

## Reviewer's report

**Title:** Comparison of *Crocus sativus* L. and imipramine in the treatment of mild to moderate depression: A pilot double-blind randomized trial.

**Version:** 1 **Date:** 16 June 2004

**Reviewer:** Lon S Schneider

### Reviewer's report:

General

This is a report on a six-week randomized trial of saffron compared with imipramine for outpatients with depression. The general result of the trial was that there was no difference between the groups in efficacy and that there were greater side effects with imipramine.

The manuscript is generally well written.

It is certainly appropriate for the authors to state in the abstract that "saffron may be of therapeutic benefit." However, this trial, by design, cannot provide evidence for or against its efficacy, or for or against the efficacy of imipramine for that matter. Without a placebo group there is no assay sensitivity. It cannot be determined whether either of the drugs had efficacy, whether the improvement wasn't due to time or non-specific study effects. The results are compatible with (1) both drugs having efficacy or (2) both drugs having no efficacy. As an aside, it would have been very difficult to demonstrate the efficacy of an already established antidepressant such as imipramine with a sample size of only 30.

Indeed, a dosage of 100 mg per day of imipramine is at the lower end of the effective range.

What this pilot trial does do is establish feasibility for a larger and more definitive trial and this should be emphasized by the author.

Beyond describing its historical and traditional use, the authors might speculate and discuss its mechanism of action. One consideration here is the compellingness of the hypothesized antidepressant mechanism of action.

The authors should further describe their blinding procedures, noting that the medications can easily be unblinded and should discuss how this may lead to bias in the results. They should describe the size and appearance of the imipramine capsules used, and whether they looked different from the saffron capsules. How did they insure that raters and patients were blind to the medication assignments? Did the saffron extract have an aroma or color that was different from the imipramine?

They should discuss why they chose the dose they did.

Statistical analysis is appropriate for this study.

The author should note and comment that their sample size analysis was optimistic and misconstrued. Did they really expect that there would be a 5 point Hamilton difference between groups (in either direction)? Planning to detect a difference of 5 on a Hamilton is unrealistic; many large placebo-controlled multicenter trials of established antidepressants only show an effect size

half that, and here the comparison is with an active antidepressant not a placebo. This 5 point difference would have constituted their minimal clinically significant difference.

The paper would benefit from more descriptive results of the patients at baseline, including baseline test scores on the Hamilton.

The text says that standard errors are shown in the figure but they are not.

As mentioned above, it is incorrect to state that saffron extract was found to be effective (page 10). Since they mentioned that saffron might be associated with abnormal bleeding they should discuss the evidence and the mechanism as well.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. Comment on potential mechanism of action for antidepressant efficacy and bleeding.
2. Add SE bars to the figure.
3. Describe their blinding procedures and threats to the blind
4. Clarify that efficacy cannot be determined with this design.
5. Add descriptive baseline information to Table, e.g., Ham-D scores.

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Discretionary Revisions (which the author can choose to ignore)

**What next?:** Accept after minor essential revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

None.