

Deprescribing Clonazepam in Primary Care Older Patients: A Feasibility Study

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Abstract

Background: Inappropriate use of clonazepam by the elderly patients is associated with cognitive impairment, delirium and falls. Strategies to optimize its use are important to increase patient safety.

Objective: To evaluate the feasibility of a clonazepam deprescription protocol in the elderly.

Methods: This is a quasi-experimental study. Elderly people with chronic use of clonazepam and attended in primary care units in two Brazilian municipalities were selected. A deprescription protocol was used, which included five fortnightly meetings between the older adults and the research team, to reduce the dose by 25 %. Patients received instructions on sleep hygiene behaviors and the advantages of clonazepam deprescription; family physicians followed a flowchart for gradual dose reduction. In the 1st and 5th meetings, there were medical appointments for anamnesis and discharge. The monitoring of patients and the application of tests were carried out by the research team.

Results: Of the 35 elderly people included in the study, 27 reached the end; 81.5 % achieved deprescription: 22.2 % stopped completely and 59.3 % decreased the dose. At the last meeting, 20 % of elderly patients reported an increase in blood pressure.

Conclusions: The high rate of deprescription and the little relevance of clonazepam withdrawal reactions, showed that the use of the protocol was effective. However, the increase in blood pressure and the worsening of sleep quality in the last meeting show the need for adjustment in the last stage of the deprescription process.

Trial Registration: The Brazilian Registry of Clinical Trials (ReBEC) RBR-524ys9; registered June 10, 2019.

Bullet Points

- A “very good” quality of life was declared by 17.6 % and 24 % of the elderly before and after the deprescription, respectively.
- Sleep hygiene behaviors are strong allies during the describing process.
- The average length of use of clonazepam was high (13 years), as the literature does not recommend its continuous use. This shows the need for an intervention to reduce the indiscriminate use of this drug.

Introduction

Following the global trend, Brazil has undergone important demographic and epidemiological changes [1, 2], a situation in which acute communicable diseases appear to a lesser extent in comparison to chronic non-communicable diseases (many of them associated with aging) and their complications, which were responsible for 72 % of deaths in Brazil, according to the latest National Health Survey [3]

The aging process is marked by physiological changes inherent to chronological age, which, combined with the appearance of chronic diseases and their comorbidities, makes elderly care more complex. These factors favor medication interactions and a higher occurrence of adverse medication reactions [4]. Thus, some drugs are unsuitable for geriatric use and are referred to as Potentially Inappropriate Medication for the elderly (PIM) [5]. PIMs are defined by explicit criteria and identified in lists published in several countries. Benzodiazepines are a class of medication common to all of these lists [5–11].

Brazil is the third largest global consumer of benzodiazepines and the largest consumer of clonazepam in the world [12, 13]. Its continued use is linked to an increased risk of cognitive impairment, daytime sleepiness, delirium, falls, fractures, car accidents, intoxication (especially when associated with other psychotropics) [14, 15] and suicide attempts [16]. In addition, studies show an association between long-term use of benzodiazepines and Alzheimer's disease [17–18].

Therefore, strategies that help to improve the appropriateness of the use of benzodiazepines are necessary and emerging for health systems, especially for the geriatric population that uses primary care services. As there are no evidence-based protocols in Brazil to assist clinicians in the practice of gradual withdrawal of clonazepam, the objective of the study was to evaluate the feasibility of a clonazepam deprescription protocol in elderly people treated in primary healthcare.

Methods

Study Design and Participants

This is an intervention study with a quasi-experimental design, held in 2019 to 2020 [19]. It was carried out in two municipalities in the state of Minas Gerais, Brazil, which together have an estimated population of 331,450 inhabitants [20, 21]. In relation to primary health care services, there are 65 basic health units, of which five were chosen for convenience, with the consent and participation of family physicians who already had links with potential patients.

Older adults, being chronic users of clonazepam (three months or more) [22, 23] attended at the five selected health units were included. Patients diagnosed with epilepsy, severe depression and/or who had at some point in their life suicidal ideation or had actually attempted suicide, elderly people with a history of psychosis, those dependent on alcohol and/or illicit drugs, and cognitively incapable patients without a fixed caregiver (according to the Mini Mental State Examination) were excluded [24].

