

Antidepressants and the Chemical Imbalance Theory of Depression: A Reflection and Update on the Discourse

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A DECADE AGO, WE PUBLISHED an article in *PLoS Medicine* about the serotonin deficiency theory of depression (Lacasse & Leo, 2005). We transposed the psychiatric literature on serotonin and depression with what pharmaceutical companies had been claiming in their consumer advertisements for years—that a chemical imbalance (serotonin deficiency) caused depression and this imbalance was corrected by selective serotonin reuptake inhibitor (SSRI) drugs. For instance, advertisements for fluoxetine (Prozac) had stated:

When you're clinically depressed, one thing that can happen is the level of serotonin (a chemical in your body) may drop. So you may have trouble sleeping. Feel unusually sad or irritable. Find it hard to concentrate. Lose your appetite. Lack energy. Or have trouble feeling pleasure...to help bring serotonin levels closer to normal, the medicine doctors now prescribe most often is Prozac® (Eli Lilly, 1998)

We knew that such advertisements did not accurately reflect the scientific status of the serotonin theory in the psychiatric research community (see Table 1; we have modified the original table to integrate new material that came to our attention since 2005). Some advertisements were more tentative or clever in their wording than others, but it seemed obvious that the drug companies were at least pushing the boundaries. We thought several of them were going over the line, in plain sight of the Food and Drug Administration (FDA), which ostensibly regulates direct-to-consumer advertising. Our goal was to illustrate the clear disconnect between the existing psychiatric science and what the public was being told in these advertisements, and we argued that the FDA should issue warning letters to pharmaceutical companies (Lacasse, 2005; Lacasse & Leo, 2005). Of course, there were ramifications for clinicians—if it was illegal to claim this in advertisements, wasn't it also an un-

acceptable thing to be telling vulnerable clients?

After the publication of the paper, we were interviewed by numerous journalists. Several of them thought our work was provocative and that we were “attacking” a well-accepted theory. If it was an attack, it was an inside job, as our sources included NIMH-funded scientists, an award-winning biological psychiatrist, and a popular psychiatric textbook. Anyone familiar with the history of serotonin research would find our argument unremarkable (e.g., Healy, 1997, 2004; Moncrieff, 2008; Valenstein, 1998). In the United Kingdom, psychiatrist David Healy has been making this point for decades (e.g., Healy, 1987, 1997, 2004, 2012, 2015). But the questions from journalists reminded us that the enormous marketing campaigns promoting SSRI drugs (and surely many of the physicians prescribing them) had convinced the U.S. public that the serotonin theory of depression was firmly grounded in science. This wasn't just an issue of misleading advertising. Instead, the incredulity seemed fueled by the significant number of mental health clients who had heard the chemical imbalance explanation from their prescribers.

We urged these reporters to query the FDA, American Psychiatric Association (APA), NIMH, and other official organizations about the science behind the advertisements. *New Scientist* interviewed Wayne Goodman, at the time a University of Florida psychiatrist and Chair of the FDA Psychopharmacological Committee. Dr. Goodman called the serotonin theory “a useful metaphor”—but one he never used when informing his own patients, stating, “I can't get myself to say that” (Lacasse & Leo, 2006; *New Scientist*, 2005). One has to expect that patients whose doctors *had said that* found this news upsetting.

Serotonin imbalance as metaphor is obviously a deep problem for many of the patients who have heard their physicians explain that their depression is caused by a chemical imbalance. These patients must

have assumed that they were hearing real science, and not metaphor. Goodman's public statement raised the question: How are patients with both diabetes and depression who listen to their doctor's explanation of their two conditions supposed to know that one explanation is based on scientific measurement, and one is just a metaphor?

