

Responses to the reviewer comments:

Thank you for the effort you made to revise this manuscript, and for the valuable remarks that have improved the quality of this work, and made it easier to read for a wider audience.

You can find here the responses to all your remarks and questions:

1. It is difficult to understand in the first place because there is no figure.
2. I suggest you should create a chronological table in the order of drug development and itemize the advantages and disadvantages of each.

Response: We create a table describing the chronological appearance in the market of most antidepressants, with their main contributions and disadvantages.

3. Paragraph In Tricyclic antidepressant (TCA),

You describe that tricyclic antidepressants (amitriptyline, nortriptyline, protriptyline, imipramine, desipramine, doxepin, and trimipramine) have comparable efficacy in treating major depression to other classes of antidepressants, including SSRIs, SNRIs, and MAOIs [26,27]. However, for hospitalized patients, and compared to SSRIs, TCAs may be particularly effective [28–30].

What was the differences between hospitalized patients and outpatients?

Response: The difference is explained in the revised version,
“This efficacy can be explained by the superiority of TCAs (versus SSRIs) for patients with more severe symptoms of major depressive disorder (MDD), who are the most in need of hospitalization [31–36].”

4. You describe that this advantage can be explained by the superiority of TCAs (versus SSRIs) for patients with more severe symptoms of major depressive disorder [31–33] as well as for patients with melancholia [34–36]. Yet, there was no difference in efficacy in outpatients, considered as less severely ill [26,29].

What was the differences between the advantage and the efficacy?

Response: to avoid confusion, the term “advantage” has been replaced by

“efficacy”.

5. Paragraph in Other antidepressants

You describe in conclusion, there seems to be no significant differences between all classes of antidepressants in terms of efficacy. [71] even though there was moderate to low evidence of the efficacy of some drugs [72]. Concerning acceptability, citalopram, escitalopram, fluoxetine, sertraline, and vortioxetine were more tolerable than other antidepressants, whereas amitriptyline, clomipramine, duloxetine, fluvoxamine, trazodone, and venlafaxine had the highest dropout rates [72].

What was the reason of dropout?

Response: the reason of dropout has been detailed in the manuscript: *“because of their more frequent and severe side effects. Nausea and vomiting were the most common reasons for treatment discontinuation, while sexual dysfunction, sedation, priapism and cardiotoxicity were also reported [30,46,65].”*

How long do you continue to use these medicines which are amitriptyline, clomipramine, duloxetine, fluvoxamine, trazodone, and venlafaxine?

Response: these antidepressants are used as second line treatment in patients who are not responding to SSRI, unless their adverse effects outweigh their benefit.

6. Paragraph in Overview of psychotherapy in depression

Would you make a figure how to use psychotherapy as an initial treatment.

Response: A figure was added to the paragraph, showing an overview of available psychotherapies with their indications in several clinical situations.

7. Paragraph in Electroconvulsive therapy

You describe the stigma around ECT limits its use. Would you explain about stigma around ECT?

Response: we add an explanation about stigma around ECT in the revised version: *“The stigma around ECT limits its use. The majority of misconceptions date back to the early years of ECT use, when it was performed without muscle relaxants or anesthesia. Some still feel that ECT should be left as a last option to treat depression,*

although most studies indicate that the benefit of ECT is greater in patients who have had fewer pharmacological treatment [144–146].”