The deprescription (outcome variable), defined as partial or total reduction of the medication [25], was carried out in a systematic way, according to the protocol proposed and validated by Baldoni et al [24]. This protocol has a flowchart for the deprescription of clonazepam for general practitioners, and two booklets for the elderly patients: sleep hygiene, and the advantages of clonazepam deprescription.

Five fortnightly meetings were held (totaling two and a half months of follow-up). At the first meeting there were medical appointments, at which point the family physician agreed to participate with the patient and, for those who accepted, the process of deprescription began. The complementary assessment tests were applied by the research team (Fig. 1). At each meeting, patients were instructed to reduce the dose of clonazepam by 25 %, with continuous reinforcement of sleep hygiene behaviors. If the elderly person showed marked signs and symptoms of withdrawal, the prescriber could resume the previous dose or prescribe a Selective Serotonin Reuptake Inhibitor (SSRI) [24].

Statistical Analyses

Descriptive analyzes of the results were performed by calculating the mean and standard deviation for the symmetric variables; median and interquartile range for the asymmetric variable; in addition to frequency distribution for the categorical variables.

Ethical Conduct

This study was approved by the Research Ethics Committee Involving Human Beings at the Federal University of São João del-Rei (UFSJ), campus Centro-Oeste Dona Lindu, opinion number 3,490,485. The Brazilian Registry of Clinical Trials (ReBEC), identifier code RBR-524ys9 was approved. In addition, family physicians of the participating municipalities signed the term of participation in the project. Participants who agreed to participate in the study signed the Informed Consent Term (ICT).

Results

A total of 153 potential participants were identified. Women corresponded to 86.2 % (n = 106), the median age was 67 years (64–74), with the minimum and maximum age being 60 and 93 years, respectively. The mean time schooling was four years of study (SD ± 2.3). Among these patients, 35 started deprescription and 27 reached the end of the study, with 81.5 % (n = 22) achieving deprescription (Fig. 2).

The mean time of use of clonazepam was 13.1 years (SD ± 10.3), with a minimum of one year and a maximum of 50 years. Among the 129 patients contacted, 42.6 % (n = 55) reported using it due to insomnia, 29.5 % due to anxiety (n = 38) and 16.3 % (n = 21) due to depression. Still, 6.2 % reported using the drug as emotional support for other comorbidities (n = 8), 6.2 % for grief (n = 8) and also 6.2 % for epilepsy. Headaches was the reason reported by 3.0 % (n = 3) and other reasons for using clonazepam (Tachycardia, schizophrenia, muscle relaxant, obsessive compulsive disorder, patient does not remember the reason for use) were reported by 6.2 % (n = 8).

Among the reasons for not participating, the history of ideation or suicide attempts (10.6 %) were the main causes of refusal and exclusion. In these cases, patients were referred immediately to the health team. Patients were also excluded due to epilepsy (8.6 %), older adults with cognitive impairment, without fixed caregiver (7.4 %), diagnosis of deep depression (7.4 %) and patients under treatment / use of drugs and / or alcohol (1.1 %). In relation to the refusals, 19.1 % reported, fear of withdrawal symptoms and also 17.0 % unavailability to attend meetings. Other reasons for refusal were “do not want / Do not have the patience for meetings” (8.6 %) and clonazepam was the only medication that worked (4.3%). Other reasons for refusals and exclusions were emotional support for other comorbidities; Schizophrenia; Borderline.

It was also possible to verify that 40 % (n = 14) of the patients suffered falls in the previous year (2018). Of these, 20 % (n = 7) reported having fallen because of a misstep and 37.2 % (n = 13) of the falls occurred within the patient's own residence (Table 1).

Table 1

Number, characteristics and consequences of the falls related to the previous year (2018), suffered by patients who underwent deprescription, in the period 2019–2020, in two municipalities in Minas Gerais, Brazil (n = 35).

