Master Thesis

Changes in prescribing patterns of benzodiazepines after training of General Practitioners.

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Foreword

This thesis and the paper that is being prepared to report on its results followed the **Transparent Reporting of Evaluations with Non-randomized Design (TREND) statement.** These guidelines intend to improve the reporting of theories, descriptions of interventions and comparison conditions, research design, and methods of adjusting for possible bias in evaluation studies that use experimental nonrandomised designs (Des Jarlais, Lyles, and Crepaz 2004).

These guidelines were chosen because this study followed a quasi-experimental design, as randomisation was not considered. The author considered more adequate to use the TREND Guidelines for reporting the results instead of other well known reporting guidelines such as the CONSORT List. The utilisation of these guidelines to report non-randomised studies has recently been demonstrated to have a greater reporting completeness than other similar designed studies that don´t use them (even when controlling for the year of publication and the journal impact factor) (Fuller et al. 2014). Is has also been shown a significant association between the study quality rating and the use of TREND guidelines (Fuller et al. 2014). For further detail and greater ease in understanding the chosen structure, please see the TREND statement checklist in attachment.

Abstract

Introduction: Benzodiazepines are the most utilized anxiolytic and hypnotic drugs. The high consumption of benzodiazepines has been a concern due to the reported side effects of long-term use and dependence. Portugal has the highest benzodiazepine utilisation in Europe. This study aims to analyse the change in General Practitioners' (GPs) benzodiazepine prescription pattern after an intervention period.

Methods: An educational session was delivered to a group of intervened GPs. The benzodiazepine prescription pattern of the intervened group was compared to the pattern of a non-intervened matched group from the same region, and to the pattern of another non-intervened matched group from a different region. The research time frame was 12 month before and after intervention. The analysis of the prescription trends used the Defined Daily Dose (DDD) and Defined Daily Dose per 1000 patients per day (DHD) methodology. The statistical methods consisted of segmented regression analysis.

Results: There was a decrease in benzodiazepine prescription pattern of intervened GPs after intervention ($p=0.005$). There was also a decrease in benzodiazepine prescription pattern for the non-intervened group from the same region ($p=0.037$) and for the non-intervened group from a different region ($p=0.010$). Concerning the analysis by gender, female gender prescribed a higher amount of benzodiazepines. The intervened female gender prescribers presented the highest decrease in prescription trend after intervention ($p=0.008$).

Discussion: The data demonstrated that the intervention was effective in reducing benzodiazepine prescription after intervention. The general decrease in prescription trend might be explained by a Hawthorne effect or a contamination effect between the three groups of GPs. The available data couldn´t explain the differences in prescription patterns by gender.

Conclusion: This study demonstrates how a single intervention has a positive impact on improving prescription trends. The replication of this intervention might be an opportunity to changing the worrying benzodiazepine utilisation in Portugal.

Resumo

Introdução: As benzodiazepinas são os fármacos ansiolíticos e hipnóticos mais utilizados. O elevado consumo destes fármacos tem representado uma preocupação devido aos efeitos secundários do seu uso prolongado e dependência. Portugal tem a maior utilização de benzodiazepinas na Europa. Este estudo pretende analisar a alteração do padrão de prescrição de benzodiazepinas após uma intervenção com clínicos gerais.

Métodos: A intervenção consistiu numa sessão educacional a um grupo de clínicos gerais. Foi comparado o padrão de prescrição de benzodiazepinas dos médicos intervencionados com o de um grupo de médicos não intervencionado da mesma região e com o de um grupo de médicos não intervencionados de outra região. Analisaram-se as prescrições de 12 meses antes e depois da intervenção. A análise do padrão de prescrição utilizou como metodologia a Dose Diária Definida (DDD) e a Dose Diária Definida por 1000 pacientes por dia (DHD). A análise estatística recorreu a métodos de regressão segmentada.

Resultados: Houve uma diminuição no padrão de prescrição de benzodiazepinas no grupo intervencionado após a intervenção ($p = 0.005$). Houve também uma redução no padrão de prescrição no grupo não intervencionada da mesma região ($p = 0.037$) e no grupo não-intervencionado da região diferente ($p = 0.010$). Analisando por género, prescritores do género feminino prescrevem uma quantidade maior de benzodiazepinas. Os clínicos gerais do género feminino intervencionados tiveram a maior redução na prescrição após a intervenção ($p = 0.008$).

Discussão: Os dados demonstraram que a intervenção reduziu a prescrição de benzodiazepinas após a intervenção. A diminuição geral do padrão de prescrição poderá ser explicada pelo efeito de Hawthorne ou pela contaminação entre os três grupos de clínicos gerais. Os dados disponíveis não explicam as diferenças nos padrões de prescrição por género.

Conclusão: Este estudo demonstra como uma única intervenção tem um impacto positivo na melhoria dos padrões de prescrição. A replicação desta intervenção poderá representar uma oportunidade para alterar a prescrição de benzodiazepinas em Portugal.

Keywords

Benzodiazepines; prescription pattern; educational intervention; primary health care doctors;

Palavras chave

Benzodiazepinas; padrão de prescrição; intervenção educacional; clínicos gerais;

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Acronyms and abbreviations list

ARS LVT: Administração Regional de Saúde de Lisboa e Vale do Tejo (Regional Health Administration of Lisbon and Tagus Valley).

BZD(s): benzodiazepine(s).

DDD: Defined Daily Doses

DGS: Direcção Geral de Saúde (Portuguese General Health Administration)

DHD: Defined Daily Doses by 1000 patients per day

GABA-A: Type-A γ aminobutyric acid

GP(s): General Practitioner(s).

NHS: National Health System

NUTS: Nomenclatura das Unidades Territoriais para Fins Estatísticos.

OECD: Organisation for Economic Co-operation and Development

OSPI-Europe: Optimizing Suicide Prevention Programmes and their Implementation in Europe.

PHC-D: Primary Health Care Doctors

USF(s): Unidades de Saúde Familiar (primary health care unit).

UCSP(s): Unidades de Cuidados de Saúde Primários (primary health care unit).

1. Introduction

Benzodiazepines (herein after referred as BZDs) are the most utilized anxiolytic and hypnotic drugs. The first benzodiazepine, chlordiazepoxide, was synthesized and then approved for use in 1960. Until then, barbiturates were used as hypnotics, anxiolytics and sedatives with a much unsafe profile and greater lethality in overdose, therefore the discovery of benzodiazepines, with a higher safety and less side effects was considered very positive (Lader 2011). The release of diazepam in 1963 increased benzodiazepines popularity and soon they become one of the most widely prescribed drugs (López-Muñoz, Álamo, and García-García 2011). Until then, barbiturates were used as hypnotics, anxiolytics and sedatives that were very unsafe and often lethal in overdose (2) benzodiazepines have a higher margin of safety and less side effects.

Benzodiazepines are positive allosteric modulators for GABA-A receptors in sites such as the ventral tegmental area where they are implied in reward circuits (Tan, Rudolph, and Lüscher 2011).

Differences in the pharmacological profile of different BZDs are minor. Clonazepam appears to have more anticonvulsant action in relation to other effects. Different GABA-A receptor isoforms are believed to mediate sedative and anxiolytic effects. They are active orally and differ mainly in respect to their duration of action (Rang 2005). Short acting half-lives (like oxazepam and midazolam) are metabolised to inactive compounds and are used mainly as sleeping pills. Some long-acting agents (like diazepam) are converted to an active metabolite (nordazepam) (Rang 2005).

The main effects of benzodiazepines are reduction of anxiety, sedation and induction of sleep, reduction of muscle tone, anticonvulsant effect and anterograde amnesia (Rang 2005).

Unwanted effects of these drugs can be divided into toxic effects resulting from acute overdosage; unwanted effects occurring during routine therapeutic use; tolerance and dependence (Rang 2005, Stevens and Pollack 2005).

The high consumption of benzodiazepines has been the target of recent studies that underscore the burden and consequences of their routine therapeutic use that often, and easily, become chronic and excessive (Lader 2011). Among the side effects associated with their use are included daytime drowsiness, slowness of movements and thought, dizziness, cognitive impairment, incoordination and dependence (Holbrook et al. 2000). Benzodiazepines abusive utilization has been recently related to dementia (de Gage et al.

2012), memory problems (Stewart 2005), increased number of bone fractures (Khong et al. 2012), a highest number of road accidents (Thomas 1998), and possible role in inducing the phenomenon of suicide (Carlsten et al. 2003, Neutel and Patten 1997).

According to official national literature and OECD database, BZD use in Portugal increased from 35 DHD since the late eighties to over 90 DHD in 2012 (Carmona and Bicho 2001, António et al. 2002, Furtado and Teixeira 2005, 2006, Furtado, Ribeirinho, and Gaspar 2010, Furtado 2013). Anxiolytics, hypnotics and sedatives, of which the more used and prescribed drugs are BZDs, had a 6% increase since the year of 2000. This high utilisation was signalled and considered of concern in 2006 by the International Narcotics Control Board (Furtado and Teixeira 2006).

A general comparison with 14 European countries shows that Portugal has the highest utilisation of BZDs in Europe (Matias et al. 2015). Even in a more detailed analysis, considering only countries with similar 12-month prevalence for mental disorders, with parallel results for negative mental health in the SF-36 questionnaire (Kovess 2004), and with similar standardised death rates for suicide (Gusmão et al. 2013), Portugal is still the country with the highest BZD utilisation (Matias et al. 2015).

