2015

Is Crocus Sativus L. as Effective as Fluoxetine for the Treatment of Mild to Moderate Depression in Adults Aged 18-55?

Mobina A. Noory
Philadelphia College of Osteopathic Medicine

Is *Crocus Sativus L.* as effective as Fluoxetine for the treatment of mild to moderate depression in adults aged 18-55?

Mobina A. Noory, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 19, 2014

Abstract

Objective: The objective of this EBM review is to determine whether or not *Crocus Sativus L.* is as effective as Fluoxetine for the treatment of mild to moderate depression in adults aged 18-55.

Study design: Systematic review of three English language, double-blind randomized controlled trials published between 2005-2007.

Data source: Three double-blind randomized controlled trials published in peer-reviewed journals comparing the effectiveness of *Crocus Sativus L.* vs. Fluoxetine or placebo for the treatment of mild to moderate depression in adults were found using PubMed and Ebscohost.

Outcomes measured: In all three articles the outcomes measured were improvement in depression symptoms based on 17-item Hamilton Depression rating scale.

Results: Two studies that compared saffron to fluoxetine found that saffron was as effective as fluoxetine for the treatment of mild to moderate depression. One study that compared saffron to a placebo found that patients in the saffron group had a significant improvement in their symptoms compared to the placebo group.

Conclusions: According to the three studies conducted, Saffron can be used as an alternative for the treatment of mild to moderate depression in adults.

Keywords: *Crocus sativus*; Saffron; Depression; Fluoxetine

INTRODUCTION

Depression is a major problem in the United States, affecting about 5 percent of the adults.[1] In fact, depression is one of the most common psychiatric conditions, and it is estimated that it will represent the second largest disease burden worldwide by the year 2020.[1,2] American Psychiatric Association defines depression as a heterogeneous disorder often manifested with symptoms at the psychological, behavioral and physiological levels that is thought to result from biochemical changes in the brain.[3] According to the Center for Disease Control (CDC), in 2003, national health expenditures for mental health services were estimated to be over 100 million dollars, and depression is estimated to cause 200 million lost workdays each year at a cost to employers of 17 to 44 billion dollars.[4] There are many different medications available for the treatment of depression, including monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs) and many more. Although these medications can be very effective, there are many side effects associated with them. Some side effects include anticholinergic affects, sexual dysfunction, cardiac arrhythmias, orthostatic hypotension, and many more. Also, about one-third of patients receive no benefit and one-third does not experience complete remission after monotherapy with antidepressants.[2]

In the western society medications are the mainstay of treatment for depression, however in Persian countries herbs have been used for their antidepressants affects for thousands of years. *Crocus Sativus,* a very expensive spice also known as saffron has been used around the world for many years for its antidepressants effects. The major benefits of spices and natural herbs are that there are no side affects associated with them and they are relatively safe. Although this spice has been used around the world, especially in the Middle East for thousands of years there have

been no studies done to show its effectiveness. In the recent years, researchers in Iran decided to test the effectiveness of this spice versus fluoxetine, a widely used SSRI for depression.

OBJECTIVE

The objective of this systematic review is to determine whether *Crocus Sativus (*saffron) is as effective as fluoxetine for the treatment of mild to moderate depression in adults aged 18-55.

METHODS

Three double blind, randomized controlled studies were chosen for this review based on certain specific criteria. The population that was included in these studies was men and women between the ages of 18-55 with mild to moderate depression based on the Diagnostics and Statistical Manual of Mental Disorders (DSM-IV) criteria. The intervention that was studied was the spice *crocus sativus,* more commonly known as saffron for the treatment of mild to moderate depression in these patients. Two of the articles compared saffron to the drug fluoxetine, a classic SSRI used to treat depression. One article compared saffron to placebo in order to study the effectiveness of the spice on these patients. The symptoms and severity of disease of the subjects were recorded at the beginning of the study using the Hamilton Depression rating scale (17-item HAM-D scale) and periodically throughout the study. All studies measured the improvement of depression symptoms using the same scale.

