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Clinical Trial

Efficacy of Aerobic Exercise Added to Alprazolam in Panic Disorder Treatment: Clinical Randomized Trial

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Abstract

Objective: The purpose of this study is to determine whether the combination of aerobic physical exercise and alprazolam in patients with panic disorder has a better therapeutic response than treatment with alprazolam alone.

Description: We have observed in our clinical practice that patients who practiced aerobic physical exercise had faster remissions and better improvement in their treatments than those who did not.

The objective is to compare the efficacy of a pharmacological monotherapy (alprazolam), which is one of the options for the pharmacological treatment of panic disorder, with another treatment such as the combination of aerobic physical exercise and alprazolam, and to determine if this combination results in a better therapeutic response.

Methods: 150 outpatients with panic disorder were randomly assigned to 4 mg of alprazolam or 4 mg of alprazolam associated to a programmed aerobic exercise reaching a heart rate between 50% and 75% of their maximum. Both groups completed their treatments in 12 weeks and were scored using the Hamilton Anxiety Rating Scale (H.A.R.S./14) and the Clinical Global Impression (CGI) before the study and during weeks 1, 4, 8, and 12.

Patients assigned to the pharmacological plan received 4 mg alprazolam daily for 12 weeks. Two weeks after the first interview they had their first baseline psychiatric control, where all the patients were evaluated. Then, at the same visit, all the patients were prescribed 4 mg of alprazolam. The dose was gradually increased from 1 to 4 mg throughout the first week of treatment. The test was repeated during weeks 2, 4, 8 and 12.

Patients assigned to exercise had to pass an ergometric test to determine their functional capacity expressed in METs for future indication of exercise. Two weeks after the first interview they had their first baseline psychiatric control and at the same time a 4 mg dose of alprazolam was prescribed, gradually increased from 1 to 4 mg along the first week of treatment. The test was repeated during weeks 2, 4, 8 and 12. Then they followed a protocolized aerobic exercise plan for this study for 12 weeks. The type of exercise consisted of a brisk walk for 30 minutes divided into stages. After each stage, the patient must control his own heart frequency, which must be between 50 and 75% of its maximum to ensure an aerobic condition (according yo American Cardiological Association criteria)

Results: 106 of the 150 selected patients managed to fulfill both treatments: 51 for the alprazolam + exercise group (dropout rate 32%) and 55 for the alprazolam group (dropout rate 27 %).

The group treated with alprazolam + exercise experienced a significant improvement ($p < 0.001$) respect to the group treated only with alprazolam, reaching lower Hamilton Anxiety Scale scores (4,16 ± 1,06 and 8.57 ± 2,39 respectively) and Global Clinical Evaluation scores (Severity 1,86 ± 0,60 and 2.71 ± 0,62 ; Improvement 2,19 ± 0,49 and 2,87 ± 0,63 respectively for each group). Also, the remission rates were higher for the first group.

Conclusion: Aerobic physical exercise in addition to pharmacological treatment (alprazolam) is more effective than the alprazolam treatment alone, and could be a useful alternative to treat this disorder.

Eligibility

Minimum Age: 20 Years Maximum Age: 60 Years

Sex: All

Gender Based:

Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

- Patients with panic disorder scored between 20 and 30 by the Hamilton Anxiety Rating Scale/14. (Baseline scale scores were measured during the first interview and diagnoses were made by

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a psychiatrist using the Structured Clinical Interview for DSM IV).

- Good physical health and normal results determined on a previous physical examination and routine laboratory tests (renal, hepatic, hematological and thyroid function).
- Patients who completed a written informed consent form (which was obtained from every included patient and had been fully explained before the procedure).

Exclusion Criteria:

- A history of some kind of recent somatic disease.
- Diagnosis of some other type of associated or psychiatric disease of axis I of DSM IV, such as affective disorders, drug dependency.
- Hamilton Anxiety Scale lower than 20 points or higher than 30.
- Use of some other type of medication or treatment (including psychotherapy) or having received it during last past 3 months.
- Patients who could not complete the clinical examination
- Patients who have not accepted to complete or sign the written informed consent.
- Pregnant patients or in lactation. (A pregnancy test was performed for women in fertile age)
- Patients with history of rejection to the used drug.

