**The serotonin hypothesis of depression: should people with depression continue to take antidepressants?**

Tony Kendrick [1]

Susan Collinson [2]

[1] Professor of Primary Care

Primary Care, Population Sciences & Medical Education, University of Southampton, Aldermoor Health Centre, Southampton SO16 5ST.

[2] Specialist TB Case Worker

Homerton University Hospital NHS Foundation Trust, London E9 6SR.

Tony Kendrick is the corresponding author, email: [A.R.Kendrick@Southampton.ac.uk](mailto:A.R.Kendrick@Southampton.ac.uk)

Word count: 891

The BMJ has judged that there are no disqualifying financial ties to commercial companies. The authors declare the following other interests: Tony Kendrick declares that his employer the University of Southampton has received funding from the National Institute for Health Research for his research on the assessment and treatment of depression in primary care, and on testing internet and telephone support to people wanting to come off long-term antidepressants. Susan Collinson declares a personal history of depression and long-term antidepressant use.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material wherever it may be located; and vi) licence any third party to do any or all of the above.

The results of a recent systematic umbrella review published in *Molecular Psychiatry* of evidence for the serotonin theory of depression [1] were widely reported in UK media as showing that depression is not caused by low levels of serotonin or a “chemical imbalance”, and therefore casting doubt on the current use of selective serotonin reuptake inhibitor (SSRI) antidepressants by millions of people [2-5].

The study brought together existing systematic reviews, meta-analyses and large dataset analyses on: associations between depression and concentrations in body fluids of serotonin and its metabolite, 5-HIAA; serotonin 5-HT1A receptor binding; serotonin transporter (SERT) levels measured by imaging or at post-mortem; tryptophan depletion studies; SERT gene associations; and SERT gene-environment interactions. It reported no consistent evidence to support the hypothesis that depression is caused by lowered serotonin activity and called for acknowledgement that the theory is not empirically substantiated [1].

A polarising debate ensued, that risks undermining the evidence based treatment of depression, causing harm to people who take or need these agents.

Critics of the review and its coverage noted that study selection was incomplete, since an omitted 2021 meta-analysis had concluded that metabolic changes in the blood were associated with depression, notably of L-tryptophan [6]. The review of previous studies was dismissed as nothing new, and limited, because peripheral and indirect measures of serotonin tell us nothing about activity at receptors between neurones in the brain [7]. Psychiatrists argued that use of SSRIs is not based on the simplistic theory that low serotonin causes depression, but on clinical trial evidence [6,7].

Others, however, including the review’s lead author, interpreted the findings to imply that antidepressants do not work, suggesting they are barely distinguishable from placebos and may just numb emotions [8,9]. These contentions are not supported by evidence, went beyond the findings of the review, and were not expressed in its conclusions [1]. They could encourage sudden antidepressant cessation, causing patients withdrawal symptoms and risking relapse.

Public reaction on social media included fear, guilt, and feeling stigmatised for taking antidepressants on the one hand, and anger at the dismissal by experts of patients’ legitimate concerns about medication on the other.

How should patients and clinicians navigate these challenges?

First and foremost, there is good evidence from randomised controlled trials that antidepressants are effective in treating people with new episodes of both less severe and more severe depression [10-12], and that this is not merely due to the enhanced expectation of improvement among participants in active treatment arms who experience side-effects and guess their treatment allocation [13]. Around 25% of trial participants taking antidepressants experience a substantial effect, compared to around 10% taking placebos [14].

However, the review discusses an important point, that surveys indicate most of the public believe the chemical imbalance theory is established [15], and this is probably because practitioners use it to justify prescribing antidepressants, although the evidence cited was a small online survey of practitioners [16]. While most practitioners surveyed did acknowledge a chemical imbalance as one possible cause of depression, they ranked it last among 13 biological, psychological, and social factors, suggesting they believed in a much broader overall model of depression [16].

Unfortunately, the chemical imbalance explanation may have encouraged long-term use of SSRIs, because it falsely implies a serotonin deficiency needing long-term replacement, perhaps for life, and may be used to justify prescribing antidepressants long after people have recovered from their depression. This false belief was identified in 10 qualitative studies of barriers and facilitators to discontinuing antidepressants when appropriate [17]. SSRIs may cause side effects including gastrointestinal bleeding and sexual dysfunction [12]. Long-term use of antidepressants may lead to increasing difficulty in eventually coming off treatment [18] and is associated with an increased risk of serious adverse events in older adults [19]. Therefore we should not tell people with depression that antidepressants correct an imbalance or deficiency of serotonin, or that they should necessarily need them long-term.

Open and honest discussions with patients about the remaining uncertainties is essential.  We do not know why antidepressants work well for some people and not others, or cause harm, and research into their biological and psychosocial mechanisms of action needs to continue. Trial evidence makes clear that their effect is on average modest [10], so the National Institute of Health and Care Excellence (NICE) recommends that psychological therapy should be offered first (if available) to people with a new episode of less severe depression unless they prefer antidepressant treatment, and a combination of antidepressant and psychological therapy for more severe depression [12].

NICE recommends that clinicians advise people taking antidepressants for a first episode to take them for at least six months after recovery [12]. After nine months or longer, around half of patients may be able to taper off treatment without relapsing and needing to restart [20]. People needing treatment for a second episode of depression are at greater risk of relapse following discontinuation, particularly if symptoms persist that are serious enough to impair daily activities, and they have an ongoing underlying cause of their depression. They may be advised to continue antidepressants for two years before considering stopping treatment again [12].

Trust between the prescriber and the person with depression is of paramount importance for a good outcome. So an initial time frame for treatment should be agreed, with frequent contact until symptoms have receded [12]. Personal continuity of care should be offered at six-monthly regular reviews of longer term treatment, to optimise knowledge of the person and their situation [12].

