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A DRY EXTRACT OF *PASSIFLORA INCARNATA* L. USED FOR THE MANAGEMENT OF BENZODIAZEPINES WITHDRAWAL

Dry extract of Passiflora incarnata L. for benzodiazepine withdrawal therapy

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Introduction

Benzodiazepine withdrawal is often accompanied by anxiety, which carries a risk of relapse and the need to prescribe additional medication. Treatment based on dry extract of Passiflora incarnata L. has already shown potential as a first line treatment for symptoms of anxiety.

Equipment and method

We conducted a three-month longitudinal study. Patients undergoing benzodiazepine withdrawal were treated with Passiflora incarnata L. All patients enrolled on the study were sufficiently stable and had been under medical care foar at least three months. Their benzodiazepine intake was reduced by 25% of the initial dose every two weeks. No special support measures were used either before or during the study. The change in anxiety score and frequency of sexual activity was assessed during the withdrawal period.

Results

Overall, 91 patients participated in this study, with eventually 27 men (36.5%) and 47 women (63.5%) included, with an average age of 44.1±11.0 years. The withdrawal success rate was 78.4% (CI95%: 69.0-87.8%). There was a marked and highly significant reduction in Hamilton anxiety score. The monthly frequency of sexual activity increased slightly but significantly. After stopping or reducing their benzodiazepine dose, 70.3% of patients continued the Passiflora incarnata L. therapy.

Conclusions

Dry extract of Passiflora incarnata L. is a safe and proven anxiolytic which appears to improve the outcome of benzodiazepine withdrawal.

What is already known about the topic?

- Management of benzodiazepine withdrawal is often accompanied by anxiety symptoms and prescription of additional drugs. A dry Passiflora incarnata L. extract has previously shown its beneficial effects in the treatment of anxiety symptoms.

What does this article bring up for us?

- Based on the results of this article, we believe that a Passiflora incarnata L. dry extract may play a role in the management of benzodiazepine withdrawal symptoms.

KEY WORDS ▶ Benzodiazepine, withdrawal, passiflora, anxiety, sexuality

INTRODUCTION

Successful benzodiazepine withdrawal requires a slow, gradual dose reduction (10–25% a week), and possibly replacement therapy with an equivalent dose of a medium- or long-acting benzodiazepine. The anxiety and distress that come with withdrawal and the possibility of the anxiety present prior to the benzodiazepine therapy returning (rebound effect) can trigger a relapse and require further benzodiazepine use. Psychoeducation, psychotherapy and adjuvant therapy are often prescribed to manage the anxiety and sleep disorders. For example, some studies report a withdrawal success rate of approximately 70% with valproate, trazodone or even imipramine vs. only 20–30% in patients given placebo. However, the research is highly diverse with sometimes contradictory results concerning the efficacy of such adjuvant therapy for withdrawal (1). It is therefore impossible to identify the best molecule and decisions are often made on a case-by-case basis.

Studies in recent years have identified the potential benefits of dry extract of Passiflora incarnata L. as a first line treatment for the symptoms of anxiety (2). One study even demonstrated a similar reduction in anxiety score for both oxazepam and passionflower in patients with general anxiety disorder (3). Other studies have also shown the efficacy of passionflower extract for the control of acute anxiety in situations such as surgery or dental extraction (3,4).

The goal of this study was to assess the efficacy of passionflower dry extract for benzodiazepine withdrawal therapy and to measure change in anxiety scores and sexual activity as an indicator of quality of life. We are not aware of any other published study of this nature on benzodiazepine withdrawal. We have identified one study demonstrating the efficacy of passionflower as an adjuvant to clonidine for opiate withdrawal (5,6).

EQUIPMENT AND METHOD

STUDY DESIGN AND DATA COLLECTION

The 91 patients enrolled on this study were all sufficiently stable with no decompensation of mental health. They had been under the care of the Psychosomatic Medicine Unit at the CHU UCL Namur University Hospital (Godinne site) for at least three months between 30 March 2015 and 25 May 2018. They took one 200mg tablet of Passiflora incarnata L. dry extract (Sedistress® 200) twice daily from the start of the trial. For the first two weeks, patients made no change to the dose of the benzodiazepine that was to be withdrawn, then gradually reduced the dose by 25% of the initial dose every fortnight.