The Problematic Advertisements Disappear

In the early 2000s, the serotonin metaphor of depression was widely advertised by the makers of antidepressants, including advertisements for citalopram, escitalopram, fluoxetine, paroxetine, and sertraline (Lacasse & Leo, 2005). In particular, Zoloft (sertraline) advertisements featuring the miserable ovoid creature were unavoidable in U.S. television and magazines. An on-line repository of direct-to-consumer advertisements for psychiatric drugs lists many from 1997–2007 referring to a chemical imbalance, across many drugs and diagnostic categories (Hansen, 2015a, 2015b).

A 2010 study compared on-line drug advertising of antidepressants regarding the issue of chemical imbalance in both 2004 and 2009 (Lacasse & Hughes, 2010). The number of websites making such claims dropped, with some websites going dark or minimalist as the drug patents ran out. Interestingly, some on-patent drug websites had simply removed the chemical imbalance claims. Newer medications were promoted as “adjusting” or “affecting” neurotransmitter levels, in contrast to “correcting a chemical imbalance.”

From 2014–2015, we collected further data, finding that the simplistic narrative of chemical imbalance that was so common in direct-to-consumer advertising in the 2000s is not widespread any longer. Consumers are no longer informed that antidepressants will normalize their neurotransmitter levels. The Abilify thermostat is gone (Lacasse & Leo, 2006) and drugs are now advertised as “affecting” neurotransmitters. This is mostly true for other classes of medications as well, as advertisements for psychostimulants (Leo & Lacasse, 2009) have also moderated their language substantially. While we still see problematic advertisements, the overall situation has obviously improved.

There is no public explanation for why this happened. To our knowledge, FDA has never sent a warning letter to a pharmaceutical company over claims that antidepress-

sants correct a chemical imbalance. In our assessment, the promotion of chemical imbalance theory in advertisements for SSRI drugs was wildly successful for the drug companies and the psychiatric profession alike. While it's difficult to imagine that they pulled them arbitrarily, we don't know why they largely disappeared.

By roughly 2007, anyone who Googled “serotonin and depression” could easily find articles explaining the mythical nature of serotonin imbalance, or at least the argument. We don't claim that our one little article was responsible, or even original (see Breggin, 1998; Glenmullen, 2000; Healy, 1997, 2004). But given that the public had accepted the serotonin theory as fact (Pescosolido et al., 2010), the widespread public criticism of it and emerging transparency of information on the Internet would obviously create problems, or at least a dilemma. Below, we highlight a few examples of the recent discourse on these issues (see also Levine, 2014; Lynch, 2015; Whitaker, 2010, 2015; Whitaker & Cosgrove, 2015).

I Don't Really Believe It, but I Say It to Patients Anyway

Psychiatrist Daniel Carlat is a practicing psychiatrist, a clinical instructor at Tufts University, and editor of *The Carlat Psychiatry Report*, which we have read for years. On July 13, 2010, he appeared on National Public Radio (NPR; Davies, 2010) to promote his book, *Unhinged* (2010), in which he describes psychiatry as a profession in crisis. Carlat had received some attention in *The New York Times*, candidly reporting his experience pitching venlafaxine (Effexor) to other doctors as a paid consultant for Wyeth. He found himself “tweaking and pruning the truth to stay positive about the product” and eventually resigned (Carlat, 2007). We find that Carlat is unusually transparent, providing interesting insights into uncomfortable issues.

Carlat was asked what we know about psychiatric medication. He responded:

What we don't know, is we don't know how the medications actually work in the brain. . . . I'll often say something like the way Zoloft works, is, it increases the level of serotonin in your brain (or synapses, neurons), and, presumably, the reason you're depressed or anxious is that you have some sort of a deficiency. And I say that [chuckles] not because I really believe it, because I know the evidence really isn't there for us to understand the mecha-

nism—I think I say that because patients want to know something. And they want to know that we as physicians have some basic understanding of what we're doing when we're prescribing medications. They certainly don't want to know that a psychiatrist essentially has no idea how these medications work. (Davies, 2010)

This is surely a remarkable public admission. Carlat continues:

