Official title: Prescription of benzodiazepines by Primary health care doctors: characteristics of prescribing trend and implementation of an online educational program

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Abstract

BZD excessive prescription has long been considered a serious mental health concern in many countries. A large number of interventions using different methodologies have been implemented to change BZD prescription pattern at primary health care settings, with limited positive results.
We aimed to propose the implementation of an effectiveness-implementation hybrid type 1 intervention. In our study we developed an online platform, named ePrimaPrescribe, which was delivered using a Digital Behavior Change Intervention(DBCI).
We included in our study all primary health care units from one region in Portugal which were randomly allocated to receive a Digital Behavior Change Intervention (DBCI) in the format of an online platform to reduce BZD prescription (ePrimaPrescribe) or an online platform concerning communication techniques (control).
We primarily aimed to evaluate the effectiveness of our Digital Behavior Change Intervention (DBCI) using as outcome measure the frequency of BZD prescriptions issued per month. Secondarily we aimed to analyze the effect of ePrimaprescribe on antidepressant prescriptions, to study the effect of ePrimaprescribe on diagnosis definition associated with BZD and antidepressant prescription; to perform a cost analysis considering the monthly National Health Service spending with BZD co-payment. We finally aim to analyze the implementation process using quantitative and qualitative methods.

Ethics and dissemination

This trial was approved by the Ethics Commission for Health of the Regional Administration of Health for Alentejo Region (Portugal) (02/2016(CES) and the Nova Medical School, Nova University Lisbon, Portugal Ethics Commission (47/2016/CEFCM). The results will be submitted for publication in peer-reviewed journals.

Introduction

Benzodiazepines (BZD) are commonly used psychotropic drugs for treating insomnia and anxiety (1). Their long-term use is associated with considerable adverse effects (2), such as increased number of falls and bone fractures (2–4), a higher number of road accidents (2,5), and possible role in inducing the phenomenon of suicide (6–8).
Numerous studies have shown that BZD are still overprescribed and commonly used long-term (9,10), despite the existence of clinical guidance advising the use of non-pharmacological psychological treatments first-line, and to restricting BZD prescription to a maximum of 8-12-weeks.
The consistently high prescription of BZD in Portugal has been the target of references in national and international publications for the last 20 years, with this fact being recognized as a sign of inadequate management of mental disorders and considered a serious public health concern (11). It is also a documented fact that BZD in Portugal

are mostly prescribed in primary health care (12), hence pointing to this setting as crucial to implementation of interventions aiming to change BZD prescription pattern.
A large number of interventions using different methodologies have been implemented to change BZD prescription pattern at primary health care settings, such as minimal educational interventions (13–15), systematic discontinuation interventions (16,17), audit and feedback interventions (18), and policy interventions (19,20). The results are inconsistent; when positive, the effect is frequently lost after a short period and seems closely related to each country's primary healthcare setting's particular characteristics.
An educational outreach intervention previously implemented in Portugal had a small effect on BZD prescribing trend and pointed as a primary limitation the lack of staff to implement face-to-face educational sessions to a larger number of General Practitioners (GPs) and with adequate frequency (21). Online interventions, namely targeting a behavioral change, with a low cost and high possibility of wide distribution, were considered a possible way to surpass time and limited resources in primary health care settings to implement an intervention of this nature.
BZD prescription has been reported as a complex behavior influenced by personal values, beliefs, attitudes, experiences, patients' characteristics and demands (22–24). Therefore, besides the relevance of adequately implementing an intervention aiming to change BZD prescription pattern, it is also crucial to gather information about barriers to this implementation, and consider influence factors such as acceptability, practicability, effectiveness, affordability and equity.
This study aimed to evaluate the impact of Digital Behavior Change Intervention tailored online program, ePrimaPrescribe, on changing BZD prescription patterns and, at the same time, to test its implementation in a real-world situation, using an effectiveness-implementation hybrid type 1 design. BZDs are often wrongly chosen to treat anxiety disorder symptoms, at the expense of the adequate pharmacological treatment with antidepressants (25,26). Thus, this study also aimed to verify the effect of our effectiveness trial on antidepressant prescription trends and on diagnoses definition associated with BZD prescription.

