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The serotonin theory of depression: a systematic umbrella review of the evidence

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Abstract

The serotonin hypothesis of depression is still influential. We aimed to synthesise and evaluate evidence on whether depression is associated with lowered serotonin concentration or activity in a systematic umbrella review of the principal relevant areas of research. PubMed, EMBASE and PsycINFO were searched using terms appropriate to each area of research, from their inception until December 2020. Systematic reviews, meta-analyses and large data-set analyses in the following areas measured by imaging or at post-mortem, tryptophan depletion studies, SERT gene associations and SERT gene-environment interactions. Studies of depression associated with physical conditions and specific subtypes of depression (e.g. bipolar depression) were excluded. Two independent reviewers extracted the data and assessed the quality of included studies using the AMSTAR-2, an adapted AMSTAR-2, or the STREGA for a large genetic study. The certainty of study results was assessed using a modified version of the GRADE. We did not synthesise results of individual meta-analyses because they included overlapping studies. The review was registered with PROSPERO (CRD42020207203). 17 studies were included: 12 systematic reviews and meta-analyses, 1 collaborative meta-analysis, 1 meta-analysis of large cohort studies, 1 systematic review and narrative synthesis, 1 genetic association study and 1 umbrella review. Quality of reviews was variable with some

genetic studies of high quality. Two meta-analyses of overlapping studies examining the serotonin metabolite, 5-HIAA, showed no association with depression (largest n = 1002). One meta-analysis of cohort studies of plasma serotonin showed no relationship with depression, and evidence that lowered serotonin concentration was associated with antidepressant use (n = 1869). Two meta-analyses of overlapping studies examining the 5-HT_{1A} receptor (largest n = 561), and three meta-analyses of overlapping studies examining SERT binding (largest n = 1845) showed weak and inconsistent evidence of reduced binding in some areas, which would be consistent with increased synaptic availability of serotonin in people with depression, if this was the original, causal abnormaly. However, effects of prior antidepressant use were not reliably excluded. One meta-analysis of tryptophan depletion studies found no effect in most healthy volunteers (n = 566), but weak evidence of an effect in those with a family history of depression (n = 75). Another systematic review (n = 342) and a sample of ten subsequent studies (n = 407) found no effect in volunteers. No systematic review of tryptophan depletion studies has been performed since 2007. The two largest and highest quality studies of the SERT gene, one genetic association study (n = 115,257) and one collaborative meta-analysis (n = 43,165), revealed no evidence of an association with depression, or of an interaction between genotype, stress and depression. The main areas of serotonin research provide no consistent evidence of there being an association between serotonin and depression, and no support for the hypothesis that depression is caused by lowered serotonin activity or concentrations. Some evidence was consistent with the possibility that long-term antidepressant use reduces serotonin concentration.

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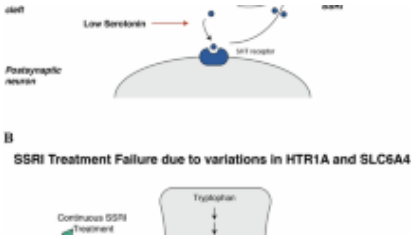

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Introduction

The idea that depression is the result of abnormalities in brain chemicals, particularly serotonin (5-hydroxytryptamine or 5-HT), has been influential for decades, and provides an important justification for the use of antidepressants. A link between lowered serotonin and depression was first suggested in the 1960s [1], and widely publicised from the 1990s with the advent of the Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants [2,3,4]. Although it has been questioned more recently [5, 6], the serotonin theory of depression remains influential, with principal English language textbooks still giving it qualified support [7, 8], leading researchers endorsing it [9,10,11], and much empirical research based on it [11,12,13,14]. Surveys suggest that 80% or more of the general public now believe it is established that depression is caused by a 'chemical imbalance' [15, 16]. Many general practitioners also subscribe to this view [17] and popular websites commonly cite the theory [18].

It is often assumed that the effects of antidepressants demonstrate that depression

must be at least partially caused by a brain-based chemical abnormality, and that the apparent efficacy of SSRIs shows that serotonin is implicated. Other explanations for the effects of antidepressants have been put forward, however, including the idea that they work via an amplified placebo effect or through their ability to restrict or blunt emotions in general [19, 20].