Falls	Frequency (%)
Quantity	
1 fall	8 (22.9%)
2 falls	2 (5.7%)
3 falls	2 (5.7%)
More than 3 falls	2 (5.7%)
Fall characteristics	
Missed step	7 (20.0%)
Fell while walking	5 (14.3%)
Fell from the chair	1 (2.9%)
Others ^a	6 (17.1%)
Fall locations	
inside home	13 (37.2%)
on the street (sidewalk, curb)	7 (20.0%)
backyard / garden	3 (8.6%)
Gymnasium	2 (5.7%)
Consequences of falls	
Hospitalization	5 (14.3%)
Fracture	5 (14.3%)
Walking is compromised	5 (14.3%)
Taking care of yourself is compromised ^b	4 (11.4%)
Everyday activities are compromised ^c	2 (5.7%)
None	2 (5.7%)
^a Fell out of bed, slipped and fell, fell while running. ^b Combing hair, dressing, shower or eating alone. ^c Washing dishes, tidying up the house, shopping, cooking, answering the door, making a journey. ^d More than one response per patient was permitted.	

Throughout the process of deprescription, the incidence of withdrawal signs and symptoms (when grouped in blocks) achieved an average of 50 % (with the exception of psychiatric symptoms) of patients per meeting, but were not clinically relevant, especially when evaluated separately (Table 2). The symptom with the greatest clinical relevance was anxiety, reported in all meetings by about 30 % of patients. At the last meeting, all the elderly people

had some type of psychiatric symptom. It is important to highlight that the number of elderly participants and the number of patients who answered the questionnaires were different, since patients with cognitive deficits and with a fixed caregiver had only the main outcome (deprescription) analyzed, due to the impossibility of responding to the tests.

Table 2

Frequency (%) of elderly participants in the study who presented signs and symptoms of withdrawal more than three times a week, from the second to the fifth meeting, in the period 2019–2020, in two municipalities in Minas Gerais, Brazil.

Signs and symptoms	Meeting 2 n = 27	Meeting 3 n = 26	Meeting 4 n = 26	Meeting 5 n = 25
Sensory System	12 (44.4%)	13 (49.9%)	7 (26.8%)	5 (20.0%)
Greater sensitivity to noise ^a	2 (7.4%)	5 (19.2%)	0 (0%)	1 (4.0%)
Greater sensitivity to light ^a	2 (7.4%)	3 (11.5%)	1 (3.8%)	2 (8.0%)
Greater sensitivity to smell ^a	4 (14.8%)	2 (7.7%)	2 (7.7%)	0 (0%)
Greater sensitivity to touch ^a	1 (3.7%)	1 (3.8%)	1 (3.8%)	1 (4.0%)
Different taste in the mouth ^a	3 (11.1%)	2 (7.7%)	3 (11.5%)	1 (4.0%)
Musculoskeletal System	7 (25.9%)	9 (34.6%)	6 (23.1%)	4 (16.0%)
Muscle pains ^b	6 (22.2%)	8 (30.8%)	4 (15.4%)	8 (32.0%)
Involuntary movements ^b	1 (3.7%)	1 (3.8%)	2 (7.7%)	3 (12.0%)
Central Nervous System	11 (40.7%)	12 (46.1%)	5 (19.2%)	12 (48.0%)
Tremor ^f	2 (7.4%)	2 (7.7%)	1 (3.8%)	0 (0.0%)
Vertigo ^c	0 (0.0%)	2 (7.7%)	1 (3.8%)	3 (12.0%)
Lethargy ^c	2 (7.4%)	3 (11.5%)	4 (15.4%)	5 (20.0%)
Headache ^c	2 (7.4%)	2 (7.7%)	5 (19.2%)	2 (8.0%)
Difficulty in concentrating ^c	5 (18.5%)	3 (11.5%)	3 (11.5%)	2 (8.0%)
General symptoms	16 (59.2%)	14 (53.7%)	12 (46.1%)	7 (28.0%)
Weakness / fatigue ^d	5 (18.5%)	5 (19.2%)	2 (7.7%)	3 (12.0%)
Indisposition ^d	4 (14.8%)	3 (11.5%)	3 (11.5%)	1 (4.0%)
Pain in the eyes ^d	2 (7.4%)	1 (3.8%)	0 (0.0%)	0 (0.0%)
Excessive night sweats ^d	4 (14.8%)	3 (11.5%)	4 (15.4%)	1 (4.0%)
Palpitations / irregular heart beat ^d	1 (3.7%)	2 (7.7%)	3 (11.5%)	2 (8.0%)
Gastrointestinal System	3 (11.1%)	5 (19.2%)	2 (7.7%)	4 (16.0%)
Nausea and / or vomiting ^e	1 (3.7%)	0 (0.0%)	1 (3.8%)	2 (8.0%)

