Effects of Passion Flower Extract, as an Add-on Treatment to Sertraline, on Reaction Time in Patients with Generalized Anxiety Disorder: a Double-blind Placebo-Controlled Study

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Objective: Because of functional impairment caused by generalized anxiety disorder and due to cognitive side effects of many anti-anxiety agents, in this study we aimed to evaluate the influence of Passion flower standardized extract on reaction time in patients with generalized anxiety disorder.

Method: Thirty patients aged 18 to 50 years of age, who were diagnosed with generalized anxiety disorder and fulfilled the study criteria, entered this double-blind placebo-controlled study. Reaction time was measured at baseline and after one month of treatment using computerized software. Correct responses, omission and substitution errors and the mean time of correct responses (reaction time) in both visual and auditory tests were collected. The analysis was performed between the two groups and within each group utilizing SPSS PASW- statics, Version 18. P-value less than 0.05 was considered statistically significant.

Results: All the participants were initiated on Sertraline 50 mg/day, and the dosage was increased to 100 mg / day after two weeks. Fourteen patients received Pasipy (Passion Flower) 15 drops three times daily and 16 received placebo concurrently. Inter-group comparison proved no significant difference in any of the test items between assortments while a significant decline was observed in auditory omission errors in passion flower group after on month of treatment using intra-group analysis.

Conclusion: This study noted that passion flower might be suitable as an add-on in the treatment of generalized anxiety disorder with low side effects. Further studies with longer duration are recommended to confirm the results of this study.

Key words: *Generalized Anxiety Disorder, Mental Processing, Passion Flower, Reaction Time, Sertraline*

The Generalized Anxiety Disorder (GAD) is defined as the basic anxiety disorder, which may reflect the fundamental process of all emotional disorders and significant degree of functional impairment (1). GAD is hyper-reactivity and a fear of negative emotional shifts and unmanageable worry about preventing these perceptive contrasts (2). The symptoms are difficult to control and last for more than six months. GAD is associated with three or more of diagnostic items from DSM-IV (Diagnostic and Statistical manual of Mental illnesses-4th edition) including: Feeling keyed up or on edge, easily getting fatigue, mind going blank, agitation, somatic tension and sleep disturbances. Treatment choices include psychological therapies such as cognitive behavioral therapy (CBT) as the main non-pharmacological therapy (3), acceptance and commitment therapy (4), intolerance of uncertainty

therapy and motivational interviewing (5) as well as pharmacotherapy including Selective Serotonin Reuptake Inhibitors (SSRIs) (6), Benzodiazepines (7), Pregabalin (8) and Gabapentin (9), Tricyclic Antidepressants (TCAs), Buspirone and Hydroxyzine (6). Reaction Time (RT) is defined as the time elapsed between offering stimuli and the indication of comprehension by the subject (10). RT is claimed to be the main dependent variable for analyzing perceptive models (11).

Response procedure is directly based on circumstances (12). Many factors may be responsible for reaction time fluctuations, specially a great number of drugs and substances e.g., Caffeine (13), alcohol (14), psychostimulants (15), sedative-hypnotic and anti-epileptic drugs (16, 17) and many of cognitive side

effects, which are raised by psychiatric pharmacotherapies (18, 19).

Passion flower symbolizes the passion of Jesus in Christian theology because of its unique structure (20). Traditionally its extract has been used as an herbal remedy for nervous anxiety (21) and insomnia, tenderness, restlessness, irritability (22) and hysteria (23). Passion flower has been reported to affect GAD (24). Most of these effects are believed to be related to benzoflavone, which is the active constituent of the plant extract (25). We aimed to investigate the effects of passion flower extract on perceptual processing toward threats via reaction time test since its advantage on mental function did not receive specific reflections in previous studies.

Materials and Method
Research Participants
Thirty outpatients entered this randomized double-blind placebo-controlled study (Ethical approval number 7408 - by Ethics Committee at Islamic Azad University of Pharmaceutical Sciences). The participants were included in the study from Roozbeh and Baharloo hospitals and private psychiatric offices during 2010- 2012. Patients were diagnosed with Generalized Anxiety Disorder (GAD) based on DSM-IV criteria and clinical interviews. Their family history was considered as well. They were tested using Hamilton Anxiety Rating Scale Form A (HARS). Hamilton Rating Scale for Depression (HRSD) was utilized to determine the patients' comorbid depression. The Hamilton Scales were standardized for Iranian patients.