Some keywords used in the search for RCT's included depression, *crocus sativus*, saffron, and fluoxetine. The chosen articles were all written in English and published in peer-reviewed journals between 2005 and 2007. The articles were found using PubMed and EBSCOHOST databases, and chosen based on their relevance to the clinical question and for their emphasis on patient-oriented evidence based medicine. The inclusion criteria consisted of

males and females between the ages of 18-55 with mild to moderate depression with a baseline HAM-D 17 item score of at least 18 and ≤ 25. Exclusion criteria consisted of anyone under the age of 18 and over the age of 55, anyone with current cognitive disorder in the last year, or anyone with current or past history of bipolar disease, schizophrenia, schizotypal personality disorder, and/or borderline personality disorder. Patients who scored greater than 2 on the suicide item of the HAM-D scale, and those with suicidal ideation were excluded as well. Pregnant women, or women of child-bearing age not on accepted form of birth control were also excluded (Table 1). In the Basti et el. study the statistical data reported were P-value, RBI, ABI, and NNT. In Noorbala and Moshiri studies only a P-value was reported.

Table 1- demographics and characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Basti (2007)	Double blind RCT	40	18-55	Pts who met the DSM-IV criteria for major depression. pts have a baseline HAM-D 17 item score of at least 18 and ≤ 25.	Current cognitive disorder in the last year, current/past history of bipolar disease, schizophrenia, schizotypal personality disorder and border line personality disorder. Excluded if pt posed a significant risk of suicide. Pregnant woman or woman not using medically approved method of birth control were excluded.	2	C. Sativus 15 mg bid or fluoxetine 10 mg bid.
Moshiri (2006)	Double blind RCT	40	18-55	Pts who met the DSM-IV criteria for major depression. pts have a baseline HAM-D 17 item score of at least	Current cognitive disorder in the last year, current/past history of bipolar disease, schizophrenia, schizotypal personality disorder and border line personality disorder. Excluded if pt posed a significant risk of suicide. Pregnant woman or woman not using medically approved	4	C. Sativus 30mg/day or Placebo

				18	method of birth control were excluded.		
Noorbala (2005)	Double blind RCT	40	18-55	Pts who met the DSM-IV criteria for major depression. pts have a baseline HAM-D 17 item score of at least 18	Current cognitive disorder in the last year, current/past history of bipolar disease, schizophrenia, schizotypal personality disorder and border line personality disorder. Excluded if pt posed a significant risk of suicide. Pregnant woman or woman not using medically approved method of birth control were excluded.	2	C. Sativus 30mg/day or Fluoxetine 20 mg/day

OUTCOMES MEASURED

All three studies measured the improvement of depression symptoms using the Hamilton Depression scale. In all three of the studies, all patients had a baseline psychiatric evaluation, a structured diagnostic interview and a medical history. Patients were randomized to receive either a capsule of C. *sativus* or fluoxetine in two of the studies, and a placebo pill in the third study. The patients were then followed and evaluated by a psychiatrist after 1, 2, 4, 6, and 8 weeks in one study[1] and 1, 2, 4, and 6 weeks in the other two studies.[2,3] The principle measure of the outcome was the 17-item HAM-D scale; the mean decrease in HAM-D score from baseline was used as the main outcome measure of response of depression to treatment.[1,2,3]

