen pop-up decision support has been shown to be an effective measure against PIMs. Terrell et al found that 43% of advice given in this way was followed and

OR for prescribing PIPs in the intervention group was 0.55 compared to the odds for prescribing PIPs in the control group. The most frequently stated reason not to follow pop-up advice was that the patient had no negative experiences with the drug (Terrell et al. 2009).

The effects of the introduction of lists of explicit criteria on PIMs have not been studied per se. However, Fastbom et al found signs of improvement of the quality of drug prescribing to elderly persons in Sweden in that PIMs decreased by 36% between 2006 and 2012 in persons aged 80 years and older. The authors state that "… the indicators have likely contributed to this", citing the Swedish Socialstyrelsen's criteria (Fastbom et al. 2015).

7.8 Why the need for explicit criteria especially for the nursing home population?

Norway had in 2015 a total of 40.708 nursing home beds for its population of 5.165.802 million people (Statistics-Norway 2016), among them 556.600 (10.8%) persons 70 years or older. There are approximately 1000 nursing homes. Average age among residents is 85 years (Helvik et al. 2015). The average resident is not capable of walking without assistance and also needs assistance for other ADL. The majority of residents have dementia, with a prevalence rate of 71.6%, as compared to 16.3% in the home-dwelling population >75 years, in a study from 1993 (Engedal et al. 1993). In later years, even higher prevalence rates have been reported. In a study from 2004-5, 81% of nursing home residents had dementia, 72% of them with clinically significant psychiatric and behavioral symptoms (Selbaek et al. 2007). In a comparative study, Helvik et al found that the odds of the occurrence of a greater severity of dementia were higher in 2010/2011 than in 2004/2005 (Helvik et al. 2015). A similar pattern is seen in the rest of Europe. Over the past decades, residents in European nursing homes have become increasingly frail and ill (Onder et al. 2012), often with multiple active diagnoses, and often with more than one disease in their late stages. Thus, the clinical setting in nursing homes differs substantially from what we see in the home-dwelling population.

Due to the high prevalence of dementia and comorbidities such as impairment to sensory functions or earlier cerebral vascular catastrophes, a substantial percentage of nursing home residents have impeded communication skills. Thus, the possibility for the prescribing doctor of getting direct information from the patient about their symptoms and

experience of ongoing medical treatment is limited. The average time of NH residency is 2 years. This means that nursing home residents most often are in the latest stages of their lives, and that focus should be towards preserving a maximum QoL here and now. The indication for medication for preventive purposes must often be reconsidered. These factors all imply that there are many considerations regarding medication use in nursing home residents that are specific to this population.

Helvik et al found that the participants in the 2010/11 study had a significantly higher number of drugs prescribed for regular use than in 2004/5 (on average 7.0 vs. 6.0) (Helvik et al. 2015). Halvorsen et al have compared the number of medications given on a regular basis to Norwegian nursing home residents in the years 1997 (4.7 on average), 2005 (6.0 on average) and 2011 (6.7 on average) (Halvorsen et al. 2016). Thus, there is a trend towards an increasing number of drugs given to this population.

Employing the NORGEP-NH criteria that we developed in the second part of this thesis, Halvorsen et al found negative trends with increasing prescribing of PIMs for seven of the 36 criteria, positive trends towards a reduction in PIMs for 13 criteria, and no change for 3 criteria from 2005 to 2011. For the rest of the criteria the number of observations was too small to conclude (more on the use of NORGEP-NH will follow under Discussion). Noteworthy is that the use of three or more psychotropic substances concomitantly increased over the period, from 11.9% to 19.9% ($p<0.001$), and half of the patients received at least one PIM in 2011. This shows that PIM use is prevalent in the nursing home sector, a finding supported by a systematic review showing that the overall weighted point prevalence of potentially inappropriate medication use in nursing homes was 43.2%, increasing from 30.3% in studies conducted during 1990-1999 to 49.8% in studies conducted after 2005 ($p<0.001$) (Morin et al. 2016).

The nursing home population is frail and thus especially prone to side effects and interactions from medication use, and not as able to discuss medication related problems with their prescribers, but all the while more exposed to polypharmacy and PIMs. Tools for evaluation of prescribing quality especially designed for this population is therefore in place.

7.9 The pharmacological reasoning behind the NORGEP-NH criteria

For the pharmacological background to the different proposed NORGEP-NH criteria, see the full NORGEP-NH table with comments and references in Appendix 3. In addition, some of the reasoning can be found in Appendix 6, which shows the full survey as it was sent to participants in the Delphi study, including comments and references (represented here as Round 3, in Norwegian only). For methods, see following section. Here, I will mention a few selected topics that relate especially to the elderly nursing home population.

7.9.1.1 Anticholinergic substances

Ataraxia (Greek: ἀταραξία): a lucid state characterized by ongoing freedom

from distress and worry, used to describe the ideal mental state

for soldiers entering battle

https://en.wikipedia.org/wiki/Ataraxia (Collaboration 2016) (Atarax is the name under which hydroxyzinehydrochloride is marketed in Norway.)

Anti-cholinergic substances have been shown to increase the risk for side-effects that can be especially harmful in an elderly population, among them problems with cognition, vision, constipation, gait and balance (Rudolph et al. 2008). The cognitive side effects are especially important to consider in the often cognitively impaired nursing home population (Gerretsen et al. 2011). The negative effect on cognition of anticholinergic drugs can have important clinical implications also in elderly without dementia. In a French study from general practice the OR of having mild cognitive impairment (MCI) was 5.12 ($p<0,001$) for participants using anti-cholinergic substances regularly as opposed to those without such medication, although in the 8 year follow-up there was no difference between the two groups in the risk for developing dementia (Ancelin et al. 2006). The groups were not very large but the findings were statistically significant, with the anti-cholinergic group having a risk of 80% for being diagnosed with MCI at study start, compared to 35% for the non-users. Several other anticholinergic side effects are especially unwanted in this population, among them constipation in a population where this is a common complaint, and the increased risk of falls (Aizenberg et al. 2002) in

elderly that have a higher risk of fractures due to frequent decreased bone density and poorly functioning musculature.

7.9.1.2 Problems regarding the use of anti-psychotics in treating NPS

Neuropsychiatric symptoms in dementia (NPS) are common in NH residents – in Selbaek's study, 73.8% of the patients exhibited at least one NPS, and 65.2% exhibited clinically significant symptoms (Selbaek et al. 2007). Finding ways to handle these symptoms is an ongoing challenge in NH wards. Instances of agitation, delusion and aggression can demand acute intervention and imply a heavy staff burden (Sourial et al. 2001). No pharmacological substances have proved very successful in treating these symptoms, but in many instances, anti-psychotics are prescribed in a hope to relieve symptoms. Anti-psychotics have been prescribed to 20-30% of the Norwegian NH population (Nygaard 2004). In their earlier mentioned study, Selbaek et al found that antipsychotics were more frequently used in patients with dementia, and the use became more prevalent with increasing severity of the disease.

However, there is not solid evidence of efficacy of these substances in treating NPS symptoms, they are not approved for this use, and side effects are frequent and potentially serious, including a possible increased risk of death from both conventional and atypical formulations (Schneider et al. 2005, Gill et al. 2007). The FDA in the U.S. has warned against this off-label use (Kuehn 2008). In recent years, many efforts are undertaken to find better ways of handling this matter, including Fossey et al who found that enhanced psychosocial care can be an effective alternative to anti-psychotics in treating NPS (Fossey et al. 2006).

7.9.1.3 The efficacy of anti-depressants in a NH population

There is a lack of evidence regarding the efficacy of anti-depressants in nursing home populations. Almost all clinical trials on these drugs have been conducted on substantially younger and healthier individuals. In a randomized, placebo-controlled, double-blinded study of patients 70 years or older with major depression and initial response to paroxetine, recurrent depression was less likely if patients received two years of maintenance therapy with paroxetine (Reynolds et al. 2006). In another RCT, discontinuation of antidepressants in patients with dementia and NPS lead to a significant increase in Cornell depression score in the discontinuation group compared to the control group (Bergh et al. 2012). However, a systematic review of people with

depression and dementia in out- and inpatient clinics found that evidence of efficacy for antidepressant treatment in this population could not be confirmed. All of the trials in the review were underpowered (Nelson et al. 2011).

7.9.1.4 The use of preventive medication in patients with limited life expectancy

As shown above, the average length of residency in Norwegian NHs is around 2 years. Thus, nursing home residents on average have a limited life expectancy. When also taking into account that a number of residents are incapable of expressing personal preferences and experienced side effects, it is clear that the use of medication intended to prevent future symptoms rather than treat present symptoms may have more negative than positive consequences. However, preventing a stroke is preferable also in situations with a limited life expectancy, likewise a hip fracture. Thus, individual considerations where the (personal and economic) cost and risk of treatment are assessed must be weighed against the cost and risk of refraining from treatment. Still, it is common for patients with a limited life expectancy to continue medication for preventive purposes, with lipid-lowering drugs most frequently used (Poudel et al. 2017). Guidelines are lacking.

8 OBJECTIVES

Through this study, our aim has been to quantify the extent and distribution of potentially inappropriate medication use among elderly people in Norway, both home-dwelling and those living in nursing facilities. By developing a tool for assessing the appropriateness of medication use in nursing homes, we hope to contribute to a reduction of such potentially inappropriate drug prescription.

9 MATERIAL AND METHODS

Our aim would be achieved through two pharmacoepidemiological surveys, one for home-dwelling elderly (Article 1), and one for elderly living in nursing homes (Article 3). In this section, I will describe the material and methods used, also covering factors not included in the articles.

9.1 Article 1: PIM prevalence among home-dwelling elderly in Norway

9.1.1 Material

In the first article, we tried to answer the question of the magnitude of PIMs among home-dwelling elderly in Norway. Data were provided via the Norwegian Prescription Database (NorPD, No.: Reseptregisteret),

The NorPD was established in 2004. The national database contains data on all drugs dispensed by Norwegian pharmacies and can be used for scientific purposes, as a management tool for authorities, and as a means of internal control for prescribers (Furu 2008). As a national database, this opens up for possibilities to study aggregated data, and we could in this way get an overview of the prescription practices for home-dwelling elderly throughout the country. At the time of this study, the NorPD did not collect information from institutions (incl. hospitals and nursing homes), or on medications sold over the counter.

We received data on all dispensings to elderly ≥ 70 years made by all prescribers from outside of institutions, in the whole country, for the whole year of 2008.

9.1.1.1 Quality control of the NorPD data file

The mere size of the original data file opened for some practical challenges. The file was too large for both Word and NotePad, and had to be imported directly from zipped format into SPSS via Read text file. Still, the programs had problems due to the size of the files and we went several rounds before all data were satisfactorily imported to the resulting SPSS (PASW Statistics 18 (SPSS, Chicago, IL) file, containing over 12 million dispensings. Statistical analyses had to be undertaken to check the files for improbabilities and systematic errors. When these analyses yielded unexpected results, we returned to the original files and scrutinized the data themselves. All statistical

analyses were time consuming; performing one single operation in SPSS on the original files would take up to 15 minutes. In the process, we discovered a number of duplicates in the original data file from the NorPD. This turned out to be caused by a faulty file merging process at the NorPD before delivering the original file to us. It turned out that when merging the file containing information about the prescriptions with the file containing information on the prescribers' specialty, prescriptions from prescribers registered with more than one specialty were included more than once. As the NorPD was recently operative at the time, ours was the first such merged file to be delivered and procedures were under development. The first data set consisted of 12.209.517 different dispensings. The corrected file from the NorPD consisted of 11.491.065 dispensings, disclosing a discrepancy of several hundred thousand in the original file that could potentially have affected results, and that would have been hard to disclose without these procedures.

This is illustrative of a kind of systematic error that may arise from using datasets generated from databases, and underlines the importance of using statistical analyses to check the underlying data when manually overlooking the data set is impossible due to volume.

9.1.1.2 Data set for Article 1

The final data set consisted of information on all prescriptions, made by all physicians working in Norway, to all home-dwelling elderly ≥70 years for the whole of 2008, a total of 11,491,065 dispensings from 24,540 prescribers to 445,900 individuals, equivalent to 88.3% of the total Norwegian population in that age group.

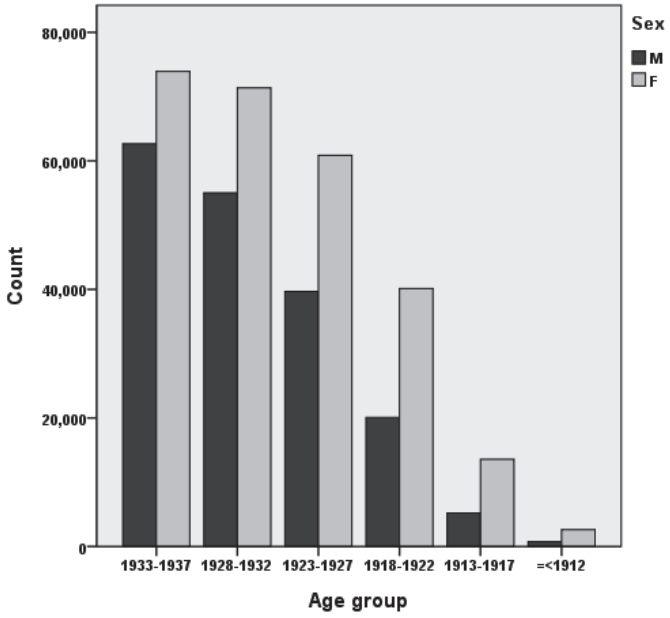
Prescriptions to patients not identified by their unique Social Security Number were excluded. Out of the recorded dispensings, 99.49% were included in the analyses.

Data were pseudonymized. We had data on the users' gender and year of birth. Substances were classified according to the WHO Anatomical Therapeutical and Chemical (ATC) Classification System, and included name, date, the prescribed amount (including number of defined daily doses DDD).

This material was notable in its volume and comprehensiveness, as are many studies relying on register data. However, we had no access to clinical data, as these are not collected in the NorPD, or sociodemographic data. Data on geographic location is

collected in the NorPD, but were not available to us due to anonymity causes, as some local communities in Norway consist of few individuals and our data would not guarantee anonymity in these cases.

The age distribution for Article 1 is shown below:



For more detailed information on the data set, see Article 1.

9.1.2 Methods

We used the then newly developed NORGEP criteria (Rognstad et al. 2009) to assess PIMs. The NORGEP criteria are independent of diagnosis and other clinical data and are thus well suited for use in large register studies like this. For the complete NORGEP criteria, see Appendix 1.

We analyzed prevalence rates and predictors for all potentially inappropriate prescriptions according to the NORGEP criteria. Then we collected only those NORGEP criteria that involved psychotropic substances, and repeated some analyses for this sub-set.

9.1.2.1 The software

Computer-based techniques were implemented for extracting and analyzing relevant dispensings according to the relevant explicit criteria. The program was developed, especially for this study, in Microsoft's Visual Studio program by Svein Gjelstad at Mediata AS (Tønsberg, Norway). This software also had to go through quality control and we developed systematic strategies in order to check for errors. The aggregation of dispensing of similar generic substances, and the calculation of timing for each dispensing were controlled. Adjustments were made in the Visual Studio program accordingly, for instance where we originally had set a cut-off value too high in doses for the computation of concurrent use. The whole process of checking data files and the corresponding data program was technically challenging but equally important.

The procedure for the calculation of concomitant use of substances, and the average dose for zopiclone and oxazepam, was based on the information on the number of defined daily doses (DDD) in each dispensing, and the time between dispensings. The program would calculate the average consumption for each patient between two or more dispensings from the pharmacy. For instance, if a patient is given a NSAIDs cure in March and another in September, the average DDD will be very low, and below our set cut-off for that substance. In this case, these prescriptions will not be assessed as regular medication, but rather as singular cases. To establish the cut-off, Svein Gjelstad went through all substances to decide the least probable DDD/day that could be considered regular medication. Normally, that would be the amount of DDD in the smallest tablet for the substance, or similar, alternatively the half of this amount if the tablet had a dividing line. To allow for some deviation in compliance, cut-off was calculated at 80% of the value before mentioned. If a prescription by these means would stretch into the month where the next dispensing was made, the substance was defined as in regular use. If this was the case for two substances, present in the NORGEP criteria 22-35, for instance warfarin and SSRI, the program would identify this as a hit for the relevant combination criterion. For three or more substances relevant to criteria 36, the program would identify this as a hit for this criterion.

A similar procedure was followed in the calculation of the indicators 12 (oxazepam > 30 mgs/day) and 13 (zopiclone > 7.5 mgs/day). In the case of two dispensings, mean daily dose was calculated as the total amount per time between these dates. If the case was more than two dispensings for one patient, mean daily dose was calculated as the mean of the dose for all periods. The last dispensing is not included in the calculation. If this number exceeds the limit set in the relevant NORGEP criterion, it is registered as one PIM. This means, that someone with three dispensings will have their mean daily dose calculated from the time between first and third dispensings and the amount of drug dispensed in the first and second dispensing. Cut-off was set at > 35 mg/day for oxazepam and > 8 mg/day for zopiclone, in order to avoid including individuals who did not represent true overuse, for instance patients with only two dispensings who collected the last dispensing earlier than needed. We only included those with more than two dispensings through the year, and those who were dispensed enough drug to last as the lowest mean daily dose over at least nine months or more.

9.1.3 Statistical analyses

Logistic regression was used for the predictor analyses. This assumes that there is a linear relationship between the outcome and the predictor variable. When we checked this in our material, we found some discrepancies from a strict linear relationship, although no clear pattern. To adjust for this, we created groups within the different predictor variables, grouping them according to a logical outcome and so that the groups be of comparable size, the latter of these arguments being that of least priority. Grouping of variables are found in the regression table. Due to the large sample size, we were able to set a p-value of 0.01 as a limit to reject the null hypothesis that there is no relationship between the response variable and explanatory variable.

We found a clear relationship between the number of medications to each patient (measured by the number of ATC codes) and the number of doctors prescribing, the number of ATC codes acting as an intermediate variable. Thus, the number of medications was omitted as a variable in the final regression analysis. This means that the number of total medications given to each patient is correlated to other variables that we are interested in studying (e.g. the number of prescribers for each patient) so that including this variable in the regression would imply a risk over over-adjusting. However, it does not mean that the number of ATC codes is irrelevant: We also found a direct relationship between the number of ATC codes and the number of PIMs, as shown in Fig. 2 in Article 1.

9.2 Article 2: The Delphi consensus process

9.2.1 Material and methods

We wanted to develop a new set of explicit criteria for inappropriate medication use especially for the nursing home setting. This was done through a three-round consensus validation, using the Delphi Method, resulting in The Norwegian General Practice – Nursing Home (NORGEP – NH) criteria for potentially inappropriate medication use.

9.2.1.1 The Delphi method

A modified Delphi technique (Linstone et al. 2002) was used for the development of the NORGEP-NH criteria. The Delphi technique is a structured communication technique

where a panel of experts can answer questions to which there are no scientific proven correct answers. The technique was originally developed by the Pentagon for forecasting new war strategies during the cold war. A facilitator creates the survey and handles the answers that are all anonymous.

9.2.1.2 Participants

We sent open invitational letter to all members of the Norwegian Geriatrics Society (n=122), Norwegian Society of Clinical Pharmacology (n=48), Norwegian College of General Practitioners' Reference Group for NH medicine (n=11), a sample of nursing home doctors in Oslo (n=55), and five selected pharmacists with known expertise in the field of drug prescribing to elderly people.

Out of a total number of eligible panellists of 241, 92 responded to the invitation, and 80 entered the Delphi process' first round. For more details on the selection process and the outcome, see Article 2.

9.2.1.3 Development of the proposed criteria

The full consensus process, including the invitational letters and the survey rounds 1-3, was performed using the survey software SurveyMonkey® (www.surveymonkey.com, Madison, WI, US).

The authors of the article acted as facilitators in the Delphi process. The proposed criteria for round 1 were developed in a joint effort between the authors, and based on the existing NORGEP criteria (Rognstad et al. 2009). An extensive literature search was conducted, to supplement these criteria with recent evidence. The facilitators had several meetings where the drafts were discussed, using their clinical experience and theoretical knowledge. The result was 27 proposed criteria, which were included in Round 1 and sent to the participants of the panel via the survey software.

9.2.1.4 The three rounds of the Delphi process

In the first round, participants were given the proposed criteria and asked to score them according to their judgment of their clinical relevance in a nursing home setting. Two to three references were given with each criterion, and optional space was provided for

comments or suggestions of additional references. At the end of the survey was an extra optional space for general comments.

After round 1, the responses were analysed using the survey software. All comments and suggestions from the panel were collected. Additional literature searches were performed where needed. The facilitators then had another round of meetings to finalize the survey for round 2. Altogether, seven of the proposals from participants were included as extra criteria in round 2, and the wording of some of the original criteria was slightly edited according to comments from the panel. Then Round 2 was sent, again via SurveyMonkey. In this round, there was still space for participants to comment, but this round was not open to new criteria. The mean score for each criterion from previous rounds was presented, as is done in some Delphi processes. Important comments from the panel were also included. Proposed criteria that were rejected by the facilitators were not included in the survey sent to participants. However, some of these proposals were quite similar to the accepted ones. The rest of the rejected criteria were deemed non-relevant by the facilitators unanimously.

Round 3 was created in a similar manner, but without room for comments, only the score of the clinical relevance of each proposed criterion. Here too, the mean score for each criterion from the previous round was included in the survey. Round 3, as it was sent to the panel, is found in Appendix 6.

A link for opting out was provided with each round.

For an overview over the participants through the three rounds, see Article 2, Figure 1.

9.2.2 Statistical analyses

Main outcome measures were the panelists' evaluation of the clinical relevance of each suggested criterion on a digital Likert scale from 1 (no clinical relevance) to 10 (highly clinically relevant).

After the third round, results from the Delphi process were exported from SurveyMonkey and into SPSS. We then discovered a technical glitch in the survey; somehow, in rounds 2 and 3, an extra step to our Likert scale had appeared, making it now possible to score from zero to 10, instead of 1 to 10 as intended. To look into this, we constructed a syntax to compute and count the number of 0, and found that one participant scored 0 twice and

three participants scored 0 once, altogether 5 times. We changed the syntax to count the number of times the score was 1:

```
COMPUTE count=0.
VECTOR v=v1 TO v95.
LOOP #vecid=1 TO 95.
Do if (v(#vecid)=1).
COMPUTE COUNT=Count+1.
End if.
End loop.
EXECUTE.
```

In this manner, we found that no participants scored 1 for any of the 34 suggested criteria. The 5 scores of 0 were then recomputed to 1. We then ended up with a scale of 10 points, from 1 to 10, and the analyses were done on this material. In considering a possible bias in results from this error, we noted that only 5 out of 34x49=1666 scores were scored as “0” originally. Matell et al have found that both reliability and validity can be independent of the number of scale points used for Likert scales (Matell 1971). After consideration, we viewed this error not to influence the results.

The degree of discordance was measured via the standard deviations (SDs). Statements were included in the final list if (mean-SD>5) in round 3. We also considered the inclusion criterion that was used in the development of the original NORGEP criteria, namely that a criterion is accepted if the inter quartile range (IQR) was within the upper third, rejected if the IQR was within the lower third, and either rejected or accepted depending on the mean score combined with comments from the panel if the IQR for a criterion fell in the middle range. However, when using a digital Likert scale like this, including only whole numbers, using the IQR would mean considerable renunciation of precision.

We used the Mann-Whitney U-tests to analyze differences in consensus between the nursing home doctors and the other specialist groups. When comparing the resulting mean scores from the two groups we tested different statistical methods to correct for a high number of tests (95). When the number of tests is high, some of these will turn out statistically significant by pure chance. In 100 tests with $p<0.05$, 5 of these will come out as statistically significant by chance. Using the ordinary statistical cut-off at $p<0.05$ would not give a just picture.

We tried running the analyses with the Bonferroni correction. In this case, we found only one mean score that was significantly different between the two groups, namely the response to the panelists' assessment in the first round of the clinical relevance of the statement: "The use of NSAIDs in general should be discouraged". After comparing tests, our statistics advisor Magne Thoresen recommended performing the analyses with $p<0.01$ instead of using the Bonferroni correction, as the latter would risk excluding too many possibly truly significant results.

As some authors of Delphi studies have used Cronbach's alpha (Cronbach et al. 1951) as a measure of internal consistency or reliability (Tomasik 2010) we did consider employing the Cronbach's @ in order to look at reliability of our scores. Sjitsma et al. argues that Cronbach's @ to only a small degree corresponds with actual reliability (Sijtsma 2009) and that alpha is not a measure of the internal structure or internal consistency of the test. We did perform these analyses, calculating the inter-rater reliability in rounds 1, 2 and 3. However, in our study alpha added little information.

9.3 Article 3: Application of the NORGEP-NH Criteria

9.3.1 Material

We used the newly developed NORGEP-NH Criteria to study the prevalence of PIMs for elderly nursing home residents in the county of Vestfold, Norway by conducting a pharmacoepidemiological study similar to the one in Article 1. The data were taken from a large ongoing interventional study led by Romøren at the Department of General Practice in Oslo.

For this part of the study, we initially planned to use medication lists from Farmaka, a firm delivering unit dose packaging of medication for elderly living at home and in nursing homes. However, Farmaka only had information on medications packaged by their system, lacking information on medication given on demand, medication given as liquid or plaster, warfarin, and morphine. Thus, several of the criteria on the list would not be possible to assess, and the prevalence of PIMs would be found to be systematically too low.

Instead, we chose to analyze data from the 3iV-study (Romoren et al. 2016). The 3iV-study is a stepped-wedge, cluster-randomized trial in the form of a structured training program in intravenous treatment with fluids and antibiotics in nursing homes with the aim to reduce hospital admissions. The participants constituted the part of the nursing

home population in need of some antibiotic or intravenous fluid therapy during the study period. Exclusion criteria for the 3iV-study were serious infection, septicaemia, or co-morbidities in need of more thorough diagnostics or treatment than the nursing home could offer. We found this data set to be valuable, not only in assessing our newly developed criteria, but also in studying these criteria in the setting of an acute episode of infection or dehydration. In addition, this material also provided some clinical information.

Some patients were included in the 3iV-study more than once. The total number of cases from the 3iV-study was 1522. Of these, 1192 cases were data from patients treated with peroral antibiotics from November 2009 to December 2010, and 330 cases were data from patients treated either in hospital or in the nursing homes with intravenous antibiotics or fluid between November 2009 and December 2011. In total, we found data for 914 patients.

For 33 subjects medication lists were not available. Some of these patients were deceased shortly after their inclusion in the study, but we suspect that some did in fact not receive any medication, and some could be missing for other reasons. As the total number of missing is low compared to the total number of participants (3.6% of the 914), the exclusion of these 33 is not likely to have significantly altered our results.

The original data file given to us from the 3iV-study consisted of 493 variables, including detailed clinical information collected for the antibiotics/intravenous fluid intervention. A little less than 300 of these variables were considered relevant, and brought into our study for further assessment.

We had access to the residents' ADL as of 14 days prior to the acute infection/dehydration episode. These were thorough assessments of ten questions according to the Barthel index scale (Collin et al. 1988) (for questionnaire, see Appendix 4, in Norwegian). The questionnaire was filled out by a nurse with knowledge of the resident, at the residents' nursing home ward.

We were interested in checking if there was any relationship between PIMs and falls among elderly in an acute episode of dehydration or infection. For this, there were two variables relevant to us from the 3iV-study; one of these was the variable "Falls with fracture or injury" within the course of 30 days into the acute episode, the other was "Fall/Tendency of falls" as an "unspecific new symptom". The responses for these two

variables did not always overlap. We thus combined the two variables into one variable, “Falls”.

The variable “Death” was recorded as “Death on day x after the start of the episode”, cut-off set to 30 days after the episode.

For the variable “Dementia” a majority of records were missing. This variable was thus excluded from our regression analyses.

9.3.2 Methods

This is a cross-sectional observational study. Main outcome was the prevalence of PIMs according to the NORGEP-NH tool. We also examined the prevalence of hits for each indicator, excluding and including PRN medication. In the medication lists, the drugs were given by generic or brand name. With the help of Svein Gjelstad, we created a system for coding these into the equivalent ATC codes. The entries that were not recognized by this system were manually coded.

In order to extract the medication lists relevant to our outcome, we constructed one SPSS syntax for use for only regular medications, and one for the use of regular and PRN medications (see Appendix 5).

We could not assess the criterion regarding the need for any preventive medication in a situation with a short expected life span, the Criterion 34 of the NORGEP-NH, as we did not have information on whether different medication was prescribed for prevention or treatment purposes. Thus, the analyses were based on Criteria 1-33.

For the deprescribing criterion regarding drugs that lower blood pressure, we only included substances that have lowering of blood pressure as an approved indication for use. Thus, for instance alpha-blockers and anti-Parkinson drugs are not included in the figures although they may have the lowering of blood pressure as a side effect.

9.3.3 Statistical analyses

Main outcome was the prevalence of PIMs according to NORGEP-NH. We checked each indicator both including and excluding PRN drugs. We also looked at the number of PIMs per person.

For analyses of factors associated with PIMs, we did a multi-level regression analysis with stratification on the nursing home level, with odds ratio (OR) as measure of effects size. For an overview over possible variables to include in the model (Exchange 2017), see Table 1. As measure of the between-cluster variance we used the intra-class correlation coefficients (ICCs) - the ratio of the between-cluster variance to the total variance, e.g. the proportion of the total variance that is accounted for by the clustering (Grace-Martin 2017).

Table 1. Frequencies, variables assessed for inclusion in regression analysis

	No. of residents		Missing	
Included in the final regression:	**N**	**%**	**N**	**%**
Age:	881	100	0	0
Gender:	881	100	0	0
Male	277	31.4		
Female	604	68.6		
Barthel[b]:	807	91.6	74	8.4
0-5	314	35.6		
6-10	259	29.4		
11-20	234	26.6		
Falls:	830	94.2	51	5.8
No	663	75.3		
Yes	167	19.0		
Delirium[c]:	877	99.5	4	0.5
No	807	91.6		
Yes	70	7.9		
Death[d]:	879	99.8	2	0.2
No	782	88.8		
Yes	97	11.0		
Ward:	840	95.3	41	4.7
Rehabilitation	58	6.6		
Short-time	158	17.9		
Long-time	364	41.3		
Comb. short-/long-time	100	11.4		
Dementia	114	12.9		
Palliative	46	5.2		
Not included in the final regression:				
Dementia:	135	15.3	746	84.7
Yes	63	7.2		
No	72	8.2		
Type of doctor:			35	3.9
NH doctor	305	34.6		
GP w part time NH work	463	52.6		
Combination of above	78	8.9		
Doctor hours/week per resident[b]:				
1	287	33.9	35	3.9
2	299	35.3		
3	260	30.7		
Nurse work year per resident[b]:				
1	296	34.0	35	3.9
2	270	30.6		
3	280	31.8		

[a] Continuous variable. [b] No. of residents in each tertile. [c] In the course of the infection.
[d] Within 30 days of study inclusion

For age, we ran analyses with the variable as continuous, and divided into tertiles, quartiles, quintiles, six, and ten groups. None of these methods yielded significantly different results, and in the final model, age was entered as a continuous variable.

We ran tests with the Barthel score as continuous variable, and grouped in tertiles, and quartiles. The final choice was tertiles, also because tertiles is a logical division in that the questionnaire often is divided in three, where

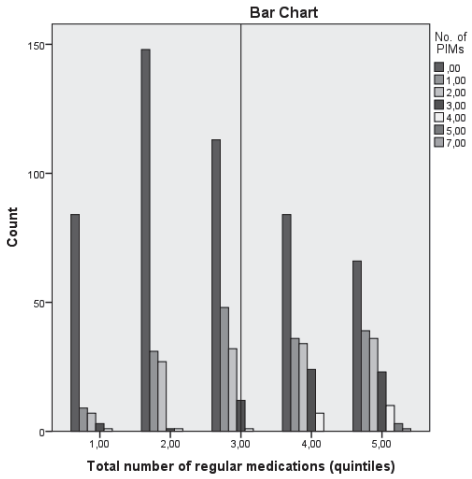
0 – Completely dependent on assistance
1 – Dependent on some assistance in ADL
2 – Completely self-sufficient.

Contingency tables were used to check subdivisions of the different categories to ensure that all contained a sufficient number of observations. In addition to clinical relevance, we used the Akaike Information Criterion (AIC) to check the relevance of the data.

Variables that were not included in the model were doctors' hours/week per resident, nurses' work years per resident, and the type of doctor working in the NH (full time NH doctors, part time GP/part time NH doctors, or a combination). The variables were of theoretical interest, however, the residents' clinical condition could act as a confounder in these analyses, about which we had lacked data. Since PIMs and the total number of drugs are related, wards with more frail residents may also imply more regular medications, hence more PIMs. If these wards have higher staff presence, an erroneous conclusion from not correcting for this confounder could be that a higher staff presence increased the risk of PIMs.

Pearson's r was used to check for relationship between the Barthel score and the number of drugs given on a regular basis, and between the total number of drugs given on a regular basis and the amount of PIMs. We knew from the work for Article 1 and from other surveys that the number of PIMs is associated with the total number of drugs, as later also shown both when using the NORGEP-NH (Halvorsen et al. 2012) and in a systematic review (Morin et al. 2016). There is an absolute logic to this; when only using one medication, there is rarely more than one PIM (exceptions can be criteria related to dosage and criteria related to classes of medications). When using two medications, only this and the combination criteria can open for the possibility for having more than two PIMs. If the total number of drugs acted as an intermediate variable for PIMs, including the total number of drugs as a variable in the regression analysis could mean over-adjusting. To check for linearity in the Vestfold data we grouped the total number of drugs into quintiles. We did find a close relationship between the total number of drugs and PIMs (see Figure 1). Thus, the variable was omitted from the regression model.

Figure 1. Total number of medications and total number of PIMs



There is considerable variation in the dispensing of PRN medications. To avoid uncertainty, predictor analyses was performed for regular medications only.

10 ETHICS AND FUNDING

Data for Article 1 were pseudonymized and categorized so that individual recognition was not possible. The project did not include interventions. Ethics application for the study was sent to and approved by the Norwegian Social Sciences Data Services (NSD). The NSD assessed the study not to require extra approval by the Regional Committees for Medical and Health Research Ethics (REK).

In the Delphi process, participants were not anonymous to the facilitators, but to each other. When comments and additional suggestions were included in the later rounds of the survey, the proposers were anonymous to the rest of the panel. The survey did not include patient data and did not involve any interventions. The study was approved by the NSD. The study did not need explicit approval by REK.

The project behind article 3 was a part of the 3iV-study, a collaborative project between 30 participant nursing homes in Vestfold, Norway, the Vestfold Hospital Trust, Centre for Development of Institutional and Home Care Services, the University College of Southeast Norway, and the University of Oslo. The 3iV-study was approved by REK (reference no. 2009/1584a-1, see Appendix 9). Written consent was obtained from all patients involved or from next of kin in cases where decision-making ability was lacking. The 3iV-study is reported in accordance with the Consort 2010 extension and registered with ClinicalTrials.gov: NCT01023763.

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11 RESULTS

11.1 Article 1

Median number of prescriptions dispensed to each individual was 18 (IQR 10, 30; range 1–654). (Data on the patient receiving 654 dispensings was controlled and found plausibly correct. This patient was included in the unit-dose packaging system.) Median number of different drugs prescribed to each individual was 7 (IQR 4, 10; range 1–45). Median number of prescribers for each individual was 2 (IQR 4, 10; range 1–24).

According to our criteria, a total of 155,341 (34.8% of survey population) elderly people >70 years received one or more PIP in Norway in 2008, among them 103,080 (66.4%) female and 52,261 (33.6%) male. Of the PIPs found, 59.9% represented psychoactive substances; 107.725 (24.2%) of the home-dwelling Norwegian population ≥ 70 years received at least one PIP involving psychotropic drugs. Among those included, 64331 (14.4%) received two or more PIPs with a maximum of 12 different PIPs over the year. Twenty percent were prescribed more than 10 medications; among these two-thirds had at least one PIP.

For prevalence figures on the different NORGEP criteria, see Article 1, Table 3.

We then looked at factors associated with the prescription of PIPs.

Table 2. Distribution of predictors

For each individual	Median	Interquar	Min, max	p-value
No. of prescriptions handled by pharmacy, total survey population	18	10 to 30	1, 654	
No. of prescriptions among those with at least one PIPx	32	21 to 48	1, 654	
No. of prescriptions among those without PIPx	14	7 to 24	1, 642	
No. of prescriptions among those with and without PIPx* are not the same				0.000
No. of ATC-codes, total survey population	7	4 to 10	1, 45	
No. of ATC-codes among those with at least one PIPx	11	7 to 14	1, 45	
No. of ATC-codes among those without PIPx	5	3 to 8	1, 36	
No. of ATC-codes among those with and without PIPx* are not the same				0.000
No. of doctors involved in prescribing, total survey population	2	1 to 4	1, 24	
No. of doctors involved in prescribing among those with at least one PIPx	3	2 to 5	1, 24	
No. of doctors involved in prescribing among those without PIPx	2	1 to 3	1, 21	
No. of doctors among those with and without PIPx* are not the same				0.000

In multivariate regression analysis (Article 1, Table 4), odds for receiving PIPs were higher for women than for men (OR 1.60, 99% C.I. 1.58-1.64). These figures were corrected for differences in age and the number of doctors involved in prescribing to each person. In a regression model only including the criteria addressing psychoactive substances, the odds ratio of females versus males regarding PIPs increased further

(OR 1.90, 99% CI 1.86–1.93). The odds for receiving PIPs increased with the number of doctors involved in prescribing to each person (OR 3.52, 99% CI 3.44–3.60 for those with ≥5 compared to those with 1 or 2 prescribers).