Patients were seen for three visits: upon enrolment to the trial (Visit 1), approximately one month later (Visit 2), then approximately two months after withdrawal (Visit 3). Data collected during Visit 1 (V1): age (years); gender; smoking (>10 cigarettes per day); alcohol intake (men > 3 glasses per day; women > 2 glasses per day); frequency of sexual activity (number of times per month); name, dose (mg), duration (months) and "diazepam 10mg" equivalents (number) of the drug to be withdrawn; and the name, dose (mg) and duration (months) of any other medication. During Visit 2 (V2), the investigator recorded the number of weeks of withdrawal and any changes in medication. During Visit 3 (V3), the investigator also collected details about frequency of sexual activity (number of times per month), the outcome of the withdrawal (success, reduction, abandonment, failure), and whether the patient was still taking Sedistress® 200, with the dose (number of tablets per day) and reason. Satisfaction was also recorded (1 = Patient satisfied; 2 = Patient not satisfied; 3 = No need or desire to continue; 4 = Discontinued due to external reason; 5 = Protocol non-compliance). Other than collecting this information and monitoring any withdrawal signs, no other special support measures were used, either before or during the study.

Anxiety was measured during V1 and V3 using the Hamilton Anxiety Scale, taken as the total score (0 = not present; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) for all 14 items: anxious mood, tension, fears, insomnia, intellectual, depressed mood, somatic (muscular) symptoms, somatic (sensory) symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, autonomic symptoms and behaviour at interview. The total score range was therefore 0 to 56 points. The higher the score, the greater the level of anxiety. A score of <17 indicates mild anxiety; 18–24 mild to moderate anxiety; 25–30 moderate to severe anxiety; and > 30 very severe anxiety.

STATISTICAL METHODS

The results are expressed as mean and standard deviation (SD) or median and interquartile range (IQR, Q1-Q3) for quantitative variables, and as frequency tables for categorised variables. The means for each quantitative variable were compared before and after withdrawal using a paired-sample t-test. The means of two groups were compared using an independent samples t-test or a Kruskal-Wallis test. The chi-squared or Fisher's exact test was used to compare proportions. Single or multiple linear regression was used to compare the effect of patient profile on change in Hamilton score. However, to predict treatment success based on patient profile, logistic regression was used. The link between each covariable and the outcome was quantified using the odds ratio (OR) and its 95% confidence interval. The statistical analysis was performed once, using the maximum available data. Missing data were not replaced. The level for statistical significance was 5% ($p<0.05$). We used the software packages SAS version 9.4 and R v.3.5 for the calculations and graphs.

RESULTS

BASELINE PATIENT PROFILES

Of the 91 patients on the study, 17 (18.7%) were eliminated from the analysis due to non-compliance with the protocol or an interruption to the withdrawal process for external reasons (e.g. major health issue, highly anxiety-inducing life event). Data were therefore analysed from 74 patients. Table 1 gives descriptive details for the 74 patients at baseline (Visit 1). Mean sexual activity was 2.4±3.7 episodes per month (range 0–16). Mean Hamilton anxiety score was 25.2±8.8 (range 4–45). Table 2 gives a list of the benzodiazepines to be withdrawn. Patients had been taking their respective benzodiazepine for a median duration of 12 months (IQR 3–24 months).

PATIENT PROFILES AT VISIT 2

The second visit took place an average of 4.9±1.2 weeks (range 2–11 weeks) i.e. just over a month after Visit 1. Table 3 shows the changes in medication between visits 1 and 2.

END PATIENT PROFILES

Table 4 gives descriptive details for the patients at their final visit. The average interval between visits 1 and 3 was 9.8±2.3 weeks (range 5–24 weeks) i.e. 2–3 months. The mean number of intercourse episodes was 3.9±4.2 (range 0–16) per month, and the mean total Hamilton anxiety score was 15.2±9.3 (range 2–38). At the final visit, the withdrawal was rated a success for 53 patients (71.6%), with 5 patients (6.8%) having succeeded in reducing the dose; one patient (1.4%) had left the trial and the withdrawal was rated a failure for 15 patients (20.3%). The success rate (success or dose reduction) was therefore 78.4% (CI95% 69.0–87.8%) and there were significantly more successes than failures. Of the patients, 52 (70.3%) continued to take the passionflower dry extract, 51 unchanged and one only to aid sleep. Most (82.7%) took two tablets a day. Of the 38 comments recorded (reasons or remarks), 21 patients (55.3%) were satisfied, six (15.8%) were not satisfied, 5 (13.2%) felt no need to continue and six (15.8%) stopped the withdrawal process for external reasons.

