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Crocus Sativus L. (saffron) versus sertraline on symptoms of depression among older people with major depressive disorders–a double-blind, randomized intervention study

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ABSTRACT

Background: While there is sufficient evidence that Crocus Sativus L. (saffron) improves symptoms of depression in young and middle-aged adults, research on older people are missing. The purpose of the double-blind, randomized intervention study was to compare the effect of saffron and sertraline on MDD among a sample of older people.

Methods: A total of 50 older out-patients with MDD (mean age = =65 years; 70% males) were randomly assigned either to the saffron condition (60 mg/d) or to the sertraline condition (100 mg/day) for six consecutive weeks. Experts employed the Hamilton Depression Rating Scale (HDRS) to rate participants' degree of depression. Timepoints were baseline, week 2, week 4 and week 6, the end of the study.

Results: Symptoms of depression decreased over time, with no advantages or disadvantages for the saffron or sertraline condition.

Conclusion: The pattern of results suggests that both saffron and sertraline have the potential to significantly decrease symptoms of depression. The results are clinically relevant, because major depressive disorders in older people is a health concern. The results are further relevant, because saffron appears to be a powerful antidepressant for older people, who might be more reluctant to the use of synthetic drugs.

1. Introduction

Major depressive disorder (MDD) is a common and disabling disorder, leading to an increase in disability and mortality (American Psychiatric Association, 2013). According to the American Psychiatric Association (2013) depression is a heterogeneous disorder, with symptoms at physiological, behavioral and psychological levels, along with chronic lifelong risk for recurrent relapse, and high morbidity, co-morbidity and mortality. On the basis of data using the Disability-Adjusted-Life-Years (DALYs) instrument to assess "the sum years lost due to premature mortality and years lived with disability adjusted for severity", Murray and Lopez (1997) estimated that MDD will be the third leading cause of burden worldwide by 2020. By contrast, in the meanwhile there is also increasing consensus that the epidemiologic prevalence rates of MDD did not increase within the 30 years (Jorm et al., 2017), but it appears that the awareness of symptoms of depression did.

While treatments consist mainly on the administration of anti-depressants, and among those most often serotonin-reuptake inhibitors (SSRIs), more recent reviews and meta-analyses questioned about their efficacy (Boesen et al., 2018; Hengartner, 2019; Hengartner and Ploderl, 2018, 2019; Munkholm et al., 2019), which might lead patients to quit medication treatment. Alternative and complementary treatment options to antidepressants are neuromodulation (Gaynes et al.,

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2014; Ren et al., 2014; Salehi et al., 2016), cognitive-behavioral interventions (Cuijpers et al., 2013; Li et al., 2018), regular physical activity (Schuch et al., 2017, 2016, 2015; Stubbs et al., 2016), and the intake of omega-3-polyunsaturated fatty acids (Deacon et al., 2017; Hallahan et al., 2016; Jahangard et al., 2018). Further, above all older people feel reluctant to use synthetic drugs, and rely rather on herbal products such as St. John's Wort (Apaydin et al., 2016). In the present study, we focused on the efficacy of Crocus Sativus L. ("saffron") on symptoms of depression among older people, as it appears that such a study has not been performed so far in this age group.

Apart from its traditional value as a spice, saffron has gained increasing attraction as an antidepressant (Akhondzadeh Basti et al., 2007; Hausenblas et al., 2015; Lopresti and Drummond, 2014, 2017; Lopresti et al., 2018; Moshiri et al., 2006), while it's beneficial effects for a broad variety of somatic complaints have been already repeatedly described (Hausenblas et al., 2015; Moshiri et al., 2015): Hausenblas et al. (2015) concluded in their systematic review that saffron has the potential to improve symptoms of premenstrual syndrome, sexual dysfunction and infertility, and excessive snacking behaviors. Kashani et al. (2018) observed improvements of flashes in postmenopausal women when treated with saffron, compared to placebo.

As regards symptoms of MDD, Lopresti and Drummond (2014) concluded in their systematic review of six studies, that saffron has the potential to improve symptoms of mild to moderate depressive states. Talaei et al. (2015) randomized 40 individuals with major depressive disorders aged between 24 and 50 years, and performed a double-blind, randomized clinical study with adjuvant saffron or adjuvant placebo to an SSRI (sertraline or fluoxetine at therapeutic dosages) for four consecutive weeks. At the beginning and at the end of the study, participants completed questionnaires on depression, anxiety and general health. Self-rated symptoms of depression and anxiety increased over time, but more so in the adjuvant saffron, compared to the adjuvant placebo group.

