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PEER-REVIEW REPORT

Name of journal: *World Journal of Psychiatry*

Manuscript NO: 69430

Title: THE ROLE OF SERENDIPITY IN THE DISCOVERY OF CLASSICAL ANTIDEPRESSANT DRUGS: APPLYING OPERATIONAL CRITERIA AND PATTERNS OF DISCOVERY

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02445281
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Senior Scientist
Reviewer's Country/Territory: Mexico
Author's Country/Territory: Spain

Manuscript submission date: 2021-09-06

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-13 19:52

Reviewer performed review: 2021-09-13 20:21

Review time: 1 Hour

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection

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Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is an excellent manuscript, interesting and readable, well written and well documented, I have no more comments.

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Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 02192131
Position: Editorial Board
Academic degree: BSc, PhD

Professional title: Associate Professor, Honorary Research Fellow

Reviewer's Country/Territory: Australia

Author's Country/Territory: Spain

Manuscript submission date: 2021-09-06

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-09-13 04:48

Reviewer performed review: 2021-09-17 11:55

Review time: 4 Days and 7 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection

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Re-review	[ ] Yes [Y] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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. 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. Definitions aside there are some points on which readers may disagree with the authors statements. Some of these are: 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 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. 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! P 4: the first SSRI was in fact zimelidine which was withdrawn from the market; fluoxetine was the first commercially

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(very) successful SSRI (see Healey The Antidepressant Era, p138). 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. Some other issues which might be addressed: P 4 the drug is viloxazine not viloxacin P 7 the bridge in phenothiazines is a sulphur not sulphate P 7 Would it be more correct to describe these as psychotic symptoms not schizophrenic? 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” P 10: Although it can be described as a TCA, iprindole is fundamentally different chemically from the “classic” imipramine like drugs in chemical structure 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 P 14 The principal safety concern with nomifensine was immune related haemolytic anaemia P 16: eutimising Is this a word? I do not find it in the Shorter Oxford Dictionary. Do you mean euthymic or mood stabilising?