We're in a paradoxical situation, I think, where we prescribe medications that do work according to the trials. And yet as opposed to essentially all other branches of medicine, we don't understand the pathophysiology of what generates mental illness and we don't understand exactly how our medications work. (Davies, 2010)

A practicing psychiatrist could understandably report that they see the medications working in their practice and find them useful. Invoking the clinical trials is perhaps a strange direction to go here, because the consistent lack of difference between SSRI and placebo in the clinical trial literature is one of the most compelling arguments against the serotonin deficiency theory. So Carlat is aware of the clinical trials, which essentially refute the serotonin theory, yet still tells patients that they have a serotonin imbalance. And while some prescribers of psychiatric medication object to misleading SSRI advertisements (Rickels, 2006), Carlat sees widespread pharmaceutical propaganda as an opportunity:

One thing that has happened is that because there's been such a vacuum in our knowledge about mechanism, the drug companies have been happy to sort of fill that vacuum with their own version of knowledge, that usually if you see a commercial for Zoloft on TV, you'll be hearing the line about serotonin deficiencies and chemical imbalances, even though we don't really have the data to back it up. It becomes a very useful marketing line for drug companies, and then it becomes a reasonable thing for us to say to patients to give them more confidence in the treatment they're getting from us—but it may not be true. (Davies, 2010)

Carlat's straightforward admissions are likely to cause reactions, and we think they mostly speak for themselves. It's worth noting that he sometimes frames the serotonin issue as one of scientific uncertainty:

we “essentially” or “exactly” don't know how SSRI medications work, and the serotonin theory “may not be true.” Such statements need to be evaluated in light of the existing literature (see Table 1). In fact, scientists have known for a long time that the serotonin theory presented by the drug companies and Carlat is not true (see Healy, 2004, 2012, 2015; Lynch, 2015). Claiming scientific uncertainty about the issue could reflect a lack of familiarity with the scientific literature, or a need to justify the use of such statements. In our opinion, neither option is flattering or desirable in an era of shared clinical decision-making. The simple alternative would be to tell patients the truth—that the pathophysiology of depression is unknown and that we have no idea how SSRIs work.

The Positive Aspects of Misinformed Thinking

On January 23, 2012, NPR Morning Edition aired “When it Comes to Depression, Serotonin Isn't the Whole Story” (Spiegel, 2012). While Carlat states that the serotonin theory “may not be true,” psychiatrist Joseph Coyle makes a much clearer statement: “I don't think there's any convincing body of data that anybody has ever found that depression is associated to a significant extent with a loss of serotonin.” Yet part of the segment focuses on the positive aspects of telling patients that a serotonin imbalance causes depression (see Levine, 2014). For instance, Alan Frazer, Professor of Pharmacology and Psychiatry, stated that the serotonin theory allowed patients to:

Feel better about themselves if there was this biological reason for them being depressed, some deficiency, and the drug was correcting it. They had a chemical imbalance and the drug was correcting that imbalance . . . yeah it's like, I have depression but I have a chemical imbalance, and you have hypothyroidism and you have a chemical imbalance, and my chemical imbalance just happens to affect my brain. (Spiegel, 2012)

Psychiatrist Pedro Delgado added, “When you feel that you understand it, a lot of the stress levels dramatically are reduced. So stress hormones and a lot of biological factors change.”

Not surprisingly, there were many angry comments on the NPR website. Apparently, many psychiatric patients never realized they were hearing a

metaphor and not science. They didn't know that the chemical imbalance metaphor was used in an attempt to reduce stigma, or stress hormones, rather than being accurate information presented by their trusted health-care provider. Since chemical imbalance is often presented as a rationale for taking SSRIs, some such patients now understandably feel lied to by their clinicians. Levine (2014) calls this "Psychiatry's Manufacture of Consent."

