Tobe EH. 2020. *Journal of Scientific Practice and Integrity*. 2(1). DOI: 10.35122/jospi.2020.966381

Letter to the Editor

The Iceberg of Improbity

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This Letter to the Editor is in response to an article published in this journal in November 2019 by Jay D. Amsterdam and Leemon McHenry entitled The Paroxetine 352 Bipolar Study Revisited: Deconstruction of Corporate and Academic Misconduct. The authors of this original research article did not wish to respond at this time.

Through authors such as Jay D. Amsterdam and Leemon McHenry, readers are hopefully becoming more aware of the necessity for critical thinking when evaluating scientific medical publications. In 2012 and in 2019, Amsterdam and McHenry published papers dissecting a fraudulent publication in *The American Journal of Psychiatry* (Nemeroff et al., *Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression*, 2001).[1,2,3] Both Amsterdam and McHenry papers deconstruct intentional falsification of data. Their 2012 report, published in *The International Journal of Risk & Safety in Medicine,* "describes how a 'negative' clinical trial was published as a 'positive' study with unsubstantiated claims of efficacy and safety."[1] They write in their 2012 paper:

> The problem of truth and transparency in published scientific reports of corporate-sponsored clinical trials has been an on-going concern in the medical and bioethics literature. The difference between what a trial should report and what is actually reported in the medical journals in the past 30 years is so alarming that some editors have declared a crisis of credibility.[1]

In their 2019 follow-up, published in this journal, Amsterdam and McHenry write:

> Because ghostwriting is designed to evade detection and is only revealed as a result of litigation or government inquiries, it is therefore imperative to document the cases in which ghostwriting has facilitated misrepresentation of clinical trial results.[2]

The first Amsterdam and McHenry paper "is based upon public evidence presented in a complaint of research misconduct filed with the Office of Research Integrity (ORI) of the Department of Health and Human Services (HHS) [4]."[1] The second paper benefited from "newly-publicized documents." The documents contain verbatim emails that describe the naked ambitions of a corporation, a prominent scientific journal, colluding specious academics, ghost writers, and pharmaceutical company marketers. The colluders reaped profits at the expense of medical and academic integrity.

According to the U.S. Department of Justice Office of Public Affairs, in 2012 GSK plead guilty to criminal and civil charges of unlawful promotion, failure to report safety data, and alleged false price reporting, in reference to Paxil, Wellbutrin, Avandia, and other drugs. The company agreed to a 3-billion-dollar settlement. The fines represent the cost of doing business. Although medical care was jeopardized, those responsible for creating such jeopardy face no consequences. The corporation is a mirror reflecting the values of those selling human dignity.

Physicians and patients must skeptically review medical papers regardless of author or publisher. The corrupt Nemeroff et al. paper has never been retracted. At the date of this written response, according to Google Scholar, there have been 500 citations of the Nemeroff et al. fraudulent publication, 15 citations of the 2012 Amsterdam and McHenry paper and no citation of the latest 2019 Amsterdam and McHenry paper. The editors of *The American Journal of Psychiatry* have elected to not inform their readers that the information in the Nemeroff et al. paper is flawed.

The Catecholamine Hypothesis: A Treatment Monopoly

Over the last quarter of a century, pharmaceutical companies have adopted the catecholamine hypothesis to direct research and marketing. In 1965, Joseph Schildkraut described that the "'catecholamine hypothesis of affective disorders proposes that some, if not all, depressions are associated with an absolute or relative decrease in catecholamines, particularly norepinephrine, available at central adrenergic receptor sites."[4] However, Schildkraut

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Received: December 18, 2019
Accepted for Publication: January 2020
Published Online: January 2020

recognized that the evidence supporting the co-relationship of biogenic amines to mood disorder was only indirect evidence, which faced obstacles in daily life such as, "the significant effects which social and interpersonal factors have on the clinical response to antidepressant drugs."[4] Yet, pharmaceutical companies market antidepressants as if the pharmacodynamic profile of the marketed drug were a perfect reflection of the pathophysiology of mood disorder. Because mood disorders lack reproducible organic markers, pharmaceutical companies have employed rating scales that do not measure a biological disorder but rather rate phenomenological presentation, as if such were equivalent to the biology of an illness. Changes in the phenomenological presentation are assumed to be related to the drug's effects on brain function. More likely, depression is a biologically heterogeneous group of illnesses with distinct mitochondrial dysfunction.[5] It would be more productive to start from the metabolism to predict phenomenology.

A positive response to a psychotropic is measured by a 50% reduction in the selected phenomenological rating scale. Yet, many studies find that over half of the participants respond to placebo. Perhaps a placebo should be offered FDA approval. Even if the psychotropic were associated to a 50% reduction of the rating score, such may not prevent the individual from suicide or enable them to function in the workplace.