As previously introduced, the problem of benzodiazepine over-prescription has long been recognized (Furtado and Teixeira 2006).

In this sense, many interventions have been tried in order to encourage doctors to reduce the amount of benzodiazepines they prescribe, avoiding long-term prescription to naïve patients, reducing and discontinuing prescription to patients already with a dependence problem (Mugunthan, McGuire, and Glasziou 2011).

A 2008 Cochrane review demonstrated that educational outreach visits can be effective in improving practice, namely that personal visits by a trained person to health professional are effective in changing prescription patterns (O'Brien et al. 2008). More specifically, a 2010 non-systematic review showed that educational interventions targeted at General Practitioners (GPs) had significantly decreased benzodiazepine use (Smith and Tett 2010). The same study indicated that education aiming long term care staff about alternative methods to treat insomnia and anxiety, and cutting back on the use of benzodiazepines would enhance the success of intervention (Smith and Tett 2010).

The Optimizing Suicide Prevention Programmes and their Implementation in Europe (OSPI-Europe) was an EU financed intervention for suicide prevention focussed on improving awareness and care for depression implemented in four countries: Ireland, Germany,

Hungary and Portugal (Hegerl et al. 2009). In Portugal, the project was implemented by the department of Mental Health in NOVA Medical School and consisted in the implementation of the 4-level model, following best evidence guidelines (Van Der Feltz-Cornelis et al. 2011): (1) training sessions and practice support aiming primary health care professionals, (2) public relations activities and media campaigns, (3) training sessions aiming community facilitators and (4) outreach and support aiming high-risk individuals through self-help groups (Hegerl et al. 2009, Hegerl et al. 2008).

The interventions in the OSPI Europe project were implemented in a standardized way to ensure comparability across the regions. The intervention was evaluated according to a prospective and controlled design. Therefore, for each intervened region, a comparable control region was chosen. The primary outcome for evaluating the effect of the intervention was the rate of suicidal acts in the intervention and control regions, during the 18 months of intervention and the six months after. As intermediate outcomes, the study aimed at measuring the effectiveness of each of the single interventions, namely public attitudes and knowledge towards depression and suicidality, effects of training for community facilitators and GPs through questionnaires, quantitative and qualitative evaluation of media reporting on suicide and evaluation on the quality of the treatment provided for depression through monitoring of antidepressants and other psychotropic prescription (Hegerl et al. 2009).

In Portugal, the region of Amadora was chosen as the intervention group and the region of Almada as the control group. These regions were chosen because they have similar suburban context (the NUTS II[1] region of Lisbon) and are very similar in socio-demographic structure and population pyramids for both genders, and also because the Tagus River separates them, reducing the possibility of contamination. Moreover, both have a comparable socio-economic development and ethnic minorities with a similar distribution (Gusmão 2013). According to the investigators involved in the OSPI-Europe project, Amadora was selected as the intervention area because there was already a consistent work performed over the years in the area of specialized mental health care, community intervention and articulation with primary health care professionals. Thus, if positive results would appear, they could be derived from the add-ons of the 4-level implementation on a well-fit set of resources already in place (Gusmão 2013).

[1] This nomenclature was originally designed by the Eurostat to define units of territory statistical analysis.

Considering specifically the training session delivered to Primary Health Care Doctors (PHC-D) or General Practitioners (GPs)[2], the focus was to improve their capacity to recognise signs and symptoms of depression and suicidal ideation and to adequately choose an antidepressant treatment simultaneously avoiding the utilization of benzodiazepines exceeding the national guidelines, or stimulating BZD weaning in patients routinely using them for long periods. In this context, exemplary clinical cases were presented, such as the patient with marked depression and anxiety symptoms, the patient with insomnia, or the patient with abuse and/or dependency. Suggestions for anxiety and depressive disorders treatment were also included. In addition, the approach to the patient abusing benzodiazepines was considered, with suggestions of ways for reducing and stopping abusive utilisation: dose reduction through a slow step-down process, beginning of antidepressant therapy and avoidance of purchase without a prescription. This study focuses the previous described intervention. The training was 8-hours long, credited and led by an expert and senior psychiatrist consultant.

A similar intervention to the one performed in this study was developed in Australia in 1999 (Dollman et al. 2005), showing that a multi-strategic intervention in a regional setting was associated with a 19% reduction in dispensing of benzodiazepines over the three years from the pre-project to follow-up period.

The choice for defining the study outcomes was enriched by the know-how from other studies developed at NOVA Medical School. These studies focused the effectiveness of educational outreach visits to improve family physician prescribing by analysing the change in prescription trend of anti-inflammatory drugs, using a similar dataset to the one selected to the present study (Pinto, Caetano, Heleno, Faria-Vaz, et al. 2012, Pinto, Caetano, Heleno, Rodrigues, et al. 2012, Pinto et al. 2014).

As explained in the following sections, it is hypothesised that this specific training to general practitioners changed their benzodiazepine prescription pattern. Therefore, the quality of benzodiazepine prescription would improve with a significant reduction of prescription in the intervention group after training, compared with the two non-intervened groups.

[2] The terms Primary Health Care Doctors (PHC-D) and General Practitioners (GPS) will be used as synonyms

2. Methods

This study follows a longitudinal analysis with a quasi-experimental design.

2.1. Participants

The OSPI-Europe project included training sessions to GPs. This intervention aimed at improving their ability to recognise and treat adequately depressive and anxiety disorders as well as identifying suicidal ideation.

The doctors included in the intervention group were contacted, by email, by their primary health care unit coordinator and were instructed to attend a single training session. Both the primary health care unit coordinator and the GPs were informed about the duration of the session, the trainer skills and it's content (practical clinical training on how to better recognise signs and symptoms of depression and to better treat anxiety and depressive disorders). There were quotas for professionals to fill in the trainings that were negotiated with the coordinators: at least 50% of those fully active. The rationale was consensual and based on the need to improve primary health care in the units which was deemed to be an ethical issue.

The GPs organised among themselves to participate and comply with the quotas. No incentive or reward was given but there was a professional obligation to be present complying with the quotas secondary to the ethical imperative. The doctors were allowed by their unit coordinator to attend the session during their clinical work schedule. All the doctors willing to attend the session were accepted for training. Randomisation was not performed, neither of the GPs included nor of the primary care units from where they came from.

Seventy-one doctors volunteered for attending the training and authorized the evaluation of the knowledge acquired through the training session. They also authorised the monitoring of their prescription and were specifically informed about the intention to evaluate the change in their BZD prescription pattern after the training though anonymity was assured.

This study includes two non-intervened groups of GPs: one coming from Amadora (the same region as the intervention group) and another coming from Almada.

The goal of having a non-intervened group of GPs coming from the same region as the intervention group was to identify the effect of the OSPI-Europe project on the prescription pattern of doctors from the same location which, although not subjected to training, might have been influenced by their intervened colleagues comments and also by public relations

activities and mass media campaigns held in Amadora. This group included 148 doctors prescribing in Amadora (in the period from January 2009 to December 2013). Its has to be highlighted that these numbers corresponds to the total number of doctors, included in the ARS LVT database, that prescribed at least for a one month period during the time this study was developed.

In fact, Amadora's primary health care centres lost almost 50% of the GPs from the preparation period of the OSPI-Europe in September 2008 until the beginning of the trainings in may 2010, hence the much smaller number of doctors included in training (as it is further detailed). Actually, in May 2010 there were 90 GPs in Amadora of which 71 were trained.

The non-intervened group of GPs coming from Almada, due its geographical location (other side of Tagus river) was expected not to be influenced during the time that the OSPI-Europe project was developed in Amadora. This group originally included 303 doctors prescribing in Almada.

For each control group, the director of the clinical council for the primary health care units was asked the permission to access the overall benzodiazepine prescription of all doctors working in them.

Doctors' distribution		
Amadora		Almada
Intervened	Non-intervened	Non-intervened
71	148	303

Table 1. Distribution of General Practitioners by intervention and non-intervention groups, considering the total of doctors included in the original ARS ALT database.

2.2. Intervention

Under the OSPI-Europe project, one training session was delivered to intervened GPs. The OSPI-Europe research project was executed with the principles laid down in the Helsinki declaration (2000). In Portugal, the Ethical Committee of NOVA Medical School approved the research protocol (ref. CE/DP/7-2009)

The intervention consisted of one eight-hour training session. The content focused on detecting signs of depression and anxiety, on how to diagnose depressive disorders and on how to specifically search any signs of suicidal ideation. Another topic emphasised during the training session was the need for adequate treatment and which drugs should be prescribed. Role modelling was used as well as guidelines.

Specifically concerning adequate prescription choices, the focus was the conscientious prescription of benzodiazepines and antidepressants. In the case of antidepressants, their clinical goal, their major effects and pharmacological actions as well as the rate of clinical response, good-practice monitoring, treatment phases, prototypical comorbid clinical pictures, were all explored. According to Portuguese and international literature, selective serotonin reuptake inhibitors (SSRIs) should be used as the first choice treatment (Simon 2002, MacGillivray et al. 2003, Pestana and Figueira 2012).

Moreover, some details of other antidepressant subclasses were discussed and it was explained when it was adequate to consider their utilisation. Concerning benzodiazepines, firstly, their utilisation was reviewed in patients suffering from insomnia and anxiety. Secondly, the different utilisations were exposed and the need for limiting the prescription to a treatment of less than 8 to 12 weeks long was highlighted, according to international guidelines and national recommendations (Pestana and Teixeira 2011). Additionally, the approach to the patient abusing benzodiazepines was considered, with suggestions of ways for reducing and stopping abusive utilisation: dose reduction, switching for antidepressant treatment, and avoidance of purchase without a prescription.