According to the questionnaire on signs and symptoms of withdrawal from clonazepam. ^aSensory Block. ^bMusculoskeletal Block. ^cCentral Nervous System Block. ^dGeneral Symptoms. ^eGastrointestinal Block. ^fPsychiatric Symptoms Block.

Signs and symptoms	Meeting 2 n = 27	Meeting 3 n = 26	Meeting 4 n = 26	Meeting 5 n = 25
Loss of appetite ^e	2 (7.4%)	5 (19.2%)	1 (3.8%)	2 (8.0%)
Psychiatric Symptoms	22 (83.2%)	22 (84.6%)	18 (69.1 %)	25 (100%)
Hallucinations ^f	1 (3.7%)	0 (0.0%)	1 (3.8%)	3 (12.0%)
Worsening memory ^f	3 (11.1%)	4 (15.4%)	3 (11.5%)	3 (12.0%)
Insomnia ^f	6 (22.2%)	2 (7.7%)	1 (3.8%)	5 (20.0%)
Nightmares ^f	1 (3.7%)	2 (7.7%)	1 (3.8%)	3 (12.0%)
Irritation ^f	3 (11.1%)	6 (23.0%)	4 (15.4%)	3 (12.0%)
Anxiety ^f	8 (29.6%)	8 (30.8%)	8 (30.8%)	8 (32.0%)
According to the questionnaire on signs and symptoms of withdrawal from clonazepam. ^a Sensory Block. ^b Musculoskeletal Block. ^c Central Nervous System Block. ^d General Symptoms. ^e Gastrointestinal Block. ^f Psychiatric Symptoms Block.				

It was observed that between the fourth and the fifth meetings, 19.2 % (n = 5) of the patients (already hypertensive) reported changes in blood pressure, with three of them seeking the emergency service. After the episodes, they were examined by doctors from their respective health units, who did not consider it necessary to return with a full dose of clonazepam, thus proceeding with the deprescription according to the protocol (dose immediately before the signs and symptoms presented).

An average variation in sleep quality was observed with each reduction in the dose of clonazepam. In the first meeting, before the intervention, 64.7 % of the older adults had poor sleep quality and 20.6 % had some sleep disorder. Comparing pre and post-intervention, 14.7 % of the participating patients had good sleep quality and at the end of the deprescription this number rose to 28 %. Sleep disorders in contrast, had lower levels in intermediate meetings (Fig. 3).

Regarding the average daily dose of clonazepam, before the intervention (n = 34) it was 1.8 mg (SD ± 1.2); in the 2^o meeting (n = 27) it was 1.4 mg (SD ± 0.9); it was 1 mg (SD ± 0.7) in 3^o meeting (n = 26); it was 1.2 mg (SD ± 1.8) 4^o meeting (n = 26); and at the end this dose was 1 mg (SD ± 1.6) (n = 25). The frequency of patients with good sleep quality was 14.7 % in the first meeting; 11.1 % in 2^o meeting; 23.1 % in 3^o meeting; 26.9% in 4^o meeting; and by the end, it had risen to 28 % (according to the Pittsburgh Sleep Quality Index) [26].

Before the intervention, 61.75 % of the patients self-perceived their quality of life “as good” and at the end, that rate was 72%. In addition, 64 % self-reported “satisfied” with their health status at the end of the intervention (Table 3)

Table 3

Percentage on the perception of quality of life and satisfaction with health assessed by the elderly, before and after the deprescription of clonazepam, according to the WHOQOL-bref, in the period 2019–2020, in two municipalities in Minas Gerais, Brazil (n = 25)^a.

