The serotonin hypothesis of depression: both long discarded and still supported?

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We thank the authors of all the letters for their interest in our paper [1]. The reason our paper is important is that the pharmaceutical industry, along with many doctors and academics, have been telling the public for decades that depression is caused by a neurochemical abnormality in order to justify the use of antidepressants, and to overcome some people's reluctance to use mood-modifying medicines [2, 3]. Our paper exposed this claim as untrue. The main areas of research do not provide support for the most well-known neurochemical hypothesis, the serotonin theory of depression – the idea that depression is caused by low levels or low activity of serotonin.

There are always further studies that can be presented to support the serotonin theory, and research on other possible biological mechanisms, which may or may not involve serotonin. However, we synthesised all existing studies from the main areas of research on serotonin and depression. The onus is on others to present a convincing case based on other types of research or alternative hypotheses, not on us to disprove every speculation.

As a whole, the letters paint a confusing picture of the status of the serotonin theory. On the one hand it is argued that it has long been abandoned, on the other that it is valid and that we missed some studies, and some authors argue both points of view. Bartova et al suggest that depression is the result of a complex 'dysbalanced dynamic system' involving almost every biological system and aspect of brain function [4]. We would agree that many brain processes, including the serotonin system likely play a complex, though poorly understood, role in emotion and behaviour, including depression. Yet such ideas are different from the specific claim that depression is caused by low serotonin levels or serotonin activity (often communicated to patients) that our review specifically examines. Whilst appearing scientific, the hypotheses proffered are so vague and overinclusive as to be completely untestable [4], as is the claim that the serotonin 'system is perturbed' [5]. It seems as if the situation is the same as in 1987 when David Healy described the monoamine hypothesis of depression as a failed Kuhnian paradigm [6]. No one believes it, but no one wants to let it go either.

It is also important that while a drug class that increases serotonin activity in the short term might seem a sensible approach to a condition caused by a serotonin deficiency, we might reasonably be concerned about the effects of modifying the complex, poorly understood serotonin system in the absence of clear evidence of a specific, underlying abnormality.

In response to criticisms of our methodology, we followed published guidance on conducting umbrella reviews, including Cochrane guidance [7, 8] and we challenge the imputation that we did

not use accepted and validated methods. Jauhar et al suggest that summarising different research areas together was mistaken but we were clear in our protocol that this approach was necessary to facilitate a comprehensive assessment of the heterogenous areas of research that have been thought to support the serotonin theory of depression.

Although Jauhar et al state that we included 'some primary studies at the expense of others,' we were transparent about our study's inclusion and exclusion criteria which were published in a protocol pre-registered on PROSPERO (CRD42020207203). We included one primary genetic study, which was much larger in terms of numbers of included participants than any systematic review, and which, as we explain, would have been quite misleading to omit, since it provides more definitive evidence than any single review.

There are various proposed ways to manage overlapping reviews, with no clear consensus [7]. The Cochrane guidance suggests that 'if the purpose is to present and describe the current body of systematic review evidence on a topic, it may be appropriate to include the results of all relevant systematic reviews as they were presented in the underlying systematic reviews' without conducting a repeat meta-analysis, and it is appropriate to 'include the results of all relevant systematic reviews, regardless of topic overlap'[7].

It is not true, as Jauhar et al, suggest, that we did not use validated processes to evaluate our findings. We used the AMSTAR to evaluate the quality of included systematic reviews, and the STREGA for the genetic study, and we used the GRADE to assess the certainty of findings, all of which are validated and widely used measures [7]. Indeed the review of risk factors cited by Jauhar et al as an example of an exemplary umbrella review uses the same quality assessment measure, the AMSTAR, and a similar classification of credibility to the GRADE that includes criteria related to sample size and presence of bias [9].