Objectives

Main objective
To evaluate the effectiveness of a Digital Behavior Change Intervention (DBCI) at a primary health care setting, in which GPs are given access to an online program, ePrimaPrescribe, aiming to reduce BZD prescription.

Secondary objective
To analyze the effect of ePrimaprescribe on antidepressant prescriptions.
To study the effect of ePrimaprescribe on diagnoses registration associated with BZD and antidepressant prescription.
To perform a cost analysis considering the monthly National Health Service spending with BZD co-payment.
To analyze the implementation process using quantitative and qualitative methods.

Methods and analysis

Study design and setting

We choose an effectiveness-implementation hybrid design taking a dual focus a priori in assessing clinical effectiveness and implementation (27).
A hybrid type 1 study tests a clinical intervention, while gathering information on its delivery during the effectiveness trial, and its potential for implementation in a real-world situation.
We performed our hybrid type 1 effectiveness-implementation using as methodology for intervention implementation a two-arm cluster randomized clinical trial. The cluster design was selected because the allocation and intervention were implemented at the healthcare unit level.
The setting for our intervention was primary health care units at a rural region in Portugal, an area of 7393 km², an estimated population of 166 706 inhabitants (2011), a population density of 22.5 inhab./km², and approximately 250 GPs working in primary health care units (of which 110 were included in our study). Portugal has a public accessible national health service, but mental health indicators are alarming (28). BZD prescription in Portugal is very high, as introduced in our background section, and the consumption of these drugs is particularly significant in the region where our intervention was implemented (11).

Eligibility criteria and recruitment

All primary healthcare units from the Portuguese Central Alentejo region were considered eligible. A researcher contacted each healthcare unit coordinator, explained the project's nature, and invited to participation.
The primary inclusion criteria were healthcare units with acceptance of at least 90% of GPs to participate in the study. We chose a higher acceptance rate than usually reported in the literature since we expected, although accepting to participate in the study, a significant number of GPs in each cluster would not actively use the DBCI ePrimaPrescribe platform.

Sample size

The unit of observation for primary analysis was at the individual GP prescription level. Data collected from a previous research implemented in a similar setting (29) allowed performing estimation for sample size (SS) calculation. We started by doing an SS calculation based on all observations' independence and an effect size of 20% reduction. We obtained a total of N=58 participants, N=29 participants per study arm. To adjust for the intra-cluster correlation coefficient (30), we then calculated the design effect (Deff) expressed as:
Deff= 1+r(m-1) - where r denotes the ICC and m is the size for each cluster.
Considering an average cluster of m=5 and an ICC of 0.02, Deff=1.08.
The SS adjusted for ICC was then be given by:
N*= N(1+r (m-1)), so N*=29(1+0.02(5-1)=31.3, hence approximately 32 per study arm.
The number of clusters (k) was given by:
k= N(1+r (m-1))/m, so k=6.4≅ 7

Considering an ICC of 0.02, a 1:1 ratio of allocation of controls per intervention unit, an alpha type error of 0.05, a cluster size of 5 doctors per unit, a minimal difference 20% reduction in the number of BZD prescriptions, the study would have to include 7 clusters per study arm in order to have an 80% power.

Random allocation

Randomization was stratified according to the organizational type of primary health care unit (UCSP vs. USF), the number of GPs per unit, the average number of appointments, and the number of patients per unit per month. We further included in our randomization criteria primary health care unit's proximity, meaning that when distinct units functioned on the same location/building, we allocated them to the same study arm.
In previous research, using similar baseline BZD prescription data from primary health care units, there was a large spread of monthly BZD prescription (29). Since this spread was similar throughout different units, no stratified randomization (or matching for similar prescribing patterns) was considered to be necessary (31).
Healthcare units were included if 90% of the GPs accept participation.
For concealment of allocation, after all eligible healthcare units accepted participation, we allocated them simultaneously to intervention or control group using a computer-generated random number of tables.
The distribution of participants after randomization is presented in the following figure.