Patients between 18 to 24 years of age were included. In addition, sertraline consumption was considered the best treatment for their current disease per decision of the psychiatrist. All patients were initiated on Sertraline. The exclusion criteria were as follows: Having difficulty including allergic reactions to sertraline or active ingredients of passion flower, renal or hepatic impairment, age under 18, pregnancy and lactation, consuming Warfarin, Hexobarbital, Pantobarbital, Levothyroxine or other thyroid medications, using alcohol or hallucinogens and history of tachycardia. The patients with a history of kidney or liver dysfunction were excluded. An informed consent was obtained from the patients prior to the initiation of the examination.

Medication
The first-line treatment for GAD patients was 50 mg Sertraline tablet for both groups. Pasipy® Drop - Iran Darouk Co. was the standardized hydroalcoholic extract of passion flower as an add-on therapy.

Placebo consisted of 20% aqueous solution of absolute edible alcohol and natural coloring agents. The placebo mixture was filled in amber glass bottles with dropper identical to the drug container.

Assortment

The participants were randomly assigned into two groups to receive either Sertraline + Pasipy (S-drug group), or Sertraline + placebo (S-placebo group) for one month. All patients were initiated on Sertraline 50 mg/day; the dosage was increased to 100 mg/day after two weeks. Pasipy and its placebo were given at 15 drops three times daily.

Data Collection Tools
The Reaction Time (RT) test was utilized as the standard computerized software. These process measured psycho-neural responses toward visual and auditory stimuli. The input variables were the number of correct responses, omission and substitution errors and the mean time of correct responses (mean reaction time) (26). After receiving each of the visual or auditory stimuli, the participants were asked to hit the correct keys, which were designed on a computer keyboard. The sign on each key was related to a specific visual or auditory threat in the tests. The stimuli were presented continuously on the screen during the test procedure. Correct responses were made when the participants had chosen the key that was the same as the presented stimulus, whereas choosing an incorrect answer was considered as a substitution error. When the patient ignored a visual or auditory stimuli, the answer was recorded as an omission error. Reaction time was the mean time of correct responses to stimuli in each of the visual or auditory tests. Test items were measured at baseline and after one month of S-drug or S-placebo administration. A questionnaire of adverse effects or possible drug interactions was filled at the end of the study.

Statistical Analysis
Demographic characteristics were compared between the two groups. The RT test outputs were analyzed once in comparison between S-drug and S-placebo groups using independent sample t-test (inter-group comparison); then reaction time changes after one month was determined in each group using a paired sample t-test (intra-group comparison). Scores from the Hamilton anxiety scale form A (HAM-A) were compared between S-drug and S-placebo groups using an independent sample t-test. The aim was to reconfirm the positive effect of passion flower on GAD and the possible improvement of the add-on therapy encountered with the SSRI monotherapy. All the comparisons were performed utilizing SPSS software (PASW – statistics 18). A p-value of less than 0.05 was considered as the minimal level of statistical significance in all measures.

Results
Seventy patients were selected for the study; of whom, 24 were excluded as they did not meet our criteria, and 16 did not follow the medication protocol because of low compliance and drug incompatibility. The patients who met the inclusion criteria were randomized by permeated block randomization (Table 1).

Table1. Demographic characteristics of patients in both groups

Group Item	Sertraline + drug N = 14	Sertraline + placebo N = 16	P-value
Age(mean±SD ¶)	29.07 ± 8.60	32.19 ± 11.43	0.410
Gender (Percent)	F: 85.7% - M: 14.3%	F: 87.5% - M: 12.5%	0.891
Caffeine intake (mg/day)	173.54 ± 99.17	130.46 ± 67.98	0.203

*: Significant difference (P-value < 0.05)
¶ SD: Standard deviation

Table2. Comparison of Reaction time parameters between the Two study Groups after One Month

Group Visual test	Sertraline + drug N = 14 mean ± SD¶	Sertraline + placebo N = 16 mean ± SD	P-value
Correct responses	8.43 ± 6.00	9.69 ± 0.09	0.663
Substitution errors	10.57 ± 4.85	8.19 ± 4.04	0.153
Omission errors	11.00 ± 5.94	12.13 ± 7.90	0.666
Mean response time (second)	0.65 ± 0.12	0.64 ± 0.12	0.720
Auditory test	**mean ± SD**	**mean ± SD**	
Correct responses	3.64 ± 1.69	4.25 ± 3.51	0.561
Substitution errors	10.93 ± 5.84	8.44 ± 4.94	0.216
Omission errors	15.43 ± 6.76	17.31 ± 7.43	0.476
Mean response time (second)	0.49 ± 0.12	0.55 ± 12	0.467