The intervention was repeated to seven groups of GPs in five different months (May 2010, June 2010, October 2010, November 2010 and March 2011) and was delivered always by the same team, which was composed by a psychiatrist and a psychologist as co-trainer. They always presented the same slides, performed the same role-modelling sessions, distributed the same videos and made an effort to replicate the training in a similar way.

The training was set in a conference room specifically prepared for that event.

Each participant was exposed to a single intervention. This was the only session delivered, and besides the moment of evaluation of the acquired knowledge, no further contact was established between the investigation team and the intervened GPs, but desktop placards with memos and core information were distributed.

All GPs included in the OSPI-Europe project gave their informed consent. This document included authorization to analyse the BZDs and antidepressant prescriptions of the

intervened doctors, and to evaluate the effectiveness of training in the acquisition of new knowledge and changing attitudes. Concerning the non-intervened groups of GPs, an authorisation was obtained from the primary health care centres' executive president in order to analyse the same content coming from their prescriptions.

2.3. Objectives

The primary objective of this study was to evaluate the change in benzodiazepine prescription pattern after a training session delivered to GPs. The secondary objective was to compare the prescription trend in the intervened group of doctors with the trend of two other groups of non-intervened doctors prescribing in the same type of primary health care centres, globally and by gender.

2.4. Outcomes

The primary outcome for this investigation was the change in the prescription pattern (globally and by gender) of intervened GPs who were given training about correct benzodiazepine prescription.

A secondary outcome for this study was the change in the prescription trend of non-intervened GPs coming from the same region as the intervened group and of the non-intervened GPs coming from a different region.

For the analysis of the trends in the prescription the Defined Daily Dose (DDD) methodology proposed by the World Health Organization (WHO) was used, which allows aggregation of data across drug groups and comparisons between countries, regions and health facilities (WHO 2003).

The Defined Daily Doses (DDD) for the monthly-prescribed benzodiazepines was computed as follows:

$$DDD = \sum \frac{(\#\,items.per.package) * (amount.of.drug.per.item(mg)) * (\#\,packages)}{Defined.Daily.Dose(for.each.drug)}$$

Equation 1. Formula used to compute benzodiazepine DDD

This methodology was preferred to the more straightforward analysis of the number of prescriptions or the number of packages prescribed because each prescription could correspond to a very different quantity of drug. To exemplify, the difference between prescribing a package of 0.5mg dosage of alprazolam with 30 pills (15 DDDs) and a package of 1mg dosage of the same substance with 60 pills (60 DDDs), could only be taken into account using the chosen methodology.

Then, for comparison and trend analysis, the Defined Daily Doses per 1000 patients per day (DHD) was computed as follows:

$$DHD = \frac{(total.DDD.prescribed.in.a.month.by.GP)X1000\,patients}{(30days)X(\#\ patients.observed.in.each.month.by.GP)}$$

Equation 2. Formula used to compute benzodiazepine DHD

It has to be highlighted that the previous equation usually uses the overall number of inhabitants to whom the drug might be offered in the specific period of time. However, the total number of patients observed by month by each doctor was chosen instead, as a significant proportion of the population in 2009-2012 still hadn´t an assigned GP. The ARS LVT also provided this data. In some cases, the data provided for the number of patients observed was missing or the number provided was substantially low compared to the number of prescriptions included in the original prescription database. In those cases, it was chosen to replace the number of patients observed by the number of patients to whom any prescription had been included in the original database.

In order to perform the statistical analysis concerning the comparison of prescription trends between the three groups of GPs (intervened GPs coming from Amadora; non-intervened GPs coming from Amadora; and non-intervened GPs coming from Almada) the Defined Daily Doses by 1000 patients per day (DHD) were aggregated according to the following formula:

$$DHD = \frac{(total.DDD.prescribed.in.a.month.by.GP.group)X1000\,patients}{(30days)X(total.patients.observed.in.each.month.by.GP.group)}$$

Equation 3. Formula used to compute benzodiazepine DHD aggregated by group of GP included in the analysis

For the general analysis by group of GPs, the mean monthly DHD was found through the following method: since intervened doctors were not trained on the same moment in time (the interventions happened in 5 different months through a period of 10 months), each group of doctors intervened on the same month and the two matching non-intervened groups had a specific time scale (so for each group there might be 5 different timescales). In order to have a single time scale for the intervened group in Amadora, the non-intervened group in Amadora and the non-intervened group in Almada, the mean value for the prescribed DHD corresponding to the same moment in the time scale was computed (meaning that for the same timescale moment a single DHD value corresponding to the mean monthly prescribed DHD was found for every group of doctors intervened in the same moment).

For the analysis of the trend in benzodiazepine prescription by gender for each group of GPs the mean monthly-prescribed DHD by females and the mean monthly-prescribed DHD by males were calculated for each group of GPs.

2.5. Sample size

This study included the total benzodiazepine prescriptions coming from the doctors selected for analysis between the 12 months before and after the intervention period (please see next section for further detail on the assignment of participants). This included 146.284 individual benzodiazepine prescriptions, 51.342 from the intervened GP group from Amadora, 30.572 from the non-intervened group of GPs from Amadora and 64.370 from the non-intervened group of GPs from Almada.

2.6. Assignment method

Of the original 71 trained doctors, only 57 could be included in this study because 14 hadn´t their prescriptions associated with the Regional Health Administration of Lisbon and Tagus Valley (Administração Regional de Saúde de Lisboa e Vale do Tejo, herein after referred to as ARS LVT) database for primary health care prescriptions. This happened mostly because in 2009 the ARS LVT system missed some prescriptions (for example prescriptions filled by hand that were not introduced in the computerised database system), and also because some doctors were not primarily prescribing at a primary health care unit of Amadora (so the bulk of their prescriptions was performed elsewhere), or because some were first year residents (so during the follow-up period their prescriptions changed to another location). In one case, although the doctor was trained, there weren´t any prescriptions included in the ARS LVT database in the follow-up period.

Of the total 57 GPs intervened, 22 came from "Family Health Units" – herein after referred as USFs, the Portuguese acronym. A slightly higher number of GPs (35) came from "Primary Health Care Units" – herein after referred as UCSPs, the Portuguese acronym. It is important to stress that these two types of primary health care units have significantly different management criteria. The USFs are based in a more regulated model of care, and doctor practicing in this type of unit receive monetary incentives based on better clinical performance, which is defined by an annually signed agreement between the Regional Health Administration and the USF's regional executive director. The UCSPs are less regulated and organised.

The doctors chosen to integrate the two control groups (Amadora non-intervened and Almada) were firstly selected taking into account that they were practicing and prescribing

in the same month that the intervention was held. Since the original dataset contained benzodiazepines prescriptions data from January 2009 to December 2013, some doctors whose prescriptions ended before or started after the date of the training sessions were excluded.

For each group of doctors that were trained in the same month, two matching groups of non-intervened doctors were selected. This selection took into account the type of primary health care facility where the GPs were prescribing.

Doctors' distribution after matching					
Amadora				Almada	
Intervened		Non-intervened		Non-intervened	
total=57		total=44		total=57	
35 UCSPs	22 USFs	30 UCSPs	14 USFs	35 UCSPs	22 USFs

Table 2: Distribution of general practitioners included in the analysis after matching.

More specifically: for every GP trained in Amadora at a specific month, it was matched a non-intervened GP from Amadora and a non-intervened GP from Almada prescribing in the same type of primary care unit, either USF or UCSP. It has to be highlighted that for Almada it was possible to obtain a 1-1 match, however regarding Amadora, the number of doctors available was insufficient so we used average DHD (see above table).

2.7. Units of Analysis

A database provided by the Information System of the ARS LVT was used. This database initially included all benzodiazepines' prescriptions reimbursed by the National Health System (NHS) beneficiaries from GPs working at primary health care centres in Almada and Amadora from January 2009 to December 2013. It did not considered prescriptions reimbursed by other health care reimbursements systems.

The sample selected for this study derived from the previously mentioned dataset. Prescriptions included for statistical analysis came from the 158 GPs selected after matching and corresponded to the designated time frame for the investigation: 12 months before to 12 month after the intervention period.

ARS LVT provided the dataset after the study protocol for the present investigation was evaluated and approved by the ARS LVT Ethics Committee for Health (please see document in attachment).

The original database contained 635.216 entries. Each database entry corresponded to a prescription containing BZDs to an individual patient.

The benzodiazepines included in this study are detailed in the following table:

List of benzodiazepines included in data analysis

Alprazolam	Estazolam	Midazolam
Bromazepam	Ethyl Loflazepate	Oxazepam
Brotizolam	Flurazepam	Potassium Clorazepate
Chlordiazepoxide	Halazepam	Prazepam
Clobazam	Ketazolam	Temazepam
Clonazepam	Loprazolam	Triazolam
Cloxazolam	Lorazepam	Zolpidem
Diazepam	Mexazolam	

Table 3: List of benzodiazepines included in data analysis.

For each entry in the dataset, the following information was originally included: the region and specific primary health care unit where the prescription was performed; the year, month and day of prescription; the number of registration in the Portuguese Medical Board that was utilised to identify each prescriber; an encrypted identification code for every patient; patient´s age; patient's gender; the benzodiazepine generic name; the benzodiazepine brand name; dosage per formulation (in milligrams); number of pills (or equivalent if liquid formulation) per package; the number of packages prescribed.

