

Journal of Complementary and Integrative Medicine

Volume 8, Issue 1

2011

Article 32

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Recommended Citation:

Pakseresht, Siroos; Boostani, Hatam; and Sayyah, Mehdi (2011) "Extract of Valerian Root (*Valeriana Officinalis* L.) vs. Placebo in Treatment of Obsessive-Compulsive Disorder: A Randomized Double-Blind Study," *Journal of Complementary and Integrative Medicine*: Vol. 8: Iss. 1, Article 32.

DOI: 10.2202/1553-3840.1465

Extract of Valerian Root (*Valeriana Officinalis* L.) vs. Placebo in Treatment of Obsessive-Compulsive Disorder: A Randomized Double-Blind Study

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Abstract

Objective: Obsessive–Compulsive Disorder (OCD) is a common neuropsychiatric condition. Many herbs with psychotropic effects exist which can have fewer side effects compared to more conventional medications. *Valeriana Officinalis* L. is a well-known medicinal plant with a long history of usage in the world with an effect on GABA. This plant is reported to be safe on humans. Our objective in this study was to compare the efficacy of the extract of *Valeriana Officinalis* L. with placebo in the treatment of OCD.

Methods: The study was an 8-week pilot double-blind randomized trial. Thirty-one adult outpatients who met the DSM-IV-TR criteria for OCD based on the structured clinical interview participated in the trial. In this double-blind and randomized trial, patients were randomly assigned to receive either capsule of the extract (765 mg/day) or placebo (30 mg/day) for 8 weeks.

Results: The results showed significant difference between the extract and placebo in the end of treatment ($P=0.000$). Somnolence was the only significant difference between the two groups in terms of observed side effects ($P=0.02$).

Conclusion: The results suggest that *Valeriana Officinalis* L. has some antiobsessive and compulsive effects. However, further studies are needed to confirm these findings. Psychiatrists often find that many patients cannot tolerate the side effects of psychiatry medicine *Valeriana Officinalis* L. is a well-known medicinal plant with a long history of usage in world with effect on GABA. The results showed significant difference between the extract and placebo in the treatment of OCD. There was also no significant difference between the two groups in terms of observed side effects.

KEYWORDS: Obsessive–Compulsive Disorder, *Valeriana Officinalis* L., GABA

Author Notes: No financial support was provided for conducting this study or preparing of this manuscript. The authors thank the staff of the outpatient psychiatry clinic of Imam Khomeini General Hospital for their contribution in conducting this study.

1. Introduction

Valerian (*Valeriana Officinalis* L. is, Valerianaceae) is a hardy perennial flowering plant, with heads of sweetly scented pink or white flowers (Jose et al., 1999). The flowers bloom in the northern hemisphere from June to September. Valerian was used as a perfume in the sixteenth century (Margery, 1993). It is consumed as food by the larvae of some Lepidoptera (butterfly and moth) species including Grey Pug. Other names used for this plant include Garden Valerian (to distinguish it from other Valerian species), Garden Heliotrope (although not related to Heliotropism) and All-heal. The garden flower Red Valerian (*Centranthus ruber*) is also sometimes referred to as "Valerian" while it is a different species, from the same family and not particularly closely related. Valerian, in pharmacology and phytotherapy medicine, is the name of a herb or dietary supplement prepared from roots of the plant, which, after maceration, triturating, and dehydration processes, are conveniently packaged, usually into capsules and may be used for certain purposes including sedation and anxiolytic effects. *Valeriana Officinalis* L. roots have valproic acid (Sash et al., 2010) and Valpotriates (Thies, 1967). Valproic acid is a potent modulator of GABA_A receptors expressed in *Xenopus* Oocytes (Khom et al., 2007), while Valpotriates is effective on the psychotic symptoms of anxiety (Andreatini et al., 2002). Valerian historically used as sedative, pain reliever and for its anti-convulsive effects. It is also used for insomnia and migraine treatment. Most basic science research about Valerian has been conducted on the interactions between Valerian constituents and the GABA neurotransmitter receptor system. These studies remain inconclusive and all require independent replication. The mechanism of action of Valerian in general, and as a mild sedative in particular, remains unknown. Valerian extracts appear to have some affinity for the GABA_A receptor, a class of receptors on which benzodiazepines are known to act (Holzl et al., 1989; Mennen et al., 1993). Valerian also contains Isovaltrate, which has been shown to be an agonist for adenosine A₁ receptor sites (Svenja et al., 2007). This action may contribute to the herb's sedative effects. *Valeriana Officinalis* L. is used in Iran as a sedative and anti anxiety agent (Shahraz, 2004).