Despite the fact that the serotonin theory of depression has been so influential, no comprehensive review has yet synthesised the relevant evidence. We conducted an 'umbrella' review of the principal areas of relevant research, following the model of a similar review examining prospective biomarkers of major depressive disorder [21]. We sought to establish whether the current evidence supports a role for serotonin in the aetiology of depression, and specifically whether depression is associated with indications of lowered serotonin concentrations or activity.

Methods

Search strategy and selection criteria

The present umbrella review was reported in accordance with the 2009 PRISMA statement [22]. The protocol was registered with PROSPERO in December 2020 (registration number CRD42020207203) (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=207203). This was subsequently updated to reflect our decision to modify the quality rating system for some studies to more appropriately appraise their quality, and to include a modified GRADE to assess the overall certainty of the findings in each category of the umbrella review.

In order to cover the different areas and to manage the large volume of research that

has been conducted on the serotonin system, we conducted an 'umbrella' review. Umbrella reviews survey existing systematic reviews and meta-analyses relevant to a research question and represent one of the highest levels of evidence synthesis available [23]. Although they are traditionally restricted to systematic reviews and meta-analyses, we aimed to identify the best evidence available. Therefore, we also included some large studies that combined data from individual studies but did not employ conventional systematic review methods, and one large genetic study. The latter used nationwide databases to capture more individuals than entire meta-analyses, so is likely to provide even more reliable evidence than syntheses of individual studies.

We first conducted a scoping review to identify areas of research consistently held to provide support for the serotonin hypothesis of depression. Six areas were identified, addressing the following questions: (1) Serotonin and the serotonin metabolite 5-HIAA–whether there are lower levels of serotonin and 5-HIAA in body fluids in depression; (2) Receptors - whether serotonin receptor levels are altered in people with depression; (3) The serotonin transporter (SERT) - whether there are higher levels of the serotonin transporter in people with depression (which would lower synaptic levels of serotonin); (4) Depletion studies - whether tryptophan depletion (which lowers available serotonin) can induce depression; (5) SERT gene – whether there are higher levels of the serotonin transporter gene in people with depression; (6) Whether there is an interaction between the SERT gene and stress in depression.

We searched for systematic reviews, meta-analyses, and large database studies in these six areas in PubMed, EMBASE and PsycINFO using the Healthcare Databases Advanced Search tool provided by Health Education England and NICE (National Institute for Health and Care Excellence). Searches were conducted until December 2020.

We used the following terms in all searches: (depress* OR affective OR mood) AND (systematic OR meta-analysis), and limited searches to title and abstract, since not doing so produced numerous irrelevant hits. In addition, we used terms specific to each area of research (full details are provided in Table S1, Supplement). We also searched citations and consulted with experts.

Inclusion criteria were designed to identify the best available evidence in each research area and consisted of:

1. Research synthesis including systematic reviews, meta-analysis, umbrella reviews, individual patient meta-analysis and large dataset analysis.

2. Studies that involve people with depressive disorders or, for experimental studies (tryptophan depletion), those in which mood symptoms are measured as an outcome.

3. Studies of experimental procedures (tryptophan depletion) involving a sham or control condition.

4. Studies published in full in peer reviewed literature.

5. Where more than five systematic reviews or large analyses exist, the most recent five are included.

Exclusion criteria consisted of:

1. Animal studies.

2. Studies exclusively concerned with depression in physical conditions (e.g. post

stroke or Parkinson's disease) or exclusively focusing on specific subtypes of depression such as postpartum depression, depression in children, or depression in bipolar disorder.

No language or date restrictions were applied. In areas in which no systematic review or meta-analysis had been done within the last 10 years, we also selected the ten most recent studies at the time of searching (December 2020) for illustration of more recent findings. We performed this search using the same search string for this domain, without restricting it to systematic reviews and meta-analyses.

Data analysis

Each member of the team was allocated one to three domains of serotonin research to search and screen for eligible studies using abstract and full text review. In case of uncertainty, the entire team discussed eligibility to reach consensus.