TABLE 1. Baseline profile for 74 subjects

Variable	N	Average SD number (%)	Minimum-Maximum
Years	74	44.1 ± 11.0	20 – 70
Sex	74		
Woman		47 (63.5)	
Men		27 (36.5)	
Smoking	74		
No		37 (50.0)	
Yes		37 (50.0)	
Alcohol	74		
No		64 (86.5)	
Yes		10 (13.5)	
Sexual activity (number of times per month)	74	2.4 ± 3.7	0 – 16
Total Hamilton anxiety score	74	25.2 ± 8.8	4 – 45
1. Anxious mood (0–4)	74	2.9 ± 0.82	1 – 4
2. Tension (0–4)	74	2.5 ± 0.89	1 – 4
3. Fears (0–4)	74	2.0 ± 1.08	0 – 4
4. Insomnia (0–4)	74	2.5 ± 1.23	0 – 4
5. Intellectual function (0–4)	74	2.1 ± 1.20	0 – 4
6. Depressed mood (0–4)	74	2.0 ± 1.19	0 – 4
7. Somatic (muscular) symptoms (0–4)	74	1.9 ± 1.23	0 – 4
8. Somatic (sensory) symptoms (0–4)	74	1.4 ± 1.22	0 – 4
9. Cardiovascular symptoms (0–4)	74	1.4 ± 1.07	0 – 4
10. Respiratory symptoms (0–4)	74	1.5 ± 1.16	0 – 4
11. Gastrointestinal symptoms (0–4)	74	1.2 ± 1.22	0 – 4
12. Genitourinary symptoms (0–4)	74	0.8 ± 1.06	0 – 4
13. Autonomic symptoms (0–4)	74	1.2 ± 1.12	0 – 4
14. Behaviour at interview (0–4)	74	1.5 ± 1.01	1 – 6
Number of medicines taken at baseline	74	3.0 ± 1.2	1 – 6

TABLE 2. Distribution of benzodiazepines to be withdrawn (N=74)

Variable	N	Average SD number (%)
Medicine to be withdrawn	74	
Cloxazolam		1 (1.4)
Bromazepam		2 (2.7)
Lorazepam		10 (13.5)
Lormetazepam		10 (13.6)
Oxazepam		1 (1.4)
Prazepam		7 (9.5)
Clorazepate		5 (6.8)
Diazepam		4 (5.5)
Alprazolam		15 (20.3)
Alprazolam retard		11 (14.9)
Zolpidem		6 (8.1)
Zopiclone		1 (1.4)
Equivalent numbers of Diazepam	73	1.5 ± 3.4
Dose to be discontinued (mg)	74	19.6 ± 77.6
Median (IQR)		2.0 (1.0-10.0)
Treatment duration (months)	74	26.8 ± 52.9
Median (IQR)		12 (3-24)

TABLE 3. Visit 1-Visit 2 change in medication V2 (N=74)

Variable	N	Average SD number (%)	Minimum-Maximum	P-value
Time limit since V1 (weeks)	71	4.9 ± 1.2		
Median (IQR)		5 (4-5)	2-11	
benzodiazepines to be withdrawn	69			
Change in the benzodiazepines to be withdrawn				
no change		3 (4.3)		
Dose reduction	66	66 (95.7)	25.0-100	<0.0001
Dose reduction (%)		46.9 ± 16.3		
Median (IQR)		50 (33.3-50)		
Medicines other than the benzodiazepine to be withdrawn	141			
Total number of other medicinal products				
no change		125 (88.7)		
Dose reduction	7	7 (5.0)	0-100	0.016
Dose reduction (%)		83.3 ± 28.9		
Median (IQR)		100 (50-100)		
Dose increase/New medicine		9 (6.4)		

TABLE 4. Patient profiles at final visit V3 (N=74)

Variable	N	Average SD number (%)	Minimum-Maximum	P-value
Duration of withdrawal since V1 (weeks)	66	9.8 ± 2.3	5-24	
Median (IQR)		10.0 (9.0-10.0)		
benzodiazepines to be withdrawn	64			
Change in the benzodiazepines to be withdrawn				
no change		6 (9.4)		
Dose reduction	56	56 (87.5)	33.3-100	<0.0001
Dose reduction (%)		92.2 ± 19.1		
Median (IQR)		100 (100-100)		
Dose increase/New medicine		2 (3.1)		
Medicines other than the benzodiazepine to be withdrawn	140			
Total number of other medicinal products				
no change		123 (87.9)		
Dose reduction	8	8 (5.7)	25-100	0.0078
Dose reduction (%)		61.5 ± 33.0		
Median (IQR)		50 (33.3-100)		
Dose increase/New medicine		9 (6.4)		