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: Alprazolam Patients assigned to the pharmacological plan	Drug: Alprazolam The patients assigned to the pharmacological plan will receive 4 mg alprazolam daily for 12 weeks. Two weeks after the first interview they have their first baseline psychiatric control, where all the patients are tested. Then, at the same visit, all the patients are indicated 4 mg of alprazolam. The dose is gradually increased from 1 to 4 mg along the first week of treatment. The test is repeated during weeks 2, 4, 8 and 12. Other Names: • Non exercise group
Active Comparator: Alprazolam + Aerobic exercisePatients assigned to mix plan	Drug: Alprazolam + Aerobic exercise The patients assigned to exercise have to pass an ergometric test to determine their functional capacity expressed in METs for future exercise indication. Two weeks after the first interview they have their first baseline psychiatric control and at the same time they are indicated a 4 mg dose of alprazolam, gradually increased from 1 to 4 mg along the first week of treatment. The test is repeated during weeks 2, 4, 8 and 12. Then they follow a protocolized aerobic exercise plan for this study for 12 weeks. The type of selected exercise consists of a rapid walk for 30 minutes divided in stages. After each stage the patient must control his own heart frequency that has to be between 50 and 75% of their maximum to assure an aerobic condition (American Cardiological Association). Other Names: • Exercise group

Baseline Characteristics

Reporting Groups				
	Description			
Alprazolam	Patients receiving only alprazolam			
Alprazolam + Aerobic Exercise	Patients receiving alprazolam + aerobic exercise			
		Alprazolam	Alprazolam + Aerobic Exercise	Total
Overall Number of Participants		75	75	150
Age, Categorical Count of Participants	Number Analyzed	75 participants	75 participants	150 participants
	<=18 years	0 0%	0 0%	0 0%
	Between 18 and 65 years	75 (100%)	75 (100%)	150 (100%)
	>=65 years	0 0%	0 0%	0 0%
Age, Continuous Mean (Standard Deviation)	Number Analyzed	75 participants	75 participants	150 Participants
		34.01 (8.07)	35.68 (7.67)	34.85 (7.89)

		Alprazolam	Alprazolam + Aerobic Exercise	Total
Sex: Female, Male Measure Count of Type: Participants	Number Analyzed	75 Participants	75 Participants	150 Participants
	Female	57 (76%)	55(73.33%)	112 (74.67%)
	Male	18 (-24%)	20 (26.67%)	38 (25.33%)
Enrollment Measure Number Type:	Number Analyzed	75 Participants	75 participants	150 participants
		75	75	150

Baseline demographic and clinical characteristics of each group were similar in terms of age and sex distribution after the randomization procedure.

In both groups most of the patients were women and education levels were almost similar. The presence of agoraphobia was greater in the exercise group (32% versus 26,67%).

Study Results

Participant Flow

Recruitment Details	180 patients were preselected for the study and 150 were eligible for the study. They were outpatients from the office practice.
Pre-assignment Details	30 selected patients were not included: 12 did not match the 20 points for the Hamilton Anxiety Scale; 10 hadhistory of medical diseases (5 of hypothyroidism, 4 of hypertension, and 1 of chronic fatigue syndrome); 8 had other associated psychiatric diseases: (5 had major depressive disorder and 3 had social anxiety disorder).

Those assigned to the exercise group had to pass a treadmill ergometric test to determine functional capacity measured in METS, using a modified Bruce protocol that is used primarily in healthy subjects [1-4]

Patients withdrew from the study when they had serious adverse effects, or if they did not attend the stress test (if they were assigned to the exercise group) or if they showed cardiovascular abnormalities during exercise testing. Of the 75 initially assigned to exercise, 63 patients attended the trial. 12 patients had to abort it due to physical discomfort.

The maximum heart rate achieved was measured for each patient [5]. There are also charts of maximum heart rate ranges for each age. Only 19 patients exceeded the expected maximum heart rate for their own age in stage IV of the stress test, but the maximum heart rates considered for the exercise plan were those obtained from the exercise stress test.

