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PROTOCOL FOR A MULTICENTRE, LONGITUDINAL, SINGLE ARM STUDY EVALUATING AN ALGORITHM FOR DEPRESCRIBING STATINS AND PROTON PUMP INHIBITORS IN NURSING HOME RESIDENTS

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ABSTRACT

Introduction: A range of adverse events, including drug interactions, unplanned hospitalisation and increased all-cause mortality, may occur in frail old people due to polypharmacy. Deprescribing using an evidence-based patient-centred implicit deprescribing algorithm might reduce unnecessary polypharmacy. However, the effectiveness of such an implicit deprescribing algorithm to reduce potentially inappropriate medication has not been proven so far. This article describes the protocol of a study, aiming to determine the effect and feasibility of an implicit deprescribing algorithm to cease potentially inappropriate medication (statins and PPIs) for nursing home residents. **Method**: The study is a multicentre, longitudinal, single arm study. The aim is to include 125 nursing home residents using a statin and/or Proton pump inhibitor. People in a hospice, geriatric rehabilitation or short-stay unit will be excluded. All participants will receive the deprescribing intervention from their nursing home physician. The primary outcome will be the percentage of patients whose medication has been successfully deprescribed three months (T1) after the intervention. Secondary outcomes include sustainable deprescribing six months (T2) after the intervention, and all possible adverse events after deprescribing. Another secondary outcome measure is related to the feasibility of performing the intervention for physicians and involves the answer on the question "Is deprescribing". **Ethics and dissemination**: Ethical approval was obtained from the Zuyderland Human Research Ethics Committee. This study will enable an improved understanding of the feasibitity of deprescribing statins and PPIs in nursing home residents by using an implicit deprescribing algorithm. **Trial registration number**: NCT04204590

KEYWORDS: Deprescribing, nursing home residents, polypharmacy.

INTRODUCTION

A range of adverse events, including drug interactions, unplanned hospitalisation and increased all-cause mortality, may occur in frail old people, at least partly due to polypharmacy.[1] The prevalence of chronic diseases increases with age, and this enhances the number of medicines older people usually use.[2] This so-called polypharmacy often leads to inappropriate medication use.[3] Moreover, at higher age, medication is often less effective, with more side effects and drug interactions, increasing the risk of side effects and complications.[4,5] Nursing home residents represent an example of a target group of in general very frail and disabled old persons, extra vulnerable for negative consequences of polypharmacy and needing attention with regard to preserving patient safety.

A possible solution for reducing inappropriate polypharmacy is called "deprescribing": a planned and supervised process of dose reduction or stopping of medication that might be causing harm, or no longer be of benefit.[6] Garfinkel's prospective cohort study in nursing homes proved that the number of hospital admissions and 1-year mortality decreased significantly after using a deprescribing tool.[1] In another study Garfinkel et al. showed that sustainable deprescribing succeeded in 83% of the geriatric study population.[7] Several other studies in frail old people showed significantly improved health outcomes, reduced pill burden and decreased mortality.[8,9] Nevertheless, it has been difficult for physicians to sustainably stop potentially inappropriate medication, mainly because guidelines often describe when to start medication and not when to stop.[10]

On the one hand, studies focus on deprescribing tools based upon explicit criteria.[11,12] These tools detect the use of potentially inappropriate medication and they are user friendly, but they represent a rigid system with closed questions and answers that often do not fit well within the personalized care that is being pursued in nursing homes.

On the other hand, deprescribing tools based on implicit criteria (such as pill burden, fatigue or increased fall risk), may fit better within offering personalized care for nursing home residents, but these tools are sparse and the underlying evidence is still lacking.[14]

Therefore, there is a demand for a more general deprescribing strategy, to support physicians to deprescribe unnecessary medicines.[13] We developed an evidence-based patient-centred implicit deprescribing algorithm for physicians working in nursing homes, which provides a systematic approach to review current medication, to identify potentially inappropriate medicines, to plan a deprescribing regimen, to create partnership with patient and family and to monitor the sustainability of the deprescribing process.[15] This algorithm is suitable for all kinds of medicine, not for one specific medication group. However, the effectiveness of this implicit deprescribing algorithm to reduce potentially inappropriate medication has not been proven yet.

The current study will focus on its use in deprescribing statins and proton pump inhibitors(PPI) only, because they are widely and not always appropriately used in nursing homes. This protocol article outlines this study in which we aim to determine the effect and feasibility of an implicit deprescribing algorithm to cease potentially inappropriate medication (statins and PPIs) for nursing home residents.