For included studies, data were extracted by two reviewers working independently, and disagreement was resolved by consensus. Authors of papers were contacted for clarification when data was missing or unclear.

We extracted summary effects, confidence intervals and measures of statistical significance where these were reported, and, where relevant, we extracted data on heterogeneity. For summary effects in the non-genetic studies, preference was given to the extraction and reporting of effect sizes. Mean differences were converted to effect sizes where appropriate data were available.

We did not perform a meta-analysis of the individual meta-analyses in each area because they included overlapping studies [24]. All extracted data is presented in Table 1. Sensitivity analyses were reported where they had substantial bearing on

interpretation of findings.

Table 1 Study characteristics and results.

The quality rating of systematic reviews and meta-analyses was assessed using AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews) [25]. For two studies that did not employ conventional systematic review methods [26, 27] we used a modified version of the AMSTAR-2 (see Table S3). For the genetic association study based on a large database analysis we used the STREGA assessment (STrengthening the REporting of Genetic Association Studies) (Table S4) [28]. Each study was rated independently by at least two authors. We report ratings of individual items on the relevant measure, and the percentage of items that were adequately addressed by each study (Table 1, with further detail in Tables S3 and S4).

Alongside quality ratings, two team members (JM, MAH) rated the certainty of the results of each study using a modified version of the GRADE guidelines [29]. Following the approach of Kennis et al. [21], we devised six criteria relevant to the included studies: whether a unified analysis was conducted on original data; whether confounding by antidepressant use was adequately addressed; whether outcomes were pre-specified; whether results were consistent or heterogeneity was adequately addressed if present; whether there was a likelihood of publication bias; and sample size. The importance of confounding by effects of current or past antidepressant use has been highlighted in several studies [30, 31]. The results of each study were scored 1 or 0 according to whether they fulfilled each criteria, and based on these ratings an overall judgement was made about the certainty of evidence across studies in each of the six areas of research examined. The certainty of each study was based

on an algorithm that prioritised sample size and uniform analysis using original data (explained more fully in the supplementary material), following suggestions that these are the key aspects of reliability [27, 32]. An assessment of the overall certainty of each domain of research examining the role of serotonin was determined by consensus of at least two authors and a direction of effect indicated.

Results

Search results and quality rating

Searching identified 361 publications across the 6 different areas of research, among which seventeen studies fulfilled inclusion criteria (see Fig. 1 and Table S1 for details of the selection process). Included studies, their characteristics and results are shown in Table 1. As no systematic review or meta-analysis had been performed within the last 10 years on serotonin depletion, we also identified the 10 latest studies for illustration of more recent research findings (Table 2).

Fig. 1

Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagramme.

Table 2 Recent depletion studies comparing acute tryptophan depletion drink with amino acid balance drink (sham drink) - characteristics and

results.

Quality ratings are summarised in Table 1 and reported in detail in Tables S2–S3. The majority (11/17) of systematic reviews and meta-analyses satisfied less than 50% of criteria. Only 31% adequately assessed risk of bias in individual studies (a further 44% partially assessed this), and only 50% adequately accounted for risk of bias when interpreting the results of the review. One collaborative meta-analysis of genetic studies was considered to be of high quality due to the inclusion of several measures to ensure consistency and reliability [27]. The large genetic analysis of the effect of SERT polymorphisms on depression, satisfied 88% of the STREGA quality criteria [32].

Serotonin and 5-HIAA

Serotonin can be measured in blood, plasma, urine and CSF, but it is rapidly metabolised to 5-hydroxyindoleacetic acid (5-HIAA). CSF is thought to be the ideal resource for the study of biomarkers of putative brain diseases, since it is in contact with brain interstitial fluid [33]. However, collecting CSF samples is invasive and carries some risk, hence large-scale studies are scarce.

Three studies fulfilled inclusion criteria (Table 1). One meta-analysis of three large observational cohort studies of post-menopausal women, revealed lower levels of plasma 5-HT in women with depression, which did not, however, reach statistical significance of $p < 0.05$ after adjusting for multiple comparisons. Sensitivity analyses revealed that antidepressants were strongly associated with lower serotonin levels independently of depression.

Two meta-analyses of a total of 19 studies of 5-HIAA in CSF (seven studies were included in both) found no evidence of an association between 5-HIAA concentrations and depression.

