

Serotonin: How Psychiatry Got Over Its “High School Crush”

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If serotonin was once American psychiatry’s “high school crush,” the field now appears wedded to a more mature model of biological and psychosocial understanding.

We’ve had 6 or 7 decades with this paradigm, what I call the “high school crush” on serotonin.

—Roger S. McIntyre, MD¹

I owe the cheeky title of this piece to Roger McIntyre, MD, Professor of Psychiatry and Pharmacology at the University of Toronto, who was interviewed at the recent American Psychiatric Association (APA) meeting in Toronto. But before providing some context for Dr McIntyre’s quip, I invite you to consider 2 claims relating to mental illness:

- Psychiatrists think that most mental illnesses are caused by a “chemical imbalance”
- Psychiatrists think that some mood disorders are associated with abnormal serotonergic neurotransmission, among other functional or structural brain abnormalities, which may or may not be the “cause” of the disorder

Since there are light years of conceptual space between these 2 claims, you might imagine, or naively hope, that psychiatry’s most strident critics would be able to distinguish claim 1 from claim 2. Alas, antipsychiatry bloggers continue to bang away at the notion that “Psychiatry” (that sinister, monolithic corporate entity) deliberately duped the public by promoting a bogus “chemical imbalance theory,” in cahoots with “Big Pharma.” Suffice it to say that this line of argumentation is itself bogus, for reasons I have reiterated at length in several venues.^{2,3} For example, in 2005, on a publicly available website, the APA clearly stated, “The exact causes of mental disorders are unknown . . . [but] we can say that certain inherited dispositions interact with triggering environmental factors.”⁴ At that time, the same APA website also indicated that “several factors can play a role in the onset of depression,” including “biochemistry” (abnormalities in brain chemicals or brain networks), genetics, personality, and environmental factors. To my knowledge, no professional psychiatric organization has ever publicly promoted a “chemical imbalance theory” of mental illness in general. (And, no, the original biogenic amine hypothesis was not a “theory”—the scientific distinction is important.⁵) That antipsychiatry bloggers assiduously comb the Internet and find a handful of “celebrity psychiatrist” quotes to the contrary neither surprises nor impresses me. But there is a sense in which some of psychiatry’s critics have a point, and this brings us back to Dr McIntyre and our old friend (or “frenemy”?), serotonin. It was not hard for the general public—and, alas, some doctors—to pick up the skein of serotonin and weave an entire tapestry with it, ultimately producing the threadbare “chemical imbalance theory.” No doubt, this was abetted by drug company “illustrations” of serotonergic synapses, complete with little packets of neurotransmitters whose reuptake is inhibited by the company’s ace antidepressant.⁶ Even today, some non-pharma websites continue to post misleading diagrams that attribute depression to a “chemical imbalance,” as Dr John Grohol recently discovered.⁷

So, to be clear: in order to establish, for a particular patient, a bona fide imbalance of neurotransmitters, we would need a “God’s-eye view,” in real time, of the dozens (hundreds?) of neurotransmitters in her brain; their relative concentrations in relation to well-validated norms; and their deviations from the patient’s normal baseline. Clearly, we have no such divine insight into the brain’s chemical constituents, even though we have learned a great deal about the brain’s “circuitry” and neural networks in recent years.⁸

Furthermore, all this focus on serotonin—while heuristically useful in some respects—may have delayed more fruitful inquiries into the biological bases of depression. Indeed, when asked about the role of serotonin in depression, Dr McIntyre replied:

I think there’s been inertia in the field insofar as we had a paradigm based on serotonin. We’ve had 6 or 7 decades with this paradigm, what I call the “high school crush” on serotonin, and we’ve had treatments that fit into that paradigm, such as the Prozac-type drugs, the serotonin agents, etc. Although that paradigm/treatment applies to a subset of around 10% to 20% of patients remarkably

well, we need to think of ways to reach other subpopulations of patients.¹

I agree with Dr McIntyre. And, as I recently stated:

There is little question that the role of serotonin in depression was over-emphasized and over-marketed in the 1990s, though most psychopharmacologists understood that the neurobiology of depression was much more complicated. Indeed, the term “SSRI” is itself a misnomer, since some of these agents also affect other brain chemicals (eg, sertraline has mild effects on dopamine).⁹

The neurobiology of depression is, of course, far more complicated than a simple deficiency of one or more neurotransmitters. In this regard, Dr McIntyre went on to elaborate an intriguing hypothesis that links some forms of depression to immune dysfunction, inflammation, and glucose dysregulation—what he calls the “immune inflammatory metabolic model.”¹ But it turns out that this model may link up with the serotonin hypothesis. Dr McIntyre notes, for example, that inflammation reduces serotonin in the brain. In principle, pharmacologic agents (eg, cytokine antagonists) that alleviate certain inflammatory conditions might amplify serotonergic function and reduce some types of depression.¹⁰ All this is just to say that, while the serotonin story has been greatly overblown, there are still reasons to retain some role for serotonin in at least a subset of persons with mood disorders.

No, this does not necessarily mean that mood disorders are caused by an imbalance of serotonin—or any other brain chemical. Over 50 years ago, the fathers of the biogenic amine hypothesis, Drs Joseph Schildkraut and Seymour Kety, recognized the complexities of sorting out psychosocial causes from biological effects—which can in turn become new causes or predispositions. They wrote: . . . it is . . . conceivable that early experiences of the infant or child may cause enduring biochemical changes, and that these may predispose some individuals to depressions in adulthood. It is not likely that changes in the metabolism of the biogenic amines [dopamine, norepinephrine, and serotonin] alone will account for the complex phenomena of normal or pathological affect.¹¹

The causal chain in the genesis of major depression is almost certainly long and complex—probably beginning with a genetic predisposition to depression, exacerbated by psychosocial stressors and losses, and worsened by dysfunctional personality traits and poor social supports. And while the “self-defeating cognitions” posited by cognitive theorists may not be a proximal cause of depression, their presence may deepen or prolong the person’s depression.¹² Recently, psychiatrists have also focused on socio-economic, educational, and cultural factors that contribute to the risk, and perhaps the onset, of clinical depression. In their recently released book, *The Social Determinants of Mental Health*, psychiatrists Michael T. Compton, MD, and Ruth S. Shim, MD,¹³ cite the following risk factors for depression: racial discrimination, poverty, unemployment, lack of social skills, reduced frustration tolerance and self-regulation, and food insecurity.¹⁴

All this is nothing radically new—it’s really an elaboration of the biopsychosocial model that has dominated academic psychiatry since the 1980s. Clearly, this multi-level model bears little resemblance to a simplistic chemical imbalance theory. And it gives the lie to those who claim that psychiatry has become reductionistic, hostile to the role of the “mind,” or void of psychodynamic understanding. On the contrary, this expanded biopsychosocial model opens the possibility for therapeutic interventions at several links in the causal chain. Thus, antidepressants—and perhaps, someday, anti-inflammatory agents—may ameliorate the biological components of depression, while psychotherapy reduces the experiential aspects of the illness, such as pathological guilt and self-loathing.

In short, if serotonin was once American psychiatry’s “high school crush,” the field now appears wedded to a more mature model of biological and psychosocial understanding.

This article was originally posted on 9/15/2015 and has since been updated.



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