The claim that presenting the chemical imbalance metaphor is in the best interests of patients needs to be considered in light of the existing empirical research. This in fact is not what the literature shows (e.g., Deacon & Baird, 2009). For instance, in a rare controlled experiment on this topic, one group of depressed students were told they had a confirmed serotonin imbalance underlying their depression, while a control group was not (Kemp, Lickel, & Deacon, 2014). The group who was told they had abnormal serotonin levels found medication more credible than psychotherapy and expected it to be more effective. They also had more pessimism about their prognosis and a lower perceived ability to regulate negative mood states, yet experienced no reduction in self-blame. These results suggest that the chemical imbalance explanation may indeed be helpful in persuading patients to take medication but that this is likely accompanied by undesirable effects. Data such as this should be a major part of the conversation regarding informed consent in psychiatry.

The Role of Journalism

Perhaps the most interesting part about both of these NPR pieces is that neither reporter questioned the experts about the ethics of telling a falsehood to patients because you think it is good for them. In contrast to how, say, a foreign-policy expert might be grilled on NPR, the tone was deferential and accepting. We would have liked both reporters to have asked the following questions: (a) Do you believe it is ethical to present a falsified scientific theory as a fact to a patient? (b) What are the possible negative effects of doing so? (c) Should the information you tell your patients be consistent with the psychiatric textbooks on your shelf? (d) How does it affect the psychiatrist-patient relationship when your patients look up serotonin imbalance on the Internet and conclude that they have been misled?

It Wasn't Us, It Was the Drug Companies

Ronald Pies is a psychiatrist at Tufts University and served as editor of the prominent trade journal *Psychiatric Times* from 2007–2010. From 2011 on, he authored several pieces on the chemical imbalance issue, which we recommend (Pies 2011a, 2011b, 2014). These are available on the web, cited frequently, and Pies is the most prominent figure in U.S. psychiatry to take up this issue publicly. Pies doesn't believe that the chemical imbalance metaphor should be attributed to psychiatry:

... opponents of psychiatry . . . mendaciously attribute the phrase ["chemical imbalance"] to psychiatrists themselves . . . And yes [it has] been vigorously promoted by some pharmaceutical companies, often to the detriment of our patient's understanding. . . . In truth, the "chemical imbalance" notion was always a kind of urban legend—never a theory seriously propounded by well informed psychiatrists. (Pies, 2011a)

We suspect that Pies had no idea how many of his fellow psychiatrists he was throwing under the metaphorical bus by making this claim. While we don't know exactly how many clinicians have told their patients they were suffering from a chemical imbalance over the last 25 years, we believe that the number is significant and consequential. Among 237 psychology students, Frances, Lysaker, and Robinson (2007) found that 46% had heard the chemical imbalance explanation from a physician. Empirical studies report use of the chemical imbalance theory by prescribers, including psychiatrists (e.g., Cohen & Hughes, 2011; Schreiber & Hartwick, 2002; see also Acker, 2013). Also, over the years, we've been in touch with many people who reported hearing "it's a chemical imbalance" from psychiatrists: people in our social circles; "consumers" at conferences; our students who work in community mental health settings; subjects in our research (Lacasse, Lietz, Hayes, Rider & Hess, in press); and people who emailed us in response to our work. And, one of the authors once worked with a talented psychiatrist and heard this explanation given weekly. If Pies is correct, that's an awful lot of uninformed clinicians.

A Bumper-Sticker Slogan to Educate Patients

In subsequent articles Pies moderates his tone and concedes that practicing psychiatrists may have used the chemical imbalance explanation at times (Pies, 2011b). He claims that it is the result of overbooked clinicians looking for quick explanations to accompany medication, perhaps to reduce self-blame on the part of patients (he acknowledges that this may backfire). He states:

My impression is that most psychiatrists who use this expression feel uncomfortable and a little embarrassed when they do so. It's kind of a bumper-sticker phase that saves time, and allows the physician to write out that prescription while feeling that the patient has been "educated." (Pies, 2011b)

To us, this sounds similar to what Carlat was reporting. Pies also notes that academic psychiatry hasn't done a great job of communicating with Primary Care Physicians (PCPs), who write most of the prescriptions for SSRIs. This might be seen as a question of priorities, because academic psychiatry in general has done a highly effective job of convincing PCPs to diagnose and treat depression with antidepressants.