Two weeks after the first assignment interview, both groups had their first baseline psychiatric control, where all patients were assessed with the Hamilton Anxiety Scale and CGI Scales.

Then, at the same visit, all patients were prescribed 4 mg of alprazolam. The dose was gradually increased from 1 to 4 mg during the first week of treatment [6,7].

Patients in the exercise group had to follow an exercise plan specially designed for this study.

The plan was based on a previously established protocol and consisted of the practice of aerobic physical exercise 3 times a week for 12 weeks. The type of exercise selected was brisk walking (both on a non-incline treadmill or natural routes) for 30 minutes. Each exercise session was divided into 5-minute periods and had a gradual increase over the following days.

After each period, the patient had to control his own heart rate.

For this stage, they were previously instructed on how to measure their own heart rate (taking the radial or carotid pulse in case the radial could not be detected). For those patients using pollards, they had to calibrate them with their heart rate values from manual pulse measurement.

Each patient had to maintain a heart rate between 50 and 75% of their maximums obtained in the ergometric test. To do this, they were instructed on how to speed up or slow down their pace to maintain the expected heart rate range. This proposal is based on the exercise guidelines of the American Cardiological Association [8].

In these guidelines, the range between 50% and 75% of the maximum achievable heart rate for each patient is called "Target Heart Rate", and it is found that beyond that 75% physical exercise becomes anaerobic [8,9] .

Patients in both groups (with or without exercise) were treated for 12 weeks.

Adverse effects were assessed during patient controls in weeks 1, 4, 8, and 12 after baseline control. Patients who could not tolerate adverse effects were excluded from the study.

Reporting Groups		
	Description	
Alprazolam	Patients receiving only alprazolam	
Alprazolam + Aerobic Exercise	Patients receiving alprazolam + aerobic exercise	
Overall Study		
	Alprazolam	Alprazolam + Aerobic Exercise
Started	75	75
Completed	55	51
Not Completed	20	24

Outcome Measure

Table 5. *Primary Outcome Measure:*

Measure Title	Participants 'Endpoint Change from Baseline in Hamilton Anxiety Rating Scale
Measure Description	The Hamilton Anxiety Rating Scale is a test that consists of 14 items measuring the severity of anxiety symptoms. Each item is rated on a 5-point ordinal scale, ranging from 0 (not present) to 4 (severe). Each of the 14 items measure both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety)with a total score range of 0–56, where 17 indicates mild severity, 18-24 mild to moderate severity, and 25-30 moderate to severe.
Time Frame	12 weeks

Hamilton Anxiety Scale

The final mean Hamilton Anxiety Scale scores were also highly and significantly smaller for exercise group than for the non-exercise one. The final scores were 4.16 ± 1.06 for the first group and 8.57 ± 2.39 for the second one, while the basal mean scores were of 22.59 ± 2.09 and 22.73 ± 1.98 respectively. The p value was also less than 0,001. (Table 6.).

Reporting Groups		
	Description	
Alprazolam	Patients receiving only alprazolam	
Alprazolam + Aerobic Exercise	Patients receiving alprazolam + aerobic exercise	
Measured Values		
	Alprazolam	Alprazolam + Aerobic Exercise
Overall Number of Participants Analyzed	75	75
Participants 'Endpoint Change in Hamilton Anxiety Rating Scale (Mean + Standard Deviation)		
Baseline	22.59 ± (2.09)	22.73 ± (1.98)
Final	8.57 ± 2.39	4.16 ± 1.06

Remission analysis

The Hamilton Anxiety Scale was also used in this study to measure the patients' remissions at the end of the study.

It was considered remission when the patient reached at least 5 points or less in the Hamilton Anxiety Scale rate at the end of the respective treatment. [10].

The percentage of remission for those assigned to exercise was of 90.20% against 12.73% for the patients not assigned to an exercise plan. 46 patients remitted in the first group against 7 for the second one. The value was highly significant and corresponded to a value of $p <$ to 0.001

The exercise group showed a faster clinical response than the non exercise group all along the study.

