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Exploring the impact of innovative deprescribing and medication review service on quality of care and morbidity/mortality of older patients with polypharmacy and multiple comorbidities in Italian hospital and long-term care facilities settings: a cluster randomized clinical trial

UO coinvolte

Nome	UO	Ruolo	Partecipanti
Regione Veneto/AOUI Verona	UO1	Capofila – sviluppo servizio deprescribing e arruolamento pazienti geriatria e medicina interna e in partnership con Uni Bicocca coinvolgimento rete di RSA affiliate a KOS	Gianluca Trifirò – PI Mauro Zamboni – Co-PI Elena Zoico Salvatore Crisafulli – to hire Nicoletta Luxi – to hire
Regione Campania/Azienda Ospedaliera Universitaria Vanvitelli	UO2	Sviluppo servizio deprescribing e arruolamento pazienti geriatria	Annalisa Capuano Rosanna Ruggiero – to hire
Friuli Venezia Giulia/ Azienda Ospedaliera di Udine	UO3	Sviluppo servizio deprescribing e coinvolgimento in RCT con RSA/case di cura ASFO	Jacopo Angelini – under40
Regione Sicilia/ARNAS Civico -Palermo	UO4	Arruolamento pazienti medicina interna	Salvatore Corrao Luigi Mirarchi – under 40 Salvatore Scibetta – to hire
IRCCS Mario Negri	UO5 autofinanziamento	Sviluppo servizio deprescribing per RSA	Luca Pasina

Progetto di 24 mesi – budget richiesto: 950.000 euro

Abstract

The aging process is associated with an increased probability of accumulating chronic conditions and geriatric syndromes, leading to a growing prevalence of multimorbidity. One of the most frequent consequences of multimorbidity, especially amongst older adults, is polypharmacy, a condition characterized by the concomitant use of five or more drugs per day. Polypharmacy is one of the main risk factors for adverse clinical outcomes, such as drug-drug interactions (DDIs), adverse drug reactions (ADRs), and hospitalizations. Preventive strategies, such as deprescribing and medication review services, can help optimize medication use and improve health outcomes. Deprescribing, defined as the stopping or dose reduction of medications that are either inappropriate or unnecessary, and medication review, which is the process of reviewing patients' therapies based on their clinical conditions, are two potential approaches to optimize medicines use and improve patients' health outcomes. Polypharmacy and related consequences emphasize the importance of tailoring these interventions to the specific needs and challenges of different care settings. Evidence gaps concerning deprescribing and medication review interventions efficacy and their impact on patient's health highlight the importance of conducting large-scale studies to assess the clinical and economic impact of such services in both hospital and long-term care facility settings. These studies are crucial for generating robust evidence and informing best practices in optimizing medication use and improving patient outcomes.

This research project aims at evaluating the impact of innovative, multidisciplinary and evidence-based deprescribing and Medication Review Services on the quality of care and clinical outcomes among elderly patients in both hospital and long-term care facility settings. The project will be structured into three different and inter-related activities as itemized below.

First, a comprehensive systematic literature review of experimental and observational studies that evaluated deprescribing and medication review interventions among elderly patients in hospitals and long-term care setting will be conducted. The objective of this task will be to identify the most effective tools and strategies for implementing these services in the abovementioned settings, also integrated with the expertise and previous experience about this approach of the Project's Consortium. As final output, a setting-specific and multidisciplinary deprescribing and medication review service will be newly developed and tested in randomized clinical trials in different settings, as described below.

Second, a stepped-wedge cluster RCT in hospital setting will be carried out. Elderly patients regularly taking five or more medications will be enrolled. The intervention will consist of a multidisciplinary team-led deprescribing and medication review process. The impact on clinical outcomes, such as reducing ADRs, potentially inappropriate medication (PIM) prescriptions, re-hospitalizations, and mortality, as well as the patients' quality of life, will be evaluated.

Third, in parallel, a similar stepped-wedge cluster RCT in long-term care facilities will be carried out. Patients will be recruited from nursing homes, and the multidisciplinary deprescribing and medication review process will be adapted to that setting as needed. The impact on clinical outcomes and quality of life will be evaluated as above.

Overall Summary

Aging is linked to multimorbidity and polypharmacy, increasing the risk of negative outcomes. Strategies like deprescribing and medication review services can optimize medication use and improve health outcomes. Large-scale studies are needed to evaluate the clinical and economic impact of these services in hospitals and long-term care facilities.

