Deprescribing: a portrait and out-comes of the reduction of Polypharmacy in Portugal (DePil17-20)

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ABSTRACT

Introduction: Polypharmacy is defined as the simultaneous taking of five or more drugs. Deprescribing can be defined as the withdrawal of potentially inappropriate medications under medical supervision and there are several tools that aid identifying this meditation in older adults. The direct involvement of patients and their caregivers in the choice and administration of drugs has long been known to be very important, but it isn't usually applied. The aim of this study is to assess the enablement of older adults while being deprescribed, the rise of willingness to be deprescribed and its quality of life outcome.

Methods and Analysis: This study protocol comprises three phases. The first two phases will be nationwide and aim to evaluate the prevalence and patterns of polypharmacy and assess the barriers and facilitators of deprescribing perceived by older adults, as well as their willingness to be deprescribed and to self-medicate. The third and last phase will be a non-pharmacological randomised clinical study to measure the impact of enablement of older adults in their willingness to be deprescribed and related quality of life.

Ethics and dissemination: The study will be conducted in accordance with the principles expressed in the Declaration of Helsinki. It has been submitted to approval from the Ethics Committee of University of Beira Interior, portuguese National Data Protection Commission and the Ethics Committee of all Health Region of Portugal. Study results will be published in peer-reviewed journals and presented at national and international conferences.

STRENGHTS AND LIMITATIONS OF THIS STUDY

- This will be the first study to assess prevalence and patterns of polypharmacy in older adults in Portugal and one of the first to assess the impact of deprescribing in quality of life of older adults in the world.
- The results will help clinicians to understand patient's perception regarding polypharmacy and deprescribing.
- The relatively small sample will be a methodological limitation because it won't allow getting so strong conclusions as if the sample was bigger, due to medical short adherence to such a kind of out of the box work.

INTRODUCTION

Polypharmacy is defined as the simultaneous taking of five or more drugs. It's present in 30-70% of older adults (1) and it's a significant predictor of the risk of falls (2) and other iatrogenic complications (3), inappropriate prescriptions (4), reduced patient's adherence (5), drug interactions (6), hospital admissions (7) and mortality (8). It is estimated that at least 75% of this adverse event is potentially preventable (9).

It is necessary to distinguish between appropriate and inappropriate medications (10), because as people get older the benefit/risk ratio of medications changes meaning that medications that were once appropriately prescribed may have become inappropriate (11). Potentially Inappropriate Medications (PIMs) are those for which the harms outweigh the benefits (12). Available data indicate that 20 to 65% of older adults are taking at least one PIM, leading to a high risk of adverse drug reactions, morbidity and mortality (13). There is a lot of information available to guide prescribers to start and maintain drug therapies that are safe and effective, but there is lack of knowledge concerning its reduction and/or withdrawal so maintaining safety and effectiveness (3, 8).

Deprescribing can be defined as the withdrawal of PIMs, under medical supervision, with the objective of managing the polypharmacy and improving health outcomes (14). However, it isn't risk's deprived, it can cause abstinence syndrome, rebound effects, pharmacokinetic/pharmacodynamic changes in the metabolism of not interrupted drugs and recurrence of symptoms that were in treatment by the withdrawn drug (1, 2).

So the decision to deprescribe results from a careful weighting between the therapeutic objectives and the risk/benefit ratio (15, 16).

Several deprescribing processes have been proposed in the literature (2, 17) and involve revision of all actual medications, identification of inappropriate medications (considering harms and benefits of medication use in the individual and in the setting of life expectancy and care goals), prioritisation of medications for withdrawal, withdrawal of medications (often with tapering) and close monitoring and support and also with documentation of the improvement in health and quality of life and the reduction of adverse effects (18).

There are several tools which have been developed in order to aid identifying PIMs in older adults. The most commonly employed explicit tools are the Beers criteria and the

STOPP/START criteria (Screening Tool of Older Person's Prescriptions and Screening Tool to Alert Doctors to Right Treatment) that are lists of medications which are generally inappropriate in older adults (or in the presence of certain conditions) due to an increased risk and/or decreased need/benefit. The STOPP/START criteria also offer a list of medications that should be initiated in older adults with certain conditions. However, there are also implicit tools, which are questions to take in account during our clinical judgement, to assess the medication appropriateness, for example the Medication Appropriateness Index (19).