METHODS AND ANALYSIS

Study design. In this multicentre, longitudinal, single arm study all included nursing home residents will receive the same deprescribing intervention within six weeks after inclusion and baseline data collection. The study will take place in ten nursing homes and is monitored by the Clinical Trial Center Maastricht (CTCM) to guarantee high quality data control. The study's trial registration number is NCT04204590 (*ClinicalTrials.gov*).

Participants. (1) All residents of nursing home long-stay wards of care home organisation Zuyderland Elderly Care, with or without dementia (staying in respectively somatic and psychogeriatric wards), using a statin and/or a PPI are eligible to participate. We aim to include 125 participants. Nursing home residents in hospices, geriatric rehabilitation or short-stay wards (expected stay is less than three months) will be excluded. Residents may also be excluded for any other reason at the discretion of their regular treating physician or legal representative. (2) All physicians working at Zuyderland Ouderenzorg (specialised nursing home physicians and physicians without this specialisation) are able to participate. The physicians willing to contribute in this study and to follow the introduction program (about informed consent, the algorithm and data collection) will be included.

Recruitment and consent process of nursing home physicians. All participating nursing home physicians will be trained in the informed consent process, to use the implicit deprescribing algorithm and how to collect data.

Recruitment and consent process of residents. The inclusion period for residents will be six months. Participating physicians will obtain a list of their residents using a statin and/or a PPI, and will inform patients and their legal representative and seek written informed consent to participate in this deprescribing study. The process will be performed in accordance with the ethical principles for involving vulnerable elderly in research studies outlined in Ephor.[16] The study will be conducted according to the international standards of the Declaration of Helsinki and subsequent amendments.[17] Ethical approval has been obtained from the Medical Ethical Committee of Zuyderland and Zuyd University of Applied Science (METC-Z). For nursing home residents who have the capacity to provide consent to participate, written consent will be obtained directly from themselves. If the resident is unable to provide written consent to participate, consent will be sought from the person's legal representative.

Baseline data collection. For each resident, data will be collected out of the resident's files at baseline, at three months and six months after the deprescribing intervention. Table 1 shows which data will be collected. The data involve: demographic data (including gender and age), main diagnosis underlying reason for admission to the nursing home and which ward (somatic or psychogeriatric department), medication used (including total number of medicines, defined daily dose (DDD) and indication for starting statins and/or PPIs), hospital admissions and reasons for hospital admission.

For each nursing home physician, data will be collected at three months (T1) and six months (T2) after the deprescribing intervention. We will ask the nursing home physicians for each of their participating patients whether deprescribing was sustainably successful and if not, why it was not successful.

Table 1: Data collected in participating nursing home residents.

Baseline (T0)	3 months after intervention (T1)	6 months after intervention (T2)
Gender (M/V), Age	Was deprescribing possible? If not, why?	Was deprescribing possible and/or sustained? If not, why?
Ward (somatic/psychogeriatric), main diagnosis underlying reason for admission to nursing home	Recurrence of symptoms, hospital admission and reason for hospital admission	Recurrence of symptoms, hospital admission and reason for hospital admission
Total number of medicines	Total number of medicines	Total number of medicines
Statin use (defined daily dose), indication	Statin use (defined daily dose)	Statin use (defined daily dose)
PPI use (defined daily dose), indication	PPI use (defined daily dose)	PPI use (defined daily dose)

Intervention The deprescribing intervention will take place during a regular medication review by the nursing home physician, which takes place every six weeks. The intervention consists of 5 steps, including: 1) reviewing the current medication, 2) identifying potentially inappropriate medication, 3) planning a deprescribing regimen, 4) creating partnership with patient and family and 5) monitoring the sustainability of the deprescribing process. For more detailed information about this intervention, see Visser et al.[15] The implicit deprescribing algorithm is shown in figure 1.[15]

These five steps help the physician to identify potentially inappropriate use of statins and/or PPIs. After identification, this medication will not be deprescribed immediately. The participant's physician will discuss this thoroughly with the participant or his/her legal representative, before deprescribing takes place. Residents will remain eligible for all usual care services during the study period.