In multivariate analyses stratified by gender (Article 1, Table 5), the odds for females for receiving PIPs peaked at age group 85-89 years (OR 1.20, 99% C.I. 1.16-1.24), subsequently falling for the older age groups. The oldest women had no higher odds for receiving PIPs than the youngest (OR 1.01, 99% C.I. 0.90-1.12, where the youngest is the reference group). For men however, adjusted OR for PIPs increased steadily with age and was highest in the age group 95+ years (OR 1.22, 99% C.I. 0.99-1.50). Still, a higher percentage of women received PIPs at any age up until the two highest age groups, for whom the percentage receiving PIPs was identical for both genders (30.7% for 90-94 year age group and 30.4% for the 95+ age group).

When analyzing only the NORGEP criteria involving psychoactive substances, and stratifying by gender, the same pattern of increasing OR with age was seen for men, but this time the increase in OR was larger (OR 1.78, 99% C.I. 1.42-2.23, Article 1, Table 5). For women, OR for receiving potentially inappropriate psychoactive substances for the 95+ age group was 1.21 (99% C.I. 1.08-1.36), the odds ratio falling with age after 85-89 years. However, in spite of a more positive development in the highest age groups for women, a higher proportion of the oldest women still received potentially inappropriate psychoactive substances than men did (29.2% vs. 23.5% for the 95+ age group, see Table 3).

Table 3. Gender * Psychoactive PIPs * Age group Crosstabulation

Age group				Psychoactive PIPs 0	1	Total
1933-1937	Gender	M	Count	53454	9211	62665
			% within Gender	85,3%	14,7%	100,0%
		F	Count	54941	18979	73920
			% within Gender	74,3%	25,7%	100,0%
	Total		Count	108395	28190	136585
			% within Gender	79,4%	20,6%	100,0%
1928-1932	Gender	M	Count	45564	9458	55022
			% within Gender	82,8%	17,2%	100,0%
		F	Count	51056	20297	71353
			% within Gender	71,6%	28,4%	100,0%
	Total		Count	96620	29755	126375
			% within Gender	76,5%	23,5%	100,0%
1923-1927	Gender	M	Count	32084	7613	39697
			% within Gender	80,8%	19,2%	100,0%
		F	Count	42095	18763	60858
			% within Gender	69,2%	30,8%	100,0%
	Total		Count	74179	26376	100555
			% within Gender	73,8%	26,2%	100,0%
1918-1922	Gender	M	Count	15823	4255	20078
			% within Gender	78,8%	21,2%	100,0%
		F	Count	27282	12864	40146
			% within Gender	68,0%	32,0%	100,0%
	Total		Count	43105	17119	60224
			% within Gender	71,6%	28,4%	100,0%
1913-1917	Gender	M	Count	4067	1151	5218
			% within Gender	77,9%	22,1%	100,0%
		F	Count	9384	4194	13578
			% within Gender	69,1%	30,9%	100,0%
	Total		Count	13451	5345	18796
			% within Gender	71,6%	28,4%	100,0%
=<1912	Gender	M	Count	576	177	753
			% within Gender	76,5%	23,5%	100,0%
		F	Count	1849	763	2612
			% within Gender	70,8%	29,2%	100,0%
	Total		Count	2425	940	3365
			% within Gender	72,1%	27,9%	100,0%
Total	Gender	M	Count	151568	31865	183433
			% within Gender	82,6%	17,4%	100,0%
		F	Count	186607	75860	262467
			% within Gender	71,1%	28,9%	100,0%
	Total		Count	338175	107725	445900
			% within Gender	75,8%	24,2%	100,0%

11.2 Article 2

Altogether 80 participants had agreed to participate in the Delphi process, and all were included in Round 1. We received 65 responses, 62 of them complete (77.5%). All responses were included in Round 2. All the originally 27 proposed criteria were kept in Round 2. In addition, 7 new criteria were added, based on suggestions from the panel. Some participants withdrew by not responding to the survey. Of those choosing to withdraw after the survey was initiated, seven participants gave reasons for withdrawal; workload, family matters, or feeling of lack of knowledge.

Round 2 was sent to 62 participants. We received 55 responses, 52 of them complete, forwarded to Round 3. All 34 criteria were still included. In round 3 we got 49 responses, all complete. Thus, 60% of the original 80 completed all three rounds of the survey, and 74% of those starting the survey completed it. The final result was a list of 34 criteria, consisting of the 27 original suggestions from the facilitators, and the seven additional criteria proposed by the panel in Round 1. No criterion was voted out through the process.

There was a high degree of accord with the suggested criteria from the beginning, with 26 criteria getting a mean score of >8.0 regarding the clinical relevance of the criterion (scale 1-10) from Round 1. Relevance scores increased for each round, and in Round 3, 28 of the 34 criteria had a mean score >9.0. Discord decreased over the three rounds in that standard deviations decreased. See Article 2, Table II.

The Delphi consensus process resulted in the NORGEP-NH criteria (Table 4), a set of 34 explicit criteria consisting of

A. 11 single substance criteria
B. 15 combination criteria, and
C. 8 deprescribing criteria.

Table 4. The Norwegian General Practice Nursing Home (NORGEP-NH) criteria for potentially inappropriate medication use in elderly (≥70 years) nursing home residents

	A: Single substance criteria *Regular use should be avoided*	**Comments, adverse effects**
1.	Combination analgesic codeine/paracetamol	Poor long-term effects. Constipation, sedation, falls
2.	Tricyclic antidepressants (TCAs)[1]	Anticholinergic effects, cardiotoxicity
3.	Non-steroid anti-inflammatory drugs (NSAIDs)	High risk of side effects and interactions
4.	1. generation antihistamines[2]	Anticholinergic effects, prolonged sedation
5.	Diazepam	Oversedation, falls, fractures
6.	Oxazepam: Dosage > 30 mg/day	Oversedation, falls, fractures
7.	Zopiklone: Dosage > 5 mg/day	Oversedation
8.	Nitrazepam	Oversedation, falls, fractures
9.	Flunitrazepam	Oversedation, falls, fractures, addiction
10.	Chlometiazole	Poor safety record. Risk of cardiopulmonal death
11.	Regular use of hypnotics	Oversedation, falls, fractures
	B: Combination criteria. *Combinations to avoid*	
12.	Warfarin + NSAIDs	Increased risk of bleeding
13.	Warfarin + SSRIs/SNRIs[3]	Increases risk of bleeding
14.	Warfarin + ciprofloxacin/ofloxacin/ erythromycin/clarithromycin	Increased risk of bleeding
15.	NSAIDs/coxibs[4] + ACE-inhibitors[5]/AT2-antagonists[6]	Increased risk of kidney failure
16.	NSAIDs/coxibs + diuretics	Reduced effect of diuretics, risk of heart and kidney failure
17.	NSAIDs/coxibs + glucocorticoids	Increased risk of bleeding, fluid retention
18.	NSAIDs/coxibs + SSRI/SNRIs	Increased risk of bleeding
19.	ACE-inhibitors/AT2-antagonists + potassium or potassium-sparing diuretics	Increased risk of hyperkalemia
20.	Beta blocking agents + cardioselective calcium antagonists	Increased risk of atrioventricular block, myocardial depression, hypotension, orthostatism
21.	Erythromycin/clarithromycin + statins	Increased risk of adverse effects of statins
22.	Bisphosphonate + proton pump inhibitors	Increased risk of fractures
23.	Concomitant use of 3+ psychotropics[7]	Increased risk of falls, impaired memory
24.	Tramadol + SSRIs	Risk of serotonin syndrome
25.	Metoprolol + paroxetine/fluoxetine/ bupropion	Hypotension, orthostatism
26.	Metformin + ACE-inhibitor AT2-antagonists + diuretics	Risk of impaired renal function and metformin-induced lactacidosis, especially in dehydration
	C: Deprescribing criteria. Need for continued use should be reassessed[8]	
27.	Anti-psychotics (incl. “atypical” substances[9])	Frequent, serious side effects. Avoid long-term use for BPSD[10]
28.	Anti-depressants	Limited effect on depression in dementia
29.	Urologic spasmolytics	Limited effect for urinary incontinence in old age. Risk of anticholinergic side effects
30.	Anticholinesterase inhibitors	Temporary symptomatic benefits only. Frequent side effects
31.	Drugs lowering blood pressure	Hypotension, orthostatism, falls

32.	Bisphosphonates	Assess risk-benefit in relation to life expectancy
33.	Statins	Assess risk-benefit in relation to life expectancy
34.	Any preventive medicine	Assess risk-benefit in relation to life expectancy

D. [1]Amitriptyline, doxepine, chlomipramine, trimipramine, nortryptiline; [2]dexchlorfeniramine, promethazine, hydroxyzine, alimemazine (trimeprazine); [3]Selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors; [4]cyclooxygenase-2-selective inhibitors; [5]angiotensin-converting enzyme inhibitors; [6]Angiotensin II receptor antagonists; [7]From the groups centrally acting analgesics, antipsychotics, antidepressants, and/or benzodiazepines; [8]This should be undertaken at regular intervals. For criteria 27-29, a safe strategy for re-evaluation is first to taper dosage, then stop the drug while monitoring clinical condition; [9] risperidone, olanzapine, quetiapine, aripiprazole; [10]Behavioural and Psychological Symptoms in Dementia

The NORGEP-NH criteria are freely available and can be used for research purposes, by health administrators, and as prescribing assistance for health professionals in nursing homes. The full NORGEP-NH with comments and references to each criterion can be found in Appendix 3.

For results from the Mann-Whitney U-tests, see Appendix 2. In brief, there was a significant difference between the specialist group and the nursing home doctor group for only 6 out of the total 95 scores. The relevant criteria involved NSAIDs and/or SSRI/SNRI, and treatment with statins. For no criterion was the difference persistent over all three rounds and only in one case was there a difference over two rounds (1 and 3), concerning the combination of NSAIDs with SSRI/SNRI.

In the Delphi process, we also received some general advice from the participants, some of which was incorporated into the NORGEP-NH criteria. A short excerption is cited below:

“In addition one should recommend that when a patient is being admitted to a nursing home, one should as a routine measure include the full medication list in www.interaksjoner.no. The same should be done as a routine whenever a new drug is introduced to the patient.” Interaksjoner.no is a Norwegian web page analyzing relevant drug interactions.

"Start low and go slow"

”I miss a focus towards a dynamic approach towards drug treatment in the elderly; what changes/controls should be done in inter-current disease, change in weight/nutritional status, change in prognosis.”

“Indication for all medical treatment of elderly should be regularly reconsidered, as illnesses and symptoms may “burn out”.”

“We should be restrictive when starting or continuing drugs that often give physical discomfort and side effects where we are dependent upon information about this from the patient themselves, in nursing home patients with poor language function and marginal function in many areas”.

11.3 Article 3

For sample characteristics, see Article 3, Table 1.

Of the 881 patients from 30 institutions that were included in the survey, 43.8% were prescribed at least one PIM regularly, according to the NORGEP-NH Single substance and Combination Criteria. 9.9% received three or more PIMs concomitantly on a regular basis. The prevalence of psychotropic drugs was especially high, with 69.7% of participants receiving this regularly, and 14.5% receiving three or more psychotropic substances on a regular basis. For prevalence figures on each criterion, see Article 3, Table 2.

Only 12.3% of participants were not affected by the NORGEP-NH criteria 1-33 (including the Deprescribing criteria), when looking at only regular medications. Almost one in ten (9.1%) were affected by four or more criteria (regular drugs only) (Article 3, Table 3).

Female residents had higher odds for receiving PIMs in general (OR 1.60, p=0.007), and 3+ psychotropic drugs concomitantly (OR 1.79, p=0.03), than their male counterparts. When only looking at residents in long-term facilities, OR for 3+ psychotropics for females vs. males was 2.91 (p=0.006).

Residents with 3+ psychotropic drugs had a higher risk of falls in the course of the infection or dehydration episode (OR 1.70, p=0.04).

Residents were categorized into tertiles regarding ADL score. Residents in the highest tertile (i.e. mostly self-sufficient) had a significantly higher risk of being prescribed 3+ psychotropics than those in the lowest tertile (i.e. mostly dependent on help in ADL) in multivariate analyses (OR 2.16, p=0.006). For long-term residents (i.e. residents living in long-term, combined long- and short-term, and dementia wards), the risk of receiving 3+ psychotropics was 3.07 (p= 0.002) for the best functioning tertile compared to those with the lowest ADL score. Considering the possibility of the lowest functioning group to have seen more deprescribing than the others, we checked for correlation between the

number of drugs and the ADL score but found no such correlation. Thus, the lowest functioning group did not receive fewer drugs than the best functioning group.

There was a significantly higher risk for long-term residents to be prescribed 3+ psychotropic drugs, than for those living in short-term, palliative, and rehabilitation wards.

In the multilevel analysis the intra-cluster correlation coefficient (ICC) for PIMs was 0.06, meaning there was a residual variance between nursing homes that was not explained by the factors in our regression model. ICC for 3+ psychotropics was 0.16. For long-term residents the unexplained differences between the nursing homes as measured by the ICC increased to 0.14 for PIMs and 0.26 for 3+ psychotropics.

12 DISCUSSION

First in this section, I will discuss general principles regarding explicit criteria like the NORGEP-NH developed in this thesis, and their use. Then I will look at methodological considerations and discuss the results from the studies behind articles 1-3.

12.1 General discussion regarding explicit criteria

As seen in Background, lists of explicit criteria are often developed especially with pharmacoepidemiological research in mind. Surveys can be helpful also in clinical practice, in detecting specific problems in local prescribing traditions, both for individual doctors, for institutions, and for health authorities. However, in these endeavours it is imperative to keep in mind that due to the way lists of external criteria are created, the "optimal" value for PIMs can not be zero, but rather a figure somewhat higher than zero, and this figure is not known or defined by the criteria. There are several reasons for this. Examples are when

- a patient may have had side-effects from other medications earlier, thus being better off using medications or combinations represented in these lists than receiving no treatment for a condition
- a patient may suffer from a combination of conditions that limits the number of medications that can be combined safely, either due to interactions or increased risk of side effects (i.e. in epilepsy, bleeding disorders, Parkinson's disease, rheumatoid arthritis)
- a patient may use the substance for other indications than the most common indication, i.e. using amitriptyline in low dose as an adjuvant analgesic and not antidepressant. In these instances, the medication use may be appropriate, but will still be classified as inappropriate in many studies, including those behind articles 1 and 3 in this thesis. This problem may be reduced in surveys where more clinical and subject data is supplied.

Another challenge that may lead to a systematic bias towards too high prevalence rates is for instance if a patient who regularly uses statins gets a prescription of an antibiotic like erythromycin. Due to interactions, this leads to a risk of accumulation of statin. However, the physician may have taken appropriate steps to follow up in terms of temporarily stopping or reducing the dose of statin during the antibiotics treatment. Such

precautionary measures could not be corrected for in Article 1, as in many studies. This adds to an impression of a higher rate of potentially inappropriate medication use than the actual use. In the study behind Article 3, medication lists were in the form of comprehensive lists given at a certain point in time, and precautionary actions like these would have been possible to detect.

The transfer value of different lists of criteria between different countries is limited by differences in pharmaceutical tradition. One example is France, a country with a pharmaceutical tradition unlike the Norwegian in that a number of substances in use in one country is not marketed in the other, as seen in the French list of external criteria (Laroche et al. 2007). In a study from Sweden, prescriptions to both home-dwelling elderly and nursing home residents (n=346 709) were assessed using all drug-specific criteria included in the 2012 Beers Criteria, the Laroche list, the PRISCUS list, the NORGEP criteria and the Swedish National Board of Health and Welfare criteria, finding prevalence rates from 16% (NORGEP criteria) to 24% (2012 Beers criteria) (Morin et al. 2015). In Taiwan, a population of 193 patients in an outpatient hospital clinic was assessed using six different lists of criteria, including NORGEP, Beers and STOPP, with prevalence rates ranging from 24 to 73% (Chang et al. 2011). Oliveira found in a study from Brazil a prevalence rate of PIMs of 51.8% according to the 2012 Beers criteria versus 33.8% when using the STOPP criteria (Oliveira et al. 2015) and in a study from an acute care Hong Kong tertiary hospital, a prevalence rate of 38.6% was found according to the Beers 2012 criteria versus 31.6% according to the STOPP criteria (Lam et al. 2015). A higher prevalence rate for one set of criteria vs. the other can be seen as the former having a higher sensitivity. However, these results show that a comparison of PIM prevalence from different studies must take into account the explicit criteria in use and the country in question. Ideally, such lists should be adapted for each national market. As the NORGEP-NH criteria are developed for the Norwegian pharmaceutical market, its use may be limited by differences in pharmaceutical traditions in other countries, unless the pharmaceutical spectrum is fairly similar to that of Norway.

We strongly recommend that measures for the reduction of PIMs be implemented. However, for the prescribing physician it is also important to bear in mind the personal cost for a patient of old age in changing medications. The advantage of a medication change must be weighed against an increased risk of user error, not to be underrated in an elderly population with medication lists of substantial lengths. Cessation of inappropriate psychoactive medications can be stressful not only mentally but

physiologically (e.g. sleep disturbances, changes in appetite), situations that can add to the severity of a situation that is already fragile. Prescribers need to take the full situation of each individual into consideration before choosing to alter medications or deprescribe. They should try to minimize this sort of stress, for instance by introducing change gradually over a longer period. In some cases, the best clinical choice may be to maintain status quo.

It is important that considerations and limitations like the above mentioned are known to those taking lists of explicit criteria into practical use. As stated in a guide accompanying the 2015 Beers update: “Many clinicians misunderstand the purpose of the criteria, mistakenly believing that the criteria deem all uses of the listed drugs to be universally inappropriate. Health systems have often reinforced this perception, implementing quality improvement and decision support systems that implicitly consider any use of these medications to be problematic. … Implementation of the criteria in inflexible, dogmatic ways can breed resentment and lack of faith in the recommendations” (Steinman et al. 2015).

To sum up;

- Explicit criteria can never replace clinical judgement and individual considerations.
- Potentially inappropriate medications may be appropriate for the individual
- Extra vigilance is needed when a doctor chooses to prescribe drugs represented on these lists.

For external criteria to be useful, they need to be updated frequently. In the pharmacological science, where both knowledge and available drugs change rapidly, lists like these will be outdated after few years without frequent updating.

12.1.1 Validity and reliability of explicit criteria

There is a question whether the validity of these kinds of lists is satisfactory. As seen above, there are many instances where the use of a substance on any of these lists of external criteria will be most appropriate and of vital importance to the person’s well-being. One example is diazepam, most commonly used as a tranquilizer in the elderly, a use that is deemed inappropriate due to its very long half-life of up to 100 hours in this population. However, it is still the drug of choice in acute treatment of epileptic seizures.

It can also be helpful in the terminal phase, to lessen anxiety for a dying person. In this latter situation, the long half-life of diazepam may indeed be of benefit to the patient, thus not having to repeat the administration so often, leading to a more peaceful setting.

It is important that explicit criteria for PIMs be used with the knowing of this. The risk of a too dutiful employing of criteria like these is that patients can be deprived of substances that would be of benefit. We will then hit the target of getting a high quality health care on paper, but miss our true goal of maximizing the patients' relief from suffering. In this respect, you can say that a certain degree of inherent low validity is present in these lists; we tend to habitually "miss the target" to a certain degree. The criteria will have a high degree of reliability as measuring variables in that different studies will yield comparable results. However, as the "optimal" level of PIMs will be higher than zero, one can argue that these criteria will systematically shoot a little to the side for the target due to the above-mentioned circumstances, meaning that the validity of the criteria will be less than 100%.

This leads to the question of validity of the NORGEP-NH and the NORGEP criteria employed in Article 1, compared to other such criteria. How good are the criteria in identifying those individuals who are in reality exposed to harmful medication use? That is – how high is the sensitivity of the criteria? And how high specificity do they have – i.e., how likely are the criteria to correctly identify individuals who are not exposed to harmful medications?

No validity studies have yet been performed using the NORGEP or the NORGEP-NH criteria. In order to assess the validity of explicit criteria for potentially inappropriate medication use, one needs to compare the results from applying the criteria to the "true" value. One study has attempted to validate three such sets of criteria, namely the Swedish National Board of Health and Welfare's criteria, the French criteria and the PRISCUS list (Wallerstedt et al. 2015). The quality of prescribing for 200 hip fracture patients > 65 years was assessed using the STOPP/START criteria and clinical judgment of one general practitioner and one geriatrician as a "gold standard". They found that 22-41% of patients were exposed to PIMs according to the three chosen sets of criteria. Using this "gold standard", they found that 71% of patients received suboptimal drug treatment. Thus, all lists had low sensitivity according to this chosen method to assess the gold standard. However, in this approach to the gold standard the number of drug omissions were also included, a problem not addressed by the three lists under validation. Employing this method, the authors found that all three lists had high

sensitivity in that the likelihood of the lists pinpointing individuals with sub-optimal drug treatment was high. They also concluded that the specificity of all lists was relatively high. They also found that the Swedish list had higher sensitivity than the other two lists, not surprisingly, in that the study was performed on Swedish patients. As the NORGEP-NH criteria were developed to identify potentially harmful medications, but not drug omissions, the gold standard used in this validity study is not as well suited for evaluation of these criteria. In the validity study of Wallerstedt et al, sensitivity scores were reported to improve somewhat in analyses when medication omissions were excluded, though figures on this were not given.

Another article that studied the predictive validity of the 2003 and 2012 Beers Criteria and the STOPP tool in predicting ADRs and hospitalizations found that Beers had relatively higher sensitivity and lower specificity and the STOPP criteria lower sensitivity and higher specificity. “All three criteria were modestly prognostic for ADEs, EDs, and hospitalizations, with the STOPP criteria slightly outperforming both Beers criteria.” (Brown et al. 2016).

12.2 Observational studies and pharmacoepidemiological research

“Life can only be understood backwards; but it must be lived forwards.”

— Søren Kierkegaard

Articles 1 and 3 of this thesis are based on observational, cross-sectional surveys. These may be suitable for the chief purposes in this thesis, namely to observe the prevalence of PIMs among elderly people at a given point in time. We can also use these methods for assessing factors associated with PIMs. In this work, these factors are sometimes referred to as predictors. However, this methodology does not allow us to study the *causes* for PIMs. We can only say whether factors are associated with one another, not whether the one or the other factor is causing this relationship, or whether a common third variable (confounder) is the cause of the association (von Elm et al. 2004).

12.3 Article 1

12.3.1 Methodological considerations

The strength of this study is the comprehensiveness. Thanks to the NorPD, we were able to do a national survey with prescriptions from 24.500 prescribers, lacking only prescriptions from institutions like hospitals and nursing homes. If we had included prescriptions made by hospital and nursing home doctors, the prevalence of PIMs would have increased.

The large number of participants led to very small statistical uncertainty. We were able to give results with p-values of 99% and still have narrow confidence intervals. The database material also eliminated problems of recall bias.

On the negative side, we could not adjust for sociodemographic factors. In a country like Norway, with mountains and fjords dividing people geographically and where the distance from Oslo to Hammerfest in the north equals the distance from Oslo to Rome, sociodemographic differences prevail, although economic differences are less than in most other countries. Our study could not illustrate any sociodemographic differences in PIMs.

In the work behind Article 1 we had access to extensive information, but for only a few variables. This trait is frequent in data sets from register databases such as the NorPD, where the researchers have to rely on the data that is already collected in the database. This means that results will be very accurate, but one can only ask a limited number of questions. There is also a risk that you lack information on significant confounders. This is important to bear in mind when interpreting results. This also affected the number of research questions we could ask in this study. However, the limitation of the data was not considered to lead to bias in the analyses that were performed.

The lack of clinical data was not so much a limitation to the results in our study, as a limitation to the scope. In combining a large data set like this one with clinical information, one could explore the clinical consequences of potentially inappropriate prescribing and assess economic results thereof. An option would be to merge files from NorPD with other registers, holding information on hospital admissions, or specific diagnoses. For instance, Norway has established a national database for hip fractures, Nasjonalt hoftebruddsregister, and studying the relationship between hip fractures and

PIPs on a national scale is one of the possibilities that could be explored. However, at the time of the preparation of Article 1, the other registers relevant for this kind of task were not yet operative.

Technically, the data tells us what prescriptions were dispensed by the pharmacies, but we have no information about compliance or to what extent the medication were ingested. Our method only addresses pharmacological inappropriateness and does not allow for analyzing other medication related problems, such as indication, dosage, administration form or monitoring.

The lack of information about over-the-counter drugs affected the combination criteria regarding NSAIDs, but was otherwise not thought to influence results much, as Norway has a very strict policy and few substances are permitted for sale over-the-counter.

In international literature, a cut-off of 65 years is more common in studying PIMs in the elderly. However, as the general health situation among elders in Norway has improved over the past few decades, 65-year-olds of today are more often in good health. The NORGEP criteria used for the assessment of PIPs in this article were developed for elderly ≥ 70 years. For this reason, we chose a cut-off of ≥ 70 years in this article. The downside to this approach is the lesser comparability with other studies.

12.3.2 Discussion of results

The main result from Article 1 was that 34.8% of the home-dwelling Norwegian population ≥ 70 years received at least one PIP over the year 2008. We also found that about one in four of the home-dwelling elderly were being subject to PIPs involving psychoactive substances, with a risk of affecting cognitive abilities, balance and sedation and consequently QoL. This demonstrates the dimension of the problem of PIMs in the modern elderly population, and is important evidence for the medical profession and health authorities.

We found that men have increasing odds for receiving PIPs with age, where females have falling odds from the 85-89 years group onwards, and these differences increased more for psychoactive PIPs than for PIPs in total (see Results). This may point towards differences in how pathophysiology changes with increasing age between the old men and women who are still healthy enough to reside at home at a high age. Another possible explanation behind these findings is the existence of differences between

genders in behavioral changes towards seeking medical help with increasing age. However, the underlying causes for this pattern can not be determined from our study, as we have noted earlier, this study design does not open for results on causal relationships.

A possible confounder to PIPs and age, for which we could not correct, was general frailty, which rises with increasing age. The total number of medications can to some extent be seen as a substitute measure for frailty. The total number of medications was omitted as a factor in our final regression model. However, in our preliminary analyses, we also ran adjusted models that included the total number of medications. The distribution of total number of medications can be seen in Figure 2, and results from unadjusted logistic regression in Table 5.

Figure 2. Distribution of number of different ATC codes per patient

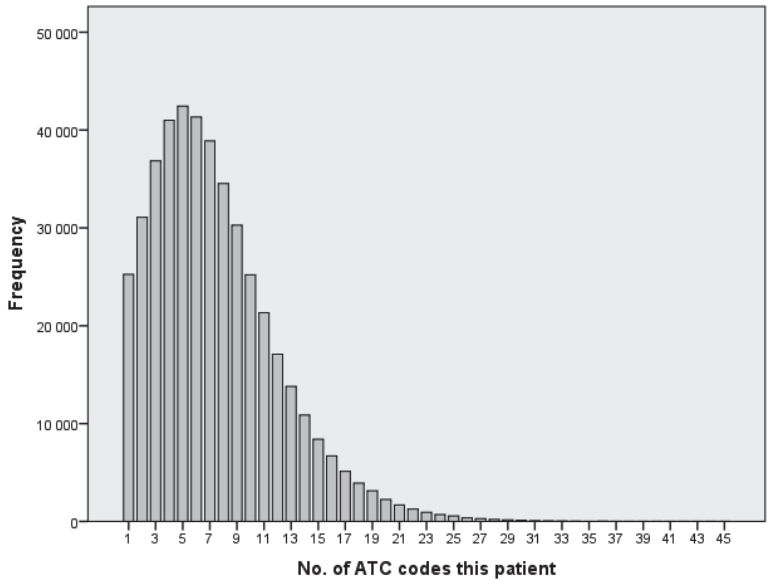

Table 5. Logistic regression model with total number of ATC-codes

Factor	Characteristic	No. of persons in subgroup	No. of persons in subgroup with PIMs (%)	Unadjusted odds ratio (95% C.I.)	Adjusted odds ratio (95% C.I.)
Gender	Male	183 433	52 261 (28.5)	1 (ref)	1 (ref)
	Female	262 467	103 080 (39.3)	1.62 (1.60-1.64)	1.53 (1.50-1.55)
Age	70-74 years	136 585	43 289 (30.6)	1 (ref)	1 (ref)
	75-79 years	126 375	43 821 (28.3)	1.14 (1.12-1.17)	0.98 (0.96-1.00)
	80-84 years	100 555	37 143 (37.4)	1.26 (1.23-1.29)	0.98 (0.96-0.99)
	85-89 years	60 224	22 957 (38.1)	1.33 (1.29-1.36)	0.97 (0.95-0.99)
	90-94 years	18 796	6 952 (37.0)	1.26 (1.21-1.31)	0.97 (0.93-1.00)
	≥95 years	3 365	1 179 (35.0)	1.16 (1.06-1.28)	0.98 (0.90-1.06)
No. of doctors prescribing to this person	1 to 2	247 844	65 457 (26.4)	1 (ref)	1 (ref)
	3 to 4	133 823	53 962 (40.3)	1.88 (1.86-1.91)	0.96 (0.94-0.97)
	5 or more	64 233	35 922 (55.9)	3.54 (3.47-3.60)	1.04 (1.02-1.07)
No. of different ATC-codes prescribed to this person	1 to 3	93 196	8 001 (8.6)	1 (ref)	1 (ref)
	4 to 5	83 442	17 037 (20.4)	2.73 (2.66-2.81)	2.74 (2.66-2.82)
	6 to 7	80 235	25 271 (31.5)	4.90 (4.76-5.03)	4.91 (4.77-5.04)
	8 to 10	90 019	40 209 (44.7)	8.60 (8.37-8.83)	8.56 (8.33-8.79)
	11 to 45	99 008	64 823 (65.5)	20.19 (19.67-20.73)	19.75(19.19-20.32)

We see from Table 5 that there is a strong relationship between the total number of ATC codes given to each person, and the number of PIPs, as discussed above. When including the number of different ATC-codes in the full regression model and thus correcting for this factor, we no longer found age to be associated with PIPs. Thus, the correlation between age and PIPs may be reflecting the degree of frailty.

Likewise, the alternative model shows that there is no longer a relationship between the number of doctors prescribing to each patient, and PIPs. Patients with comorbidities are more likely to see several doctors, and more likely to need more medications. Thus, morbidity may also be a confounder for the variable “number of doctors prescribing to this person”.

The choice of model thus shows the same picture from two different angles, and in some ways, the models give alternative information. We see that including the total number of medications in the regression model would indeed mask other correlations, as could be

expected when including an intermediate variable, however omitting the variable also has its limitations. If length had not been an issue, the preferred solution might have been to include both models in the article. Other studies have reported the similar strong relationship between PIMs and the total number of medications prescribed, and often included the total number of medications as a factor in the regression (Guaraldo et al. 2011, Morin et al. 2016). Some of these studies have found higher age to be associated with PIMs.

However, the results regarding gender were clear. We found females to have higher odds for PIPs. This finding was consistent through all models that were tested and we considered it a very robust finding. The OR for gender difference was higher when analyzing PIPs related to any psychoactive substance than for PIPs in general. Thus, we found that older females are more prone to be prescribed potentially harmful psychoactive medications than males. In this study, no confounders were identified that could explain these differences. There seemed to be a true difference between the genders. This correlates with what often, but not always has been found in other studies (Guaraldo et al. 2011), keeping in mind that studies are not directly comparable due to use of different criteria developed for different markets.

12.4 Article 2

12.4.1 Methodological considerations

One of the benefits of the Delphi method is that all participants' views are given the same weight, regardless of rank. Due to the habit of excluding elderly people from RCTs on medication effects and side effects, there is still little scientific evidence to potentially inappropriate medication use in this age group. Thus, the Delphi technique could be a fruitful method, and is the most commonly used method for development of explicit criteria (Dimitrow et al. 2011).

Many different Delphi processes have been performed, in various settings and for various problems. One of the issues that facilitators have to resolve is whom to include in the panel. The selection of participants is of importance for the relevance of the results from Delphi processes. For the Beers 2012 criteria, the panel consisted of "an 11-member interdisciplinary expert panel with relevant clinical expertise" (American Geriatrics Society Beers Criteria Update Expert 2012). For Beers 2015, a panel of 13 was gathered with expertise in geriatric medicine, nursing, pharmacy practice, research,

and quality measures, with special regard to representation from different practice settings, including long-term care (American Geriatrics Society Beers Criteria Update Expert 2015).

In the case of NORGEP-NH, it was essential to include the knowledge and experience of the nursing home doctors. The clinical issues that nursing home doctors face are in fact quite different from those of the hospital physician. In order to find a common ground between these professionals, we included both nursing home doctors, geriatricians, and clinical pharmacologists. We also had worked with several especially skilled pharmacists on several other occasions, and their competency was included in our panel.

The risk in choosing an approach where the panelists were not exclusively selected on basis of their personal achievements or positions was that we might include doctors with little experience in the particular field. If too many were in this category, we would risk lesser quality of the consensus process. Our hope was that our strategy would attract those with a special interest for the cause, which indeed did happen. To check for bias due to the selection of participants we planned to perform statistical analyses (discussed below), analyzing outcome after grouping the panel into two groups. Those in direct clinical contact with the nursing home residents in their normal environment (the nursing home doctors) on one side, and the hospital based or more theoretically oriented health professionals (the rest of the panel) on the other.

The Delphi process in itself is based on expert knowledge. However, the facilitators' initial 27 suggestions, and the 7 criteria later added on basis of suggestions by the panel, were based on a combination on experience and knowledge among both the facilitators and the panel in combination with a thorough, non-systematic literature search. The relevant literature was also offered as references to the panel during the consensus process itself. It is therefore correct to say that evidence based knowledge played an important part in this Delphi consensus process. The same applies to the Delphi processes for the updated Beers criteria from 2012 (American Geriatrics Society Beers Criteria Update Expert 2012) and 2015 (American Geriatrics Society Beers Criteria Update Expert 2015), in which literature searches made the theoretical framework for the following Delphi processes. As the amount of evidence in the field of pharmacogeriatics is increasing, all available knowledge should be incorporated in the consensus processes. This modification strengthens the Delphi processes.

In this study, the researchers were based at the Department of General Practice, and the participants received study material through e-mails. There was never direct contact between the researcher and the participants, nor between the participants themselves, except if they coincidentally knew each other and could discuss informally between themselves. However, to the extent that there was contact between participants during the consensus process this was not considered problematic, as the idea was to reach consensus also through hearing what the rest of the panel scores, and adjusting your own score in the light of this knowledge.

Regarding the choice of the web-based SurveyMonkey survey tool, there were some practical difficulties in communicating and in getting good overviews among the facilitators. Some facilitators were familiar with the interface of this program while others were not, and being an early version of the software, finding survey results and exporting them in practical formats was sometimes a challenge. These practical issues hampered the work within the facilitator group to some extent, but SurveyMonkey proved to be a very efficient tool in reaching out to the respondents and in keeping track of them.

12.4.2 Discussion of results

The NORGEP-NH Delphi process resulted in 34 criteria, 27 as proposed by the facilitators and 7 after suggestions by participants. None of the proposed criteria were voted out. For all the suggested criteria, the degree of discord as measured by the standard deviations of the mean score fell with each round. The degree of consensus was especially high in the third round.

There may be several reasons for the high degree of consensus seen throughout the process. Firstly, a thorough literature search and discussions within the facilitator group both before preparing the initial 27 criteria and in selecting the 7 additional criteria, meant that the criteria were in fact thoroughly tested before being presented to the panel. Secondly, the exact phrasing of each criterion was amended according to suggestions from the panel for each round. A third reason is that the Delphi method in itself can lead to a tendency of consensus in that participants are presented the average score from the former round in scoring the next round. This can influence the scores in later rounds, especially for participants who are more theoretically insecure. In our design, the nursing home doctors did not have the prerequisite of a medical specialty – namely because a specialty of nursing home medicine does not yet exist in Norway. The younger or less

experienced nursing home doctors in the panel could theoretically be more prone to being influenced by the average score.

This leads to the argument that the Delphi method is a conservative technique for acquiring consensus, in that it takes a lot for a criterion to be rejected. However, this can be adjusted for in deciding on outcome measures. In our study, we decided that a criterion be included in the final list only if (mean – 1SD) > 5 in the final round. Thus, a criterion with a relatively high mean score could still be voted out if the discordance was high in the last round. This still did not lead to the rejection of any suggested criterion, however, bearing in mind that the criteria were constructed with the purpose of being as much on the target as possible.

The final NORGEP-NH criteria can be divided into three groups. One group consists of single substance criteria. The second group consists of different drug combinations to avoid whenever possible. Group 1 and 2 are easily applicable in pharmacoepidemiological research. Although one of the statements ideally requires information about diagnosis: “Tricyclic antidepressants for depression”, in practice there is one way around this, in that TCAs used against neuropathic pain normally require a much lower daily dose than antidepressant treatment does. Having information about daily dose will therefore be a way to approximate the target.