Academic Psychiatry as Silent Partner in the Promotion of Chemical Imbalance

Pies admits that both he and official psychiatric associations should have done more to dispel the chemical imbalance myth (Pies, 2014). He adds that there "were sincere attempts to do just that, by several prominent psychiatrists." Unfortunately, he doesn't provide any recent examples (he does cite Shildkrauddt & Kety, 1967). It is easy to imagine that a single prominent academic psychiatrist, authoring an Op-Ed in *The New York Times*, could have set the record straight on serotonin imbalance decades ago. Yet, to our knowledge, no one did so.

We have long been concerned about how conflicts-of-interest with the pharmaceutical industry might shape the behavior (unconsciously or not) of academic psychiatrists, including the promotion of the chemical imbalance metaphor. In 2009, we wrote about misleading direct-to-consumer advertising of psychostimulants such as Adderall, where the claims were at

least as misleading as SSRI advertisements (Lacasse & Leo, 2009). Noting the lack of objections to these advertisements from within academic psychiatry, we asked, “Is it possible that the flow of money from the pharmaceutical companies to influential academic psychiatrists . . . has brought with it a certain willingness to remain silent?” We doubt Ronald Pies would find this irrationally conspiratorial, or a crazy question to ask—because we published this in *Psychiatric Times* (Editor: Ronald Pies, M.D.).

Thus, while we don’t know why Ronald Pies himself didn’t speak out on the chemical imbalance issue decades ago, readers should be aware of his past financial relationship with pharmaceutical companies. He sounds vaguely critical of the drug industry in his recent articles and never discloses any history of financial conflicts-of-interest. However, Pies has received funding from GlaxoSmithKline, Abbot Laboratories, and Janssen Pharmaceuticals—the makers of Paxil, Wellbutrin, Lamictal, Depakote, and Risperdal (Chaudron & Pies, 2003; Pies & Rogers, 2005). For years, Paxil and Wellbutrin were advertised as correcting a chemical imbalance in the brain. These three companies have recently been fined a combined \$6.7 billion for illegal marketing of their products.¹ Pies has also consulted for ApotheCom, a “Medical Communications Agency” that “provides services to support the commercialization of new products . . . [including] . . . publications planning, [and] promotional communications . . .” (Pharma Voice Marketplace, 2015). While useful context, this isn’t uncommon among academic psychiatrists, and some would say it was par for the course in the 2000s. However, in a public forum, more transparency is preferable. Pies blames the drug companies for running misleading advertisements about

chemical imbalance, belatedly admits he should have said something sooner, but fails to mention that he was paid to help them promote their products at the time the advertisements were running.

It’s important to realize that organized psychiatry doesn’t always remain silent, such as when the interests of psychiatric prescribers and pharmaceutical companies converge. In the mid-2000s, press releases endorsed by some of the most prominent psychiatrists in the United States were issued objecting to the FDA black box warning on SSRIs (e.g., American College of Neuropsychopharmacology, 2006; Healy, 2012). The APA also issued a press release defending antidepressants (APA, 2004; Healy, 2006). This was at a time when the chemical imbalance metaphor was omnipresent in direct-to-consumer advertising. While that was seen as a pressing issue to present to the public, misleading messages on chemical imbalance were not.

But We Never Promoted the Theory

Remaining silent is one thing, promoting chemical imbalance theory is another. Pies has also stated, “I am not aware of any concerted effort by academic psychiatrists, psychiatric textbooks, or official psychiatric organizations to promote a simplistic chemical imbalance hypothesis of mental illness” (2014). In the age of the Internet, it didn’t take long for MadinAmerica.com blogger Philip Hickey (2014) to make him aware of some. We added to the list by consulting Lynch (2015, Chapter 5) and searching the Internet. The resulting list (Table 2) is admittedly incomplete but sufficient to address Pies’ point.

