

# BMJ Open Deprescribing in primary care in Portugal (DePil17-20): a three-phase observational and experimental study protocol

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## ABSTRACT

**Introduction** Polypharmacy is commonly defined as the simultaneous taking of five or more drugs. Deprescribing is the process of tapering or stopping medications with the aim of improving patient outcomes and optimising current therapy, and there are several tools aiming at identifying potentially inappropriate medications, especially in the elderly. 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 is not usually applied. The aim of this study is to assess the knowledge of older adults about deprescription, the effect on willingness to have regular medications 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 have regular medications deprescribed and to self-medicate. The third and last phase will be a non-pharmacological randomised clinical study to measure older patients' acceptance to have regular medications 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 approved by the Ethics Committee of the University of Beira Interior and Portuguese National Data Protection Commission. Study results will be published in peer-reviewed journals and presented at national and international conferences. In short, no action will be taken without written consent from patients and doctors.

**Trial registration number** >NCT03283735.

## INTRODUCTION

Polypharmacy is commonly defined as the simultaneous taking of five or more drugs,<sup>1</sup> but it can also be defined as using medication that is not indicated, not effective or is therapeutic duplication.<sup>2</sup> It is present in 30%–70% of older adults<sup>3</sup> and it is a significant predictor of the risk of falls,<sup>4</sup> inappropriate prescriptions, reduced patient adherence, drug interactions, hospital admissions<sup>5,6</sup> and mortality.<sup>7</sup>

## Strengths and limitations of this study

- Phase I and II will be nationwide and will be the first ones to take place in Portugal.
- This will be one of the first to assess the impact of deprescribing in health and quality-of-life outcomes on older adults.
- Study methodology comprehensively aims at getting the whole picture of the problem from its epidemiological study, through the understanding of what polymedicated patients feel about being on less medication load, until the perception of quality-of-life study when deprescription has been made.
- The relatively small sample will be a methodological limitation because it will not allow getting so strong conclusions as if the sample was bigger, due to medical short adherence because of the workload.
- The possible contamination of the intervention in phase III, due to parallel sources of information, taking place as a confounding variable.

It is estimated that at least 75% of this adverse event is potentially preventable.<sup>8</sup>

Potentially inappropriate medications (PIM) are those for which the harms outweigh the benefits, namely those that are not indicated or lack evidence of efficacy and those that do not align with patients goals/preference and values.<sup>9</sup> So, it is necessary to distinguish between appropriate and inappropriate medications<sup>10</sup> because as people get older the benefit:risk ratio of medications changes, meaning that medications that were once appropriately prescribed may have become inappropriate.<sup>11</sup> An Australian study reported that 60% patients had at least one PIM, leading to a high risk of adverse drug reactions, morbidity and mortality.<sup>12</sup> There are a lot of guidelines about when to start medication that is safe and effective, but there is a lack of similar guidelines for ceasing inappropriate medication.<sup>13</sup>

Deprescribing is the process of tapering or stopping medications with the aim of

improving patient outcomes and optimising current therapy.<sup>14</sup> However, it is not free of risks, namely withdrawal syndromes, rebound effects, pharmacokinetic/pharmacodynamic changes in the remaining drugs and recurrence of the symptoms.<sup>3,15</sup> So, the decision to deprescribe results from a careful weighting between the therapeutic objectives and the risk:benefit ratio.

Many deprescribing processes have been proposed in the literature.<sup>15,16</sup> One of the most widely used is a simple five-step protocol consisting of a comprehensive medication history, identifying PIM (attending to the harms and benefits of medication, as well as to the life expectancy and care goals), determining whether medication can be ceased and prioritisation (taking into account the patient's preferences), planning and initiating medication withdrawal (one at a time and often with tapering) and close monitoring and documenting the improvement in health and quality of life and the reduction of adverse effects.<sup>17</sup>

Almost a dozen medication screening tools exist in order to aid identifying PIM in older adults and improve their care. The most widely used are Beers criteria and the Screening Tool of Older Person's Prescriptions and Screening Tool to Alert Doctors to Right Treatment (STOPP/START) criteria. Both the Beers criteria and the STOPP component of the STOPP/START criteria are lists of medications that should be avoided in older adults because of its adverse effects and drug–drug and drug–disease interactions. On the other hand, the START component of the STOPP/START criteria consists of a list of medications that should be considered to initiate in the presence of certain conditions. Another useful tool is the Medication Appropriateness Index that consist of issues to be taken into account before prescribing a medication.<sup>18</sup>

Many studies have recognised that the implementation of a deprescribing process is feasible in practice and acceptable to participants<sup>19,20</sup> and, hypothetically, may result in favourable patient health and quality-of-life outcomes<sup>21</sup>; further studies are needed to confirm it. There are already a few number of strategies that appear to be effective and promising,<sup>22</sup> however assessing the effectiveness of these interventions is difficult because different studies have different study designs, settings and types of interventions. Many of these studies have short follow-up periods (2 months to 1 year), so they may not provide information about the long-term impact of these interventions, and/or lack of clinical outcome measurements.<sup>23</sup> One outcome measurement rarely used was the effect on health-related quality of life.