Several studies have established that the implementation of a deprescribing process is feasible in practice (20, 21) and may result in favourable patient health and quality of life outcomes (22) and a few strategies seem effective or promising (23). Most of these studies are limited by variable methodologies, single settings, short follow-up periods and/or lack of clinical outcome measurements (24).

But there is inconsistent reporting of the patient willingness to have a medication deprescribed (2, 18). The direct involvement of patients and their caregivers in the choice and administration of drugs has long been known to be very important, but it isn't usually applied, so many patients complain about lacking this opportunity in the decision-making process (25, 26). It is assumed that older people generally do not like to take multiple medications, but there is also evidence that they may be reluctant to accept their doctor's proposal to stop some of them (13, 16, 18). So it's important to understand this incongruity between not liking to take multiple medications and reluctance to accept the proposal to stop them.

Terminology

For the purpose of defining polypharmacy, we will use the list of active principles of drugs and consider two definitions: ≥5 drugs vs ≥ the median number.

Study objectives

The primary objective of this Thesis is to assess the enablement of older adults while being Deprescribed, the rise of Willingness to be Deprescribed and their Quality of Life outcome.

Specific objectives are:

- To identify the prevalence of polypharmacy in older adults in Portugal;
- To evaluate the proportion of PIMs in older adults in Portugal;
- To describe the sociodemographic and clinical profiles of older adults with polypharmacy in Portugal;
- To identify the main Barriers to and the Facilitators of Deprescribing in Portuguese older adults;
- To correlate the main Barriers to and Facilitators of Deprescribing with socio-demographic and clinical profiles of older adults;
- To evaluate the Portuguese older adults Willingness to be Deprescribed;
- To correlate the Willingness to be De-prescribed with socio-demographic and clinical profiles of older adults;
- To evaluate the percentage of older adults that take medication without medical recommendation (including over-the-counter medication and other medications derived from non doctor orientation), and also taking remedies.
- To evaluate the proportion of self-medication on older adults;
- To correlate the Self-medication with the Willingness to be Deprescribed;
- To evaluate if Quality of Life increases after being Deprescribed;

- To elaborate and validate a flowchart with the De-prescribing process, in the patient's perspective.

METHODS AND ANALYSIS

Study design

This is a three-phase study:

1. Cross-sectional, analytical study of the prevalence and patterns of polipharmacy, namely sociodemographic and clinical profiles (age, genre, area of residence and years of study) and about medication (number of drugs and their active component), in older adults attending Primary Care in Portugal.
2. Cross-sectional, triangulation study of older adults' perception of Barriers to and Facilitators of Deprescribing, Willingness to be Deprescribed and Willingness to Self-medicate.
3. Non-pharmacological randomised clinical study of the impact of enablement of older adults in their willingness to be Deprescribed and related Quality of Life.

Phase I: prevalence of polypharmacy in older adults attending primary care in Portugal

Design

Cross-sectional, analytical study.

Setting

Primary Care Centres in Portugal will be randomly selected from the five main-land Portuguese Healthcare Administrative Regions and two Autonomous Regions (Madeira and Azores), in order to obtain a national geographical representative sample.

Sample size

Since the prevalence of polypharmacy in older adults is unknown, we used as base of population all older adults in Portugal. For the study, we used a 95% confidence interval (CI) and a maximum precision error of 5%, so a minimum of 385 patients should be recruited.

Study procedures

This phase of the study starts in November 2017.

General Practitioners (GPs) sampling is made according to existing files of previous projects adherent GPs, in other epidemiological studies. After the selection of GPs, those who accept to participate will recruit their own patients. Assuming that a GP will be able to include at least 6 patients in a 3-week period, a total of 65 GPs will be enrolled in the study: 21 in North of Portugal (31.7%), 16 in Centre of Portugal (24.7%), 18 in Lisbon-Tejo Valley (27.4%), 5 in Alentejo (8.4%), 3 in Algarve (4.3%), 1 in Azores (1.6%) and 1 in Madeira (1.9%) in accordance with the distribution of Portuguese old adult population (≥65 years) in Portugal according with Pordata (www.pordata.pt).