In order to answer the investigation objectives, based on the original available data, the following information was added to every entry on the database: a continuous variable with the calculation of the Defined Daily Dose (DDD) corresponding to each prescription (calculation performed as previously detailed in the outcomes section, using the dosage per pill or equivalent formulation (in milligrams); number of pills or equivalent formulation per package and the number of packages which was available in the original dataset); a binary variable (NO/YES) identifying the doctors that were intervened; GP's gender; number of patients observed by each doctor per month (additional information asked to the ARS LVT, essential to compute the total benzodiazepine quantity prescribed by month as previously detailed further the outcomes section); a binary variable (UCSP/USF) allowing to identify the type of primary health care unit; a monthly time scale (from -12 to 12) in which the "0"

moment corresponds to the month of intervention, “1” corresponds to one month after intervention and “-1” corresponds to one month before intervention (and so on for the total 25 months-time included in this investigation).

The final dataset used to perform the overall analysis excluded the following data: prescriptions coming from GPs that were not prescribing by the time the interventions were delivered; prescriptions not concerning the study timeframe (from -12 to 12 months after training). This dataset comprised 146.284 entries.

2.8. Statistical Methods

For the general analysis on the prescription trend of each group of GPs, a segmented regression analysis was performed. This is a statistical method suitable for estimating effects in interrupted time series studies in order to conclude about the impact of an intervention on the measure of interest (DHD in this study).

For the analysis of the prescription trend of each group of GPs by gender, a descriptive graphical analysis was performed in order to verify the influence of gender on the general prescription trend.

The statistical analyses were performed using *STATA (StataCorp 2013)* and the *R Project for statistical computing software (Team R 2013)*.

3. Results

3.1. General analysis

This study included 51.342 prescriptions from intervened Amadora GPs group, 30.572 prescriptions from non-intervened Amadora GPs group and 64.370 prescriptions from Almada GPs group. In the following figure a decreasing trend in benzodiazepines prescription is shown in the intervened group and also, more slightly, in the prescription trend of non-intervened groups from Amadora and Almada.

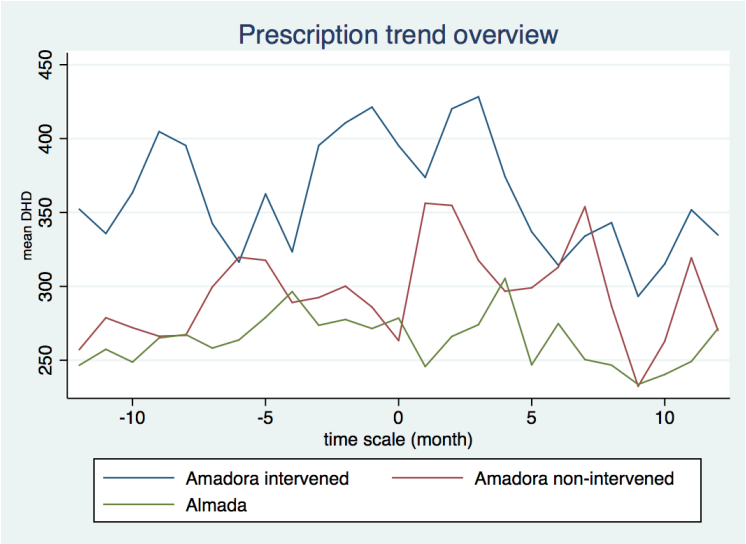


Figure 1. Graphical descriptive analysis of the mean DHD values trend by group of GPs.

In order to verify the change in the prescription pattern after training, a segmented regression analysis was performed and the following graphical analysis demonstrates the slopes for the fitted DHD values.

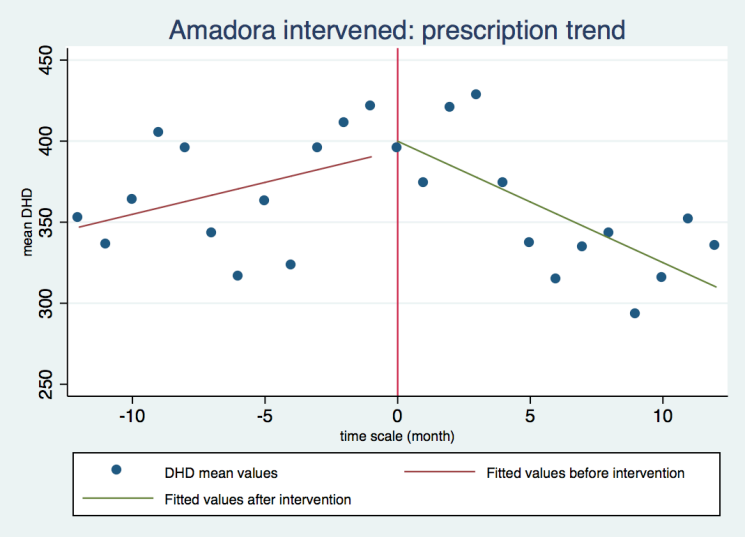


Figure 2. Graphical analysis of DHD mean values trend for the intervened Amadora group.

The graphical analysis for the benzodiazepines prescription trend in the intervened group shows that there was a decrease in the trend just after the intervention.

The following regression analysis demonstrates that there was a non-statistically significant increasing prescription trend before intervention (slope before intervention=3.937; p=0.161) and a significant decreasing prescription trend after the intervention (slope after intervention=-7.488 with a p=0.005).

Mean DHD	Coef.	95% conf. interval	Std. Err.	p
Intercept (before) intervention	394.231	352.739 - 435.723	19.952	<0.001
Intercept (after) intervention	399.917	364.581 - 435.253	16.991	<0.001
Slope (before) intervention	3.937	-1.700 - 9.575	2.711	0.161
Slope (after) intervention	-7.488	-12.485 - 2.491	2.403	0.005

Table 4. Regression analysis for prescriptions of intervened group from Amadora. Intercept before intervention is the predicted mean at time -1; Intercept after intervention is the predicted mean at time 0; Slope before intervention is the slope when the time scale is less than 0; Slope after intervention is the slope when the time scale is 0 or higher.

Furthermore, an analysis was performed to compare the slopes before and after the intervention and a significant difference between slopes was found (difference between slopes = -11.43 with a p=0.005). Since this difference is negative, a decrease in benzodiazepine prescription after the intervention was demonstrated.

In order to verify the prescription trend in the non-intervened group of GPs prescribing in the same area as the intervened group (Amadora), the same analysis was performed, as previously described.

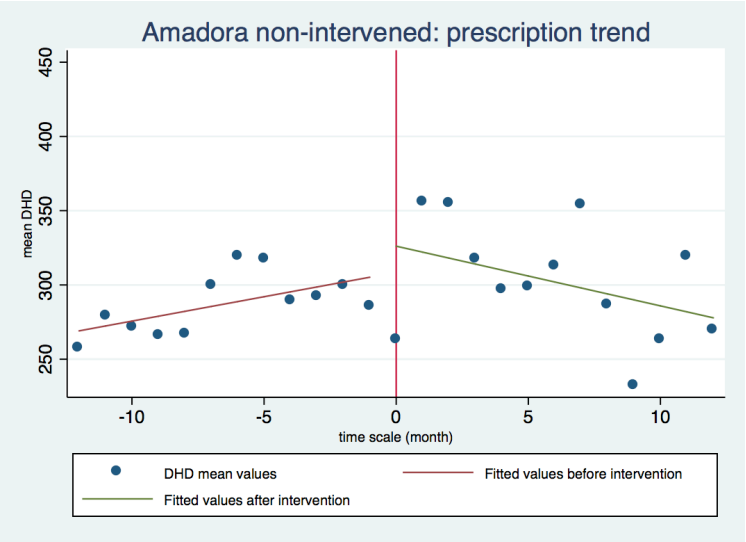


Figure 3. Graphical analysis of DHD mean values trend for the non-intervened Amadora group.

The following regression analysis demonstrates that there was a non-significant increasing prescription trend before the intervention period (slope before intervention =3.282 with a p=0.193) and a decreasing prescription trend after the intervention (slope after intervention =-4,020 with a p=0.079).

Mean DHD	Coef.	95% conf. interval	Std. Err.	p
Intercept (before) intervention	308.478	270.843 - 346.112	18.097	<0.001
Intercept (after) intervention	326.104	294.054 - 358.155	15.412	<0.001
Slope (before) intervention	3.282	-1.831 - 8.396	2.459	0.196
Slope (after) intervention	-4.020	-8.553 - 0.5122	2.179	0.079

Table 5. Regression analysis for prescriptions of non-intervened group from Amadora. Intercept before intervention is the predicted mean at time -1; Intercept after intervention is the predicted mean at time 0; Slope before intervention is the slope when the time scale is less than 0; Slope after intervention is the slope when the time scale is 0 or higher.

As previously, an analysis was performed to compare the slopes before and after the intervention period and a significant difference between slopes was found (difference between slopes =-7.30 with a p=0.037). Since this difference is negative a decrease in benzodiazepine prescription after the intervention period was demonstrated.

In order to verify the prescription trend in the non-intervened group of GPs prescribing in Almada, once again the same analysis was performed.