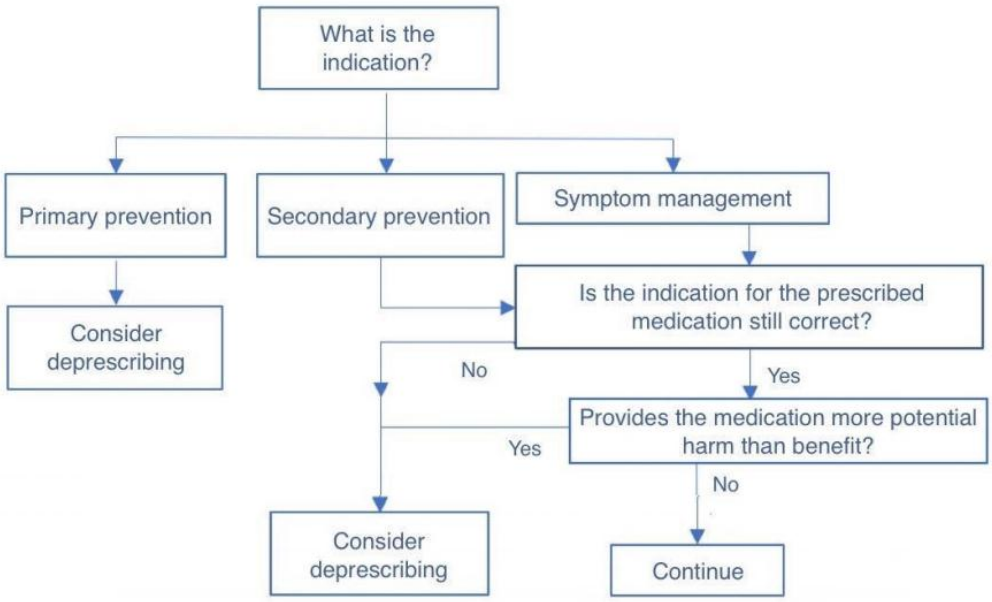

Figure 1: Algorithm for identifying potentially incorrect medication. From: Visser et al, WJPLS 2019; 5 (10): 10-17.

Outcome measures. To find out whether deprescribing of statins and/or PPIs is possible with this implicit algorithm, the primary outcome will be the percentage of patients whose medication has been successfully deprescribed three months (T1) after the intervention. Deprescribing is successful in case of stopping or a decrease in daily dose of statins and/or PPI. The following secondary outcomes will be assessed:

1. All possible adverse events after deprescribing, reported as harms due to for instance recurring, worsening or new onset of original symptoms.
2. The success rate of deprescribing after six months (T2): has the deprescribed medication still been ceased and is deprescribing sustainable?

The last outcome measure is related to the physicians: After three and six months, the physician will answer for every participant whether deprescribing was successful and if not, why?

Sample size. To assess the effect of the deprescribing intervention, we will aim to recruit a sample of 125 participants. Evidence from previous studies suggests

that in 65% of patients using a PPI and 90% of patients using a statin, physicians can safely deprescribe this medication.[18] Assuming a significance level of 5% and a deprescribing success rate of 50% (conservative estimate), at least 97 participants are required to be able to estimate this success rate with enough precision (margin of error of 10%).

Nursing home studies are associated with a high loss to follow up because of death. Therefore, we expect a loss to follow up of approximately 20% at T2. To ensure enough participants at T2, we aim to recruit a sample size of 125 participants.

Data analysis. Numerical variables will be presented as mean with standard deviation or median with interquartile range where appropriate, while number and percentage of participants will be used for categorical variables. The proportion of participants in which medication successfully has been deprescribed will be assessed together with a 95% confidence interval at 3 months after intervention. The difference in participant characteristics between participants who successfully deprescribed versus those who did not, will be compared using independent-samples t-test or Mann Whitney U-test for numerical variables and chi-square or Fisher's exact test for categorical variables. For statins and PPI separately, the longitudinal trend in daily dose will be assessed using a linear mixed model, with an unstructured covariance structure for repeated measures and a random intercept on nursing home level to account for potential correlation between participants within the same nursing home. In addition, a mixed model analysis accounts for drop-out using a likelihood-based method, assuming missing at random (MAR), i.e. missingness may depend on observed variables. All analyses will be performed using SPSS Statistics for Windows (version 26.0, Armonk, N.Y., USA, IBM Corp.). A two-sided p-value ≤ 0.05 will be considered statistically significant.

Data management Participants will be assigned a unique code to enable data linkage throughout follow up. All data will be entered into an electronic management system by research team members who are trained in data entry. To ensure accurate data entry, CTCM will check data entry for all participants. Data collection and study conduct will be monitored two-weekly with the research team to ensure protocols are implemented consistently. Data collected as part of this study will be treated confidentially and stored securely at Research Manager. Two nursing home physicians will have access to the final dataset.