Enrolled GPs will be instructed to collect all necessary data about all older adults (≥65 years) patients attending a primary care consultation during the period of study: 5 days on 3

consecutive weeks (Monday and Tuesday on week 1; Wednesday and Thursday on week 2; and Friday on week 3).

Data collection

The collection of the data will occur in November 2017.

GPs will be responsible for collecting all data about patients' sociodemographic characteristics, as well as morbidity and medication, during their consultations.

Data will be electronically stored in a database specifically designed for this study using MS Access 2010. Data will be encrypted and password protected. Information will be treated in strict confidentiality to protect the privacy of patients. The investigators will have no access to the data of the patient, except the one provided by the GP meaning that the only person to know who is being studied is the GP.

Before the collection of data, there will be online reunions with the GPs participating in the study.

Statistical analysis

A descriptive analysis will be performed to all study variables, namely the number of valid observations, mean±SD, median and range for quantitative variables and absolute and relative frequencies for qualitative variables. Prevalence of polypharmacy (considering definition: ≥5 drugs vs ≥ the median number) will be calculated together with corresponding 95% CI. Moreover, the prevalence of polypharmacy will be estimated by subgroups, namely age, gender, residence area and formal education. Univariate analysis will be conducted to study the associations between those characteristics and polypharmacy using $\chi 2$ test (qualitative characteristics) or t test/Mann-Whitney (quantitative characteristics). Multiple logistic regressions will be carried out considering the presence of polypharmacy as the dependent variable and patients' characteristics as the independent variables in order to calculate odds ratio (ORs) and corresponding 95% CI. Total number of drugs taken by patient and their pharmacological classes will also be summarised together with 95% CI, and multiple regressions may be performed to analyse its association with patients' characteristics. All tests will be two-sided using a significance level of 0.05. Statistical analysis will be conducted using SPSS V.23.0 or higher.

Results perspective

Authors' hypotheses are that:

The prevalence of polypharmacy is higher than 59%, with no difference between genre;

There is higher prevalence in people with lower education;

There is high prevalence in multimorbidity in polipharmacy;

There is an association between Non-Steroidal Anti-inflammatory Drugs (NSAIDs) and polypharmacy;

There is no geographical difference distribution of polypharmacy in Portugal.

Phase II: patients' perception of barriers to and facilitators of deprescribing, willingness to be deprescribed and actual self-medication in adult patients with polypharmacy attending primary care in Portugal

Objectives

To assert reasons and facilitators, willingness to be deprescribed and actual self-medication

Design

Cross-sectional, analytical study.

Setting

It will be the same of the phase I.

Sample size

A minimum of 385 patients will be included in phase II in order to obtain a sample with a 95% CI and a maximum precision error of 5%.

Study procedures

This phase of the study is expected to start in June 2018.

Again, GPs sampling will be made according to existing files and those who accept to participate will recruit their own patients. Patients from phase I can be enrolled in phase II. Assuming that a GP will be able to include at least 6 patients in a 3-week period, a total of 65 GPs has to be enrolled in the study, with the same distribution of the phase I. Enrolled GPs will be instructed to invite all older adult (≥65 years) patients attending the primary care consultation to participate in the study during 5 days on 3 consecutive weeks (Monday and Tuesday on week 1; Wednesday and Thursday on week 2; and Friday on week 3). Those willing to participate in the study must give written informed consent and present willingness and ability to comply with the study requirements.

Exclusion criteria will be: Being acutely unwell in the last three weeks, and refuse to participate.

Data collection

The collection of the data will occur in June 2018.

Patient's socio-demographic and clinical characteristics and medication will be registered using the same methodology as described in phase I.

Perception of medication will be evaluated using Portuguese general Beliefs about Medicines Questionnaire (BMQ), the willingness to be deprescribed will be assessed with two open-questions (one to assess the facilitators and the other to assess the barriers), and the actual self-medication will be evaluated with an analogic visual scale (0 to 10) about the need to self-medicate and its justification.

For those not knowing how to write or read, someone of their knowledge, will fill in the open questions, with their answers.

In case of less than 5% of answers of the open questions, two patient groups will be invited to make a focus group asserting reasons for accepting deprescribing.