Clearly, mainstream psychiatry (including academic psychiatry and professional organizations) has promoted the chemical imbalance theory. Comparing Table 1 and Table 2, it is apparent that there are often

two different conversations occurring (Whitaker, 2010; Whitaker & Cosgrove, 2015). One is the actual scientific discourse, as exemplified in the APA’s *Textbook of Psychiatry* (Hales, Yudofsky, & Talbott, 1999), which accurately describes the empirical status of serotonin imbalance theory 16 years ago. The other conversation is between influential psychiatrists and the public, or between psychiatrists and primary care physicians. In this second conversation, the drug company advertising line about SSRIs correcting chemical imbalances is repeated as fact by psychiatric authorities, including the APA.

The Chemical Imbalance Theory as a Little White Lie

Pies started out enthusiastically critiquing the chemical imbalance theory. We obviously believe he tried to rewrite some history along the way. But, by 2014, Pies refers to the use of the chemical imbalance metaphor as “a little white lie”² (Pies, 2014; see also Hickey, 2014). While previously psychiatrists who used this language were not well-trained, or knowledgeable, or well-informed, now they are just telling white lies—little ones.

We found this disappointing. When our physicians are educating us, we prefer they not tell us any lies, white or otherwise. Unfortunately, characterizing the chemical imbalance metaphor as a “little white lie” communicates a paternalistic, hierarchical approach that sounds suspiciously like the days of medicine that we thought we had left behind. It’s a “little white lie” if you’re a psychiatrist; if you’re a confused, vulnerable depressed person who agrees to take an SSRI after hearing it, you might not consider it so little. After all, if your trusted physician tells you that you have a chemical imbalance in your brain that can be corrected with medication, not doing so sounds foolish, if not scary (Lacasse, 2005). How many patients with reservations about SSRIs have agreed to take medication after being told this “little white lie”?

Discussion

In the last decade, widespread claims of chemical imbalance in depression have essentially been withdrawn by both the profession of psychiatry and the pharmaceutical industry. We believe the profession of psychiatry should be strongly critiqued for withdrawing the serotonin theory belatedly, long after the science was in, and for not speaking up while drug advertisements

¹We want to be clear that we are not accusing Ronald Pies of anything. Conflicts-of-interest are routine in academic psychiatry and many of the major pharmaceutical companies have been fined in the recent past. We do believe that readers deserve to know of his past financial relationships with the drug companies that promoted their products as correcting a chemical imbalance. The details of these financial relationships are not publicly available.

²Pies’ (2014) original quote reads as follows: “In the narrative of the antipsychiatry movement, a monolithic entity called ‘Psychiatry’ has deliberately misled the public as to the causes of mental illness, by failing to debunk the chemical imbalance hypothesis. Indeed, this narrative insists that by promoting this little white lie, psychiatry betrayed the public trust and made it seem as if psychiatrists had magic bullets for psychiatric disorders.” It’s important to realize that “little white lies” is Pie’s characterization of chemical imbalance, not how it is presented in the critical narrative. Writers like Whitaker (2010) vigorously critique the idea of chemical imbalance exactly because they do not see it as a “little white lie.”

