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Personal Perspective on the Systematic Review of Serotonin Imbalance Hypothesis for depression and Mechanism of Action for Antidepressants

An Interview with Trainee Psychiatrist Mark Horowitz

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ABSTRACT
Fauzia Khan meets Dr Mark Horowitz, Trainee Psychiatrist and Clinical Research Fellow in the NHS. Mark talks about his journey into psychiatry, his personal experience of using antidepressants and the withdrawal effects he experienced. Mark also discusses his research interests and the recent umbrella systematic review he co-authored with Professor Joanna Moncrieff on the serotonin theory of depression. [1]

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Tell me about your background and journey into psychiatry.
I grew up in Sydney, Australia and come from a very neurotic Jewish family – similar to those portrayed in Woody Allen's films. I decided to become a psychiatrist early in medical school, aiming to fix my family and myself. Medical school did not suit me very well, and I was miserable, leading to my being diagnosed with depression and prescribed antidepressants. I was also interested in neuroscience, the mind, and psychoanalysis, so I think it was inevitable that I ended up in psychiatry. In the early 2010s, I undertook a PhD looking at the biology of depression in the brain using a model of stem cells from the human brain. I was interested in stress, stress hormones, and why antidepressants work, and as I was also on antidepressants at the time, I was interested in working out whether we could improve these drugs.

As well as researching the neurobiology of depression, the pharmacology of antidepressants, and how antidepressants work, you also have personal experience of using antidepressants

Unhappy in medical school, I had been diagnosed with depression, and at the time, I was reading many self-help books on cognitive behaviour therapy (CBT) but did not find them helpful enough. I was aware of people around me taking antidepressants. Through lectures, I had heard that they were effective for depression, so I visited my doctor in Sydney. Following a short consultation, I was told that antidepressants would be helpful. I remember being excited about taking medication to improve my mood because I felt down, depleted and pessimistic. I thought this medication would be the solution to these problems. In the first few months of taking the antidepressants, I was experiencing a lot of side effects: I felt dizzy, 'out of it, and woozy – it felt like a mild version of recreational drugs. I didn't think these drugs suited me and so I returned to my doctor to be prescribed a different antidepressant. I had similar side effects with this, which made me feel nauseous and funny, so I went back to my doctor for the third time. However, I continued experiencing the same side effects and decided this was as good as it would get. I'm unsure if the drugs helped my mood, but I thought the side effects showed that the drug was quite potent and must be doing something, so I accepted them and stayed on them for the next two decades.

You speak about the withdrawal affects you experienced from taking antidepressants, and much of your work indeed centres around this

Over the next few years, after commencing antidepressants, I experienced many health problems. I found that I was constantly tired and had great trouble with my concentration and memory. I had always had a good memory. I was academically inclined, had done well in exams, and got into medical school with a scholarship. However, in the period after starting antidepressants, I found myself increasingly unable to stay awake during the day. I would sneak away during class, my placements in the hospital to have naps in the bathroom or on patient examination tables, or I would go to my car to sneak naps. I had trouble focusing in lectures, and my memory was not what it once was. I come from a very medical family, we had a lot of faith in doctors, so I went to my doctor, who diagnosed me with narcolepsy, a sleeping disorder that makes you tired during the day. The specialist explained the issues I was having with my memory and concentration were due to this condition. I was prescribed medications for narcolepsy, including stimulant medication, which made me anxious, so I took more drugs to manage my anxiety. My diagnoses of depression and narcolepsy had a very significant effect on my life. I ended up working part-time because I was so tired, and it ended up affecting my relationships. I was very insecure in my ability to keep working, which greatly affected my self-image and self-confidence. I ended up undertaking a PhD partly to give myself more flexibility in my time so that I could nap; I found it challenging to keep up with the intense daily schedules of being a doctor. These symptoms of tiredness, poor concentration and memory problems played a huge role in my life for over a decade.

Towards the end of my PhD, I came across a paper discussing withdrawal symptoms from antidepressants, which I hadn't heard about before. I was shocked because I thought drugs that cause withdrawal symptoms couldn't be very healthy for you, drugs like Valium(r) or opioids like Oxycontin. I thought I was not sure I should be on a drug that causes withdrawal symptoms, so I decided to try and come off them while I was writing up my PhD. To that end, I started researching all the academic papers about coming off antidepressants and browsing Google. I found a mixture of different information about the time it would take to come off antidepressants. I also came across people saying that being on antidepressants caused them to experience symptoms of tiredness, memory and concentration problems. I did then try to go off them over about four months. However, things became very disturbed then - I had great trouble sleeping and started having panic attacks.