Obsessive-Compulsive Disorder (OCD) is a heterogeneous disorder of unknown etiology, characterized by the presence of upsetting, persistent worries, images or impulses, which are experienced as intrusive and senseless (obsessions) and/or excessive repetitive behaviors (compulsions) performed in response to these obsessions, or according to rigid rules (American Psychiatric Association, 2000). The hypothesis that alterations in benzodiazepine receptor function play a role in the pathology of the anxiety disorders is supported by many preclinical evidences (Kaplan and Sadock, 2005). There is increasing evidence that the major inhibitory neurotransmitter, gamma amino butyric acid in OCD (Gwyneth et

al.,2005). In recent years, interest in complementary and alternative medicine has grown rapidly in different parts of the world. The reason for this increased interest is in dissatisfaction with conventional allopathic therapies and willingness in patients to be more involved in their own health care. In addition patients find these alternatives more congruent with their own philosophical orientations (Austin, 1998; Boon et al., 2000). The Center for Diseases Control and Prevention has recently published data indicating that 62% of the adult population in the United States has used complementary and alternative medicine within the preceding 12 months, and almost 19% have used an herbal remedy (Barnes et al., 2002).The purpose of the present investigation was to assess the efficacy of *Valeriana Officinalis* L., as uptake inhibitor of GABA, in the treatment of OCD.

2. Methods

2.1. Trial design

The study was a prospective, double-blind, eight-week trial. Two groups of outpatients with OCD in Imam Khomeini Hospital of Ahwaz, Iran participated in the study from October, 2008 through June, 2009.

2.2. Participants

Participants were patients in the outpatient clinic of Imam Khomeini Hospital, Jundishaur University of Medical Sciences, with complaint of OCD-related symptoms. Participants were eligible for the study if they met DSM-IV-TR criteria for OCD (American Psychiatric Association, 2000), had baseline score of 21 or higher in the Yale-Brown scale (Y-BOCS) for OCD (Goodman et al., 1989), did not receive psychiatric medication during the 2 weeks prior to the trial, were between 18 and 60 years of age. Written informed consent for participation in the study was obtained from all participants. Subjects were disqualified if they had psychotic symptoms or suicidal thoughts, had concomitant psychiatric or neurological disorder, had significant cardiac, renal or hepatic disease, had a history of sensitivity to medications with plant origin, were pregnant or breast-feeding, or were developmentally delayed.

The study was conducted from October of 2008 through June of 2009, in the outpatient clinic of Imam Khomeini Hospital. Patients could withdraw from the study at any time during the trial and transfer to a conventional treatment. Those completing the trial were also guaranteed transfer to a conventional treatment after the study. The study was conducted in accordance with the Declaration of Helsinki and Tokyo for humans and was approved by the ethical committee at Jundishapur University of Medical Sciences.

2.3. Preparation of medication

The fresh roots of *Valeriana Officinalis* L. were collected from the Azerbaijan province in Iran in May, 2008. Each 40 g of air-dried root of the plant was boiled with 300 ml water for 10 min. The mixture was then filtered and the filtrate was concentrated with ethanol bath at 37 °C. Each 40 g of the dried roots yielded 5.6 g of extract. In order to preserve the double blind condition, *Valeriana Officinalis* L. extract and placebo was dispensed in identical-appearing capsules. *Valeriana Officinalis* L. capsules were filled with 250 mg of the extract and talcum powder while placebo capsules were only filled with talcum powder.

2.4. Procedures

After obtaining written informed consent, participants entered either of the parallel groups, randomized, double blind, with a fixed-schedule for 8-week clinical trial. Patients were randomly assigned to treatment with the *Valeriana Officinalis* L. (750 mg/day) or placebo, using a computer-generated list of random numbers. All patients received one oral capsule 3 times a day. The dosage regimen was selected based on previous study about the efficacy of *Valeriana Officinalis* L. (Mirabel et al.,2010).If the patients had insomnia, they were given oxazepam 5 mg, one oral tablet to be taken at night. No other psychotropic medication was prescribed. Participants did not receive any concomitant psychological treatment or psychosocial support. The patients were visited at weeks 0, 2, 4, 6, and 8 of treatment course. Efficacy was assessed using the Y-BOCS (Goodman et al., 1989) .Treatment-induced adverse effects were assessed systematically at each visit by a score sheet designed for the study.

2.5. Statistical analysis

Repeated measures analysis of variance (ANOVA) with a two-tailed post-hoc Tokay mean comparison test was performed on the change in Y-BOCS scores from baseline. To compare the outcome of two groups in the same week, an unpaired two sided Student's t-test was used. Results are presented as mean± SEM Differences were considered significant when $P < 0.05$. To compare the demographic data and the frequency of side effects between the two groups, Pearson Chi-square test was performed.

3. Results

3.1. Demographic characteristics

Thirty-three patients enrolled in the study; 16 were assigned to the extract group and 17 to the placebo group. The characteristics of the two study groups are summarized in Table 1. The two groups were well matched and there were no statistically significant differences between the groups regarding demographic characteristics.