The final NORGEP-NH also includes a third group, the Deprescribing criteria. These criteria consist of drugs for which continued need should be reassessed frequently. These criteria are different, in that medications on the Deprescribing criteria may be highly appropriate, such as drugs lowering blood pressure for serious hypertension, bisphosphonates in newly discovered osteoporosis, or statins in the first three months following a cerebral vascular catastrophe. These instances should obviously not be counted when assessing inappropriate medication use. However, in the nursing home population, with an average of two more life years and often considerably less, the risk of a patient experiencing negative side effects from the drug – that they may not be capable of expressing clearly - may indeed be higher than the chance of him or her benefiting from the drug. A trial in which patients with life expectancy of 1 month to 1 year were randomized to either discontinue or continue statin use, found no significant difference in the number of participants who died within 60 days (23.8% vs 20.3%, p=0.36), and total QoL was better for the group discontinuing statin therapy (Kutner et al. 2015). The need for preventive medications must be reconsidered often, and the long-term continuation of preventive medication may indeed be determined inappropriate. When developing

criteria especially for the nursing home population, these deprescribing criteria were thus considered essential, in spite of their limitations in pharmacoepidemiological research. The Deprescribing criteria can also act as important reminders to prescribers to reassess the need for continued anti-depressant medical treatment, and even more important, anti-psychotic treatment. However, in calculating frequencies from the NORGEP-NH criteria, these limitations have to be borne in mind. Including all the drugs on this list in frequency estimates will not give a correct figure for truly inappropriate medication use. For this, an estimate based on the A. Single substance criteria, and B. The combination criteria, is more correct. However, including the Deprescribing criteria gives an impression of the amount of prescriptions that need special attention from prescribers in the follow-up of these patients. This information can be of use also for health administrators and will reflect the complexity7 of the medical treatment in the population studied.

Of the 80 participants who initiated the Delphi survey, 49 (61%) completed all three rounds. 49% of those completing the survey were nursing home doctors. The majority of those withdrawing did not enter the first round, in spite of agreeing to participate (see Article 2, Figure 1). Out of the 65 entering the first round, 75.4% finished all three rounds. The in total six participants, three in each round, who delivered partial responses, were not included since all six only responded to a few initial questions. A few participants gave reasons for withdrawing, including retirement, change of work place, a subjective feeling of not having the appropriate qualifications, and personal matters. The remaining withdrew by not responding to the questionnaire. Email reminders were sent twice for each round, to those not having responded. The responders were generally active throughout the process. The number of comments, suggestions for further references, and suggestions for new criteria were numerous. The final criteria were not only approved by the participants, but also influenced by their participation.

Regarding the deprescribing criterion “Cessation of treatment with statins should be considered with markedly reduced life span. Exception: Patients with a recent cerebrovascular thrombosis of <3 months”, Mann-Whitney U-tests showed that NH doctors were significantly more in agreement with this statement in Round 1. The exception to the criterion was added after Round 1, and this exception may have increased consensus from geriatricians seeing patients after acute stroke, in situations where evidence shows that statins have a plaque stabilizing effect that is important in the first phase after an acute cerebral ischemic stroke regardless of expected life span

(Hong et al. 2015). The wording was cut short in the last version of the criteria as published in Article 2. The shortening of the phrases made the criteria easier to read and use, but have a side effect of increasing risk of misunderstandings and incorrect use. The full NORGEP-NH is found in Appendix 3.

However, the Mann-Whitney tests showed an overall substantial agreement between the two groups of participants, showing no significant difference in the scoring between the groups, for 89 out of the total 95 scores in the survey. The resulting NORGEP-NH list would have been unaltered if either one of the two groups alone had participated in the Delphi consensus process.

Developing a tool that can be useful in a busy clinical setting, implies creating a list of criteria that is not too detailed. The downside to this is the risk that simplification may indeed lead to the wrong conclusions on some occasions. For instance, criterion 13. Warfarin + SSRIs/SNRIs, and 18. NSAIDs/coxibs + SSRIs/SNRIs, both with reasoning the increased risk of bleeding, did not distinguish between the different SSRIs/SNRIs or NSAIDs/coxibs. The risk of bleeding does seem to vary for different subtypes of these drugs, for SSRIs/SNRIs part due to differences in serotonin inhibition for the different substances (RELIS 2011), and for NSAIDs/coxibs due to different impact on the gastric mucosa. For instance, cipramil seems to have a lower risk profile than some of the other SSRIs. However, the risk is still present, and the need to remind prescribers of the risk is thus important. Another example is that of different statins interact with different macrolid antibiotics in different ways via CYP450 and CYP3A4 (RELIS 2004).

One systematic review has reported an association between SSRIs and falls (Hartikainen et al. 2007), with the risk of hip fracture increasing with an OR of 6.30 (95% CI, 2.65–14.97) within two weeks of a new prescription of fluoxetine or paroxetine. Bakken et al showed in a national Norwegian study based on the Nor-PD in 2013 that the risk of hip fracture was higher among those using anti-depressants, and higher among those using SSRIs than TCAs (Bakken et al. 2013). We did not address the relation between SSRIs and falls in our NORGEP-NH criteria, again underlining the importance of a continuous effort of updating criteria like the NORGEP-NH.

As discussed earlier, treatment omissions will not be covered by external criteria like the NORGEP-NH. Pain treatment in nursing home residents may be one area in need of extra focus from prescribers. There is some evidence that stepping up pain treatment positively affects NPS in this population (Husebo et al. 2011), indicating that prescribers

not always uncover significant pain in these residents. There is a trend over the past few years for increased use of strong opioids in Norwegian nursing homes (Fredheim et al. 2010), in line with what these findings would imply. However, the relationship is not clear-cut; a systematic review and meta-analysis from 2012 found no clear relationship between pain and NPS (van Dalen-Kok et al. 2015). The NORGEP-NH criteria underline the risk of the use of several analgesics and thus may theoretically lead to increased skepticism among prescribers towards these substances. Hence, it is essential to emphasize that adequate pain treatment is important and not considered in any way inappropriate.

12.5 Article 3

12.5.1 Methodological considerations

As seen in Material, the selection of participants in this study was based on residents in need of acute intervention in the form of peroral and/or intravenous antibiotic and/or fluid treatment. Theoretically, this selection could imply that our participants were in a poorer clinical condition than average.

If this is the case, and increased frailty implies increased total number of drugs and hence increased PIMs, there is a risk of bias towards higher prevalence of PIMs in our study population than the average NH population. However, our study found a lower PIM rate than found elsewhere (see below). Thus, comparing the results from our study to other randomly selected nursing home populations may be justifiable. We also know that infections are highly prevalent in this population (Tobiassen et al. 2002, Sundvall et al. 2015). The proportion of residents in the relevant Vestfold nursing homes receiving such treatment in the course of our study period will thus be considerable. It can be argued that the selected population in general was not necessarily significantly more ill and frail than average, but that they at the time of this study were in a setting of acute illness. However, we did not have means to quantify these factors. As some of the nursing home beds in question here are short-term residencies, it was not possible for us to calculate the exact proportion of NH residents in Vestfold over the period that was included in our study. The total number of NH beds in Vestfold was 1379, as compared to the 881 patients included in our study.

We had access to comprehensive clinical data of value. However, dementia had to be omitted from the analyses due to too many missing values (see Methods, Table 1).

Information on preexisting conditions was to be filled in by the nursing home doctors and not the research nurse, a possible explanation for the discrepancy between this and the comprehensive collection of data for other variables. This meant we were not able to analyze the relationship between dementia and PIMs, or dementia and the number of psychotropic drugs.

For the other variables included in the regression, numbers missing were within acceptable limits. However, we found that patients who had been admitted to hospital, especially those who were admitted outside regular work hours when the especially designated nurses were not at work, were more likely to be represented with some missing data. These patients may have some traits in common, such as a more abrupt evolving condition, and maybe a more serious clinical condition. This constitutes therefore a theoretical risk of systematic bias in the analyses. However, there is no a priori reason to believe that this specific sample of patients would have a divergent distribution of PIMs and 3+ psychotropics than the rest of the sample.

12.5.2 Discussion of results

In this study, we found a prevalence of PIMs of 43.8%, excluding PRN medication, including the NORGEP-NH single substance and combination criteria, i.e. the “true” PIMs. These results are comparable to prevalence rates reported from other studies. A prevalence rate of 43.8% is slightly lower than the 49.8% found among 553,814 NH residents from 18 countries after 2005 as reported by Morin et al (Morin et al. 2016). This systematic review covered 19 different sets of explicit criteria. As noted, differences between different tools and different pharmaceutical substances available in each country implies that figures are not directly comparable.

When including the deprescribing criteria, and including PRN drugs, 92.7% of the residents examined received at least one medication that merit a place in the NORGEP-NH list. This can serve as a reminder as to the complexity of nursing home medicine.

In Norway, a population of about 5 million reside over a geographic area stretching north to south the equivalent as the distance between Oslo and Rome, Italy. In some areas, physician recruitment is challenging. Thus, looking at quality of care in different parts of the country, including PIM prescribing, would be of interest. The data in our study come from the county of Vestfold, located in the southern central parts of the country, an area

where the GP pool has been traditionally stable. Prevalence of PIMs in NH residents from six nursing homes in the north of Norway - four in Tromsø and two in Lofoten - according to the NORGEP-NH criteria was assessed in a master thesis from University of Tromsø (Kucukcelik 2016). This survey reported that 61% of the residents received at least one PIM according to the NORGEP-NH single substance and combination criteria. This exceeds the findings in our study, and may be an implication that there are regional differences in Norway, although more research is needed to verify this.

PIMs in Norwegian NHs from 1997 to 2011 as assessed by the NORGEP-NH Criteria have been shown to increase, as have the total number of drugs given to residents over these years (Halvorsen et al. 2016). This finding may in part reflect the increasing frailty of NH residents and the general increasing use of pharmacological substances as seen over these years. The study does not report whether PIMs have increased relative to the total number of drugs. However, the demonstrated increase in the total burden of PIMs in this population is of concern.

Computerized alert systems have showed to be useful tools in reducing PIMs in general practice settings (Tamblyn et al. 2008, Terrell et al. 2009, Tamblyn et al. 2012). The efficacy of these tools may differ in the even more complex prescribing setting of nursing homes. This kind of resources was not available at the nursing homes included in this study.

Of importance and concern is the high prevalence of the use of psychoactive substances: 85.2% of the nursing home residents used one or more psychotropic drug regularly or on demand. This warrants increased focus on exploring effective non-pharmacological measures in the follow-up of the needs of these patients.

Also reflecting this pattern, the NORGEP-NH criterion regarding the use of three or more psychotropic drugs concomitantly was shown in this study to be of high prevalence, affecting 14.5% of residents on a regular basis and 41.5% when including PRN medications. This is markedly higher than the 4.8% affected by the equivalent criterion in our study of home-dwelling elderly (Article 1). These results underline the importance of reminding prescribers to reduce the number of psychotropic acting drugs whenever possible. However, for instance in treating depression, better results can sometimes be reached, with fewer side effects, when combining low doses of more than one

substance, instead of using higher doses of one substance. Another example is lower than optimal pain treatment, reducing patients' QoL. Hence, this criterion, as all, is to serve as a reminder of extra caution, not avoidance.

We also found that 10.3% of the NH residents used anti-psychotics on a regular basis. Among elderly with cognitive impairment, an increased risk of serious ADRs from antipsychotics has been found to lead to an increased mortality risk (Ballard et al. 2009). A large European study recently published (Liperoti et al. 2017) found an increased mortality hazard ratio of 1.71 for those residents in nursing homes with dementia using anti-psychotics, who also were exposed to antipsychotic drug interactions, compared to those not exposed to such interactions. This implies that at least some of the increased mortality that is observed in nursing home residents using antipsychotics come from drug interactions. These drug interactions often come from concomitant psychotropic drugs, but also from cardiovascular drugs. This further necessitates caution in prescribing these substances to elderly with cognitive impairment.

12.5.2.1 Discussing factors associated with PIMs and 3+ psychotropic drugs

The higher odds for female NH residents to receive PIMs as found in this study (OR 1.60, p=0.007), coincides with the similar figure for home-dwelling elderly as found in Article 1 (OR 1.60, 99% CI 1.58–1.64). It seems a substantial proportion of this consists of psychotropic drugs; odds for 3+ psychotropic drugs concomitantly was 1.79 (p=0.03) for females vs. males, rising to 2.91 (p=0.006) when only analysing residents in long-term facilities. The study design chosen for this thesis do not allow us to explore the basis for these gender differences, however, one would encourage that such research be conducted. Possible explanations includes differences in disease spectrum between genders, differences in patients' own preference for and understanding of available treatment that can be tracked to societal gender differences, and doctors' perception of gender and gender differences.

We found the residents with the best preserved ADL to have a significantly higher odds of being prescribed 3+ psychotropics (OR 2.16, p=0.006), the odds ratio increasing to 3.07 (p=0.002) for residents in long-term wards. At first, we found this result counter-intuitive. We thus looked at the relationship between the total number of regular medications and the ADL as measured by the Barthel Index (see Methods), to check if

the total number of medications might act as a confounder, in case the residents with the lowest ADL could have stopped some of their medications. However, no such relationship of clinical relevance was found (OR 1.10, p= 0.46). The higher OR for the best functioning residents could therefore not be explained through a higher use of medications in general. The most likely explanation to our findings is thus that the better functioning residents receive more psychotropic drugs, at least partly, as treatment for agitation, confusion and other NPS in dementia. This interpretation is consistent with the findings of Selbaek et al., where the patients with the most severe form of dementia received the most psychotropic drugs (Selbaek et al. 2007, Selbaek et al. 2008). There is reason to believe that the prevalence of dementia is even higher in long-term facilities than in all facilities as a total, since short-term wards will have a higher prevalence of cancer patients and patients in rehabilitation, another argument in favour of this theory. Yet another factor pointing in this direction is the fact that the inter-facility variance of the prescribing of 3+ psychotropics, as measured by the intra-cluster correlation coefficient (ICC), increased from 0.16 to a considerable 0.26 when only looking at long-term wards. This points to different traditions between the facilities, or other individual non-systematic differences, as earlier found in the US (Chen et al. 2010). This again means that targeted educational efforts towards prescribers in this topic may be effective in reducing these PIMs.

As seen above, we had information about three administrative variables of theoretic interest that were not included in the final regression model. They were “work time employed by the nursing home doctor per resident on each ward”, “work time employed by nurses per resident in each ward”, and “type of doctor working in each ward” (nursing home doctor, general practitioner with nursing home medicine as part time job, or a combination of these). None of these variables yielded significant results in bi- or multivariate models when tested. However, when testing the multivariate model including these factors, ICC fell to 6.1×10^{-12} regarding total PIMs, meaning there was very little variance between the nursing homes that was not accounted for in the extended model. Still, for three or more psychotropics, the ICC was 0,6. Thus; this model strengthened the interpretation that the majority of the variance between the nursing homes concerns the prescribing of psychotropic drugs.

In our study, residents with 3+ psychotropic drugs had a higher risk of falls in the course of the infection or dehydration episode (OR 1.70, p=0.04). This is in line with the above, and with Hartikainen and Bakken’s studies mentioned before reporting associations

between SSRI's and falls (Hartikainen et al. 2007, Bakken et al. 2013). However, Sylliaas et al found that a high Neuropsychiatric Inventory score as measure for NPS was an independent predictor of falls, after correcting for use of neuroleptics and the number of drugs in total (Sylliaas et al. 2012), and another study has found that dementia and depression increased risk of falls in a general elderly population (Gostynski et al. 2001). Nygaard et al found in a study of 118 NH long-term residents that restricted mobility was independently associated with increased risk of falling (OR 4.8), but also found that residents with restricted mobility using anxiolytics/hypnotic or antidepressants had a lower tendency to fall than non-users (Nygaard 1998). Hence, there are several possible confounders here, and the picture is complex. However, one possible confounder in analyses regarding mortality and the use of multiple psychotropic drugs is shown to be ADL. One strength of this study was the meticulous recording of ADL by staff with knowledge to the participants.

13 CONCLUSIONS

Explicit criteria can be used as tools to survey the prevalence of drugs determined to be of high risk in an elderly population. In this thesis, we developed the NORGEP-NH criteria, a list of explicit criteria for potentially inappropriate medication use in elderly nursing home residents, through a Delphi consensus process that was completed by a panel consisting of 49 doctors and pharmacists.

In two pharmacoepidemiological studies, we found our original hypothesis - that many elderly people are using drugs that can be harmful to them – to be strengthened. We found that potentially inappropriate medications affected more than one out of three home-dwelling Norwegians 70 years or older in the year 2008, as measured by the NORGEP criteria. In nursing homes, the prevalence was found to be even higher: 43.8% of the study population from Vestfold nursing homes were using at least one potentially inappropriate medication on a regular basis, this time as measured by the NORGEP-NH criteria. Almost all the nursing home residents (92.7%) were using drugs that according to the NORGEP-NH criteria should be monitored closely. The use of three or more psychoactive drugs at the same time was widespread among the home-dwelling (4.8%), and even more so in the nursing home setting (14.5%).

Elderly females were found to be especially at risk for being prescribed potentially inappropriate medications. This finding was consistent through all analyses, and valid for both home-dwelling and nursing home residents. Elderly females were also found to have higher odds than males for using three of more psychotropic drugs at the same time, in both study populations.

14 THEORETICAL AND CLINICAL IMPLICATIONS

This thesis demonstrates the need for increased research on the benefit/harm ratio for medication use in the elderly, independently of pharmaceutical industry. There is also a need for studies that can shed more light on the use of psychotropic drugs in treatment of NPS in dementia and its consequences. It is important that we keep our focus on the topic of adverse effects and interactions.

The concept of PIMs is useful in understanding the dangers that lie in careless prescribing. Evidence to support any specific interventions to reduce PIM prescribing is inconclusive, but data support the efficacy of prescriber education in geriatric pharmacotherapy, and also the use of explicit criteria, electronic prescribing tools, and cooperation between prescribers and pharmacists.

The guidelines that prevail in modern medicine focus on single diseases, not on comorbidities, and are not always suited as prescriptions guides in the elderly. The very high prevalence of polypharmacy and PIMs demonstrated here might be one consequence of the use of such single disease guidelines. Where comorbidity and frailty is frequent, this approach will often be what Dee Mangin has called a “procrustean approach to good quality care” (Mangin 2012) – referencing Greek mythology and Procrustes, who has an iron bed in which he invites travellers to spend the night. If they were too short, he would stretch them to fit the bed. If they were too long, he would amputate their legs. For elderly, and especially for the frail and nursing home residents, sometimes the bed does not fit. In these cases, the total drug burden and risk of accumulation of side effects must be weighed against the possible benefits of following established guidelines. Following an individual approach may be of preference.

One consequence of the extent of the problem of PIMs in the elderly is that revision of medication lists should be a prioritized task among physicians. In many instances, this will be best done in especially designated consultations. Geriatricians are often focused on this and have the advantage of specific knowledge in the field. However, often the task will naturally fall on the general practitioners or nursing home doctors, being in a unique position to weigh patients’ situations and preferences. Monitoring over time is important when stopping or changing drug treatment. For this, the general practitioners and nursing home doctors are uniquely positioned. General practitioners sometimes follow patients and their families over years and through different phases in their lives,

acquiring valuable non-medical knowledge that will assist in prescribing to meet individual needs, and allowing for evaluation of changing medical needs over time. Such revisions should not fall shy of stopping drugs that are no longer needed; many of the results demonstrated in this thesis imply that in the case of medication use in the elderly, sometimes less is more. Maybe the time has come for a paradigmatic shift within medical treatment of the elderly, where prescribers consider the individual above the disease.

15 EPILOGUE

During the age of the pharmacological revolution, we have over time developed habits of prescribing pharmacological substances as one of the most common means to alleviate various kinds of health problems in the population.

At present, we see that a large proportion of the elderly population use many such substances regularly and at the same time, all the while being prone to comorbidities but with few physiological reserves. The use of medications that have a high-risk profile is also very common, as shown in this thesis. In this, there is a risk that many of our elders are carrying an extra burden in their lives, of side effects from pharmacological treatment, some subtle and hard to acknowledge for both user and caregiver, and some of them likely preventable.

It is fair to say that potentially inappropriate medication use in the elderly is indeed - a modern epidemic.

In the years to come, there is a need for the medical community to further explore non-pharmacological intervention possibilities to address ailments in the growing elderly population. Can we hope for a humanistic revolution?

'And in the end it's not the years in your life that count.

It's the life in your years.'

— Abraham Lincoln

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Artikkel 2

II

Scandinavian Journal of Primary Health Care, 2015; 33: 134–141

ORIGINAL ARTICLE

The Norwegian General Practice – Nursing Home criteria (NORGEP-NH) for potentially inappropriate medication use: A web-based Delphi study

GUNHILD NYBORG, JØRUND STRAAND, ATLE KLOVNING & METTE BREKKE

Department of General Practice/Family Medicine, Institute of Health and Society, University of Oslo, Norway

Downloaded by [University of Oslo] at 13:00 04 February 2016

Abstract

Objective. To develop a set of explicit criteria for pharmacologically inappropriate medication use in nursing homes. *Design.* In an expert panel, a three-round Delphi consensus process was conducted via survey software. *Setting.* Norway. *Subjects.* Altogether 80 participants – specialists in geriatrics or clinical pharmacology, physicians in nursing homes and experienced pharmacists – agreed to participate in the survey. Of these, 62 completed the first round, and 49 panellists completed all three rounds (75.4% of those ultimately entering the survey). *Main outcome measures.* The authors developed a list of 27 criteria based on the Norwegian General Practice (NORGEP) criteria, literature, and clinical experience. The main outcome measure was the panellists' evaluation of the clinical relevance of each suggested criterion on a digital Likert scale from 1 (no clinical relevance) to 10. In the first round panellists could also suggest new criteria to be included in the process. For each criterion, degree of consensus was based on the average Likert score and corresponding standard deviation (SD). *Results.* A list of 34 explicit criteria for potentially inappropriate medication use in nursing homes was developed through a three-round web-based Delphi consensus process. Degree of consensus increased with each round. No criterion was voted out. Suggestions from the panel led to the inclusion of seven additional criteria in round two. *Implications.* The NORGEP-NH list may serve as a tool in the prescribing process and in medication list reviews and may also be used in quality assessment and for research purposes.

Key Words: *Delphi technique, explicit criteria, general practice, inappropriate medication use, Norway, nursing homes, pharmacoepidemiology*

Introduction

The nursing home (NH) population of Western countries has become increasingly frail and ill, with specific and extensive needs in terms of health care. A recent UK survey found that 56% of the residents in 38 NHs died within a year of admission [1]. In Norway, only 29% of long-term residencies in NHs exceeded two years' length in 2012 [2]. The majority of patients have multiple diseases with an average of four active diagnoses, four out of five residents have extensive needs for assistance in carrying out activities of daily living [2], and four out of five have dementia [3].

In general, the elderly population is more prone to medication side effects and drug–drug interactions [4]. Still there is often limited research evidence of effects and side effects, because most randomized, controlled trials on drug treatment are conducted in younger populations where comorbidities and polypharmacy are common exclusion criteria.

Various lists of explicit criteria for pharmacological inappropriateness have been developed to guide clinical practice and for assessing the extent of potentially inappropriate medication (PIM) use in the elderly [5,6]. The Beers criteria were developed in the US in 1991 for NH residents [7] and later for a general population [8–10]. In Europe the STOPP-START criteria, designed for a general elderly population, were published in 2008 [11] and the German PRISCUS list was developed in 2010 [12].

Correspondence: Mette Brekke, Department of General Practice/Family Medicine, Institute of Health and Society, University of Oslo, Norway. Tel. +47 92832865. E-mail: mette.brekke@medisin.uio.no

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Nursing home residents are frail and thus are especially prone to medication side effects and drug interactions.

- This paper describes a three-round Delphi process, resulting in a list of drugs, dosages, and drug combinations to be avoided in nursing home residents for safety reasons.
- The list may serve as a tool in the prescribing process and in medication reviews.
- The list may also be used in quality assessment and for research purposes.

The Norwegian General Practice (NORGEP) criteria are another list of explicit criteria for pharmacological inappropriateness, targeting home-dwelling elderly seen in general practice [13]. The NORGEP list consists of 36 statements including 21 single drugs and 15 drug–drug combinations. The list is partly based on the Beers' criteria and it was derived through a three-round Delphi consensus process carried out in 2006 by a large expert panel consisting of geriatricians, GP specialists, and clinical pharmacologists. According to the NORGEP criteria, one-third of the total population of home-dwelling elderly in Norway was exposed to at least one PIM over the course of one year in 2008 [14]. A study from Norwegian NHs based on 28 of the 36 NORGEP criteria revealed a prevalence of PIM of 31% [15].

Some studies have shown an impact of inappropriate drug regimens on health care outcomes like hospital admission rates [16,17], self-perceived health status [18], and health-care utilization [19], while others have found no association between PIMs and the length of hospital stay [18]. Two studies found no association between PIMs and mortality [16,20]. In one study, inappropriate medication use increased the risk of adverse drug events when measured by the STOPP criteria; however, when applying the Beers criteria the correlation was not significant [21]. There is a need for more evidence as to the clinical relevance of the different lists of explicit criteria when it comes to effect on patient-related health outcomes. In the present study we aimed at establishing an updated and clinically relevant tool for assessing medication use in NH residents.

Material and methods

We conducted a three-round consensus process using the Delphi technique [22]. The Delphi technique is a structured communication technique where a panel of experts answers questions, most often in the form of a questionnaire, to which there are no scientifically proven correct answers [22]. The idea is that a group of experts, participating individually and anonymously, will give a more valid approach than experts one by one, and that consensus is reached through consecutive rounds in which participants are shown average responses made by the panel in previous rounds.

In August 2011 we invited by e-mail all members of the Norwegian Geriatrics Society (NGS, n = 122) and the Norwegian Society of Clinical Pharmacology (NFKF, n = 48) to participate. We also invited five pharmacists known to have particular expertise in medication safety, a convenience sample of NH physicians working in Oslo (n = 55), and all members of the Norwegian College of General Practitioners' Reference Group for NH medicine (n = 11). Altogether, the number of eligible doctors in the five groups was 241. A total of 92 doctors responded to the invitation, and 80 agreed to participate (Figure 1).

The three rounds of the Delphi process were completed between August 2011 and March 2012. The survey was conducted via the software SurveyMonkey® (Madison, WI, US), and the participants were sent an e-mail with a link to the survey. In first round they were exposed to 27 statements, suggesting criteria for inappropriate medication use in NH residents. The proposed criteria were based on the NORGEP criteria [13] and the knowledge and experience of the authors, who also carried out a comprehensive literature search for each suggested criterion. A few of the criteria from the NORGEP list have since their publication been taken off market and a few of them were shown to be of little clinical relevance in a subsequent pharmacoepidemiological national study [14] and these criteria were not included here. Other criteria given as single drug criteria in the NORGEP were here listed as drug classes (first-generation tricyclic antidepressants [TCAs], first-generation antihistamines, and neuroleptics). Each statement was presented with a brief explanation and up to three literature references. A commentary box was provided beneath each criterion. In addition, the participants were encouraged to suggest additional criteria and references.

A new literature search was performed before the authors decided whether or not to include criteria proposed by the panellists in the first round. The revised list of criteria was presented to the panellists in round two, in which average relevance scores from the first round were included. In the second round there was still room for comments but not for suggesting additional criteria. In the third round average scores for each criterion in round two were enclosed and the panellists were asked only to score without comments. A link for opting out was provided in each mail.

Main outcome was the panellists' evaluation of the clinical relevance in an NH setting of each statement

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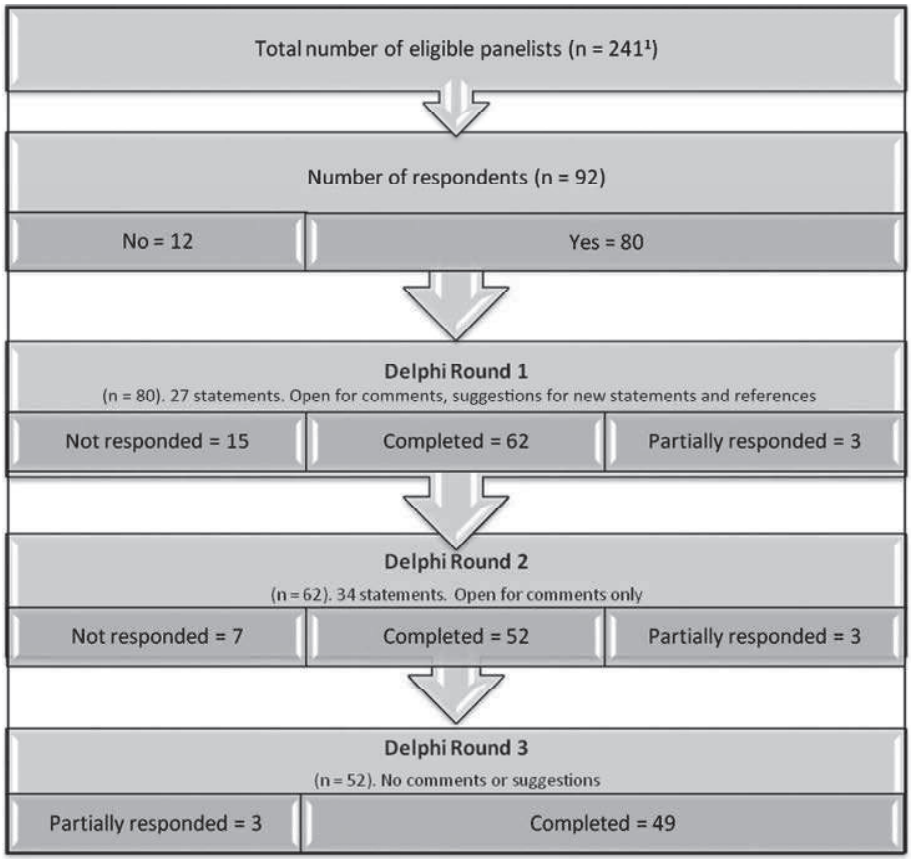

Figure 1. The Delphi process, setting, and participants. [1]Nursing home physicians (n = 55), members of the Clinical Reference Group for Nursing Homes (n = 11), geriatricians (n = 122), clinical pharmacologists (n = 48), pharmacists (n = 5). Two of the doctors in the CRGNH were also nursing home physicians in Oslo and are represented in both groups here.

as scored on a digital Likert scale from 1 (no clinical relevance) to 10 (highly clinically relevant) [23,24].

Statistics

For each criterion, degree of consensus was based on the average Likert score and corresponding standard deviation (SD). SDs described the degree of discordance through the three rounds. Statements were included in the final list if the mean score minus one SD exceeded 5 in round three.

Subgroup analyses were performed comparing scores made by the NH physician group with corresponding scores made by the rest of the panel. Because frequency distributions were skewed towards the right and thus were not normally distributed, Mann–Whitney U-tests were employed to analyse differences in consensus between the two groups. The participants were assumed independent of each other, since the survey was conducted via Internet and not in a face-to-face group. Because of the large number of statistical tests significance was set to $p < 0.01$. Analyses were performed using IBM SPSS Statistics version 20.

Ethics

The study protocol was presented to and approved by the Norwegian Social Sciences Data Services (NSD). Since there was no intervention as such and all correspondence and comments were anonymous the NSD assessed that the study did not need explicit approval by the Regional Committee for Medical and Health Research Ethics.

Results

We received altogether 92 responses from 34 Oslo nursing home physicians, nine members of the Reference Group for NH medicine (some of whom also were physicians in Oslo nursing homes), 13 members of NFKF, 38 members of NGF, and all five pharmacists. Of these, 80 participants agreed to take part in the survey out of which 52 completed all three rounds and 49 provided complete data (see Figure 1). The first round comprised 27 statements to be scored while the second and third rounds held a total of 34 statements, seven of which were based on the panellists' suggestions in the first round. Five participants

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gave reasons for not completing the survey; the rest opted out by not responding to it. Of the 49 participants completing all three rounds, 15 (30.6%) were specialists in geriatrics, five (10.2%) specialists in clinical pharmacology, and five (10.2%) pharmacists, thus making up a group of 25. The other 24 (49.0%) respondents were NH physicians, some members of the General Practitioners' Reference Group for NH medicine.

All proposed criteria were included in the final list (Table I). There was generally a high score for clinical relevance for most criteria, 26 of them receiving a mean score > 8.0 for the first round the criterion was included (Table II). For all criteria the relevance

Table I. Norwegian General Practice Nursing Home (NORGEP-NH) criteria for potentially inappropriate medication use in elderly (> 70 years) nursing home residents.

A: Single substance criteria	Comments, adverse effects
Regular use should be avoided	
1. Combination analgesic codeine/paracetamol	Poor long-term effects. Constipation, sedation, falls
2. Tricyclic antidepressants (TCAs)[1]	Anticholinergic effects, cardiotoxicity
3. Non-steroid anti-inflammatory drugs (NSAIDs)	High risk of side effects and interactions
4. First-generation antihistamines[2]	Anticholinergic effects, prolonged sedation
5. Diazepam	Over-sedation, falls, fractures
6. Oxazepam: Dosage > 30 mg/day	Over-sedation, falls, fractures
7. Zopiklone: Dosage > 5 mg/day	Over-sedation
8. Nitrazepam	Over-sedation, falls, fractures
9. Flunitrazepam	Over-sedation, falls, fractures, addiction
10. Chlometiazole	Poor safety record. Risk of cardiopulmonary death
11. Regular use of hypnotics	Over-sedation, falls, fractures
B: Combination criteria	
Combinations to avoid	
12. Warfarin + NSAIDs	Increased risk of bleeding
13. Warfarin + SSRIs/SNRIs[3]	Increased risk of bleeding
14. Warfarin + ciprofloxacin/ofloxacin/erythromycin/ clarithromycin	Increased risk of bleeding
15. NSAIDs/coxibs[4] + ACE-inhibitors[5]/AT2-antagonists[6]	Increased risk of kidney failure
16. NSAIDs/coxibs + diuretics	Reduced effect of diuretics, risk of heart and kidney failure
17. NSAIDs/coxibs + glucocorticoids	Increased risk of bleeding, fluid retention
18. NSAIDs/coxibs + SSRI/SNRIs	Increased risk of bleeding
19. ACE-inhibitors/AT2-antagonists + potassium or potassium-sparing diuretics	Increased risk of hyperkalaemia
20. Beta blocking agents + cardioselective calcium antagonists	Increased risk of atrioventricular block, myocardial depression, hypotension, orthostatism
21. Erythromycin/clarithromycin + statins	Increased risk of adverse effects of statins
22. Bisphosphonate + proton pump inhibitors	Increased risk of fractures
23. Concomitant use of 3 or more psychotropics[7]	Increased risk of falls, impaired memory
24. Tramadol + SSRIs	Risk of serotonin syndrome
25. Metoprolol + paroxetine/fluoxetine/bupropion	Hypotension, orthostatism
26. Metformin + ACE-inhibitor AT2-antagonists + diuretics	Risk of impaired renal function and metformin-induced lactacidosis, especially in dehydration
C: Deprescribing criteria. Need for continued use should be reassessed[8]	
27. Anti-psychotics (incl. "atypical" substances[9])	Frequent, serious side effects. Avoid long-term use for BPSD[10]
28. Anti-depressants	Limited effect on depression in dementia
29. Urologic spasmolytics	Limited effect for urinary incontinence in old age Risk of anticholinergic side effects
30. Anticholinesterase inhibitors	Temporary symptomatic benefits only. Frequent side effects
31. Drugs lowering blood pressure	Hypotension, orthostatism, falls
32. Bisphosphonates	Assess risk–benefit in relation to life expectancy
33. Statins	Assess risk–benefit in relation to life expectancy
34. Any preventive medicine	Assess risk–benefit in relation to life expectancy

Notes: [1]Amitriptyline, doxepine, chlomipramine, trimipramine, nortryptiline; [2]dexchlorfeniramine, promethazine, hydroxyzine, alimemazine (trimeprazine); [3]selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors; [4]cyclooxygenase-2-selective inhibitors; [5]angiotensin-converting enzyme inhibitors; [6]angiotensin II receptor antagonists; [7]from the groups centrally acting analgesics, antipsychotics, antidepressants, and/or benzodiazepines; [8]this should be undertaken at regular intervals. For criteria 27–29, a safe strategy for re-evaluation is first to taper dosage, then stop the drug while monitoring clinical condition; [9]risperidone, olanzapine, quetiapine, aripiprazole; [10]behavioural and psychological symptoms in dementia.

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Table II. Norwegian General Practice Nursing Home (NORGEP-NH) criteria for potentially inappropriate medication use in nursing home residents.[1] Mean scores with standard deviations and final score.