Receptors

Fourteen different serotonin receptors have been identified, with most research on depression focusing on the 5-HT$_{1A}$ receptor [11, 34]. Since the functions of other 5-HT receptors and their relationship to depression have not been well characterised, we restricted our analysis to data on 5-HT$_{1A}$ receptors [11, 34]. 5-HT$_{1A}$ receptors, known as auto-receptors, inhibit the release of serotonin pre-synaptically [35], therefore, if depression is the result of reduced serotonin activity caused by abnormalities in the 5-HT$_{1A}$ receptor, people with depression would be expected to show increased activity of 5-HT$_{1A}$ receptors compared to those without [36].

Two meta-analyses satisfied inclusion criteria, involving five of the same studies [37, 38] (see Table 1). The majority of results across the two analyses suggested either no difference in 5-HT$_{1A}$ receptors between people with depression and controls, or a lower level of these inhibitory receptors, which would imply higher concentrations or activity of serotonin in people with depression. Both meta-analyses were based on studies that predominantly involved patients who were taking or had recently taken (within 1–3 weeks of scanning) antidepressants or other types of psychiatric medication, and both sets of authors commented on the possible influence of prior or current medication on findings. In addition, one analysis was of very low quality [37], including not reporting on the numbers involved in each analysis and using one-sided p-values, and one was strongly influenced by three studies and publication bias was present [38].

The serotonin transporter (SERT)

The serotonin transporter protein (SERT) transports serotonin out of the synapse, thereby lowering the availability of serotonin in the synapse [39, 40]. Animals with an inactivated gene for SERT have higher levels of extra-cellular serotonin in the brain than normal [41,42,43] and SSRIs are thought to work by inhibiting the action of SERT, and thus increasing levels of serotonin in the synaptic cleft [44]. Although changes in SERT may be a marker for other abnormalities, if depression is caused by low serotonin availability or activity, and if SERT is the origin of that deficit, then the amount or activity of SERT would be expected to be higher in people with depression compared to those without [40]. SERT binding potential is an index of the concentration of the serotonin transporter protein and SERT concentrations can also be measured post-mortem.

Three overlapping meta-analyses based on a total of 40 individual studies fulfilled inclusion criteria (See Table 1) [37, 39, 45]. Overall, the data indicated possible reductions in SERT binding in some brain areas, although areas in which effects were detected were not consistent across the reviews. In addition, effects of antidepressants and other medication cannot be ruled out, since most included studies mainly or exclusively involved people who had a history of taking antidepressants or other psychiatric medications. Only one meta-analysis tested effects of antidepressants, and although results were not influenced by the percentage of drug-naïve patients in each study, numbers were small so it is unlikely that medication-related effects would have been reliably detected [45]. All three reviews cited evidence from animal studies that antidepressant treatment reduces SERT [46,47,48]. None of the analyses corrected for multiple testing, and one review was of very low quality [37]. If the results do represent a positive finding that is independent of medication, they would suggest that depression is associated with

higher concentrations or activity of serotonin.

Depletion studies

Tryptophan depletion using dietary means or chemicals, such as parachlorophenylalanine (PCPA), is thought to reduce serotonin levels. Since PCPA is potentially toxic, reversible tryptophan depletion using an amino acid drink that lacks tryptophan is the most commonly used method and is thought to affect serotonin within 5–7 h of ingestion. Questions remain, however, about whether either method reliably reduces brain serotonin, and about other effects including changes in brain nitrous oxide, cerebrovascular changes, reduced BDNF and amino acid imbalances that may be produced by the manipulations and might explain observed effects independent of possible changes in serotonin activity [49].

One meta-analysis and one systematic review fulfilled inclusion criteria (see Table 1). Data from studies involving volunteers mostly showed no effect, including a meta-analysis of parallel group studies [50]. In a small meta-analysis of within-subject studies involving 75 people with a positive family history, a minor effect was found, with people given the active depletion showing a larger decrease in mood than those who had a sham procedure [50]. Across both reviews, studies involving people diagnosed with depression showed slightly greater mood reduction following tryptophan depletion than sham treatment overall, but most participants had taken or were taking antidepressants and participant numbers were small [50, 51].