Patients are uncertain about their willingness to have a medication deprescribed because they are confused by conflicting advice on benefit and harm from different healthcare professionals.<sup>15</sup> The majority of patients want to be involved in the decision-making process,<sup>17,24</sup> and this has long been known to be very important, but shared decision-making is not routine.<sup>25</sup> It is assumed that older people generally consider they take a lot of

medications and complain about it, but they are reluctant to cease specific medications in practice.<sup>26,27</sup> So it is important to understand this incongruity between not liking to take multiple medications and reluctance to accept the proposal to stop them. In particular for Portuguese context, there are no studies on these matters, so it is necessary to understand such ambivalence, because it will help us solve many problems arising from polypharmacy, such as adverse drug reactions.<sup>28</sup>

There are only some studies about the prevalence of polypharmacy in some region of Portugal, none nationwide. Also, there are no studies about the Portuguese older adults' attitudes and beliefs regarding medication, and there are very few studies around the world. Finally, most of the studies focus on the effect of deprescribing in clinical outcomes such as falls, consultations rates, hospitalisations and/or mortality. Very few focus on the effect on quality of life and older adults' willingness. In order to study the phenomenon, as well as to create rationales, this work is necessary.

### Terminology

For the purpose of defining polypharmacy, we will use the list of active ingredient of drugs and consider three definitions:  $\geq 5$  drugs versus  $\geq$  the median number of drugs versus presence of at least one PIM. The rationale for such resides in the scarcity of studies on the number of medications simultaneously taken. In fact, due to multimorbidity, many elderly patients are taking more and more drugs.<sup>29</sup> So, we want to compare the international accepted definition ( $\geq 5$  drugs) with this new approach to see if there are differences.

### Study objectives

The primary objective is to assess the knowledge of older adults about deprescription, the effect on willingness to have regular medications 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 PIM 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 evaluate the Portuguese older adults willingness to have regular medications deprescribed.
- ▶ To correlate the self-medication with the willingness to have regular medications deprescribed.
- ▶ To evaluate the effect in quality of life after having regular medications deprescribed.
- ▶ To elaborate and validate a flow chart with the deprescribing 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 polypharmacy, namely sociodemographic and clinical profiles (age, gender, 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 have regular medications deprescribed and willingness to self-medicate.
3. Non-pharmacological randomised clinical study of older patients' acceptance to have regular medications deprescribed and related quality of life.

### Phase I

#### Objectives

To assert the prevalence of polypharmacy in older adults attending primary care in Portugal and describe their sociodemographic and clinical profiles.

#### Design

Cross-sectional, analytical study.

#### Setting

Primary care centres in Portugal will be randomly selected from the five mainland 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 will use as base of population all older adults in Portugal. For the study, we will use a 95% CI and a maximum precision error of 5%. According to Pordata ([www.pordata.pt](http://www.pordata.pt)), the population of Portugal is around 10.33 million, of which 2.18 million are over the age of 65. Since the literature suggests that the range of polypharmacy is 30%–70% and we think that it is over 50%, we estimate that we would need at least 742 patients.

#### Study procedures

This phase of the study will start in March 2018.

We will ask the information department of the ministry of health for the data of 757 randomised patients (electronically stored): 245 in North of Portugal, 190 in Centre of Portugal, 211 in Lisbon-Tejo Valley, 65 in Alentejo, 33 in Algarve, 6 in Azores and 7 in Madeira in accordance with the distribution of Portuguese old adult population ( $\geq 65$  years) in Portugal according to Pordata.

#### Data collection

The collection of data will occur in March 2018.

Data will be electronically stored in a database specifically designed for this study. It will be encrypted and password protected. Information will be treated in strict

confidentiality to protect the privacy of the patients. The investigators will have no access to the data of the patients, except the one provided by the information department of the ministry of health.

#### Statistical analysis

A descriptive analysis of all study variables will be performed, namely the number of valid observations, mean $\pm$ SD, median and range for quantitative variables and absolute and relative frequencies for qualitative variables. Prevalence of polypharmacy (considering the three definitions) 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 Student's t-test/Mann-Whitney U test (quantitative characteristics). Multiple logistic regressions will be carried out considering the presence of polypharmacy as the dependent variable and patients' characteristics as the independent variable in order to calculate the OR and corresponding 95% CI. Total number of drugs taken by the patients 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.