Hamilton Anxiety Rating Scale items that improved in a greater proportion with the exercise treatment were general somatic symptoms such as fatigability, weakness, or functional alterations of the senses, as well as the genitor-urinary symptoms, the autonomic ones, fears, difficulties in memory and concentration and the insomnia. Then, in a lower proportion cardiovascular symptoms, respiratory symptoms, and state of tension and anxious mood.

Table 7. *Statistical Analysis 1 for Participants 'Endpoint Change from Baseline in Hamilton Anxiety Rating Scale*

Statistical Analysis Overview	Comparison Group Selection	Alprazolam, Alprazolam + Aerobic Exercise
	Comments	A p-value less than 0.05 (≤ 0.05) is statistically significant. It indicates strong evidence against the null hypothesis, as there is less than a 5% probability the null is correct (andthe results are random)
	Type of Statistical Test	Other
	Comments	[Not specified]
Statistical Test of Hypothesis	P-Value	<0.001
	Comments	[Not specified]
	Method	t-test, 1 sided
	Comments	[Not specified]
Method of Estimation	Estimation Parameter	Mean Difference (Final Values)
	Estimated Value	1
	Estimation Comments	[Not specified]

Secondary Outcome Measure

Response to treatment

According to the Global Clinical Impression Severity Scale (CGI-S), 13 patients (25.49%) achieved the scale category ""not at all ill"" in the exercise group and only 4 (7.27%) for the group treated alone with medication.

Final mean scores on the CGI-S and CGI-I scales were significantly lower for the exercise group, starting with similar baseline values. In all cases, the level of significance was lower than that indicated in the study objectives, with a value of p <0.001.

According to the Clinical Global Impression Improvement (CGI-I) rating scale, 43 patients (84.31%) in the group treated with exercise + alprazolam achieved the "very much improved" scale category at the end of treatment, compared to 15 patients (27.27%) in the non exercise group. The rest of the patients in both groups had "very much improved" and there were no patients in both groups who were unchanged.

Table 8.

Measure Title	Participants 'Endpoint Change from Baseline in Clinical Global Impression Severity Scale (CGI-S)	
Measure Description	The Clinical Global Impression Severity scale is a 7-point ordinal scale that rates the severity of the patient's illness, assessing on the severity of a patient's mental illness. It ranges from 1 to 7 (1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, extremely ill).	
Time Frame	Baseline and 12 weeks	
Reporting Groups		
	Description	
Alprazolam	Patients only receiving alprazolam	
Alprazolam + Aerobic Exercise	Patients receiving alprazolam + aerobic exercise	
Measured Values		
	Alprazolam	Alprazolam + Aerobic Exercise
Overall Number of Participants Analyzed	75	75
Participants 'Endpoint Change from Baseline in Clinical Global Impression Severity Scale (CGI-S) Mean (Standard Deviation)	4.05 ± (0.23)	4.06 ± (0.24)

Table 9. *Secondary Outcome Measure:*

Measure Title	Participants 'Endpoint Change from Baseline in Clinical Global Impression Improvement Scale (CGI-I)
Measure Description	The Clinical Global Impression Improvement Scale is a 7-point ordinal scale that assesses how much the patient's illness has improved or worsened relative to a baseline state before the intervention. Rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.
Time Frame	Baseline and 12 weeks

Analysis Population Description

Table 10: *Patients with history of Panic Disorder*

Reporting Groups		
	Description	
Alprazolam	Patients receiving only alprazolam	
Alprazolam + Aerobic Exercise	Patients receiving alprazolam + aerobic exercise	
Measured values		
	Alprazolam	Alprazolam + Aerobic Exercise
Overall Number of Participants Analyzed	55	51
	Alprazolam	Alprazolam + Aerobic Exercise
Participants 'Endpoint Change from Baseline in Clinical Global Impression Improvement Scale (CGI-I) (Mean ± Standard Deviation)	2.70 ± (0.62)	1.86 ± (0.60)

Reported adverse effects

51 patients in the exercise group (68%) and 55 in the non-exercise group (73%) were able to complete the study.

44 patients were withdrawn from the study due to poorly tolerated side effects, all due to alprazolam, in similar proportions for both groups.

The most frequently reported side effect that prompted exclusion in both groups was drowsiness. Others were dizziness and ataxia (17 cases), 1 sexual dysfunction and 1 paradoxical anxiety.

