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Antidepressants and the serotonin hypothesis of depression

Antidepressants remain an effective treatment for depression, even without the "chemical imbalance" explanation

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A recent umbrella review of evidence for the serotonin theory of depression[1] was 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 use of selective serotonin reuptake inhibitor (SSRI) antidepressants by millions of people.[2-5]

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

The polarising debate that ensued risks undermining the evidence based treatment of depression and causing harm to people who take or need SSRI antidepressants. Critics of the review and its coverage noted that study selection was incomplete, as an omitted 2021 meta-analysis had concluded that changes in blood biochemistry, notably of L-tryptophan, were associated with depression.[6] The umbrella review was dismissed as nothing new and limited because peripheral and indirect measures of serotonin concentration or activity tell us nothing about activity at receptors between neurons 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 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 experts' dismissal of the legitimate concerns of patients about medication on the other.

Clinical response

How should patients and clinicians navigate these challenges? First and foremost, good evidence from randomised controlled trials shows 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 because of 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 with around 10% taking placebos.[14]

However, the review discusses an important point—that most of the public believes the chemical imbalance theory is established,[15] and this is probably because general practitioners use it to justify prescribing antidepressants, although the only evidence cited to support this assertion was a small online survey.[16] While most GPs surveyed acknowledged 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. 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 make it more difficult to come 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 will necessarily need long term treatment.

Open and honest discussion with patients about the remaining uncertainties is essential. We do not know why antidepressants work well for some people and not others, or why they cause harm to some people, not others. Research into their biological and psychosocial mechanisms of action must continue. Trial evidence makes clear that the effect of antidepressants is on average modest.[10] The National Institute for Health and Care Excellence (NICE) therefore 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 that people with more severe depression are given a combination of antidepressant and psychological treatment.[12]

NICE recommends that clinicians advise people taking antidepressants for a first episode to take them

for at least six months after recovery.[12] Roughly half of patients treated for nine months or more may be able to taper off antidepressants without relapsing and needing to restart.[20] People needing treatment for a second episode of depression are at greater risk of relapse after discontinuation, particularly if symptoms persist that are serious enough to impair daily activities, or their depression has an ongoing underlying cause. 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. An initial time frame for treatment should therefore 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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