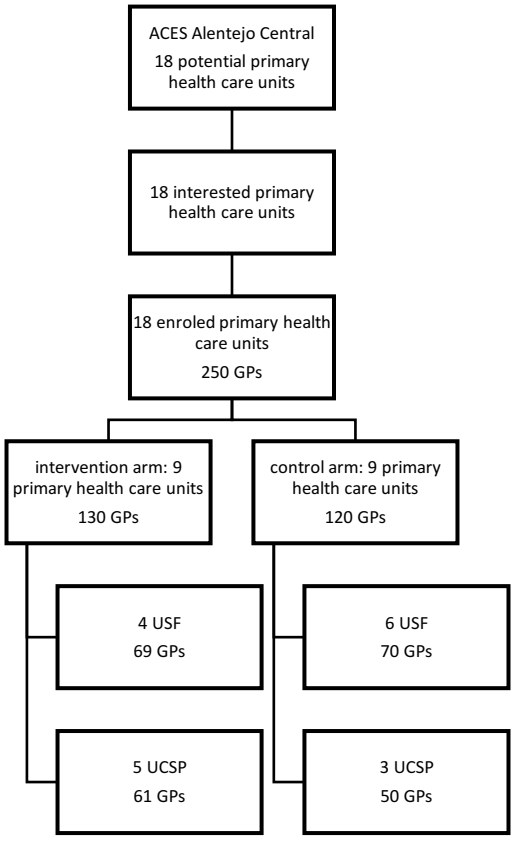

Figure 1: Distribution of participants after randomization

Blinding

GPs could not be blinded due to the fact that they were asked to participate actively in a study seeking to change their prescription practice. Both GPs included in intervention and control arm were asked to access an online platform. However, they were blinded to the existence of alternative content to the platform presented in their primary health care unit.

The authors were not blinded to primary health care unit allocation.

The primary and secondary outcomes were assessed by analysis of the electronic prescription and diagnosis registration database for each GP. These data were extracted and anonymized (except to primary health care unit identification) by a data manager at the central Shared Services of the Portuguese Ministry of Health, who was not involved in the study and was blinded to participant allocation.

Intervention

Development of Digital Behavior Change Intervention (DBCI) online programs

The online programs were designed based on Behavior Changing Wheel theory (32) theory, considering that behavior change is key to improving healthcare and health outcomes. We used a Digital Behavior Change Intervention (DBCI) mode of delivery. The ePrimaPrescribe program, designed to be implemented in the intervention group, was developed based on guidelines for anxiety and depression treatment and benzodiazepines withdrawal. Our primary sources of information were National Institute for Health and Care Excellence (NICE) guidelines (33), guidelines issued by the Portuguese National Health Directorate (DGS) (34,35), and other relevant literature specifically addressing deprescribing evidence-based practice guidelines (36,37). The program comprised three e-learning modules, each with approximately 30 minutes of duration and with the following subjects: pharmacological effect and clinical use of BZD; how to treat anxiety disorder avoiding the continuous use of BZD; how to manage BZD dependence and BZD withdrawal proposals.

The primary health care units included in the control arm of our study were also offered an online platform, named ComunicaSaudeMental. This DBCI platform's content was developed based on literature concerning general communication techniques and more specific communication techniques for addressing light to moderate mental health disorders or patient's emotional management at primary health care settings. This program comprised (similarly to the one offered to the intervention arm) three e-learning modules, each with approximately 30 minutes.

After the development phase, modules were uploaded to two moodle platforms (one for the intervention educational platform, ePrimaPrescribe; another for the control educational platform, ComunicaSaudeMental), and an individual coded access was created to each participant.

Before the implementation phase, both programs were tested by three GPs and three psychiatrists. Two of the GPs were members of the Primary Health Care Research Department at NOVA Medical School, and one was also a member of the Mental Health Research Department at NOVA Medical School. Two of the three psychiatrists were specialists in substance misuse. These experts were asked to comment on the accuracy and quality of the e-learning modules critically. Their suggestions were carefully considered, and when appropriate, were integrated into the module's final version.