The purpose of GRADE ratings are to determine the certainty or quality of evidence. They are acknowledged to be inherently subjective, but aim to provide a reproducible and transparent framework for grading certainty of evidence [10]. We modified the GRADE quality assessment, as we recorded in PROSPERO, in order to generate a measure of certainty with the greatest relevance to the domains of interest. We followed the approach of Kennis et al (2020)[11] who used an approach appropriate to assessing observational studies examining the certainty of association between depression and various biological characteristics, with clear relevance to our review. For example,

the criteria highlighted by Jauhar et al regarding whether a study is a randomised controlled trial or an observational study lacks relevance to the research we examined because except in the case of tryptophan depletion, all of these studies are observational in nature. This criteria in GRADE derives from its original purpose to evaluate clinical interventions for guideline development [12, 13]. Instead we focused on more relevant criteria such as sample size (also focused on in the umbrella review favoured by Jauhar) since the occurrence of false positive results due to small sample size has been noted to be a problem [14, 15].

We included whether results reflected potential effects of antidepressants in our ratings of bias only if an effect was found since we were rating the certainty of a result in terms of whether it supported the serotonin hypothesis. The main point here, however, is that the potential effects of antidepressants have usually been ignored.

On tryptophan depletion, we did not 'miss' the Yatham study as Jauhar et al. claim. It is not a meta-analysis or systematic review and it was not among the 10 most recently published studies that we surveyed as an example of recent research in the area. It involved only 17 people who had been recently treated with antidepressants. We also did not omit the result of the subgroup analysis of drug-free patients with remitted depression in the Ruhe review [16]. This was presented in Table 1 but not described in the text because the main point of tryptophan depletion is to establish whether it induces depression in people without depression. If lowered serotonin levels or activity were the cause of depression then this intervention should be able to induce depression. On this point we all agree the data is consistent and tryptophan depletion has no effect. Despite Jauhar et al and Jacobsen's suggestions, effects in patients on and off medication are inconsistent, numbers are small, heterogeneity is significant, and results may have been influenced by prior use of medication since antidepressant effects on the brain can persist for long periods after they are stopped [17].

We did not include reviews of circulating tryptophan described by Jauhar, and Maes and Almulla [18] because they did not fulfil the inclusion criteria as pre-specified in our protocol. There are several reasons why peripheral levels of a precursor amino acid may not be informative about central serotonin levels: it is affected by diet, its relationship to central levels is unclear, and the majority (90%) of tryptophan is metabolised in the kynurenine pathway [19] with only 1% of dietary tryptophan contributing to serotonin in the brain [20]. As Maes and Almulla point out, tryptophan plays biological roles that are likely to be independent of serotonin or only distantly related to it. In any case, the potential impact of antidepressant treatment in the two meta-analyses cited by Jauhar has not been excluded since the majority of studies involved people who were taking

antidepressants, with only a few studies involving people who had stopped taking medication and then for only short periods prior to measurement (mostly weeks)[21, 22]. None were conducted with people who were explicitly medication naïve. In addition to this, one analysis had clear publication bias and used an unusual approach to adjust for this (which led to a larger overall effect after adjustment)[22], but when data was requested from the authors and adjusted using the standard trim and fill method the effect disappeared (analysis presented here [23]), consistent with the observation that by far the largest included study had an effect that was nearly perfectly zero. Moreover, the number of people studied is relatively low, and we showed how in the genetic research early studies that reported positive results were later contradicted by larger, higher-quality studies.

On serotonin receptors, we analysed all the systematic reviews that have been conducted to date and reported the metrics used by the studies, which mostly were BP_{ND}. Jauhar argue on the one hand that lower levels of $5HT_{1A}$ activity in depressed subjects would be consistent with lower serotonin and on the other hand they highlight a small study that took a different approach to measuring receptors which found higher levels of $5HT_{1A}$ in depressed subjects [24]. Although Jauhar et al and Jacobsen are correct to point out that there are $5HT_{1A}$ heteroreceptors as well as autoreceptors, nevertheless a considerable amount of evidence points to the overall effect of these receptors being inhibitory. For example, in animals give non-selective $5HT_{1A}$ agonists (affecting both autoreceptors and heteroreceptors) a pro-sexual (i.e. anti-serotonin) effect is seen [25]. Some evidence points to $5HT_{1A}$ receptors being reduced in people with depression in some brain areas, consistent with higher levels of serotonin if this receptor were the 'origin' of depression, but effects are highly uncertain, since confounding effects of medication have not been excluded and numbers are relatively small.