DISCUSSION

This study will determine the effect, safety and feasibility of a deprescribing intervention using an implicit algorithm to deprescribe potentially inappropriate statins and/or PPIs in nursing home residents. Deprescribing has the potential to improve clinical outcomes, but there is a lack of safety and success rate evidence to support most methods to conduct deprescribing.[18] In the nursing home population, it is difficult to conduct a RCT: Recruiting is tough: nursing home residents often are in the last years of their lives and are more reluctant to join an intervention study. And to reduce any risk of complications, legal representatives often prevent their clients from participating as well. Also, there is a high loss to follow up due to residents who die during the study period. That is what makes it difficult to include enough participants in nursing home research to ensure enough power.[19] Therefore, the design of a longitudinal, single arm study has been chosen, taking into account its limitations.

In this study, we only focus on the deprescribing of statins and PPIs in Dutch nursing home residents. Therefore, the study findings may not be generalizable to all medicines and/or residents of nursing homes in other countries. We further acknowledge that there may be practical difficulties in using the algorithm, such as obtaining a comprehensive and complete medical history. In addition, the deprescribing intervention might be time-consuming in older individuals with polypharmacy and multiple comorbidities. Nevertheless, we do not think this will limit our findings.

Overall, this study will provide important information and insight in the possibility and safety to (sustainably) deprescribe potentially inappropriate statins and PPIs in nursing home residents and also in the feasibility of the chosen intervention. The findings may therefore be useful for all nursing home residents and their physicians.

REFERENCES

1. Garfinkel D, Mangin D. Feasibility Study of a systematic approach for discontinuation of multiple medications in older adults; Archives of Intern Medicine, oct 11-2010; 170(18): 1648-1654.
2. Jyrkkä J, Enlund H. Polypharmacy status as an indicator of mortality in an elderly population. Drugs Aging, 2009; 26(12): 1039-48.
3. Huizer-Pajkos A, Kane AE, Howlett SE, Mach J, Mitchell SJ, Cabo R de, et al. Adverse geriatric outcomes secondary to polypharmacy: the influence of aging. J Gerontol. Series A: Biol. Sci. Med. Sci., 2015; 4-6.
4. Schenker V, Park S, Jeong K, et al. Associations between polypharmacy, symptom burden and quality of life in patients with advanced, life limiting illness. J Gen Intern Med, 2019; 34: 559–66.
5. Poudel A, Hubbard RE, Nissen L, Mitchell C. Frailty: A key indicator to minimize inappropriate medication in older people. QJM, 2013; 106: 969-975.
6. Thompson W, Farrell B. Deprescribing: What is it and what does the evidence tell us? Can J Hosp Pharm, 2013; 66(3): 201-202.

7. Garfinkel D, Ilhan B, Bahat G. Routine deprescribing of chronic medications to combat polypharmacy. Ther. Adv. Drug Saf., 2015; 6: 212-233.
8. Gnjidic D, Hilmer SN, Blyth FM, Naganathan V, Waite L, Seibel MJ, et al. Polypharmacy cutoff and outcomes: Five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J. Clin. Epidemiol., 2012; 65: 989-995.
9. Jamsen KM, Bell JS, Hilmer SN, Kirkpatrick CMJ, Ilomäki J, LeCouteur D, et al. Effects of changes in number of medications and drug burden index exposure on transitions between frailty states and death: The concord health and ageing in men project cohort study. J. Am. Geriatr. Soc., 2016; 64: 89-95.
10. Todd A, Holmes H. Recommendations to support deprescribing medications late in life. Int J Clin Pharm, 2015; 37: 678–81.
11. American Geriatrics Society Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc, 2019; 67: 674-694.
12. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age and ageing*, 2015; *44*(2): 213–218.
13. Farrell B, Richardson L, et al. Self-efficacy for deprescribing: a survey for health care professionals using evidence-based deprescribing guidelines. Res Social Adm. Pharm., Jan, 2018; 14(1): 18-25.
14. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Review of deprescribing processes and development of an evidence-based, patient-centred deprescribing process. British journal of clinical pharmacology, 2014; 78(4): 738–747.
15. Visser A, Schols J, Janknegt R, Prevoo M. Deprescribing in nursing home residents: an implicit algorithm. WJPLS, 2019; 5(10): 10-17
16. Ephor Leidraad voor medisch wetenschappelijk onderzoek bij ouderen. https://ephor.nl/wp-content/uploads/2018/12/leidraad-medisch-wetenschappelijk-onderzoek-bij-ouderen-2017.pdf, 2017.
17. World Medical Association "Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects". JAMA, 2013; 310(20): 2191–2194.
18. Page AT, Clifford RM, Potter K, Schwartz D, Etherton-Beer CD. The feasibility and the effect of deprescribing in older adults on mortality and health: A systematic review. British J. Clin. Pharmacol, 2016.
19. Knechel N. A. The challenges of enrolling older adults into intervention studies. The Yale journal of biology and medicine, 2013; 86(1): 41–47.