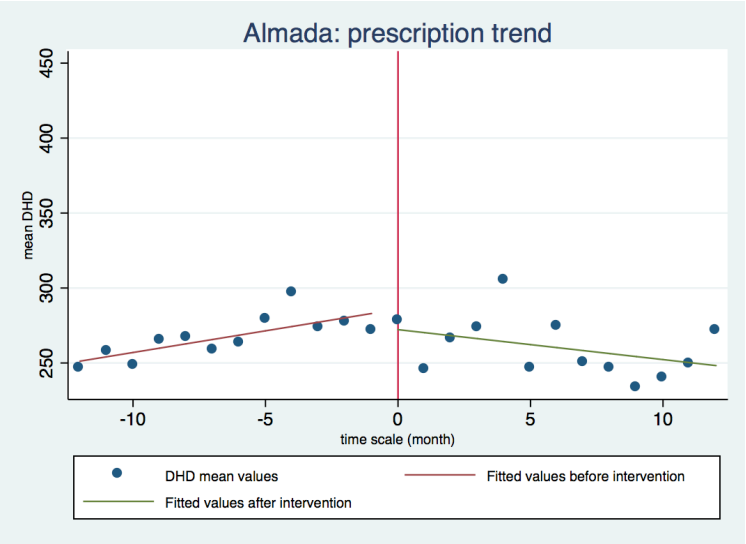


Figure 4: Graphical analysis of DHD mean values trend for the non-intervened Almada group.

The following regression analysis demonstrates that there was an increasing trend in benzodiazepine prescription before intervention (slope before intervention =2.889 with a p=0.036) and a decreasing prescription trend after the intervention (slope after intervention =-1.997 with a p=0.096).

Mean DHD	Coef.	95% conf. interval	Std. Err.	p
Intercept (before) intervention	285.886	266.093 - 305.679	9.518	<0.001
Intercept (after) intervention	272.231	255.375 - 289.087	8.106	<0.001
Slope (before) intervention	2.889	0.199 - 5.578	1.293	0.036
Slope (after) intervention	-1.997	-4.381 - 0.387	1.146	0.096

Table 6. Regression analysis for prescriptions of non-intervened group from Almada. Intercept before intervention is the predicted mean at time -1; Intercept after intervention is the predicted mean at time 0; Slope before intervention is the slope when the time scale is less than 0; Slope after intervention is the slope when the time scale is 0 or higher.

An analysis to compare the slopes before and after intervention was performed and there was a significant difference between these slopes (difference between slopes =-4.886 with a p=0.010). Since this difference is negative a decrease in benzodiazepine prescription after the intervention was demonstrated.

Finally, a comparison between the slopes for the different groups of GPs included in this study was performed. This analysis demonstrated that there was no significant difference in the slopes before (p=0.859) and the slopes after intervention (p=0.290) for intervened and non-intervened groups in Amadora. Also there was no significant difference between the

slopes before (p=0.889) and the slopes after intervention (p=0.417) for the non-intervened group of Amadora and for the group from Almada.

When comparing the slopes before and the slopes after intervention for the intervened group in Amadora and the non-intervened group in Almada, the same analysis demonstrates no significant different in the slopes before the intervention (p=0.728), but there is a significant difference in the slopes after intervention (p<0.001).

Finally, it should be highlighted that all the graphical analysis showed an increase in benzodiazepine prescription around the 10th month after the intervention period.

3.2. Analysis by prescribers' gender

A more in depth analysis was performed in order to study the prescription pattern according to prescribers' gender.

Of the total benzodiazepines prescribed by the intervened group from Amadora, 31.249 came from 37 female prescribers and 20.093 came from 20 male prescribers. Of the total benzodiazepines prescribed by the non-intervened group from Amadora, 21.011 came from 28 female prescribers and 9.561 came from 16 male prescribers. Of the total benzodiazepines prescribed by the non-intervened group of GPs coming from Almada, 36.228 came from 33 female prescribers and 28.142 came from 24 male prescribers.

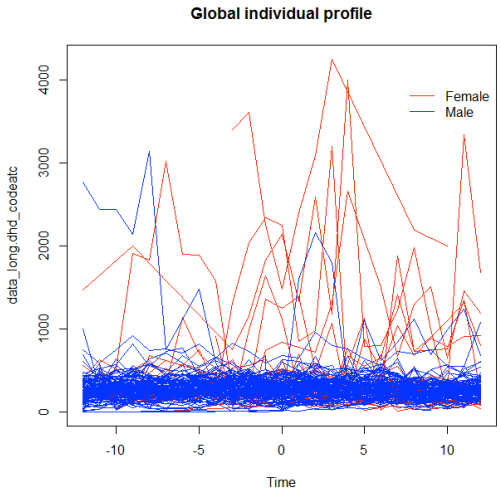


Figure 5. Spaghetti plot for individual benzodiazepine prescribing profile of all doctors involved in the study.

Figure 5 illustrates the individual prescribing profile of all the doctors involved in this study. This analysis demonstrates that female prescribers have higher benzodiazepine prescription. To further investigate differences in prescription trends between genders, a detailed analysis was performed for each group included in the study.

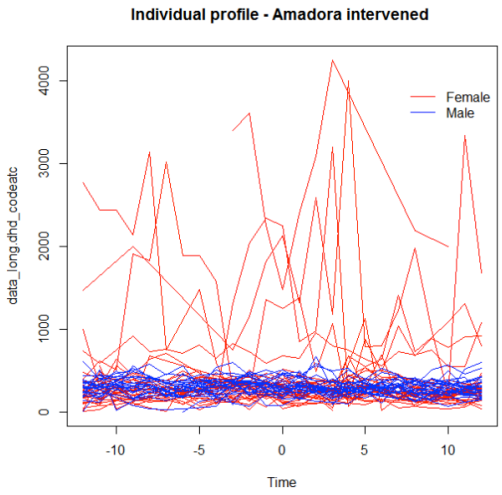


Figure 6: Spaghetti plot for individual benzodiazepine prescribing profile of intervened GPs from Amadora.

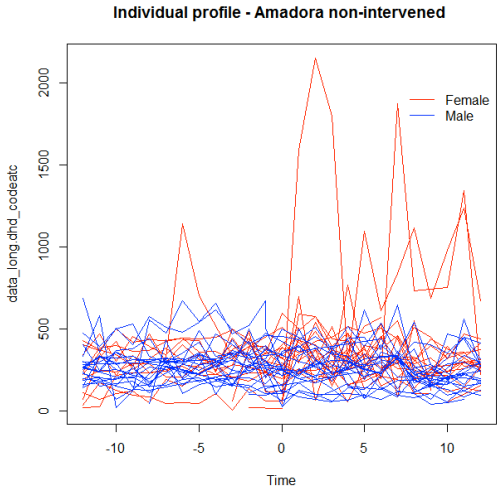


Figure 7: Spaghetti plot for individual benzodiazepine prescribing profile of non-intervened GPs from Amadora

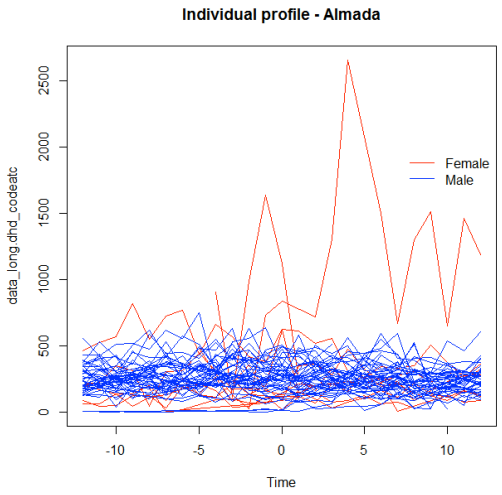


Figure 8: Spaghetti plot for individual benzodiazepine prescribing profile of non-intervened GPs from Almada

This analysis brought to light the existence of a difference between prescription trends in female and male prescribers. In order to explore this difference, an analysis of prescription trend by gender and a comparison of the slopes for the prescription trend before and after the intervention period were performed for each group.

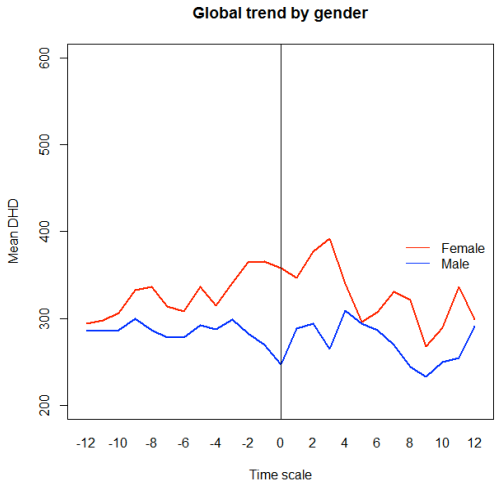


Figure 9: Graphical analysis of the mean DHD prescribing pattern by gender – overall trend for all the doctors included in the study.

The previous graph illustrates the overall mean prescribing trend of benzodiazepines of all doctors included in this study by gender. One can state that these results again demonstrate differences in benzodiazepine prescribing pattern by gender. Females generally prescribe more benzodiazepines, but their prescribing patterns have a more deep decrease after intervention than male prescription patterns.

The following figures regard the mean DHD prescription trend by gender, specifically for the intervened GPs in Amadora.