TABLE 4. Patient profiles at final visit V3 (N=74)

Variable	N	Average SD number (%)	Minimum-Maximum
Sexual activity (number of times per month)	64	3.9 ± 4.2	0 – 16
Total Hamilton anxiety score	69	15.2 ± 9.31	2 - 38
1. Anxious mood (0–4)	69	1.8 ± 1.04	0 – 4
2. Tension (0–4)	69	1.5 ± 0.98	0 – 4
3. Fears (0–4)	69	1.4 ± 1.16	0 – 4
4. Insomnia (0–4)	69	1.6 ± 1.17	0 – 4
5. Intellectual function (0–4)	69	1.4 ± 1.20	0 – 4
6. Depressed mood (0–4)	69	1.2 ± 1.14	0 – 4
7. Somatic (muscular) symptoms (0–4)	69	1.3 ± 1.06	0 – 4
8. Somatic (sensory) symptoms (0–4)	69	0.80 ± 1.01	0 – 4
9. Cardiovascular symptoms (0–4)	69	0.70 ± 0.93	0 – 4

10. Respiratory symptoms (0–4)	69	0.90 ± 0.99	0 – 4
11. Gastrointestinal symptoms (0–4)	69	0.65 ± 0.92	0 – 4
12. Genitourinary symptoms (0–4)	69	0.55 ± 0.92	0 – 4
13. Autonomic symptoms (0–4)	69	0.65 ± 0.95	0 – 4
14. Behaviour at interview (0–4)	69	0.78 ± 0.84	0-3
Conclusion	74	15.2 ± 9.31	
Success		53 (71.6)	
Dose reduction		5 (6.8)	
Abandonment		1 (1.4)	
Failure		15 (20.3)	
Treatment continued	74		
Yes		22 (29.7)	
No		51 (68.9)	
Yes, to aid sleep		1 (1.4)	
Sedistress® 200 dose (number/day)	52		
0		3 (5.8)	
1		3 (5.8)	
1.5		2 (3.8)	
2		43 (82.7)	
4		1 (1.9)	
Satisfaction	38		
Patient satisfied		21 (55.3)	
Patient not satisfied		6 (15.8)	
No need or desire to continue		5 (13.2)	
Interrupted withdrawal for external reason		6 (15.8)	

V1-V3 CHANGE IN FREQUENCY OF SEXUAL ACTIVITY AND HAMILTON SCORE (N=69)

Patients for whom both the baseline and final figures were available were included in this analysis. Other subjects were excluded. Table 3 shows the change in sexual activity, total Hamilton anxiety score and Hamilton item scores between Visit 1 and Visit 3. The number of sexual intercourse episodes per month increased slightly but significantly during the study, from 2.8±3.8 to 3.9±4.2 times per month (p=0.021). There was a marked and highly significant reduction in Hamilton anxiety score, which fell from 25.0±9.0 to 15.2±.3 i.e. a reduction of 9.8±8.9 or 40% (p=0.0001). The changes in these two variables are also given in graph form in Figures 1 and 2.

FACTORS AFFECTING THE DRASTIC FALL IN ANXIETY SCORE

The Hamilton anxiety score fell significantly after withdrawal, so it was important to examine whether this reduction was influenced by patient factors such as gender, age, smoking, alcohol intake, number of medicines taken previously, the duration of the medicine to be withdrawn, baseline anxiety score and the number of "Diazepam 10mg" equivalents to be withdrawn. The results are shown in Table 6 and relate to the 68 patients for which all data were available. For these 68 subjects, the Hamilton score went from 25.2±9.0 at V1 to 15.3±9.37 at V3 (reduction of 9.9±8.91; p<0.0001). The regression coefficient and standard error (SE) are given for each variable on both a univariate basis (i.e. for each variable taken separately) and a multivariate basis (i.e. for all variables taken together).

