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## COMMENT OPEN



# A leaky umbrella has little value: evidence clearly indicates the serotonin system is implicated in depression

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A recent “umbrella” review examined various biomarkers relating to the serotonin system, and concluded there was no consistent evidence implicating serotonin in the pathophysiology of depression. We present reasons for why this conclusion is overstated, including methodological weaknesses in the review process, selective reporting of data, over-simplification, and errors in the interpretation of neuropsychopharmacological findings. We use the examples of tryptophan depletion and serotonergic molecular imaging, the two research areas most relevant to the investigation of serotonin, to illustrate this.

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Moncrieff et al. [1] aimed to synthesise and evaluate evidence on serotonin (5-hydroxytryptamine, 5-HT) in the context of the monoamine hypothesis of depression, into an umbrella review. They concluded, “there is no convincing evidence that depression is associated with, or caused by, lower serotonin concentrations or activity.” The review included investigations of 5-HT and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in “body fluids”, 5HT<sub>1A</sub> receptor and serotonin transporter protein (SERT) availability in imaging and post-mortem studies, investigations of SERT gene polymorphisms, interactions between SERT and stress in depression, and effects of tryptophan depletion on mood. Given the complexity of the serotonergic system and importance of the subject, great care and transparency are essential when reviewing, synthesising and interpreting such data. Clear guidance is available for conducting umbrella reviews, cited in the current review [2].

Putting aside concerns about the antiquated concept of single-gene polymorphisms and the current view of polygenetic architecture of Major Depressive Disorder (MDD), and discussion of antidepressant efficacy in a review that did not present any

such data, we highlight substantial methodological weaknesses that make interpretation of the current review challenging.

## METHODOLOGICAL WEAKNESSES IN THE REVIEW

The evidence synthesis approach adopted [1] has several inherent methodological weaknesses. Whilst umbrella reviews typically split their study-unit into previous meta-analyses/systematic reviews of primary studies vs. umbrella reviews of meta-analyses/systematic reviews (also termed “meta-umbrella” reviews) [3], the authors summarised these different study units together, appearing to include some primary studies at the expense of others (see below, exclusion of Yatham et al. [4], for example). This makes comparative interpretation of effect sizes potentially unreliable. This is complicated by heterogeneity of the summarised measures (genetic, neuroimaging, biochemical) and methodological choices, such as not synthesising ‘results of individual meta-analyses because they included overlapping studies’ [1]. This is in contrast to umbrella reviews that have selected non-overlapping primary studies from overlapping meta-analyses [3]. Validated criteria are established to

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classify levels of evidence in umbrella reviews of biomarkers, to avoid selective reporting and post-hoc manipulation [3]. The authors did not use these: interpretation of evidence was undertaken with a mixture of metrics, including a “modified” version of GRADE quality assessment, introduced in a *post-hoc* protocol amendment. GRADE initially categorises observational studies as “low”, and these are downgraded or upgraded based on pre-specified criteria. The authors rate certainty of evidence determined “by consensus of at least two authors and a direction of effect indicated” [1]. The authors cite an original meta-analysis [5] to justify their choice, but there is little similarity between the two studies. Criteria in the current review were unified statistical analysis of original data, confounding by antidepressant use adequately excluded where effect found, outcomes of interest pre-specified, consistent results, little likelihood of publication bias (in funnel plots or tests) and large sample ( $n > 500$ , non-genetic studies,  $>10,000$  for genetic studies). It is unclear why confounding effects of antidepressants would not apply to all studies, i.e. not just where positive outcomes were seen: antidepressants are as likely to confound studies with negative results (a point acknowledged by the authors in the review).

### A DEPLETED ACCOUNT OF TRYPTOPHAN DEPLETION

These methodological weaknesses are manifested in the consideration of tryptophan depletion studies. The authors include a meta-analysis, systematic review and 10 recent studies involving healthy volunteers, but missed a clinical and molecular imaging study, which showed an effect in people with MDD [4]. The authors state, “studies involving people diagnosed with depression showed slightly greater mood reduction following tryptophan depletion...but most participants were taking antidepressants and participant numbers were small.” However, in the meta-analysis they cite [6], the effect size for the effects of tryptophan depletion on mood in depressed people not taking antidepressants, from 8 samples, was large (Hedge’s  $g = -1.9$  (95% CIs  $-3.02$  to  $-0.78$ ). Admittedly, a number of these studies came from the same group, and confidence intervals were wide (removal of a potential outlier decreased Hedge’s  $g$  to  $-1.06$  (95% CIs  $-1.83$  to  $-0.29$ ). Notwithstanding this, omission of these data in the current review is questionable. A more accurate interpretation is that tryptophan depletion studies suggest a role for 5-HT in people vulnerable to depression and in those remitted on SSRI treatment. In contrast, by citing a series of individual negative studies in healthy participants, the authors give the impression tryptophan depletion has no effect.