This research project aims to assess the impact of these services on the quality of care and clinical outcomes for elderly patients in the abovementioned settings. This will generate robust evidence and inform best practices in optimizing medication use. The project will include a comprehensive systematic literature review, to identify the most effective tools and strategies for implementing these services, and two stepped-wedge cluster RCT in both settings, with the purpose to evaluate the impact on clinical outcome, such as reducing ADRs, PIMs, and hospitalizations, as well as the patients' quality of life and related economic consequences.

Background/State of the art and Preliminary data (if available)

Senescence is associated with an increased probability of accumulating chronic conditions, thereby leading to a surging prevalence of multimorbidity, which is defined as the coexistence of at least two chronic conditions The presence of multimorbidity frequently results in polypharmacy, posing a significant risk of inappropriate prescribing practices. Consequently, the occurrence of adverse clinical consequences such as drug-drug interactions (DDIs) and adverse drug reactions (ADRs) is amplified, subsequently leading to higher morbidity, hospitalizations, and mortality rates.

Within the hospital setting, it has been reported that ADR-related hospitalizations of geriatric patients varied from 5% to 46%, with a mean prevalence of 11%. In any case, hospital admission requires a comprehensive therapy reassessment, particularly for hospitalized frail older patients, wherein deprescribing interventions are generally considered safe and were proved to be effective in reducing potentially inappropriate medications (PIM).

In long-term care facilities, the risk of ADRs is further heightened, primarily due to the prevalent use of PIMs, which exceeds a 40% prevalence rate. A systematic review evaluating the impact of deprescribing interventions on clinical outcomes found that deprescribing successfully reduced the number of nursing home residents with PIMs by 59%, thereby reducing the risk of ADRs and reasonably improving overall clinical health outcomes.

Description and distribution of activities of each operating unit

Hypothesis and specific aims

- **Specific Aim 1**: As a first step, during the first six months of the Project, a comprehensive systematic literature review will be conducted to identify all randomized controlled trials (RCTs) and prospective cohort studies that described and evaluated the impact of various deprescribing and medication review interventions in the hospital and/or long-term care facilities settings. The main aim will be to identify and elucidate the most effective tools and strategies used to implement deprescribing and medication review services in the two aforementioned settings. This endeavor will provide valuable insights for organizing the Deprescribing and Medication Review Service, also taking into account previous expertise and experience of the Project's Consortium. The impact of such a service on both clinical and economic outcomes will be evaluated by carrying out two different RCTs (**Specific Aims 2** and **3**). If possible, a meta-analysis summarizing the global impact of these services on both clinical (e.g., hospitalizations, PIMs prescriptions, ADRs and quality of life) and economic (e.g., cost savings resulting from the discontinuation of PIMs, the prevention of ADRs, and reductions hospitalizations) outcomes will be conducted. This systematic review and meta-analysis will be carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Potentially relevant articles will be searched in three different bibliographic databases, including PubMed, Embase and Web of Science. These databases will be searched for terms related to deprescribing, medication review, elderly patients and the specific settings (i.e., hospital and long-term care facilities). Only RCTs and prospective cohort studies written in English and describing the methodologies of deprescribing and medication review interventions in hospitalized or long-term care facilities resident elderly patients (age ≥65 years) will be included. For each of the studies included in the systematic review the following information will be extracted: author(s) and year of publication, study design, type of healthcare professionals

involved and its role, setting and country, number of participants enrolled (age and gender), description of the intervention, deprescribing algorithms and tools, medication commonly stopped or reduced, comparator (if any), study follow up, outcome measures and results.
This systematic review and meta-analysis will be conducted by the operating units of the AOUI Verona, the University of Udine, the AOU "Luigi Vanvitelli" and the IRCCS "Mario Negri". These Units have been already involved in deprescribing and medication review activities in different settings. Evidence from systematic review, in combination with the expertise of these Operating Units, will allow to develop an innovative and setting-specific deprescribing and medication review services for the comprehensive assessment of the polypharmacy received by older people in different settings. IRCCS "Mario Negri" developed Intercheck-web, which is one of the tools that will be considered for the Deprescribing and Medication Review service.