Perception of quality of life	Very bad	First meeting	Last meeting	Satisfaction with health	First meeting	Last meeting
		0%	0%		Very Dissatisfied	0%
	Bad	11.76%	8%	Dissatisfied	17.6%	16%
	Neither bad nor good	26.47%	20.0%	Neither satisfied nor dissatisfied	44.1%	20.0%
	Good	44.12%	48%	Satisfied	29.4%	52%
	Very good	17.65%	24%	Very satisfied	8.8%	12%

^a27 participants reached the end of the study, and 25 responded to the WHOQOL-bref on both occasions (before and after intervention).

Discussion

At the end of the study, 81.5 % of elderly patients achieved deprescription, with clinically irrelevant signs and symptoms. This rate of deprescription was similar to that observed in a study carried out in a long-term institution in Belgium (84 %), however, the frequency of total deprescription was higher than the present study: 65.8 % stopped consuming benzodiazepine compared to 22.2% of the present work [33]. The fact that the Belgian study presented a total deprescription greater than our study can be explained by the fact that in long-term institutions, the health professional has greater control over the daily dose used and can offer more constant care to the elderly, and in the case of the present study the elderly are in the community, which can make it difficult to control the daily dose and have immediate access to information.

In another study, carried out in health centers in Spain, the general rate of deprescription (67.1 %) was lower when compared to our data. However, the total withdrawal rate was higher (45.2 %) than our study [34]. Another research team, also in Spain, obtained as a result 64.3 % of total benzodiazepine deprescription with the help of melatonin [35]. Other possible reasons for this difference observed among the individuals who achieved total deprescription in the aforementioned studies are different follow-up times, sociodemographic and economic differences between research participants, different clinical conditions, and medications in use, in addition to covering the entire class of benzodiazepines and not just a single medication, as is the case with our protocol.

The main reasons for using clonazepam (anxiety, insomnia and depression) found in our study were the same reported in studies conducted in the United States and Spain, which pointed out that insomnia and anxiety are the reasons why 75 % of patients (older adults or not) use benzodiazepines [34, 36]. The chronic use of these medications is not indicated for the causes mentioned [5–11], and may lead to serious adverse reactions, such as falls and fractures. Our study found a prevalence of 40 % of falls. Falls associated with the use of benzodiazepines have been reported by several authors; Coutinho and Dutra concluded that the risk of a benzodiazepine user suffering falls is 109 % higher than those who do not use this class of medication [37–40]. A study conducted in the Netherlands found that approximately 60 % of patients using medication suffered one or more falls, and exposure to psychotropic drugs increases the chance of an individual falling by 96 % [41].

Regarding the signs and symptoms of withdrawal from clonazepam, these were uncommon and of no clinical relevance. Several authors report that withdrawal syndrome, when using long duration benzodiazepines (as is the case with clonazepam), is milder than in relation to short duration benzodiazepines, which show symptoms of lack of medication more quickly and intensely [42–45]. However, the increase in some symptoms such as insomnia, nightmares and hallucinations, in addition to the change in blood pressure in some patients in the two weeks after the last withdrawal of the dose (between the fourth and fifth meetings), highlights the need to review the last fraction of withdrawal of the medication, since in the tested protocol, 25 % of the initial dose was withdrawn, and other benzodiazepine protocols in general recommend that the last and penultimate withdrawal be 12.5 % [46–47].

Analyzing this last withdrawal of the dose of clonazepam, it was observed that sleep disorders, which obtained their lowest rates in intermediate meetings, practically returned to the numbers before the intervention. Several studies show that sleep quality improves with the use of melatonin [34, 48–49]. The systematic review conducted by Reeve et al. evidenced that the majority of the studies did not show significant difference in the quality of the sleep before and after deprescription, but that during the process of the gradual withdrawal, there can be a worsening of the quality of sleep, a fact that we observed only in the last withdrawal of the dose, between the fourth and fifth meetings [48].

Regarding the average daily dose of clonazepam, it is important to note that the increase in the average dose observed in the fourth meeting can be explained by the behavior of a patient, who at the beginning of the study used 7 mg of the drug, and went to 5.3 mg and 4 mg in the second and third meetings, respectively. On the fourth meeting they doubled the dose and ended the follow-up using 8 mg of clonazepam per day.