Criterion:	Round 1 MS (SD)	Round 2 MS (SD)	Round 3 MS (SD)	Final score[2]
A: Single substance criteria. The following should be avoided for regular use whenever possible:				
1. Combination analgesic with codeine/paracetamol	6.5 (2.3)	8.3 (1.8)	8.5 (1.4)	7.1
2. Tricyclic antidepressants (TCAs) for depression	7.2 (2.1)	9.1 (1.2)	9.5 (0.7)	8.8
3. NSAIDs	8.8 (2.0)	9.8 (0.6)	9.8 (0.5)	9.3
4. First-generation antihistamines	7.6 (2.4)	8.6 (1.6)	9.3 (1.0)	8.3
5. Diazepam	9.1 (1.7)	9.6 (1.0)	9.7 (1.0)	8.7
6. Oxazepam: Dosage > 30 mg/day	8.8 (1.5)	9.4 (1.2)	9.6 (1.0)	8.6
7. Zopiklone: Dosage > 5 mg/day	7.6 (2.4)	8.1 (2.0)	8.5 (1.8)	6.7
8. Nitrazepam	8.7 (1.9)	9.5 (1.0)	9.7 (0.8)	9.1
9. Flunitrazepam	9.3 (1.5)	9.8 (0.6)	9.9 (0.2)	9.7
10. Chlometiazole	8.6 (1.9)	9.1 (1.2)	9.2 (1.3)	7.9
11. Regular use of hypnotics	N/A[3]	8.5 (2.0)	9.2 (1.3)	7.9
B: Combination criteria. The following drug combinations should be avoided whenever possible:				
12. Warfarin + NSAIDs	9.6 (1.1)	10.0 (0.1)	10.0 (0.3)	9.7
13. Warfarin + SSRI/SNRI	7.3 (2.5)	7.8 (1.5)	8.1 (1.4)	6.7
14. Warfarin + ciprofloxacin/ofloxacin/ erythromycin/ clarithromycin	8.1 (2.4)	9.1 (1.3)	9.2 (1.1)	8.1
15. NSAIDs/coxibs + ACE-inhibitors/AT2-antagonists	9.1 (1.3)	9.4 (1.1)	9.6 (1.0)	8.6
16. NSAIDs/coxibs + diuretics	8.0 (2.2)	8.6 (1.8)	9.2 (1.6)	7.6
17. NSAIDs/coxibs + glucocorticoids	8.2 (2.1)	9.2 (1.3)	9.5 (0.9)	8.6
18. NSAIDs/coxibs + SSRI/SNRIs	7.2 (2.5)	8.1 (1.9)	8.8 (1.5)	7.3
19. ACE-inhibitors/AT2-antagonists + potassium or potassium-sparing diuretics	8.4 (2.0)	9.2 (1.3)	9.6 (0.8)	8.8
20. Beta blocking agents + cardioselective calcium antagonists	8.5 (2.0)	9.3 (1.2)	9.6 (0.8)	8.8
21. Erythromycin/clarithromycin + statins	8.3 (2.0)	9.5 (0.9)	9.6 (0.8)	8.8
22. Bisphosphonate + proton pump inhibitors	6.6 (2.4)	6.8 (2.1)	7.4 (1.8)	5.6
23. Concomitant use of three or more psychotropic drugs	9.6 (0.7)	9.9 (0.5)	10.0 (0.1)	9.9
24. Tramadol + SSRIs	N/A[2]	8.5 (1.8)	9.2 (0.9)	8.3
25. Metoprolol + paroxetine/fluoxetine/bupropion	N/A[2]	8.9 (1.1)	9.1 (1.0)	8.1
26. Metformin + ACE-inhibitors/AT2-antagonists + diuretics	N/A[2]	8.4 (1.8)	8.6 (1.4)	7.2
C: De-prescribing criteria. Need for continued use should be reassessed[4]				
27. Anti-psychotics	7.6 (1.9)	9.5 (1.4)	9.7 (0.8)	8.9
28. Anti-depressants	8.6 (0.9)	9.9 (0.2)	10.0 (0.0)	10.0
29. Urologic spasmolytics	8.9 (1.6)	9.7 (0.7)	9.9 (0.4)	9.5
30. Anticholinesterase inhibitors	9.4 (1.1)	9.8 (0.4)	9.9 (0.7)	9.2
31. Drugs that lower blood pressure	N/A[2]	9.9 (0.5)	10.0 (0.2)	9.8
32. Bisphosphonates	N/A[2]	9.7 (0.9)	9.9 (0.4)	9.5
33. Statins	9.1 (1.3)	9.7 (0.9)	9.9 (0.5)	9.4
34. General use of preventive medication	N/A[2]	9.6 (1.0)	9.9 (0.4)	9.5

Notes: [1]The clinical relevance for each of the criteria is scored (from 1 to 10) by a panel of experts during a three-round consensus process. Figures are mean scores with standard deviation, MS (SD). [2]Final score (column to the right) is mean score in round 3 minus 1 SD in round 3. To be included on final NORGEP-NH list, final score should be > 5. [3]Not available, this denotes criteria first entered into the Delphi process in round 2. [4]More details are given in Table I.

scores increased through the second and third rounds: 28 of the 34 criteria attained a final average score > 9 in round three. For all criteria the SD was reduced from first to third round, reflecting fewer outliers at the lower end of the scale. Three criteria with an average score < 8 in the first round had a final score > 9 in the third round, namely non-steroidal anti-inflammatory drugs (NSAIDs) in general, anti-psychotics in absence of psychosis, and first generation of antihistamines. Only the criterion regarding concurrent use of proton pump inhibitors (PPIs) and bisphosphonates still had a score < 8 in round three.

Through all three rounds 27 criteria were assessed three times by the panel while seven were scored twice, resulting in 95 means altogether (see Table II). When comparing mean scores made by NH physicians with those made by the group of geriatricians, clinical pharmacologists, and pharmacists (Mann–Whitney U-test with $p < 0.01$ to correct for the large number of tests) we only found a significant but small

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difference for five out of 95 mean scores. For one criterion there was a difference in round 1 ($p = 0.002$) and 3 ($p = 0.004$), but not round 2 ($p = 0.06$), namely the combination of NSAIDs with selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors (SSRIs/SNRIs), where the nursing home physicians scored higher compared with the other group. The nursing home physicians were also more restrictive regarding NSAIDs in general ($p = 0.001$), statins ($p = 0.001$), and the combination of systemic NSAIDs/coxibs + systemic glucocorticoids ($p = 0.008$) in round 1 than the other group, but in later rounds no such difference was found.

Discussion

This three-round Delphi process, carried out among 80 participants, resulted in a list of 34 criteria for potentially inappropriate medication use in NHs. Both the degree of consensus and the average scores for clinical relevance increased throughout the Delphi process. A corresponding trend was also seen in the NORGEP Delphi process [13]. A Delphi technique is said to be useful when a problem does not lend itself to precise analytical techniques, but can benefit from subjective judgements on a collective basis [22]. However, the initial 27 suggestions, and the seven criteria suggested by the panel, are all based on a combination of experience among both the authors and the panel and evidence from the literature. All suggestions have been scrutinized through literature searches and relevant references were provided to the panel during the consensus process.

The standard deviations of the means can be interpreted as a measure of the degree of discord among the participants. However, our data did not follow a normal distribution, as most participants' scores were in the high range (right skewed distribution), especially in round 3, thus the SD will be inflated and not give an exact measure of the variance [25]. Still, a larger SD implies that a larger number of participants scored well below the mean. The Delphi technique in itself can be said to be conservative in the respect that it takes quite a lot for a proposed criterion to be rejected. The main reasons for the Delphi method to fail are imposing monitor views and preconceptions upon the respondent group, and ignoring and not exploring disagreements [22]. In order to avoid falling into these traps and including criteria for which there was substantial discord, we decided that a criterion be included in the final list only if (mean -1SD) > 5, so that not only was the mean score taken into consideration but also the degree of discord. In a case with a high degree of disagreement, as seen by a high SD, the average minus SD will thus be lower than in a case with a high general agreement (and thus a low SD). In this way, a controversial criterion will be less likely to be included in the list than a less controversial. Still no criterion was voted out through the three rounds.

Out of the 80 doctors who initially agreed to take part in the survey, 49 (61%) completed all three rounds. Of these 24 (49%) were nursing home physicians. The survey was lengthy, with a lot of text and many references, and this might have added to the withdrawal percentage. However, participants who completed all three rounds were in large part active throughout the process, providing numerous comments and suggestions for further references in both rounds one and two, thus giving the impression of an involved and independent panel.

It has been argued that one of the most critical aspects when designing a Delphi survey is the selection of qualified experts [22]. In some earlier surveys, among them the Beers consensus process and its later updates [7,8,10], the recruitment process differed from the present study in that the panel consisted of considerably fewer, hand-picked experts: 12 and six in the case of Beers criteria for NHs. The Delphi process leading to the NORGEP criteria, however, included a panel of 47 doctors [13]. At present there is no vocational training leading to a clinical speciality within NH medicine in Norway. Thus we do not know NH doctors' level of expertise and experience. To check for robustness with regard to this matter we tested the average scores and the development of consensus throughout the survey's three rounds for these participants versus the rest of the panel. Using the Mann–Whitney U-test with $p < 0.01$ to correct for the large number of tests, we found only minor differences between the two groups of panellists. The final list of explicit criteria would have been unaltered had only either one of the two participant groups undertaken the survey.

The final 34 criteria can roughly be divided into three groups: single-substance criteria, drug–drug combination criteria, and criteria where regular consideration of "de-prescribing" is of uttermost importance in this population. The term "de-prescribing" can be defined as cessation of long-term therapy, supervised by a clinician [26]. It has been suggested that the term should be adopted internationally by researchers and practitioners engaged in this area [27]. Three criteria in this latter group concern preventive drug use when expected remaining life span is short: one concerning the use of preventive medication in general, the other two concerning the use of, respectively, bisphosphonates and statins. One can argue that the two latter criteria are redundant. However, since there was consensus to include all three criteria throughout the survey, they were included in the final list. A similar argument applies to using NSAIDs in

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different combinations, all of which could have been substituted by a single general criterion. However, since some of the combinations are particularly risky, the combination criteria still may serve a purpose in attracting attention to these potential threats.

The criterion concerning the combination of PPIs and bisphosphonates, suggested by one of the participants, was the only criterion with a mean score < 8 in the final round. Because this represented relatively new knowledge at the time of the survey, the lower score can be viewed as healthy scepticism, as one could argue that more research was needed. After this study was completed, new research has strengthened the evidence for the clinical relevance of avoiding this combination, which is associated with increased risk for fractures [28,29].

The criteria concerning concomitant use of SSRI/SNRI, and warfarin and NSAIDs respectively, do not distinguish between different SSRI/SNRI. However, different SSRI/SNRI represent a varying increase in the risk of bleeding when combined with anticoagulants due to differences in serotonin inhibition [30].

The Norwegian General Practice Nursing Home (NORGEP-NH) criteria resulting from this survey can be used as a reminder for NH physicians in their daily clinical work, and may also be useful for pharmacoepidemiological research and quality assessment work. In a previous study we found that one-third of the total population of home-dwelling elderly in Norway were exposed to at least one PIM over the course of one year, according to a modified version of the NORGEP criteria [14]. The present list, although primarily developed for the especially frail patients in nursing homes, can also be useful as a tool for GPs undertaking medication reviews for elderly patients outside institutions.

There is a need for more research on the effects of implementing the NORGEP-NH and similar lists with explicit criteria in clinical practice on outcomes like quality of life, morbidity, and mortality.

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Declaration of interest

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

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Artikkel 3

III

Potentially inappropriate Medication Use in Nursing Homes. An observational study using the NORGEP-NH Criteria

Gunhild Nyborg[1], Mette Brekke[1], Jørund Straand[1], Svein Gjelstad[1], Maria Romøren[1]

[1] Department of General Practice/Family Medicine, Institute of Health and Society, University of Oslo

Abstract

Background: Frail residents in the nursing home sector call for extra care in prescribing. The Norwegian General Practice Nursing Home (NORGEP-NH) list of 34 explicit criteria for potentially inappropriate medication use in nursing homes was developed explicitly for this population. The aim of this study was to employ the NORGEP-NH Criteria to study the extent of potentially inappropriate medication use among nursing home residents and explore possible associated factors.

Methods: Cross-sectional observational pharmacoepidemiological study from residents in nursing homes in the county of Vestfold, Norway. Data collected 2009-11 included residents' demographic and clinical status and all medications, regular and on demand.

Results: 881 patients from 30 institutions (mean 85.9 years, 68.6% female), were included. According to NORGEP-NH, 43.8% were prescribed at least one potentially inappropriate regular medication, and 9.9% regularly received three or more PIMs. When also including a) the NORGEP-NH Deprescribing Criteria and b) including drugs prescribed for use as needed, 92.7% of all residents received medication that needs particular surveillance according to the NORGEP-NH. 69.7% of the nursing home residents used at least one psychotropic drug regularly. Female residents received more often than males at least one potentially inappropriate regular medication (OR 1.60, p=0.007). Regarding the prescription of three or more concomitant psychotropic medications, odds ratio for females was 1.79 (p=0.03) compared to males. Residents with the best performance in activities of daily living, and residents residing in long-term wards, had higher risk of using three or more psychotropic drugs. Use of multiple psychoactive drugs increased the risk of falls in the course of an acute episode of infection or dehydration (odds ratio 1.70, p=0.009).

Conclusions: Prevalence of potentially inappropriate medications in nursing homes according to the NORGEP-NH was extensive, and especially the use of multiple psychotropic drugs. The high prevalence found in this study shows that there is a need for higher awareness of medication use and side effects in the elderly population. Data obtained from clinical trial NCT01023763 registered with ClinicalTrials.gov 12/01/2009.

Keywords

Inappropriate medication use, elderly, nursing homes, drug safety, explicit criteria, NORGEP-NH, psychotropic medications.

Background

Over the past decades, residents in European nursing homes have become increasingly frail, often with multiple active diagnoses [1]. The situation is similar in Norway, where a recent study found that the prevalence of dementia among Norwegian nursing home residents increased from 80.4% in 2004 to 84.3% in 2010-11, the average resident is incapable of walking without assistance, and also needs assistance for other activities of daily living (ADL). [2]. Meanwhile, development in the field of pharmacology has given doctors a broader palette in their effort to treat diseases. As a result, it is now common for nursing home residents to have medication lists of substantial length. A cross sectional study in eight European countries found that almost one out of four nursing home residents were subject to excessive polypharmacy (10 or more medications), whereas polypharmacy (5-9 drugs) was observed in one out of two [3]. A US study from 2004 found polypharmacy, defined as 9 or more medications, in 40% of nursing home residents [4].

Elderly are especially prone to side-effects and drug interactions due to physiological changes like reduced kidney, cognitive and sensory function, and altered pharmacokinetics and pharmacodynamics [5]. While medication use is crucial for symptom relief and reduction of morbidity and mortality, polypharmacy also involve an increased risk of adverse reactions (ADRs) [6, 7]. However, due to dementia and other conditions, many nursing home residents can have problems expressing their opinion and experience regarding medication use, increasing the risk of ADRs being unrecognized. Consequently, it is important that nursing home physicians are aware of the risks involved in medication use in this population, and that medication reviews and deprescribing are prioritized tasks [8, 9].

Potentially inappropriate medications (PIMs) can be defined as drugs that pose more risks than benefits to the patients [10]. Several lists of explicit and implicit criteria have been developed for the surveillance of PIM use in a general elderly population [11-13]. The US Beers criteria have been widely used and were last updated in 2015 [14]. The Beers list reflects prescribing patterns and drugs marketed in the US. The STOPP list developed in Ireland in 2008, updated in 2015 [15], has gained increased popularity in Europe. The STOPP criteria require access to clinical information, giving rise to concern that the tool may be too comprehensive for some clinical and research purposes [16]. The NORGEP Criteria were developed in Norway in 2008, intended for use in general practice and for a home-dwelling elderly population [17].

However, multi-morbidity, frailty, and the end-of-life setting, imply that the nursing home population requires especially targeted tools for medication surveillance. For many years, the Beers 1991 list of explicit criteria for inappropriate medication use in nursing homes was the only list especially developed for the nursing home setting [10]. According to these criteria, about half of all nursing home residents have been reported to be exposed to PIMs [18, 19]. The use of psychotropics is substantial in the nursing home setting, and in some research, the variable of three or more concomitant psychotropic drugs has been used as a substitute variable for PIMs [20, 21].

In order to have an updated tool designed for the Norwegian pharmaceutical market, the Norwegian General Practice – Nursing Home (NORGEP-NH) criteria for potentially inappropriate medication use especially for elderly in nursing homes were developed through a three-round Delphi consensus process

in 2012 [22] (see Table 3). In addition to the “Single substance” and “Combination” criteria parallel to those found in the original NORGEP criteria, the NORGEP-NH criteria also introduced a third category – the “Deprescribing” criteria. This category contains substances that are not inappropriate per se, but that need special attention in that the need for their continued use should be reassessed frequently. The NORGEP-NH criteria have not yet been validated per se.

Aims

The purpose of this study was to assess the level of potentially inappropriate medication use in elderly nursing home residents in Norway according to the newly developed NORGEP-NH criteria and to look at factors associated with PIM use. This is the first study to explore resident characteristics and clinical factors associated with PIMs according to these criteria.

Methods

Norway had in 2015 a total of 40.708 nursing home beds for its population of 5.165.802 million [23], among them 556.600 (10.8%) persons 70 years or older. This study was carried out in one of Norway’s 19 counties. Eligible units were all 34 nursing homes in the county (a total of 1611 beds), of which four nursing homes declined to participate. The 30 participating nursing homes had 12-124 beds (median 41), in total 1379 beds. They had one to eight departments, and either one type of wards or a combination of wards: for rehabilitation, short term and long term care, palliative care and special departments for patients with dementia.

This is a cross-sectional observational study based on medication data collected for a comprehensive interventional trial of peroral and intravenous treatment with antibiotics and intravenous fluids in nursing homes [24]. The main purpose of the trial was to study how introducing intravenous therapy with fluids and antibiotics in the nursing homes, as an alternative to hospitalization, affected the total outcome of the incident in nursing home residents with a case of acute infection or dehydration. The trial followed a cluster-randomized, stepped wedge design with randomization on the nursing home level. The intervention was in form of a structured program with training of the nursing homes’ personnel in intravenous treatment so that they could offer this treatment locally. Nursing homes were allocated to the control group before the intervention and to the intervention group after, so that patients in the nursing homes received only peroral therapy before the intervention, and peroral or intravenous therapy according to medical need after.

The participants in our study constitute the part of the nursing home population in need of antibiotic or intravenous fluid therapy during the study period. Data were collected from nursing home residents treated with peroral antibiotics from November 2009 to December 2010 (1192 cases), and residents treated with intravenous fluids and/or intravenous antibiotics either in the nursing home or in the local hospital from November 2009 to December 2011 (330 cases). Some patients were represented several times in the interventional study: 66.1% were registered once during the study period, 20% with two episodes, and the remaining with three or more episodes requiring antibiotic or intravenous treatments. For the purpose of this study, we included data from only the first treatment episode (990 individual residents). Exclusion criteria in the intervention trial were serious infection, septicemia, or co-morbidities in need of more thorough diagnostics or treatment than the nursing home could offer.

Further, we excluded patients less than 70 years, as the NORGEP-NH criteria were developed for residents of nursing homes ≥ 70 years, leaving a total number of 914 patients.

For 33 subjects (3.6% of those eligible) medication lists were not available. For some of these, original reports were marked "Deceased, information no longer available" or equivalent. For most, there was no information as to why medication lists were not present in the records. Some of these may have been using no medications. All of these patients had been included with only one case (occurrence) in the Vestfold study. These were also excluded from our study, leaving a total of 881 short-term as well as permanent nursing home residents in 30 of the 34 nursing homes in the county.

In each nursing home and in each hospital department, a nurse served as primary contact for the study team. The nurses were responsible for including the patients and recording patient information in data collection forms, and photocopying the patients' medication charts with both regular and pro re nata (PRN, as needed) drugs. For all cases, clinical data were recorded at enrollment (day 1 in the treatment course) and at predefined days during the course of the acute illness, including delirium assessed with Confusion Assessment Method (CAM) [25]. Activity of daily living (ADL) was measured by the Barthel Index [26] which was retrospectively estimated (score 1 to 20 with increasing level of ADL) by a nurse familiar with the patient as of 14 days before the disease onset, thus representing the resident's habitual level of functioning.

Statistics and analyses

IBM SPSS Statistics 22® (Armonk, New York, USA) statistical software was used for the prevalence analyses. Two SPSS syntaxes were developed for the calculation of PIMs according to the NORGEP-NH, one for substances in regular use only, and one also including PRN drugs.

STATA® (College Station, Texas, USA) was used for predictor analyses in form of bivariate and multivariate regression, with odds ratio (OR) as measure of effects size and ICC as a measure of variability between clusters.

Main outcome was the prevalence of PIMs according to the NORGEP-NH tool. We looked at each indicator, and at the sum of hits per person, with and without PRN drugs.

We performed predictor analysis for PIMs and for the concomitant use of three or more psychotropic medications. All predictor analyses concern the use of regular medications (exclusive PRN drugs) and were stratified with nursing homes acting as clusters.

Variables with statistical significance in bivariate analyses and/or clinical relevance (such as death or delirium) were chosen for the final regression model. Contingency tables showed that the subdivisions of the categories made in the final model were meaningful in the sense that all categories contained an appropriate number of observations. The Akaike Information Criterion (AIC) was also employed when deciding which variables to include in our final, multivariate, mixed effects regression model. Dementia could not be assessed as a possible explanatory variable due to poor quality of the underlying data.

Pearson's r was used to check for relationship between the Barthel score and the number of drugs given on a regular basis, and between the total number of drugs given on a regular basis and the amount of PIMs.

The total number of medications was shown to have a close, approximately linear relationship to both the number of PIMs and the prescribing of 3 or more psychotropic drugs and we found a positive correlation between total number of drugs and both PIMs (Pearson's r=0.36, p=0.000) and 3+ psychotropic drugs (r=0.338, p=0.000). Therefore, the total number of medications given was treated as an effect mediator and was omitted as a variable in the regression analyses in order to avoid over-adjustment bias in the estimate of OR [27].

Barthel ADL scores were categorized in tertiles.

To examine the amount of variability between the nursing homes that was not explained by the variables in the model, an estimate of the intra-cluster correlation coefficient (ICC) was obtained.

Results

Overall mean age was 85.9 (range 70-102), and 604 of the 881 (68.6%) were female. 97 of the participants (11.0%) died within 30 days into the study period.

For sample characteristics, see Table 1.

Table 1: Sample Characteristics.

	Total number (%) in data set	Number with medication list (%). Included in study	Number without medication list (%). Not included in study	Mean (range) among those included in study
Participants	914 (100)	**881** (100)	33 (100)	
Gender:				
Female	623 (68.2)	604 (68.6)	19 (57.6)	
Male	291 (31.8)	277 (31.4)	14 (42.2)	
Age (years):				85.9 (70-102)
< 85	401 (43.9)	382 (43.4)	19 (57.6)	
> 85	513 (56.1)	499 (56.6)	14 (42.4)	
Institutions	30	30[a]	16[a]	
No. of beds	1379			46.0[b] (12-124)
No. of incl. cases		881 (100)		29.4[b] (3-170)
No. of NH doctors	57			1.9[b] (1-6)

[a] No. of institutions represented among patients with/without medication lists. [b] Per institution.

The average number of medications given to each patient on a regular basis was 6.7 (range 0-19). When including PRN medications, the average number of medications for each patient was 9.7 (range 1-25).

For those without medications lists, age range was 74-97, mean age 84.1 years. Of these, 21 (60%) were female and 14 (40%) were male, and they were residents in 16 different nursing homes. Associations between gender and age with group between residents with and without medication lists were established using the Chi-square test. The results showed no statistical difference between those without medication lists, who were excluded from our study, and the included group ($p > 0.05$) (Table 1).

The NORGEP-NH Criteria and the prevalence of PIMs are given in Table 2.

Table 2: Prevalence of Potentially Inappropriate Medication Use in Nursing Home Residents ≥70 years according to NORGEP-NH

NORGEP-NH[a] List of Explicit Criteria	Freq., regular med. only, in %	Freq., incl. PRN[b] medication, in %
A: Single Substance Criteria. The following should be avoided for regular use whenever possible:		
1. Combination analgesic with codeine/paracetamol	0.8	6.8
2. Tricyclic antidepressants (TCAs) for depression	0.9	0.9
3. NSAIDs	1.1	7.7
4. First generation antihistamines	4.5	6.0
5. Diazepam	1.4	10.7
6. Oxazepam: Dosage > 30 mg/day	0.8	N/A
7. Zopiclone: Dosage > 5 mg/day	14.1	N/A
8. Nitrazepam	2.8	3.6
9. Flunitrazepam	0.3	0.3
10. Chlometiazole	1.2	8.7
11. Regular use of hypnotics	30.9	N/A
B: Combination Criteria. The following drug combinations should be avoided whenever possible:		
12. Warfarin + NSAIDs	0.0	0.5
13. Warfarin + SSRI/SNRI	1.6	1.6
14. Warfarin + ciprofloxacin/ofloxacin/ erythromycin/ clarithromycin	0.3	0.5
15. NSAIDs/coxibs + ACE-inhibitors/AT2-antagonists	0.2	1.1
16. NSAIDs/coxibs + diuretics	0.6	3.9
17. NSAIDs/coxibs + glucocorticoids	0.0	0.0
18. NSAIDs/coxibs + SSRI/SNRIs	0.2	2.0
19. ACE-inhibitors/AT2-antagonists + potassium or potassium-sparing diuretics	1.9	1.9
20. Beta blocking agents + cardioselective calcium antagonists	0.0	0.1
21. Erythromycin/clarithromycin + statins	0.1	0.1
22. Bisphosphonate + proton pump inhibitors	1.6	1.7
23. Concomitant use of three or more psychotropic drugs	14.5	41.5
24. Tramadol + SSRIs	1.4	6.1
25. Metoprolol + paroxetine/fluoxetine/bupropion	0.0	0.0
26. Metformin + ACE-inhibitors/AT2-antagonists + diuretics	1.0	1.0
C: Deprescribing criteria. Need for continued use should be reassessed:		
27. Anti-psychotics	10.3	14.2
28. Anti-depressants	35.3	35.5
29. Urologic spasmolytics	0.7	0.7
30. Anticholinesterase inhibitors	5.9	6.0
31. Drugs that lower blood pressure[c]	62.5	65.2
32. Bisphosphonates	5.4	5.6
33. Statins	12.1	12.1
34. General use of preventive medication	N/A[d]	N/A[d]

[a] The Norwegian General Practice criteria for assessing potentially inappropriate prescriptions to elderly patients in Nursing Homes. [b] Pro re nata, drugs given as needed. [c] Incl. in the figures: All drugs that have the lowering of blood pressure as primary outcome (i.e. hypertensives). Excl. drugs with lower blood pressure as side effect, wanted or unwanted. [d] Criterion 34 on the NORGEP-NH list, "General use of preventive

medication", was not assessed in this paper, as information was lacking on whether medication was given for the purpose of treatment or prevention. Abbreviations: NSAIDs: Non-steroid anti-inflammatory drugs. SSRIs: Selective serotonin re-uptake inhibitors. SRNIs: selective norepinephrine reuptake inhibitors. Coxibs: Cyclooxygenase-2-selective inhibitors. ACE-inhibitors: Angiotensin-converting enzyme inhibitors. AT2-antagonists: Angiotensin II receptor antagonists.

Over 10% of the residents used antipsychotics, 30.9% used hypnotics, and 35.3% used anti-depressants on a regular basis. Three or more psychotropic drugs were used concomitantly by 14.5% of residents on a regular basis. When including the drugs on the PRN medication list, 41.5% used three or more, and one out of ten (10.5%) used five or more psychotropic drugs concomitantly (Table 3). 85.2% received one or more psychotropic substances, regularly or on demand.

Table 3: Prevalence of PIMs per Person According to the NORGEP-NH Criteria. Number of people affected, with percentages.

No. of PIMs per person	NORGEP-NH A[1]+B[2]+C[3], prevalence (%),		NORGEP-NH A[1]+B[2], prevalence (%)		No. of psychotropic drugs per person, prevalence (%)	
	Excl. drugs on demand	Incl. drugs on demand	Excl. drugs on demand	Incl. drugs on demand	Excl. drugs on demand	Incl. drugs on demand
0	108 (12.3)	64 (7.3)	495 (56.2)	265 (30.1)	267 (30.3)	130 (14.8)
1	253 (28.7)	163 (18.5)	163 (18.5)	185 (21.0)	290 (32.9)	182 (20.7)
2	211 (24.0)	161 (18.3)	136 (15.4)	181 (20.5)	196 (22.2)	203 (23.0)
3	142 (16.1)	151 (17.1)	63 (7.2)	138 (15.7)	86 (9.8)	160 (18.2)
4	80 (9.1)	130 (14.8)	20 (2.3)	72 (8.2)	37 (4.2)	113 (12.8)
5	52 (5.9)	104 (11.8)	3 (0.3)	22 (2.5)	4 (0.5)	53 (6.0)
6	26 (3.0)	57 (6.5)	0	13 (1.5)	1 (0.1)	29 (3.3)
7	5 (0.6)	29 (3.3)	1 (0.1)	2 (0.2)	0	8 (0.9)
8	3 (0.3)	13 (1.5)	0	3 (0.3)	0	2 (0.2)
9	0	3 (0.3)	0	0	0	1 (0.1)
10	1 (0.1)	5 (0.6)	0	0	0	0
11	0	1 (0.1)	0	0	0	0
SUM	881 (100%)	881 (100%)	881 (100%)	881 (100%)	881 (100%)	881 (100%)

[1]A: Single substance criteria [2]B: Combination criteria [3]C: Deprescribing criteria

Of the nursing home residents in this study, 43.8% had at least one PIM, according to the NORGEP-NH Criteria parts A and B (Table 3). When including PRN drugs the percentage of residents affected by at least one PIM rose to 69.9%. One in ten (9.9%) was given three or more PIMs concurrently on a daily basis. Only 7.2% of residents did not receive any medication according to the NORGEP-NH Single substance, Combination, and Deprescribing criteria.

Factors associated with potentially inappropriate medication

As the prevalence of receiving 3+ concomitant psychotropic drugs in this study was substantial, and this factor in other studies as shown above has been used as a proxy to PIMs, we ran analyses for both the PIMs in total and for 3+ psychotropics in the regression models. Bivariate and multivariate mixed effects regression results for all residents are shown in Table 4. The results commented below are all from multivariate analyses.

Table 4. Factors associated with potentially inappropriate medications, and 3+ concomitant psychotropic medications according to NORGEP-NH Single Substance and Combination Criteria[a].

		PIMs according to NORGEP-NH Criteria 1-26				3+ concomitant psychotropic drugs			
Variable	No. of residents n (valid cases, %)	Bivariate analyses OR (95% C.I.)	p	Multivariate analyses OR (95% C.I.)	p	Bivariate analyses OR (95% C.I.)	p	Multivariate analyses OR (95% C.I.)	p
Age[a] **n= 881**	881	0.99 (0.97-1.01)	0.34	0.98 (0.96-1.01)	0.17	0.99 (0.96-1.02)	0.59	0.98 (0.95-1.01)	0.18
Gender: **n= 881 Male**	277 (31.4)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Female	604 (68.6)	1.38 (1.02-1.86)	**0.03**	1.60 (1.14-2.24)	**<0.01**	1.72 (1.09-2.71)	**0.02**	1.79 (1.06-3.01)	**0.03**
Barthel[b] **n=807 0-5**	314 (35.6)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
6-10	259 (29.4)	1.28 (0.91-1.80)	0.16	1.36 (0.95-1.94)	0.09	1.26 (0.75-2.10)	0.38	1.41 (0.83-2.42)	0.21
11-20	234 (26.6)	1.30 (0.91-1.85)	0.15	1.32 (0.91-1.92)	0.15	1.83 (1.11-3.04)	**0.02**	2.16 (1.25-3.73)	**0.01**
Falls: **n= 830 No**	663 (75.3)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Yes	167 (19.0)	1.09 (0.77-1.54)	0.47	1.10 (0.76-1.36)	0.60	1.84 (1.16-2.91)	**<0.01**	1.70 (1.03-2.80)	**0.04**
Delirium[c]: **n= 877 No**	807 (91.6)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Yes	70 (7.9)	0.93 (0.56-1.55)	0.78	0.95 (0.51-1.76)	0.88	1.22 (0.62-2.42)	0.57	1.21 (0.52-2.83)	0.66
Death[d]: **n=897 No**	782 (88.8)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Yes	97 (11.0)	0.75 (0.48-1.17)	0.21	0.80 (0.47-1.36)	0.41	0.97 (0.52-1.78)	0.91	1.67 (0.82-3.38)	0.16
Ward: **n=837 Rehabilitation**	58 (6.6)	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Short-time	158 (17.9)	0.74 (0.30-1.39)	0.44	0.87 (0.39-1.94)	0.73	2.30 (0.54-9.87)	0.26	2.75 (0.60-12.60)	0.19
Long-time	364 (41.3)	1.25 (0.52-2.35)	0.57	1.61 (0.72-3.62)	0.25	5.08 (1.27-20.23)	**0.02**	7.48 (1.74-32.08)	**<0.01**
Short-/longtime	100 (11.4)	1.56 (0.59-3.17)	0.31	2.12 (0.86-5.26)	0.10	5.92 (1.34-26.27)	**0.02**	7.20 (1.51-34.36)	**0.01**
Dementia	114 (12.9)	1.11 (0.41-2.16)	0.80	1.19 (0.50-2.83)	0.70	7.24 (1.68-31.27)	**<0.01**	7.70 (1.68-35.32)	**<0.01**
Palliative	46 (5.2)	1.51 (0.56-3.61)	0.38	1.98 (0.73-5.40)	0.18	1.88 (0.30-11.71)	0.50	2.04 (0.30-13.99)	0.47

[a]Bivariate and multivariate mixed effects regression analyses stratified on the nursing home level. [b] Continuous variable. [c] No. of residents in each tertile. [d] In the course of the infection. [e] Within 30 days of study inclusion.

Resident's age was not a significant predictor of PIMs or 3+ psychotropic drugs when looking at residents in all wards. However, when looking only at residents in long-term and dementia wards, the odds for receiving 3+ psychotropic drugs significantly decreased with increasing age (OR 0.95, 95% C.I. 0.92-0.99, p=0.02). We did not find clear non-linear associations when age was tested as categorical variable in various groupings.

Female residents had higher odds of receiving PIMs than male residents (OR 1.60, p=0.007). When analysing for 3+ psychotropic medications the gender difference increased (OR 1.79, p=0.03). When analysing gender difference and including only residents living in long-term wards (comprised of long-time and dementia wards), OR for PIMs for female residents vs. male residents was 1.63 (p=0.04). However, for 3+ psychotropic drugs the odds for females increased to 2.91 (95% C.I. 1.36-6.23, p=0.006) when only including residents in long-term facilities.

The odds of receiving PIMs were higher for the group with the highest ADL score. The odds of receiving 3+ psychotropic drugs was even higher for those with the highest ADL score, with an OR=2.16 (p=0.006) for the best functioning tertile compared to the group with the lowest ADL score. For only residents in long-term wards, this tendency was even stronger: The best functioning elderly in long-term care had an OR of 3.07 (95% C. I. 1.5-6.3, p=0.002, not shown in table) of receiving 3+ psychotropic drugs compared to the group with the lowest ADL score. They also had an OR of 2.64 (95% C. I. 1.56-4.46, p=0.000) of receiving PIMs compared to the lowest functioning group. When checking for relationship between the ADL score and the number of drugs given on a regular basis we did not find such correlation.

There were no significant differences between the different types of wards regarding total numbers of PIMs. However, when looking at the prescribing of 3+ psychotropic drugs, the odds were significantly higher for residents in long-term wards, dementia wards, and in wards with combined long- and short-term beds, as compared to residents in short-term wards, rehabilitation wards and palliative wards.

In the multilevel model, an ICC estimate of 0.06 was obtained. This means that 6% of the variability in PIMs total could be attributed to differences between nursing homes. ICC increased to 0.16 when analysing residents receiving 3+ psychotropic drugs. When looking at only residents in long-term facilities, the difference between the nursing homes measured by the ICC increased to 0.14 for PIMs and 0.26 for 3+ psychotropic drugs.

Residents receiving 3+ psychotropic drugs had higher odds of falls in the course of the infection or dehydration episode, with or without fracture (OR 1.70, p=0.04). We found no significant results on either PIMs or psychotropic drugs regarding delirium or death following in the course of the infection.

We tested a regression model where the outcome variable was medications lowering blood pressure, to see if residents using these substances were more prone to falls than other residents, but we did not find any such relationship in these data.

Discussion

Summary of results and comparison to previous literature

The prevalence of PIMs according to the NORGEP-NH Single Substance and/or Combination Criteria was 43.8% excluding, 69.9% including PRN medication. The use of psychotropic medications was extensive.

Females were at higher risk of receiving PIMs and multiple psychotropic drugs, especially when in long-term facilities. Those with good ADL-functioning were at higher risk of receiving multiple psychotropic drugs. The use of multiple psychotropic drugs increased the risk of falls in the course of an infection or dehydration episode.

The use of first generation antihistamines is not included in the criterion regarding "Concomitant use of three or more psychotropic drugs". Among the 4.5% using first generation antihistamines, 45% also used three or more psychotropics. Thus, these residents had yet an additional burden regarding risk of falls and over-sedation [28].

Clomethiazole is still in use for neuropsychiatric symptoms like agitation and aggression in Norway, as one of few countries. Almost one in ten (8.7%) had clomethiazole listed as a regular or PRN drug.

When analyzing "The use of TCA against depression", we did not have information on whether the resident was using TCA to treat depression or as adjuvant treatment of chronic pain. The prevalence for this indicator may therefore be higher than the number actually using TCAs for depression. The basis for this indicator is that the anti-cholinergic effects of TCAs are potentially harmful for the frail elderly [29, 30]. However, Coupland et al. found newer anti-depressants to be associated with an even higher risk of falls than TCAs [31]. The efficacy of anti-depressants in this population is not clearly established [31-33]. There is a need for further research into effects and side effects of anti-depressant drugs in this population.

The total PIM prevalence of 43.8% in our study is in accordance with a nursing home study that according to the STOPP criteria reported a prevalence rate of 46.2% [34], one study employing the Beers criteria that found a prevalence rate of 46.5% [19], and another 50%, the latter looking at residents with a minimum of three months' stay [18]. A Norwegian study reporting prevalence rates of PIMs in nursing homes based on 28 of the 36 original NORGEP criteria developed for home-dwelling elderly found a prevalence of PIM use at 30%. A recent study employing the NORGEP-NH criteria found that PIMs in Norwegians nursing homes have increased over the years 1997-2011, while the average number of drugs also increased over the same time period [35].