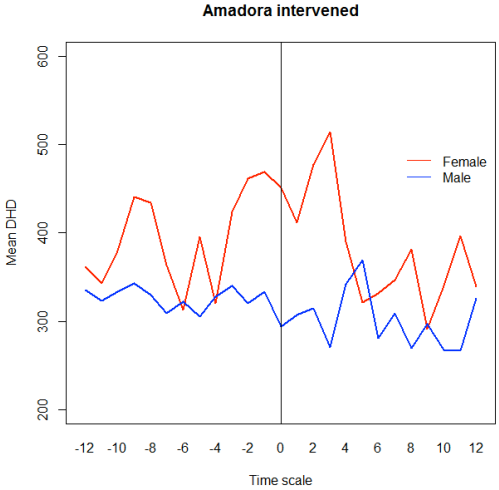
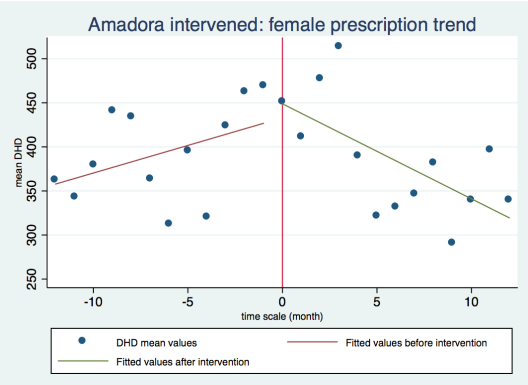


Figure 10: Graphical analysis of the mean DHD prescribing pattern of intervened GPs from Amadora by gender



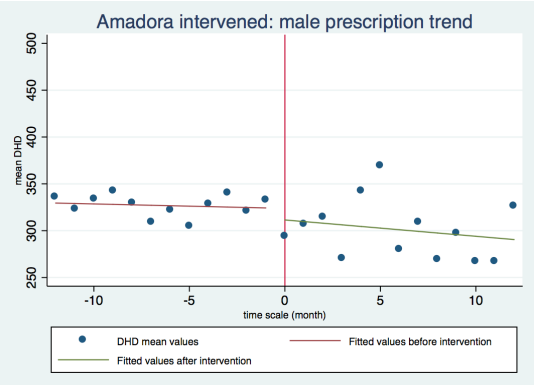


Figure 11: Graphical comparison of DHD mean values trend for the intervened Amadora group, by gender.

	Female gender			Male gender		
Mean DHD	**Coef.**	**95% conf. interval**	**p**	**Coef.**	**95% conf. interval**	**p**
Intercept (before) intervention	433.015	366.427 – 499.604	<0.001	323.806	292.168 – 355.444	<0.001
Intercept (after) intervention	448.889	392.181 – 505.598	<0.001	311.461	284.517 – 338.405	<0.001
Slope (before) intervention	6.264	-2.783 – 15.312	0.165	-0.474	-4.772 – 3.825	0.821
Slope (after) intervention	-10.784	-18.804 – 2.764	0.011	-1.743	-5.553 – 2.068	0.352

Table 7: Regression analysis for prescriptions of intervened group from Amadora, by gender. Intercept before intervention is the predicted mean at time -1; Intercept after intervention is the predicted mean at time 0; Slope before intervention is the slope when the time scale is less than 0; Slope after intervention is the slope when the time scale is 0 or higher.

Figures 10 and 11 show that female intervened gender GPs from Amadora were prescribing more before intervention, with an increasing trend in the year before intervention (slope before intervention =6.264 with p=0.165), and they kept prescribing more than male prescribers, although with a reduction in benzodiazepine prescription immediately after the intervention period (slope after intervention =-10.784 with p=0.011). There is a significant difference between slopes before and after intervention for female gender (difference between slopes =-17.05 with p=0.008). Concerning male gender, their BZD prescription is lower than for females. Before intervention, male gender presents a very small and non-significant decreasing trend in prescription (slope before intervention =-0.474 with p=0.821). After intervention, male gender maintains a non-significant decreasing trend in prescription (slope after intervention =-1.743 with p=0.352). There was no significant difference in the prescription trend for male gender before and after intervention (difference in slopes =-1.269 with p=0.651).

The following figures regard the mean DHD prescription trend specifically for the non-intervened GPs in Amadora by gender.

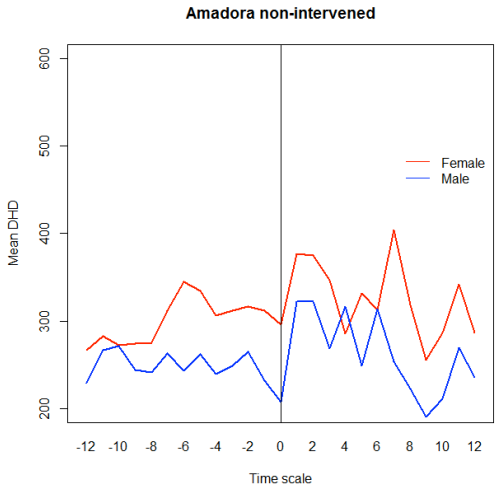
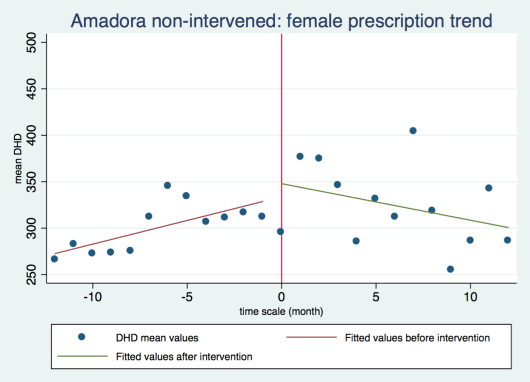


Figure 12: Graphical analysis of the mean DHD prescribing pattern of non-intervened GPs from Amadora by gender



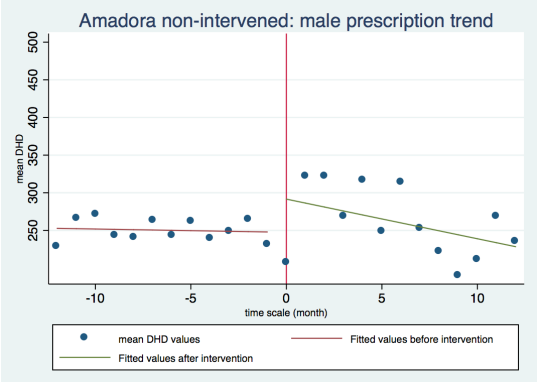


Figure 13: Graphical comparison of DHD mean values trend for the non-intervened Amadora group by gender.

	Female gender			Male gender		
Mean DHD	**Coef.**	**95% conf. interval**	**p**	**Coef.**	**95% conf. interval**	**p**
Intercept (before) intervention	333.747	290.737 – 376.757	<0.001	247.560	204.728 – 290.392	<0.001
Intercept (after) intervention	347.906	311.277 – 384.535	<0.001	291.5867	255.109 – 328.064	<0.001
Slope (before) intervention	5.092	-0.752 – 10.936	0.084	-0.436	-6.255 – 5.383	0.878
Slope (after) intervention	-3.937	-9.117 – 1.243	0.129	-5.260	-10.419 – 0.102	0.046

Table 8: Regression analysis for prescriptions of non-intervened group from Amadora, by gender. Intercept before intervention is the predicted mean at time -1; Intercept after intervention is the predicted mean at time 0; Slope before intervention is the slope when the time scale is less than 0; Slope after intervention is the slope when the time scale is 0 or higher.

As previously, the same analysis was performed to describe the slopes of the trend in prescription for non-intervened GPs from Amadora.

Figures 12 and 13 demonstrate there is also a difference in prescribing patterns by gender in the non-intervened GPs from Amadora.

Female GPs were prescribing more before intervention, with an increasing trend in the year before intervention (slope before intervention =5.092 with p=0.084), and they keep prescribing more than men, although with a non-significant reduction in benzodiazepine prescription after the intervention period (slope after intervention =-3.94 with p=0.129). There is a significant difference between slopes before and after intervention for female gender (difference between slopes =-9.028 with p=0.026).

Concerning male GPs, their BZD prescription is lower than for females. Before intervention, non-intervened male gender GPs present a non-significant decreasing trend in prescription (slope before intervention =-0.436 with p=0.878), which is very similar to the prescription trend of intervened male GPs. After intervention, male gender GPs presents a significant decreasing trend in prescription (slope after intervention =-5.260 with p=0.046). There was non-significant difference in the prescription trend for male gender before and after intervention (difference between slopes =-4.824 with p=0.211).

Finally, the following figures analyse the mean DHD prescription trend for the non-intervened GPs in Almada, by gender.