I would wake up in the morning in sheer terror of feeling as though I had been chased by a wild animal. It was the first time in my life that I thought life was not worth living anymore because I was in a constant state of panic. Along with this were physical symptoms like dizziness, and I sensed that things were not real. A feeling, unlike anything I had ever experienced before, so I was sure these were withdrawal effects. My experience became so distressing that I moved back from London to my family's house in Sydney. It was the most disturbing experience of my life, and I ended up going back on the medication because I just needed it to end.

When I restarted the drug, the withdrawal effects took a few weeks to subside. I was too frightened to try again for a long while after that experience. But four years ago, I decided to try stopping again, taking a much slower approach than before. After more gradual reductions, I noticed that overall, I felt less tired, and my concentration and memory improved. And that process made me strongly suspect that the symptoms I had been experiencing for years were due to the medication I had been on and were very unlikely due to narcolepsy, which I think may have been a misdiagnosis. I am still in the process of coming off medication. I also wrote about the principles I learned, which I published in *The Lancet Psychiatry*. Since then, my research and clinical practice have focused on how to stop antidepressants and other psychiatric medications safely.

You were involved with the recent systematic umbrella review led by Professor Joanna Moncrieff entitled 'The serotonin theory of depression: a systematic umbrella review of the evidence. [1]

A prevalent hypothesis in the 1960s was that low levels of the neurotransmitter serotonin might cause depression. This hypothesis was amplified and widely propagated in the 1980s and 1990s when the pharmaceutical companies first marketed their drugs SSRIs (selective serotonin reuptake inhibitors) that increase levels of serotonin. If low serotonin levels cause depression, taking a medication that increases serotonin makes sense. There were advertisements in the United States and education for doctors. Psychiatrists wrote books and articles about the hypothesis, which influenced further research. It was an extremely successful message because surveys in some Western countries demonstrated that 85-90% of the public think depression is due to a chemical imbalance (the colloquial term for the serotonin hypothesis).

There has been a lot of academic debate in the last two decades about whether there is robust evidence to support this hypothesis. We explored significant areas of research that supported the serotonin hypothesis via a systematic review. We investigated serotonin levels in the blood and the cerebrospinal fluid in patients with depression compared to healthy volunteers, amongst other measures of serotonin activity.

We found that serotonin levels were variable in different cohorts. People taking antidepressants had lower serotonin levels after long-term use, but we found no consistent evidence of low serotonin in people with clinical depression. We found no relationship between low serotonin levels and depression in the last 50 years of research.

What are the implications of this review, how can it be put into practice?

We conclude that we should no longer tell patients that they have a chemical imbalance or low serotonin levels. Some psychiatrists believe that the chemical imbalance theory helps to reduce stigma and encourages patients to take their medication. However, we must be open and transparent with our patients about the evidence, which shows that depression is unlikely to be causally related to low serotonin.

The review seems to have been positively received by many; however, it has also generated some critique. How would you respond?

Many psychiatrists have agreed that the robust research evidence does not support the idea that low serotonin causes depression, and that this was not news to them. However, this is in stark contrast to how shocking our paper was to the public. It is now one of the 400 most shared scientific articles out of 21 million published, reflecting this paper's interest among the public and the general medical community.

We should reflect on how much the messaging by the pharmaceutical industry influences what doctors and the public think. In some ways, this is reminiscent of the scandal with 'Purdue pharma and OxyContin' -in that this involved the spread of misinformation (in the case of OxyContin that it was not an addictive substance) through paid academics.[2] If we do not take stock of this lesson, we are bound to repeat it. Indeed, some academics are now discussing the 'glutamate hypothesis of depression'[3] related to the antidepressant agent, Esketamine (Spravato).[4]

Millions have been historically misinformed about the likely cause of their depression, leading them to inappropriate treatment choices, a self-perception of being emotionally fragile, and a pessimistic outlook on their chance for recovery.

As the psychiatric community, I think we owe people an apology for the misinformation.

Some experts have responded to our paper, arguing that despite the serotonin hypothesis not being supported by evidence, antidepressants are still effective interventions. Many people taking antidepressants get better, but whether they 'work' or not is contested. Antidepressants reduce depression scores slightly more than placebo on average, but the difference is slight: 2 points on a 52-point depression scale. Analyses of patient responses have determined that this is not a big enough difference to be noticeable by patients or doctors. At the same time, the side effects and other, more subtle psychological or physiological changes are evident and may even falsely amplify the placebo effects.

