Ansiedad y Estrés

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Original

Pilot psychotherapy program for the deprescription of benzodiazepines for anxiety disorders

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A B S T R A C T

Introduction: The objective was to implement a pre-experimental pilot psychotherapy program for benzodiazepine deprescription in patients with anxiety disorders in primary care.
Methods: Before-after clinical trial without a control group performed in two urban health centers. Patients aged 18-60 years with a diagnosis of anxiety disorder on benzodiazepine treatment were included. The program consisted of seven sessions of individual psychotherapy, and an individualized deprescription schedule. The Goldberg test and SF-12 questionnaire were administered in the first, third and final sessions.
Results: Of the 123 patients included, 107 (87%) finished the study, of whom 93 (86.9%) were women, with a mean age of 44.7 years. Most had generalized anxiety disorder diagnosed in the past year. After completing the program, benzodiazepines were withdrawn in 54 out of 86 participants (62.8%); in 14 (16.3%) the dose was decreased, in 6 (7.0%) the dose was maintained and in 12 (13.9%) the dose was increased. There were significant improvements in the mental dimension of the SF-12 and the Goldberg test score.
Conclusions: The intervention was useful in deprescibing benzodiazepines, reducing anxiety and improving the quality of life. Introducing such a program in primary care could allow a better approach to anxiety disorders, avoiding polypharmacy.

Programa piloto de psicoterapia para la deprescripcion de benzodiacepinas en trastornos de ansiedad

R E S U M E N

Introducción: El objetivo fue implementar un programa piloto preexperimental de psicoterapia para deprescribir benzodiacepinas en pacientes con trastornos de ansiedad en Atención Primaria.
Método: Ensayo antes-después sin grupo control realizado en dos centros de salud urbanos. Pacientes de 18 a 60 años con trastorno de ansiedad en tratamiento con benzodiacepinas. El programa fueron 7 sesiones de psicoterapia individual y pauta individualizada de deprescripción. Se administró el test de Goldberg y QoL(SF-12) en primera, tercera y última sesión.
Resultados: Participaron 123 pacientes, 107(87%) finalizaron el estudio, siendo 93(86.9%) mujeres, con una edad media de 44.7 años. La mayoría presentaban trastorno de ansiedad generalizada diagnosticado en el último año. Tras completar el programa, en 54(62.8%) de los 86 pacientes analizados se pudieron retirar benzodiacepinas, en 14(16.3%) se disminuyó la dosis, en 6(7.0%) se mantuvo y en 12(13.9%) se aumentó. Asimismo, se observó una mejoría significativa en la dimensión mental del SF-12 así como en la puntuación del test de Goldberg.

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Conclusiones: El programa ha demostrado ser una herramienta útil para deprescribir benzodiacepinas, disminuir la ansiedad y mejorar la calidad de vida. Implementar dicho programa en Atención Primaria permitiría un mejor abordaje de los trastornos de ansiedad, evitando la polifarmacia.

Introduction

Mental health disorders cause an important social and economic burden. Among them, anxiety disorders are associated with significant levels of disability and have a considerable impact on personal well-being and social and work relationships (Ministerio de Sanidad, 2008).

Anxiety is defined as an anticipation of future harm or misfortune accompanied by a feeling of dysphoria and/or somatic symptoms of tension. When it exceeds a certain intensity or the individual's adaptive capacity it becomes pathological. Anxiety disorders are a group of diseases characterized by worry, fear/excessive fear, tension or stress that causes notable discomfort or a clinically-significant deterioration in activity (Gale et al., 2019; López-Ibor & Valdés, 2004). The causes include biological, environmental and psycho-social factors (Lobo & Campos, 1997). Anxiety disorders alone or associated with other pathologies are one of the most frequent causes of consultation in primary care. There are variations in their management, the lack of a common pattern of presentation, somatization and an association with chronic diseases (Bandelow et al., 2017; Thibaut et al., 2017).