TABLE 5. V1-V3 Change in frequency of sexual activity and Hamilton score (N=74)

Variable	N*	V1 Average ± SD	V3 Average ± SD	Average difference ± SD	P-value
Sexual activity (number of times per month)	64	2.8 ± 3.8	3.9 ± 4.2	1.05 ± 3.33	0.021
Total Hamilton anxiety score	69	25.0 ± 9.01	15.2 ± 9.31	9.80 ± 8.87	<0.0001
1. Anxious mood (0–4)	69	2.90 ± 0.83	1.83 ± 1.04	1.07 ± 0.99	<0.0001
2. Tension (0–4)	69	2.54 ± 0.85	1.51 ± 0.98	1.03 ± 1.00	<0.0001
3. Fears (0–4)	69	2.03 ± 1.06	1.43 ± 1.16	0.59 ± 1.19	<0.0001
4. Insomnia (0–4)	69	2.43 ± 1.21	1.55 ± 1.17	0.88 ± 1.06	<0.0001
5. Intellectual function (0–4)	69	2.14 ± 1.22	1.41 ± 1.20	0.74 ± 1.02	<0.0001
6. Depressed mood (0–4)	69	2.00 ± 1.18	1.19 ± 1.14	0.81 ± 1.22	<0.0001
7. Somatic (muscular) symptoms (0–4)	69	1.97 ± 1.18	1.28 ± 1.06	0.70 ± 1.13	<0.0001
8. Somatic (sensory) symptoms (0–4)	69	1.35 ± 1.21	0.80 ± 1.01	0.55 ± 0.96	<0.0001
9. Cardiovascular symptoms (0–4)	69	1.38 ± 1.06	0.70 ± 0.93	0.68 ± 0.88	<0.0001
10. Respiratory symptoms (0–4)	69	1.57 ± 1.16	0.90 ± 0.99	0.67 ± 0.85	<0.0001
11. Gastrointestinal symptoms (0–4)	69	1.23 ± 1.21	0.65 ± 0.92	0.58 ± 1.06	<0.0001
12. Genitourinary symptoms (0–4)	69	0.80 ± 1.08	0.55 ± 0.92	0.25 ± 0.83	0.016
13. Autonomic symptoms (0–4)	69	1.23 ± 1.14	0.65 ± 0.95	0.58 ± 1.02	<0.0001
14. Behaviour at interview (0–4)	69	1.45 ± 1.01	0.78 ± 0.84	0.67 ± 0.87	<0.0001

**Number of subjects for which data are available from both V1 and V3*

FIGURE 1. V1-V3 change in monthly sexual activity (N=64). The graph on the right shows the distribution of individual differences between the two visits

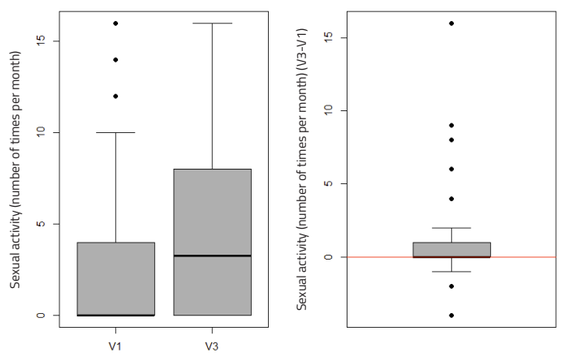


FIGURE 2. V1-V3 change in Hamilton anxiety score (n=69). The graph on the right shows the distribution of individual differences between the two visits

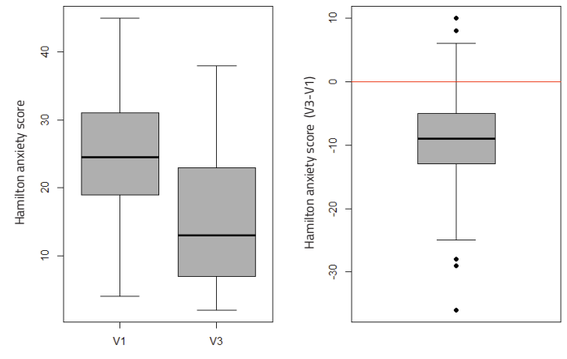


TABLE 6. Analysis of variables influencing the reduction in Hamilton anxiety score post benzodiazepine withdrawal (n=68 complete subjects)