### Phase II

#### Objectives

To determine older peoples' attitudes and beliefs regarding medication use and their willingness to have regular medications deprescribed.

#### Design

Cross-sectional, analytical study.

#### Setting

It will be the same as phase I.

#### Sample size

Since the prevalence of polypharmacy in older adults is unknown, we will consider that it is around 60% of the older adults' population. So, we need at least 385 patients with polypharmacy, 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 October 2018.

For general practitioners (GPs) sampling we used existing files of previous projects adherent GPs, in other epidemiological studies, in order to have an higher adherence rate. After the selection of GPs, those who agree to participate will recruit their own patients, after their consent. Assuming that a GP will be able to include at

least six patients, a total of 65 GPs will be enrolled in the study: 21 in North of Portugal, 16 in Centre of Portugal, 18 in Lisbon-Tejo Valley, 5 in Alentejo, 3 in Algarve, 1 in Azores and 1 in Madeira in accordance with the distribution of Portuguese old adult population ( $\geq 65$  years) in Portugal according to Pordata ([www.pordata.pt](http://www.pordata.pt)).

Enrolled GPs will be instructed to give the questionnaire and the informed consent to all older adults ( $\geq 65$  years) patients, with polypharmacy, attending a primary care consultation during the period of study: we will randomise six consultation days for data collection. GPs will collect all necessary data about the patients who sign the informed consent and fill all questions of the questionnaire. After that, we will randomise the pool of data according to gender and region, in order to obtain a sample in accordance with Portuguese distribution of old adult population ( $\geq 65$  years).

GPs and patients willing to participate in the study must give written informed consent and present ability to comply with the study requirements.

Exclusion criteria will be: being acutely unwell in the last 3 weeks and refusal to participate.

#### Data collection

The collection of data will occur in October 2018.

GPs will be responsible for collecting all data about patients' sociodemographic characteristics, as well as morbidity and medication, during their consultations. Moreover, the perception of medication will be evaluated using Portuguese general Beliefs about Medicines Questionnaire (BMQ), the willingness to have regular medications deprescribed will be assessed with one open-question ('What do you think about withdrawing medication?'), to evaluate the qualitative knowledge about the patient's acceptance, and the need to self-medicate with over-the-counter medication will be evaluated with a Visual Analogue Scale (0–10) about the need to self-medicate and its justification.

Those who do not know how to write or read can choose someone they know (eg, a family member or a friend) to write the answer.

In case of less than 50% of answers of the open questions, two patient groups will be invited to make a focus group asserting reasons for accepting deprescribing.

Data will be electronically stored in a database specifically designed for this study using MS Excel 2010. It 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 patients. The only person to know who is being studied will be the GP.

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

We have been authorised to use BMQ by the authors.

#### Statistical analysis

A descriptive analysis of all study variables will be performed, namely the number of valid observations,

mean $\pm$ SD, median and range for quantitative variables and absolute and relative frequencies for qualitative variables. We will categorise the willingness to have regular medications deprescribed in two groups (high and low). The perception of medication, willingness to have regular medications deprescribed and need to self-medicate 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 the perception of medication, willingness to have regular medications deprescribed and need to self-medicate using  $\chi^2$  test (qualitative characteristics) or t-test/Mann-Whitney (quantitative characteristics). Multiple logistic regressions will be carried out considering the perception of medication, willingness to have regular medications deprescribed and need to self-medicate as the dependent variable and patients' characteristics as the independent variable in order to calculate the OR and corresponding 95% CI. All tests will be two-sided, considering a significance level of 0.05.

#### Null hypothesis

The people with more willingness to have their regular medications 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 do not think they have polypharmacy.

#### Phase III

##### Objectives

To measure older patients' acceptance to have regular medications deprescribed and related quality of life.

##### Design

Non-pharmacological cluster randomised clinical study, intended to last for 6 months.

##### Outcomes

Primary outcome will be the quality of life.

Secondary outcome will be the willingness to have regular medications deprescribed.