Intervention implementation

We used as guidance to the following intervention implementation report, the Template for Intervention Description and Replication (TIDieR) checklist and guide (38).

ePrimaPrescribe online platform was implemented in primary health care setting since this is where most BZD initial and renovation prescriptions are issued. A Digital Behavior Change Intervention (DBCI) was chosen as the delivery method since we hypothesized that a free, easily accessible platform might have a higher and longer-term effect changing BZD prescription pattern.
Both primary health care units allocated to intervention and control arm had an initial face-to-face visit to present to GPs the online platform, delivery of personal identification access code, explanation on how to access and use it. Informed consent was asked during this initial face-to-face visit.

We expected GPs to start accessing and hence actively participating in the study in the weeks following the first face-to-face visit to their unit. Access to the platform was free, available at any convenient time and frequency, through any digital device with internet connection.

We performed all face-to-face visits to allocated primary health care units in a six-week time frame.

We sent an email to GPs every three months, at three, six and nine months after implementation, as a reminder for participation and as a strategy to improve adherence to the intervention. The platform was not tailored, personalized, adapted, or modified in any way during the intervention implementation period.

To assess how well the intervention was actually implemented, and hence to evaluate the extension to which the intervention was delivered as planned, we performed another face-to-face visit to all participating primary health care units, 12 months after the initial intervention. During this visit, GPs included in the intervention arm were asked to answer a survey exploring their motivations and expectations regarding the use of the ePrimaPrescribe program; a questionnaire for evaluating the barriers and facilitators to the Implementation of the ePrimaPrescribe online platform; and to participate in an exploratory group discussion over the general perception of their study participation and platform implementation.

All face-to-face visits, and hence intervention procedures explanation and monitoring were provided by the first author, who has a background as a psychiatrist and regularly performs her clinical work in the same geographical area where the intervention was implemented.

We performed semi-structured in-depth interviews with an intentional sample of participants from the intervention arm to explore perceptions on the feasibility and implementation of the study.

Outcome assessment

Primary outcome measure

We used as primary outcome measure the frequency of BZD prescriptions issued per month, the proportion of prescriptions issued by participants included in intervention and control units over the study time frame and more specifically at baseline, six and 12 months after intervention.
We included BZDs from the following Anatomical Therapeutic Chemical classification system-coded groups: N05B; N05C and N03AE.

Secondary outcome measures

Effectiveness

We used the frequency of antidepressant prescriptions issued per month, the proportion of prescriptions issued by participants included in intervention and control units over the study time frame and more specifically at baseline, six and 12 months after intervention.
We included antidepressants from the following Anatomical Therapeutic Chemical classification system-coded groups: N06A.

To study the effect of ePrimaprescribe on diagnosis registration, we used the monthly registration distribution of psychological symptoms, complaints, and diagnoses coded at the same month as BZD and antidepressant prescriptions. The GP's diagnosis registration used the International Classification of Primary Care, second edition (ICPC-2) developed and updated by the World Organization of Family Doctors' (WONCA) International Classification Committee (WICC).

We further performed a cost analysis considering the monthly National Health Service spending with BZD co-payment. This cost was compared with the amount that would need to be spent to comply with needs and solutions suggested when evaluating GP’s perceptions of the feasibility and implementation.

Implementation

We studied the implementation process using quantitative and qualitative methods.

Quantitative data

We developed a standardized onsite survey aiming to explore the following themes: GP's self-evaluation of knowledge about the management of patients with anxious and depressive symptomatology; reasons for prescribing BZDs and antidepressants; subjective assessment of the amount of BZDs and antidepressants prescribed; reasons for keeping long-term BZD prescription; difficulties for changing long-term BZDs prescription; the degree of concern with continued BZD prescription; knowledge and degree of adequacy of the existing Portuguese guidelines on BZD prescription; motivations and expectations regarding the use of the ePrimaPrescribe program in clinical practice and participation in the study. This questionnaire had 18 multiple questions and 14 short answer questions. The development and testing of this questionnaire is detailed in Part 5, section 1.

We adapted the Barriers and Facilitators Assessment Instrument (BaFAI)(39) to the implementation of the DBCI ePrimaPrescribe program. This questionnaire is organized into four categories: barriers deriving from the characteristics of the practice/innovation; barriers deriving from the characteristics of the professionals; barriers due to patient characteristics; barriers arising from the intervention context. It has twenty-five questions of a five-point Likert scale type.