Variable	Univariate model		Multivariated model (R^2=0.32)	
	Coefficient ± SE	P-value	Coefficient ± SE	P-value
Years	-0.02 (0.10)	0.84	0.05 (0.10)	0.60
Sex	-0.20 (2.28)	0.93	-0.29 (2.08)	0.89
Smoking	-1.60 (2.17)	0.46	-1.63 (2.01)	0.42
Alcohol	2.95 (3.19)	0.36	1.92 (2.95)	0.52
Initial anxiety score	0.45 (0.11)	0.0001	0.45 (0.11)	0.0001
Number of medicinal products	-1.62 (0.88)	0.068	-1.40 (0.83)	0.10
Duration of benzodiazepine therapy to be withdrawn (log)	-1.63 (0.76)	0.035	-1.33 (0.73)	0.073
"Diazepam 10mg" equivalents	-0.14 (0.31)	0.66	-0.22 (0.28)	0.44

A positive coefficient accentuates the reduction and a negative coefficient mitigates it. At univariate level, the only variables significantly correlated to a reduction in anxiety are baseline anxiety score and how long the patient had been taking the benzodiazepine to be withdrawn. These observations were confirmed for anxiety score at multivariate level when all variables are combined. The duration of benzodiazepine therapy is no longer significant but there is a trend (p=0.073). The multiple regression coefficients show that the higher the baseline anxiety score, the greater the reduction (p=0.0001); the correlation between baseline anxiety score and post-withdrawal reduction in score is r=0.45. On the other hand, a long duration of benzodiazepine therapy tends to counter this reduction (p=0.073); the correlation between the two variables is r=-0.26, and this is therefore an inhibiting factor. None of the other variables were significantly correlated to a fall in anxiety score, in particular the number of "Diazepam 10mg" equivalents to be withdrawn (p=0.44).

FACTORS AFFECTING THE INCREASE IN SEXUAL ACTIVITY

The monthly number of intercourse episodes increased significantly after withdrawal, so it was important to examine whether this increase was influenced by patient factors such as gender, age, smoking, alcohol intake, number of medicines taken previously, the duration of the medicine to be withdrawn, baseline anxiety score, baseline sexual activity and the number of "Diazepam 10mg" equivalents to be withdrawn. The results are shown in Table 7 and relate to the 63 patients for which all data were available. For these 63 subjects, the frequency of sexual activity rose from 2.7±3.74 at Visit 1 to 3.8±4.2 at Visit 3 (increase of 1.1±3.3, 41%; p=0.012). The regression coefficient and standard error (SE) are given for each variable on both a univariate basis (i.e. for each variable taken separately) and a multivariate basis (i.e. for all variables taken together). A positive coefficient contributes to increasing the number of instances of sexual intercourse and a negative coefficient contributes to a decrease.

TABLEAU 7. Analysis of variables influencing the increase in sexual activity post benzodiazepine withdrawal (n=63 complete subjects)

Variable	Univariate model		Multivariated model (R^2=0.32)	
	Coefficient ± SE	P-value	Coefficient ± SE	P-value
Years	0.014 (0.042)	0.75	0.013 (0.042)	0.76
Sex	0.62 (0.89)	0.49	1.08 (0.88)	0.22
Smoking	-1.08 (0.84)	0.20	-0.60 (0.86)	0.49
Alcohol	1.19 (1.15)	0.30	1.39 (1.15)	0.23
Initial anxiety score	0.002 (0.049)	0.96	-0.015 (0.047)	0.76
Sexual activity (number of times per month)	-0.28 (0.11)	0.012	-0.33 (0.12)	0.0063
Number of medicinal products	-0.50 (0.33)	0.14	-0.61 (0.35)	0.086
Duration of benzodiazepine therapy to be withdrawn (log)	-0.30 (0.30)	0.33	-0.42 (0.32)	0.20
"Diazepam 10mg" equivalents	-0.041 (0.12)	0.72	-0.043 (0.12)	0.72

On a univariate level, it is clear that the only variable significantly connected to the frequency of sexual intercourse is the initial frequency. This observation is confirmed on a multivariate level when all the variables are combined. The regression coefficients show that the higher the initial frequency of sexual intercourse is, the smaller the increase (p=0.0063); the correlation between the initial number of instances of sexual intercourse and the increase in the score after withdrawal is r=-0.31. The other variables are not significantly connected to the frequency of sexual intercourse apart from a trend for the number of medications at the beginning of the withdrawal process, where the higher the number is, the smaller the increase is (p=0.086).

PREDICTED SUCCESS OF WITHDRAWAL

As a reminder, withdrawal was regarded as a success in 58 patients and as a failure in 16 of them. A comparison of the two groups can be seen in Table 8.