Mazidi et al. (2016) assigned in their double-blind, randomized and placebo-controlled study 60 participants (mean age about 43 years) with major depressive disorders either to the adjuvant saffron or to the adjuvant placebo condition. Participants completed a series of self-rating questionnaires on symptoms of depression and anxiety. Twelve weeks later, symptoms of self-rated depression and anxiety decreased, but more so in the saffron condition, compared to the placebo condition.

Further, two systematic reviews and meta-analyses compared the influence of saffron on symptoms of depression, compared to placebo. Marx et al. (2019) analyzed 23 studies and showed that saffron had a large positive effect size when compared with placebo for depressive symptoms ($g = = 0.99$) and anxiety symptoms ($g = = 0.95$). Saffron also had a large positive effect size, when used as an adjunct to antidepressants for depressive symptoms ($g = = 1.23$). Marx et al. (2019) concluded that saffron appeared to be superior to placebo, either alone or as adjuvant, though due to the publication bias, results should be interpreted with caution.

Yang et al. (2018) analyzed seven randomized and placebo-controlled trials, and concluded that saffron was effective in the treatment of MDD and had comparable efficacy to synthetic antidepressants. Saffron was also a safe drug without serious adverse events reported.

Khakasarian et al. (2019) compared the efficacy of saffron on symptoms of depression, compared to placebo and fluoxetine. From the eight randomized clinical trials included in their review, it turned out that the effect of saffron was comparable to that of fluoxetine (and placebo).

To summarize, saffron, either alone or as adjuvant, appears to have the potential to improve self-rated symptoms of depression, when compared to placebo or synthetic drugs. Limitations are the short period of interventions (often four to eight weeks; (Marx et al., 2019; Talaei et al., 2015; Yang et al., 2018), the use of placebo as comparator (for exceptions see Yang et al., 2018), self-assessed symptoms of depression (Marx et al., 2019; Mazidi et al., 2016; Talaei et al., 2015; Yang et al., 2018), and samples aged between 18 and 60 years. To counter these limitations and to gain further insight into the efficacy of saffron, we investigated the influence of saffron vs. sertraline among older people. Further, experts' rated participants' degree of depression. We hold that the results might be clinically relevant, as they might give to professionals further treatment options in older individuals with MDD. Further, older people with MDD and reluctant to use synthetic medications might opt for to using saffron.

Based on previous results (Ghajar et al., 2017; Hausenblas et al., 2015; Kashani et al., 2018; Khaksarian et al., 2019; Lopresti and Drummond, 2014, 2017; Lopresti et al., 2018; Marx et al., 2019), we expected improvements of symptoms of depression over time, but more so in the saffron condition, compared to the sertraline condition.

2. Methods

2.1. Procedure

Outpatients of Farshchian Psychiatric Hospital in Hamadan (Hamadan University of Medical Sciences, Hamadan, Iran), aged 60 years or more and suffering from MDD were approached to participant in the present double-blind, randomized and medication-controlled study. Eligible participants were fully informed about the aims of the study and the anonymous data handling. Participants signed the written informed consent and were randomly assigned either to the saffron condition or to the sertraline condition. Experts' blind to participants' study assignment rated participants' intensity of depression. Assessments were performed at baseline, two weeks later, four weeks later, and eight weeks later at the end of the study (= four timepoints). The local ethical committee approved the study, which was performed in accordance with the rules laid down in the Declaration of current (2013) Declaration of Helsinki. The study has been registered at the Iranian register for clinical trials: IRCT20120215009014N204 irct.ir.