Research on SERT involves only small numbers of people who are drug naïve (and we were well aware of the number of drug naïve people included which we presented in Table 1 in our paper, despite our correspondents' suggestion otherwise) and it makes little sense to suggest that lower levels of SERT produce depression - as Jauhar and Jacobsen speculate - if SSRI antidepressants are designed to reduce SERT activity. Jauhar et al dispute our ratings on GRADE, but confuse quality ratings with certainty ratings. Efforts were made to examine publication bias in the review cited [26], but the GRADE is not a measure of whether a test or procedure was done, but of whether the results of the review are likely to be affected by sources of bias. In the review in question, significant publication bias was found in critical areas such as the hippocampus, which when adjusted for led to

disappearance of the detected effect. Even if the GRADE rating for this review was adjusted to 1 from 0, however, this meta-analysis would be upgraded from 'very low certainty' to 'low certainty', evidence, changing the overall GRADE rating for this area from 'very low certainty evidence of increased serotonin activity' to 'low certainty evidence of increased serotonin activity.' Our assessment that results may have been affected by prior drug treatment is due to the fact that all but three of the 25 included imaging studies involved people who had been previously treated with antidepressants, and it is increasingly apparent that antidepressants and other drugs have long-lasting effects on brain structure and function [17, 27].

The other studies mentioned by Jauhar et al consist of a small study of a potential, indirect measure of serotonin synthesis published in 2004 including just 17 patients who could have taken antidepressants up to two weeks prior to the study [28]. Since this area of research does not appear to have been frequently replicated, we can only assume that it was concluded to be irrelevant or that future findings were negative. The recent study cited (published after our review) provides little evidence of anything, since it employed a highly indirect method of measuring serotonin activity: reduction in $5HT_{2A}$ receptor non-displaceable binding in a single brain region (without a pre-specified protocol) following amphetamine challenge [29, 30]. The study involved only 17 depressed patients, five of whom also had Parkinson's disease. Findings were not statistically significant before exclusion of an outlier (supplementary materials), and the results presented then were only significant with a 1-sided statistical test [29, 30]. Bayesian analysis of this data suggests that the evidence presented was weak and not much more likely under the alternative hypothesis (some difference) than under the null-hypothesis (no difference).[30]

Finally, Jauhar et al argue that serotonin must be involved in depression because drugs which target the serotonin system are effective and other authors also argue that antidepressants 'work'. However, whether antidepressants produce a genuine and useful pharmacological effect that is independent of the placebo effect, has not been established. Antidepressants show marginal differences from placebo, which do not fulfil criteria for clinical relevance, and may represent amplified placebo effects due to unblinding [31–33]. It is hard to reconcile even the most generous appraisal of their efficacy with the vast numbers of people now taking them. Contrary to Bartova et al's claims, the idea that antidepressants reduce suicide has not been established, and evidence from randomised trials suggests they increase the risk of suicidality in some age groups [34, 35].

Moreover, antidepressants could affect people's emotions without having anything to do with their ability to modify the putative mechanisms that underpin depression. Antidepressants are psychoactive compounds that change people's thoughts and feelings by modifying normal brain chemistry, irrespective of whether people have a mental disorder or not. Alcohol, for example, induces an altered mental state which, when superimposed on underlying feelings, can temporarily over-ride symptoms of low mood or anxiety. Antidepressants produce varied and more or less subtle effects on arousal, sensations, thoughts and feelings, commonly including numbing of emotions [36], now demonstrated even in healthy volunteers [37] . These provide a plausible way in which antidepressants may reduce depression scores (along with placebo and amplified placebo effects), and we have referred to this elsewhere as the 'drug centred model' of drug action [38]. Such an obvious explanation needs to be excluded before unsubstantiated hypotheses, such as that antidepressants affect abnormalities of neurotransmitters, neurogenesis, inflammation or neural networks, are adopted.