We asked all participating GPs to complete the onsite survey and BaFAI questionnaires at the end-of-study face-to-face visit that was performed after completion of the twelve-month intervention period.

At the end-of-study face-to-face visit, we also collected GPs sociodemographic data.

Qualitative data

During our end-of-study face-to-face visit, we performed a group discussion in each primary health care unit included in the intervention group, to explore GP's perceptions over their participation.

We finally performed semi-structured in-depth interviews with an intentional sample of participants from the intervention arm to explore perceptions of the study's feasibility and implementation. The interview guide structure was developed after an exploratory analysis of the themes emerging from the answers to the onsite survey questionnaire, from the answers to the BaFAI, and from the group discussion occurring during the end-of-study visit.

Data management

Each prescription data was coded using an individual GP and patient numerical identification, in a secured and validated electronic database, directly extracted by the central Shared Services of the Portuguese Ministry of Health.

Data concerning clinical diagnosis was extracted by the same method as the prescription database. Matching of prescription and diagnosis database was

performed using the coded patient's numerical identification and prescription/diagnosis registration month.

Data obtained through questionnaires and interviews was collected after participants signing an informed consent during the initial implementation face-to-face visit.

Statistical analysis

We performed an exploratory descriptive analysis using number of prescriptions as primary measure of outcome, considering as main influencing factors the patient's age and sex, by units of intervention and control.

We performed most analysis at the level of intervention versus control clusters (so compared together the set of intervened units vs the set of control units), since the available data did not allow for the author to identify each of the participating GP, hence also not allowing to distinguish in the intervention units, which GPs were compliant with the intervention (i.e. the doctors that actually used the DBCI), from those that, although initially agreeing to participate, finally didn't use the platform.

We tested for significant differences among the baseline characteristics of the intervention and control group. We performed descriptive analysis, with continuous variables summarized using means and standard deviations for normal distributions, and by medians and the 25th and 75th percentiles for non-normal distributions.

Estimated effects were calculated by comparing number of prescriptions in the intervention and control groups at baseline, six months, and 12 months after intervention.

All analyses were performed on an 'intention-to-treat' basis (i.e., all initially enrolled GPs were included in the analysis according to the group to which they were assigned). This approach reduces the bias that may occur when participants not receiving assigned treatments are excluded from analysis.

The intervention and control groups were compared at the defined time points accounting for clustering by unit.

We tested for significant differences in the baseline characteristics of the control and intervention groups using t-tests or one-way ANOVA. This included calculation of means and/or proportions with confidence intervals, and on robust standard deviations (to account for clustering).
We performed a secondary analysis where we explored the association between the frequency of BZD and antidepressant prescription with diagnoses using Chi-Squared tests for testing independence in two-way contingency tables. The Cochran-Armitage trend test was employed to assess how the proportion of two ordinal successes varies across the levels of a binary variable. And when both variables in a contingency table had ordered categories, the linear-by-linear test was used instead (40).

We finally performed a cost analysis considering the monthly National Health Service spending with BZD co-payment, using t-tests or one-way ANOVA.

Statistical significance was considered for p-values < 0.05.

The R statistical software (41,42) was used to perform all the statistical analyses within the RStudio integrated development environment for R, RStudio Team (2019). The graphs and plots were obtained with use of the *ggplot2* R package (43).

We performed a descriptive analysis to correlate data from the onsite survey questionnaire and BaFAI questionnaire with GP's sociodemographic characteristics using Chi-Squared tests for testing independence in two-way contingency tables.

We used qualitative methods, namely content analysis, to explore data from in-depth interviews using ATLAS.ti.

Data was reported elsewhere according to the 2010 Consolidated Standards of Reporting Trials guidelines.