Ruths et al. found an increase in the regular use of psychotropic drugs among Norwegian nursing home residents from 57.6% in 1997 to 70.5% in 2009 [36]. This is in accordance with our finding of 69.7%. It has been shown that deprescribing of anti-psychotic drugs in nursing home populations may improve inhabitants' function [37]. The high level of psychotropic medication use in the nursing home population is concerning, considering the limited effects and the high probability for serious side effects. This especially applies to anti-psychotics used for behavioural and psychological symptoms of dementia (BPSD) [37-45].

In a recent multinational European study, the strongest correlate of antipsychotic drug use was found to be severe behavioral symptoms [46], and Lovey et al [47] found that the use of anti-psychotics was correlated to aggressive, verbally disruptive and wandering behavior and the ability to rise from a chair. We found that residents living in long-term facilities had higher odds of receiving multiple psychotropic drugs than elderly in rehabilitation wards or in palliative care units, and among these, the elderly with the best level of functioning had the highest odds of receiving three or more psychotropic drugs. We did

not find a correlation between the ADL score and the number of drugs given on a regular basis. Thus, a higher rate of deprescribing in the lowest functioning group does not seem to explain the results. This finding suggests that the level of ADL could act as a confounder in analyses regarding the use of multiple psychotropic drugs in studies where one cannot correct for ADL as a variable as was done here.

There was an unexplained variability between the nursing homes regarding the prescribing of multiple psychotropic substances, as shown by the larger ICC between nursing homes, suggesting some degree of individual differences in prescription practice between doctors. This is consistent with findings of Chen et al in a study revealing large unexplained variance between nursing homes regarding prescribing of anti-psychotics to residents often lacking a clear indication [48].

Some studies have demonstrated increased levels of falls with increasing levels of PIMs [49, 50]. In this study, we found the risk of falls in the course of an acute infection or dehydration to increase for those who received multiple psychotropic drugs, but there was no clear such association when looking at the number of PIMs as a whole. We did not find a relationship between a tendency of falls and the number of blood pressure lowering substances. Hartikainen et al found in a systematic review from 2007 [51] antihypertensive drugs to be weakly associated with falls, and psychotropics – mainly benzodiazepines, antidepressants, and antipsychotics – to be strongly associated with falls in the elderly.

The gender differences found in our study are consistent with results from a large national study of home-dwelling elderly in Norway conducted in 2008 [52], in which an odds ratio for females for receiving one or more PIMs of 1.60 was found. There is still a need to explore further the reasons behind these differences.

Strengths and limitations

This study is based on comprehensive information about both regular medications and medications given on demand. In addition, the clinical information provided gave an opportunity to study some clinical factors related to PIM use in this setting. The different statistical models yielded robust results regarding significant and non-significant outcomes.

The patients included in this study were selected based on their need of antibiotic or fluid treatment for acute infection or dehydration. This selection could imply a bias towards the more frail of the residents. However, infections are common among nursing home residents and the proportion that receive antibiotic treatment each year is substantial [53, 54]. We do not have access to the exact number of those included in this study in relation to the total number of residents in the 30 nursing homes, partly due to high turnover of residents and partly because this was beyond the scope of the intervention trial [24]. The county of Vestfold has 1379 nursing home places in total (for all 34 nursing homes and all age groups). Our selection of 881 patients implies that this study encompasses a fairly high proportion of the residents in the participating nursing homes. Importantly, the study design opened up for a chance to study how PIMs may affect the frail population of nursing home residents when they encounter acute illness.

Medication lists were recorded on day 1 of inclusion into the original interventional trial, from the nursing home for patients treated there, and from the hospital for patients who were hospitalized. This means that the medication lists were already revised somewhat at the time of inclusion into our study,

in that antibiotics and/or fluids had been added. Additional adjustments to the residents' medications may also have been made before upon the clinical encounter leading to the inclusion in the interventional study, for instance to correct for electrolyte imbalances and/or creatinine elevation. Such imbalances may appear as consequence of PIMs, for instance relating to concurrent use of metformin, ACE-inhibitors/AT2-antagonists, and diuretics, represented in the NORGEP-NH criterion 26. Such adjustments could affect the calculated prevalence rates of PIMs. However, whereas adjustments like the termination of some of the above-mentioned substances could lead to lower prevalence rates, the adding of antibiotics could lead to higher prevalence rates, as can for instance the adding of drugs to treat acute confusion related to acute illness and/or hospitalization. The results from this study should be interpreted with this setting in mind.

The observational design allows us to analyse factors that are related to PIMs, and to 3+ psychotropics. However, this methodology does not allow us to say whether the one or the other factor is causing this relationship, or whether a common third variable (confounder) is the cause of the association [55].

Implications for further research and practice

The highly prevalent use of PIMs in nursing homes found in this study shows that there is a need for intensified measures towards this problem. The topic should be prioritized in educational efforts towards prescribers and caregivers. The complexity of the task of prescribing to this population should be recognized by health administrators to ensure that prescribers are given sufficient resources.

However, although the high prevalence of psychotropic drugs and of PIMs in general shown here is of concern, it is important that elderly people not be withheld from efficient pharmacological treatment. Notably, adequate management of pain has been shown to reduce other use of psychotropic medications [56]. There may well be instances where the use of substances on lists as the NORGEP-NH may be appropriate. Explicit criteria like the NORGEP-HN and Beers' criteria are meant to heighten the awareness of clinicians and caregivers to the use of these substances and the risk involved: "The criteria are designed to support, rather than supplant, good clinical judgment." [57]

Studies over the past few years have demonstrated the widespread problem of potentially inappropriate prescribing in elderly throughout the world [52, 58-63], and there is a known relationship between ADRs and hospitalization and death [7, 64]. So far, there is conflicting evidence as to the effect of PIMs on mortality, morbidity and quality of life (QoL) [65-75]. Some studies find increased hospitalization and mortality rates and reduced QoL with increasing drug burden [73]. Medication reviews has been advocated as a means to reduce the prevalence of PIMs in nursing homes [76]. However, a recent systematic review and meta-analysis that looked at the effect of medication reviews on nursing home resident's mortality or hospitalization found no clear correlation [77]. There is thus a need for more research into the impact of PIMs, and how we best are to reduce their prevalence [78, 79].

Conclusion

This study analyzed potentially inappropriate medication use in nursing homes according to the NORGEP-NH criteria. We found a high prevalence of PIMs, and among these, the use of psychotropic drugs was especially prevalent. Females were at higher risk of receiving both PIMs and multiple

psychotropic drugs concurrently. Residents in long-term wards, and residents with a better-preserved ADL, had a higher risk of receiving multiple psychotropic drugs. The use of multiple psychotropic drugs increased the risk of falls in the course of an infection or dehydration episode.

A prevalence of PIMs of this magnitude reveals a need for targeted measures.

Abbreviations

OR = odds ratio
NH = nursing home
ADR = adverse drug reaction
PIM = potentially inappropriate medication
NORGEP-NH Criteria = Norwegian General Practice – Nursing Home Criteria
BPSD = Behavioural and Psychological Symptoms of Dementia
PRN = pro re nata (medication given on demand only)
QoL = quality of life
RCT = randomized controlled trial
ACE-inhibitors: Angiotensin-converting enzyme inhibitors
ARB: Angiotensin receptor blockers
AT2-antagonists: Angiotensin II receptor antagonists
Coxibs: Cyclooxygenase-2-selective inhibitors
NSAIDs: Non-steroid anti-inflammatory drugs
SRNIs: selective norepinephrine reuptake inhibitors
SSRIs: Selective serotonine re-uptake inhibitors
TCAs: Tricyclic antidepressants

Declarations

Ethics and Consent Statement

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) (reference no. 2009/1584a-1). Written informed consent was obtained from all patients. In patients lacking decision-making capacity, written consent was collected from next of kin. (The 3iV study is reported in accordance with the Consort 2010 extension to cluster randomised trials and the suggested modifications to the Consort 2010 cluster extension for reporting of stepped wedge cluster randomised trials [24, 80]. Trial registration with ClinicalTrials.gov: NCT01023763.

Consent for publication

Not applicable.

Availability of Data and Materials

The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request, likewise the SPSS syntaxes used in the NORGEP-NH analyses.

Dr. Nyborg, Dr. Romøren and Dr. Gjelstad have had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The original data are those of Dr. Romøren.

Competing Interests

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

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Authors' contributions

Acquisition of data: MR, SG
Study concept and design: GN, MR, MB, JS, SG
Analysis of data: GN, SG
Interpretation of data: GN, MR, SG, MB, JS
Drafting of the manuscript: GN
Revision of the manuscript: GN, MR, MB, JS, SG
Funding: GN, MB, JS

Project supervision: GN, MR, MB, JS

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19 APPENDIX 1: The NORGEP criteria

Suggested list of explicit criteria (n=36) regarding pharmacologically inappropriate prescriptions in elderly patients (≥70 years) in general practice and the reasons why. Numbers in superscript refer to the reference list while numbers in parentheses refer to the numbers in the left column representing the drug for which the statement is valid.

	Criteria	Comments
	Tricyclic antidepressants:	
1.	Amitryptiline	Anticholinergic effects, risk of impaired cognitive function[20, 21, 31, 33, 44]. (1-4)
2.	Doxepine	Amitryptiline may be cardiotoxic. Better alternatives exist (1)
3.	Clomipramine	
4.	Trimipramine	
	1st generation low potency antipsychotics:	
5.	Chlorpromazine	Anticholinergic effects, extrapyramidal effects [19, 41].(5-8)
6.	Chlorprothixene	
7.	Levomepromazine	
8.	Prochlorperazine	Often prescribed for dizziness despite lack of documentation [(22, 30)].(8)
	Long acting benzodiazepines	
9.	Diazepam	Prolonged elimination half-life, risk of accumulation, muscular weakness, falls and fractures [39, 40, 43, 45, 52].(9-11)
10.	Nitrazepam	
11.	Flunitrazepam	
	High doses of benzodiazepines and benzodiazepine-like agents:	
12.	Oxazepam > 30 mg/24 h	Risk of muscular weakness, falls and fractures [39, 40, 43, 45, 52].(12-13)
13.	Zopiclone > 7.5 mg/24 h	
	Centrally acting muscle relaxants:	Anticholinergic effects, risk of addiction [10-12].
14.	Carisoprodol	
	Analgesics:	More toxic than its comparators [12].
15.	Dextropropoxyphene	
	Pulmonary drugs:	
16.	Theophylline	Risk of arrhythmias, No documented effect in COPD, better alternatives exist [24, 29].
	Cardiovascular drugs:	
17.	Sotalol	Risk of arrhythmias, better alternatives exist if the indication for treatment is beta-blockade [27].
	1st generation antihistamines:	
18.	Dexchlorfeniramine	Anticholinergic effects, prolonged sedation [44, 50, 45]. (18-21)
19.	Promethazine	
20.	Hydroxyzine	
21.	Alimemazine (trimeprazine)	

	Warfarin combinations:	
22.	Warfarin + NSAID	Increased risk of bleeding [37].
23.	Warfarin + ofloxacin or ciprofloxacin	Increased risk of bleeding due to inhibition of warfarin metabolism [28, 37] (23-25).
24.	Warfarin +erythromycin or clarithromycin	
25.	Warfarin + SSRI	For SSRIs, also increased risk of bleeding due to a direct platelet-inhibiting effect [37].
	NSAIDs combinations:	
26.	NSAID (or coxib) + ACE inhibitor (or ARB)	Increased risk of renal failure [34, 56, 57].
27.	NSAID + diuretic	Reduced effect of diuretics [35].
28.	NSAID + glucocorticoid	Increased risk of intestinal bleeding. Risk of fluid retention [48].
29.	NSAID + SSRI	Increased risk of gastrointestinal bleeding [25, 26, 36, 46, 54, 55].
	Other combinations:	
30.	Erythromycin or clarithromycin + statin	Increased risk of adverse effects of statins, including rhabdomyolysis, due to inhibition of statin metabolism [32, 47, 51]. Highest risk for simvastatin and lovastatin.
31.	ACE inhibitor + potassium or potassium-sparing diuretic	Increased risk of hyperkalemi [42, 53].
32.	Fluoxetine or fluvoxamine + TCA	Increased risk of adverse effects of TCAs due to inhibition of TCA metabolism [38].
33.	Beta blocker + cardioselective calcium antagonist	Increased risk of atrioventricular block and myocardial depression [23].
34	Diltiazem + lovastatin or simvastatin	Increased risk of adverse effects of statins, including rhabdomyolysis, due to inhibition of statin metabolism [71, 72] .
35	Erythromycin or clarithromycin + carbamazepine	Increased risk of adverse effects of carbamazepine due to inhibition of its metabolism [38].
36.	Concomitant prescription of 3 or more drugs within the groups centrally acting analgesics, antipsychotics, antidepressants and/or benzodiazepines	Increased risk of muscular weakness, falls, fractures and cognitive impairment [45].

Abbreviations: NSAID: Non-steroid antiinflammatory drug; ACE: Angiotensin converting enzyme; SSRI: Selective serotonin reuptake inhibitor; TCA: Tricyclic antidepressant; COPD: Chronic obstructive pulmonary disease; ARB: Angiotensin receptor blocker.

20 APPENDIX 2: Mann-Whitney test of Delphi study

	Criterion:	Mean score (S.D.) Round 1 NH doctors	Mean score (S.D.) Round 2 NH doctors	Mean score (S.D.) Round 3 NH doctors	Mean score (S.D.) Round 1 Others[4]	Mean score (S.D.) Round 2 Others[4]	Mean score (S.D.) Round 3 Others[4]	Sig. (Mann-Whitney U[2]) Round 1	Sig. (Mann-Whitney U[2]) Round 2	Sig. (Mann-Whitney U[2]) Round 3
1.	Regular use of the combination drug codein/paracetamol should be avoided.	6.5 (2.6)	8.5 (2.2)	8.3 (1.6)	6.4 (2.0)	8.1 (1.4)	8.6 (1.3)	0.58	0.07	0.58
2.	Tricyclic antidepressants (TCAs): Regular use as anti-depressant should be avoided.	7.8 (2.0)	9.2 (1.1)	9.6 (0.7)	6.7 (2.1)	9.1 (1.3)	9.4 (0.7)	0.02	0.92	0.19
3.	Systemic NSAIDs: Should be avoided.	9.6 (1.3)	9.8 (0.7)	9.8 (0.7)	8.0 (2.2)	9.9 (0.4)	9.9 (0.3)	0.001	0.61	0.34
4.	1. generation antihistamines: Regular use should be avoided.	7.7 (2.8)	8.8 (1.7)	9.3 (1.2)	7.5 (2.0)	8.4 (1.6)	9.3 (0.9)	0.39	0.20	0.55
5.	Diazepam: Should be avoided (except in terminal phase and for convulsions).	9.0 (2.1)	9.8 (0.8)	9.7 (0.9)	9.1 (1.4)	9.5 (1.1)	9.6 (1.1)	0.66	0.18	0.73
6.	Oxazepam: Dosage > 30 mg/day should be avoided.	9.0 (1.3)	9.3 (1.2)	9.5 (10.0)	8.6 (1.6)	9.5 (1.1)	9.6 (1.1)	0.54	0.73	0.94
7.	Zopiclone: Dosage > 5 mg/day should be avoided.	6.7 (2.8)	7.7 (2.4)	8.5 (2.1)	8.4 (1.8)	8.4 (1.6)	8.5 (1.5)	0.02	0.32	0.60
8.	Nitrazepam: Should be avoided.	8.9 (1.7)	9.5 (0.7)	9.9 (0.3)	8.4 (2.0)	9.4 (1.2)	9.6 (1.1)	0.34	0.78	0.13
9.	Flunitrazepam: All use should be avoided.	9.1 (1.9)	9.8 (0.5)	10.0 (0.2)	9.5 (1.1)	9.8 (0.6)	9.9 (0.3)	0.80	0.63	0.58
10.	Chlormetiazole: Should only be used in cases where other options have been tried and failed. Regular use should be avoided.	8.3 (1.9)	8.9 (1.1)	9.0 (1.4)	8.8 (1.9)	9.2 (1.3)	9.5 (1.1)	0.31	0.24	0.11
11.	Hypnotics: Regular use should be avoided.	N/A[3]	8.5 (1.7)	9.4 (1.1)	N/A[3]	8.4 (2.3)	9.0 (1.4)	N/A[3]	0.82	0.19
12.	Warfarin + NSAIDs: Should be avoided.	9.8 (0.5)	10.0 (0.2)	9.9 (0.4)	9.4 (1.4)	10.0 (0.0)	10.0 (0.0)	0.25	0.31	0.15
13.	Warfarin + SSRI/SNRI: Should be avoided.	8.0 (2.2)	8.1 (1.8)	8.7 (1.2)	6.6 (2.6)	7.4 (1.2)	8.5 (1.3)	0.04	0.04	0.003
14.	Warfarin + ciprofloxazine/ofloxazine/erythromycine/clarithromycine: Should be avoided.	8.4 (2.2)	9.3 (1.1)	9.3 (1.0)	7.8 (2.7)	8.8 (1.5)	9.0 (1.2)	0.34	0.31	0.30
15.	Systemic NSAIDs/coxibs + ACE-inhibitor/AT2-antagonists: Should be avoided.	9.2 (1.1)	9.3 (1.1)	9.7 (0.6)	9.0 (1.5)	9.5 (1.1)	9.4 (1.2)	0.57	0.43	0.52
16.	Systemic NSAIDs/coxibs + diuretics: Should be avoided.	8.0 (2.7)	8.5 (2.2)	9.3 (1.2)	8.0 (1.6)	8.7 (1.3)	9.2 (1.2)	0.45	0.65	0.89
17.	Systemic NSAIDs/coxibs + systemic glucocorticoids: Should be avoided.	8.9 (1.7)	9.2 (1.4)	9.6 (0.9)	7.4 (2.2)	9.1 (1.3)	9.4 (0.9)	0.008	0.40	0.54
18.	Systemic NSAIDs/coxibs + SSRI/SNRIs: Should be avoided.	8.3 (2.1)	8.5 (2.0)	9.2 (1.4)	6.2 (2.4)	7.8 (1.8)	8.4 (1.4)	0.002	0.06	0.004
19.	ACE-inhibitor/AT2-antagonists + potassium or potassium-sparing diuretics: Should be avoided.	8.7 (1.5)	9.0 (1.5)	9.5 (0.9)	8.0 (2.3)	9.4 (1.2)	9.6 (0.7)	0.32	0.26	0.63
20.	Beta blocking agents + cardioselective calcium antagonist (verapamil/diltiazem): Should be avoided.	9.6 (1.8)	9.1 (1.3)	9.4 (0.9)	8.4 (2.1)	9.4 (1.2)	9.8 (0.6)	0.70	0.21	0.10
21.	Erythromycine/clarithromycine + statins: Should be avoided.	8.7 (1.9)	9.7 (0.7)	9.7 (0.9)	8.0 (2.0)	9.3 (1.1)	9.5 (0.8)	0.19	0.27	0.18
22.	Bisphosphonate + proton pump inhibitors: Should be avoided.	7.0 (2.5)	7.0 (2.3)	8.0 (1.7)	6.1 (2.3)	6.6 (1.9)	6.8 (1.8)	0.21	0.40	0.02
23.	Concomitant use of three or more drugs from the groups centrally acting analgesics, antipsychotics, antidepressants, and/or benzodiazepines: Should be avoided.	9.6 (0.7)	9.8 (0.7)	10.0 (0.2)	9.6 (0.8)	10.0 (0.2)	10.0 (0.0)	0.88	0.26	0.31
24.	Tramadole + SSRIs: Should be avoided.	N/A[3]	8.6 (1.9)	9.4 (0.8)	N/A[3]	8.3 (1.7)	9.1 (1.0)	N/A[3]	0.45	0.21
25.	Metoprolol + paroxetine/fluoxetine/buproptione: Should be avoided.	N/A[3]	9.0 (1.0)	9.2 (0.9)	N/A[3]	8.8 (1.2)	9.0 (1.1)	N/A[3]	0.60	0.54
26.	Metformine + ACE-inhibitors/AT2-antagonists + diuretics: Should be avoided.	N/A[3]	8.6 (1.7)	9.1 (1.2)	N/A[3]	8.1 (1.9)	8.2 (1.4)	N/A[3]	0.24	0.03
27.	Anti-psychotics should not be used in patients without psychosis.	7.2 (2.5)	9.1 (2.0)	9.7 (0.9)	8.0 (1.2)	9.8 (0.5)	9.7 (0.7)	0.66	0.31	0.55
28.	All use of anti-depressants should be monitored with respect to effect and side-effects.	8.5 (0.8)	10.0 (0.2)	10.0 (0.0)	8.6 (1.0)	10.0 (0.2)	10.0 (0.0)	0.65	0.98	1.00
29.	Urologic spasmolytics: Need and effect should be carefully weighed against potential side-effects. Trial cessation of medication should be considered to assess indication for continued use.	9.1 (1.4)	9.6 (0.8)	9.9 (0.3)	8.6 (1.7)	9.8 (0.6)	9.8 (0.5)	0.32	0.63	1.00
30.	All use of anticholinesterase inhibitors and similar drugs for dementia should be monitored with documentation of effect and cessation of medication should be effectuated where effect is non-satisfactory or there are inacceptable side-effects.	9.6 (1.0)	9.8 (0.5)	9.8 (1.0)	9.2 (1.1)	9.8 (0.4)	10.0 (0.2)	0.09	0.90	0.52
31.	Drugs that lower blood pressure: All use should be monitored with regards to orthostatism, hypotension and fall tendency.	N/A[3]	10.0 (0.2)	10.0 (0.2)	N/A[3]	9.8 (0.6)	10.0 (0.2)	N/A[3]	0.16	0.98
32.	Cessation of treatment with bisphosphonates should be considered in patients with markedly reduced life span.	N/A[3]	9.9 (0.3)	9.8 (0.5)	N/A[3]	9.5 (1.3)	9.9 (0.3)	N/A[3]	0.70	0.58
33.	Cessation of treatment with statins should be considered with markedly reduced life span. Exception: Patients with a recent cerebrovascular thrombosis of <3 months.	9.7 (0.7)	9.8 (0.5)	10.0 (0.0)	8.5 (1.5)	9.5 (1.1)	9.7 (0.7)	0.001	0.17	0.02
34.	Cessation of the use of preventive medicine should always be considered when the patient's remaining life span is short.	N/A[3]	9.6 (0.8)	10.0 (0.2)	N/A[3]	9.5 (1.1)	9.8 (0.5)	N/A[3]	0.74	0.09

[1]: Specialists in geriatrics and clinical pharmacology and selected pharmacists [2]: Difference non-NH doctors/NH doctors [3]: Not applicable.

21 APPENDIX 3: The full NORGEP-NH list with comments and references

The NORGEP-NH Explicit Criteria for drugs, dosages, or combinations of drugs considered inappropriate in elderly (>70 years) living in nursing homes

	A: Single Substance Criteria *The following should be avoided whenever possible:*	**Comments:**
1.	Regular use of the combination drug codeine/paracetamol	Poorly documented effect when in regular use. Risk of addiction. Frequent side effects (constipation, sedation, falls). Risk of treatment failure or overdose due to individual differences in CYP2D6 metabolism. The fixed combination of paracetamol and codeine can be inappropriate due to different dosage regimens for the two substances. However adequate pain relief is important and some residents of nursing homes may not be able to express pain. In cases where paracetamol alone does not have the desired effect one should supplement the treatment, e.g. by adding morphine or another opiate. (1, 2)
2.	Use of TCAs[a] as anti-depressant	Tricyclic antidepressants: Anticholinergic effects, risk of impaired cognitive function. Low doses of TCA used as a pain reliever in e.g. neuropathic pain can be appropriate. In some patients with depression a TCA can be appropriate, in these cases nortriptyline can be recommended. (3-8)
3.	NSAIDs[b]	High risk of side effects and interactions. Should only be used on strong indications. Should not be used in patients with heart failure and/or kidney failure. (9-12)
4.	Regular use of 1. generation antihistamines	Anticholinergic effects, prolonged sedation. (4, 6)
5.	Diazepam: Should be avoided (except in terminal phase and for convulsions).	Long-acting benzodiazepines: Prolonged elimination half-life, risk of accumulation, muscular weakness, falls and fractures. (13-15)
6.	Oxazepam: Dosage > 30 mg/day	High doses of benzodiazepines and benzodiazepine-like agents: Risk of muscular weakness, falls and fractures. (13, 14)
7.	Zopiklone: Dosage > 5 mg/day	Increased risk of side effects e.g. falls and sedation. Non-pharmacological measures like exposure to light, daytime activities and adjustment of sleep routines should be emphasized. (16, 17)
8.	Nitrazepam: All use	Long half-life. High risk of side effects and addiction. Better alternatives are available. (13, 14, 16)

9.	Flunitrazepam: All use	Long half-life. High risk of side effects and addiction. Better alternatives are available. (13, 14, 16)
10.	Chlometiazole: Should only be used in cases where other options have been tried and failed. Regular use should be avoided.	Considerable higher mortality than other substances used on same indications. Poor documentation on safety partly due to the fact that the drug is out of use in many countries. (18, 19)
11.	Regular use of hypnotics	Risk of side effects e.g. falls and sedation. Non-pharmacological measures like exposure to light, daytime activities and adjustment of sleep routines should be emphasized. (16, 17, 20, 21)
	B: Combination Criteria. *The following drug combinations should be avoided whenever possible:*	
12.	Warfarin + NSAIDs[b]	Warfarin combinations: Increased risk of gastrointestinal and intracerebral hemorrhage, increasing with increasing age.(22-27)
13.	Warfarin + SSRIs/SNRIs[c]	Increases risk of gastrointestinal bleeding due to SSRIs/SNRIs inhibition of uptake of serotonin in platelets. The effect is independent of level of INR and probably dependent on the degree of serotonine inhibition, and varies between different SSRIs/SNRIs. Citalopram, escitalopram, and fluvoxamine have lower serotonine inhibition than fluoxetine, paroxetine and sertraline. Fluvoxetine is in addition an inhibitor of CYP2C9, CYP2C19 and CYP1A2 all involved in metabolism of warfarine and the combination should be avoided.(7, 28-30)
14.	Warfarin + ciprofloxacin/ofloxacin/erythromycin/clarithromycin.	Increased risk of bleeding due to inhibition of warfarin metabolism and reduced production of vitamin K from intestinal flora. If strong indication INR should be monitored closely.(24, 25)
15.	Systemic NSAIDs[b]/coxibs[d] + ACE-inhibitors[e]/AT2-antagonists[f]	NSAIDs combinations: Increased risk of drug induced kidney failure.(31)
16.	Systemic NSAIDs[b]/coxibs[d] + diuretics	Reduced effect of diuretics, increased risk of heart failure and kidney failure. Increased risk of hyperkalemia in combinations with potassium-sparing diuretics. (32, 33)
17.	Systemic NSAIDs[b]/coxibs[d] + systemic glucocorticoids	Risk of intestinal bleeding and fluid retention(26, 34)
18.	Systemic NSAIDs[b]/coxibs[d] + SSRI/SNRIs[c]	Each drug increases the risk of gastrointestinal bleeding individually. Some studies but not all show an added effect when the two substances are combined. (28, 29, 35-37)
19.	ACE-inhibitors[e]/AT2-antagonists[f] + potassium or potassium-sparing diuretics	Increased risk of hyperkalemia. Should only be used on strong indication (e.g. severe heart failure) and under close

		monitoring of potassium serum levels.(38, 39)
20.	Beta blocking agents + cardioselective calcium antagonists	Increased risk of atrioventricular block and myocardial depression. Should only be used on strong indication. (32, 40)
21.	Erythromycin/clarithromycin + statins	Increased risk of adverse effects of statins, including rhabdomyolysis, due to inhibition of statin metabolism. Highest risk for simvastatin and lovastatin. In case of indication for both substances the statin dose should be considered reduced or temporarily stopped.(41)
22.	Bisphosphonate + proton pump inhibitors	Concomitant use can reduce the effect of bisphoshonates and increases the risk of fractures. (42-47)[g]
23.	Concomitant use of three or more drugs from the groups centrally acting analgesics, antipsychotics, antidepressants, and/or benzodiazepines	Increased risk of muscular weakness, falls, fractures and cognitive Impairment (7, 48-51)
24.	Tramadol + SSRIs[c]	Risk of serotonin syndrome, increasing with increasing age and dose. However, care should be taken not to undertreat pain in the elderly. (2, 52, 53)
25.	Metoprolol + paroxetine/fluoxetine/bupropion	Interaction resulting in significantly increased serum levels of metoprolol and the combinations should be avoided. When combining metoprolol with citalopram, escitalopram, or duloxetine, the same interaction occurs but less pronounced; in such cases a reduced dose should be considered.(54)
26.	Metformin + ACE-inhibitors[e]/AT2-antagonists [f] + diuretics	Significant risk of impaired renal function and metformin-induced lactacidosis, especially in situations of dehydration. Metformin is eliminated through tubular filtration. If this decreases, metformin accumulates. If indication, e.g. for diabetics with heart failure, diuretics and ACE-inhibitors/AT2-antagonists should be considered stopped during situations of acute illness. (55, 56)
	C: Criteria Dependent on Clinical Condition	
27.	Anti-psychotics should not be used in patients without psychosis.	All antipsychotics are hazardous in the elderly due to side effects that can be potentially serious including increased mortality. No documented effect on BPSD[h]. It has been shown that increasing of pain treatment can have effect on BPSD. Care should be taken not to undertreat pain in the elderly.(2, 3, 6, 57-59)
28.	All use of anti-depressants should be monitored with respect to effect and side effects.	Due to interactions and side effects. (7, 8, 60, 61)

29.	Urologic spasmolytics: Indication and effect should be carefully weighed against potential side effects. Trial cessation of medication should be considered to assess indication for continued use.	Risk of anticholinergic side effects. Limited benefit when incontinence and use of incontinence equipment. Concomitant use with other drugs with anticholinergic properties should be avoided.
30.	All use of anticholinesterase inhibitors and similar drugs for dementia should be monitored with documentation of effect and cessation of medication should be effectuated where effect is non-satisfactory or there are inacceptable side effects.	Risk of side effects. (62-64)
31.	Drugs that lower blood pressure: All use should be monitored with regards to orthostatism, hypotension and fall tendency.	E.g. nitrates, alpha-blockers, calcium antagonists, beta-blockers, ACE-inhibitors, AT2-antagonists, anti-parkinson drugs and anticholinergics, due to increased risk of hypotension and orthostatism. Concomitant use of more than one of these is assumed to increase the risk further, but little documentation on this is available. (48, 65-67)
32.	Cessation of treatment with bisphosphonates should be considered in patients with markedly reduced life span.	Risk of perforation of esophagus in dysphagia. Risk of side effects that must be held up against little expected benefit from treatment. (68)
33.	Cessation of treatment with statins should be considered in patients with markedly reduced life span.	Side effects that potentially reduce quality of living, e.g. myopathy. Marginal benefit can be expected in patients with limited life span. Exception: Patients with at recent cerebrovascular thrombosis of < 3 months due to statins' effect on inflammation and plaque stabilization. (69, 70)
34.	Cessation of the use of any preventive medicine should always be considered when the patient's remaining life span is short.	Marginal expected benefit and high risk of side effects. The patient may not be capable of expressing subjective side effects. (71, 72)

[a] tricyclic antidepressants [b]non-steroidal anti-inflammatory drugs [c]selective serotonin reuptake inhibitors/selective norepinephrine reuptake inhibitors [d]cyclooxygenase-2-selective inhibitors [e]angiotensin-converting enzyme inhibitors [f]angiotensin II receptor antagonists [g]References 45-47 accessed after the Delphi process was finished [h]Behavioral and psychological symptoms of dementia
All criteria concern substances for systemic administration.

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22 APPENDIX 4: The Barthel questionnaire used in the 3iV-study

Barthel ADL-Indeks (status for 14 dager siden) **Skjema 1 – Felles pasientinformasjon s5**

Mahoney FI, Barthel DW. Maryland State Med J 1965;14:61-65.
Denne norske versjonen er redigert i 2008 av Ingvild Saltvedt, Jorunn L. Helbostad, Unni Sveen, Pernille Thingstad, Olav Sletvold og Torgeir Bruun Wyller på grunnlag av flere tidligere norske oversettelser og med hovedvekt på originalpublikasjonen fra 1965.

GENERELT
Barthel ADL-indeks er først og fremst beregnet på å bli brukt av sykepleiere, ergoterapeuter og fysioterapeuter i deres daglige kontakt med pasientene. Det skal registreres hva pasienten faktisk gjør, ikke hva man tror pasienten kan mestre. Svarene skal baseres på egen kjennskap til pasienten eller samtale med personale eller pårørende som kjenner vedkommende. Pasienten skal ikke "testes". Poengene representerer grad av uavhengighet av hjelp fra annen person, uansett årsak. Hvis det er nødvendig med *tilsyn* eller *tilrettelegging*, er personen **ikke** uavhengig, men hvis en aktivitet mestres med *hjelpemidler,* **er** personen uavhengig i denne aktiviteten.