— **Specific Aim 2**: To perform a stepped-wedge cluster RCT to evaluate the impact of innovative Deprescribing and Medication Review Services on the quality of care and clinical outcomes among hospitalized elderly patients (i.e., aged ≥ 65 years) who are regularly taking 5 or more different medications daily. During the initial three months of the Project, the study protocol for this RCT will be presented to the AOUI Verona Ethics Committee for approval. It is likely that by this time, valuable insights pertaining to the methodology of deprescribing and medication review will have already been obtained from the systematic review.
After completing systematic review and development of the best fit for use tools/strategies for deprescribing and medication review services, during the following 9 months (that is from month 6 to month 15), patients admitted to the Internal Medicine and Geriatric Units of the AOUI Verona, AOU "Luigi Vanvitelli" and the ARNAS Civico Hospital or accessing the ambulatories for outpatients affiliated to these Units who will provide informed consent and will have inclusion criteria as specified in the study protocol will be recruited in the RCT. Overall, around 400 older people that are monthly admitted to the above mentioned hospitals and ambulatories could be recruited. Readmitted patients will be considered eligible only if they have not been previously enrolled in the study. Patients who are not competent to provide informed consent and/or whose caregivers do not agree to their participation in the study, and patients in the final terminal stages of cancer or other serious disease will be excluded from this study. During the control period, patients will receive usual care, with medication reconciliation at hospital admission and discharge, as normally carried out. The order of entry into the intervention will be determined centrally by a randomized sequence generated by statistical software. The deprescribing and medication review services will be led by a multidisciplinary team including physicians taking care of the patients, clinical pharmacologists, and other health professionals, such as hospital pharmacists and nurses. The intervention of deprescribing and medication review will consist of four different phases, including: (i) clinical evaluation of the patient at hospital admission, with a comprehensive clinical and pharmacological anamnesis; (ii) the evaluation of the appropriateness of the prescribed drug therapies using validated tools (e.g., INTERCheck Web). In particular, this evaluation will be performed before discharge, once the patient is clinically stable. The following critical elements will be assessed: the risk of DDIs, the risk of ADRs, the presence of potential prescribing cascades, and the use of PIMs; (iii) discussion and sharing of treatment choices with the patient/caregiver; (iv) monitoring the impact of deprescribing process and medication review: at this stage, the patient's adherence to the medical therapy, the possible occurrence of symptoms associated with the change in medical therapy, and the discontinuation/switch of medications independently or based on the prescription from other physicians will be assessed. In particular, the efficacy of deprescribing and medication review interventions in reducing the incidence rate of ADRs, PIMs prescriptions and re-hospitalizations as well as the mortality rate among elderly patients during the follow-up periods (i.e., at 30, 60 and 180 days after discharge) will be evaluated. The impact on patients' quality of life

will be also evaluated using the EQ-5D-5L questionnaire. Furthermore, the maintenance of the revised medical therapy during the follow-up periods will be evaluated.

Specific Aim 3: To perform a stepped-wedge cluster RCT to evaluate the impact of innovative Deprescribing and Medication Review Services on the quality of care and clinical outcomes among elderly patients in long-term care facilities. This RCT will be conducted by the operating units of the AOUI Verona, the University of Udine and the IRCCS "Mario Negri". The study protocol of this RCT will be submitted to the Ethics Committee of the AOUI Verona for approval during the first three months of the Project.
Patients will be enrolled from a network of nursing homes and long-term care facilities, including those being part of KOS and 22 nursing homes affiliated with the Azienda Sanitaria Friuli Orientale (ASFO) : a) KOS may enroll up to 31 nursing homes from 4 Regions – the involvement of KOS in the project will be allowed through an agreement between University of Bicocca (Giampiero Mazzaglia and Chiara Monti from Hygiene Department) and AOUI VR as University of Bicocca has already in place a scientific collaboration with KOS. ASFO (which will have as main collaborator Barbara Basso, the chief of pharmaceutical Department) has already an agreement with AOUI Verona as being part of the postgraduation school of clinical pharmacology and toxicology network.
Patients who are not competent to provide informed consent and/or whose caregivers do not agree to their participation in the study, and patients in the final terminal stages of cancer or other serious disease will be excluded from this study.
During the control period, patients will receive usual care. The order of entry into the intervention will be determined centrally by a randomized sequence generated by statistical software. The deprescribing and medication review services will be led by a multidisciplinary team including physicians taking care of the patients, clinical pharmacologists, and other health professionals, such as nurses. The intervention of deprescribing and medication review will consist of four different phases, including: (i) clinical evaluation of the patient, with a comprehensive clinical and pharmacological anamnesis; (ii) the evaluation of the appropriateness of the prescribed drug therapies using validated tools. In particular, the following critical elements will be assessed: the risk of DDIs, the risk of ADRs, the presence of potential prescribing cascades, and the use of PIMs; (iii) discussion and sharing of treatment choices with the patient/caregiver; (iv) monitoring the impact of deprescribing process and medication review: at this stage, the patient's adherence to the medical therapy, the possible occurrence of symptoms associated with the change in medical therapy, and the discontinuation/switch of medications independently or based on the prescription from other physicians will be assessed. In particular, the efficacy of deprescribing and medication review interventions in reducing the incidence rate of ADRs, PIMs prescriptions and hospitalizations as well as the mortality rate among elderly patients during the follow-up periods (i.e., at 30, 60 and 180 days after the intervention) will be evaluated. The impact on patients' quality of life will be also evaluated using the EQ-5D-5L questionnaire. Furthermore, the maintenance of the revised medical therapy during the follow-up periods will be evaluated.