Discussion

Strengths and limitations

The concerning reality of excessive BZD prescription in Portugal suggests the need for effective interventions, at minimal cost and with a low need for professional time. A maximally effective withdrawal strategy is especially important in primary care settings because of budgetary limitations and the small amount of GP time available per consultation (44).
BZD (de)prescription is considered a complex behavior. Behavior change is key to improving healthcare and health outcomes. Therefore, we have chosen to design our intervention based on a behavior changing theory, the Behavior Changing Wheel theory (32), hoping that using a validated and reviewed framework would strengthen the quality of our approach.
Concerning our effectiveness trial, this paper describes the protocol for a cluster-randomized trial to assess, primarily, whether a Digital Behavior Change Intervention (DBCI) would have a significant effect on BZD prescription. It also describes two secondary analyses regarding antidepressant prescription trend and reporting of diagnoses registration associated to BZD prescription, hoping that the implementation of our DBCI could secondarily translate in the improvement of anxiety disorder registration and adequate treatment (with an increasing antidepressant prescription).
Randomized trials are the gold standard to assess intervention effects, and cluster-randomized trials are an appropriate design when interventions need to be introduced to groups of individuals (in our case groups of GPs prescribing in the same primary health care unit), which are randomly allocated to different study arms (30,45).

We chose as delivery method a DBCI because these online interventions have the potential for low unit-cost, high reach, effective and acceptable ways to benefit individuals and society (46).
We chose to include both prescription-related outcomes and diagnosis outcomes. Regarding prescription-related outcomes, we recognize the limitation of presenting our prescription-related outcome as the frequency of prescription. In the specific case of BZDs, this limitation is minimized by the fact that, in Portugal, the prescription of BZDs cannot be placed in chronic prescriptions. This means that when a BZD prescription is issued it has to be dispensed during the next 30 days, and that each prescription might have a maximum of two boxes of drug. Hence, we considered that, since there is the need for frequent prescription renewal, the number of prescriptions issued is an adequate measure to estimate our intervention effect.
Regarding clinical diagnosis outcomes, we recognize that our data might be a fairly inexact approach, since most prescriptions are not associated with a diagnosis, and also because even when this association was found, it didn't mean that symptoms or disorders were identified at the moment of prescription. Despite this limitation, we considered relevant to report the analysis of the change in clinical diagnosis, since it might indicate significant secondary effects coming from the intervention implementation.
We recruited GPs to participation taking into account all the available characteristics that might influence our primary and secondary outcomes: sex, years of clinical experience, type of primary health care unit and previous training in mental health.
We recognize as a limitation and possible bias the fact that it was the first author that was mainly responsible for implementation, and at the same time responsible for collecting data from the questionnaires and in-depth interviews. We minimized this limitation by having all data, its categorization, content and theme identification reviewed by a researcher which was not involved with data collection.

Relationship to other studies and expected contribution

The excessive BZD prescription is a reality for many countries other than Portugal. For this reason, a large body of evidence already exists, with extended research assessing the effectiveness of interventions aiming to change BZD prescription pattern. From simple methodologies, such as sending letters to long-term BZD users, to more complex ones, such as multi-step tailored interventions, most studies show limited short-term effects. Most studies also lack a more profonde understanding of the facilitators and barriers to implementation.
We consider that our trial is innovative since it presents a methodology that was carefully prepared to reach a maximum effectiveness, at minimal cost and low need for professional time, and it also has an important focus on factors influencing implementation. We also consider our research to be of particular national interest because no matter how well structured an intervention might be, if it is not accepted by the public for whom it is designed, the results are inevitably scarce and limited.
When dedicating a significant effort to explore GP's perceptions over their participation experience, we expected to contribute for two important areas of knowledge. On one hand, to better understand the factors influencing the act of BZD prescription, and possibly on a larger perspective, what this prescription

means/represents in the management of mental health issues in the primary health care setting. On the other hand, in a time and setting where online interventions are becoming more common, to explore the factors influencing acceptance and practicability of our Digital Behavior Changing Intervention. Concerning specifically this mode of delivery, we also expected for our research to contribute for an in-depth exploration of perceptions, liable to be applied on other areas besides mental health and hence helping to shape digital interventions that are adjusted to what GPs want and feel motivated to comply.

Ethics and dissemination

This trial was approved by the Ethics Commission for Health of the Regional Administration of Health for Alentejo Region (Portugal) (02/2016(CES) and the Nova Medical School, Nova University Lisbon, Portugal Ethics Commission (47/2016/CEFCM). The results of this study were disseminated via peer-reviewed publications and conference presentations. All data will be available on request.

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