1. Spising
- ☐ 2 Helt selvhjulpen. Kan bruke nødvendige hjelpemidler og spiser innen rimelig tid
- ☐ 1 Behov for noe hjelp, f.eks. til å skjære opp maten
- ☐ 0 Helt avhengig av hjelp

2. Bading/dusj
- ☐ 1 Helt selvhjulpen
- ☐ 0 Trenger hjelp

3. Personlig hygiene
- ☐ 1 Selvhjulpen. Klarer å vaske ansiktet, kjemme håret, pusse tenner og barbere seg
- ☐ 0 Trenger hjelp til en eller flere oppgaver

4. Påkledning
- ☐ 2 Selvhjulpen i av- og påkledning. Klarer selv glidelås, knapper og skolisser
- ☐ 1 Trenger hjelp, men klarer halvparten innen rimelig tid
- ☐ 0 Trenger hjelp til mer enn halvparten

5. Tarmkontroll
- ☐ 2 Kontinent. Klarer selv evt. å sette stikkpille/klyx
- ☐ 1 Nedsatt kontroll og enkelte "uhell" eller trenger hjelp til evt. å sette stikkpiller/klyx
- ☐ 0 Helt inkontinent eller hyppige "uhell"

6. Blærekontroll
- ☐ 2 Kontinent. Holder seg evt. tørr ved bruk av uridom eller mestrer bruk av kateter på egen hånd
- ☐ 1 Nedsatt kontroll og enkelte "uhell" eller holder seg tørr med uridom eller kateter, men trenger hjelp for å bruke dette
- ☐ 0 Helt inkontinent eller trenger permanent kateter

7. Toalettbesøk
- ☐ 2 Selvhjulpen ved toalettbesøk eller bruk av toalettstol. Ordner klær, tørker seg, spyler toalettet eller tømmer bekken
- ☐ 1 Trenger hjelp til forflytning, klær, tørke seg
- ☐ 0 Kan ikke bruke toalett

8. Forflytning mellom seng og stol
- ☐ 3 Selvhjulpen. Klarer også å låse rullestol og bevege fotstøtte
- ☐ 2 Klarer forflytningen med litt hjelp eller tilsyn
- ☐ 1 Kan sitte, men må ha mye hjelp ved forflytning
- ☐ 0 Kan ikke sitte. Sengeliggende

9. Mobilitet
- ☐ 3 Klarer å gå 50 meter, kan bruke stokk eller krykker, men ikke annet ganghjelpemiddel
- ☐ 2 Kan gå 50 meter med rullator og/eller støtte/tilsyn av en person
- ☐ 1 Kan ikke gå, men kan kjøre rullestol uten hjelp 50 meter
- ☐ 0 Kan ikke kjøre rullestol uten hjelp

10. Trappegang
- ☐ 2 Selvhjulpen. Kan evt. bruke ganghjelpemidler
- ☐ 1 Trenger hjelp/tilsyn av en person
- ☐ 0 Kan ikke gå i trapp

	Sumskår (maksimal skår 20 poeng)

23 APPENDIX 5: SPSS Syntax for computing PIMs according to the NORGEP-NH criteria in Article 3

```
String atc1 (A7).
String atc2 (A7).
String atc3 (A7).
String atc4 (A7).
String atc5 (A7).
String atc6 (A7).
String atc7 (A7).
String atc8 (A7).
String atc9 (A7).
String atc10 (A7).
String atc11 (A7).
String atc12 (A7).
String atc13 (A7).
String atc14 (A7).
String atc15 (A7).
String atc16 (A7).
String atc17 (A7).
String atc18 (A7).
String atc19 (A7).
String atc20 (A7).
string atcInd23 (A200).
*The following 3 are antibiotics.
String atc21 (A7).
String atc22 (A7).
String atc23 (A7).

compute atc1 = FastAtc1.
compute atc2 = FastAtc2.
compute atc3 = FastAtc3.
compute atc4 = FastAtc4.
compute atc5 = FastAtc5.
compute atc6 = FastAtc6.
compute atc7 = FastAtc7.
compute atc8 = FastAtc8.
compute atc9 = FastAtc9.
compute atc10 = FastAtc10.
compute atc11 = FastAtc11.
compute atc12 = FastAtc12.
compute atc13 = FastAtc13.
compute atc14 = FastAtc14.
compute atc15 = FastAtc15.
compute atc16 = FastAtc16.
compute atc17 = FastAtc17.
compute atc18 = FastAtc18.
compute atc19 = FastAtc19.
compute atc20 = FastAtc20.
compute atc21 = AB1Atc.
compute atc22 = AB2Atc.
compute atc23 = AB3Atc.
execute.

COMPUTE dose1 = 0.
COMPUTE dose2 = 0.
COMPUTE dose3 = 0.
COMPUTE dose4 = 0.
COMPUTE dose5 = 0.
COMPUTE dose6 = 0.
COMPUTE dose7 = 0.
COMPUTE dose8 = 0.
COMPUTE dose9 = 0.
COMPUTE dose10 = 0.
COMPUTE dose11 = 0.
COMPUTE dose12 = 0.
COMPUTE dose13 = 0.
COMPUTE dose14 = 0.
COMPUTE dose15 = 0.
COMPUTE dose16 = 0.
COMPUTE dose17 = 0.
COMPUTE dose18 = 0.
COMPUTE dose19 = 0.
COMPUTE dose20 = 0.
COMPUTE dose21 = 0.
COMPUTE dose22 = 0.
COMPUTE dose23 = 0.

compute dose1 = Fastdose1.
compute dose2 = Fastdose2.
compute dose3 = Fastdose3.
compute dose4 = Fastdose4.
compute dose5 = Fastdose5.
compute dose6 = Fastdose6.
compute dose7 = Fastdose7.
compute dose8 = Fastdose8.
compute dose9 = Fastdose9.
compute dose10 = Fastdose10.
compute dose11 = Fastdose11.
compute dose12 = Fastdose12.
compute dose13 = Fastdose13.
compute dose14 = Fastdose14.
compute dose15 = Fastdose15.
compute dose16 = Fastdose16.
compute dose17 = Fastdose17.
compute dose18 = Fastdose18.
compute dose19 = Fastdose19.
compute dose20 = Fastdose20.
execute.

COMPUTE Ind1 =0.
COMPUTE Ind2 =0.
COMPUTE Ind3 =0.
COMPUTE Ind4 =0.
COMPUTE Ind5 =0.
COMPUTE Ind6 =0.
COMPUTE Ind7 =0.
COMPUTE Ind8 =0.
COMPUTE Ind9 =0.
COMPUTE Ind10 =0.
COMPUTE Ind11 =0.
COMPUTE Ind12 =0.
COMPUTE Ind13 =0.
COMPUTE Ind14 =0.
COMPUTE ind15=0.
COMPUTE Ind16 =0.
COMPUTE Ind17 =0.
COMPUTE Ind18 =0.
COMPUTE Ind19 =0.
COMPUTE Ind20 =0.
COMPUTE Ind21 =0.
COMPUTE Ind22 =0.
COMPUTE Ind23 =0.
COMPUTE Ind24 =0.
COMPUTE Ind25 =0.
COMPUTE Ind26 =0.
COMPUTE Ind27 =0.
COMPUTE Ind28 =0.
COMPUTE Ind29 =0.
COMPUTE Ind30 =0.
COMPUTE Ind31 =0.
COMPUTE Ind32 =0.
COMPUTE Ind33 =0.
COMPUTE Ind23Count = 0.
COMPUTE atcInd23 = ''.
COMPUTE Warfarin=0.
COMPUTE SSRI_SNRI=0.
COMPUTE ACEAT2 =0.
COMPUTE DIURETIC =0.
```

```
COMPUTE POTASSIUM =0.
COMPUTE MAKROLID =0.
COMPUTE MAKROLID_KINOLON =0.
COMPUTE STATIN =0.
COMPUTE TRAMADOL =0.
COMPUTE PARFLUBU =0.
COMPUTE METFORMIN =0.
COMPUTE BP =0.
COMPUTE STEROID =0.
COMPUTE BETABLOCK=0.
COMPUTE CALCIUMANTAG=0.
COMPUTE BISPHOSPH=0.
COMPUTE PPI=0.
COMPUTE SSRI=0.
COMPUTE METOPROLOL=0.
COMPUTE BP2=0.
EXECUTE.

VECTOR atc = atc1 to atc23.
VECTOR dose = dose1 to dose23.
loop # = 1 to 23.
  IF (atc(#)='B01AA03') Warfarin=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='N06AB' | (atc(#)=
'N06AX16') | (atc(#)= 'N06AX21' )) SSRI_SNRI=1.
  IF CHAR.SUBSTR(atc(#),1,3)='C09' ACEAT2=1.
  IF (CHAR.SUBSTR(atc(#),1,3)='C03' ) DIURETIC=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='C03AB' |
CHAR.SUBSTR(atc(#),1,4)= 'A12B' |
CHAR.SUBSTR(atc(#),1,4)= 'C03D' |
CHAR.SUBSTR(atc(#),1,4)= 'C03E' ) POTASSIUM=1.
  IF (atc(#)='J01FA01') | (atc(#)= 'J01FA09' )
MAKROLID=1.
  IF (atc(#)='J01MA02') | ((atc(#)= 'J01MA01') | (atc(#)=
'J01FA01') | (atc(#))= 'J01FA09' )
MAKROLID_KINOLON=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='C10AA' |
CHAR.SUBSTR(atc(#),1,4)= 'C10B' ) STATIN=1.
  IF (atc(#)='N02AX02') | (atc(#)= 'N02AX52' )
TRAMADOL=1.
  IF (atc(#)='N06AB05') | (atc(#)= 'N06AB03') | (atc(#)=
'N06AX12' ) PARFLUBU=1.
  IF (atc(#)='A10BA02') | (CHAR.SUBSTR(atc(#),1,5)=
'A10BD' ) METFORMIN=1.
  IF (CHAR.SUBSTR(atc(#),1,3)='C02' |
CHAR.SUBSTR(atc(#),1,3)= 'C03' |
CHAR.SUBSTR(atc(#),1,3)= 'C04' |
CHAR.SUBSTR(atc(#),1,3)= 'C07' |
CHAR.SUBSTR(atc(#),1,4)= 'C08C' |
CHAR.SUBSTR(atc(#),1,3)= 'C09' ) BP=BP+1.
  IF (CHAR.SUBSTR(atc(#),1,5)='G04CA' |
CHAR.SUBSTR(atc(#),1,4)= 'N04B') BP2=BP2+1.
  IF (CHAR.SUBSTR(atc(#),1,5)='H02AB')
STEROID=1.
  IF (CHAR.SUBSTR(atc(#),1,4)='C08D')
CALCIUMANTAG=1.
  IF (CHAR.SUBSTR(atc(#),1,3)='C07')
BETABLOCK=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='M05BA')
BISPHOSPH=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='A02BC') PPI=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='N06AB') SSRI=1.
  IF (atc(#)='C07AB02') METOPROLOL=1.
  IF (atc(#)='N02AA59') Ind1=1.
  IF ((atc(#)='N06AA09') | (atc(#)= 'N06AA12') | (atc(#)=
'N06AA04') | (atc(#)= 'N06AA06') | (atc(#)= 'N06AA10' ))
Ind2=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='M01AB' |
CHAR.SUBSTR(atc(#),1,5)= 'M01AC' |
CHAR.SUBSTR(atc(#),1,5)= 'M01AE' |
CHAR.SUBSTR(atc(#),1,5)= 'M01AG' |
CHAR.SUBSTR(atc(#),1,5)= 'M01AH' | (atc(#)=
'M01AX01')) Ind3=1.
  IF (atc(#)='R06AB02') | (atc(#)= 'R06AD02') | (atc(#)=
'N05BB01') | (atc(#)= 'R06AD01' ) Ind4=1.
  IF (atc(#)='N05BA01') Ind5=1.
  IF (atc(#)='N05CD02') Ind8=1.
  IF (atc(#)='N05CD03') Ind9=1.
  IF (atc(#)='N05CM02') Ind10=1.
  IF (atc(#)='N05CD02') |
(CHAR.SUBSTR(atc(#),1,5)='N05CF') Ind11=1.
  IF (CHAR.SUBSTR(atc(#),1,4)='N05A' ) Ind27=1.
  IF (CHAR.SUBSTR(atc(#),1,4)='N06A' ) Ind28=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='G04BD' ) Ind29=1.
  IF (CHAR.SUBSTR(atc(#),1,5)='N06DA' ) Ind30=1.
  DO IF (atc(#)='N05BA04').
    IF (dose(#)>30) ind6 =1.
  End if.
  DO IF (atc(#)='N05CF01').
    IF (dose(#)>5) ind7 =1.
  End if.
  DO IF (CHAR.SUBSTR(atc(#), 1,3)='N05') |
(CHAR.SUBSTR(atc(#), 1,4)='N02A') |
(CHAR.SUBSTR(atc(#), 1,4)='N06A').
    DO IF CHAR.INDEX(atcInd23,atc(#)) = 0.
      COMPUTE Ind23Count= Ind23count+1.
      COMPUTE atcInd23 = CONCAT(atcInd23, ' ',
atc(#)).
    end if.
  End if.
end loop.

IF (warfarin=1 and Ind3=1) Ind12=1.
If (warfarin=1 and SSRI_SNRI=1) Ind13=1.
IF (warfarin=1 and MAKROLID_KINOLON=1) Ind14=1.
IF (Ind3=1 and ACEAT2=1) Ind15=1.
IF (Ind3=1 and DIURETIC=1) Ind16=1.
IF (Ind3=1 and STEROID=1) Ind17=1.
IF (Ind3=1 and SSRI_SNRI=1) Ind18=1.
IF (ACEAT2=1 and POTASSIUM=1) Ind19=1.
IF (BETABLOCK=1 and CALCIUMANTAG=1) Ind20=1.
IF (MAKROLID=1 and STATIN=1) Ind21=1.
IF (BISPHOSPH=1 and PPI=1) Ind22=1.
If (ind23count>=3) Ind23=1.
IF (TRAMADOL=1 and SSRI=1) Ind24=1.
IF (METOPROLOL=1 and PARFLUBU=1) Ind25=1.
IF (METFORMIN=1 and DIURETIC=1 and ACEAT2=1)
Ind26=1.
IF (BP>0 | BP2>0) Ind31=1.
COMPUTE Ind31B=BP+BP2.
IF (BISPHOSPH=1) Ind32=1.
IF (STATIN=1) Ind33=1.
execute.

COMPUTE Indtreff1=(Ind1 + Ind2 + Ind3 + Ind4 + Ind5
+ Ind6 + Ind7 + Ind8 + Ind9 + Ind10 + Ind11 + Ind12 +
Ind13 + Ind14 + Ind15 + Ind16 + Ind17 + Ind18 + Ind19
+ Ind20 + Ind21 + Ind22 + Ind23 + Ind24 + Ind25 +
Ind26).
COMPUTE Indtreff2=(Ind27 + Ind28 + Ind29 + Ind30 +
Ind31 + Ind32 + Ind33).
COMPUTE Indtreff=Indtreff1 + Indtreff2.
EXECUTE.

COMPUTE AntallFaste = 0.
IF  (Length(Fast1Atc) > 0) AntallFaste=1.
IF  (Length(Fast2Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast3Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast4Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast5Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast6Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast7Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast8Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast9Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast10Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast11Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast12Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast13Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast14Atc) > 0) AntallFaste=AntallFaste+1.
```

```
IF  (Length(Fast15Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast16Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast17Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast18Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast19Atc) > 0) AntallFaste=AntallFaste+1.
IF  (Length(Fast20Atc) > 0) AntallFaste=AntallFaste+1.
EXECUTE.

COMPUTE AntallFaste2 = 0.
COMPUTE AntallFaste3 = 0.
COMPUTE AntallFaste4 = 0.
COMPUTE AntallFaste5 = 0.
COMPUTE AntallFaste6 = 0.
COMPUTE AntallFaste7 = 0.
COMPUTE AntallFaste8 = 0.
COMPUTE AntallFaste9 = 0.
COMPUTE AntallFaste10 = 0.
COMPUTE AntallFaste11 = 0.
COMPUTE AntallFaste12 = 0.
COMPUTE AntallFaste13 = 0.
COMPUTE AntallFaste14 = 0.
COMPUTE AntallFaste15 = 0.
COMPUTE AntallFaste16 = 0.
COMPUTE AntallFaste17 = 0.
COMPUTE AntallFaste18 = 0.
COMPUTE AntallFaste19 = 0.
COMPUTE AntallFaste20 = 0.

*Number of medications for use when needed, this
syntax can be run for both files both excl and incl drugs
on demand, as this does not involve the computing of
indicator hits.
COMPUTE AntallEvt = 0.
IF  (Length(EvtAtc1) > 0) AntallEvt=1.
IF  (Length(EvtAtc2) > 0) AntallEvt=AntallEvt+1.
IF  (Length(EvtAtc3) > 0) AntallEvt=AntallEvt+1.
IF  (Length(EvtAtc4) > 0) AntallEvt=AntallEvt+1.
IF  (Length(EvtAtc5) > 0) AntallEvt=AntallEvt+1.
IF  (Length(EvtAtc6) > 0) AntallEvt=AntallEvt+1.
IF  (Length(EvtAtc7) > 0) AntallEvt=AntallEvt+1.
IF  (Length(EvtAtc8) > 0) AntallEvt=AntallEvt+1.
IF  (Length(EvtAtc9) > 0) AntallEvt=AntallEvt+1.
IF  (Length(EvtAtc10) > 0) AntallEvt=AntallEvt+1.
EXECUTE.

COMPUTE AntallEvt2 = 0.
COMPUTE AntallEvt3 = 0.
COMPUTE AntallEvt4 = 0.
COMPUTE AntallEvt5 = 0.
COMPUTE AntallEvt6 = 0.
COMPUTE AntallEvt7 = 0.
COMPUTE AntallEvt8 = 0.
COMPUTE AntallEvt9 = 0.
COMPUTE AntallEvt10 = 0.

COMPUTE AntallMed = 0.
COMPUTE AntallMed = AntallFaste + AntallEvt.
```

Riktig legemiddelbruk i sykehjem - runde 3

Velkommen til 3. runde i studien for utvikling av kriterier for riktig legemiddelbruk i sykehjem!

På de følgende skjermbildene skal du ta stilling til 34 kriterier for rasjonell forskrivning/ordinering av legemidler i sykehjem. Dette er tredje og siste runde i denne konsensusundersøkelsen. Vi ønsker at du, i lys av det som fremkom i 1. runde, skal skåre hvordan du nå vurderer den kliniske relevansen av hvert kriterium. Alle spørsmålene må skåres, også der hvor du opprettholder ditt svar fra forrige runde.

Du kan gå inn igjen og redigere på svarene dine så mange ganger du vil frem til 22. februar.

Vi takker for ditt bidrag til arbeidet med å forbedre legemiddelforskrivningen i sykehjem!

Vennlig hilsen

Gunhild Nyborg, Atle Klovning, Jørund Straand og Mette Brekke

Riktig legemiddelbruk i sykehjem - runde 3

Forslag til kriterier for potensielt uhensiktsmessig forskrivning til pasienter i sykehjem

Du skal, som sist, på en enkel skala angi i hvilken grad du mener hvert enkelt av et antall kriterier er relevant for å fange opp potensielt uhensiktsmessig legemiddelbruk i sykehjem. Resultatene fra denne rundens skåringer vil være avgjørende for hvilke kriterier som blir værende på listen og hvilke som blir tatt ut.

Vi har nå lagt ved panelets vurderinger fra 2. runde. Det er gjort noen få endringer i ordlyd i kriteriene på grunnlag av deres innspill. Som i forrige runde finner dere referansene nedenfor skåringstabellen, og nederst alle kommentarer fra panelet. Vi bemerker spesielt at den gjeldende ordlyden på kriteriene kommer under skåringstabellen, etter en asterisk (*). Forrige rundes ordlyd finner dere på bildet med forrige rundes skåringstabell.

Det er ikke åpnet for kommentarer i denne runden. Det er mulig å manøvrere seg bakover i surveyen dersom du ønsker å gjøre endringer i det du har svart.

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 1. Antipsykotika

Slik fordelte svarene seg i andre runde:

1. Kriterium 1: Antipsykotika som fast forskrivning bør unngås til pasienter uten psykose. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	1,9% (1)	5,8% (3)	9,6% (5)	**78,8% (41)**	52

* Kriterium 1: Antipsykotika bør unngås til pasienter uten psykose.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse: Alle former for antipsykotika er risikomedikamenter hos eldre på grunn av høy forkomst av til dels alvorlige bivirkninger og dårlig dokumentasjon av effekt ved "senil uro" (BPSD). Det er vist at urolige eldre ofte har smerter og at intensivert smertebehandling ofte har god effekt på uroen (se ref). Det er vist økt mortalitet ved bruk av både typiske og atypiske antipsykotika. De eldre preparatene har betydelige antikolinerge bivirkninger.

Anbefaling: Behandling skal være på indikasjon og bør være så lavdosert og kortvarig som mulig. Klinisk effekt skal evalueres og dokumenteres innen fire uker. Forsøk på nedtrapping og seponering skal dokumenteres senest etter 6 måneder.

Referanser for deg som vil lese mer:
Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. BMJ. 2011;343:d4065.

Gerretsen P, Pollock BG (2011) Drugs with anticholinergic properties: a current perspective on use and safety. Expert opinion on drug safety 10 (5):751-765. doi:10.1517/14740338.2011.579899Ballard C, Hanney ML, Theodoulou M, et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009 Feb;8(2):151-7.
http://www.ncbi.nlm.nih.gov/pubmed/19138567

Gill SS. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med. 2007;146(11):775-86.
http://www.annals.org/content/146/11/775.full.pdf+html

Trifiro G, Gambassi G, Sen EF, et al. Association of community-acquired pneumonia with antipsychotic drug use in elderly patients: a nested case-control study. Ann Intern Med. 2010 Apr 6;152(7):418-25, W139-40.
http://www.ncbi.nlm.nih.gov/pubmed/20368647

Kuehn BM. FDA: Antipsychotics risky for elderly. JAMA. 2008;300:379-80. http://www.ncbi.nlm.nih.gov/pubmed/18647971

Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008;168:508-13.
http://archinte.ama-assn.org/cgi/reprint/168/5/508.pdf

Her er paneldeltagernes kommentarer:

"Viktig å ta med anbefaling nedenfor og allikevel gi rom for å bruke antipsykotika på indikasjon. Jeg har jobbet med geriatriske pas. i flere år og ser nok fra tid til annen at vi er nødt til å bruke - gjerne nyere- antipsykotika. Mange avdelinger har i sine prosedyrer " bare " valg mellom Haldol (uheldig ved hvilken som helst type parkinsonisme) og Heminevrin (OBS ved KOLS) - dette er for dårlig mtp de som sliter med mye slim (KOLS, Pneumoni - og samtidig agitert uro.). Det blir problemer med mye slim og økt tetthet samt panikk og evt. enda mer uro. Om dere kan legge til en anbefaling å helst IKKE bruke Heminervrin ved slimplagete KOLS pas. / pneumoni, kaan gi økt CO2-retensjon (resp. svikt type II) .

Hos eldre med akutt konfusjon hvor nevroleptika er indisert bør prepaartet brukes så lenge det er symptomer tegn. Avsluttes etter uker måneder gitt omstendigheter og antakelser.

Definer "Fast forskriving". Dersom det menes daglig bruk på ubestemt tid er score 10, dersom det menes inntil to uker ved akutt delir, og så revurdering, der underliggende årsak samtidig behandles er score 5

Stikkordet her er vel "bør", noen ganger kan det være indisert med antipsykotika medisinering men i kortest mulig tid, og dokumentere effekt i skjema selv om ikke psykoer er tilstedet, men slike medisiner bør være sistevalget. Husebø sin studie synes jeg ikke er relevant her, og bidrar med ikke noe nytt.

Bra at Bettinas, Dags og Clive Bs artikkel fra BMJ er fremhevet. Rosenbergs og Lyketsos lederkommentar til artikkelen kunne forsåvidt også vært nevnt / sitert"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 2. Antidepressiva

Slik fordelte svarene seg i andre runde:

1. Kriterium 2. All antidepressiv behandling skal evalueres med tanke på effekt og bivirkninger. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	3,8% (2)	**96,2% (50)**	52

* Kriterium 2. All antidepressiv behandling skal evalueres med tanke på effekt og bivirkninger.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Preparatene har bivirkninger og interaksjonspotensiale.

Referanse for deg som vil lese mer:
Nelson JC, Devanand DP (2011) A systematic review and meta-analysis of placebo-controlled antidepressant studies in people with depression and dementia. J Am Geriatr Soc 59 (4):577-585. doi:10.1111/j.1532-5415.2011.03355.x

Reynolds CF, 3rd, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, Houck PR, Mazumdar S, Butters MA, Stack JA, Schlernitzauer MA, Whyte EM, Gildengers A, Karp J, Lenze E, Szanto K, Bensasi S, Kupfer DJ (2006): Maintenance treatment of major depression in old age. N Engl J Med 354 (11):1130-1138

Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J (2011) Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ 343:d4551. doi:10.1136/bmj.d4551

Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. Drugs & aging. 2002;19(4):299-320. http://www.ncbi.nlm.nih.gov/pubmed/12038880

Her er paneldeltagernes kommentarer:

"jeg evaluerer effekten etter 2, 4 og 6 uker , Ikke noen dokumentasjon for respans, da seponeres etter 6 uke. ved dokumentert effekt , vurdering for doseøkning ellers forsettes med samme dose. ny vurdering etter 2, 4 , 6 og 9 mnd. Vurdering for nedtraping og seponering.

Antidepressiva bruk vurderes utfra toleranse og effekt. De sførste ukene forsøker man å oppmuntre til fortsatt bruk om milde bivirkninger grunnet håp om forbigående samt økende grunn til effekt etter 2-4 uker. Om toleranse effekt samt premorbiditet og alvolighetsgrad av asktuelle indikasjonen ønsket minst kontinuert i 1/2 år.

Geriatrisk depresjonsskala er en validert skår som jeg har god erfaringer med. Cornellskala bør brukes i tillegg, da den fanger opp komparentopplysninger om depresjonssymptomer.

vanskeliggjøres av at behandlingen startes av en lege og skal evalueres av en annen, når pasienten flytter mellom omsorgsnivåer.

Depresjonsdiagnosen er vel alltid en utfordring hos sykehjemspasienter. Hverken GDS eller MADRS er egnet hos pasienter med demens. Cornell er et alternativ, men da må den utføres i samsvar med veiledningen. Det er åpenbart okfte IKKE tilfelle.

Til slik evaluering bør det brukes validerte spørreskjema som MADRS eller Beck*s inventory

Serumkonsentrasjonsmåling og CYP testing kan bidra til å forklare effekt/bivirkninger og hvordan doseringen bør være. Det bør vurderes om dette skal med som et ledd i evalueringen"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 3. Statiner

Slik fordelte svarene seg i andre runde:

1. Kriterium 3. Statinbehandling bør seponeres hos eldre med sterkt reduserte livsutsikter. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

Lag diagram | Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	0,0% (0)	7,7% (4)	11,5% (6)	**78,8% (41)**	52

* Kriterium 3. Statinbehandling bør seponeres hos eldre med sterkt reduserte livsutsikter.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse: Statiner har bivirkninger som kan redusere livskvaliteten, inkludert muskelsvekkelse og -smerter. Deres bruk i en sykehjemspopulasjon er ikke undersøkt i randomisert-kontrollerte studier. Det forventes marginal helsegevinst hos personer med sterkt reduserte livsutsikter.

Behandling i 3 måneder etter en sikker trombotisk hendelse kan likevel være indisert på grunn av statinenes plakkstabiliserende og inflammasjonshemmende effekt.

Referanser for deg som vil lese mer:

Silveira MJ, Kazanis AS, Shevrin MP. Statins in the last six months of life: a recognizable, life-limiting condition does not decrease their use. Journal of palliative medicine. 2008 Jun;11(5):685-93.
http://www.ncbi.nlm.nih.gov/pubmed/18588398

Hindler K, Cleeland CS, Rivera E, Collard CD. The role of statins in cancer therapy. Oncologist. 2006 Mar;11(3):306-15.
http://www.ncbi.nlm.nih.gov/pubmed/16549815

Her er paneldeltagernes kommentarer:

"Primærforebyggende statinbehandling er sjelden indisert til personer over 75 år. Selv sekundærprofylakse bør ha god indikasjon. Postmenopausale kvinner, selv med kolesterol over 8 og uten andre risikofaktorer skal ikke ha statin primærforebyggende. Jf. retningslinjer side 47. Og uansett: lav dose!

unntak burde være de pas. med carotisstenose bilateral eller annen alvorlig symptomgivende karsykdom og hyperkolesterolemi

tenk på livskvaliteten!

Om ikke akutt hendelse sekundært til arteriell sykdom med fortsatt mulighet for bedret prognose og ikke unødvendig polyfarmasi kontinueres kolesterol senkende i en begrenset tid. Kolseterolsenkende hos ledre enn 80 år er forbundet med mer dødlighet/morbiditet enn i andre aldersgrupper. Der forebygging ikke hører hjemme blir indikasjonen dårlig.

Generelt kan det ikke anbefales å seponere statinbehandling hos alle sykehjemspasienter som har langtkommen demens. De har sin plass inntil 3 måneder etter en sikker trombotisk hendelse, men skal så seponeres i en sykehjemspopulasjon."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 4. Demensmidler

Slik fordelte svarene seg i andre runde:

1. Kriterium 4. Demensmidler (antikolinesterasehemmere/andre): Behandling krever oppfølging med dokumentasjon av effekt og seponering ved ikke tilfredsstillende effekt eller uakseptable bivirkninger. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	13,5% (7)	**84,6% (44)**	52

* Kriterium 4. Demensmidler (antikolinesterasehemmere/andre): Behandling krever oppfølging med dokumentasjon av effekt og seponering ved ikke tilfredsstillende effekt eller uakseptable bivirkninger.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:

Referanser for deg som vil lese mer:

Kim DH, Brown RT, Ding EL, Kiel DP, Berry SD. Dementia medications and risk of falls, syncope, and related adverse events: meta-analysis of randomized controlled trials. J Am Geriatr Soc. 2011 Jun;59(6):1019-31.

Winblad B, Kilander L, Eriksson S, Minthon L, Batsman S, Wetterholm AL, et al.
Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet. 2006 Apr 1;367(9516):1057-65.
http://www.ncbi.nlm.nih.gov/pubmed/16581404

Winblad B, Wimo A, Engedal K, Soininen H, Verhey F, Waldemar G, et al. 3-year study of donepezil therapy in Alzheimer's disease: effects of early and continuous therapy. Dement Geriatr Cogn Disord. 2006;21(5-6):353-63.
http://www.ncbi.nlm.nih.gov/pubmed/16508298

Her er paneldeltagernes kommentarer:

"jeg anser dette som en selvfølge, men effekt kan bare bedømmes av de som følger pas. opp i de daglige og over tid- det betyr investere tid for komparent-anamnese-ikke alt kan måles med MMS/ KT. Når en Alzheimers ikke blir verre ila 1 år etter påbegynt medisinering, ser jeg det som pos. effekt , antatt at de gjennomførte miljøtiltakene ikke bare er koblet til medisinering og oppfølgningen som følger med legekontroller ift medisin. Man kan tenke seg at de som blir følgt opp pga medisinering evt. få generelt et bedre og allsidig geriatrisk tilbud ift de som ikke blir medisinert og ikke kontrollert - innsats er evt. større når man vet at det kommer en kontroll?? Så har vi da iallfall " placebo-effekt"- som ikke rettferdiggjør bivirkninger, dvs. kontroll og sep. ved bivirkninger er et " must"

Enig, men bråseponering burde unngås. Pasienter kan oppleve uønskede seponeringseffekter.

evaluering av effekt i 1, 2 , 3 , og 4. uke , ikke dokumentert effekt da seponeres medisin. vedvarende alvorlig bivirkninger , da bør seponering vurderes.

Ikke nødvendigvis MMS og ny kognitiv utredning da spesielt da forventet effekt på MMS er lav. Tilbakemelding fra pårørende / nødvendig omsorgsnivået gir oss en indikasjon på om det er effekt eller forringelse etter oppstarten.

Evaluering skal skje med 6 måneders intervaller med validerte skåringsverktøy som MMSE og klokketest, verbal fluency eller animal naming test. Dersom raskt fall i MMSE definert som >2 poeng på 6 mndr, bør det gjøres seponeringsforsøk. Medikamentet skal alltid seponeres ved plagsomme bivirkninger.

vanskeliggjøres også når pasienten flyttes mellom omsorgsnivåer.

NNT ligger vel mellom 8-10 og det er viktig at effekt vurderes av en spesialist innen demensfeltet, spesielt hos yngre med demens. Det er for mange ikke spesialister som tolker virkninger av medisiner uten rett kompetanse eller oppfølging. Det er også et poeng å starte opp så tidlig som mulig etter stilt demendiagnose, dersom slike medisiner er indisert. Premorbid tilstand og BPSD spiller også inn på målt kognitiv effekt, og må vurderes i den kliniske helheten. Enkle mål som tap av skår ADAS cog og MMSE, og ADL funskjon må ses sammen med pasient og pårørende sin opplevelse av sykdommen.

en bør gjøre et kontrollert seponeringsforsøk hvis man mener det ikke virker. Hvis pasientens kognitive funksjon eller atferd forverres ila de første ukene etter seponering bør behandlingen vurderes reinnsatt"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 5. Trisykliske antidepressiva (TCA)

Slik fordelte svarene seg i andre runde:

1. Kriterium 5. Trisykliske antidepressiva (TCA): Fast bruk mot depresjon anbefales ikke. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

Lag diagram | Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	7,7% (4)	9,6% (5)	25,0% (13)	**53,8% (28)**	52

* Kriterium 5. Trisykliske antidepressiva (TCA): Fast bruk mot depresjon anbefales ikke.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Sederende med betydelige antikolinerge bivirkninger, og kontraindisert ved hjerte-karlidelser.

Hos enkeltpasienter kan nytten likevel oppveie risikoen og Nortriptylin kan da være et alternativ. Kan være indisert i lav dose ved nevropatisk smerte, spesielt ved samtidig depresjon og søvnproblemer.

Referanser for deg som vil lese mer:
Gerretsen P, Pollock BG (2011) Drugs with anticholinergic properties: a current perspective on use and safety. Expert opinion on drug safety 10 (5):751-765. doi:10.1517/14740338.2011.579899

Fox C, Richardson K, Maidment ID, et al. Anticholinergic Medication Use and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study. Journal of the American Geriatrics Society. 2011 Aug;59(8):1477-83.
http://www.ncbi.nlm.nih.gov/pubmed/21707557

Aizenberg D, Sigler M, Weizman A, Barak Y. Anticholinergic burden and the risk of falls among elderly psychiatric inpatients: a 4-year case-control study. Int Psychogeriatr. 2002;14:307-10.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12475091

Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008;168:508-13.
http://archinte.ama-assn.org/cgi/reprint/168/5/508.pdf

Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. Drugs & aging. 2002;19(4):299-320.
http://www.ncbi.nlm.nih.gov/pubmed/12038880

Ny stor kohortstudie som finner at TCA har færre bivirkninger enn SSRI:
Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. BMJ. 2011;343:d4551.
http://www.bmj.com/content/343/bmj.d4551.full.pdf
Kommentar: Egne preliminære funn fra Reseptregisteret viser at av de 7023 personene > 70 år som hentet ut amitriptylin fra apotek i Norge i 2008 var det kun 638 som fikk ekspedert preparatet mer enn en gang. Gjennomsnittlig døgndose for disse var 8,8 mg. Det kan diskuteres om resultatene fra BMJ-studien delvis kan reflektere ulikheter i compliance for de ulike medikamentgruppene.

Her er paneldeltagernes kommentarer:

"Nortriptylin kan være et unntak.

Til kommentarene nedenfor: Nortriptylin er den aktive metabolitten til amitriptylin så det er vel ingen spesiell grunn til å fremheve den som noe annerledes. Likevel, dersom TCA er indisert, vil jeg også mene den er et mer rasjonelt valg enn pro-drug'en amitriptylin. Disse midlene har i lav dose en rolle i behandling av nevropatisk smerte, jf. diverse retningslinjer (Sverige, Kanada etc).

Bra erfaring hos noen pasienter med lav til moderat dose Nortriptylin, hvor ingen andre med. hadde tilsv. effekt.

det bør vurderes individuel hos eldre, noen får god effekt av det.

Ugunstige bivirkninger som er uttalte hos denne gruppen pasienter.

kan være nyttig hos pasienter med god erfaring av effekt fra tidligere.

Fast mot depresjon - bør ikke brukes pga fins bedre alterantiv, samt antikolinerge bivikrninger hvor eldre er spesielt utsatt. Men ved kronisk smerte av neuropatisk type og samtidig søvnproblem kan TCA (amitritylin) være indisert, f.eks for å unngå benzodiazepiner (søvn) og opioider (smerte). Men man bør evaluere jevnlig TCA mht efekt og bivirkninger

DEt finnes mange alternativer til TCA som ikke har lik bivirkningsprofil men som er effektive i beh av depresjon

-Anbefales ikke som første valg, bør teksten her være. Da er score 10.

kriteriet bør stå, men med noen modifikasjoner slik som anført i kommentarene gitt forrige gang (ved alvorlig depresjon der behandling er initiert innen psykiatrien, dosereduksjon bør allikevel vurderes)"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 6. NSAIDs

Slik fordelte svarene seg i andre runde:

1. Kriterium 6. Systemisk NSAID: Bør bare brukes på sterk indikasjon. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	5,8% (3)	**90,4% (47)**	52

* Kriterium 6. Systemisk NSAID: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Betydelige bivirkninger og stort interaksjonspotensiale. Kontraindisert ved alvorlig hjertesvikt og/eller nyresvikt.

Ved overfladiske symptomer kan gel forsøkes.

Referanse for deg som vil lese mer:
Page J, Henry D. Consumption of NSAIDs and the development of congestive heart failure in elderly patients: an underrecognized public health problem. Archives of Internal Medicine. 2000 Mar 27;160(6):777-84.
http://www.ncbi.nlm.nih.gov/pubmed/10737277

Blix HS, Viktil KK, Moger TA, Reikvam A. Use of renal risk drugs in hospitalized patients with impaired renal function--an underestimated problem? Nephrol Dial Transplant. 2006 Nov;21(11):3164-71.
http://www.ncbi.nlm.nih.gov/pubmed/16880181

Johnson AG, Simons LA, Simons J, Friedlander Y, McCallum J. Non-steroidal anti-inflammatory drugs and hypertension in the elderly: a community-based cross-sectional study. Br J Clin Pharmacol. 1993 May;35(5):455-9.
http://www.ncbi.nlm.nih.gov/pubmed/8512757

Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Annals of Internal Medicine. 1991 Feb 15;114(4):257-63.
http://www.ncbi.nlm.nih.gov/pubmed/1987872

Her er paneldeltagernes kommentarer:

"Ved indikasjon muskel-/skjelettsmerter er det riktig at utvortes bruk har bra effekt og mye lavere risiko. Det er riktig at Albyl-E er i samme båt, jf. kommentar nedenfor. Derfor viktig at dette aldri brukes i høyere dose enn 75 mg, dessuten mener flere nå at det brukes hos for mange. 160 mg må dessuten ut!

Hvis unntaksvis betyr at en har tatt høyde for at pasienten ikke har dårlig nyrefunksjon, astma, hjerte/karsykdom, har eller har hatt mavesår eller GI-blødning, ikke bruker samtigig ACE-hemmere/AT-antagonister eller medisiner som øker risikoen for GI-blødninger eller legemidler som øker risiko for nyresvikt er jeg enig. Samtidig spiller NSAIDs en viktig rolle i behandling av muskel- og skjelettsmerter og andre mulige alternativer som opiodanalgetika har også mange uønskede effekter.

Skal heller ikke unntaksvis brukes som fast medikasjon. Hos pasienter med sterke smerter bør heller opiater brukes.

Eldre bruker ofte flere medisiner og man bør derfor alltid sjekke interkajsonsmuligheter. Økt blødningsrisiko, nefrotoksisitet osv. Bruk av lokale NSAID som gel er vist å ha god absorpsjon i hudnære områder som skuldre, knær og ankler.

Eller "ikke i det hele tatt"....?

Bør absolutt unngås, kan dog vurderes ved cansersmerter

Bør ikke brukes som fast medikasjon over lengre tid hos eldre. Men kan ha indikasjon som supplement."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 7. Førstegenerasjons antihistaminer

Slik fordelte svarene seg i andre runde:

1. Kriterium 7. Førstegenerasjons antihistaminer: Fast bruk bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	3,8% (2)	1,9% (1)	19,2% (10)	11,5% (6)	19,2% (10)	**42,3% (22)**	52

* Kriterium 7. Førstegenerasjons antihistaminer: Fast bruk bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Betydelig risiko for antikolinerge bivirkninger. Sterkt sederende. Bedre alternativer finnes.

Referanser for deg som vil lese mer:
Fox C, Richardson K, Maidment ID, et al. Anticholinergic Medication Use and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study. Journal of the American Geriatrics Society. 2011 Aug;59(8):1477-83.
http://www.ncbi.nlm.nih.gov/pubmed/21707557

Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008 Mar 10;168(5):508-13.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?

Her er paneldeltagernes kommentarer:

"atarax har sin plass ved sterk kløe som gir kraftige rivmerker og forstyrret nattsøvn når ikke f.eks cetirizin hjelper nok, bør da observere tegn til antikolinerge bivirkninger som f.eks. økt forvirring

Enig med kommentarer om at det er forskjell på antihistaminer og at deksklorfeniramin og hydroksyzin (Atarax, prodrug til cetirizin) ikke er så 'farlige' som fentiaziner. Men også hydroxyzin har antikolinerge bivirkninger. Er urolig over relativt hyppig bruk av Vallergan (alimemazin (USA: trimeprazin) til eldre. Det er et fentiazin. Kan synes som forbruket har økt?