2.2. Samples

From January 2018 to July 2019, a total of 65 individuals with MDD were approached. Inclusion criteria were: 1. Age of at least 60 years and higher; 2. Diagnose of MDD, as ascertained by an experienced psychiatrist or clinical psychologist, and based on the DSM 5 criteria (American Psychiatric Association, 2013). 3. Hamilton Depression Rating Score of 7 points or higher; 4. Willing and able to comply with the study conditions, and specifically to complete questionnaires and to attend the assessments. 5. Signed written informed consent. Exclusion criteria were: 1. Acute suicidality; 2. Other serious psychiatric disorders such as bipolar disorders, substance use disorder, anxiety disorders, veterans with posttraumatic stress disorder (PTSD); 3. Intake of antidepressants during the last 4 weeks; 4. Intake of aspirin, anti-coagulant drugs or non-steroidal anti-inflammatory drugs (NSAID). 5. Participants withdraw from the study. 6. Undergoing other treatments for MDD such as psychotherapy, neuromodulation, regular, supervised physical activity trainings, or specific nutritional regimen; 7. Other somatic complaints such as diabetes, known and severe sleep issues such as obstructive sleep apnea, restless legs syndrome or insomnia, as referred from the patient and from medical records. 8. An expert not otherwise involved in the study decided to exclude a participant due to most probably study-related adverse effects.

Fig. 1 (flow chart) shows that from the 65 eligible participants 5 did not meet the inclusion criteria, and 10 refused to participate. At the end, 50 participants were randomly assigned either to the saffron condition or to the sertraline condition.

2.3. Sample size calculation

Sample size calculation was performed with G*Power (Faul et al.,

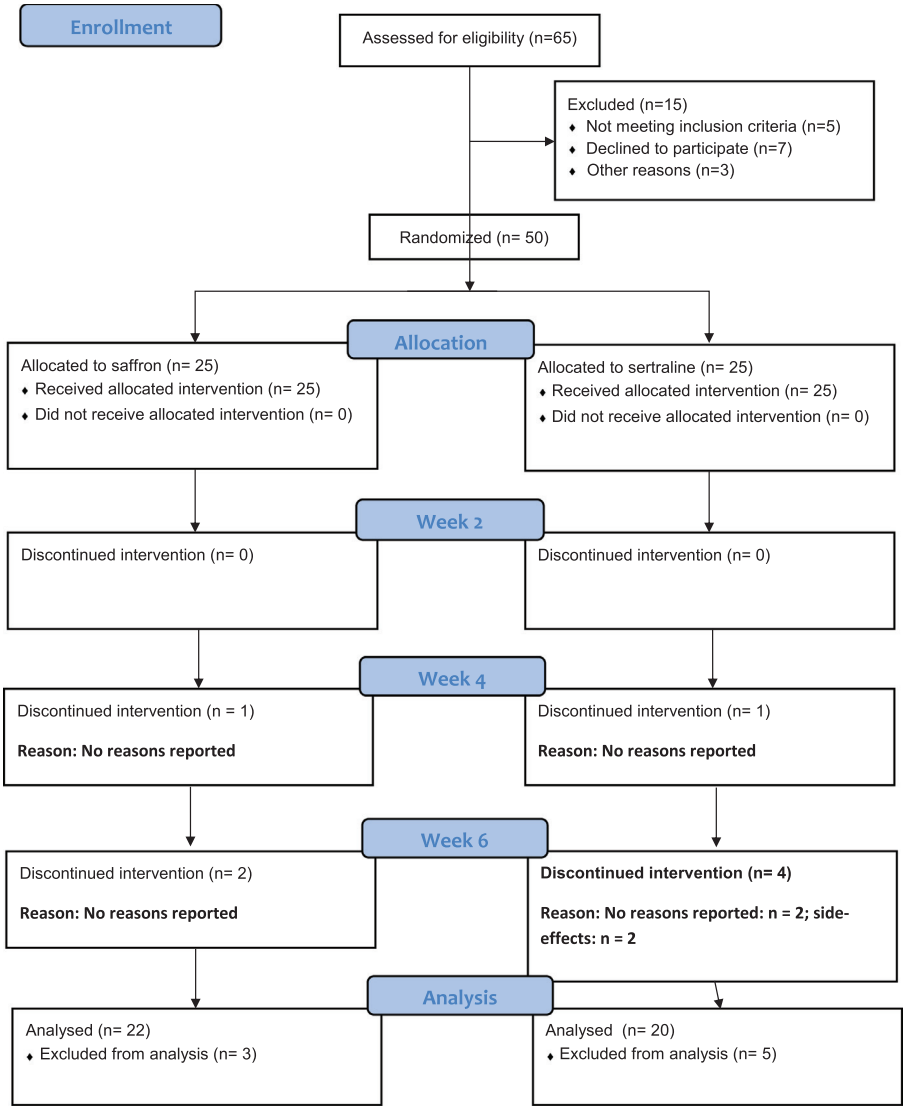

Fig. 1. Flow chart; recruitment, eligibility, randomization, patients' group assignments, and number of patients per group at all timepoints.