— **Hypothesis and significance**: According to the latest National Report on Medicines use in Italy report, about 67% of the elderly (i.e., patients aged 65 years or more) in Italy are on polypharmacy, and approximately a quarter of them takes more than ten different medications daily. In addition to medicines, the high consumption of dietary supplements in this population should also be considered. Polypharmacy increases the risk of drug-drug interactions as well as of ADRs in all care settings, including the hospital and long-term care facilities settings. As such, it is associated with a high risk of hospitalization and adverse post discharge outcomes. According to a recent systematic review of observational studies, the proportion of preventable in-hospital ADRs accounted for 38% of the total cases, and these percentages rose in the elderly population, where preventable ADRs

exceeded 70%. Based on the same systematic review, the healthcare costs for preventable ADRs due to hospital admission or prolonged length of stay ranged from € 2.851 to € 9.015 per patient, with a mean prolonged length of hospital stay of 8.5 ± 4.2 days. An increasing body of evidence from all healthcare settings demonstrates that reducing the number of PIMs taken by the patient in turn reduces the risk of ADRs and related consequences (e.g., emergency department admissions, hospitalizations and prolonged hospital stay, healthcare costs). Given these premises, it is crucial to adopt preventive strategies that could help reduce potentially inappropriate prescriptions and the complexity of the daily therapeutic regimens. Deprescribing, defined as the stopping or dose reduction of medications that are either inappropriate or unnecessary, and medication review, which is the process of reviewing patients' therapies based on their clinical conditions, are two potential approaches to optimize medicines use and improve patients' health outcomes.

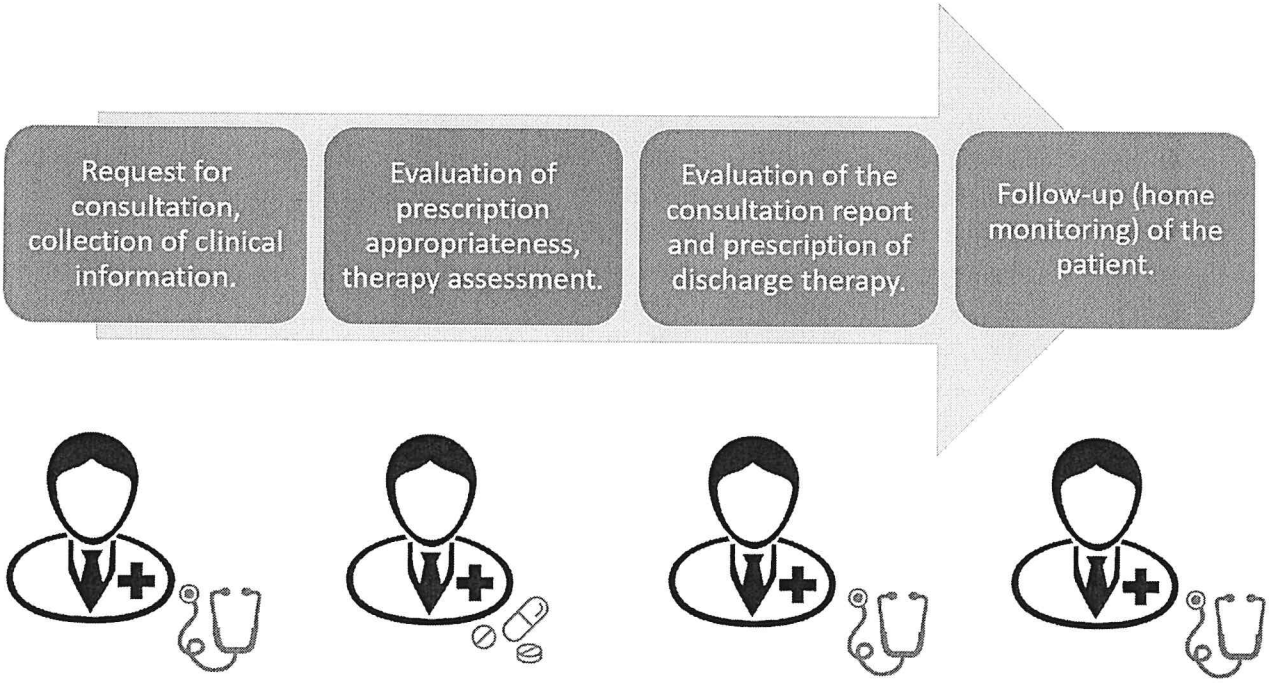
As such, the implementation of Deprescribing and Medication Review Services may allow to review and potentially reduce the number or dose of PIMs, in order to promote patients' adherence to appropriate medical therapies and, as a consequence, improve the quality of care, and reduce the financial burden associated with medication management. Considering the high prevalence of polypharmacy and multimorbidity among elderly patients, they are likely to benefit most from deprescribing and medication review interventions.

