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Benzodiazepine dependency treatment in a patient using diazepam capsules with decreasing doses

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KEYWORDS

Benzodiazepines, community pharmacy, dependence treatment

ABBREVIATIONS

BZD: benzodiazepines
DDED: daily dosage equivalent of diazepam

Presentation of clinical case/History

Consumption of benzodiazepines (BZD) has been growing steadily in Spain since the 90s. Half of patients over age 85 and 2% of adolescents between ages 15 and 19 have been treated with BZD (1). No clinical indication justifies prolonged prescription of BZD; however, long-term use is very common (2).

The patient had been in treatment with alprazolam for 14 years. For one year, she reduced the dose by splitting 0.5 mg alprazolam tablets until reaching a dose of 0.25/0/0.25. She wanted to stop the medication and asked her doctor to prescribe an alternative.

The treatment for benzodiazepine (BZD) dependency is gradual dose reduction, but the non-existence of commercialized presentations with the required doses complicates implementing the treatment. The doctor asked if there is anything we could do about this.

Study and evaluation

The patient had a physical and psychological dependence caused by prolonged use of the medication and met the diagnostic criteria of dependence. The risks of dependency increase with the dose and the time of use, and the lower the half-life of the BZD the higher the risk. Addictive past behavior also increases the risk (3).

A rapid dose reduction or abrupt withdrawal can cause withdrawal symptoms consisting of headaches, muscle aches, acute anxiety, confusion, irritability, mild dysphoria and insomnia. In severe cases there can be depersonalization, hyperacusis, tingling, muscle cramps, abdominal pain, vomiting, sweating, trembling, intolerance to light and physical contact, hallucinations and seizures (4).

At the time of intervention, the patient had a stable life with plans for the future, no mental illness, was not taking any other medications and had no drug addictions. She wanted to stop taking alprazolam.

According to the doctor, it was decided to adjust the dose and establish a plan for gradual dose reduction, preparing the necessary capsules from tablets in the pharmacy laboratory due to the patient's circumstances (5). The protocol from the University of Newcastle in the United Kingdom (6) was used as a reference, which first establishes a change to an equivalent dose of long-acting BZD (diazepam), followed by 10% reductions of the dose in the early phases and 25% in the last phases. The protocols establish a final dose of 1 mg, but in agreement with the doctor, we set the final dose at 0.5 mg diazepam. The initial dose regimen can be seen in table 1.

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Table 1 *Initial dose proposed*

		Morning	Midday	Evening	Night	DDED mg
Inicial dose	**Start/end date**	**Alprazolam 0.25 mg**			**Alprazolam 0.25 mg**	**10**
Stage 1		Alprazolam 0.25 mg			Alprazolam 0.25 mg	10
(2 weeks)						
Stage 2		Alprazolam 0.25 mg			Diazepam 5 mg	10
(2 weeks)						
Stage 3		Diazepam 5 mg			Diazepam 5 mg	10
(2 weeks)						
Stage 4		Diazepam 4 mg			Diazepam 5 mg	9
(1 week)						
Stage 5		Diazepam 3 mg			Diazepam 5 mg	8
(1-2 weeks)						
Stage 6		Diazepam 2 mg			Diazepam 5 mg	7
(1-2 weeks)						
Stage 7		Diazepam 1 mg			Diazepam 5 mg	6
(2 weeks)						
Stage 8		Diazepam 0.5 mg			Diazepam 5 mg	5.5
(1-2 weeks)						
Stage 9					Diazepam 5 mg	5
(1-2 weeks)						
Stage 10					Diazepam 4 mg	4
(1-2 weeks)						
Stage 11					Diazepam 3 mg	3
(1-2 weeks)						
Stage 12					Diazepam 2,5 mg	2.5
(1-2 weeks)						
Stage 13					Diazepam 2 mg	2
(1 week)						
Stage 14					Diazepam 1.5 mg	1.5
(1 week)						
Stage 15					Diazepam 1 mg	1
(1 week)						
Stage 16					Diazepam 0.5 mg	0.5
(1 week)						
Stage 17					Placebo	0
(1 week)						
Stage 18					Placebo	0
(1 week)						

DDED: daily dosage equivalent of diazepam.

Table 2 *Weight of the different tablets and capsules used in the test. Mean and standard deviation*

Nº	Split	Capsules
1	0.137	0.124
2	0.106	0.123
3	0.139	0.111
4	0.141	0.125
5	0.099	0.115
6	0.142	0.112
7	0.142	0.109
8	0.113	0.124
9	0.106	0.123
10	0.137	0.121
11	0.106	0.111
12	0.100	0.120
13	0.124	0.120
14	0.119	0.117
15	0,100	0.122
16	0.100	0.118
17	0.139	0.120
18	0.142	0.120
19	0.131	0.117
20	0.146	0.124
Data number	20	20
M Mean	0.123	0.119
Std Deviation	0.01782	0.00503