A positive impact on the quality of life of patients who achieved deprescription has been reported in several studies [50–52], corroborating our results. It should be noted that quality of life, sleep, and the signs and symptoms of withdrawal from clonazepam and other benzodiazepines were measured in different instruments in different studies, making the comparison between studies limited.

Regarding the difference between the number of potential patients identified and those who achieved deprescription (only 27.2 % continued in the study), it was observed that this also occurs in other studies. Research carried out in Belgium and Finland obtained results of 28 % and 24 %, respectively, showing how low the proportion of eligible patients is and who accept the process of deprescription [33, 35].

This loss is mainly due to the fear of not being able to sleep and/or increased anxiety. These too, were the main reasons reported in other studies [53, 54]. Analyzing the causes of exclusion of patients from the study, the history of suicidal thoughts and attempts at suicide stood out for their frequency and clinical relevance. In the literature there is a meta-analysis carried out in 2019, which explains the association between the use of benzodiazepines and ideation and suicide attempts. The authors identified that these suicide attempts also occur when psychiatric symptoms are already under control [35]. This spells out the need for caution before and during the benzodiazepine deprescription process.

Regarding the limitations of this study, the small number of participants stands out, in addition to the absence of a control group and a random sample. Patient availability and the involvement of the entire primary health care team are also major challenges to implement this type of protocol in the real world. However, among the potentialities, it is important to highlight that this is the first study that analyzes the applicability of a specific clonazepam deprescription protocol, and that considers the reality of elderly Brazilians attended in the primary care of the Brazilian Unified Health System (SUS). Finally, it is important that the effectiveness of this protocol is tested in a

randomized clinical trial, with a significant sample, and with the necessary adjustments so that it is widely used in health systems.

Conclusions

The result of the deprescription process, in which 81.5 % of the elderly patients managed to reduce or cease the use of the medication, in line with the low frequency and low clinical relevance of clonazepam withdrawal reactions, showed that the protocol is feasible to be used in the context of primary health care. However, the increase in blood pressure and the increase in sleep disturbances between the fourth and fifth meetings, show that the dose reduction in the penultimate meeting, when the patients were without the medication, should be more gradual.

Declarations

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Competing interests:

The authors declare that they have no competing interests.

Data availability

Availability of data and materials: The datasets generated during and/or analysed during the current study are available in the League of Clinical Pharmacy Academy of the Federal University of São João del-Rei (LAFarC/UFSJ) repository, <https://ufsj.edu.br/lafarc/arquivos.php> (Items 37, 55 and 56).

Consent for publication;

Not applicable.

Consent to participate:

Not applicable.