De er slettes unødvendige, etter min erfaring er det ofte brukt " på gammel vane", pas. har stått på det i mer enn ti år og tror på dette som på fjell. Meget vanskelig å få dette vekk fra liste...til og med ved påviste bivirkninger. Likte " Unntaks-beskrivelsen" i slutten av kommentarfeltet.

All bruk er for kategorisk.

Det er en bedre formulering med "fast bruk bør unngås". Det finnes gode indikasjoner som bruk av Vallergan som sovemedisin og Atarax som kløestillende.

Ingen regel uten unntak. Det hender at en pasient har brukt den samme type tablett i årevis og bare "vil ha den som hjelper" og da må det være greit.

Jeg bruker Vallergan av og til mot uttalte sovnvansker , Atarax mot plagsomt kløe om natten.

alimemazin kan være aktuelt ved søvnvansker som alterantiv til benzodiazepiner

Ser av kommentarer at det er mye erfaringsbasert og ikke evidens basert argumentasjon. Dette er et problem og resulterer i svært forskjellig behandlingsmessig tilnærming av sykejhemspasienter i mine øyne.

Det er høyst relevant å si "bør", hvilket ikke utelater bruk etter spesiell indikasjon.

følgeteksten bør nyanseres. Bruk som sedativa bør unngås, kun unntaksvis brukes ved kløe og allergi der man ikke kommer til målet med nyere antihistaminer"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 8. Urologiske spasmolytika

Slik fordelte svarene seg i andre runde:

1. Kriterium 8. Urologiske spasmolytika: Behov og effekt må vurderes nøye mot potensielle bivirkninger. Prøveseponering anbefales for å avklare indikasjon for fortsatt bruk. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	7,7% (4)	7,7% (4)	**82,7% (43)**	52

* Kriterium 8. Urologiske spasmolytika: Behov og effekt må vurderes nøye mot potensielle bivirkninger. Prøveseponering anbefales for å avklare indikasjon for fortsatt bruk.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Betydelig risiko for antikolinerge bivirkninger. Begrenset nytte ved samtidig inkontinens og bruk av inkontinensutstyr. Samtidig bruk med andre preparater med antikolinerge bivirkninger må unngås.

Referanser for deg som vil lese mer:
Gerretsen P, Pollock BG (2011) Drugs with anticholinergic properties: a current perspective on use and safety. Expert opinion on drug safety 10 (5):751-765. doi:10.1517/14740338.2011.579899

Kay GG, Granville LJ. Antimuscarinic agents: implications and concerns in the management of overactive bladder in the elderly. Clin Ther. 2005 Jan;27(1):127-38; quiz 39-40.
http://www.ncbi.nlm.nih.gov/pubmed/15763613

Fox C, Richardson K, Maidment ID, et al. Anticholinergic Medication Use and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study. Journal of the American Geriatrics Society. 2011 Aug;59(8):1477-83.
http://www.ncbi.nlm.nih.gov/pubmed/21707557

Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008 Mar 10;168(5):508-13.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?

Her er paneldeltagernes kommentarer:

"Det er i så fall en stor forskjell om pas. er dement eller ikke og hvilken komorbiditet foreligger. Ikke demente vet selv om de har hatt nytte av det, det kan bety livskvalitet!!. Bivirkninger kan delvis måles - økt resturin, økt frekvens på UVI, - hos moderat demente seponeres medisinen fordi da tilkommer det andre faktorer som gi inkontinens og disse pas. skal ikke ha enda mindre acetylcholin / økt ortostatisme osv.. Viktig poeng med å sjekke indikasjon for loop -diuretica. Det går en del pas. uten hjertesvikt med venøs insuffisiens på loop-diuretica ...

indikasjon for bruk må være sterk"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 9. Kodein og paracetamol

Slik fordelte svarene seg i andre runde:

1. Kriterium 9. Fast bruk av kombinasjonspreparatet kodein/paracetamol bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	1,9% (1)	3,8% (2)	5,8% (3)	9,6% (5)	28,8% (15)	15,4% (8)	**32,7% (17)**	52

* Kriterium 9. Fast bruk av kombinasjonspreparatet kodein/paracetamol bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Dårlig dokumentert effekt ved langtidsbruk, tilvenningsfare og hyppige bivirkninger (obstipasjon, sedasjon, fall). Ulike doseringsprinsipper for paracetamol og opioider gjør at kombinasjonsbehandling ofte er uhensiktsmessig. Kodein er et inaktivt prodrug som metaboliseres til aktivt morfin via CYP2D6-systemet og individuelle forskjeller i CYP2D6-metabolismen gir stor variasjon i reell dose aktivt opiat. Ultraraske metaboliserere kan få en utilsiktet høy dose aktivt morfin, mens defekt CYP2D6 vil føre til at kodein ikke omdannes til aktivt morfin, med påfølgende behandlingssvikt.

Anbefaling: Det er viktig med adekvat smertelindring. Spesielt kan noen sykehjemsbeboere ha vanskeligheter med å uttrykke smerte. Dersom man ikke kommer til mål med paracetamol bør man trappe opp behandlingen, for eksempel ved å legge til et opioid.

Referanser for deg som vil lese mer:
Solomon DH, Rassen JA, Glynn RJ, et al. The comparative safety of opioids for nonmalignant pain in older adults. Archives of Internal Medicine. 2010 Dec 13;170(22):1979-86.
http://www.ncbi.nlm.nih.gov/pubmed/21149754

Husebo BS, Ballard C, Sandvik R, Nilsen OB, Aarsland D. Efficacy of treating pain to reduce behavioural disturbances in residents of nursing homes with dementia: cluster randomised clinical trial. BMJ. 2011;343:d4065.

Her er paneldeltagernes kommentarer:

"Vi har sett en del eksempler på at pasienter får paracetamol/kodein og samtidig gir sykepleiere paracetamol alene. Da kan totaldosen paracetamol bli over det anbefalte med de effekter det har (påvirkning av INR hos warfarinpasienter, levertoksisitet). Det er en grunn til at faste kombinasjoner er uheldig. Og hvis pasienten bare bruker kombinasjonen, tilsier det at vedkommende kan få for sjeldne doseringer av paracetamol eller for store doser kodein (som har mye lengre virketid).

Unntak: kreftsmerte i første trinn på smertetrapp og artrosepas. som bare bruker 1 tab P.f. fast om kvelden i kombin. m. 500 mg Paracet. De trenger da ikke sovepille fordi de slapper av på minidose Codein- bare 1 gang om dagen kan være bedre enn Paracet 1 g pluss Apodorm fast.

de fleste eldre er plaget av kroniske smerter med god virkning av de 2 preparater, da bør vurderes individuelt.

Det er et mye bedre alternativ å tilpasse smertebehandlingen med paracetamol og opiat hver for seg. Er pasienten opiatkrevende, skal man være liberal med å forskrive det. Dette gjelder i særlig grad sykehjemspasienter, som B Husebø har vist er underbehandlet for smerteplager.

dette er ofte pasientens eget ønske

På sykehjemmet mitt starter jeg aldri med denne kombinasjonen, men jeg ser at pasienter kommer fra sykehus eller legevakt eller tannlege og er satt på Paralgin Forte/Pinex Forte som en kortvarig behadnling.

Bør om mulig unngås.

Smerteanamnese viktig. Ikke-farmakologisk tilnærming også aktuelt. obs toleranse, avhengighet, samt fall risiko. Vurderes opp mot smertebildet til pasient Vurder depotformuleringer dersom opioider må brukes

DEt er i prinsippet ingen midler som skal brukes FAST hos eldre sykehjemspasienter

Kan være aktuelt med fast bruk, hvis nytte og effekt av medisiner oppveier bivirkninger.

ut fra kommentarene gitt nednefor blir jeg betenkt over hvordan dette kriteriet oppfattes. Det er kjempeviktig at sykehjemspasienter (også demente) får god nok smertebehandling, flere studier tyder på at dette ikke er tilfelle. "bivirkningene" av å være underbehandlet er større enn medikamentbivirkningene! Etter min mening bør kombinasjonspreparat unngås fordi kodein uansett er et opiod, hos 1/10 vil det ikke virke. Dvs er det ikke tilstrekkelig med paracet i adekvate doser (4 g per dag!) legger man til et opiod."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 10. Diazepam

Slik fordelte svarene seg i andre runde:

1. Kriterium 10. Diazepam: Fast bruk bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	0,0% (0)	3,8% (2)	11,5% (6)	**80,8% (42)**	52

* Kriterium 10. Diazepam: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Tilvenningsfare og bivirkningspotensiale (sedasjon, svekket hukommelse, muskelrelaksasjon, fall). Halveringstid på opptil 100 timer hos eldre.

Unntak: Behandling av ulike typer krampetilstander.

Hvis man til tross for bivirkningene ønsker å forskrive et benzodiazepin bør medikament med kortere halveringstid benyttes (oxazepam).

Referanser for deg som vil lese mer:
Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry. 2001;158:892-8.
http://www.ncbi.nlm.nih.gov/pubmed/11384896

Pariente A, Dartigues JF, Benichou J, Letenneur L, Moore N, Fourrier-Reglat A. Benzodiazepines and injurious falls in community dwelling elders. Drugs Aging. 2008;25(1):61-70.
http://www.ncbi.nlm.nih.gov/pubmed/18184030

http://www.irf.dk/dk/rekommandationsliste/baggrundsnotater/nervesystemet_analgetika_og_psykofarmaka/atc-gruppe_n05b_og_n05c_-_angstdaempende_midler_og_sovemidler.htm (accessed 25 May 2011)

Her er paneldeltagernes kommentarer:

"En deltager spør hva alternativet er. Det er jo f.eks. oksazepam (Sobril) - hvis benzodiazepin er indisert. Og ikke fast, se neste kriterium

Absolutt. Har sett en del pas. med skikkelig abstinenser når de ble innlagt på sykehus og ingen visste at de tok fast diazepam, man trengte delvis detektiviske ferdigheter for å finne ut om dette...jeg vil anta at det er en del eldre som går i åresvis på dette stoff og jeg har opplevd " lege-tourisme" av eldre i 70-årene for å kunne øke dosen uten at egen lege, som trodde han hadde kontroll på dette, visste om dette... jeg er slettes lei av å se dette gang på gang...Viktig at , når det oppdages, man få mulighet å trappe ut, det er ikke de gamles feil at de fikk den medisinen en gang som trøst når nærstående mennesker døde- her må legestanden ta seg i nesa!! Har vi ikke noe annet å tilby i så fall?- Vi må ikke bare ta vekk noe, vi må ha noe bedre å tilby.

Urolige demente som ikke responderer på miljøtiltak, skal ikke medisineres med diazepam grunnet fallfaren og forverring av kognitiv svikt. Det finnes bedre alternativer med nevroleptisk behandling ved APSD. Dette bør diskuteres med alderspsykiater i hvert tilfelle.

Ved behov for benzodiazepin for angst, uro er oksazepam førstevalg. Kan også brukes ved kombinert angst og søvnpoblem med en kveldsdose som i flg halveringstid vil være angstdempende dagen derpå. Ved kun søvnvansker bør zolpidem velges pga kort halveringstid.

obs lang halveringstid og aktive metabolitter med enda lengre halveringstid. Oxazepam bedre, ikke doser denne for lavt ved overgang fra diazepam.

begrunnelsen bør nyanseres. Hvis man til tross for bivirkningene ønsker å forskrive et benzodiazepin bør medikament med kortere halveringstid benyttes (ozazepam)."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 11. Oxazepam

Slik fordelte svarene seg i andre runde:

1. Kriterium 11. Oxazepam: Fast dosering >30 mg/d bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	3,8% (2)	0,0% (0)	7,7% (4)	19,2% (10)	**67,3% (35)**	52

* Kriterium 11. Oxazepam: Dosering >30 mg/d bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Tilvenningsfare og bivirkningspotensiale (sedasjon, svekket kognisjon, muskelrelaksasjon, fall). Fast bruk bør unngås.

Referanser for deg som vil lese mer:
Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry. 2001;158:892-8.
http://www.ncbi.nlm.nih.gov/pubmed/11384896

Pariente A, Dartigues JF, Benichou J, Letenneur L, Moore N, Fourrier-Reglat A. Benzodiazepines and injurious falls in community dwelling elders. Drugs Aging. 2008;25:61-70.
http://www.ncbi.nlm.nih.gov/pubmed/18184030

Her er paneldeltakernes kommentarer:

"Mange pasienter med demens fratas ytterligere kognitiv fungering med høye oxazepandoser, resultatet kan bli økt uro p.g.a. dårligere kognitiv fungering

Også for oxazepam gjelder i sykehjemspopulasjonen de samme følgene som ved diazepam: fallfare, kognitiv svekkelse, sedasjon og forstyrret døgnrytme.

obs fall

Dette bør være individuelt, og det bør være aktuelt med serumkontroller, siden noen pasienter metaboliserer raskere/saktere (cyp) virkestoffet og kan trenge en høyere dose enn andre for å oppnå virkning. Derfor lite egnet som generell regel, men viktig å huske hos eldre at en starter og prøver med lavest mulig dose altså: start low, go slow.

Fast dosering bør generelt unngås. SOm regel bør det gis som behovsmedisin. Hvis det skal gies fast bør lavest mulig dose tilstrebes. 30 mg er ganske mye på en liten dame!"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 12. Zopiklon

Slik fordelte svarene seg i andre runde:

1. Kriterium 12. Zopiklon: Dosering >5 mg/d bør unngås. På en skala fra 0 til 10, hvor relevant er dette kriteriet? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	0,0% (0)	9,6% (5)	9,6% (5)	9,6% (5)	17,3% (9)	15,4% (8)	**34,6% (18)**	52

* Kriterium 12. Zopiklon: Dosering >5 mg/d bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Bivirkninger (oversedering, hangover). Økt risiko for fall. Fast bruk bør unngås. Ikke-farmakologiske tiltak som lyseksponering, aktivisering på dagtid og tilpasning av leggerutiner/tidspunkter bør vektlegges.

Referanser for deg som vil lese mer:
Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ. 2005 Nov 19;331(7526):1169.
http://www.bmj.com/content/331/7526/1169

Allain H, Bentue-Ferrer D, Polard E, Akwa Y, Patat A. Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. Drugs & aging. 2005;22(9):749-65.
http://www.ncbi.nlm.nih.gov/pubmed/16156679

Her er paneldeltagernes kommentarer:

"Noen trenger 7,5mg f.eks. store pas. eller pas. som har brukt det en tid og ellers har begrenset forevntet levetid f.eks. kreftpas. Bør likevel som hovedregel prøve å unngå fast bruk eller doser over 5 mg

Gi rom for økt dose ved pas. rundt 100 kilo som ikke ha OSAS eller Pickwick og skal opereres neste dag eller til noe som stresser dem og så ikke kan få sove...Burde sees ifb. med nyrefunksjon, reell fallrisiko, leverfunksjon. alkoholbruk og vekt

Fast bruk bør generelt unngås, vurdering av effekt med seponeringsforsøk regelmessig. Ved bruk bør doser under 5 mg/d tilstrebes

Zopiklon bør ikke brukes fast hos noen. Dette er et dårlig kriterium og bør fjernes fra lista!

høyere dose er ofte pasientens ønske

vurderes ut fra historikk Obs eldre mer følsomme, reduser dose

Igjen bør dette være individuelt, noen vil trenge høyere dose for samme virkning med god søvn."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 13. Flunitrazepam

Slik fordelte svarene seg i andre runde:

1. Kriterium 13. Flunitrazepam: All bruk bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	7,7% (4)	**88,5% (46)**	52

* Kriterium 13. Flunitrazepam: All bruk bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Lang halveringstid. Betydelig tilvenningsfare. Bedre alternativer finnes.

Referanser for deg som vil lese mer:
Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ. 2005 Nov 19;331(7526):1169.
http://www.bmj.com/content/331/7526/1169

Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry. 2001;158:892-8.
http://www.ncbi.nlm.nih.gov/pubmed/11384896

Pariente A, Dartigues JF, Benichou J, Letenneur L, Moore N, Fourrier-Reglat A. Benzodiazepines and injurious falls in community dwelling elders. Drugs Aging. 2008;25:61-70.
http://www.ncbi.nlm.nih.gov/pubmed/18184030

Her er paneldeltagernes kommentarer:

"Helt enig. Nesten ikke til å få ut av systemet og stor avhengighetspotensiale. Pas. bruker ofte alkohol ved siden av , de bruker det i åresvis , kan ikke skjønner at det hooper seg opp med økende alder og er i slutten overdosert med samme dose over tid, kjører delvis fortsatt bil

Flunitrazepam har som de andre benzodiazepiner en betydelig fallfare som bivirkning, i tillegg til forverring av kognitiv svikt."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 14. Nitrazepam

Slik fordelte svarene seg i andre runde:

1. Kriterium 14. Nitrazepam: All bruk bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	1,9% (1)	7,7% (4)	19,2% (10)	**69,2% (36)**	52

* Kriterium 14. Nitrazepam: All bruk bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Bedre alternativer finnes.

Referanser for deg som vil lese mer:
Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ. 2005 Nov 19;331(7526):1169.
http://www.bmj.com/content/331/7526/1169

Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Hazardous benzodiazepine regimens in the elderly: effects of half-life, dosage, and duration on risk of hip fracture. Am J Psychiatry. 2001;158:892-8.
http://www.ncbi.nlm.nih.gov/pubmed/11384896

Pariente A, Dartigues JF, Benichou J, Letenneur L, Moore N, Fourrier-Reglat A. Benzodiazepines and injurious falls in community dwelling elders. Drugs Aging. 2008;25:61-70.
http://www.ncbi.nlm.nih.gov/pubmed/18184030

Her er paneldeltakernes kommentarer:

"Man kan jo bruke oxazepam om man må- i begrenset tid, mmed eksklusjonskriterier (OSAS).

ofte pasientenes eget ønske"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 15. Klometiazol

Slik fordelte svarene seg i andre runde:

1. Kriterium 15. Klometiazol (Heminevrin): Bør bare brukes unntaksvis der andre behandlingsalternativ ikke har ført frem. Skal ikke brukes som fast medisin. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	9,6% (5)	21,2% (11)	11,5% (6)	**55,8% (29)**	52

* Kriterium 15. Klometiazol (Heminevrin): Bør bare brukes unntaksvis der andre behandlingsalternativ ikke har ført frem. Skal ikke brukes som fast medisin.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Betydelig overdødelighet ved bruk av klometiazol sammenlignet med andre preparater med samme bruksområde. I en studie var antall dødsfall per million resepter for klometiazol 95,7 (95% k.i. 88-103) mot 3,1 (2,7-3,5) for diazepam og 2,0 (1,1-3,4) for oxazepam (se ref.). Medikamentet er i dag lite brukt ved delir og APSD hos eldre internasjonalt og det finnes lite dokumentasjon på sikkerhet ved bruk. Ved bruk av klometiazol mot alkoholabstinens er rapporterte fatale tilfeller ofte knyttet til respirasjonsdepresjon.

Referanser for deg som vil lese mer:
Buckley NA, McManus PR. Changes in fatalities due to overdose of anxiolytic and sedative drugs in the UK (1983-1999). Drug Saf 2004; 27(2): 134-41.
http://www.ncbi.nlm.nih.gov/pubmed/14717623

Pentikainen PJ, Valtonen VV, Miettinen TA. Deaths in connection with chlormethiazole (heminevrin) therapy. Int J Clin Pharmacol Biopharm. 1976 Oct;14(3):225-30
http://www.ncbi.nlm.nih.gov/pubmed/1002357

Her er paneldeltagernes kommentarer:

"Brukes likevel unntaksvis ved APSD med fysisk utagering og delirproblematikk. Pas. med Levy Body demens og fysisik utagering kan ikke bruke nevroleptika. Langvarig bruk ikke indisert da det raskt taper effekt.

Klometiazol kan brukes for å indusere søvn ved akutt delir og hos demente med sterkt forstyrret døgnrytme.

Noen av mine sykehjemspasienter med demenslidelse og agitert uro har glitrende effekt av Heminevrin ved behov, enkelte ganger - og da er jeg glad for at den fins.

Definer "fast medisin". Ubestemt tid = score 10, kortvarig bruk daglig er OK

Kun hvis ikke effekt av miljøtilltak og andre mediskamenter."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 16. Warfarin + NSAIDs

Slik fordelte svarene seg i andre runde:

1. Kriterium 16. Warfarin + NSAIDs: Skal unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	**98,1% (51)**	52

* Kriterium 16. Warfarin + NSAIDs: Skal unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Samtidig bruk gir økt fare for gastrointestinal og intracerebral blødning. Riskoen for blødning stiger med økende alder.

Referanser for deg som vil lese mer:
Narum S, Solhaug V, Myhr K, Johansen PW, Brors O, Kringen MK (2011) Warfarin-associated bleeding events and concomitant use of potentially interacting medicines reported to the Norwegian spontaneous reporting system. Br J Clin Pharmacol 71 (2):254-262. doi:10.1111/j.1365-2125.2010.03827.x

Battistella M, Mamdami MM, Juurlink DN, Rabeneck L, Laupacis A. Risk of upper gastrointestinal hemorrhage in warfarin users treated with nonselective NSAIDs or COX-2 inhibitors. Archives of Internal Medicine. 2005 Jan 24;165(2):189-92. http://www.ncbi.nlm.nih.gov/pubmed/15668365

Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005;165:1095-106. http://archinte.ama-assn.org/cgi/reprint/165/10/1095.pdf

Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ. 2007;177:347-51. http://pubmedcentralcanada.ca/picrender.cgi?accid=PMC1942107&blobtype=pdf

Mellemkjaer L, Blot WJ, Sorensen HT, Thomassen L, McLaughlin JK, Nielsen GL, et al. Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. Br J Clin Pharmacol. 2002;53:173-81. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1874281/pdf/bcp0053-0173.pdf

Cheetham TC, Levy G, Niu F, Bixler F. Gastrointestinal safety of nonsteroidal antiinflammatory drugs and selective cyclooxygenase-2 inhibitors in patients on warfarin. The Annals of Pharmacotherapy. 2009 Nov;43(11):1765-73. http://www.ncbi.nlm.nih.gov/pubmed/19809010

Her er paneldeltagernes kommentarer:

"NSAIDS alene er som regel kontraindisert i seg selv og i hvert fall sammen med Marevan

Hos pasienter som bruker warfarin og får sterke smerter, bør det brukes opiater, ikke NSAIDS. Ved leddplager kan lokalbehandling med steroider gis.

alt for stor interaksjonsfare

Men gjelder ikke kombinasjonen Albyl-E og Marevan. Indisert ved koronarsykdom og atrieflimmer."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 17. Warfarin + SSRI/SNRI

Slik fordelte svarene seg i andre runde:

1. Kriterium 17. Warfarin + SSRI/SNRI: Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	3,8% (2)	11,5% (6)	23,1% (12)	**28,8% (15)**	13,5% (7)	17,3% (9)	52

* Kriterium 17. Warfarin + SSRI/SNRI: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Øker faren for gastrointestinal blødning. Serotonin reopptakshemmere hemmer opptak av serotonin i blodplater. Blodplater produserer ikke eget serotonin. På den måten hemmes blodplatenes funksjon. Effekten er uavhengig av INR-verdi. Risikoen avhenger sannsynligvis av graden av serotoninhemming.

Av SSRIene har fluoksetin, paroksetin og sertralin sterkest serotoninhemming. Fluvoksamin, citalopram og escitalopram har intermediær serotoninhemming. Av andre antidepressiva har klomipramin høyest serotoninhemming, venlafaksin, amitriptylin og imipramin intermediær serotoninhemming og mirtazapin, mianserin, bupropion, nortriptylin og desipramin lavest serotoninhemming. I tillegg til økt blødningsrisiko på grunn av SSRI/SNRIenes effekt på blodplateaggregasjonen, bør også eventuelle farmakokinetiske interaksjoner tas med i betraktningen. Warfarin metaboliseres via CYP2C9, CYP2C19 og CYP1A2, hvorav CYP2C9 er det viktigste enzymet. Fluvoksetin er en moderat/potent hemmer av både CYP2C9, CYP2C19 og CYP1A2, og er vist å kunne gi betydelig økning i serumkonsentrasjon av warfarin og kombinasjonen bør om mulig unngås.

Referanser for deg som vil lese mer:
RELIS database 2011; spm.nr. 2567, RELIS Nord-Norge. http://relis.arnett.no/Utredning_Ekstern.aspx?Relis=5&S=2567

Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Archives of Internal Medicine. 2003 Jan 13;163(1):59-64. http://www.ncbi.nlm.nih.gov/pubmed/12523917

Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. Am J Gastroenterol. 2009 Jun;104(6):1475-82. http://www.ncbi.nlm.nih.gov/pubmed/19491861

Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. Drugs & aging. 2002;19(4):299-320. http://www.ncbi.nlm.nih.gov/pubmed/12038880

Her er paneldeltagernes kommentarer:

"Hva med de med psykisk lidelse, bra effekt på SNRI og Atrieflimmer? Ikke skriv " bør unngåes", men legg inn varsel

bør vurderers individuel

Ikke 100 % kontraindikasjon. Bør være klar over muligheten for uøanske bivirkning.

Bør individualiseres, forskjellige individer reagerer forskjellig på antidepressiva. Hvis det er indisert og pas. har bare god effekt av en bestemt SSRI så bør den ikke seponeres men man må følge nøye med.

Enig i at det bør stå "bør brukes med forsiktighet". Kan være vanskelig å unngå kombinasjonen

Dette har jeg ikke tenkt mye over, dessverre."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 18. Warfarin + ofloxacin/ciprofloxacin/ erythromycin/clarithromycin

Slik fordelte svarene seg i andre runde:

1. Kriterium 18. Warfarin + ofloxacin/ciprofloxacin/ erythromycin/clarithromycin: Bør bare brukes på sterk indikasjon/mikrobiologisk resistensbestemmelse under nøye kontroll av INR. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	5,8% (3)	3,8% (2)	13,5% (7)	21,2% (11)	**53,8% (28)**	52

* Kriterium 18. Warfarin + ofloxacin/ciprofloxacin/ erythromycin/clarithromycin: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Økt blødningsfare grunnet hemning av warfarinmetabolismen og redusert syntese av vitamin K fra bakterier i tarmen. Bør bare brukes på sterk indikasjon under nøye kontroll av INR.

Referanser for deg som vil lese mer:
Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. CMAJ. 2007;177:347-51.
http://pubmedcentralcanada.ca/picrender.cgi?accid=PMC1942107&blobtype=pdf

Holbrook AM, Pereira JA, Labiris R, McDonald H, Douketis JD, Crowther M, et al. Systematic overview of warfarin and its drug and food interactions. Arch Intern Med. 2005;165:1095-106.
http://archinte.ama-assn.org/cgi/reprint/165/10/1095.pdf

Her er paneldeltagernes kommentarer:

"Hyppige INR-kontrollar dersom slike antibiotika er indiserte.

Gi rom for unntak (harepest), men legg inn varsel Kriterium 18

All antibiotika kan påvirke INR, men verst er makrolidene unntatt azitromycin. Hvis man er klar over faren kan man monitorere INR ekstra nøye.

Bør ikke dette være to ulike punkter? kinoloner og warfarin, makrolider og warfarin. Også interaksjon mellom flagyl og marevan (økt INR, ses raskt, dels via vit K antagonist, dels via påvirket metabolisme av warfarin) Uansett bør INR måles hyppigere under en antiobiotika kur Vil ofte være andre antibiotika valgmuligheter enn makrolider

Med forsiktighet, og da med hyppige INR kontroller (vi måler selv på sykehjememt)

Greit. Men ved alle antibiotika kan en oppleve høy INR pga endret syntese av vit K i tarm. Derfor: ved antibiotikabehandling hos warfarinbrukere- kontroller INR hyppig!"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 19. Systemiske NSAIDs/koksiber + ACE-hemmer/AII-hemmer

Slik fordelte svarene seg i andre runde:

1. Kriterium 19. Systemiske NSAIDs/koksiber + ACE-hemmer/AII-hemmer: Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	1,9% (1)	5,8% (3)	19,2% (10)	**69,2% (36)**	52

* Kriterium 19. Systemiske NSAIDs/koksiber + ACE-hemmer/AII-hemmer: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Fare for medikamentindusert nyresvikt.

Referanser for deg som vil lese mer:
Witczak BJ, Asberg A, Hartmann A. [Acute dialysis-dependent renal failure at the Rikshospital in 1998]. Tidsskr Nor Laegeforen. 2001;121:1216-9.
http://www.ncbi.nlm.nih.gov/pubmed/11402747

Her er paneldeltagernes kommentarer:

"Bruker nesten aldri NSAIDs mere til mine pasienter i sykehjem

Interaksjoner bør alltid sjekkes. "Kontraindisert" ved hjerte og/eller nyresvikt, særlig kiksiber. Hvis noe skal brukes bør man anbefale Naproxen.

Bør unngås som langtidsforskriving, kun til kortvarig bruk (<1 uke) og med preparater med kort halveringstid, forutsatt at pasienten er nyrefrisk og kan innta rikelig med drikke."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 20. Systemiske NSAID + diuretikum

Slik fordelte svarene seg i andre runde:

1. Kriterium 20. Systemiske NSAID + diuretikum: Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	0,0% (0)	1,9% (1)	3,8% (2)	5,8% (3)	19,2% (10)	23,1% (12)	**42,3% (22)**	52

* Kriterium 20. Systemiske NSAID + diuretikum: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Kombinasjonen gir redusert effekt av diuretikum og økt risiko for hjerte- og nyresvikt. NSAIDs og kaliumsparende diuretika gir økt risiko for hyperkalemi.

Referanser for deg som vil lese mer:
Stockley's Drug Interaction Pocket Companion 2010, Baxter K. (ed), 2010.

Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A. NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med. 1998;158:1108-12.
http://archinte.ama-assn.org/cgi/reprint/158/10/1108.pdf

Her er paneldeltagernes kommentarer:

"jfr tidligere, NSAIDs bør unngås til eldre (unntak terminale, cancersmerter)

støtter kommenater om NSAIDS hos skrøpelige eldre, det er bare unntaksvis lurt!"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 21. Systemisk NSAID + systemisk glukokortikoid

Slik fordelte svarene seg i andre runde:

1. Kriterium 21. Systemisk NSAID + systemisk glukokortikoid: Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	3,8% (2)	9,6% (5)	5,8% (3)	19,2% (10)	**59,6% (31)**	52

* Kriterium 21. Systemisk NSAID + systemisk glukokortikoid: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Kombinasjonen kan føre til gastrointestinal blødning og væskeretensjon.

Referanser for deg som vil lese mer:
Mellemkjaer L, Blot WJ, Sorensen HT, Thomassen L, McLaughlin JK, Nielsen GL, et al. Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. Br J Clin Pharmacol. 2002;53:173-81.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1874281/pdf/bcp0053-0173.pdf

Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Annals of Internal Medicine. 1991 May 1;114(9):735-40.
http://www.ncbi.nlm.nih.gov/pubmed/2012355

Her er paneldeltagernes kommentarer:

"RELIS Sør-Øst sammen med kliniske farmakologer holder på med en systematisk gjennomgang av blødningsrisiko.

Forbeholdes spesielle indikasjoner : R.A. / M. addison og akutt nyresteinkolikk / giktanfall e.l. , bør da gis PPI samtidig så lenge NSAID gis

Husk PPI hvis absolutt nødvendig etter nøye vurdering."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 22. Systemisk NSAID + SSRI

Slik fordelte svarene seg i andre runde:

1. Kriterium 22. Systemisk NSAID + SSRI: Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	1,9% (1)	7,7% (4)	5,8% (3)	11,5% (6)	17,3% (9)	23,1% (12)	**30,8% (16)**	52

* Kriterium 22. Systemisk NSAID + SSRI: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Bruk av NSAIDs og bruk av SSRI øker begge risikoen for gastrointestinal blødning hver for seg. Noen studier viser at samtidig bruk øker faren for gastrointestinal blødning ytterligere. Andre finner ikke samme økning i risiko.

Referanser for deg som vil lese mer:
Dalton SO, Johansen C, Mellemkjaer L, Norgard B, Sorensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. Archives of Internal Medicine. 2003 Jan 13;163(1):59-64. http://www.ncbi.nlm.nih.gov/pubmed/12523917

Loke YK, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther. 2008 Jan 1;27(1):31-40. http://www.ncbi.nlm.nih.gov/pubmed/17919277

Tata LJ, Fortun PJ, Hubbard RB, Smeeth L, Hawkey CJ, Smith CJ, et al. Does concurrent prescription of selective serotonin reuptake inhibitors and non-steroidal anti-inflammatory drugs substantially increase the risk of upper gastrointestinal bleeding? Aliment Pharmacol Ther. 2005 Aug 1;22(3):175-81. http://www.ncbi.nlm.nih.gov/pubmed/16091054

de Abajo FJ, Garcia-Rodriguez LA. Risk of upper gastrointestinal tract bleeding associated with selective serotonin reuptake inhibitors and venlafaxine therapy: interaction with nonsteroidal anti-inflammatory drugs and effect of acid-suppressing agents. Arch Gen Psychiatry. 2008 Jul;65(7):795-803. http://www.ncbi.nlm.nih.gov/pubmed/16091054

Targownik LE, Bolton JM, Metge CJ, Leung S, Sareen J. Selective serotonin reuptake inhibitors are associated with a modest increase in the risk of upper gastrointestinal bleeding. Am J Gastroenterol. 2009 Jun;104(6):1475-82. http://www.ncbi.nlm.nih.gov/pubmed/19491861

Her er paneldeltagernes kommentarer:

"Enig med siste kommentar fra panelet om at det blir mange NSAID-kriterier i lys av at vi alt har sagt at denne gruppen bør unngås hos eldre.

unntak burde begrunnes og tids-begrenses

Behandlingsvarighet og individuell vurdering av blødningsrisiko er av stor betydning

Ikke hvis det er sterk indikasjon og man er klar over mulige bivirkninger

se tidl NSAIDs bør unngås til eldre

Støtter den siste kommentaren på dette punktet. NSAIDs bør generelt unngås.

Jeg tenker at all NSAID bør så langt som mulig, unngås på sykehjemspasienter.

begrens antall kriterier på NSAIDS"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 23. ACE-hemmer/ATII-antagonist + kalium eller kaliumsparende diuretikum

Slik fordelte svarene seg i andre runde:

1. Kriterium 23. ACE-hemmer/ATII-antagonist + kalium eller kaliumsparende diuretikum: Bør bare brukes ved sterk indikasjon og under kontroll av serum-kalium. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	5,8% (3)	0,0% (0)	15,4% (8)	13,5% (7)	**63,5% (33)**	52

* Kriterium 23. ACE-hemmer/ATII-antagonist + kalium eller kaliumsparende diuretikum: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Risiko for hyperkalemi. Kan være indisert i noen tilfeller, blant annet ved alvorlig hjertesvikt. Bør bare brukes ved sterk indikasjon og under kontroll av serum-kalium.

Referanser for deg som vil lese mer:
Kurisu S, Inoue I, Kawagoe T, Ishihara M, Shimatani Y, Nakama Y, et al. Role of medications in symptomatic hyperkalemia. QJM. 2007;100:591-3.
http://qjmed.oxfordjournals.org/content/100/9/591.full.pdf

Schepkens H, Vanholder R, Billiouw JM, Lameire N. Life-threatening hyperkalemia during combined therapy with angiotensin-converting enzyme inhibitors and spironolactone: an analysis of 25 cases. Am J Med. 2001;110:438-41.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11331054

Her er paneldeltagernes kommentarer:

"tillegg av kriterium 23 er ok.

Det finnes bedre antihypertensiva enn diuretika. Diuretika er generelt risikabelt hos gamle.

Bør ikke benyttes til til pasienter som ikke selv er i stand til å innta drikke"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 24. Betablokker + kardioselektiv kalsiumantagonist

Slik fordelte svarene seg i andre runde:

1. Kriterium 24. Betablokker + kardioselektiv kalsiumantagonist (verapamil, diltiazem): Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	3,8% (2)	3,8% (2)	5,8% (3)	19,2% (10)	**65,4% (34)**	52

* Kriterium 24. Betablokker + kardioselektiv kalsiumantagonist (verapamil, diltiazem): Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Risiko for AV-blokk + myokarddepresjon. Bør kun brukes på spesiell indikasjon.

Referanser for deg som vil lese mer.
Zeltser D, Justo D, Halkin A, et al. Drug-induced atrioventricular block: prognosis after discontinuation of the culprit drug. Journal of the American College of Cardiology. 2004 Jul 7;44(1):105-8.
http://www.ncbi.nlm.nih.gov/pubmed/15234417

Baxter K, editor. Stockley's drug interactions. 7th ed: The pharmaceutical press; 2006.

Her er paneldeltagernes kommentarer:

"Behandlingen blir av og til initiert av Kardiolog.

Kardiologene bruker dette en del, men det bør være de og bare de som initierer slik behandling pga faren for kardigent sjokk!

Kan ikke forstå at BT i det hele tatt bør beh aggressivt i en fase av livet der kvalitet i dagene er langt viktigere enn om en er i mål med BT-beh.

Hjertebahandling på sykhjemspasienter synes jeg at er meget vanskelig.

revider teksten: bør kun brukes på spesiell indikasjon og være initiert av spesialist"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 25. Erythromycin/clarithromycin + statin

Slik fordelte svarene seg i andre runde:

1. Kriterium 25. Erythromycin/clarithromycin + statin: Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	7,7% (4)	5,8% (3)	15,4% (8)	**69,2% (36)**	52

* Kriterium 25. Erythromycin/clarithromycin + statin: Bør unngås.

Anbefaling: Dersom det er indikasjon for bruk av makrolidantibiotika bør statin seponeres i behandlingsperioden.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Interaksjon gir økt statineffekt med bivirkninger (obs rhabdomyolyse). Ved behov for makrolid bør statindosen reduseres eller midlertidig seponeres.