2007). The effect size for F-tests was set at 0.22, alpha at 0.05, beta at 0.8, and two groups, and four time points, the calculated sample size was 46; to counterbalance possible drop-outs, the sample size was set at $N = = 50$.

2.4. Randomization

Randomization was achieved using the software randomization.com. Based on this list, a psychologist not otherwise involved in the study assigned participants to the two study conditions (saffron vs. sertraline). To do so, the psychologist prepared 2 × 25 sealed envelopes containing two different colored points, which represented the two study conditions. The envelopes were stirred in an opaque box, and once an envelope was drawn, it was put aside. Participants and staff members involved in the study were fully blind as regards participants' study assignment.

2.5. Saffron and sertraline

Participants in the saffron condition received saffron in capsules of 60 mg/d in the morning for six consecutive weeks. Participants in the sertraline condition received sertraline also in specially manufactured capsule containing 100 mg sertraline. Both saffron and sertraline capsules were identical in shape, color, weight and scent.

2.6. Tools

2.6.1. Sociodemographic information

Participants reported on their age (in years), gender, highest achieved educational level (illiterate/primary school/diploma/higher education), and current job position (retirement vs. part-time job).

2.6.2. Symptoms of depression; experts' ratings

To assess participants' intensity of depression, experts employed the Hamilton Depression Rating Scale (Hamilton, 1960); It consists of 21 items, and ratings are given on different scales ranging from 3, 4, or 5 points (e.g., insomnia early: 0 = =no difficulty falling asleep; 1 = complains of occasional difficulty falling asleep, i.e., more than 0.5 h; and 2 = =complains of nightly difficulty falling asleep), with higher scores reflecting more marked depressive symptoms (Cronbach's $\alpha = 0.80$).

2.6.3. Side-effects

To assess side-effects, participants were asked at each timepoint, if they thought to experience unpleasant effects most probably related to the intake of the study medication. Participants was given a list of

possible side-effects (British National Formulary, 2004).

2.7. Statistical analysis

Statistical calculations were not performed per protocol, but with the Intent-To-Treat (ITT) and the Last Observation Carried Forward (LOCF).

With a series of *t*-tests and X^2-tests sociodemographic and illness-related data were compared between the group with saffron or sertraline.

A two-way repeated measures ANOVA was performed, with one between-subjects factor Group (saffron vs. sertraline), one within-subjects factor Time (baseline, week 2, week 4, and week 6), the Group by Time-interaction, and the HDRS-scores as dependent variable. Given the deviation of sphericity, F-tests were performed using Greenhouse–Geisser corrected degrees of freedom, though the original degrees of freedom are reported with the relevant Greenhouse–Geisser epsilon value (ε). Further, for F-tests, effect sizes were reported with partial eta-squared (η_p^2), with $\eta_p^2 \leq 0.019$ indicating trivial effect sizes, $0.020 \leq \eta_p^2 \leq 0.059$ indicating small, $0.06 \leq \eta_p^2 \leq 0.139$ indicating medium, and $\eta_p^2 > 0.14$ indicating large effect sizes (Cohen, 1988). Next, at the end of the study, HDRS scores were categorized into responders (improvement of 50% of higher of HDRS scores) and remitters (HDRS scores of 8 points or lower). Two X^2-tests were performed to calculate the distribution of responders and remitters between the saffron and the sertraline condition.

The level of significance was set at alpha <0.05. All computations were performed with SPSS® 25.0 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

3.1. Sociodemographic information

A total of 50 participants took part in the study. Mean age was 65.60 years (SD = =4.32; age range: 60–69 years). Table 1 reports the descriptive and inferential statistical sociodemographic information, separately for participants in the saffron and sertraline condition. No descriptive and statistically significant differences between the two groups were observed for age, gender distribution, highest educational achievement, and current job position.

3.2. Hamilton Depression Rating scores over time and between the two intervention groups

Tables 2 and 3 report the descriptive and inferential statistical indices of depression scores over time (baseline, week 2, week 4, week 6) and between and within the saffron and sertraline condition (statistical indices are not repeated in the text).

Hamilton Depression Rating scores significantly decreased over time. No statistically significant or descriptive mean differences were observed between the two groups (saffron vs. sertraline). No statistically significant Time by Group interaction was observed (see also Fig. 2).