Table 1. Evidence the Chemical Imbalance Theory of Depression Is Not Valid: Selected Quotations

Quote	Citation
“By 1970...[biochemist and Nobel Prize Winner Julius] Axelrod had concluded that, whatever was wrong in depression, it was not lowered serotonin.”	Healy, 2004, p. 12
“I spent the first several years of my career doing full-time research on brain serotonin metabolism, but I never saw any convincing research that any psychiatric disorder, including depression, results from a deficiency of brain serotonin” (Psychiatrist David Burns, who conducted award-winning serotonin research in the 1970s).	Lacasse & Gomory, 2003, p. 393
“Tianeptine is an interesting compound with antidepressant activity thought to be related to increased rather than decreased 5HT [serotonin] uptake” [meaning, in 1989 it was known to be an antidepressant that depletes, not increases, serotonin].	Ives & Heym, 1989, p. 22
“The simplistic idea of the ‘5-HT [serotonin]’ neurone does not bear any relation to reality” (John Evenden, Astra pharmaceutical company research scientist, 1990).	Shorter, 2009, p. 204
“In the 1990s...No one knew if SSRIs raised or lowered serotonin levels; they still don’t know...There was no evidence that treatment corrected anything.”	Healy, 2015
“...Patients have been diagnosed with ‘chemical imbalances’ despite the fact that no test exists to support such a claim, and there is no real conception of what a correct chemical imbalance would look like...Yet conclusions such as ‘depression is a biochemical imbalance’ are created out of nothing more than semantics and the wishful thinking of scientists/psychiatrists and a public that will believe anything now that has the stamp of approval of medical science” (Psychiatrist David Kaiser of Northwestern University Hospital, 1996).	Kaiser, 1996; Lynch, 2015, pp. 31-32.
“Although it is often stated with great confidence that depressed people have a serotonin or norepinephrine deficiency, the evidence actually contradicts these claims” (Neuroscientist Elliot Valenstein).	Valenstein, 1998, p. 100
“The monoamine hypothesis...holds that monoamines...such as... [serotonin]...are deficient in depression and that the action of antidepressants depends on increasing the synaptic availability of these monoamines...However, inferring neurotransmitter pathophysiology from...[SSRIs]...is similar to concluding that because aspirin causes gastrointestinal bleeding, headaches are caused by too much blood...Additional experience has not confirmed the monoamine depletion hypothesis.” (American Psychiatric Association <i>Textbook of Psychiatry</i> , 1999).	Dubvosky & Buzan, 1999, p. 516
“A serotonin deficiency for depression has not been found” (Psychiatrist Joseph Glenmullen, Clinical Instructor of Psychiatry at Harvard Medical School).	Glenmullen, 2000, p. 197
“...I wrote that Prozac was no more, and perhaps less, effective in treating major depression than prior medications...I argued that the theories of brain functioning that led to the development of Prozac must be wrong or incomplete” (Brown University Psychiatrist Peter Kramer, author of <i>Listening to Prozac</i>).	Kramer, 2002
“[We must] abandon the simplistic hypotheses of there being either an abnormally high or abnormally low function of a given neurotransmitter” (Avid Carlson, Nobel Prize winner for his work on the neurotransmitter dopamine, 2002).	CINP Meeting with the Nobels (2003); Shorter, 2009, p. 204
“Indeed, no abnormality of serotonin in depression has ever been demonstrated” (Psychiatrist and historian David Healy in 2004).	Healy, 2004, p. 12

Table 2. Promotion of the Chemical Imbalance Theory of Depression as Valid: Selected Quotations