In Spain, studies estimate the prevalence of mental illness in the general population at 10-20% (Somers et al., 2006). Eurobarometer data show an estimated prevalence of any mental disorder in Spain of 17.6% (20.8% in women vs. 14.2% in men). In addition, anxiety disorders may be associated with depression, and therefore a therapeutic approach to anxiety disorders might prevent the onset of depression (Haro, 2006).

Benzodiazepines are one of the most-frequently prescribed drugs in developed countries. In 2011, the consumption of daily doses per 1,000 inhabitants/day in Spain was 82.9 (Sánchez et al., 2013). In Spain during 2003-2010, the consumption of anxiolytics and hypnotics increased by 34.3%, and was the highest in Europe (24% in Portugal, 4% in Italy and 6.1% in France) (Sánchez et al., 2013). The estimated prevalence of long-term benzodiazepine use in the general population is approximately 2.2-2.6% (Vicens et al., 2011), and is higher in women and increases progressively with age (Brendan et al., 2018). Benzodiazepines should be used at the lowest effective dose in monotherapy and only for the short-term treatment of acute disorders (Rickels & Juergen Moeller, 2019). The estimated treatment duration is 2-4 weeks for insomnia and 8-12 weeks for anxiety, including gradual withdrawal in both cases (Ministerio de Sanidad, 2008; Clinical Guideline 22 NICE, 2007). Prolonged treatment may cause tolerance, dependence, abuse and withdrawal syndrome (Kang et al., 2020). Benzodiazepines cause short- and long-term sedation, psychomotor deterioration, accidents and falls (Martinez-Cengotitabengoa et al., 2017; Nielsen, 2017), deterioration in complex abilities and driving, and paradoxical behaviors (Azparren & Garcia, 2014; Panes et al., 2018).

In Spain, according to ENSE 2017 results, 1 in 10 adults has a mental health problem, women almost twice as men and 1 in 10 people take benzodiazepines.

Deprescription is defined as the planned, standardized withdrawal of chronic medication, and is carried out on an individual basis under clinical criteria, mainly in polymedicated patients. The withdrawal regimen consists of reducing the total daily dose by between 10-25%, depending on the degree of dependence. The resulting dose is maintained for 2-3 weeks. Withdrawal is carried out using the same benzodiazepine or replacing it with an equivalent dose of diazepam, which has a long half-life and which is marketed in several doses. If symptoms of abstinence and/or withdrawal appear, the dose should be maintained for some weeks or until symptoms disappear before dropping to the next step, with rises in the dose being avoided (Azparren & Garcia, 2014; Pottie et al., 2018).

Studies of primary care patients indicate that they accept psychological interventions (Vega et al., 1999) and prefer them to drug treatments as treatment for mental health disorders.

Meta-analyzes have compared the effectiveness of benzodiazepine withdrawal strategies and found that any type of intervention improves the results obtained with routine treatment (Reeve et al., 2017). However, the best results are obtained with interventions which add psychotherapy techniques (*OR = 5.06; 95% CI 2.68-9.57*) (Azparren & Garcia, 2014). For this reason, we designed a pre-experimental pilot humanistic integrative psychotherapy program to address anxiety disorders and carry out benzodiazepine deprescription in primary care consultations. The objective of the study is to analyse the usefulness and effectiveness of this program.

Material and methods

Design

We carried out a pre-experimental pilot program designed as a before-after trial without a control group for 15 months in two urban health centers in Barcelona with an assigned population of 67,000.

Inclusion and exclusion criteria

The inclusion criteria were age 18-60 years, a diagnosis of anxiety disorder in the last five years according to DSM-5 (American Psychiatric association, 2014) criteria, and current treatment with benzodiazepines. Exclusion criteria were current treatment by a mental health professional, active addiction to drugs or alcohol and active dependence on benzodiazepines (defined as a score of 8-13 on the predictive test of dependence on hypnotics proposed by Tyrer 1993). Patients who fulfilled the inclusion criteria were recruited in a standardized manner. Each family physician considered which patients could benefit from the program. Patients were invited to participate by telephone, and gave written informed consent in the family physician's office.