Table 2
Descriptive statistical indices of depression scores (Hamilton Depression Rating Scale) over time and separately for participants in the saffron and the sertraline condition.

		Time points			
		Baseline	Week 2	Week 4	Week 6
	N	M (SD)	M (SD)	M (SD)	M (SD)
Saffron	25	21.12 (2.35)	18.04 (2.09)	14.64 (3.89)	9.92 (4.51)
Sertraline	25	21.40 (2.86)	18.12 (2.92)	14.12 (2.44)	8.76 (4.52)

3.3. Response, remission and side-effects

Table 4 reports response rates, remission rates and side-effects between the saffron and the sertraline condition. Response and remission rates did not differ between the two study conditions. Descriptively and compared to participants in the saffron condition, participants in the sertraline condition reported more side-effects. Two participants in the sertraline condition withdraw from the study due to possible side-effects (see Fig. 1).

4. Discussion

The key findings of the present study were that among older people diagnosed with major depressive disorders (MDD) both Crocus Sativus L. (saffron) and sertraline at therapeutic dosages decreased symptoms of depression over a time lapse of six weeks, as rated by experts. Treatment with saffron or with sertraline had no advantages or disadvantages as regards efficacy.

In the meanwhile, there are sufficient studies and meta-analyses (Khaksarian et al., 2019; Lopresti and Drummond, 2014; Marx et al., 2019; Yang et al., 2018) to show the favorable effect of saffron on symptoms of depression, both compared to placebo and to antidepressants. However, the present data are novel, in that we observed such favorable effects on symptoms of depression based on experts' ratings, in that we assessed older people, and in that we compared saffron to sertraline, a standard SSRI.

By contrast, the quality of the study does not allow a deeper understanding of the underlying neurophysiological mechanisms. Hausenblas et al. (2015) reported that saffron has antioxidant properties, anti-inflammatory properties, and neuroprotective effects. Further, saffron regulates the hypothalamic-pituitary-adrenocortical (HPA) axis activity, it has NMDA antagonist effects, improves the signaling of the neurotrophic brain-derived agent, and inhibits the serotonin reuptake from the synapses. Likewise, various studies have shown that saffron has anti-inflammatory, antioxidant, anti-anxiety, anti-depressant, anticonvulsant, and analgesic properties (Kashani et al., 2018; Moshiri et al., 2015). Lopresti and Drummond (2017) reported that saffron contains crocins (family of six mono-glycosylor di-glycosyl polyene esters), crocetin (a natural carotenoid dicarboxylic acid precursor of crocin), picrocrocin (monoterpene glycoside precursor of

Table 1
Descriptive and inferential statistical indices of sociodemographic dimensions, separately for participants in the saffron and sertraline condition.

	Condition		Statistics
	Saffron	Sertraline	
N	25	25	
	M (SD)	M (SD)	
Age (years)	64.48 (2.63)	66.72 (5.34)	$t(48) = =1.88$, $p = =.07$
	n	n	
Gender (female/male)	6/19	9/16	$X^2(N = = 50, df = 1) = =0.86$, $p = =.36$
Highest educational level (illiterate/primary school/diploma/higher education)	3/14/5/3	2/18/5/0	$X^2(N = = 50, df = 3) = =3.70$, $p = =.30$
Current job position (retirement/part time)	22/3	22/3	$X^2(N = = 50, df = =1) = =0.00$

Table 3
Inferential statistical indices of depression (Hamilton Depression Rating Scale) over time and between and within the group treated with saffron or with sertraline.

Factors Time	Group	Time by group- interaction	Greenhouse–Geisser epsilon
F(3, 144) = =296.85*** η_p^2 = =0.861 (L)	F(1, 48) = =0.01 η_p^2 = =0.008 (T)	F(3, 144) = 0.36 η_p^2 = =0.008 (T)	0.649

*** = $p < .001$; T = =trivial effect size; L = =large effect size.

safranal and product of zeaxanthin degradation) and safranal; the combination of these agens appear to have antioxidant and anti-inflammatory properties and neuroprotective effects, which have the potential to counteract higher oxidative stress and inflammatory concentrations typically observed in individual with MDD (for a thorough and comprehensive explanation we refer to Lopresti and Drummond, 2017).