Further, the studies of antidepressants last for 6-8 weeks while people use these drugs for months, years and even decades, and we know drugs (especially those that cause withdrawal) will have a diminishing impact over time. We also know that research funding and publication are often biased against work that is either inconclusive or does not demonstrate a positive response to an intervention.

The mechanism of action of a drug is important when we are thinking of its application. We should be cautious about long term treatment with antidepressants based on short-term trial data.

There are alternative hypotheses on the mechanism of action for antidepressants– i.e. by increasing neurogenesis, reducing inflammation or affecting neurotransmitters other than serotonin. Many of these hypotheses were derived from animal studies or cells, yet to be demonstrated in humans.

But rather than propagating an unproven hypothesis for the mechanism of action of antidepressants, there are more obvious explanations how they might affect our thoughts and feelings. Antidepressants are psychoactive chemicals – that cross the blood-brain barrier and influence our thoughts and feelings. An example of a commonly used psychoactive chemical is alcohol which makes people feel relaxed and merry and which can help reduce inhibition in people with social anxiety.

Antidepressants do not demonstrate similar subjective effects as alcohol ingestion, with effects which can vary based on a specific chemical compounds. Some cause sedation, and some cause arousal. But one common outcome is numbing emotions – which occurs in 50% of people dose-dependently. Such numbing might be experienced as a relief by people in the middle of emotional turmoil. However, we regard drugs that act by numbing as very different from those that fix an underlying chemical problem. For example we know other drugs that alter brain chemistry, such as alcohol and recreational drugs, can impair concertation, sleep and lead to withdrawal effects when used for prolonged periods- similar concerns also exist for antidepressants. [5,6]

Lastly, one response to our work has been that if low serotonin does not cause depression, what is the underlying cause? We know more about what causes depression than is often thought. The number of stressors in life – job loss, relationship breakdown, physical illness, etc. – strongly predicts who will become depressed. An overemphasis on looking for the chemical equation of depression may have distracted us from its social causes and solutions. We are perhaps making a category error and mistaking problems of the mind for issues in the brain.

And how would you respond to those that take antidepressants and find them beneficial and effective?

I'm very happy for them if they find something that helps them. I would suggest other ways of understanding why these drugs might be beneficial and effective that differ from the chemical imbalance theory. I don't think they're helpful because they rectify an underlying chemical imbalance. They may be beneficial because of either placebo effects, which are essentially about hope, or because they have a numbing effect which can be helpful to quieten down difficult emotions and thoughts.

Sometimes people believe they need antidepressants because they feel terrible when they try to stop them, and that's not proof that antidepressants are needed. Indeed, withdrawal effects are common and easy to mistake for a relapse. Withdrawal symptoms from antidepressants can include anxiety, trouble sleeping, depressed mood, and insomnia and often overlap with symptoms of depression.

However, we recognise these symptoms as withdrawal symptoms because even people taking antidepressants for non-mental health reasons, such as neuropathic pain or menopause, can experience the same withdrawal symptoms. So, feeling worse after stopping antidepressants is not necessarily a sign that you need the antidepressants. It may just be a sign that you must stop them more carefully (slower and down to lower doses than is usually done).

There is now updated guidance from the Royal College of Psychiatrists and the UK National Institute for Clinical Excellence (NICE) on safely tapering antidepressants over months or longer. Many people have managed to wean off successfully. [7]

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About Mark Horowitz

Dr Mark Horowitz (BA, BSc, MA, GDPsych, MBBS (Hons), PhD) is a Honorary Clinical Research Fellow in Psychiatry at University College London. He is a trainee psychiatrist and has completed a PhD in the neurobiology of antidepressants and depression at the Institute of Psychiatry at King's College London. His personal experience of the difficulty in coming off antidepressants led to an interest in the little understood field of de-prescribing in psychiatry, and the balance of harms and benefits of psychiatric medication. He has published papers on this topic in The Lancet Psychiatry, JAMA Psychiatry and other scientific journals. He authored the Royal College of Psychiatry guidance on 'Stopping antidepressants." He is Associate Editor of Therapeutic Advances in Psychopharmacology and is guest editing a special edition of this journal on 'Discontinuing psychotropic medications.' Twitter handle: @markhoro Website: markhorowitz.org