



## EDITORIALS

# Serotonin and depression

The marketing of a myth

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The serotonin reuptake inhibiting (SSRI) group of drugs came on stream in the late 1980s, nearly two decades after first being mooted. The delay centred on finding an indication. They did not have hoped for lucrative antihypertensive or antiobesity profiles. A 1960s idea that serotonin concentrations might be lowered in depression<sup>1</sup> had been rejected,<sup>2</sup> and in clinical trials the SSRIs lost out to the older tricyclic antidepressants as a treatment for severe depression (melancholia).<sup>3-5</sup>

When concerns emerged about tranquilliser dependence in the early 1980s, an attempt was made to supplant benzodiazepines with a serotonergic drug, buspirone, marketed as a non-dependence producing anxiolytic. This flopped.<sup>6</sup> The lessons seemed to be that patients expected tranquillisers to have an immediate effect and doctors expected them to produce dependence. It was not possible to detoxify the tranquilliser brand.

Instead, drug companies marketed SSRIs for depression, even though they were weaker than older tricyclic antidepressants, and sold the idea that depression was the deeper illness behind the superficial manifestations of anxiety. The approach was an astonishing success, central to which was the notion that SSRIs restored serotonin levels to normal, a notion that later transmuted into the idea that they remedied a chemical imbalance. The tricyclics did not have a comparable narrative.

## Serotonin myth

In the 1990s, no academic could sell a message about lowered serotonin. There was no correlation between serotonin reuptake inhibiting potency and antidepressant efficacy. No one knew if SSRIs raised or lowered serotonin levels; they still don't know. There was no evidence that treatment corrected anything.<sup>7</sup>

The role of persuading people to restore their serotonin levels to "normal" fell to the newly obligatory patient representatives and patient groups. The lowered serotonin story took root in the public domain rather than in psychopharmacology. This public serotonin was like Freud's notion of libido—vague, amorphous, and incapable of exploration—a piece of biobabble.<sup>8</sup> If researchers used this language it was in the form of a symbol referring to some physiological abnormality that most still presume will be found to underpin melancholia—although not necessarily primary care "depression."

The myth co-opted the complementary health market. Materials from this source routinely encourage people to eat foods or engage in activities that will enhance their serotonin levels and in so doing they confirm the validity of using an antidepressant.<sup>9</sup> The myth co-opts psychologists and others, who for instance attempt to explain the evolutionary importance of depression in terms of the function of the serotonin system.<sup>10</sup> Journals and publishers take books and articles expounding such theories because of a misconception that lowered serotonin levels in depression are an established fact, and in so doing they sell antidepressants.

Above all the myth co-opted doctors and patients. For doctors it provided an easy short hand for communication with patients. For patients, the idea of correcting an abnormality has a moral force that can be expected to overcome the scruples some might have had about taking a tranquilliser, especially when packaged in the appealing form that distress is not a weakness.

## Costly distraction

Meanwhile more effective and less costly treatments were marginalised. The success of the SSRIs pushed older tricyclic antidepressants out of the market. This is a problem because SSRIs have never been shown to work for the depressions associated with a greatly increased risk of suicide (melancholia). The nervous states that SSRIs do treat are not associated with increased risk of suicide.<sup>11</sup> The focus on SSRIs also coincided with the abandonment of the pursuit of research into established biological disturbances linked to melancholia (raised cortisol); the SSRIs are ineffective in mood disorders with raised cortisol.<sup>12</sup>

Over two decades later, the number of antidepressant prescriptions a year is slightly more than the number of people in the Western world. Most (nine out of 10) prescriptions are for patients who faced difficulties on stopping, equating to about a tenth of the population.<sup>13 14</sup> These patients are often advised to continue treatment because their difficulties indicate they need ongoing treatment, just as a person with diabetes needs insulin.

Meanwhile studies suggesting that ketamine, a drug acting on glutamate systems, is a more effective antidepressant than SSRIs

for melancholia cast doubt on the link between serotonin and depression.<sup>15-17</sup>

Serotonin is not irrelevant. Just as with noradrenaline, dopamine, and other neurotransmitters, we can expect it to vary among individuals and expect some correlation with temperament and personality.<sup>18</sup> There were pointers to a dimensional role for serotonin from the 1970s onwards, with research correlating lowered serotonin metabolite levels with impulsivity leading to suicidality, aggression, and alcoholism.<sup>19</sup> As with the eclipse of cortisol, this research strand also ran into the sand; SSRIs lower serotonin metabolite levels in at least some people, and they are particularly ineffective in patient groups characterised by impulsivity (those with borderline personality traits).<sup>20</sup>

This history raises a question about the weight doctors and others put on biological and epidemiological plausibility. Does a plausible (but mythical) account of biology and treatment let everyone put aside clinical trial data that show no evidence of lives saved or restored function? Do clinical trial data marketed as evidence of effectiveness make it easier to adopt a mythical account of biology? There are no published studies on this topic.

These questions are important. In other areas of life the products we use, from computers to microwaves, improve year on year, but this is not the case for medicines, where this year's treatments may achieve blockbuster sales despite being less effective and less safe than yesterday's models. The emerging sciences of the brain offer enormous scope to deploy any amount of neurobabble.<sup>21</sup> We need to understand the language we use. Until then, so long, and thanks for all the serotonin.

Competing interests: I have read and understood BMJ policy on declaration of interests and declare I am a founder member of RxISK, which works to raise the safety profile of medicines and is on the advisory board of the Foundation for Excellence in Mental Health Care. I have acted as an expert witness in cases relating to suicide and violence and SSRIs.

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