##### 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

Since the prevalence of polypharmacy in older adults in Centre of Portugal is unknown, we will consider that it is around 60% of the older adults' population in this region (around 520 000). So we need at least 380 patients with polypharmacy, to obtain a sample with a 95% CI and a maximum precision error of 5%. However, assuming a dropout rate of around 25%, we will increase the required sample by 25% in order to compensate for dropouts, so we will need at least 474 patients with

polypharmacy. Then we will create two groups with a minimum of 237 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 agree to participate will recruit their own patients, after their consent. Patients from previous phase can be enrolled. Assuming that a GP will be able to include at least 10 patients, a total of 48 GPs have to be enrolled in the study. Enrolled GPs will be instructed to invite all older adult ( $\geq 65$  years) patients with polypharmacy, attending the primary care consultation to participate in the study until we obtain the required sample size, they will be randomised as described below. The geographical areas of work, the districts, will be randomised for entry into exposed and unexposed groups, in order to minimise the contamination of the intervention that could happen if we use randomisation at patient level. The purpose is to have doctors performing only one task in each district. To make both groups as homogenous as possible, we will group similar districts in order for them to be in different branches of the study.

Patients willing to participate in the study must give written informed consent and present willingness and ability to comply with the study requirements. The patients' recruitment procedure will be the same as the one described for phase II.

Exclusion criteria: being acutely unwell in the last 3 weeks and refusal to participate.

Two groups will be created with a minimum of 237 patients each, one of which will be composed of patients from the regions of Aveiro, Coimbra and Guarda and the other from patients from the regions of Castelo Branco, Leiria and Viseu. In the intervention group, we will give empowerment tools and will talk with their GPs about how to approach the problem of polypharmacy and the control group will receive the usual care. The information given in the intervention group will result from the knowledge obtained in phase II, it will be compiled in small leaflets and other informational materials to be made according to the best practice, to be given and remembered at scheduled times to this group. To summarise, this information will be used to educate GPs about how to approach the issue of deprescribing and to provide material to participants, during a consult, so that they can learn more about it.

### Data collection

The collection of data will occur in the beginning (baseline) and end of phase III (at 6 months), in order to analyse changes from baseline.

GPs will be responsible for collecting all data. Patient's sociodemographic and clinical characteristics, and medication will be registered using the same methodology as described in phase II.

Perception of medication will be evaluated using Portuguese general BMQ, the willingness to have regular medications deprescribed will be assessed with one open question (the same as phase II), and the quality of life will be assessed with EuroQol Five Dimensions Questionnaire (EQ-5D), a validated tool for Portugal. The aim is to observe the impact of deprescription on health-related quality of life, even if, to our knowledge no study has used EQ-5D in this specific domain in Portugal.

Those who do not know how to write or read can choose someone they know (eg, a family member or a friend) to write the answer.

We have been authorised to use BMQ and EQ-5D by the authors.

### Statistical analysis

It will be similar to phase II. Comparisons between baseline and the 6-month groups regarding a quantitative variable are to be made using t-test or Sign/Wilcoxon non-parametric test, if normality assumption is not met.

### Null hypothesis

The intervention will result in higher quality of life.

### Patient and public involvement

Patients and/or public were not involved.

## DISCUSSION

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 health and quality-of-life outcomes on older adults. We hope that the results will help clinicians to better understand patient's perception regarding polypharmacy and deprescribing.

However, many Portuguese GPs are not very keen to participate in studies like this because they have a heavy workload. Therefore, special attention and care are put on the size of the sample to achieve the goal of the study and in the recruitment methodology. Moreover, we will support and interact constantly with the participant GPs, in order to maintain their motivation. Because of this anticipated short adherence, we conclude that it would be impracticable to conduct phase III at the national level.

For phase III, a strategy was thought of trying to make geographical contamination as little as possible. Therefore we randomized the geographical areas instead of GPs or patients, so that GPs wouldn't discuss the intervention between themselves. As it is an area still unknown in Portugal, we will try to control external interventions about deprescription, but, of course, in a interconnected world where the news spreads via the internet, some contamination will surely happen and may be a confounding variable, but it will be a systematic one. Also, in order to make both groups as homogenous as possible, we will group similar, but apart, districts, where doctors will perform the tasks. GPs will be the focus of meetings

and ongoing mails so that the study is completed. Since there is no access to the identification of patients, the most suitable way to conduct the study is through randomisation of patients by voluntary GPs. This will probably be a bias but, in light of the Portuguese laws, there is no other way to do it and, once again, there is no fee for task study. The fact that there is randomisation of patients, guaranteed by the size of the epidemiological representative samples, will provide a clear picture of the intended study problem.

### Ethics and dissemination

The study will be conducted in accordance with the principles expressed in the Declaration of Helsinki. Study results will be published in peer-reviewed journals and presented at national and international conferences. In short, no action will be taken without written consent from patients and doctors.

**Contributors** PAS, LMS and JARS 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** None declared.

**Patient consent** None declared.

**Ethics approval** The Ethics Committee of the University of Beira Interior and Portuguese National Data Protection Commission.

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