Variables analyzed

The main study variable was benzodiazepine withdrawal. The reduction in the number of containers, the cumulative dose, and improvements in anxiety and the quality of life were secondary variables. The number of containers and the cumulative dose were calculated using information from the electronic prescription, for the following two periods: I) the three months prior to inclusion in the program and II) the three months after the end of the program, if there are patients who did not use electronic prescription, they will be excluded from the analysis of these

variables. The mg measurement indicates what the patient takes and what depresses in each session, it is the subjective way of control and know the real dose. The box measurement represents the objective way, in Spain the electronic prescription works with boxes that are obtained in the pharmacy, depending on the prescription and consumption of the drug, certain boxes are obtained. Sociodemographic variables recorded from the medical record were: age, sex, marital status, nationality, first degree family history of anxiety disorder, educational level (primary, secondary, tertiary), occupation (student, primary sector, industrial or services), substances of abuse (tobacco, alcohol, illegal drugs), previous monitoring by mental health professional, DSM-5 classification, year of onset of anxiety disorder, benzodiazepine dependence test and concomitant treatment with selective serotonin reuptake inhibitors (SSRI).

Interventions

The program consisted of seven approximately-weekly individual one-hour psychotherapy sessions with the same psychotherapist. Figure 1 shows the stages of the program.

The instruments used were the self-administered Goldberg test, an anxiety subscale of nine questions which is a screening instrument to detect anxiety (Goldberg et al.,1989), with score of ≥ 4 indicating probable anxiety disorder; and the self-administered SF-12 (Vilagut et al., 2008) questionnaire, which measures health-related quality of life (HRQL). The SF-12 measures mental and physical components in 8 dimensions: physical function (2), social function (1), physical role (2), emotional role (2), mental health (2), vitality (1), bodily pain (1) and general health (1). The items are coded, aggregated and transformed into a scale of 0 (worse HRQL) to 100 (better HRQL) using documented scoring algorithms. Both tests were administered in the first, third and last sessions. In each session, benzodiazepine consumption was checked by asking the patient. An individualized deprescription regime was followed.

Humanistic integrative psychotherapy (Gimeno-Bayón & Rosal, 2001) uses various techniques, which have in common certain fundamental concepts such as the conflict between different ego states, unconscious motivations, defense mechanisms as strategies to modulate anguish, and therapeutic relationships as promoters of the understanding of the origin and maintenance of symptoms. The objective is to promote the understanding and integration of the aspects of the ego in conflict, finding new ways to integrate them to function and develop with more freedom and efficiency. The techniques used in the program are based on this psychotherapeutic model, and each has a specific intention:

Identification technique using the Rosebush fantast (women) or the Animal's story (men) to identify the current situation and get in touch with defense mechanisms.

Explanation of the states of the self according to transactional analysis for self-knowledge of the personality.

Fantasy technique: Visit to the Wise person, working on contact with protection mechanisms.

Fantasy technique: Project, to encourage redecision, energize and strengthen.

Explanation of emotional pipelines according to Moisso, adapted by Gimeno-Bayón; explanation of correct emotional management of the four basic emotions: fear, anger, joy and sadness.

Finally, the Focusing technique, firstly centered on the exercise "clear a space", shown to control anxiety.

The withdrawal regimen consisted of a decrease of 10-25% in the total daily dose of benzodiazepines, depending on the degree of dependence. The resulting dose was maintained for 2-3 weeks.

Withdrawal was carried out using the same benzodiazepine or replacing it with an equivalent dose of diazepam, which has a long half-life and which is marketed in several doses. If abstinence and/or withdrawal symptoms appeared, the dose was maintained for a few more weeks or until the symptoms disappeared, before dropping to the next step, while avoiding dose increases (Azparren & Garcia, 2014).

Sample size

Assuming a reduction in patients taking benzodiazepines of 15% as clinical relevant (Vicens et al., 2011), with a power of 90%, a level of confidence of 99% and a percentage of losses of 25%, it was estimated that it would be necessary to include a minimum of 120 participants in the study to have a final sample size of 90 participants.