For those who complied with the protocol, 28 had tolerable side effects due to alprazolam in the exercise group and 34 in the non-exercise group, which did not justify exclusion from the study.

Physical exercise was well tolerated in most cases. 3 patients had increased respiratory symptoms, 4 tachycardia, 4 dizziness, 3 chest pain and 5 muscle pain that remitted during treatment. None of them had to be withdrawn for these effects.

Table 11.

Time Frame	Adverse event data were collected for 12 weeks			
Adverse Event Reporting Description	Definition of adverse events are similar of those taken from clinicaltrials.gov			
Reporting Groups				
	Description			
Alprazolam	Patients receiving only alprazolam			
Alprazolam + Aerobic Exercise	Patients receiving alprazolam + aerobic exercise			
All-Cause Mortality				
	Alprazolam		Alprazolam + Aerobic Exercise	
	Affected/At Risk (%)		Affected/At Risk (%)	# Events
Total All-Cause Mortality	/		/	
Serious Adverse Events				
	Alprazolam		Alprazolam + Aerobic Exercise	
	Affected/At Risk (%)		Affected/At Risk (%)	# Events
Total	0/75 (0%)		0/75 (0%)	

Table 12. *Most frequent side effect events*

Frequency Threshold Above Which Other Adverse Events are Reported: 5%

	Alprazolam		Alprazolam + Aerobic Exercise	
	Affected/At Risk (%)	# Events	Affected/At Risk (%)	# Events
Total	32/75 (42.67%)		39/75 (52%)	
Nervous system disorders				
Dizziness *	4/75 (5.33%)	8	5/75 (6.67%)	9
Drowsiness *	28/75 (37.33%)	52	34/75 (45.33%)	60

*Indicates events were collected by non-systematic methods.

Limitations and Caveats

Panic patients may sometimes be reluctant to use medication. This could lead to early dropouts. Possible difficulties in following the exercise protocol.

Discussion

The results of this study showed that the indication of aerobical physical exercise in addition to pharmacotherapy (in this case alprazolam) had statistically significant better effects in the treatment for panic disorder than the single pharmacological treatment. Patients who practiced exercise had also a faster response than those who were treated with alprazolam alone.

They also experienced a greater improvement in concentration and memory, and also over genitourinary symptoms, insomnia, fears, and autonomic symptoms in comparison with the other group.

Many alternatives for the treatment of panic disorder have been considered for many years, including other pharmacological treatments, and cognitive and behavioral therapies.

Pharmacological treatments include antidepressants and specific anxiolytic medication.

Generally, the appearance of side effects and a certain late onset of therapeutic effects tend to delay the patient's adherence to pharmacological therapies, especially antidepressants.

Benzodiazepines can also sometimes cause different degrees of habituation [11] The dropout rate for the exercise group has been relatively low (9 out of 75) (12%). Patients with

panic disorder can often be reluctant to receive medication.

The indication of physical exercise in addition to pharmacological treatment has shown that it is possible to obtain a better and faster therapeutic response with fewer side effects. This could also help panicked patients to agree to take their medications better.

It has not yet been proven whether the only indication for physical exercise not associated with other treatments was more effective in relation to other treatments for panic disorder [1].

Beneficial effects of physical exercise have been described for patients with depressive disorders [12] Publications of the W.H.O. mention the many health benefits of physical activity [13,14].

It is well known that a sedentary lifestyle is associated with obesity and heart disease, thus increasing the costs of health expenses. Today many companies encourage their workers to practice physical exercise during the working day.

Panic patients could be included in exercise plans that could be sponsored by N.G.O. or also by Government Organizations. They have usually affected their quality of life due to their symptoms, which reduce their family, social and work performance.

Sometimes they arrive at a late diagnosis and have to consult doctors from many other specialties, thus generating an unnecessary and expensive use of medical attention before reaching a psychiatrist consultation.

The implementation of an exercise plan in addition to a traditional medication plan becomes an acceptable measure to be applied for the panic patient, reduces the drugs costs and interactions, and it also probably represents an interesting therapeutic measure to be applied also for other psychiatric disorders.

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