TITLE: "The role of serendipity in the discovery of classical antidepressant drugs: Applying operational criteria and patterns of discovery".

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Dear Lian-Sheng Ma, Editorial Office Director, Company Editor-in-Chief, Editorial Office,

Thank you very much for your comments. Following your indications, I am revised the manuscript according with the referees comments.

According to the referee's comments, the comments and changes made are as follows:

Reviewer 1:

I want to thank the reviewer 1 for all his comments and contributions to our manuscript, which will undoubtedly improve it considerably. It is perceived that he is a great expert and connoisseur of this matter.

1) "Specific Comments to Authors: This paper reports the role of serendipity in the discovery of the two early classes of antidepressants: tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). It is difficult not to agree with the general thrust of the article that serendipity played some role in the initial discovery of the clinical effects of these agents".

Indeed, the role of serendipity in the discovery of the first psychoactive drugs in the 1950s is assumed by most researchers. In our manuscript, we intend to systematize how this process of serendipity took place.

2) "There is a tendency to assume that readers will be familiar with previous work of the authors and their ratings of serendipity. Thus the working definition of serendipity is not explained so it is difficult for the reader to judge whether they agree with either the definitions per se or with the classes to which the discoveries discussed are assigned".

In principle, and to avoid that the manuscript was not too long, we would refer readers to our previous work on this topic. But, following the recommendations of the reviewer, we will incorporate the definition of serendipity that we use and the criteria of serendipity that we develop.

3) *"P 3: Although they are still available today in most jurisdictions, TA+CAs and MAOIs are probably much less likely to be used as first line treatments for MDD today. In fact they are probably well down the pecking order of most psychiatrists and GPs".*

We indicate in the manuscript that ACTs continue to be used in clinical practice, as well as in clinical research. Obviously, we share the opinion of the reviewer that they are not first-line drugs in the treatment of affective disorders, and we will indicate this in the manuscript.

4) *"P 3: It is arguable if TCAs, MAOIs forged an understanding of the biology of the illnesses. The logical of the argument from successful treatments to cause of illness is fundamentally flawed since it assumes that the drug correct an underlying deficit. It is still unclear today how MDD arises at a neurobiological level or indeed what specific pharmacological actions of antidepressants (if any) are responsible for the alleviation of depressive symptoms".*

The pharmacocentric theory of the first knowledge in relation to the etiology of mental illnesses is defended and shared by many researchers. Without knowledge of the effects of the classic neuroleptics and TCAs, it would have been impossible to postulate the monoaminergic theories of depression or the dopaminergic hypothesis of schizophrenia (in fact, some researchers won the Nobel Prize for these contributions). However, I share a certain perspective with the reviewer in the sense that we still do not know many aspects of what happens, from the neurobiological perspective, in the brain of patients with psychiatric disorders and this would explain the high rates of therapeutic failure that we still have today today with available drugs. I am very happy that our contribution generates this type of debate.

5) "*P 3: It would seem to me that the inefficacy of agents such dinitrile succinate was not due to any specific prevailing Freudian ideas but rather that the clinical studies showed they were ineffective!"*.

I share the reviewer's opinion that these pharmacological agents were quite ineffective and that they were incorporated into the therapeutic arsenal with very few clinical studies (we will correct this in the manuscript). However, it is also relevant to highlight, as many authors have pointed out, that the psychoanalytic currents that dominated in a certain way the psychiatric panorama of the time (prior to the 1950s) were opposed to the pharmacological approach to mental disorders and hindered the development of this branch of pharmacology. That is why we say in the manuscript that "this was due, in part, to Freudian ideas."

6) "*P 4: the first SSRI was in fact zimelidine which was withdrawn from the market; fluoxetine was the first commercially (very) successful SSRI (see Healey The Antidepressant Era, p138)*".

This was indeed so. The first commercialized SSRI, albeit with little success, was zimelidine. We will incorporate it into the manuscript.

7) "*P 8: Kuhn described the pharmacological effects..... seems to imply actions at central receptors and the like. More likely he was describing peripheral side effects / adverse reactions? Of course these are mediated by various receptors but at that time Kuhn was not in a position to understand the pharmacology of the Drug*".

In the work discussed by the reviewer, Kuhn describes the therapeutic and adverse effects that he observed in patients treated with imipramine. And as the reviewer very well indicates, at that time it was impossible to attribute the effects described to the mechanism of action of the drugs. Its pharmacological effects at the transporter and receptor level would be discovered during the next decade.

8) "*P 4 the drug is viloxazine not viloxacin*".

We correct this typographical error in the manuscript. Thank you very much to the reviewer for pointing it out.

9) "*P 7 the bridge in phenothiazines is a sulphur not sulphate*".

We also corrected this error in the text.

10) "*P 7 Would it be more correct to describe these as psychotic symptoms not schizophrenic? ¿Sería más correcto describirlos como síntomas psicóticos no esquizofrénicos?*".

I think the reviewer's proposal is very successful. And so we will modify it.

11) "*P 8 "Chance was not decisive....." Perhaps it is apposite to quote Pasteur here: "In the fields of observation chance favours only the prepared mind"*.

We have used this classic Pasteur quote regularly in some of our previous papers. It also has its place here: we will.

12) "*P 10: Although it can be described as a TCA, iprindole is fundamentally different chemically from the "classic" imipramine like drugs in chemical structure*".

The reviewer is absolutely right, but we have not wanted to refine too much in these aspects, since it is outside the objective of the study to establish all the chemical differences between the considered classic TCAs.

13) "*P 13:Maprotiline is a TCA even though it has a four rings they are not fused together as in a tetracyclic such as mianserin. Hence chemically it is incorrect to describe it a tetracyclic even though many people do*".

This is also true. Although most authors classify maprotiline as a tetracyclic, others classify it as a tricyclic. We will point this out in the manuscript.

14) "*P 14 The principal safety concern with nomifensine was immune related haemolytic anaemia*
El principal problema de seguridad de la nomifensina fue la anemia hemolítica relacionada con el sistema inmunitario".

We will incorporate this contribution that the reviewer makes us.

15) "*P 16: eutimising Is this a word? I do not find it in the Shorter Oxford Dictionary. Do you mean euthymic or mood stabilising?*"

Indeed, we refer to mood stabilizing. We will correct it in the manuscript.

Reviewer 2:

We thank the reviewer for his positive comments regarding the publication of the article.

We hope that this revised version meets your interest.

With best regards,

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