Although we agree with El-Mallakh et al [39] and Jacobsen [40] that medical treatments do not always reverse the primary cause of the pathology they are used to treat, most modern medical treatments in physical healthcare, including those cited, do act on biological processes associated with the mechanisms that produce the symptoms or signs in question (e.g. blood volume for diuretics in hypertension) even if they do not act on the primary mechanisms (which are sometimes unknown) in what we have called elsewhere a 'disease-centred' model of drug action [38]. This is different from the way psychoactive compounds interact with people's thoughts and feelings as suggested by the 'drug-centred' model. An example of the latter in physical medicine is the way the intoxicating effects of alcohol were used to distract people from pain before more targeted analgesics were available.

We also agree with El-Mallakh et al [39] that some abnormalities in the serotonergic system identified after long-term antidepressant treatment are consistent with adaptive changes that reduce the potency of serotonin (often called tolerance), as would be expected in a homeostatic system designed to maintain equilibrium, but which might overshoot [41]. Moreover, as El-Mallakh suggests, we must consider what are the long-term effects of perturbing neurotransmitters that exist in complex inter-dependent relationships with each other. This is particularly important given that we only have 6-12 week trial data from which to extrapolate the effects of taking antidepressants long-term, yet we know that the consequences of the long-term use of recreational drugs, which also alter brain chemistry, include mood symptoms along with issues with

concentration, memory, sleep and withdrawal effects (all of which are concerns with antidepressant use in the long term)[42].

From the public's point of view, taking a drug that is believed to reverse an underlying chemical imbalance or other brain abnormality is quite a different prospect from taking a drug that perturbs brain chemistry in incompletely known and potentially unpredictable ways, with poorly researched effects on mood and behaviour, with emotional numbing emerging as a clear effect [36, 37]. Yet, this approach to marketing drugs by drawing on unproven, implausible single neurotransmitter hypotheses to provide biological justifications for their use continues apace. The 'opioid hypothesis of depression'[43] and the 'glutamate hypothesis of depression'[44] are being promoted alongside efforts to market opioids and ketamine (which acts on glutamate), respectively, as antidepressants, often by researchers with ties to the manufacturer.

People should be making the decision whether to take antidepressants based on what is known about the drugs, rather than fanciful stories propagated by their manufacturers. We hope that our paper and the ensuing discussion will make psychiatrists and researchers find out more about the consequences of long-term use of brain-modifying chemicals, including antidepressants. If this happens, everyone will end up more informed, and people might use such drugs more selectively and cautiously.

Contribution

JM wrote the first draft of the manuscript. All other authors substantially contributed to edits and revisions of the manuscript. All authors have approved the final version of the manuscript.

Conflict of Interests

JM receives royalties for books about psychiatric drugs, and is a co-applicant on the REDUCE trial, funded by the National Institute of Health Research, evaluating digital support for patients stopping long-term antidepressant treatment. She is co-chairperson of the Critical Psychiatry Network (an informal group of psychiatrists) and a board member of the unfunded organisation, the Council for Evidence-based Psychiatry. Both are unpaid positions. MAH reports being a co-founder of Outro Health which provides digital support for patients in Canada and the US to help stop long-term antidepressant treatment using gradual, hyperbolic tapering. MAH and JM are both co-applicants on the RELEASE trial in Australia evaluating hyperbolic tapering of antidepressants against tapering as usual. He is also an Associate of the International Institute for Psychiatric Drug Withdrawal (IIPDW) and a member of the Critical Psychiatry Network. RC is a Board Member of the International Institute for Psychiatric Drug Withdrawal (IIPDW), this is an unpaid position. TS is co-chairperson of the CPN (an unpaid position). MPH receives royalties from Palgrave Macmillan for a book about antidepressants. Other authors report no potential conflicts of interest.

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