RESULTS

In the study done by Basti et el, forty adult patients with major depression that scored at least 18 and ≤ 25 on the HAM-D depression scale participated in the trial. These 40 individuals were randomly assigned into two groups, 20 of them received fluoxetine 10 mg bid, and the remaining 20 received *C. Sativus* capsule 15 mg bid. No significant differences were identified between the two groups in regards to patient demographics, age and gender. There were 2

withdraws, one from each group, thus 38 people completed the trial. The outcomes were presented as dichotomous data and intention to treat analysis was used with last observation carried forward. The Hamilton Depression Rating Scale was used to compare the two groups, and there were no significant differences in the HAM-D scale between the two groups in week 0, the baseline evaluation (t=0.86, d.f=38, P=0.39). In this study the percentage of responder was determined as 50% drop in the Hamilton Depression Rating Scale Score. Outcome measured was the mean decrease in HAM-D score from baseline as the measure of response of depression to treatment, so this negative value means that for every 10 patients that took *crocus sativus* there was one fewer 50% mean decrease from baseline in HAM-D score compared to fluoxetine. There were no significant differences between two treatments in terms of the percentage of responders, which is defined as at least 50% drop in the Hamilton Depression Rating Scale; fluoxetine 85% and *Crocus Sativus* 75% (Table 2). The data was not statistically significant (P=0.30). The relative benefit increase was calculated ot be -0.118, the absolute benefit increase was found to be -0.1, and the numbers needed to treat was calculated to be -10 (Table 2). Thus, this study found no significant differences on the change of scores of the Hamilton Depression Rating Scale at week 8 compared to baseline in the two groups, meaning *Crocus Sativus* is as effective as fluoxetine in the treatment of mild or moderate depression. Ten side effects were observed over the 8 week study, including anxiety, decreased appetite, increased apetite, sexual dysfunction, tremor, nausea, headache, sweating, heart pounding, and insomnia. However, the difference between the *crocus sativus* and fluoxetine in the frequency of side effects was no significant.[1]

Table 2: Efficacy of Saffron vs. Fluoxetine

Study	Percentage of responders in Fluoxetine group	Percentage of responders in Crocus sativus group.	P-value	RBI	ABI	NNT
Basti et el	85%	75%	P = 0.30	-0.118	-0.1	-10

RBI = relative benefit increase, ABI= Absolute benefit increase
NNT = Numbers needed to treat

Noorbala et el study was a 6 week randomized and double-blind clinical trial that compared the effectiveness of *crocus sativus* to fluoxetine for the treatment of mild to moderate depression in adults. Forty outpatient adults who me the criteria for mild to moderate depression with a baseline HAM-D scale score of at least 18 participated in this study. Patients were randomly divided into two groups, one group received capsule saffron 30mg/day, and the other group received fluoxetine 20mg/day. The patients were assessed by a psychiatrist at baseline, and then at 1, 2, 4, and 6 weeks after the medication was started. The data in this study was continuous, and to compare the two groups at baseline and the outcome of two groups at the end of the trial, an unpaired Student's t-test with a two-sided P-value was used. Differences were considered significant with $P<0.05$. In the fluoxetine group the drop in the HAM-D scale score at the end of week 6 compared to baseline was -15.00 ± 5.88, and in the saffron group it was -12.20 ± 4.67 (Table 3). The P value was calculated as 0.10, thus no significant differences was observed on the change of scores of the HAM-D scale at week 6 compared to baseline in the two groups (Table 3). Over the course of the study nine side effects were observed, including anxiety, decreased appetite, increased appetite, sedation, nausea, headache, sexual dysfunction, tremor, and sweating. Although patients in the saffron groups reported slightly less side effects

compared to the fluoxetine group, there were no significant differences between the side effects in the two groups based on the p-values (table 4).[3]

Table 3- Efficacy of Saffron vs. fluoxetine

Study	Drop in HAM-D score in fluoxetine group	Drop in HAM-D score in saffron group	P- Value
Noorbala et el.	-15.00 ± 5.88	-12.20 ± 4.67	0.10

Table 4: Side effects of saffron vs. fluoxetine

Side Effects	Saffron	Fluoxetine	P-value
Anxiety	3	6	0.45
Decreased appetite	2	5	0.40
Increased appetite	5	2	0.40
Sedation	1	0	1.00
Nausea	2	4	0.66
Headache	3	6	0.45
Sexual dysfuction	0	4	0.10
Tremor	0	4	0.10
Sweating	0	3	0.23