Statistical analysis

Categorical variables were expressed as absolute frequency and percentage (%) and continuous variables as mean and standard deviation (*SD*). Before-after comparisons were made using the t-test for repeated samples. A sensitivity analysis was carried out to compare the baseline characteristics of patients who did and did not complete the program, using the chi-square test to compare categorical variables and the t test for independent samples for continuous variables. Values of *p* <0.05 were considered statistically significant. The 95% confidence intervals (*CI*) were calculated. The statistical analysis was carried out using the R version 3.2.3.for Windows statistical program.

The study was approved by the clinical research ethics committee of the Hospital Clinic of Barcelona (registration number 0303/2015). Each participant gave signed informed consent. The methodology complied with the ethical criteria of the Declaration of Helsinki.

Results

Patient characteristics

Of the 123 patients who agreed to participate in the psychotherapy program, 107 (87%) completed it: 93 (86.9%) were female with a mean age of 44.7 years (*SD* 11.3). Sociodemographic and clinical characteristics are shown in tables 1 and 2. With respect to the type of anxiety disorder, 104 (97.2%) had generalized anxiety disorder, 14 (13.1%) panic disorder, 6 (5.6%) dysthymia, 1 (0.9%) phobia and 1 (0.9%) separation anxiety disorder: 19 (17.8%) participants presented ≥ 1 type of anxiety disorder. Dysthymia corresponds to persistent depressive disorder. There were 6 patients who had this diagnosis concomitant with another anxiety disorder. In 41 (38.3%) cases, the diagnosis of anxiety was made less than one year previously. Sixty-two (57.9%) patients had previously been under treatment by a mental health professional, 58 (54.2%) had a high risk of addiction to benzodiazepines, and diazepam was the most frequently prescribed benzodiazepine (48.6%). Twenty nine participants were taking SSRI, most frequently citalopram. There were no significant differences between patients taking SSRI and those that did not.

The sensitivity analysis showed no significant differences between patients who did and did not complete the study with respect to baseline characteristics, except for a longer duration of the disorder in patients who did not complete the study.

Table 1.
Baseline characteristics of patients who completed the study (*n* = 107).

Variable	
SEX	
Male	14 (13.1%)
Female	93 (86.9%)
AGE, mean ± SD	44.7 ± 11.3
NATIONALITY	
Spanish	85 (79.4%)
South American	19 (17.8%)
Rest of Europe	2 (1.9%)
African	1 (0.9%)
CIVIL STATUS	
Single	35 (32.7%)
Married	39 (36.4%)
Divorcee	14 (13.1%)
Widow	4 (3.7%)
Cohabiting	15 (14%)
EDUCATIONAL LEVEL	
Primary	5 (4.7%)
Secondary	27 (25.2%)
Tertiary	75 (70.1%)
DSM-5 CLASSIFICATION	
Generalized anxiety	104 (97.2%)
Panic	14 (13.1%)
Phobia	1 (0.9%)
Separation anxiety	1 (0.9%)
Dysthymia	6 (5.6%)
PROFESSION	
Student	7 (6.5%)
Industrial sector	21 (19.6%)
Service sector	79 (73.8%)
FAMILY HISTORY OF ANXIETY	80 (74.8%)
ALCOHOL	5 (4.7%)
TOBACCO	25 (23.4%)
ILLICIT DRUGS	5 (4.7%)

Table 2.
Baseline treatment and mental health status of patients who completed the study (*n* = 107).