Misinformation about the pathophysiology of depression and conjectured pharmacodynamics was well marketed with the introduction of Prozac (fluoxetine) in 1988. The argument was made that patients with depression had a lack of serotonin in the central nervous system. Fluoxetine, without significant adverse events, increases the synaptic availability of serotonin by inhibiting its natural reabsorption from the synapse once released by the neuron. With the introduction of fluoxetine, a new class of antidepressants called selective serotonin reuptake inhibitors (SSRIs) emerged. As companies developed competing SSRIs, the gambit became the more selective the SSRI, the better its effect. "Cleaner" drugs had less effect at non-serotonergic receptors. Marketing to the public encouraged the prescribing and taking of SSRIs for depression. Patients often understood their symptoms as a serotonin deficiency and felt relieved from the stigma of symptoms and signs of depression. In the mid-1990s, the next well marketed group of developed antidepressants were serotonin/ noradrenergic reuptake inhibitors (SNRIs). Pharmaceutical companies shifted "educational" marketing from SSRI drugs (i.e., the "cleaner" the better) to the SNRI drugs (whereby the "dirtier" the better). This illustrates that the pharmaceutical companies were willing to contradict themselves, making a dramatic shift in biological concept, to market the new group of drugs.

The marketing of SSRIs and related drugs convinced the medical community and the public of the catecholamine hypothesis, despite established alternative explanations and therapies. For example, although never marketed in the USA, effective drugs for the treatment of depression have been released outside the USA. In Europe, an atypical tricyclic antidepressant, Stablon/tianeptine, was released in 1988 with a suggested mechanism of action of a selective serotonin reuptake enhancer (SSRE), the opposite of a SSRI. Tianeptine was later suggested to pharmacodynamically reduce 5-HT availability, indirectly modulate adrenergic and dopaminergic systems, inhibit cholinergic hyperactivity, and modulate the effects of excitatory amino acids on N-methyl-D-aspartate receptors.[6] Tianeptine provided relief of depressive symptomatology within seven days without weight gain or sexual dysfunction. Through email correspondence dated July 21, 2010, the manufacturer, Servier International, informed me:

> Thank you for your interest in Stablon. In response to the question you raised in both your email and in your letter, please be informed that Stablon has never been submitted to the FDA and, thus, is not approved by the FDA for use in the USA.

The FDA confirmed it had no knowledge of tianeptine. Because of excellent marketing in the USA, medical schools, residencies, USA medical journals, and continuing physician educational programs never questioned the SSRI theory for the treatment of depression.

An additional extraordinary consequence of the marketing of SSRIs was to essentially end the education and training of specialists in psychiatry to value and prescribe monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs). Nescience has allowed MAOIs and TCAs to become old medicines, falsely perceived as inferior to newer putative antidepressant agents.[7] Physicians have not been trained to create a balanced algorithm of care. As a practicing psychiatrist, I have observed many instances of patients prescribed multiple SSRIs or SNRIs and then prescribed back to another SSRI without considerations outside of those groupings. I have often noted that prescriptions reflect the latest sales pitch.

Conflicts of Interest

Speakers at educational CME talks use slides designed by the sponsoring corporation. The speaker lists potential financial conflicts in a meaningless statement of a few seconds duration. I have never heard any speaker with personal or family financial conflicts provide the exact or approximate monies received or promised in order to permit the audience to access the risk of potential influence. There is a big difference between being paid $1800 in a year to offer talks and being paid over $500,000 a year.

Moreover, DSM diagnostic labels are influenced by vested financial interests. Committees with authority to create or clarify criteria for various disorders contain members receiving monies from pharmaceutical firms. In the legal profession, lawyers and judges are expected to recuse themselves when facing conflict. Why do psychiatric professionals receiving monies from sources of financial conflict not recuse themselves? The answer is arrogance and money. As Lisa Cosgrove, Ph. D, Harold J. Bursztain, M.D., and Sheldon Krimsky, Ph.D wrote:

> It is clear that transparency alone is not enough of a safeguard: approximately 68% of the members of the DSM-V task force reported having industry ties, which represents a relative increase of 20% over the proportion of DSM-IV task-force members with such ties.[8]

Meetings of the American Psychiatric Association and other medical groups are partly sponsored by pharmaceutical industry. Acceptance of such support opens the door to vested financial interest becoming the force guiding current and future medicine.

The emphasis on prescribing drugs as the major psychiatric contribution to treatment without knowing the patient has become an unfortunate consequence of insurance industry control of medical care, initially through the formation of HMOs. Today, psychiatrists perform a "med check" perhaps every few weeks to several months that may range from 10 minutes to 30 minutes during which a patient, often not in remission, is psychiatrically evaluated to determine medical and psychological changes and current mental status, response to pharmaceuticals, changes in their life, compliance, ability to function vocationally, and avocationally. The psychiatrist writes prescriptions for drugs with minimal knowledge of the patient. Drug sales benefit corporations; however, the success of treatment is compromised. Algorithms of treatment require an appreciation of the whole person in a context of their lives, family, socioeconomic strengths and weaknesses, goals, hopes, fears, etc. The high placebo rate response found in antidepressant drug trials warns the prudent physician to know the patient as a complete human being. Further, minimal contact with the patient causes a frequent complaint of physician abandonment.