Moshiri et el. study was a 6 week randomized and double-blind clinical trial that was conducted in the outpatient clinic of Roozbeh Psychiatric. Forty adult patients that met the DSM IV criteria for mild to moderate depression and had a baseline HAM-D scale score of at least 18 participated in this study. The patients were randomly assigned into two groups: saffron and placebo. The saffron group received capsule petal of *C. sativus* 30mg/day and the placebo group received a placebo capsule. The A psychiatrist assessed the patients at baseline and after 1, 2, 4, and 6 weeks after the medication started. Throughout the study, the person who administered the medications, rater and patients were blind to assignments. The data was continuous and an unpaired student's t-test with a two-sided P-value was used to compare the two groups at

baseline and at the end of the trial. Results were presented as mean ± S.E.M. Differences were considered significant with $P<0.05$. The changes in the HAM-D scale score at the endpoint compared to the baseline were found to be -14.01 ± 5.53 in the crocus sativus group and -5.05 ± 4.63 in the placebo group (Table 5). The p-value was found to be $P<0.0001$, thus a significant difference was observed on the change of scores of the Hamilton Depression Rating Scale at week 6 compared to baseline in the two groups (Table 5). There were eight side effects observed over the course of the 6-week trial, including anxiety, decreased appetite, stomach pain, tremor, nausea, headache, sweating and heart pounding. However, there was no significant difference between the frequency of side effects between the two groups.[2]

Table 5- Efficacy of *crocus sativus* vs. placebo

Study	Crocus sativus	Placebo	P value
Moshiri et el.	-14.01 ± 5.53	-5.05 ± 4.63	P <0.0001

DISCUSSION

Some type of limitation exists in almost any study that is conducted. Some limitations of these saffron studies include: age limitations, lack of placebo group, using a fixed dose of saffron, small number of participants, and short period of follow up. All three studies consisted of adults aged 18-55, however, depression is very common in the elderly and these studies do not include them. About 6 million Americans age 65 and older are affected with depression and saffron could be a good alternative treatment for them, however the safety and efficacy of it has not been studied in this age group.[6] The studies all consisted of either 6-week or 8-week trial and that is not sufficient time to asses the effectiveness of a medication for depression, therefore a longer period of study is warranted to fully asses the effectiveness and safety of *crocus sativus* for treatment of depression. A fixed dose of saffron was used in all three studies and the dosage

that was used may not be as effective as a higher dose, or a lower dose may have fewer side effects, however, these questions cannot be answered unless another study is done with differing doses of saffron. Out of the three studies, only one contained a placebo group while the other two did not. All three studies were conducted in Iran, and about 96% of world's saffron is supplied by Iran, and thus it is possible that there was a form of bias was present during the study.[7] Due to these limitations that are present in the current studies done, many more studies are warranted to be conducted in order to fully asses the effectiveness and safety of saffron for the treatment of mild to moderate depression.

CONLCUSION

In conclusion, three double-blind randomized controlled trials were evaluated in order to answer the question whether or not *crocus sativus* (saffron) is as effectives as fluoxetine for the treatment of mild to moderate depression in adults aged 18-55. Two of the studies compared the effectiveness and safety of saffron to fluoxetine, while one study compared it to a placebo. Both studies that compared the effectiveness of saffron concluded that it was as effective as fluoxetine for the treatment of depression in adults aged 18-55. In the study conducted by Moshiri et el. where saffron was compared to a placebo, it was concluded that patients that received *C. sativus* experienced statistically significant benefits in their mood after 6 weeks of treatment compared to placebo.[2] However, due to the limitations of age, small number of participants, fixed dose of saffron used, and lack of placebo group, many more studies are indicated before saffron can be used as a treatment for depression.

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