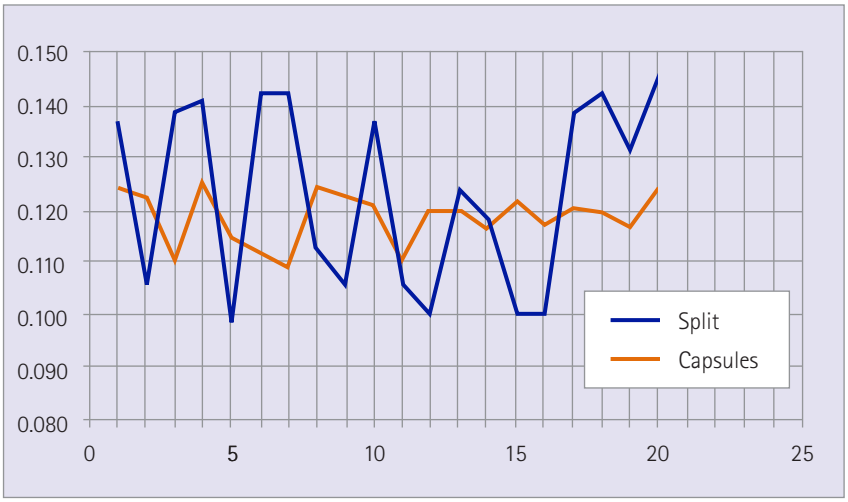

Figure 1 *Weight of the different tablets and capsules used in the test*

According to the protocols, each phase can last one or two weeks. If the patient does not tolerate the reduction, the phasing can be extended by the time necessary, but the dose is never increased. Therefore, it is not possible to know a priori the duration of treatment, even if there is an established plan, as it is the patient who sets the length of each period.

Procedure

All the procedures consulted (6) adjusted the dose by scraping and weighing the tablets one by one until reaching the indicated weight. While we did consider this method, we ruled it out because we found it to be slower and we did not have the elaboration procedure available, though for the encapsulation method (PN/L/FF/001 of the Formulario Nacional and PNT11-4 MICOF GUIA FORMULACION MAGISTRAL) by geometric dilutions (PNT11-2 MICOF GUIA FORMULACION MAGISTRAL) we did have standardized procedures available. As can be seen in the data (table 2 and figure 1), we see that when dividing the tablets the deviation of the content of the active ingredient was greater than the average for the capsules. We preferred to prepare capsules with a gradual dose reduction using the slow-reduction protocols of Professor Heather Ashton of Newcastle University (1), and if there were any withdrawal symptoms the dose would be reset without altering the DDED (daily dosage equivalent of diazepam). Dose reductions were proposed at 10% averages in the initial stages and 25% in the single dose phases. We consulted the patient and the doctor and after they agreed we began to develop the capsules. To do this we crushed the diazepam leo tablets and diluted them with excipient No.1 of the National Formulary, using riboflavin as an indicator of the dilution. To prepare the capsules we followed the appropriate SOPs.

Due to the importance of the dose in the process of breaking the dependency, we calculated the standard deviation of the content of the active ingredient of 20 tablets split by the patient (s=0.018) and 20 capsules made in the laboratory (s=0.005), and as the graphic shows, our method is more precise.

Time is shared between preparing the powder mixture and filling the capsules. As the amount of the active ingredient is always being reduced, the job is to dilute the initial powder mixture. The time spent on preparation, making the capsules and packaging the weekly requirements can vary between 3 and 5 minutes.

We set the monthly cost at €20. The price includes both preparation of the medication and the work required to complete the withdrawal programme, as well as dose recalculation, package inserts and information for the patient and coordination with the doctor.

We do not know the time needed to prepare the doses by scraping the tablets and, consequently, the possible cost of the service.

Result/Follow-up

The patient received her medication from the pharmacy every week. Also, before preparing the capsules, we consulted with her on whether to maintain or move forward the plan proposed because the duration of the phasing was her decision, always without altering the DDED. The patient responded well to treatment and decided to accelerate it. Originally 19 phases were envisaged with a total duration of 38 weeks, but this was able to be reduced to 15 phases over 18 weeks.

When she definitively suspended the BZD she changed to herbal medicine so that the withdrawal would be even less abrupt. First preparing capsules of Passiflora with hawthorn and subsequently tablets of Aquileia dream® (California Poppy, Passion Flower, Valerian and Melatonin 1.95 mg).

Final comments/ Conclusions

The procedure was fully satisfactory to all parties. The patient was very

helpful at all times. Patient-pharmacy-doctor communication is critical to the successful completion of a dependency withdrawal treatment. Not only because it is the doctor who must write the prescriptions needed to be able to use diazepam, but because the doctor also facilitates any consultation regarding prescription changes. At the same time, the patient is more at ease knowing that the doctor and the pharmacy are collaborating.

Sharing the decision-making with the patient, before and during the process, encourages them to take responsibility and comply with the treatment, which should be personalized to each case depending on their personality, living conditions and socio-environmental surroundings.

The system of gradual dose reduction is applicable to other active ingredients such as corticosteroids, antidepressants, antipsychotics, antiparkinson medications, etc. It also allows for adapting the dose for patients who are very underweight or extremely weak and need lower doses than those commercialized.

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