The authors also omit several studies included in 2 meta-analyses [7, 8] of circulating tryptophan concentrations, which directly influence central serotonin synthesis. This is far more relevant to CNS serotonin function than serotonin and 5-HIAA levels in body fluids, which are covered in the review. L-tryptophan plasma concentrations show, after adjusting for publication bias, significant decrease in people with MDD (Hedge’s  $g = -0.45$ , 95% CIs,  $-0.66$  to  $-0.23$ ), with a large effect size of  $g = -0.84$  (95% CIs  $-1.27$  to  $-0.4$ ) in unmedicated people [7]. Furthermore, using the authors’ bespoke criteria for certainty, this would presumably score quite well given that it fulfils most criteria, except pre-specification of outcome measures. The authors were aware of this meta-analysis as they state they excluded it from the section on serotonin in body fluids.

### SIMPLISTIC (MIS)INTERPRETATION OF MOLECULAR IMAGING EVIDENCE

The authors misrepresent and misinterpret molecular imaging data regarding both 5-HT<sub>1A</sub> receptor and serotonin transporter protein (SERT) binding. They cite a meta-analysis involving 10 5-HT<sub>1A</sub> receptor studies [9], most of which used BP<sub>ND</sub>, an outcome measure of receptor availability not requiring arterial input, which assumes there exists a “reference region” with no specific binding

in MDD and controls; [10] moreover, 5 studies included people with bipolar disorder or post-partum depression. The authors also make the simplistic interpretation that reduced binding would suggest increased synaptic 5-HT. However, decreased binding can be the result of several factors, including decreased receptor density or affinity. The authors state, “5HT<sub>1A</sub> receptors, known as autoreceptors”, mistakenly assuming 5HT<sub>1A</sub> receptors are exclusively pre-synaptic autoreceptors. Most are post-synaptic 5-HT<sub>1A</sub> heteroreceptors. Diminished availability of post-synaptic 5-HT<sub>1A</sub> receptors in unmedicated depression would be consistent with lowered 5-HT neurotransmission. Whilst most studies report lower 5-HT<sub>1A</sub> binding, higher binding is seen if a more sophisticated outcome measure with arterial input is used, and lower binding noted when the reference region approach taken in most studies is used. This is a replicated finding in people free of antidepressants for a period of years [10]. None of this complexity is acknowledged in the review.

### AN UNCERTAIN APPROACH TO SERT BINDING

The authors conclude, in appraising three reviews of SERT binding, that the “areas in which effects were detected were not consistent”. However, findings in a number of brain regions are consistent, with SERT reductions reported in people with MDD in all reviews. This is seen in Table 1 in the current review. A review they describe as a meta-analysis (and included twice, for 5HT<sub>1A</sub> and SERT studies) appears only to pool values, and all reviews analysed different brain regions. This question would have been legitimately answered by a conventional umbrella review, where included studies are extracted and meta-analysed. Furthermore, the modified GRADE scoring appears unclear- in one review [11], antidepressant use was an exclusion in context of a positive outcome, though scored as 0. Publication bias is reported as a test statistic, though again scored 0. The authors make another oversimplification, assuming lower SERT binding is associated with higher synaptic 5-HT. The reference cited presents other models, including lower SERT binding associated with lower 5-HT [12]. In-vivo studies have failed to show a relationship between SERT and endogenous serotonin [11, 13], and the relationship between decreased SERT and MDD could be explained through mechanisms such as decreased SERT expression in neurons and/or decreased density of serotonergic neurons [11]. The authors’ explanation is that reduced SERT in meta-analyses is due to prior antidepressant treatment but appear unaware of reductions reported in drug-naïve populations [14]. They also appear to have missed the fact that 149 of 364 people in one of the cited meta-analyses were drug naïve [15], and therefore their conclusion that these meta-analytic findings were due to antidepressants is difficult to follow.

When commenting on the molecular imaging literature and its interpretation, it is worth noting individual studies, including a PET study which suggested decreased serotonin synthesis in medication-free people with MDD compared to controls [16], and a recent [<sup>11</sup>C] Cimbi-36 PET study of serotonin release with amphetamine challenge [17], which suggested reduced serotonin release capacity in 17 antidepressant-free people with a major depressive episode, compared to controls. Whilst the latter study was not available for the original researchers to include, it emphasises that curtailing research in this area is premature.

Furthermore, almost all effective antidepressants have an effect on the 5-HT system (including ketamine, in pre-clinical models [18], and 5-HT agonism remains one of the main mechanisms for the antidepressant qualities of psychedelics.

### CONCLUSION

To summarise, the methodology is inconsistent with an umbrella review, with substantial bias created by the authors’ chosen quality

criteria, selective reporting, and interpretation of results. There is an underappreciation of the complexities of neuroscience and neuropsychopharmacology, and it is therefore impossible for the reader to draw valid or reliable conclusions.

A more accurate, constructive conclusion would be that acute tryptophan depletion and decreased plasma tryptophan in depression indicate a role for 5-HT in those vulnerable to or suffering from depression, and that molecular imaging suggests the system is perturbed. The proven efficacy of SSRIs in a proportion of people with depression lends credibility to this position.