Variable	
ONSET OF ANXIETY	
<1 year	41 (38.3%)
1-2 years	19 (17.8%)
2-3 years	10 (9.3%)
3-4 years	12 (11.2%)
4-5 years	25 (23.4%)
PREVIOUS MENTAL HEALTH TREATMENT	62 (57.9%)
Anxiety (GOLDBERG)	90 (84.1%)
BENZODIAZEPINE DEPENDENCY	
Some risk	49 (45.8%)
High risk	58 (54.2%)
TREATMENT	
Diazepam	52 (48.6%)
Lorazepam	29 (27.1%)
Alprazolam	18 (16.8%)
Bromazepam	4 (3.7%)
SSRI	29 (27%)
Citalopram	9 (8.4%)
Fluoxetine	7 (6.5%)
Paroxetine	7 (6.5%)
Sertraline	5 (4.7%)
Venlafaxine	1 (0.9%)
Escitalopram	1 (0.9%)
Duloxetine	2 (1.8%)
Imipramine	1 (0.9%)

SSRI: selective serotonin reuptake inhibitors.

Effect of the intervention on the use of benzodiazepines

Twenty-one (19.6%) patients who did not use the electronic prescription were excluded from this analysis. There was a mean reduction of 1.39 (*95% CI 0.98 to 1.81*) containers prescribed
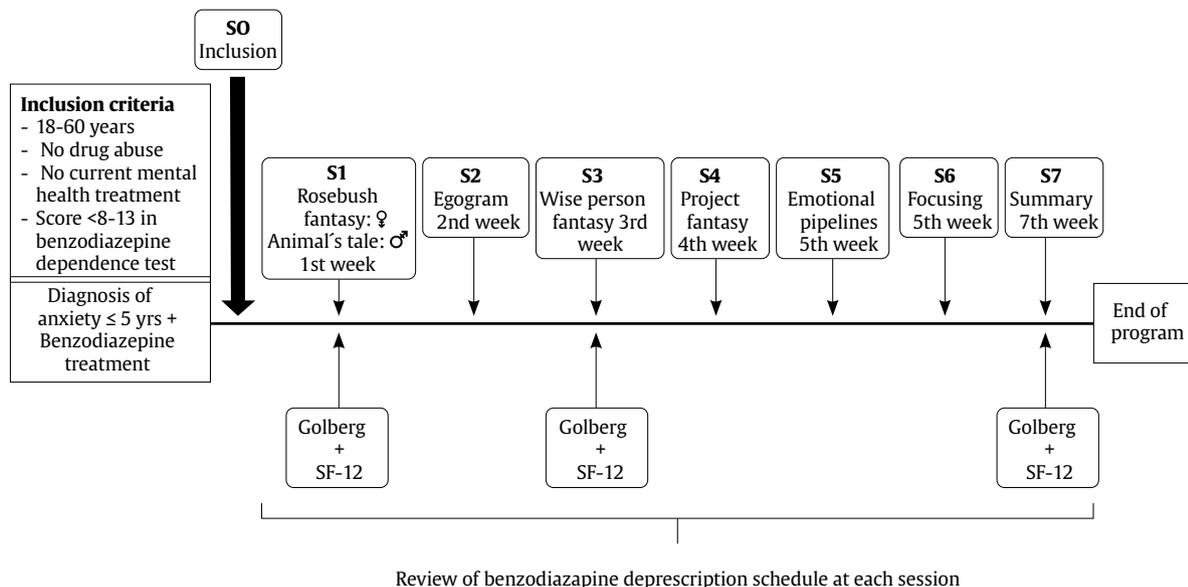
Figure 1: Stages of program

