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Short communication

An 'urban legend' remains an 'urban legend'

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Dear Drs. Mendenhall and Kohrt:

As senior academic psychiatrists in the U.S., we wish to express our concern regarding the accuracy and objectivity of the article by Ang et al. (2022). In addition, one of us (RP) has written extensively on the so-called chemical imbalance theory (CIT) (Pies, 2022), and is not accurately represented by the decontextualized quotes and paraphrases in the Ang et al. article.

Ang et al.'s interpretation of the literature bears little resemblance to the position of academic psychiatry in the U.S., over the past six decades. We acknowledge the uncontroversial point that, in the period from about 1990 to 2010, Anglo-American psychiatry was intensely focused on the possible role of serotonin in clinical depression; and that subsequent research has seriously criticized (though not conclusively refuted) the serotonin hypothesis of mood disorders (SHMD). But during this period, most academic psychiatrists and psychopharmacologists in the U.S. understood that the etiology and neurobiology of depression—much less, of mental illness in general–was much more complicated than the SHMD.

The crucial difference between a *hypothesis*—essentially, an informed guess–and a full-blown scientific *theory* is completely neglected in the Ang et al. article, and this is no mere semantic quibble. Ang et al.'s entire article erroneously conflates what they characterize as a "chemical imbalance theory" with monoaminergic *hypotheses* of depression. A detailed review by one of us (GD) found no references to a "chemical imbalance theory" of mental illness in any standard psychopharmacology textbook or peer-reviewed psychopharmacology literature over the past 30 years. Ang et al.'s conflation of monoaminergic, catecholaminergic, or indoleaminergic hypotheses of depression with a so-called "chemical imbalance theory" of mood disorders is inaccurate on its face.

For this very reason, Ang et al. err when they claim that, "the chemical imbalance theory was first proposed in the 1960s." On the contrary: to our knowledge, no major psychiatric organization in the U.S.—and no academic psychopharmacologists —ever proposed a sweeping "chemical imbalance theory" holding that the etiology of psychiatric disorders in general, or mood disorders in particular, lies solely in a "chemical imbalance" in the brain. On the other hand, there are clear examples of the "chemical imbalance" trope in pharmaceutical television advertising literature that reached a very wide audience in the period from 1990 to 2010 (Zoloft Medication Commercial, 2003).

To be clear: in the 1960s, the monoamine *hypothesis* was developed by J.J. Schildkraut, Seymour Kety and others as precisely that—a heuristic *hypothesis*, not a theory—and was carefully qualified as a *correlational*, not a *causal,* hypothesis. This distinction is crucial. In 1967, Schildkraut and Kety wrote:

> *It should be emphasized … that the demonstration of …* [a catecholamine] *abnormality would not necessarily imply a genetic or constitutional, rather than an environmental or psychological, etiology of depression … it is equally 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 …* [and] *any comprehensive formulation of the physiology of affective state will have to include many other concomitant biochemical, physiological, and psychological factors.* (Schildkraut and Kety, 1967)

This statement is essentially a harbinger of what was later developed as the "biopsychosocial model" of psychiatric illness by George Engel, and which has served as the "backbone" of academic psychiatry (at least in the U.S.) for the past forty years or more (Engel, 1980). American academic psychiatry has never espoused a simplistic "chemical imbalance theory" of mental illness (Pies, 2022). Furthermore, in 1978, the Board of Trustees of the American Psychiatric Association clearly stated that.

> "*Psychiatric disorders result from the complex interaction of physical, psychological, and social factors, and treatment may be directed toward any or all three of these areas.*" (American Psychiatric Association, 2006).

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Moreover, many psychiatrist-researchers were quite explicit in positing that depressive phenomena were very unlikely to have a direct relationship to a specific chemical event in the brain. Rather, as Akiskal and McKinney wrote in 1973,

> *"… we argue that depressive behaviors must be understood as occurring on several levels simultaneously rather than as having a one-to-one, direct relationship with a single chemical event in the brain, and that a multiplicity of genetic, developmental, pharmacological; and interpersonal factors converge in the midbrain and lead to a reversible, functional derangement of the mechanisms of reinforcement."* (Akiskal and McKinney, 1973)

Furthermore, the monoamine hypothesis of mood disorders was far from the only one put forth by psychiatrists during the past five decades. It is therefore inaccurate to describe the serotonin hypothesis of mood disorders as the dominant "Kuhnian paradigm" of psychiatry, as Ang et al. state. Our review shows that in the period of 1990–2010, there were at least 17 other hypotheses regarding depression, with 8 additional ones since then. These hypotheses entail many levels of analysis, including but not limited to the neurophysiological, neuroendocrine, chronobiological, immunological, and morphological levels (Nestler et al., 2002). To be sure, the monoaminergic hypothesis (involving serotonin and/or norepinephrine) was continuously discussed, debated and refined by researchers during this period, but was never widely accepted as a *causal theory* of mood disorders.

In sum, the attempt to link academic psychiatry—or "psychiatry" as a profession–to a generalized, causally-based, "chemical imbalance theory" of mental illness or mood disorders is not supported by the evidence presented by the authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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