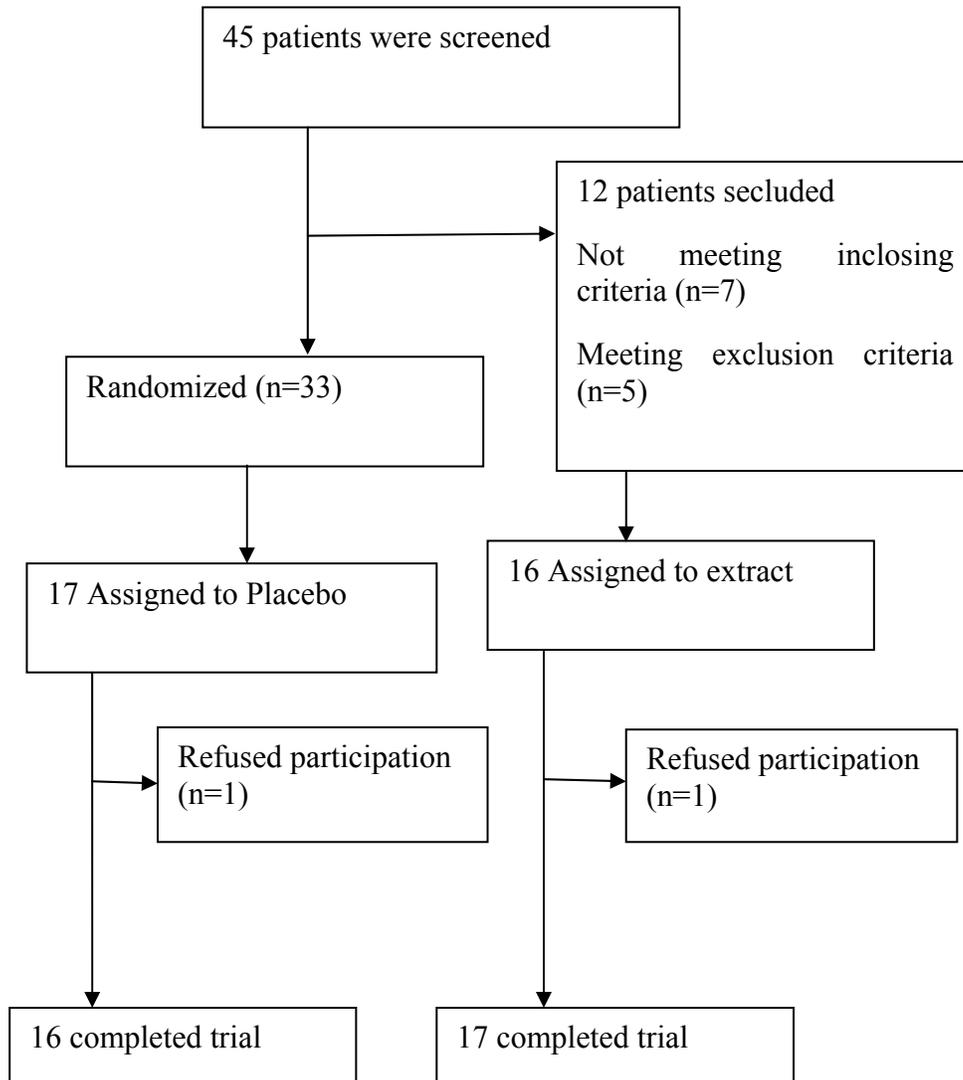
Table 1—Demographic data of the participants.

Characteristic	Extract (n=15)	Placebo (n=16)
Sex	Male:7	Male:9
	Female:8	Female:7
Marital status	Married:9	Married:8
	Single:6	Single:8
Age	31±2.13	29±1.12

3.2. Attrition

Thirty-one participants completed the 8-week trial, while 2 patients discontinued the trial. The treatment attrition did not differ between the two groups. One patient withdrew from the trial in each study group. They left study because of their unwillingness to continue the study (figure 1.) (P=0.31).

Figure 1—CONSORT diagram showing the disposition of all subjects screened for the study