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Figures

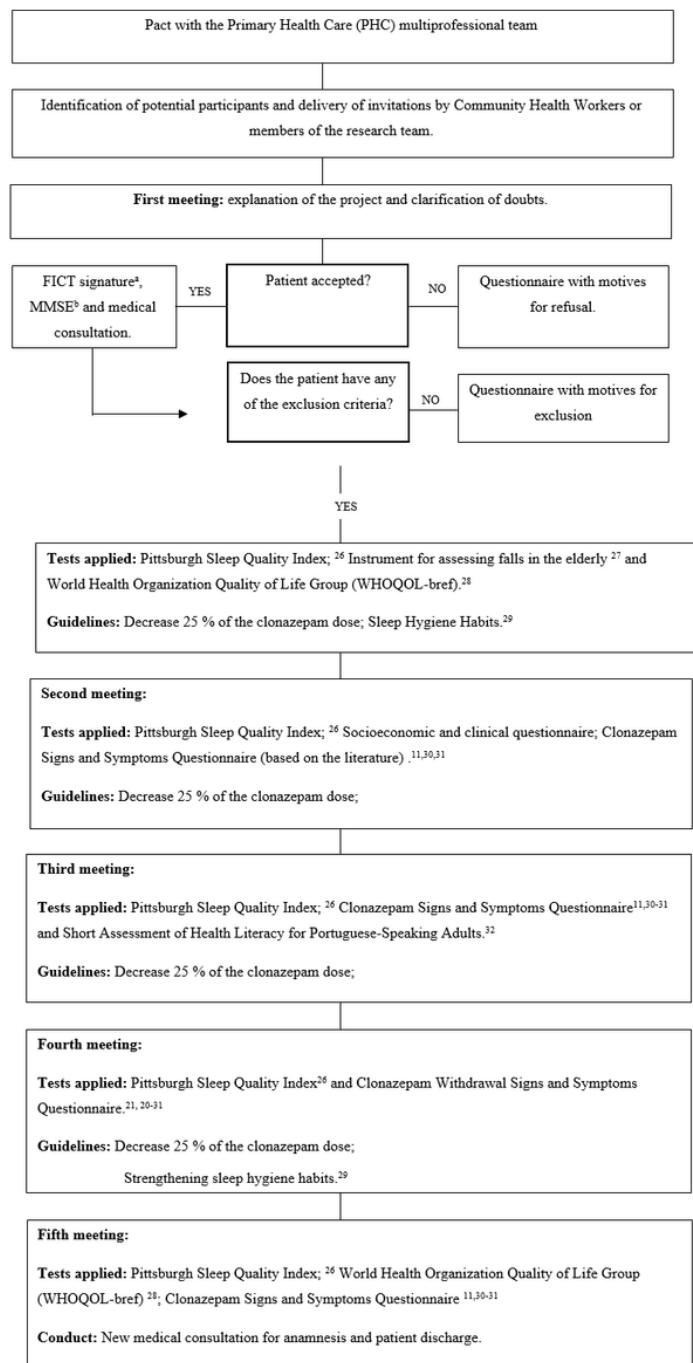


Figure 1

Representative flowchart of each meeting between patients and research team, from two municipalities in Minas Gerais, 2019-2020. aICT: Informed Consent Term; bMMSE: Mini-Mental State Examination.