Referanser for deg som vil lese mer:
Law M, Rudnicka AR. Statin safety: a systematic review. Am J Cardiol. 2006;97:52C-60C.
http://www.ncbi.nlm.nih.gov/pubmed/16581329

Her er paneldeltagernes kommentarer:

"Mulig det er lurt å tilføye: Statin kan seponeres i antibiotikaperioden. Tror kanskje mange ser seg blinde på at det skal gis daglig.

Erytromycin eller beslektede antibiotika bruker jeg hos eldre bare ved sterke indikasjoner , pga stor resiko for interaksjoner og bivirkninger, og generelt eldre tåler det meget dårlig.

Statiner skal jo likevel seponeres hos de aller fleste sykehjemspasienter. Men hos de som står på det, er det viktig å gjøre pause.

Statin bør seponeres i den tiden man bruker erytromycin/klacid hvis det er indikasjon for bruk av makrolid. Penicillin er førstevalg for alle luftveisinfeksjoner med unntak av mycoplasma og chlamydia

seponer statinet under ab-kur

JEg lengter etter en retningslinje som legger frem argumentasjon for at statiner ikke er dokumentert for en befolkning i sykehjem på overlevelse og hendelser slik at disse medikamentene kan forsvinne fra sykehjemmet. Poenget er at enten har alle indikasjon, men egentlig har vi ingen dokumentasjon for å si at vi hindrer hendelser eller at sykehjemspasienten vår lever lenger."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 26. Bisfosfonat + protonpumpehemmer

Slik fordelte svarene seg i andre runde:

1. Kriterium 26. Bisfosfonat + protonpumpehemmer: Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	1,9% (1)	0,0% (0)	0,0% (0)	5,8% (3)	**21,2% (11)**	**21,2% (11)**	11,5% (6)	13,5% (7)	3,8% (2)	**21,2% (11)**	52

* Kriterium 26. Bisfosfonat + protonpumpehemmer: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Samtidig bruk kan redusere effekten av bisfosfonater og øke risikoen for brudd.

Referanser for deg som vil lese mer:
Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. Curr Gastroenterol Rep. 2010 Dec;12(6):448-57

Abrahamsen B, Eiken P, Eastell R. Proton pump inhibitor use and the antifracture efficacy of alendronate. Archives of Internal Medicine. 2011 Jun 13;171(11):998-1004.
http://www.ncbi.nlm.nih.gov/pubmed/21321287

Yang YX, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA : the journal of the American Medical Association. 2006 Dec 27;296(24):2947-53.
http://www.ncbi.nlm.nih.gov/pubmed/17190895

Her er paneldeltagernes kommentarer:

"Vurdere om bisfosfonat fortsatt er indisert hos den enkelte i denne aldersgrupper, har sett alvorlig GI blødning på bisfosfonat hos eldre, da med fall og brudd som resultat, noe jo bisfosfonat nettopp skulle forebygge.

OJ!. kan tenke meg at mange kvinner med dyspepsi får dette på sykehjem...jeg velger å plukke bort bisfosfonat ved dyspepsi, de fleste ha hatt det en stund. I tvil og ved strk indikasjon for bisfosfonat og behov for PPI velger jeg å henvise til sykehus til poliklinisk i.v. behandling med Aredia eller Zometa.

bruk av Biforfonat hos sykehjems pasienter er noe som er i tvil og indikasjonen må være sterk.

Viktig å være klar over reduksjon av effekt og risiko for brudd - for å gjøre en individuell vurdering av risiko og potensiell og observert nytte av behandling"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 27. Samtidig bruk av tre eller flere psykoaktive preparater

Slik fordelte svarene seg i andre runde:

1. Kriterium 27. Samtidig bruk av tre eller flere preparater innen gruppene sentralt virkende analgetika, antipsykotika, antidepressiva, benzodiazepiner: Bør unngås. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	5,8% (3)	**90,4% (47)**	52

* Kriterium 27. Samtidig bruk av tre eller flere preparater innen gruppene sentralt virkende analgetika, antipsykotika, antidepressiva, benzodiazepiner: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Betydelig fare for sedasjon og fall.

Referanser for deg som vil lese mer:
Hartikainen S, Lonnroos E, Louhivuori K. Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci Med Sci. 2007 Oct;62(10):1172-81
http://www.ncbi.nlm.nih.gov/pubmed/17921433

Spina E, Scordo MG. Clinically significant drug interactions with antidepressants in the elderly. Drugs & aging. 2002;19(4):299-320.
http://www.ncbi.nlm.nih.gov/pubmed/12038880

Leipzig RM, Cumming RG, Tinetti ME. Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. J Am Geriatr Soc. 1999;47:30-9.
http://www.ncbi.nlm.nih.gov/pubmed/9920227

Weiner DK, Hanlon JT, Studenski SA. Effects of central nervous system polypharmacy on falls liability in community-dwelling elderly. Gerontology. 1998;44(4):217-21.
http://www.ncbi.nlm.nih.gov/pubmed/9657082

Koski K, Luukinen H, Laippala P, Kivela SL. Physiological factors and medications as predictors of injurious falls by elderly people: a prospective population-based study. Age Ageing. 1996;25:29-38.
http://www.ncbi.nlm.nih.gov/pubmed/8670526

Her er paneldeltagernes kommentarer:

"Her syndes det nok en del. Hos en del pas. med APSD med fysisk utagering forsøker man mye i ren desperasjon. Forløpende døgnregistrering og evaluering ved instituering/seponering av medikamenter uansett viktig!

selvsagt.

Hvis så store utfodringer bør en ha konferert med alderspsyk føre oppstart."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 28. Seponering av forebyggende legemidler ved forventet kort levetid

Slik fordelte svarene seg i andre runde:

1. Kriterium 28. Seponering av forebyggende medikamenter bør foretas når pasientens forventede levetid er kort. På en skala fra 0 til 10, hvordan vurderer du den kliniske relevansen av dette kriteriet? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	3,8% (2)	7,7% (4)	9,6% (5)	**76,9% (40)**	52

* Kriterium 28. Seponering av forebyggende medikamenter bør alltid vurderes når pasientens forventede levetid er kort.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Forventet gevinst er liten og risikoen for bivirkninger er stor. Pasienten vil ofte ikke være i stand til å melde fra om subjektive bivirkninger.

Referanser for deg som vil lese mer:
(NY): O'Mahony D, O'Connor MN. Pharmacotherapy at the end-of-life. Age Ageing. 2011;40(4):419-22. Epub 2011/05/31

(NY): Kristjansson SR, Wyller T. Avslutning av forebyggende legemiddelbruk hos eldre. Tidsskr Nor Laegeforen. 2010;130(17):1726–8.

Her er paneldeltagernes kommentarer:

"Vurder bivirkninger av disse medisiner som kan være plagsomme i siste livsfase. I tillegg bør kostnader også tas i betraktning.

Referanse er f.eks. retningslinjene for primærforebygging av hjerte/karsykdom, bisfosfonat etc. Vi må bli flinkere til å si at alle legemidler kan gi bivirkninger som kan gjøre den siste tiden mer plagsom istedenfor å bedre livskvaliteten.

Vurdering i forhold til livskvalitet og risiko for seponeringsreaksjoner - fint å seponere hvis tablettinntak oppleves som problematisk f.eks ved svelgeproblemer osv, samt bivirkninger. Kanskje modifisere kriteriet til at seponering alltid bør vurderes ved forventet kort levetid.

Et nøkkelkriterium for å forstå om legen har tatt inn over seg at sykehjemsmedisin er forskjellig fra den medisin som vedkommende har lært på doktorskolen og forskjellig fra alle andre områder av medisin. Vi har brukt det meste av opplæringen i faget på når og hvordan vi skal starte medisinering, men ikke når og hvordan vil skal avslutte den.

Her vil eg tilrå å leggja til grunn ei venta attverande levetid på < 1 år.

ofte vanskelig å gjennomføre pga pårørendes ønske

Hvor kort levetid da?

Det spørs hva vi mener med "forebyggende". Noen ganger forebygger vi jo i et svært kort perspektiv også (eks. forebygging av UVI med trimetoprim etc.), og det er det vel ikke riktig å seponere. Bør spesifisere at det dreier seg om forebyggelse av hendelser som ligger langt fram i tid.

Gjelder "rent" forebyggende - husk at f.eks. betablokker både er forebyggende mot hjerteinfarkt, men også god symptomatiskbehandling av angina

Endre fra bør foretas til bør vurderes, her vil det være mange gråsoner

Spesielt hvis fare for interaksjoner og bivirkninger.

Man bør her spesifisere hva man legger i begrepet kort forventet levetid.

presiser hva som er kort forventet levetid. Terminalomsorg er greit, men etter det?? Mindre enn 2 år? (Wyller og Kristjansson, tidsskriftet 2010). Bør Marevan for pasienter med svært høy risiko for hjerneslag allikevel gis?? Hemiparese er ikke festlig selv om man har kort forventet levetid!

'Mahony, D. and M. N. O'Connor (2011). "Pharmacotherapy at the end-of-life." Age and Ageing 40(4): 419-422."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 29. Samtidig bruk av metoprolol og antidepressiva

Slik fordelte svarene seg i andre runde:

1. Kriterium 29. Metoprolol bør ikke kombineres med paroksetin, fluoksetin eller bupropion. På en skala fra 0 til 10, hvordan vurderer du den kliniske relevansen av dette kriteriet? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	7,7% (4)	28,8% (15)	17,3% (9)	**44,2% (23)**	52

* Kriterium 29. Metoprolol bør ikke kombineres med paroksetin, fluoksetin eller bupropion.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Interaksjon med kraftig økning av serumkonsentrasjon av metoprolol som resultat. Metoprolol bør også brukes med forsiktighet i kombinasjon med citalopram, escitalopram eller duloksetin og dosereduksjon av metoprolol bør da vurderes.

"Paroksetin er vist å øke biologisk tilgjengelig dose av metoprolol i størrelsesorden 4–6 ganger. Det samme vil trolig gjelde de to andre potente CYP2D6-hemmerne i samme gruppe, fluoksetin og bupropion. Det er publisert tilfeller med alvorlig bradykardi og AV-blokk ved kombinasjon av metoprolol og disse tre midlene. Escitalopram, citalopram og duloksetin er mindre potente CYP2D6-hemmere, som er vist å gi 2–3 ganger økning i biologisk tilgjengelig metoprololdose. Sertralin, venlafaksin, mianserin og mirtazapin forårsaker begrenset eller ingen hemming av CYP2D6 og forventes ikke å gi klinisk relevante interaksjoner med metoprolol... Andre antidepressiver kan kombineres med metoprolol uten risiko for interaksjoner" (Molden og Spigset 2011).

Referanser for deg som vil lese mer:
Molden E, Spigset O (2011) [Interactions between metoprolol and antidepressants]. Tidsskr Nor Laegeforen 131 (18):1777-1779. doi:10.4045/tidsskr.11.0143

Her er paneldeltagernes kommentarer:

"Heldigvis bruker Norge lite paroksetin! Og heller ikke så mye fluoksetin og bupropion. Vi har allerede kriterium på bruk av antidepressiva til eldre og dette blir vel da enda en grunn til å unngå antidepressiva. Det at metoprolol vel er den mest brukte betablokkeren i Norge, øker relevansen av kriteriet.

Vennligst legg også inn info om 2-3 ganger økt effekt av Metoprolol ved bruk av Cipramil / Cipralex

Enig, selv om det er mulig å vurdere effekten av interaksjonen mellom metoprolol og disse SSRI klinisk ved å måle blodtrykk og puls.

Kriteriet bør heller formuleres: ved samtidig bruk av metoprolol og paroksetin, fluoksetin og bupropion bør dosen metoprolol halveres eller settes enda lavere. Det finnes pasienter som har god indikasjon for begge deler. Både hjetesvikt og depresjon er meget vanlige lidelser hos eldre, og effekter er vist å være god hos begge medikamenter. Derfor blir formuleringen "bør ikke" i dette tilfellet for absolutt.

Dette var jeg ikke klar over, skjøt det står også i Felleskatalogen.

Ut fra interksjoner bør annet antidepressivum velges.

Indikasjon for begge preparatgrupper vurderes. Mht metoprolol vurderes effekt/bivirkning og evt endring i den dersom antidepr legges til: puls, BT etc sjekkes. Cyp måling vurderes? Andre antidepr enn de nevnte kan vurderes og er vel i dag også vanligere å bruke

Man må iallefall være årvåken og følge blodtrykk, puls og EKG nøye.

Kombinasjonen må brukes bare under nøye vurdering av indikasjon og med reduksjon av metoprololdosen

bør en foreslå overgang til annen betablokker i stedet? angstsymptomer blir verre hvis en ligger med 120 i puls!"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 30. Medikamenter med blodtrykkssenkende effekt

Slik fordelte svarene seg i andre runde:

1. Kriterium 30. Medikamenter med blodtrykkssenkende effekt: All bruk bør monitoreres med henblikk på ortostatisme, hypotensjon og falltendens. På en skala fra 0 til 10, hvordan vurderer du den kliniske relevansen av dette kriteriet? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	3,8% (2)	5,8% (3)	**90,4% (47)**	52

* Kriterium 30. Medikamenter med blodtrykkssenkende effekt: All bruk bør monitoreres med henblikk på ortostatisme, hypotensjon og falltendens.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Gjelder for eksempel nitropreparater, alfablokkere, kalsiumantagonister, betablokkere, ACE-hemmere/AT2-antagonister, antiparkinsonmidler, antikolinergika. Midlene kan øke faren for ortostatisme og hypotensjon. Det kan antas at samtidig bruk av flere slike midler også øker risikoen for ustøhet og fall, men det finnes lite dokumentasjon på dette.
Totalvurdering mhp (forventet) behandlingsgevinst og risiko for bivirkninger må foretas.

Referanser for deg som vil lese mer:
McKay C, Anderson KE (2010) How to manage falls in community dwelling older adults: a review of the evidence. Postgraduate medical journal 86 (1015):299-306. doi:10.1136/pgmj.2009.093468

Hartikainen S, Lonnroos E, Louhivuori K (2007) Medication as a risk factor for falls: critical systematic review. J Gerontol A Biol Sci Med Sci 62 (10):1172-1181

Vu MQ, Weintraub N, Rubenstein LZ (2005) Falls in the nursing home: Are they preventable? Journal of the American Medical Directors Association 6 (3 Suppl):S82-87. doi:10.1016/j.jamda.2005.03.025

Ooi WL, Hossain M, Lipsitz LA (2000) The association between orthostatic hypotension and recurrent falls in nursing home residents. Am J Med 108 (2):106-111

Her er paneldeltagernes kommentarer:

"ortostatisk BT-måling blir ofte ikke tatt etter prosedyrene- det måles bare BT, ikke pulsrespons, det måles bare 1 gang etter 1 minutt- ofte med falsk negativ resultat. Kan dere i heftet med anbefalingene i et vedlegg skriver opp den egentlige, riktige prosedyren, jeg opplever gang på gang at sykepl. enten ikke vet hvordan det gjøres eller slurver pga tidspress og fordi det mangler kunnskap om betydningen av prosedyren...

Etter min efaring kan det meste, nesten alle antihypertensivae seponeres på en sykehjemspopulasjon. Jeg vil snu kriteriet helt rundt og heller postulere at alle antihypertensiva seponeres, med eller uten nedtrapping. Deretter skal det monitoreres om pas utvikler symptomgivende hypertensjon. Om BT-monitorering i denne prosedyren er viktig eller ikke er jeg ikke helt sikker på.

Antallet fall skal alltid dokumenteres. Ortostatisk blodtrykksmåling bør gjøres 2-4 ganger årlig hos sykehjemspasienter, særlig ved bruk av antihypertensiva eller L-dopa.

viktig å ta hensyn til "totalbelastning" på eldre

All bruk bør monitoreres med henblikk på ortostatisme og hypotensjon. Falltendens er en mer uspesifikk parameter og kan være forårsaket av mye annet enn blodtrykks medisiner.

De fleste som tidligere har hatt hypertensjon, har ikke behov for BT senkende da de er så svake at de må ha sykhejemsplass. Måler alltid BT x3 i 3 dager føre og etter ev endringer."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 31. Kombinasjonen metformin + ACE-hemmer/AT2-antagonist + diuretika: Bør unngås.

Slik fordelte svarene seg i andre runde:

1. Kriterium 31: Kombinasjonen metformin + ACE-hemmer/AT2-antagonist + diuretika: Bør unngås. På en skala fra 0 til 10, hvordan vurderer du den kliniske relevansen av dette kriteriet? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	3,8% (2)	5,8% (3)	17,3% (9)	15,4% (8)	11,5% (6)	**42,3% (22)**	52

* Kriterium 31: Kombinasjonen metformin + ACE-hemmer/AT2-antagonist + diuretika: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Betydelig risiko for forverret nyrefunksjon og metformin-indusert laktacidose (som har svært høy mortalitetsrate), for eksempel utløst av simple tilstander som oppkast, diare, eller dehydrering av annen årsak.

Eliminasjon av metformin skjer via tubulær filtrasjon. Når denne avtar øker akkumulasjon av metformin, som igjen øker risikoen for laktacidose. Metformin og ACE-hemmer bør vurderes seponert under akutt sykdom.

Anbefaling: Hos diabetikere med hjertesvikt og i andre indiserte tilfeller bør ACE-hemmer/AT2-antagonist og diuretika seponeres ved interkurrent sykdom som gir risiko for dehydrering.

Referanser for deg som vil lese mer:
RELIS database 2011; spm.nr. 2390, RELIS Nord-Norge
http://relis.arnett.no/Utredning_Ekstern.aspx?Relis=5&S=2390

Her er paneldeltagernes kommentarer:

"Det viktigste her er å være oppmerksom på symptomer som er tegn på metformin overdosering. Hos denne populasjonen skal kvalme, oppkast og diaré først vurderes som bivirkninger. Her er vi for dårlige! Vi må passe på at pasientene får nok væske, det gjelder ikke minst om sommeren. Metformin er et fortsatt et godt valg ved hjertesvikt: Papanas N et al. Metformin and heart failure: never say never again. Expert Opin Pharmacother 2012; 8(1): 1-8

Diabetiker med hypertensjon/ hypertensiv hjertesvikt SKAL jo få det- men hvem tenker på å seponere/ pausere ved interkurrente infeksjoner/ væskemangel etc?? dette er svært viktig å nevne !!

Det er riktig at dette en meget risikabel kombinasjon for dehydrerte pasienter. Dette er selvfølgelig også kombinasjon ACE-hemmer/ AT2-antagonist og diuretika. Diuretika burde uansett ikke gis så lenge pasienten er dehydrert. Vi ser hvert år flere sykehusinnleggelser pga nyresvikt hos dehydrerte pasienter som bruker ACE-hemmer og diuretika. Samtidig burde denne kombinasjonen kunne håndteres på sykehjem ved å midlertidig seponerer diuretika og ACE-hemmer når tilstander som fører til dehydrering oppstår.

Vel, nå er det klare anbefalinger om å seponere metformin på pasienter over 75 år i alle fall. Jeg var ikke klar over at den ovennevnte kombinasjonen er såpass risikabel.

Særlig ved nedsatt nyrefunksjon. Faren for lactacidose størst ved infeksjonstilstander hvis man bruker kombinasjonen.

Kan vel aksepteres på sykehjem forutsett klare retningslinjer for overvåking av hydreringsstatus. Nesten verre hos hjemmeboende pasienter der man ikke har samme grad av "kontroll".

Hele sykdomsbilde må vurderes, og monitorering viktig mht nyrefunksjon inkl elektrolytter, diabetes etc. Juster dose etter disse parametre. Forskjell på akutt sykdom og kronisk fase, vis ekstra forsiktighet med kombinasjonen og vurder "null ut" ved akutt sykdom som oppkast, diare og annen væskeforstyrrelse

ACE-hemmer / AT2 antagonist, metformin og evt diuretika bør vurderes seponert under interkurrent sykdom

Bør vurderes ut i fra situasjonen, men man skal være obs på evt konsekvenser ved f.eks gastroenteritter

Må individualiseres. Hvis pas.har hjertesvikt og stabil GFR > 40 må det være lov å bruke

Må følges med regelmessige kontroller og stoppordre for ACE/AT2 blokker ved interkurrent sykdom

Dette er vanskelig"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 32. Kombinasjon av tramadol og SSRI: Bør unngås.

Slik fordelte svarene seg i andre runde:

1. Kriterium 32: Kombinasjonen tramadol + SSRI: Bør unngås. På en skala fra 0 til 10, hvordan vurderer du den kliniske relevansen av dette kriteriet? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	7,7% (4)	9,6% (5)	7,7% (4)	11,5% (6)	19,2% (10)	**42,3% (22)**	52

* Kriterium 32: Kombinasjonen tramadol + SSRI: Bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Fare for serotonergt syndrom. Forekommer oftere ved høy dose og ved økende alder.

Referanser for deg som vil lese mer:
RELIS database 2008; spm.nr. 2771, RELIS Midt-Norge
http://relis.arnett.no/Utredning_Ekstern.aspx?Relis=4&S=2771

RELIS database 2008; spm.nr. 3220, RELIS Øst
http://relis.arnett.no/Utredning_Ekstern.aspx?Relis=1&S=3220&R=X

Her er paneldeltagernes kommentarer:

"Tror vi bruker for mye tramadol. Også mange andre grunner til å unngå tramadol hos eldre: RELIS Øst 2008, spm 3220. NB CYP2D6-polymorfisme

Her finnes det mange tryggere alternativer. Siden den kombinasjonen er så lett å unngå, burde det alltid gjøres.

Tramadol bør ikkje brukast hjå sjukeheimspasientar i det heile tatt, grunna faren for kognitiv svikt og falltendens. Eit betre alternativ er paracetamol og opiat.

Synes ikke dette er så dramatisk forutsatt at man holder seg unna de 2D6-hemmende SSRI-ene.

HAr aldri sett noe seretonergt syndrom. DEnne interaksjonsfaren burde tallfestes dersom faren er stor. Tramadol og SSRI brukes mye mtp å fremme livskvalitet hos sykehjemsbefolkningen.

Må individualiseres. Pas. bør og kan følges nøye etter oppstart

Tramadol bruker jeg ikke på mine sykehjemspasienter."

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 33. Bisfosfonater

Slik fordelte svarene seg i andre runde:

1. Kriterium 33. Behandling med bisfosfonater bør seponeres hos eldre med sterkt reduserte livsutsikter. I lys av fordelingen av svarene i første runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	0,0% (0)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	0,0% (0)	0,0% (0)	0,0% (0)	1,9% (1)	13,5% (7)	**82,7% (43)**	52

* Kriterium 33. Behandling med bisfosfonater bør seponeres hos eldre med sterkt reduserte livsutsikter.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse: Risiko for øsofagusperforasjon ved nedsatt svelgefunksjon ved peroral behandling. Preparatene kan gi gastrointestinale og andre bivirkninger. Ikke indikasjon hos eldre som ikke lenger er mobile. Det forventes marginal helsegevinst hos personer med sterkt reduserte livsutsikter.

Referanser for deg som vil lese mer:
RELIS database 2010; spm.nr. 4589, RELIS Øst
http://relis.arnett.no/Utredning_Ekstern.aspx?Relis=1&S=4589

Her er paneldeltagernes kommentarer:

"Enig, med mindre det er smertebehandling med i.v. bisfosfonater ved skelettmetastaser.

Venta attverande levetid på <1 år bør leggjast til grunn for seponering.

Dette hører også med til den samtalen legen må ta med pasient (dersom det er mulig) og pårørende. Det hører vel med til sjeldenheten i norske sykehjem. Behandling som har pågått i lang tid kan ikke bare i all stillhet "strykes".

kan vel integreres i kriteriet om at forebyggende behandling bør avsluttes hos eldre med sterkt reduserte livsutsikter

Er ikke dette likt tidligere punkt som peker på behov for vurdering av forebyggende behandling ved begrenset leveutsikt?"

Riktig legemiddelbruk i sykehjem - runde 3

Kriterium 34. Hypnotika

Slik fordelte svarene seg i andre runde:

1. Kriterium 34. Hypnotika: Fast bruk bør unngås. På en skala fra 0 til 10, hvor relevant er dette kriteriet? Lag diagram Last ned

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor	Antall svar
Relevans	1,9% (1)	0,0% (0)	0,0% (0)	1,9% (1)	1,9% (1)	1,9% (1)	7,7% (4)	11,5% (6)	15,4% (8)	17,3% (9)	**40,4% (21)**	52

* Kriterium 34. Hypnotika: Fast bruk bør unngås.

I lys av fordelingen av svarene i andre runde, samt de innkomne kommentarene fra paneldeltagerne, hvordan vurderer du nå den kliniske relevansen av dette kriteriet på en skala fra 0 til 10?

	0 Ingen	1	2	3	4	5	6	7	8	9	10 Svært stor
Relevans	○	○	○	○	○	○	○	○	○	○	○

Plass for eventuelle kommentarer:

Begrunnelse:
Bivirkninger (oversedering, hangover). Økt risiko for fall. Ikke-farmakologiske tiltak som lyseksponering, aktivisering på dagtid og tilpasning av leggerutiner/tidspunkter bør vektlegges.

Referanser for deg som vil lese mer:
Frey DJ, Ortega JD, Wiseman C, Farley CT, Wright KP, Jr. (2011) Influence of zolpidem and sleep inertia on balance and cognition during nighttime awakening: a randomized placebo-controlled trial. J Am Geriatr Soc 59 (1):73-81. doi:10.1111/j.1532-5415.2010.03229.x

Glass J, Lanctot KL, Herrmann N, Sproule BA, Busto UE. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. BMJ. 2005 Nov 19;331(7526):1169.
http://www.bmj.com/content/331/7526/1169

Allain H, Bentue-Ferrer D, Polard E, Akwa Y, Patat A. Postural instability and consequent falls and hip fractures associated with use of hypnotics in the elderly: a comparative review. Drugs & aging. 2005;22(9):749-65.
http://www.ncbi.nlm.nih.gov/pubmed/16156679

Her er paneldeltagernes kommentarer:

"Ofte vanskleig å unngå

hyppigere gjennomgang av medikament indikasjon/bivirkningsprofil kan unngå fast bruk uten indikasjon lengre.

Vil jo ev. erstatte noen av de kriteriene vi hadde tidligere? Men greit med disse generelle kriteriene.

terminale kreftpasienter bør nevnes som unntak

i lengre perioder bør unngås, f.eks utover 4 uker

Joda, dette er riktig og noe å tilstrebe. Men ikke så ofte lett eller mulig uten betydelig innsats overfor pas, pårørende og personale. Jeg er en svært seponeringsvillig sykehjemslege. Men akkurat dette kriteriet kan nok tenkes å være en "turn-off" på kollegaer om det formuleres for strengt. Overvei en rundere tilrådning. Så kan de foregående kriteriene forbli så tydelige som de nå er formulert.

Fallfaren er òg svært relevant, og opphav til mykje plager for sjukeheimspasienten. Difor bør kriteriet lyda: fast bruk må unngås.

dette er vanskelig gjennomførbart i praksis

Realistisk?

Ideelt sett ja, men vanskelig å gjennomføre i praksis da mange av pasientene har brukt hypnotika fast i årevis.

Hva med Circadin? Hvis pas. har brukt hypnotika i lang tid før han/hun kom på sykehjem kan det være vanskelig å seponere. Må i så fall trappes forsiktig ned. Bruke Z-preparater

Men vanskeligere å gjennomføre i praksis.

Bør unngås ja, men i praktiken ikke gjennomførbart.

I prinsippet enig, men ofte vanskelig å unngå i praksis"

Norsk samfunnsvitenskapelig datatjeneste AS
NORWEGIAN SOCIAL SCIENCE DATA SERVICES

Harald Hårfagres gate 29
N-5007 Bergen
Norway
Tel: +47-55 58 21 17
Fax: +47-55 58 96 50
nsd@nsd.uib.no
www.nsd.uib.no
Org.nr. 985 321 884

Jørund Straand
Seksjon for allmennmedisin
Institutt for allmenn- og samfunnsmedisin
Universitetet i Oslo
Postboks 1130 Blindern
0318 OSLO

Vår dato: 30.03.2009 Vår ref:21087 / 2 / GRH Deres dato: Deres ref:

TILBAKEMELDING PÅ MELDING OM BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 22.01.2009. All nødvendig informasjon om prosjektet forelå i sin helhet 25.03.2009. Meldingen gjelder prosjektet:

21087	*Forskrivning av potensielt uhensiktsmessige legemidler til eldre - vurdert etter nye, norske kriterier*
Behandlingsansvarlig	*Universitetet i Oslo, ved institusjonens øverste leder*
Daglig ansvarlig	*Jørund Straand*

Etter gjennomgang av opplysninger gitt i meldeskjemaet og øvrig dokumentasjon, finner vi at prosjektet ikke medfører meldeplikt eller konsesjonsplikt etter personopplysningslovens §§ 31 og 33.

Dersom prosjektopplegget endres i forhold til de opplysninger som ligger til grunn for vår vurdering, skal prosjektet meldes på nytt. Endringsmeldinger gis via et eget skjema, http://www.nsd.uib.no/personvern/forsk_stud/skjema.html.

Vedlagt følger vår begrunnelse for hvorfor prosjektet ikke er meldepliktig. Prosjektet kan settes i gang.

Vennlig hilsen

Bjørn Henrichsen

Grethe Halvorsen

Kontaktperson: Grethe Halvorsen tlf: 55 58 25 83
Vedlegg: Prosjektvurdering

Personvernombudet for forskning

Prosjektvurdering - Kommentar

21087

Vår vurdering er basert på følgende:
Utvalget består av alle i alderen > 70 år som har hentet ut resept registrert i Reseptregisteret i 2008.
Opplysningene som leveres ut fra Reseptregisteret skal være anonyme (jf. e-post fra Reseptregisteret til prosjektleder, 6. februar 2009). Vi minner om at anonyme opplysninger er opplysninger som verken direkte (via f.eks. løpenummer som gjør det mulig å gå tilbake til enkeltindivid i registeret) eller indirekte (via sammenstilling av bakgrunnsopplysninger som f.eks. kommune, alder og kjønn eller referanse til foreskriver, alder og kjønn på pasient eller referanse til slike opplysninger) føre tilbake til enkeltpersoner.

Norsk samfunnsvitenskapelig datatjeneste AS
NORWEGIAN SOCIAL SCIENCE DATA SERVICES

Harald Hårfagres gate 29
N-5007 Bergen
Norway
Tel: +47-55 58 21 17
Fax: +47-55 58 96 50
nsd@nsd.uib.no
www.nsd.uib.no
Org.nr. 985 321 884

Mette Brekke
Institutt for helse og samfunn
Universitetet i Oslo
Postboks 1130 Blindern
0318 OSLO

Vår dato: 24.02.2011 Vår ref: 26399 / 3 / LT Deres dato: Deres ref:

KVITTERING PÅ MELDING OM BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 14.02.2011. Meldingen gjelder prosjektet:

26399	*Kriterier for potensielt uhensiktsmessig medikamentbruk i sykehjem - en modifisert Delphi-studie*
Behandlingsansvarlig	*Universitetet i Oslo, ved institusjonens øverste leder*
Daglig ansvarlig	*Mette Brekke*

Personvernombudet har vurdert prosjektet og finner at behandlingen av personopplysninger er meldepliktig i henhold til personopplysningsloven § 31. Behandlingen tilfredsstiller kravene i personopplysningsloven.

Personvernombudets vurdering forutsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldeskjemaet, korrespondanse med ombudet, eventuelle kommentarer samt personopplysningsloven/-helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.

Det gjøres oppmerksom på at det skal gis ny melding dersom behandlingen endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering. Endringsmeldinger gis via et eget skjema, http://www.nsd.uib.no/personvern/forsk_stud/skjema.html. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet.

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database, http://www.nsd.uib.no/personvern/prosjektoversikt.jsp.

Personvernombudet vil ved prosjektets avslutning, 30.06.2012, rette en henvendelse angående status for behandlingen av personopplysninger.

Vennlig hilsen

Bjørn Henrichsen

Lis Tenold

Kontaktperson: Lis Tenold tlf: 55 58 33 77
Vedlegg: Prosjektvurdering

Personvernombudet for forskning

Prosjektvurdering - Kommentar

Prosjektnr: 26399

Det gis skriftlig informasjon og samtykke for deltakelse er ensbetydende med returnering av skjema. Personvernombudet finner skrivet mottatt 24.02.2011 tilfredsstillende.

Innsamlete opplysninger anonymiseres ved prosjektslutt, senest 30.06.2012. Med anonymisering innebærer at navnelister slettes/makuleres, og ev. kategorisere eller slette indirekte personidentifiserbare opplysninger

UNIVERSITETET I OSLO

DET MEDISINSKE FAKULTET

Maria Romøren
Institutt for allmenn og samfunnsmedisin
Universitetet i Oslo
Pb 1130 Blindern
0318 Oslo

Regional komité for medisinsk og helsefaglig forskningsetikk Sør-Øst A (REK Sør-Øst A)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 22 84 46 66
Telefaks: 22 85 05 90
E-post: jorgen.hardang@medisin.uio.no
Nettadresse: http://helseforskning.etikkom.no

Dato: 13.11.09
Deres ref.:
Vår ref.: 2009/1584a-1

2009/1584 Intravenøs behandling i sykehjem

Prosjektleder	: Førsteamanuensis Maria Romøren
Vitenskapelig tittel	: MD PhD
Arbeidssted	: Institutt for allmenn og samfunnsmedisin, UiO
Forskningsansvarlig	: Universitetet i Oslo

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional forskningsetisk komité for medisinsk og helsefaglig forskningsetikk i møtet 19. oktober 2009. Søknaden er vurdert i henhold til lov av 20. juni 2008 nr. 44, om medisinsk og helsefaglig forskning (helseforskningsloven) kapittel 3, med tilhørende forskrift om organisering av medisinsk og helsefaglig forskning av 1. juli 2009 nr 0955.

I sin behandling knyttet komiteen flere merknader til søknaden. Vedtaksbrev med merknader ble sendt ut til prosjektleder 4.11.2009. Svar på merknader ble mottatt 8.11.2009. Komiteen anser svar på merknader som tilfredsstillende slik de er forelagt i tilbakemeldingen fra søker.

Ad spørsmål nr 2 og 3; *vedrørende tillatelse til å innhente eller ta i bruk opplysninger fra henholdsvis pasientgruppen som står på peroral antibiotika og den gruppen pasienter som får intravenøs behandling med antibiotika, men som ikke deltar i studien.*

Komiteen registrerer at opplysninger om de to forannevnte grupper av pasienter skal inngå i prosjektet som anonymiserte data. Helseopplysninger kan utleveres når "individualiserende kjennetegn er fjernet", det vil si når de ikke lenger kan føres tilbake til enkeltpersoner, jfr. helsepersonelloven § 23 nr. 3. Anonymisering av opplysninger er således et eget rettsgrunnlag for å gå inn i pasientjournaler. Det er alminnelig antatt at forskningsformål ikke er uforenlig med det opprinnelige formålet for innsamlingen av personopplysninger, jfr. personopplysningsloven § 11 annet ledd, der dette fremgår.

Forskning (og undervisning) er en del av helsetjenestens oppgaver, jfr. lov om spesialisthelsetjenesten § 3-8. Bruk til undervisning og forskning faller derfor inn under formålet med opplysningene. En som allerede er kjent med opplysningene kan anonymisere disse, jf. helsepersonelloven § 23 nr. 1, og deretter utlevere de anonyme opplysningene til forskning, jfr. helsepersonelloven § 23 nr. 3.

Helsepersonell som omfattes av helsepersonelloven eller representanter for disse (databehandlerpersonell), jfr. helseregisterloven § 13, har etter dette "særskilt hjemmel i lov", og kan tilrettelegge helseopplysninger for forskning. Det vil si foreta anonymisering eller uttrekk av opplysninger som omfattes av samtykket eller dispensasjonen.

Dispensasjon fra taushetsplikt er ikke nødvendig i dette tilfellet, da opplysningene som skal brukes fra de to aktuelle pasientgruppene det ikke er innhentet samtykke fra er bearbeidet og er anonyme på forskers hånd.

Komiteen mener søker gir en tilfredsstillende begrunnelse i sitt svar på spørsmålene, og gir med dette tillatelse til benytte anonymiserte opplysninger for de to nevnte pasientgruppene uten at det innhentes samtykke.

Vedtak

Komiteen har vurdert søknaden med ovennevnte tillegg og godkjenner prosjektet med hjemmel i helseforskningsloven § 10, jfr. forskningsetikkloven § 4.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, med tilleggssvaret på merknader til opprinnelig søknad og de bestemmelser som følger av helseforskningsloven med forskrifter.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i soknaden, må prosjektleder sende endringsmelding til REK. Vi gjor oppmerksom på at hvis endringene er "vesentlige", må prosjektleder sende ny soknad, eller REK kan pålegge at det sendes ny soknad.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og **omsorgssektoren».**

Tillatelsen gjelder til 31.12.2012. Opplysningene skal deretter slettes eller anonymiseres, senest innen 31.12.2017.

Prosjektet skal sende sluttmelding, se helseforskningsloven § 12, senest 1.6.2013.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jfr. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK REK Sør-Øst A. Klagefristen er tre uker fra mottak av dette brevet, jfr. forvaltningsloven § 29.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no

Vennligst oppgi vårt saksnummer/referansenummer i korrespondansen.

Med vennlig hilsen

Gunnar Nicolaysen (sign.)
Professor
Leder

Øyvind Grønlie Olsen
Fungerende komitésekretær