1. Moncrieff J, Cooper R, Stockmann T, Amendola S, Hengartner MP, Horowitz MA. The serotonin theory of depression: a systematic umbrella review of the evidence. *Mol Psychiatry* 2022;(July). <https://doi.org/10.1038/s41380-022-01661-0>
2. Blanchard S. Depression is not caused by chemical imbalance in the brain, say experts – and pills ‘not based on science’. *The Sun* online published 1:00, 20 Jul 2022 Updated: 17:52, 21 Jul 2022. <https://www.thesun.co.uk/health/19254920/depression-chemical-imblance-pills-not-work/> (accessed 22/07/2022)
3. Ely J. Depression 'is NOT caused by low serotonin levels: Study casts doubt over widespread use of potent drugs designed to treat chemical imbalance in brain. *MailOnline* published 01:00, 20 July 2022 | updated: 01:06, 20 July 2022. <https://www.dailymail.co.uk/health/article-11027847/Depression-NOT-caused-low-serotonin-levels-study.html> (accessed 22/07/2022)
4. Knibbs J. Depression not caused by low serotonin as new study debunks chemical imbalance theory *Daily Mirror* online published 16:08, 21 Jul 2022. <https://www.mirror.co.uk/lifestyle/health/depression-not-caused-low-serotonin-27538041> (accessed 22/07/2022)
5. Hayward E. Antidepressants study casts doubt on drugs taken by 8m people. *The Times* online published 12.01am 20 July 2022. <https://www.thetimes.co.uk/article/antidepressants-study-casts-doubt-on-drugs-taken-by-8m-people-db2dsb9zf> (accessed 22/07/2022)
6. Wise, J. “No convincing evidence” that depression is caused by low serotonin levels, say study authors. *BMJ* 2022; 378:o1808 doi: <https://doi.org/10.1136/bmj.o1808> (Published 20 July 2022)
7. Science Media Centre: expert reaction to a review paper on the ‘serotonin theory of depression’. <https://www.sciencemediacentre.org/expert-reaction-to-a-review-paper-on-the-serotonin-theory-of-depression/> (accessed 22/07/2022)
8. Moncrieff J. Breakfast News, on the chemical imbalance myth. July 22: <https://www.youtube.com/watch?v=2Ub7V0RcLew> (accessed 22/07/2022)
9. Moncrieff J, Horowitz M. Depression is probably not caused by a chemical imbalance in the brain – new study. *The Conversation* July 20th 2022. <https://theconversation.com/depression-is-probably-not-caused-by-a-chemical-imbalance-in-the-brain-new-study-186672> (accessed 22/07/2022)
10. Cipriani A, Furukawa TA, Salanti G, Chaimani A, Atkinson LZ, Ogawa Y *et al*. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Lancet* 2018;391:1357-1366. doi: 10.1016/S0140-6736(17)32802-7.
11. Furukawa TA, Maruo K, Noma H, Tanaka S, Imai H, Shinohara K *et al*. Initial severity of major depression and efficacy of new generation antidepressants: individual participant data meta-analysis. *Acta Psychiatr Scand* 2018;137:450–8.
12. NICE. Depression in adults: treatment and management. June 2022. [www.nice.org.uk/guidance/ng222](http://www.nice.org.uk/guidance/ng222)
13. Hieronymus F, Lisinski A, Nilsson S, Eriksson E. Efficacy of selective serotonin reuptake inhibitors in the absence of side effects: a mega-analysis of citalopram and paroxetine in adult depression. *Molecular Psychiatry* 2017; doi:10.1038/mp.2017.147
14. Stone MB, Yaseen ZS, Miller BJ, Richardville K, Kalaria SN, Kirsch I. Response to acute monotherapy for major depressive disorder in randomized, placebo controlled trials submitted to the US Food and Drug Administration: individual participant data analysis. *BMJ* 2022;378: e067606 <https://dx.doi.org/10.1136/bmj-2021-067606>
15. Pilkington PD, Reavley NJ, Jorm AF. The Australian public's beliefs about the causes of depression: associated factors and changes over 16 years. *J Affect Disord* 2013; 5;150(2):356-62. doi: 10.1016/j.jad.2013.04.019.
16. Read J, Renton J, Harrop C, Geekie J, Dowrick C. A survey of UK general practitioners about depression, antidepressants and withdrawal: implementing the 2019 Public Health England report. *Therapeutic Advances in Psychopharmacology* 2020;10:204512532095012. <https://journals.sagepub.com/doi/full/10.1177/2045125320950124>
17. Maund E, Dewar-Haggart R, Williams S, Bowers H, Geraghty AWA, Leydon G, *et al*. Barriers and facilitators to discontinuing antidepressant use: A systematic review and thematic synthesis*. J Affect Disord* 2019;245:38–62.
18. Read J, Williams J. Adverse Effects of Antidepressants Reported by a Large International Cohort: Emotional Blunting, Suicidality, and Withdrawal Effects. *Current Drug Safety* 2018;13(3):176-186. <https://doi.org/10.2174/1574886313666180605095130>
19. Coupland C, Dhiman D, Morriss R, Arthur A, Barton G, Hippisley-Cox J. Antidepressant use and risk of adverse outcomes in older people: population based cohort study. *BMJ* 2011;343:d4551
20. Lewis G, Marston L, Duffy L, Freemantle N, Gilbody S, Hunter R, *et al*. Maintenance or Discontinuation of Antidepressants in Primary Care. *N Engl J Med* 2021;385(14):1257–67. <https://doi.org/10.1056/NEJMoa2106356>