We further hold that the present results are important for the following reasons: First, despite the availability of several antidepressants, their efficacy has been challenged: Hengartner and colleagues (Braillon et al., 2019a,b; Hengartner et al., 2019; Hengartner and Ploderl, 2018, 2019) showed that that only one out of nine people benefit from antidepressants: the remaining eight are unnecessarily put at risk of adverse drug effect. Likewise, the effect size for antidepressants is modest, plateauing at around 0.30 compared with placebo. Last, the serious adverse effects of antidepressants such as suicide attempts, cardiovascular events, and severe withdrawal reaction after discontinuation of long term pharmacotherapy have to be considered when prescribing antidepressants (Carvalho et al., 2016). On the flip side, especially in older people with depression, herbal medications are valuable alternatives to antidepressants, as side-effects are low (see Table 4).

Despite the novelty of the results, several limitations warrant against the overgeneralization of the results. First, medication adherence was not systematically assessed, though the overall results are such that a systematic bias of lack of medication intake appears unlikely. Second, it is conceivable that latent and unassessed dimensions such as sleep quality, quality of social support, along with nutritional factors such as the intake of omega-3-polyunsaturated fatty acids might have biased two or more dimensions in the same of opposite directions. Third, while the present study showed *that* saffron had a favorable effect on symptoms of depression, the quality of the data does not explain, *why* this happened. Last, a follow-up assessment might have allowed to understand, if saffron, sertraline, or both had a longer-term effect on depression.

Table 4
Response and remission rates, separately for participants in the saffron and sertraline condition.

	Condition Saffron	Sertraline	Statistics
N	25 n	25 n	
Responder (yes/no)	17/8	14/11	$X^2(N = = 50,$ df = =1) = =0.76, $p = .34$
Remitter (yes/no)	14/11	14/11	$X^2(N = = 50,$ df = =1) = =0.00
Side effects (headache/ vertigo/tiredness/ sleep changes)	0/0/1/0	3/2/3/2	–

5. Conclusion

The pattern of results suggests that compared to sertraline, daily dosages of saffron 60 mg/d for six consecutive weeks had the same effects on symptoms of depression among a sample of older people with MDD. Given that above all older people might be more reluctant to take synthetic medications, and given that the efficacy of antidepressants is more critically considered, it appears that natural medications such as saffron is a valuable alternative.

Disclosure

All authors declare no conflicts of interests. The entire study was performed without external funding.

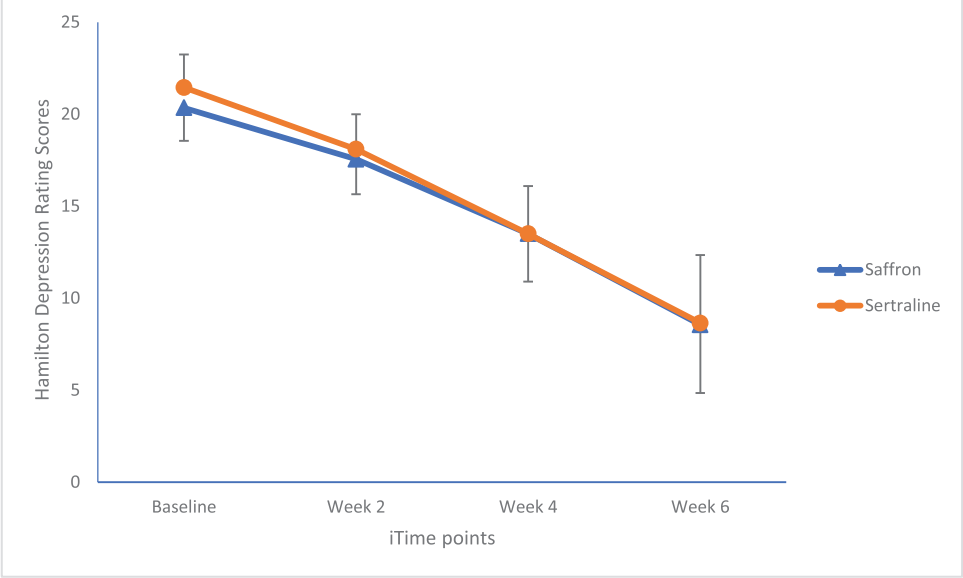

Fig. 2. Hamilton Depression Rating scores decreased significantly over time. No group differences and no Time by Group – interactions were observed. Points are means; bars are standard deviations. For clarity, standard deviations were shown only in one direction.

Declaration of Competing Interest

All authors declare no conflicts of interests. The entire study has been performed without external funding.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112613.

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