TABLE 8. Comparative analysis of patients for which the withdrawal was rated a failure (n=16) and patients for which the withdrawal was rated a success (N=58)

Variable	Withdrawal failure (N=16)		Withdrawal succes (N=58)		P-value
	N	Average ± SD Median (IQR)	N	Average ± SD Median (IQR)	
Sexual activity (number of times per month)					
V1	12	1.3 ± 2.5	52	3.2 ± 4.0	0.094
V3	12	1.4 ± 1.8	52	4.4 ± 4.4	0.019
Difference	12	0.17 ± 1.8	52	1.3 ± 3.6	0.44
P-Value (Difference)		0.99		0.020	
Anxiety score					
V1	13	23.5 ± 8.12	56	25.4 ± 9.24	0.52
V3	13	18.3 ± 9.76	56	14.5 ± 9.15	0.19
Difference	13	5.23 ± 7.12	56	10.9 ± 8.96	0.038
P-Value (Difference)		0.023		<0.0001	
Treatment continued	16		58		0.0001
No		11 (68.8)		11 (19.0)	
Yes		5 (31.2)		47 (81.0)	

The monthly sexual activity was identical between the two groups at Visit 1, but at Visit 3 it was higher for the success group than for the failure group (p=0.019). There was no real change over time for the failure group, but there was a significant increase for the success group (increase of 1.3±3.6; p=0.020). For total Hamilton anxiety score, there was a statistically significant reduction over time for both the failure group (5.2±7.1; p=0.023) and success group (10.9±9.0; p<0.0001). However, the reduction was greater if the withdrawal therapy succeeded (p=0.038). Figures 3 and 4 illustrate the change in frequency of sexual activity and anxiety score for the success and failure groups.

FIGURE 3. Distribution of frequency of sexual activity between V1 and V3, by withdrawal failure (E = failure, n=12) and withdrawal success (R = success, n=52)

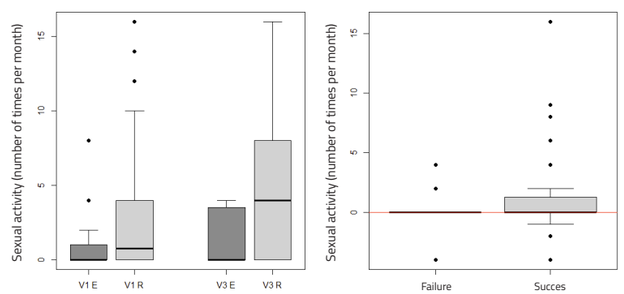
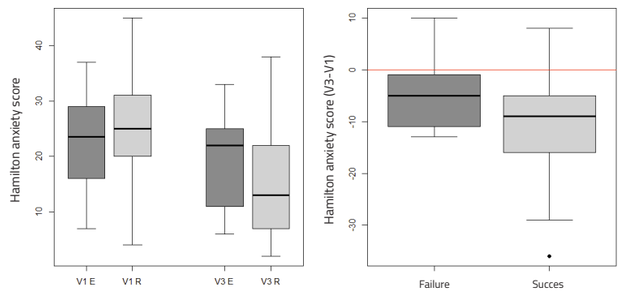


FIGURE 4. Distribution of Hamilton anxiety score between V1 and V3, by withdrawal failure (E = failure, n=12) and withdrawal success (R = success, n=52)



We see also that the proportion of patients that continued the treatment was significantly higher in the success group than in the failure group (81.0% vs. 31.2%; p=0.0001). We can therefore attempt to predict the success of withdrawal therapy based on patient profile (sex, age, smoking, alcohol intake, number of prior medicines taken, duration of medicine to be withdrawn, baseline anxiety score and number of "Diazepam 10mg" equivalents to be withdrawn). Complete data were available for 73 patients. The results are given in Table 9. At univariate level, no variable was significantly correlated with successful withdrawal. These observations were confirmed at multivariate level when all variables are combined.