Psychological Factors that Motivate Scientific Misconduct

Addressing the psychological motives for scientific misconduct is a humbling task. There are so many tributaries that feed into the rivers that lead to the seas. To manage this potentially vast subject, I select specific issues to permit at least an initial recognition of the subject of psychological causation beyond the factual data establishing misconduct.

The first question that comes to mind is what allows a culture of scientific misconduct to exist? One answer is that those involved in fraud can be rewarded in socioeconomic and academic stature. This has been the case for many centuries**.** Mahatma Gandhi is credited with a quote:

> Earth provides enough to satisfy every man's needs, but not every man's greed.[9]

Values are a commodity rationalized to favorably support the wishes of the individual and/or the culture. The refusal to retract the fraudulent ghost-written paper demonstrates an arrogance that is disassociated from the reality of fraud. As Sir Francis Bacon wrote in an essay entitled "Of Truth" in 1625, lies gratify:

> But it is not only the difficulty and labor, which men take in finding out of truth, nor again, that when it is found, it imposeth upon men's thoughts, that doth bring lies in favor, but a natural though corrupt love, of the lie itself.[10]

Culture is created by a social group. Wilfred Bion, a British psychoanalyst, recognized that to become part of a group, the individual needs to shed some element of autonomy to merge with the group. A group may search for an enemy to enhance their union.[11] The human species has a readiness to form groups and expel those not accepting the group's values and beliefs; however, unquestioning acceptance of the group's values and actions is an act of blind faith and potentially disassociation from reality. In contrast, whistleblowers, commonly lone wolves, face expulsion from the group. This expulsion is often justified by false allegations of corruption and incompetence to lessen the merit of the whistleblower's disclosure.

Those involved in misconduct in medical science either ignore or disregard the possible harm to the patient to remain loyal to the group. The denial of misconduct may reflect fears of emotional disquiet. External pain occurs through public exposure leading to social and legal ramifications. Internal pain results from shame, which is concealed or warded off by enhanced righteous arrogance. In the case of systematic medical fraud involving numerous people, some of whom gained prominence in their own mind, their idealized self needs to love their lie, as the alternative is to face their shame.

Regardless of their education, humans have always faced the reality principle versus the pleasure principle. Based upon daily observations, Freud hypothesized a pleasure principle defined as events that are set into motion by an unpleasurable tension and the direction of resolution coincides with the lowering of that tension through avoidance of unpleasure or the production of pleasure.[12] In childhood development, slowly the pleasure principle yields to reality. This is not completely resolved by adult life. The urge for greed and power is a well-recognized amoral ambition. Moral ambition is derived from achievement and

mastery, while amoral ambition disassociates from other people. The psychological make-up of the amoral ambitious person includes a promotion of self over others, implying contempt for others and repressed self-contempt. The need for what Bacon calls a "natural though corrupt love, of the lie itself" becomes discernible:

> Doth any man doubt, that if there were taken out of men's minds, vain opinions, flattering hopes, false valuations, imaginations as one would, and the like, but it would leave the minds, of a number of men, poor shrunken things, full of melancholy and indisposition, and unpleasing to themselves?[10]

There will always be those who corrupt and exploit. History has not shown a learning curve to replace greed and power with neutral scrutiny of facts. Medical science is not immune from human factors, which have been described by writers like Sir Frances Bacon over many centuries. Ideally, authors need to reflect on their ambitions and readers need to remain vigilant.

I thank Dr. Amsterdam and Dr. McHenry for providing a crucible of probity that encourages the reader's vigilance and warns against idealizations that obscure truth.

Author Bio: Dr. Tobe is an adult and child psychiatrist and psychoanalyst in private practice. His publications reflect diverse interests including the interplay of molecular, social, cultural, occupational and intrapsychic factors effecting mental function.

Acknowledgments: The author would like to thank Drs. Amsterdam and McHenry for their original research articles that this letter is a response to, and the Managing Editor of JoSPI, Dr. Tess Bird, for her editorial comments on this letter.

Declaration of Conflicts of Interest: None

Note: *A new version of this letter with minor corrections was uploaded on February 10, 2020. The original letter falsely reported that Amsterdam and McHenry's JoSPI article benefitted from documents obtained during litigation that were under court seal during research for the authors' first publication in 2012. In fact, the status of these documents during the publication of the first Amsterdam and McHenry article was unknown. The original letter also implied that the 352 study was related to the $3 billion fine against GSK. In fact, Dr. Tobe was reflecting on this fine as further evidence of misconduct.*

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