Figure 1.
Stages of the program.
MH: Mental health. // BDZ: benzodiazepines. // Dx: diagnosis. // treat: treatment. // s: session. // wk: week.
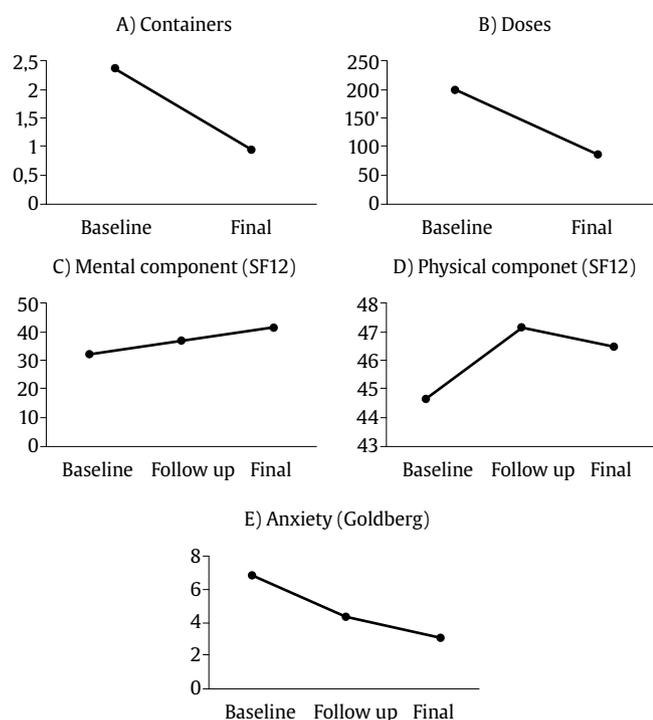
Table 3.

Effect of the intervention on benzodiazepine consumption (*n* = 86).

Variable	In the 3 months pre-intervention	In the 3 months post-intervention	Difference (pre - post)	
			Mean (95% *CI*)	*P*-value
Number of containers	2.36 (2.48)	0.97 (1.80)	1.39 (0.98 - 1.81)	<0.001
Dosage in mg	201.4 (288.6)	87.1 (225.8)	114.3 (68.2 - 160.6)	<0.001

Values are represented as mean (standard deviation) unless otherwise indicated.
95%CI: 95% confidence interval, Mg: milligrams.

during the three months after the intervention compared with the three months before (2.36 pre- vs. 0.97 post-intervention, *p* <0.001) (Table 3, Figure 2A). The intervention also had a significant effect on the dose: there was a mean reduction of 114.3 (*95% CI 68.2 to 160.6*) mg during the three months after the intervention (Figure 2B), reducing the cumulative dose to practically a third. Benzodiazepines were withdrawn after the intervention in 54 (62.8%) of the 86 patients analyzed, the dose was decreased without complete withdrawal in 14 (16.3%), maintained in 6 (7.0%), and increased in 12 (13.9%) patients.

Figure 2.
Evolution in variables: number of containers (A) (*N*=86), cumulative dose (B) (*N*=86), mental component of quality of life (C) (*N*=107), PHYSICAL COMPONENT OF QUALITY OF LIFE (d) (*n*=107) and anxiety (e) (*N*=107).

Improvements in the quality of life and anxiety

The SF-12 of participants improved after the intervention, especially in the mental component, where a mean improvement of 10.37 (*95% CI 8.05 to 12.68*) was found, with a linear increase between sessions 1, 3 and 7 (Table 4, Figure 2C). A significant improvement was also observed in the physical component (44.79 baseline session vs. 46.81 final session, *p* = 0.016) (Table 4, Figure 2D).

There was also a linear decrease in the degree of anxiety between visits 1,3 and 7, which fell by a mean of 3.62 (*95% CI 2.91 to 4.34*) units, meaning that there were 90 (84.1%) probable cases of anxiety at the beginning of the study and 40 (37.4%) cases at the end (*p* <0.001) (Figure 2E).

Discussion

As far as we know, this is the first pre-experimental pilot program using humanistic integrative psychotherapy for anxiety disorders and benzodiazepine deprescription. Studies have analyzed strategies for benzodiazepine deprescription, especially with strategies that aim at effective withdrawal at a minimum cost and with a low need for professional time, due to the limited resources available in primary care (Vicens et al., 2011). Of all the strategies used, those that provide psychological support with cognitive behavioral therapy were the most effective and gradual, but with the greatest cost and the concomitant professional time (Carr et al., 2011). Our program is not only a tool for deprescription, but also for the treatment of anxiety and, therefore, combining the two aspects ensures greater efficiency and durability, since depression itself can entail a rise in basic anxiety.

