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

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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].

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