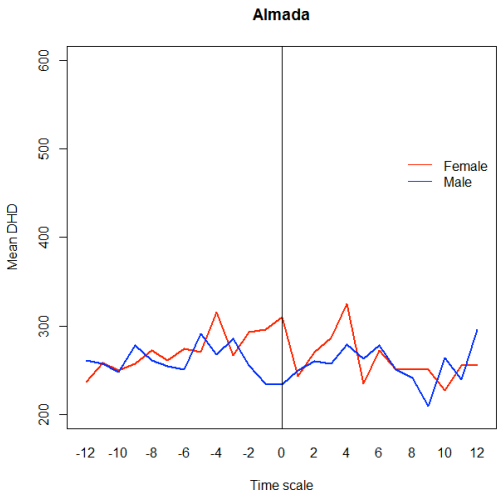


Figure 14: Graphical analysis of the mean DHD prescribing pattern of non-intervened GPs from Almada by gender

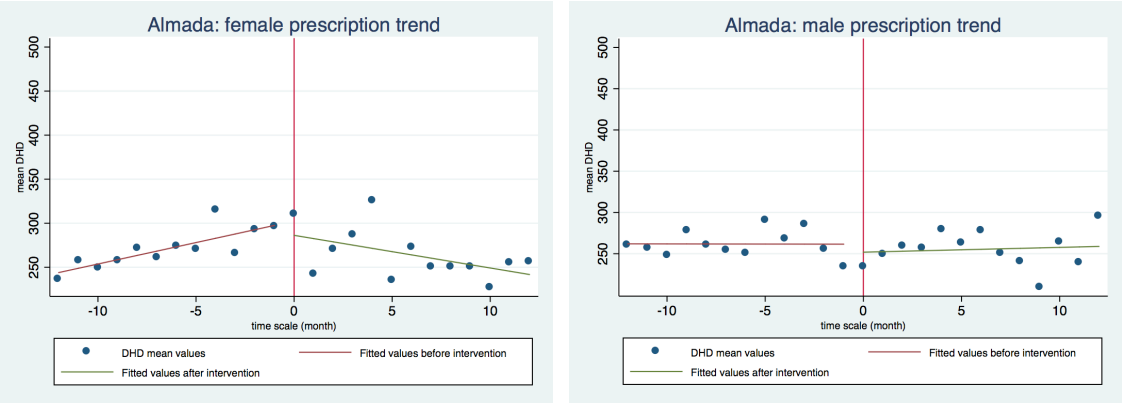


Figure 15: Graphical comparison of DHD mean values trend for the intervened Almada group by gender.

	Female gender			Male gender		
Mean DHD	**Coef.**	**95% conf. interval**	**p**	**Coef.**	**95% conf. interval**	**p**
Intercept (before) intervention	302.348	275.513 – 329.182	<0.001	261.543	235.476 – 287.61	<0.001
Intercept (after) intervention	286.234	263.381 – 309.087	<0.001	251.869	229.669 – 274.069	<0.001
Slope (before) intervention	4.867	1.221 – 8.514	0.011	-0.034	-3.576 – 3.508	0.984
Slope (after) intervention	-3.707	-6.939 – 0.475	0.027	0.579	-2.561 – 3.718	0.705

Table 9: Regression analysis for prescriptions of non-intervened group from Almada, by gender. Intercept before intervention is the predicted mean at time -1; Intercept after intervention is the predicted mean at time 0; Slope before intervention is the slope when the time scale is less than 0; Slope after intervention is the slope when the time scale is 0 or higher.

In figure 14 some results stand out when comparing with the previous similar analysis to the other groups of GPs from Amadora. Firstly, benzodiazepines' total prescription amount and trends are lower in Almada than in Amadora (for intervened and for non-intervened groups of GPs). Secondly, the differences in the amount of prescription and trends are smaller when comparing female to male prescribers.

As figure 15 and table 9 further demonstrate, female gender GPs in Almada were prescribing more than male gender GPs before intervention, with a significant increasing trend in the year before intervention (slope before intervention =4.867 with p=0.011), and they kept an higher prescription trend compared to male prescribers, although with a reduction in benzodiazepine prescription after the intervention period (slope after intervention =-3.707 with p=0.027). There is a difference between slopes before and after intervention for female gender (difference in slopes =-8.575 with p=0.001).

Concerning male gender GPs, before intervention their trend presents a non-significant decrease (slope before intervention =-0.034 with p=0.984). After intervention, male GPs present a non-significant increasing trend in prescription (slope after intervention =0.579 with p=0.705). There was no significant difference in the prescription trend for male gender before and after the intervention period (difference in slopes =0.612 with p=0.790).

A comparison between the slopes for the different groups of GPs before and after intervention was also performed by gender. This analysis demonstrated there were no significant differences between slopes by gender. Since in the general analysis it was found a significant difference between the slopes after intervention of the prescription trend for the intervened GP group in Amadora and the non-intervened group in Almada ($p<0.001$), one can state that this difference results from the combination of effects from female and male gender prescription trends.

4. Discussion

4.1. Global decrease in benzodiazepine prescription

The initial general analysis demonstrated a decrease in benzodiazepine prescription trend after the intervention period, which corresponded from May 2010 to March 2011. This decreasing trend happened in all three groups of GPs included in this study, although with a larger differences in slopes pre and post-intervention and more statistical significance for the intervened group from Amadora.

The author searched the Portuguese General Health Administration (Direcção Geral de Saúde – DGS) database for any guidelines or information advises in order to justify the general decrease in benzodiazepine prescription.

In November 2011 a non-compulsory guideline was published concerning the treatment of anxiety and insomnia (Pestana and Teixeira 2011). In this guideline it was advised to avoid long-term benzodiazepine utilisation, so one could state that its publication would probably lead to a reduction in prescription. However, the data showed a decrease right after the intervention period (from May 2010 to March 2011), which might indicate that the change in prescription pattern is due to the intervention. Nevertheless, the guideline was probably subject to public discussion – meaning, discussion between peers – before it's definitive publication.

A search on both the National Authority of Medicines and Health Products (INFARMED)[3] and on the European Medicines Agency (EMA)[4] was performed in order to verify if any information or warning was published concerning each of the active substances included in the analysis. As previously, no appropriate information was found in order to justify the global decrease in benzodiazepines in the period right after the intervention.

The author was aware that the USFs primary health care centres sign annually a contract with the governmental financing agency in which some quality goals are set[5]. A review was performed in order to verify if there was any article in these contracts concerning specifically the prescription of benzodiazepines. Contracts for Amadora and Almada in 2010 and 2011 had an explicit recommendation concerning both benzodiazepines and antidepressants. In this recommendation the combined increase of these two groups of medicines was proposed. In Amadora (the region where GPs were intervened), an increase was proposed

[3] http://www.infarmed.pt/portal/page/portal/INFARMED
[4] http://www.ema.europa.eu/ema/
[5] Contratos programa para os agrupamentos de Centros de Saúde: Agrupamento de Centros de Saúde VI: Amadora e de Almada-Seixal

from 93 DHD to 100 DHD and in Almada an increase from 112 DHD to 130 DHD. In this sense, it also cannot be assigned to these contracts the change in prescription pattern after the intervention period.

Further research was performed in order to include more recent data contained in these contracts but the 2012 contracts for Amadora and Almada were not available and in 2013 the contracts stop referring to the adequate prescription of benzodiazepines (and antidepressants).

Finally, the awareness on the negative effects of benzodiazepine long-term utilisation is relatively recent in the literature. A Medline literature search using the terms "benzodiazepines" and "side-effects" was performed to verify how many papers were published in the total period of time in which the study took place (May 2009 to March 2012) and then in the 3 months before and after the intervention period (February 2010 to June 2011). In the first mentioned period, 1180 papers were published referring this subject while in the second mentioned period, 996 papers were published. This demonstrates that by the time the intervention was taking place, the scientific/medical community was concerned about the negative effects of benzodiazepine's utilisation. This large number of papers might have influenced the GPs prescription pattern, although the author admits that this fact shouldn´t have had such an important and general impact.

An Hawthorne effect or a contamination effect between groups of GPs was also considered in order to explain the general change in prescription trend after the intervention period.

The Hawthorne effect suggests that study subject's behaviour or study results are altered by the subjects' awareness that they are being studied (Fernald et al. 2012). This is specially a concern when subjects are not blinded to randomization (Fernald et al. 2012), as it happened in this research since some GPs from each primary health care centre were trained while others weren't. In addition, as public relations activities and media campaigns were held in Amadora at a community level, although not knowing the exact study outcomes, the non-intervened doctors from Amadora might have been aware that the measures implemented by the OSPI-Europe project would be later assessed, and for this reason, they might have changed their prescription pattern due to the knowledge they were being "observed". The Hawthorne effect was already described in a multi-practice audit of benzodiazepine cessation (Holden 2001), so one might infer about the influence of this effect in the decreasing trend in BZD prescription after the intervention period for the two groups of GPs prescribing in Amadora.

Contamination in trials occurs when people who were not intended to receive an intervention, inadvertently do so (Keogh-Brown et al. 2007). Trials of educational interventions are especially prone to contamination because the active ingredients can be transportable and difficult to confine (Keogh-Brown et al. 2007). Contamination tends to reduce the magnitude of effect estimates and therefore also to increase the chance that estimates will not be statistically significant, therefore causing bias and reducing power (Keogh-Brown et al. 2007, Torgerson 2001). A 2007 consensus on contamination in clinical trials argued that contamination was more likely in trials conducted in settings where subjects worked, lived or interacted closely together and where interventions were desirable, simple or easily transferable or were aimed at increasing knowledge. It was less likely when subjects were socially or physically separate, and where interventions were complex or aimed at changing behaviours. It was more likely with interventions aimed at health professionals than with interventions aimed at patients. It was more likely with interventions based on broadcast media, audiovisuals or written information and was least likely with computer-based reminders (Howe et al. 2007).

In this sense, one can discuss that the decrease in prescription trend after the intervention period in the non-intervened group of GPs from Amadora could be due to a contamination effect. Concerning Almada, although the group of GPs from this region was physically separated from the intervened group in Amadora, both Amadora and Almada primary health care centres belong to the same Regional Health Administration (ARS LVT), therefore some information spilling would be possible and a reasonable justification to the slight decrease in BZDs prescription in Almada after the intervention period.

Another aspect that cannot be taken lightly is the effect of general national trends. In fact, we previously ascertained a reduction of BZD utilization and prescription from 2010 both at national level and at ARS LVT level (Furtado 2013). This systemic effect could help explain the downward trends in the three sites, pre and post-intervention, the differential effect in Amadora intervened GPs being due to the intervention itself.