*: Significant difference (P-value < 0.05)
¶SD: Standard deviation

Table3. Comparison of Reaction time parameters within each study group at baseline (1) and after One Month (2)

Group Visual test	Sertraline + drug Mean ± SD¶	P-value	Sertraline + placebo Mean ± SD	P-value
Correct responses 1	9.21 ± 7.99	0.555	10.69 ± 8.24	0.323
Correct responses 2	8.43 ± 6.00		9.69 ± 9.09	
Substitution errors 1	9.14 ± 3.84	0.222	8.50 ± 4.82	0.808
Substitution errors 2	10.57 ± 4.85		8.19 ± 4.04	
Omission errors 1	11.64 ± 6.79	0.585	10.81 ± 7.31	0.340
Omission errors 2	11.00 ± 5.94		12.13 ± 7.90	
Mean response time 1 (second)	0.59 ± 0.21	0.288	0.61 ± 0.21	0.549
Mean response time 2 (second)	0.64 ± 0.11		0.64 ± 0.12	
Auditory test	**mean ± SD**		**mean ± SD**	
Correct responses 1	3.36 ± 1.45	0.537	4.19 ± 4.86	0.939
Correct responses 2	3.64 ± 1.69		4.25 ± 3.51	
Substitution errors 1	8.71 ± 4.39	0.054	8.69 ± 4.76	0.845
Substitution errors 2	10.93 ± 5.84		8.44 ± 4.94	
Omission errors 1	8.71 ± 4.39	0.045 *	17.13 ± 6.11	0.898
Omission errors 2	15.43 ± 6.76		17.31 ± 7.43	
Mean response time 1 (second)	0.44 ± 0.16	0.484	0.60 ± 0.16	0.312
Mean response time 2 (second)	0.49 ± 0.21		0.54 ± 0.18	

*: Significant difference (P-value < 0.05)
¶SD: Standard deviation1: baseline
2 : One month after drug or placebo consumption

Table4. Comparison of Hamilton Anxiety Rating Scale Form (HARS) at Baseline between the Two Study Groups

Group	Sertraline + drug N = 14	Sertraline + placebo N = 16	P-value
Score	Mean ± SD ¶	Mean ± SD	
Baseline	21.54 ± 8.15	24.07 ± 10.73	0.495
After 1 month	16.44 ± 7.15	23.08 ± 8.85	0.039 *

*: Significant difference (P-value < 0.05)
¶ SD: Standard deviation

Table5. List of Reported Adverse Effects by Patients in Both Study Groups

Group	Sertraline + drug	N = 14	Sertraline + placebo	N = 16	P-value
Item	Frequency	Percent	Frequency	Percent	
Allergy	1	2.9 %	1	2.9 %	0.925
Asthma	1	2.9 %	1	2.9 %	0.925
Sinus irritation	1	2.9 %	1	2.9 %	0.925
Dermatitis	1	2.9 %	3	8.8%	0.634
Subcutaneous phlebitis	0	0%	0	0%	NS
Tachycardia	3	8.8%	3	8.8%	0.861
Nausea	7	20.6%	3	8.8%	0.319
Vomiting	2	5.9%	0	0%	0.165
Dizziness	5	14.7%	2	5.9%	0.155
Somnolence	8	23.5%	7	20.6%	0.481
Excessive sedation	2	5.9%	1	2.9 %	0.493
Abnormal bleeding	0	0%	1	2.9 %	0.333
etc.	3	8.8%	4	11.8%	0.825

Fourteen patients (85.7% female and 14.3% male) were initiated on Sertraline (50 mg/day and the dosage was increased to 100 mg/day after two weeks) + Pasipy (15 drops three times daily). The mean age ± standard deviation (SD) of these patients was 29.07 ± 8.60. Sixteen patients (87.5% female and 12.5% male) were initiated on Sertraline (50 mg/day and the dosage was increased to 100 mg/day after two weeks) + placebo (15 drops three times daily). The mean age in this group was 32.19 ± 11.43.

Inter-group analysis
After one month, independent sample t-test did not demonstrate any significant difference in any of visual or auditory items. Baseline scores were proved not to be statistically different, but they are not displayed in the tables. In the visual test for the drug group, the omission errors were less than the placebo consumers, but this difference was not statistically significant (P = 0.666). However, the mean reaction time was slightly longer in this group (P = 0.720).
In auditory analysis for the drug group, omission errors were less than the placebo group, but the difference was not significant (P = 0.476). However, the mean reaction time toward sound threats improved slightly after one month of taking Pasipy in the drug group compared to the placebo group (P = 0.467) (Table 2).