Since these research syntheses were conducted more than 10 years ago, we searched for a systematic sample of ten recently published studies (Table 2). Eight studies conducted with healthy volunteers showed no effects of tryptophan depletion on mood, including the only two parallel group studies. One study presented effects

in people with and without a family history of depression, and no differences were apparent in either group [52]. Two cross-over studies involving people with depression and current or recent use of antidepressants showed no convincing effects of a depletion drink [53, 54], although one study is reported as positive mainly due to finding an improvement in mood in the group given the sham drink [54].

SERT gene and gene-stress interactions

A possible link between depression and the repeat length polymorphism in the promoter region of the SERT gene (5-HTTLPR), specifically the presence of the short repeats version, which causes lower SERT mRNA expression, has been proposed [55]. Interestingly, lower levels of SERT would produce higher levels of synaptic serotonin. However, more recently, this hypothesis has been superseded by a focus on the interaction effect between this polymorphism, depression and stress, with the idea that the short version of the polymorphism may only give rise to depression in the presence of stressful life events [55, 56]. Unlike other areas of serotonin research, numerous systematic reviews and meta-analyses of genetic studies have been conducted, and most recently a very large analysis based on a sample from two genetic databanks. Details of the five most recent studies that have addressed the association between the SERT gene and depression, and the interaction effect are detailed in Table 1.

Although some earlier meta-analyses of case-control studies showed a statistically significant association between the 5-HTTLPR and depression in some ethnic groups [57, 58], two recent large, high quality studies did not find an association between the SERT gene polymorphism and depression [27, 32]. These two studies consist of by far the largest and most comprehensive study to date [32] and a high-quality meta-

analysis that involved a consistent re-analysis of primary data across all conducted studies, including previously unpublished data, and other comprehensive quality checks [27, 59] (see Table 1).

Similarly, early studies based on tens of thousands of participants suggested a statistically significant interaction between the SERT gene, forms of stress or maltreatment and depression [60,61,62], with a small odds ratio in the only study that reported this (1.18, 95% CI 1.09 to 1.28) [62]. However, the two recent large, high-quality studies did not find an interaction between the SERT gene and stress in depression (Border et al [32] and Culverhouse et al.) [27] (see Table 1).

Overall results

Table 3 presents the modified GRADE ratings for each study and the overall rating of the strength of evidence in each area. Areas of research that provided moderate or high certainty of evidence such as the studies of plasma serotonin and metabolites and the genetic and gene-stress interaction studies all showed no association between markers of serotonin activity and depression. Some other areas suggested findings consistent with increased serotonin activity, but evidence was of very low certainty, mainly due to small sample sizes and possible residual confounding by current or past antidepressant use. One area - the tryptophan depletion studies - showed very low certainty evidence of lowered serotonin activity or availability in a subgroup of volunteers with a family history of depression. This evidence was considered very low certainty as it derived from a subgroup of within-subject studies, numbers were small, and there was no information on medication use, which may have influenced results. Subsequent research has not confirmed an effect with numerous negative studies in volunteers.

Table 3 Modified GRADE ratings for each study and the overall rating of strength of evidence.

Discussion

Our comprehensive review of the major strands of research on serotonin shows there is no convincing evidence that depression is associated with, or caused by, lower serotonin concentrations or activity. Most studies found no evidence of reduced serotonin activity in people with depression compared to people without, and methods to reduce serotonin availability using tryptophan depletion do not consistently lower mood in volunteers. High quality, well-powered genetic studies effectively exclude an association between genotypes related to the serotonin system and depression, including a proposed interaction with stress. Weak evidence from some studies of serotonin 5-HT_{1A} receptors and levels of SERT points towards a possible association between increased serotonin activity and depression. However, these results are likely to be influenced by prior use of antidepressants and its effects on the serotonin system [30, 31]. The effects of tryptophan depletion in some cross-over studies involving people with depression may also be mediated by antidepressants, although these are not consistently found [63].