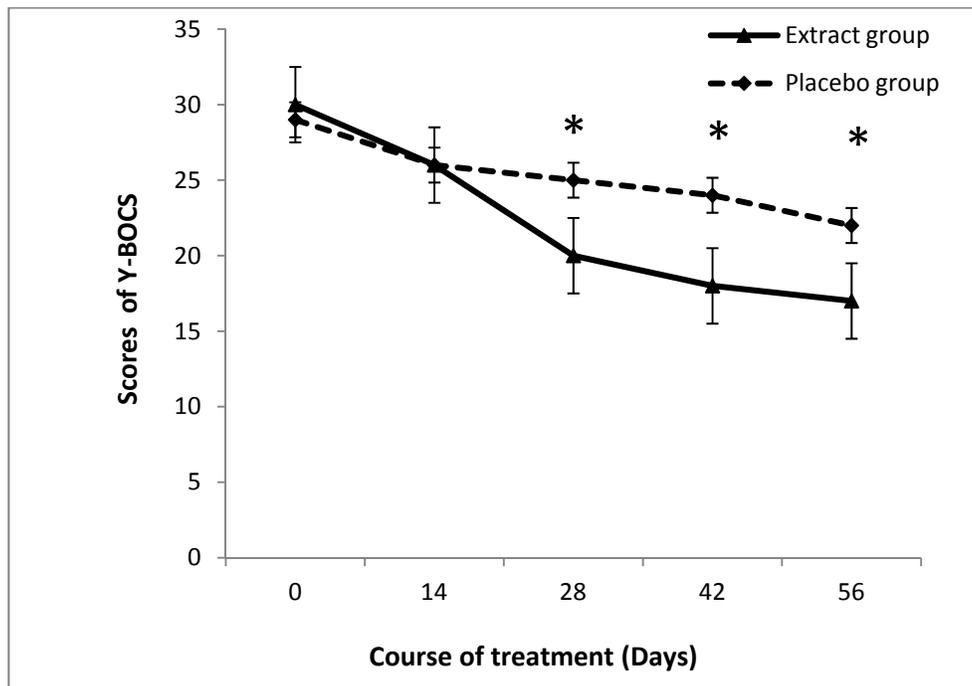


3.3. Effect on the Y-BOCS scores

As shown in Fig. 2, the mean Y-BOCS scores gradually declined in the extract group during the trial. ANOVA revealed significant effect of time ($F=29.5$,

$p < 0.01$). The effect of treatment was significant ($F = 2.32$, $p = 0.035$). Time-by-treatment interaction was not significant ($F = 2.9$, $p = 0.078$). In weeks 4, 6 and 8, patients treated with the extract had significantly lower scores than the placebo treated patients ($p = 0.043$, $p = 0.07$, $p = 0.00$).

Figure 2—Effect of extract on score of Yale-Brown Obsessive-Compulsive (Y-BOCS). Each point represents mean for 15–16 patients. *: $P < 0.05$ compared to placebo (Student's t-test).



3.4. Adverse effects

No patient discontinued the treatment because of adverse effects and the most common adverse effect was somnolence. Patients receiving the extract show more somnolence than those taking the placebo ($p=0.02$) (Table 2).

Table 2—Reported adverse effects.

Adverse effect	Placebo (n=16)	Extract (n=15)	χ^2	P
Headache	2 (12.5%)	1 (6.67%)	1.07	0.38
Somnolence	3 (18.75%)	8 (53.3%)	2.63	0.02
Nausea	1 (6.25%)	1 (6.67%)	0.11	0.92
Dry mouth	2 (12.5%)	1 (6.67%)	1.82	0.29
Blurred vision	2 (12.5%)	2(13.3%)	1.54	0.28
Constipation	1 (6.25%)	1 (6.67%)	4.22	0.51

4. Discussion

OCD is a chronic condition characterized by obsessions or compulsions that cause distress or interfere with functioning. Obsessions are repetitive thoughts or urges that may lead to distress or anxiety (Eric et al., 2010). SSRIs are considered as first line in the pharmacotherapy of OCD (Kaplan and Sadock, 2005). The untoward side-effects of SSRIs such as decreased libido, has prompted many researchers to evaluate new compounds in the hope of finding safer alternative drugs. Among these alternative drugs, medicinal plants such as *Valeriana Officinalis* L. have a special place. To the best of our knowledge, the present study is the first double-blind controlled trial of *Valeriana Officinalis* L. in the treatment of OCD. Our main finding was that *Valeriana Officinalis* L. extract is effective in the treatment of OCD. Significant difference in efficacy was observed between the two treatments. In the extract group significant effects were observed by day 28, 42 and 56. This indicates a rapid onset of action for the extract. On the other hand, the substantially lower incidence of impairment of libido could be an important advantage of *Valeriana Officinalis* L. extract. However, it should be emphasized that there was no significant difference between the two treatments in terms of the overall frequency of side-effects. We conclude that *Valeriana Officinalis* L. extract is potentially a significant improvement over placebo in the

management of OCD, particularly when drug induced impairment of libido is to be avoided. Considering the effects of *Valeriana Officinalis* L. extract on the GABA (Sascha et al., 2010) and the effect of extract on OCD treatment, the authors believe that the role of GABA in OCD should be further studied. The findings of this study should be considered with caution. The experimental group was small. In addition, the short term of the study (8 weeks) was another disadvantage of the study and it seems that longer periods of treatment and study would result in more reliable data. Use of outpatients, difficulty entering the trial and ease of withdraw from it, were among other limitations of the trial.

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