Statistical analysis

Descriptive statistics will be computed for all variables together with 95% CI whenever relevant and applicable. Associations between qualitative-independent variables will be tested using $\chi 2$ test. Comparisons between two or more independent groups regarding a quantitative variable are to be conducted using analysis of variance (ANOVA) or Kruskal-Wallis non-parametric test, if normality assumption is not met. ANCOVA may also be used to adjust for potential confounding factors. Associations between quantitative independent variables will be analysed using Pearson's or Spearman's correlation coefficient depending on normality assumption. All tests will be two-sided, considering a significance level of 0.05.

Results perspective

Authors' hypotheses are that:

The people with more willingness to be deprescribed believe that medications are harmful and overused by doctors;

The need to self-medicate is present in people with less fear of medication and less overuse belief;

People with polypharmacy see no or little harm in the medication and don't think they have polypharmacy.

Phase III: impact of enablement of older adults in their willingness to deprescribe and quality of life

Design

Non-pharmacological randomised clinical study, intended to last for six months.

Setting

Primary Care Centres in Portugal will be randomly selected from six Health Centres of Centre of Portugal (Aveiro, Castelo Branco, Coimbra, Guarda, Leiria and Viseu)

Sample size

Will be created two groups with a minimum of 190 patients each (one will be the intervention group and the other the control).

Study procedures

This phase of the study is expected to start in September 2019 and will last for 6 months.

Again, GPs sampling will be made according to existing files and those who accept to participate will recruit their own patients. Patients from previous phases can be enrolled in phase III. Assuming that a GP will be able to include at least 6 patients, a total of 64 GPs has to be enrolled in the study. Enrolled GPs will be instructed to invite all older adult (≥65 years) patients attending to the primary care consultation to participate in the study during until obtaining the sample size and being randomized according to the table for study entry. The geographical areas of work, the Districts, will be randomized for entry into exposed and unexposed groups. Those patients willing to participate in the study must give written informed consent and present willingness and ability to comply with the study requirements.

Exclusion criteria: Being acutely unwell in the last three weeks, and refuse to participate.

Two groups will be created with a minimum of 190 patients each, one of which will be composed from patients from the region of Aveiro, Coimbra and Guarda and the other from patients from the region of Castelo Branco, Leiria and Viseu. In the intervention group we will give enablement tools and talks with their GPs about how to issue the problem of polypharmacy. The information given in this group will result from the knowledge obtained in phase II in the shape of small leaflets and other information materials to be made according to the best practice, to be given and remembered at scheduled times to the intervention group.

Data collection

The collection of the data will occur in the beginning and end of phase II.

Patient's socio-demographic and clinical characteristics and medication will be registered using the same methodology as described in phase I.

Perception of medication will be evaluated using Portuguese general Beliefs about Medicines Questionnaire (BMQ), the willingness to be deprescribed will be assessed with two open-questions (the same as phase II), and the quality of life we will assessed with EuroQol Five Dimensions Questionnaire (EQ-5D).

For those not knowing how to write, someone of their knowledge, will fill in the open questions.

Statistical analysis

Descriptive statistics will be computed for all variables together with 95% CI whenever relevant and applicable. Associations between qualitative-independent variables will be tested using $\chi 2$ test. Comparisons between two or more independent groups regarding a quantitative variable are to be conducted using analysis of variance (ANOVA) or Kruskal-Wallis non-parametric test, if normality assumption is not met. ANCOVA may also be used to adjust for potential confounding factors. Associations between quantitative independent variables will be analysed using Pearson's or Spearman's correlation coefficient depending on normality assumption. All tests will be two-sided, considering a significance level of 0.05.

Results perspective

Authors' hypothesis is that:

The intervention will result in statistical higher willingness to be deprescribed and better quality of life so creating a tool for active patient deprescription.

ETHICS AND DISSEMINATION

The study will be conducted in accordance with the principles expressed in the Declaration of Helsinki. It has been submitted to approval from the Ethics Committee of University of Beira Interior, portuguese National Data Protection Commission and the Ethics Committee of all Health Region of Portugal. Study results will be published in peer-reviewed journals and presented at national and international conferences.

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AUTHORS' CONTRIBUTIONS

PAS, LMS and JAS were involved in designing of the study. PAS was involved in writing of the manuscript. All authors read and approved the final manuscript draft.

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COMPETING INTERESTS STATEMENT

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