Melinda et al. analyzed cognitive behavioral therapy for the treatment of generalized anxiety in primary care, obtaining very good results and greater durability of the improvement by means of weekly one-hour therapy (2009). Although a similar program in primary care would allow a better approach to anxiety disorders, the lack of time in consultations limits effective doctor-patient communication, which is essential in the case of mental disorders; this is an added problem for a correct approach.

Of the program participants, 29 of theme were taking selective serotonin reuptake inhibitors (SSRIs), and most often citalopram. When we compared both groups, treatment with SSRI versus those

Table 4.

Effect of the intervention on the quality of life and anxiety (*n* = 107).

Variable	Baseline (Session 1)	Session 3	Final (Session 7)	Difference (final - baseline)	
				Mean (95% *CI*)	*P*-value
Quality of life (SF-12)					
Physical component	44.79 (10.55)	47.48 (9.34)	46.81 (9.49)	2.02 (0.38 - 3.67)	0.016
Mental component	34.42 (9.56)	39.79 (10.70)	44.79 (9.92)	10.37 (8.05 - 12.68)	<0.001
Anxiety (Goldberg Test)	6.71 (2.58)	4.32 (3.23)	3.08 (3.10)	3.62 (2.91 - 4.34)	<0.001
No case (<4)	17 (15.9%)	50 (46.7%)	67 (62.6%)		
Probable case (≥4)	90 (84.1%)	57 (53.3%)	40 (37.4%)		

Values are represented as mean (95% CI) for continuous variables and as frequency (%) for categorical variables unless otherwise indicated. 95%CI: 95% confidence interval.

without, no significant differences were observed between them (Gomez et al., 2018).

Most participants were women, confirming previous studies in which anxiety disorders are more prevalent in women (Quirós et al., 2012). There may be factors of vulnerability (biochemical, hormonal, social) that explain this, but specific factors or their mechanisms of action are not specified (McHugh et al., 2021). It is not known why the rates are higher in women and little is known about the risk factors or antecedents. What is considered important is to give relevance to these data both at diagnosis and when establishing a treatment.

It is known that psychotherapy is more effective for anxiety disorders between 18 and 60 years of age. We limited the study to this age range, thus avoiding the postponement of benzodiazepine treatment. Likewise, this also allows psychotherapy to modify behaviors that are indicators of chronic anxiety disorders and associated mental disorders. Psychotherapeutic programs such as ours are important to prevent and reduce cases of mental disorders, thus avoiding the possible burden of disability.

More than half our patients were taking diazepam, in contrast with other studies in which the most frequent benzodiazepine was lorazepam (Sánchez et al., 2013). Deprescription sometimes involves a change of benzodiazepine to diazepam, as there are more dosing options and it has a longer half-life, which permits more comfortable deprescription. This would justify the greater consumption of diazepam, together with the fact that, in the guidelines for the use of benzodiazepines, the use of those with a medium-long term half-life is recommended.

The study had some limitations. First, data on the medication prescribed could not be obtained in 20% of patients because patients used private prescriptions, did not have a health card from the autonomous community or obtained medication from close relatives. This uncontrolled circumstance is encountered in other types of study and highlights the underlying problems in obtaining this type of medication. Secondly, the study did not include a control group due to problems of viability, time constraints and economic limitations. Instead we used a before-after methodology, retrospectively comparing variables in the three months before and three months after the intervention. As our results are preliminary this program has to be considered as pre-experimental study. It's not possible to know with certainty that the intervention has achieved its purpose, despite its good results, because measures have not been taken on a regular session-by-session.

Conclusion

In conclusion, a psychotherapy program in primary care was effective in deprescibing benzodiazepines in two thirds of participants. Humanistic psychotherapy helped to deprescibe benzodiazepines, improve SF-12, and reduce anxiety. Questions remain about improving efficiency and about health spending, either direct (visits, complementary tests) or indirect (sick leave). The challenge is the generalization of these programs in primary care with professionals trained to achieve a less dependent and less medicalized society.

We can conclude that the program is a promising option which needs to be challenged by future empirical studies using better control groups and methodological safeguards.

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