A comparison between the slopes for the prescription trends demonstrates that the results are consistent with the author's expectations. There is a significant difference between the slopes after intervention period for intervened GPs from Amadora and for non-intervened GPs from Almada.

Finally, since participants self-selected themselves to integrate the intervened group of GPs in Amadora, there might be a bias a selection bias influencing the results.

4.2. Gender effect and needs

A detailed analysis considering the benzodiazepine prescription trend of the three GPs groups demonstrated the existence of a difference in the prescribing pattern between female and male prescribers.

In all groups (even for Almada where the difference between genders was smaller), female GPs prescribed a greater amount of benzodiazepines.

The available dataset does not allow to further exploring the reasons and the meaning of this difference.

It would be expected to have patients with similar characteristics regardless the prescriber's gender, so one might infer that these differences are due to characteristics of the prescriber. The author performed a literature review searching for studies with similar female higher BZDs prescription trends and also for reasons for this fact. There is a lack in literature concerning these questions, since most of the papers found focussed the patient's gender (most BZDs were reported to be prescribed to women) instead of the prescriber's.

Three references were found concerning differences in attitudes towards depression identification and treatment by primary health care doctors, in which it was demonstrated that female prescribers were more insecure and might hesitate in establishing a definite diagnose when comparing to male doctors. These reasons might justify a delay in prescribing antidepressants, hence choosing to prescribe more frequently BZDs (Rollman et al. 2001, Andersson, Lindberg, and Troein 2002, Gusmão 2005).

A comparison of the slopes for the prescription trends by gender suggests that the decreasing BZD prescription pattern after intervention in Amadora is due to the changing in female doctors prescription pattern. This indicates that the effectiveness of the intervention in Amadora was mostly due to the decrease in BZD prescription from female GPs. One might infer that since females were prescribing more before intervention, it would be easier to integrate the new knowledge derived from the intervention into clinical practice.

4.3. The need for training sustainability

Finally, the author considered that the increasing trend in prescription that is shown in all graphical analysis 9 to 10 months after the intervention period (corresponding to the period from February 2011 to December 2011) is worthy of comments.

In order to find a reason for this change in pattern occurring in all three groups of GPs included in this study, the same previous review of (1) the Portuguese General Health

Administration documents database, (2) the National Authority of Medicines and Health Products (INFARMED) and of (3) the European Medicines Agency (EMA) was performed without any significant finding.

The mentioned contracts signed by Amadora and Almada in 2010 and 2011 mentioning as a goal the increasing prescription of benzodiazepines and antidepressants also shouldn´t explain that fact.

Two more possible explanations for this increase in BZD prescription trend should be considered.

The first is the possible loss of intervention effect for both groups of GPs prescribing in Amadora. Several publications point to this phenomenon happening a few months after educational interventions and point to the need for continuous intervention and monitoring in order to assure the maintenance of the effect (Smith and Tett 2010, Smith et al. 2006).

The second is the influence of the 2008 economic crisis on mental health. Allegedly, there was a direct negative effect of economic crisis on mental health, mental disorders and mental health symptoms (Kentikelenis et al. 2011, Khang, Lynch, and Kaplan 2005, Stuckler et al. 2009). The situation of unemployment and debt might have significantly increase complaints of anxiety in the Portuguese population (Escoval et al. 2012) leading to a greater demand for benzodiazepines.

On the other hand, the crisis did not impact suicide rates (Ayuso-Mateos, Barros, and Gusmão 2013). It is possible that in the short-term, BZD increase after 2011 helped to stop severe effects of increased prevalence of mental pathology thus restraining more suicides from happening. In the future, negative effects of that increase should be seen.

4.4. Limitations

Almada region seemed to be a good choice for control region for this study because of its similarities in terms of socio-demographic structure and also because the Tagus river separating the two regions would prevent the existence of contamination between them. However, the analysis performed demonstrated that doctors prescribing in Almada had a benzodiazepine prescription trend with significant differences concerning the amount and the distribution by prescriber's gender comparing to doctors prescribing in Amadora.

The study would have had higher validity if randomisation at the level of primary health care centres had been performed. In fact, since the GPs organised among themselves to participate and comply with the quotas (50% of the fully active GPs working in Amadora

were required to participate), a selection bias might have occurred. This self-selection might have led to the inclusion in this study of doctors with similar prescribing patterns or learning needs (Would intervened doctor be the ones with a larger number of anxious patients? Or the ones more aware of their inadequate prescribing patterns? Or the ones more interested in learning?) If randomisation would not again be possible, matching should be performed taking into account not only the type of primary health care centre (USFs vs. UCSP), as performed in this study, but also the baseline prescription trend, the GPs' gender and possibly the doctors' clinical experience.

The mean DHD values obtained were substantially higher than the values for DHD prescription known to Portugal: 215 DHD in our study versus 96 DHD for the year of 2012) (Furtado 2013). This was due to the fact that for computing DHD values the total number of patients observed by each doctor was chosen instead of the number of inhabitants of Amadora and Almada. This choice was made after a preliminary analysis that showed very low DHD when the number of inhabitants was used, demonstrating that a significant number of inhabitants still didn't use the primary health care services in 2009-2011.

In some cases the data provided for the number of patients observed, and used to compute the DHD values, was missing or the number provided was substantially low compared to the number of prescriptions included in the original prescription database. In those cases, it was chosen to replace the number of patients observed by the number of patients to whom any prescription had been included in the original database.

5. Conclusions

This study demonstrates how a single intervention might have a positive impact on improving prescription trends.

Since a single intervention to GPs was performed resulting in a significant change in benzodiazepine prescription pattern, surely a cost-effectiveness analysis to the results would demonstrate the benefits of this intervention and the relevance for its replication.

Considering the worrying benzodiazepine consumption in Portugal, the replication of this educational intervention in other primary health care setting would possibly be a good suggestion to the Mental Health authorities to implement in the future.

It was demonstrated that prescription trend of benzodiazepines is different for male and female prescribers. The reasons for this fact could be further explored and considered in future studies concerning interventions to improve prescription patterns.

Finally, considering that 10 months after intervention there was a slight increase in benzodiazepine prescription, these data point to the need of re-trainings, in which case e-learning training sessions could be considered in order to keep sustainability of effect.

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7. Attachments

Attachment 1

TREND Statement Checklist

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions		
		• Structured abstract recommended		
		• Information on target population or study sample		
Introduction				
Background	2	• Scientific background and explanation of rationale		
		• Theories used in designing behavioral interventions		
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)		
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented		
		• Recruitment setting		
		• Settings and locations where the data were collected		
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:		
		○ Content: what was given?		
		○ Delivery method: how was the content given?		
		○ Unit of delivery: how were the subjects grouped during delivery?		
		○ Deliverer: who delivered the intervention?		
		○ Setting: where was the intervention delivered?		
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?		
		○ Time span: how long was it intended to take to deliver the intervention to each unit?		
		○ Activities to increase compliance or adherence (e.g., incentives)		
Objectives	5	• Specific objectives and hypotheses		
Outcomes	6	• Clearly defined primary and secondary outcome measures		
		• Methods used to collect data and any methods used to enhance the quality of measurements		
		• Information on validated instruments such as psychometric and biometric properties		
Sample Size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules		
Assignment Method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)		
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)		
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)		

TREND Statement Checklist

Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.		
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)		
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)		
Statistical Methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data		
		• Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis		
		• Methods for imputing missing data, if used		
		• Statistical software or programs used		
Results				
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)		
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study		
		○ Assignment: the numbers of participants assigned to a study condition		
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention		
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition		
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition		
		• Description of protocol deviations from study as planned, along with reasons		
Recruitment	13	• Dates defining the periods of recruitment and follow-up		
Baseline Data	14	• Baseline demographic and clinical characteristics of participants in each study condition		
		• Baseline characteristics for each study condition relevant to specific disease prevention research		
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition		
		• Comparison between study population at baseline and target population of interest		
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences		

TREND Statement Checklist

Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible		
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses		
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision		
		• Inclusion of null and negative findings		
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any		
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory		
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)		
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study		
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations		
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation		
		• Discussion of research, programmatic, or policy implications		
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues		
Overall Evidence	22	• General interpretation of the results in the context of current evidence and current theory		

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/

Attachment 2

Exma. Senhora Dr.ª

Teresa Reis

alvesreisteresa@gmail.com

C/C: Dr. Prof. Ricardo Gusmão e ao Prof. Dr. Pedro Caetano

Sua Referência	Sua Comunicação de	Nossa Referência	Data
		8042/CES/2012	06-05-2013

Assunto: "Alterações dos padrões de prescrição de benzodiazepinas após formação a médicos de Centros de Saúde."

- Parecer 083/CES/INV/2013 da Comissão de Ética – Secção de Investigação

O Projecto com a designação "Alterações dos padrões de prescrição de antidepressivos após formação a médicos de Centros de Saúde", foi sujeito à apreciação da Comissão de Ética para a Saúde da ARSLVT (Secção de Investigação) na sua reunião de 03-05-2013, tendo merecido Parecer favorável.

Conflito de interesses: não identificados

O Parecer foi aprovado por unanimidade.

O Conselho Directivo, atento ao teor do Parecer emitido por aquela Comissão, entende estarem reunidas as condições para a sua concretização.

Com os melhores cumprimentos,

O Vice - Presidente do Conselho Directivo

Luis Pisco
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