Why it is important to discuss what antidepressants do

Joanna Moncrieff, Professor of Critical and Social Psychiatry[1]

Mark Horowitz, Honorary Clinical Research Fellow in Psychiatry[1]

[1] Division of Psychiatry, University College London, Maple House,149 Tottenham Court Rd, London W1T 7NF.

Email for correspondence: j.moncrieff@ucl.ac.uk

Twitter handles: @joannamoncrieff, @markhoro

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Dear Editor

We would like to respond to the suggestion that we over-stepped the data in discussion of the relevance of our serotonin paper to antidepressant use.[1] The serotonin hypothesis was propagated by drug companies and academics as a rationale for why people should take antidepressants. It is still widely disseminated,[2] but it turns out the evidence is unconvincing. No other biological hypotheses are proven or accepted.[3]

If there is no conclusive evidence that antidepressants work by reversing an underlying abnormality, we must consider other plausible explanations for how they might work. We know antidepressants, like other psychoactive drugs, produce more or less subtle mental changes[4] including emotional numbing.[5] These are likely to impact depressive symptoms and may , along with physical effects, produce amplified placebo effects (which are not refuted by the paper cited, since there is good evidence of unblinding[6] and expectation effects in antidepressant studies).[7] Currently, we suspect few patients are given this information.

The antidepressant trials referred to routinely demonstrate a drug-placebo difference of less than 2 points on the 52-point HAM-D scale,[8] a difference thought to be clinically unimportant.[9] The recent FDA modelling exercise was exploratory and probabilistic and does not exclude mental alterations or amplified placebo effects as an explanation for the slightly different, though substantially overlapping distributions of antidepressant and placebo response.[10]

Understanding that antidepressants produce mental and physical alterations that may account for their effects has quite different implications from the idea that they work by reversing an underlying abnormality, which makes the use of drugs seem necessary and reassuring. Many

people might have made different decisions about using antidepressants if they had not been led to believe this narrative.

False claims were also used to promote Oxycontin ('not addictive for people in pain'). We need to recognise the influence of drug companies on medical discourse and the effect of hiring of academics as drug advocates to avoid repeating such mistakes. Similar narratives of a drug reversing speculative biological abnormalities are currently being employed to promote the use and development of various new 'antidepressants' including esketamine[11] and opioids.[12]

References

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Competing interests: JM is a co-applicant on the NIHR-funded REDUCE trial testing internet and telephone support for people wanting to come off long term antidepressants. She receives royalties from books she has written about psychiatric drugs. JM and MH are co-Investigators on the RELEASE trial in Australia investigating supported, gradual, hyperbolic tapering of antidepressants. MH is a co-founder of Outro Health which supports people who wish to stop unnecessary antidepressant medication in Canada and the US using gradual, hyperbolic tapering.