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## AUTHOR CONTRIBUTIONS

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SJ has received honoraria for educational talks given on antipsychotics for Janssen, Lundbeck and Sunovion. He has given an educational talk for Boehringer Ingelheim on causes of schizophrenia. He has received honoraria as an adviser for LB pharmaceuticals Inc. in regard to antipsychotic medication. He is a Council Member for the British Association for Psychopharmacology and sat as a panel member for the Wellcome Trust. DSB is President of the British Association for Psychopharmacology (unpaid), Editor of Human Psychopharmacology (editors fee), Medical Patron of Anxiety UK (unpaid), consultancy to Idorsia (July 2020, unpaid: not relevant to consideration of subject matter of paper). MBrowning has received travel expenses from Lundbeck for attending conferences, and has acted as a consultant for J&J, Novartis, P1vital Ltd and CHDR. He owns shares in P1vital Products Ltd. AJC is President of The International Society for Affective Disorders (unpaid) and in the last three years has received honoraria for educational activities and/or consulting from Janssen, COMPASS Pathways and Medscape, and research grant support from the Medical Research Council (UK), Wellcome Trust (UK), the National Institute for Health Research (UK) and Protexin Probiotics International Ltd. PC is co-founder of Tetricus Labs (unrelated to this work). DE has received funding from NIHR and is scientific advisor for Mydecine, Enttheon Biomedical, Clerkenwell Health, Smallpharma Ltd and Field Trip Health Ltd. PFP has received research funds or personal fees from Lundbeck, Angelini, Menarini, Sunovion, Boehringer Ingelheim, Mindstrong, Proxym Science, outside the current study. GMG is a NIHR Emeritus Senior Investigator and Chief Medical Officer at Compass pathways, holds shares in Compass pathways, P1vital and P1vital products and has served as consultant, advisor or CME speaker in the last 3 years for Beckley Psytech, Boehringer Ingelheim, Clerkenwell Health, Compass pathways, Evapharma, Janssen, Lundbeck, Medscape, Novartis, Ocean Neuroscience, P1vital, Servier. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. ODH is a part-time employee and stock holder of Lundbeck A/s. He has received investigator-initiated research funding from and/or participated in advisory/ speaker meetings organised by Angelini, Autifony, Biogen, Boehringer-Ingelheim, Eli Lilly, Heptares, Global Medical Education, Invivo, Janssen, Lundbeck, Neurocrine, Otsuka, Sunovion, Recordati, Roche and Viatris/ Mylan. ODH has a patent for the use of dopaminergic imaging. MFJ has within the last 3 years received honoraria for lectures or consulting from Janssen, Lundbeck, EMS and Daiichi-Sankyo. MFJ has received funding from the Wellcome Innovator scheme “The first in-human, randomised, double-blinded, placebo-controlled study to investigate the safety and tolerability, PK and PD of oral ketamine in HV. RL has received honoraria for ad hoc speaking or advising/ consulting, or received research funds, from: Asia-Pacific Economic Cooperation, Bausch, BC Leading Edge Foundation, Brain Canada, Canadian Institutes of Health Research, Canadian Network for Mood and Anxiety Treatments, CAN-BIND Solutions, Carnot, Grand Challenges Canada, Healthy Minds Canada, Janssen, Lundbeck, Lundbeck Institute, Michael Smith Foundation for Health Research, MITACS, Myriad Neuroscience, Ontario Brain Institute, Otsuka, Pfizer/Viatris, Sanofi, Unity Health,

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speaker or advisory boards for, or has received research grants from, Abbvie, Alkermes, Allergan, Otsuka, Sumitomo Dainippon Pharma, GlaxoSmithKline, Intracellular Therapies, Merck, Sanofi, and Sunovion in the last 3 years. AHY is Editor of Journal of Psychopharmacology and Deputy Editor, BJPsych Open, Paid lectures and advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Boehringer Ingelheim, Eli Lilly, LivaNova, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, COMPASS, Sage, Novartis, Neurocentrx Principal Investigator in the Restore-Life VNS registry study funded by LivaNova. Principal Investigator on ESKETINTRD3004: "An Open-label, Long-term, Safety and Efficacy Study of Intranasal Esketamine in Treatment-resistant Depression." Principal Investigator on "The Effects of Psilocybin on Cognitive Function in Healthy Participants" Principal Investigator on "The Safety and Efficacy of Psilocybin in Participants with Treatment-Resistant Depression (P-TRD)" UK Chief Investigator for Novartis MDD study MJJ821A12201. Grant funding (past and present): NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); NIHR (UK). Janssen (UK) EU Horizon 2020. No shareholdings in pharmaceutical companies. RZ is a private healthcare provider, has received honoraria for talks by Janssen & Lundbeck, is a co-I on a Livanova-funded neurostimulation study, is affiliated with the D'Or Institute for Research and Education, and has collaborated with digital health companies EMIS PLC and Depsee Ltd, Alloc Modulo. All other authors declare no competing interests.

## ADDITIONAL INFORMATION

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