Intra-group Analysis
In the drug group, a significant decline in auditory omission errors was observed after one month of treatment (P = 0.045). The mean reaction time had a non-significant increase in both visual (P = 0.288) and auditory tests (P = 0.484) in drug intra-group analysis. None of the changes in test variables in placebo consumers reached the significant level. The mean reaction time was a bit longer in the visual test (P = 0.549), but had a non-significant improvement toward auditory stimuli in this group (P = 0.312) (Table 3).

Hamilton Test
Hamilton Anxiety Rating Scale Form A (HARS) questionnaires were ranged between 18 to 24 (mild to moderate). A significant improvement to relieve anxiety symptoms was observed in the add-on therapy group compared to the Sertraline + placebo after one month of administration (P = 0.039) (Table 4).

Adverse Reactions
Based on data from Table 5, no major and significant adverse effect or drug interaction was observed after Sertraline + Pasipy co-administration compared to the other group. The most remarkable side effect in Sertraline + placebo group was somnolence (F = 7, percent = 20.6%), which occurred more frequently in add-on therapy (F = 8, percent = 23.5%).

Discussion

'Fear appeal' is a brain message against threatening situations (27). It is a distinguishing characteristic in anxiety disorders (28) which persuades the suffered patient to do a warily action. This could explain reduced omission errors after add-on therapy. Therefore, passion flower seems to increase the positive risky behavior and remove hesitance features as expected. It is accompanied by the Hamilton test results that reconfirm the potential effects of this herbal medicine for GAD. Slight and non-significant prolongation in mean response time (RT) is explained by relieving pathological impulsiveness, which is one of the most distinguished features of GAD (29). Numerous studies revealed that GAD rarely achieves high end-state functioning at post-treatment, and the influence of these treatments on quality of life is not quite proved (30). Pharmacotherapy has been claimed the main stage of treatment. Despite advantages, one of the concerns about the first-line medication is cognitive side effects (31, 32). Among Benzodiazepines, which are known as one of the most promising medications, the difficulty in discontinuing these medications is a crucial dilemma (1). CBT has been believed to be the most effective treatment in GAD among the non-pharmacological management. Studies that consider CBT have some limitations; for instance, the inter-personal differences and long duration of such experiments can restrict reaching confirmed conclusions (33). The pharmaceutical industry relies on plant-based medicines significantly (34). Passion flower and its active ingredients, chrysin and pyrone derivative maltol, are responsible for the related CNS effects (35). Although the exact pharmacological mechanism is not fully known, the majority of studies indicated that the sedative-hypnotic effects of passion flower are presented through gama aminobutyric acid (GABA) neurotransmission (36). In a study by Appel et al., passion flower was shown to antagonize GABA B receptor. However, ethanol site and benzodiazepine site of GABAA receptors were not affected (37). Passion flower has been demonstrated to be an efficacious drug for GAD management when compared with Oxazepam and its undesirable side effects. The most preferences for anxiolytic effect of this phytotherapy compared to the chemical medications are the venial impairment of performance (24), lack of psychomotor dysfunction (38) or high sedation (39), which are promising in comparison with psychiatric drugs with many of cognitive side effects (18, 19). The effects of cognitive function have been reported in the literature. For example, in a study by Dimpfel et al., mathematical calculation, concentration and memory tests were performed to evaluate the effects of passion flower dry extract in a group of volunteers. The results showed no cognitive impairment even though the psychometric scales were different from the RT test used in our study (40). Passion flower 500 mg was administered before surgery and numerical rating scale (NRS) was utilized to assess anxiety and sedation; besides, Trieger Dot Test and the Digit-Symbol Substitution were used to evaluate psychomotor changes. The outcomes showed no significant difference in the psych omotor function between the two groups after anesthesia (41). This study concluded that passion flower does not affect reaction time, and therefore can be given to those patients whose level of consciousness and speed of performance is important in their professional activities. In our last trial, we found no adverse effect of passion flower on alertness in the healthy volunteers (25). However, small sample size and time limitation restricted our experiment.

Limitations

The limitations of the present study were as following: Firstly, the sample size was relatively small. Secondly, one month may not be considered long enough to precisely evaluate the effects of Passion flower extract. Thirdly, "structured interview", a more precise mean of evaluation of the patients, was not utilized in this study.

Conclusion

This study noted that passion flower might be consumed as a safe (low side effects) add-on in the treatment of generalized anxiety disorder. Further studies with longer duration are recommended to confirm the results of this study.

Acknowledgements

Conflict of interest

None.

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