For it to be effective, it is essential that the implementation of deprescribing and medication review interventions take into account the specific needs and critical issues of different care settings.

For instance, in the long-term facilities setting, despite recommendations to limit the use of PIMs such as antipsychotics, benzodiazepines, antidepressants, proton pump inhibitors, or antiplatelet agents, the use of these drugs is widespread and often inappropriate, involving about 76% of residents. On the other hand, patients with limited life expectancy have peculiar needs for deprescribing. Although a number of studies suggested that deprescribing and medication review interventions are generally safe and effective, substantial evidence gaps still remain. Indeed, the majority of the interventions described in the literature were limited to specific drug classes or medical conditions, and only a few trials evaluated the efficacy of deprescribing and medication review services implementation in the hospital and long-term care facilities settings. As such, large-scale studies assessing the clinical and economic impact of systematic deprescribing and medication review services both in the hospital and long-term facilities settings are required.

Picture to support preliminary data:

Main tasks of the Deprescribing and Medication Review Service. In blue, the activities pertaining to the physician are reported, while in green, the activities pertaining to the clinical pharmacologist/pharmacists are reported. As the follow-up phase, other health professionals, such as nurses, may also provide useful contributions.



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Translational relevance and impact for the national health system (SSN)

- **What is already know about this topic?:** The aging process increases the likelihood of developing chronic conditions, leading to a higher prevalence of multimorbidity. This often results in polypharmacy and inappropriate prescribing, which can lead to adverse outcomes such as DDIs and ADRs, increased morbidity, hospitalizations, and mortality rates. On the one hand, it has been reported that ADRs-related hospitalizations in geriatric patients ranged from 5% to 46%, with a mean prevalence of 11%, thus suggesting the need of a comprehensive therapy reassessment for hospitalized patients, especially the frailer ones. On the other hand, medical therapy management is particularly challenging in long-term facilities. With PIMs' prevalence exceeding 40%, nursing homes residents are at higher risk of experiencing ADRs. It has been documented that deprescribing interventions in this setting allow to reduce PIMs by about 60%, thereby decreasing the risk of ADRs and improving overall clinical outcomes. Some international experiences of in-hospital and long-term facilities showed that the implementation of deprescribing and medication review interventions is generally safe and effective in reducing PIMs, but evidence regarding the impact on clinical and economic outcomes (i.e., risk of drug-drug interactions and ADRs, hospitalizations, increased length of hospital stay and mortality and related economic impact) is still sparse and controversial.

- **What this research adds?:** There is a need to provide further evidence, both nationally and internationally, concerning the efficacy and safety of deprescribing and medication review interventions in frail older patients in both hospital and long-term care facilities settings. In Italy, the implementation of deprescribing services is still in its early stages, and there are currently no officially recognized services available. Data generated from this project will provide to healthcare institutions robust evidence to support the clinical and economic benefits associated with the implementation of such services.

- **What are the implications for public health, clinical practice, patient care?:** The implementation of Deprescribing and Medication Review services presents a valuable opportunity to optimize patients' pharmacotherapy, improve the quality of care, and reduce the financial burden associated with medication management. Evidence from various healthcare settings suggests that systematically reviewing medical therapies (e.g., specific pharmacological recommendations including dosage adjustments or therapy alternatives suggestions) and reducing the number of PIMs taken by patients leads to a decrease in the risk of ADRs and their associated consequences. This includes a reduction in emergency department visits, hospitalizations, duration of hospital stays, and containment of healthcare costs.