The chemical imbalance theory of depression is still put forward by professionals [17], and the serotonin theory, in particular, has formed the basis of a considerable research effort over the last few decades [14]. The general public widely believes that depression has been convincingly demonstrated to be the result of serotonin or other chemical abnormalities [15, 16], and this belief shapes how people understand their moods, leading to a pessimistic outlook on the outcome of depression and negative

expectancies about the possibility of self-regulation of mood [64,65,66]. The idea that depression is the result of a chemical imbalance also influences decisions about whether to take or continue antidepressant medication and may discourage people from discontinuing treatment, potentially leading to lifelong dependence on these drugs [67, 68].

As with all research synthesis, the findings of this umbrella review are dependent on the quality of the included studies, and susceptible to their limitations. Most of the included studies were rated as low quality on the AMSTAR-2, but the GRADE approach suggested some findings were reasonably robust. Most of the non-genetic studies did not reliably exclude the potential effects of previous antidepressant use and were based on relatively small numbers of participants. The genetic studies, in particular, illustrate the importance of methodological rigour and sample size. Whereas some earlier, lower quality, mostly smaller studies produced marginally positive findings, these were not confirmed in better-conducted, larger and more recent studies [27, 32]. The identification of depression and assessment of confounders and interaction effects were limited by the data available in the original studies on which the included reviews and meta-analyses were based. Common methods such as the categorisation of continuous measures and application of linear models to non-linear data may have led to over-estimation or under-estimation of effects [69, 70], including the interaction between stress and the SERT gene. The latest systematic review of tryptophan depletion studies was conducted in 2007, and there has been considerable research produced since then. Hence, we provided a snapshot of the most recent evidence at the time of writing, but this area requires an up to date, comprehensive data synthesis. However, the recent studies were consistent with the earlier meta-analysis with little evidence for an effect of tryptophan depletion on mood.

Although umbrella reviews typically restrict themselves to systematic reviews and meta-analyses, we aimed to provide the most comprehensive possible overview. Therefore, we chose to include meta-analyses that did not involve a systematic review and a large genetic association study on the premise that these studies contribute important data on the question of whether the serotonin hypothesis of depression is supported. As a result, the AMSTAR-2 quality rating scale, designed to evaluate the quality of conventional systematic reviews, was not easily applicable to all studies and had to be modified or replaced in some cases.

One study in this review found that antidepressant use was associated with a reduction of plasma serotonin [26], and it is possible that the evidence for reductions in SERT density and 5-HT_{1A} receptors in some of the included imaging study reviews may reflect compensatory adaptations to serotonin-lowering effects of prior antidepressant use. Authors of one meta-analysis also highlighted evidence of 5-HIAA levels being reduced after long-term antidepressant treatment [71]. These findings suggest that in the long-term antidepressants might produce compensatory changes [72] that are opposite to their acute effects [73, 74]. Lowered serotonin availability has also been demonstrated in animal studies following prolonged antidepressant administration [75]. Further research is required to clarify the effects of different drugs on neurochemical systems, including the serotonin system, especially during and after long-term use, as well as the physical and psychological consequences of such effects.

This review suggests that the huge research effort based on the serotonin hypothesis has not produced convincing evidence of a biochemical basis to depression. This is consistent with research on many other biological markers [21]. We suggest it is time to acknowledge that the serotonin theory of depression is not empirically substantiated.

Data availability

All extracted data is available in the paper and supplementary materials. Further information about the decision-making for each rating for categories of the AMSTAR-2 and STREGA are available on request.

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Contributions

JM conceived the idea for the study. JM, MAH, MPH, TS and SA designed the study. JM, MAH, MPH, TS, and SA screened articles and abstracted data. JM drafted the first version of the manuscript. JM, MAH, MPH, TS, SA, and REC contributed to the manuscript's revision and interpretation of findings. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Ethics declarations

Competing interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). SA declares no conflicts of interest. MAH reports being co-founder of a company in April 2022, aiming to help people safely stop antidepressants in Canada. MPH reports royalties from Palgrave Macmillan, London, UK for his book published in December, 2021, called "Evidence-biased Antidepressant Prescription." JM receives royalties for books about psychiatric drugs, reports grants from the National Institute of Health Research outside the submitted work, that 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. TS is co-chairperson of the Critical Psychiatry Network. RC is an

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