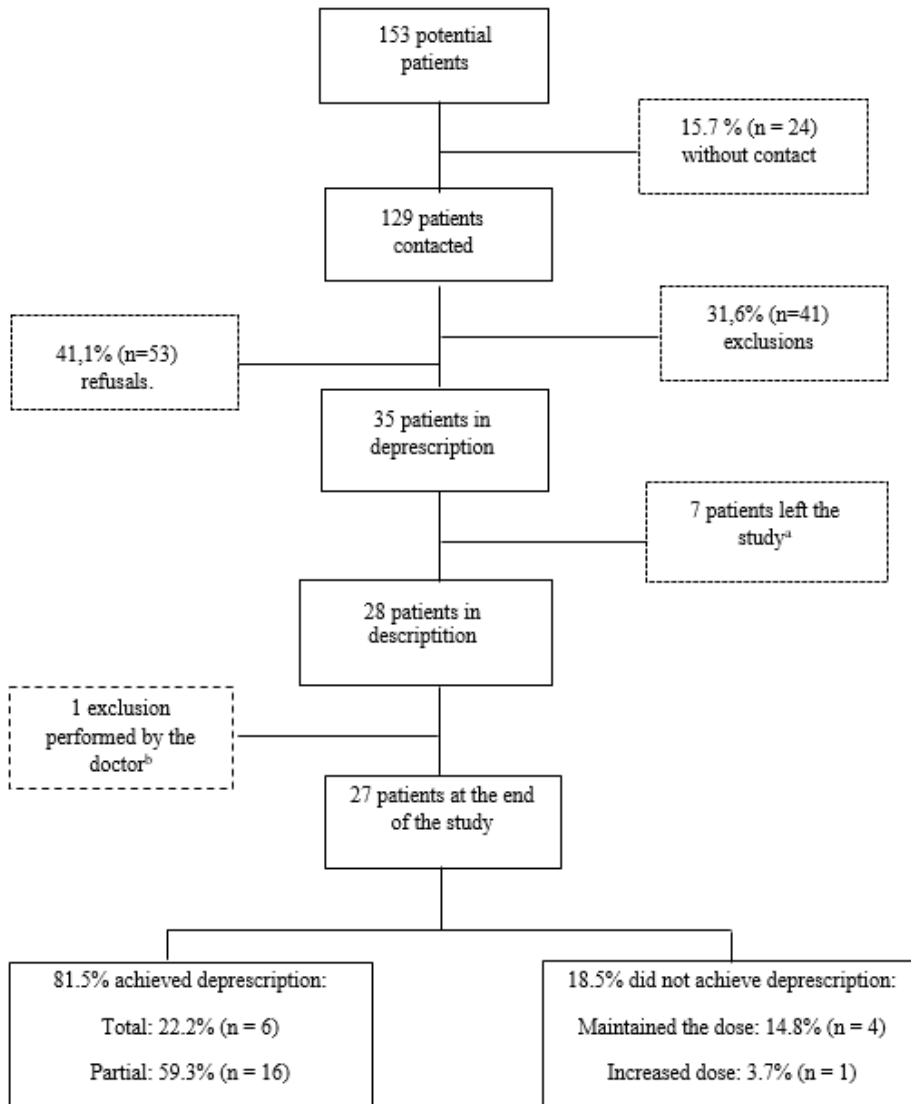


Figure 2

Flowchart representative of the number of patients and their results throughout the process of deprescription, in the period 2019-2020, in two municipalities in Minas Gerais, Brazil. a1 change of city, 4 withdrew from participating, and 2 no longer responded to researchers and/or community health workers. b Exclusion due to uncontrolled systemic blood pressure.

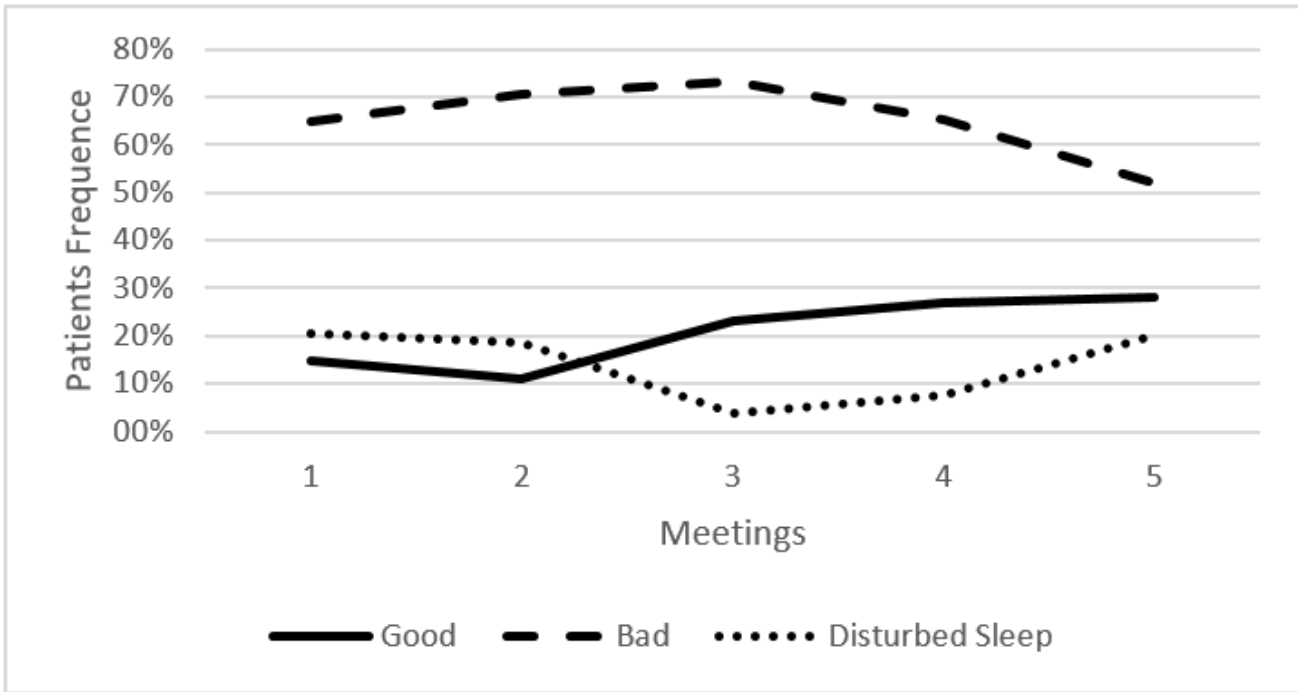


Figure 3

Sleep quality index of the elderly patients during the process of clonazepam deprescription in the period 2019-2020. Microsoft Excel © 2016.