TABLE 9. Analysis of variables affecting outcome (success/failure) of benzodiazepine withdrawal therapy (n=73)*

Variable	Univariate model			Multivariated model	
	Failure (N=16)	Succes (N=57)	P-value	OR (IC95%)	P-value
Years	42.8 ± 9.73	44.5 ± 11.5	0.57	0.014 (0.028)	0.61
Sex	5 (19.2)	21 (80.8)	0.68	0.16 (0.63)	0.80
Smoking	10 (27.0)	27 (73.0)	0.29	-0.34 (0.64)	0.59
Alcohol	2 (20.0)	8 (80.0)	0.87	0.057 (0.91)	0.95
Initial anxiety score	23.3 ± 8.37	25.5 ± 9.10	0.37	0.041 (0.035)	0.25
Number of medicinal products	3.00 ± 1.03	2.96 ± 1.25	0.92	-0.015 (0.27)	0.95
Duration of benzodiazepine therapy to be withdrawn (log)	2.33 ± 1.73	2.30 ± 1.29	0.93	-0.098 (0.24)	0.68
"Diazepam 10mg" equivalents	3.06 ± 7.23	1.09 ± 0.54	0.33	-0.42 (0.47)	0.37

** Results presented as an average +- SD or number (%), odds ratio, CI 95% Confidence interval to 95%*

DISCUSSION

This prospective interventional study analysed data from 74 of 91 patients under the care of the Psychosomatic Medicine Unit at the CHU UCL Namur University Hospital (Mont-Godinne site). The subjects received dry extract of Passiflora incarnata L. as benzodiazepine withdrawal therapy. Average patient age was 44±11 years, and two thirds of subjects (63.5%) were female. The main medicines to be withdrawn were alprazolam (normal and ER), prazepam, lormetazepam and lorazepam. These patients took on average 3.0±1.2 medicines per day, and the median duration of therapy of the benzodiazepine to be withdrawn was approximately 1 year. The mean number of "Diazepam 10mg" equivalents administered per patient was 1.5±3.4.

Both total withdrawal and a dose reduction at Visit 3 were rated a success. The withdrawal therapy was therefore a success for the majority of patients (78.4%). The 17 patients excluded from the statistical analysis were not rated failures, because the exclusion was due to the external reasons (e.g. somatic disorders, anxiety-inducing life events) or the fact that the protocol was breached (e.g. non-compliance with the passionflower therapy; benzodiazepine discontinued too abruptly). However, the analysis of change in Hamilton anxiety score and frequency of sexual activity did include the failures for which data were available.

As well withdrawal efficacy of this treatment, the study demonstrated a significant improvement in Hamilton anxiety score, which went from 25.0±9.0 to 15.2±9.3, a reduction of 9.8±8.9 or 40% (p<0.0001). Comparing patients in terms of withdrawal success or failure, the improvement in anxiety score was significant for the failure group but was significantly greater in the success group (10.9±9.0 vs. 5.2±7.1; p=0.038).

There was also a significant increase in the frequency of sexual activity, which rose from 2.7±3.7 episodes to 3.8±4.2, an increase of 1.1±3.3 or 41% (p=0.012), The number of intercourse episodes rose in the success group (p=0.020) but not in the failure group.

LIMITATIONS

The main limitation of this study was the lack of a control group. Drawing comparisons with other studies is difficult due to the differences between protocols. However, we were surprised by our 78.4% withdrawal success rate. In recent literature (1), the success rate achieved with various molecules benzodiazepine withdrawal such as trazodone, valproate and imipramine is around 70%, and only 20 -30% for placebo. As described above, no special withdrawal measures were used. We therefore hypothesise that the anxiolytic effect of passionflower and its safety profile (70.3% of patients continued taking the treatment) play an important role in the withdrawal.

This hypothesis will be tested in the future with the addition of a control group. Another limitation of the study was the lack of information about the initial indication for the benzodiazepine therapy. The drugs had been prescribed some while ago by a different practitioner. The two main indications for benzodiazepines i.e. anxiety and sleep disorders, both occur with most psychiatric illnesses and taking benzodiazepines usually masks the initial diagnosis. It was therefore impossible to obtain any post hoc objective information about the diagnosis. It would be useful to conduct a pre-benzodiazepine diagnostic analysis (e.g. questionnaire).

CONCLUSIONS

We found that 78.4% of patients who received dry extract of Passiflora incarnata L. successfully stopped or reduced the dose of their long-term benzodiazepine therapy. This withdrawal was accompanied by a significant reduction in anxiety (40%) and a significant increase in the frequency of sexual activity (41%).

PRACTICAL RECOMMENDATIONS

When withdrawing patients from long-term benzodiazepine therapy, additional medication is often necessary to treat the symptoms of anxiety. Dry extract of Passiflora incarnata L. is a safe and proven anxiolytic, making it relevant for this indication.

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