Quote	Source	Citation
“Celexa helps to restore the brain’s chemical balance by increasing the supply of a chemical messenger in the brain called serotonin.”	Celexa website, 2005	Lacasse & Leo, 2005
“Antidepressants may be prescribed to correct imbalances in the levels of chemicals in the brain.”	<i>Let’s Talk Facts About Depression</i> , a patient information leaflet distributed by APA	American Psychiatric Association, 2005, p. 2
“Antidepressants...have no effect on normal mood. They restore brain chemistry to normal.”	Nada Stotland, president of the American Psychiatric Association, 2007-2008	Stotland, 2001, p. 65
“[antidepressants work] only if there was a chemical imbalance in the brain that needed fixing”	Donald Klein, psychiatrist and psychopharmacologist	Talan, 1997
“While the patient may require a somatic therapy to correct the underlying chemical imbalance, he may also need psychotherapy...”	Nancy Andreason, psychiatrist and author of <i>The Broken Brain</i>	Andreason, 1985, p. 258
“...some depressed patients who have abnormally low levels of serotonin respond to SSRIs...”	Psychiatrist Richard Friedman in <i>The New York Times</i>	Friedman, 2007
“There is truly a real deficiency of serotonin in depressed patients.”	Psychiatrist Charles Nemeroff	Nemeroff, 2007
“The physician should stress that depression is a highly treatable medical illness caused by a chemical imbalance.”	MacArthur Foundation Depression Education Program for Primary Care Physicians	Cole, Raju, Barrett, Gerrity, & Dietrich, 2000, p. 340
“Patients with neurotransmitter dysregulation may have an imbalance of serotonin and norepinephrine...duloxetine [Cymbalta] may aid in correcting the imbalance of serotonin and norepinephrine neurotransmission in the brain.”	Madkur Trivedi, psychiatrist at University of Texas Southwest Medical School, in <i>The Primary Care Companion of the Journal of Clinical Psychiatry</i>	Trivedi, 2004, p. 13
“Restoring serotonin’s imbalances not only helps brighten mood and restore normal sleeping and eating patterns, but it also seems to promote a sense of well-being.”	Michael Thase, psychiatrist and psychopharmacology researcher at the University of Pennsylvania, and science writer Susan Lang	Thase & Lang, 2004, p. 106
“We now know that mental illnesses—such as depression or schizophrenia—are not ‘moral weaknesses’ or imagined but real diseases caused by abnormalities of brain structure and imbalances in chemicals of the brain...medications and other treatments can correct these imbalances. Talk therapy can directly improve brain functioning.”	Richard Harding, president of the American Psychiatric Association, 2000-2001	Harding, 2001, p. 66
“At some time in the course of their illness, most patients and families need some explanation of what has happened and why. Sometimes the explanation is as simplistic as ‘a chemical imbalance’...”	Robert Freedman, psychiatrist at the University of Colorado	Freedman, 2003, as cited by Hickey, 2014

(and many clinicians) were convincing the American public that the chemical imbalance theory was legitimate. We previously argued that the propagation of misleading advertising “is only possible in the absence of vigorous government regulation . . . or outcry from professional associations” (Lacasse & Leo, 2006). That outcry never came, and these issues weren’t addressed publicly until the patents for most blockbuster SSRIs had expired, and Big Pharma moved onto mood stabilizers and atypical antipsychotics. While we are hesitant to overemphasize conflicts-of-interest as an explanation for what has occurred, we can’t help but notice that the silence of psychiatry regarding chemical imbalance only ended when the profits had been extracted from the SSRI marketplace.

The new narrative will apparently be that psychiatrists recently discovered that the chemical imbalance theory was incorrect. Psychiatric researchers are changing their mind based on data, so the story goes, and it just took a while to let the public know. We believe this is empirically incorrect (Table 1; see Healy, 2015; Shorter, 2015). The idea that the withdrawal of the chemical imbalance theory was caused by recent data should be rejected.

As the theory has been withdrawn and a dialogue has taken place, many mental health clients have reacted negatively to the news that there was never any reason to believe that depression was caused by a serotonin imbalance (Healy, 2015). Many mental health clients find it unacceptable, and perhaps a violation of ethical informed consent, for clinicians to give patients metaphorical explanations for their mental health problems and promote them as scientific truth. Patients who start an SSRI because they have been told it will correct their chemical imbalance, that it is like thyroid medication for hypothyroidism, are likely to eventually conclude that they have simply not been told the truth. This obviously creates awkward dynamics in patient-prescriber relationships and also represents a potential public relations problem for the profession of psychiatry.

Previously, we argued that misleading consumer advertisements for SSRIs should end (Lacasse & Leo, 2005). A decade later, the serotonin theory of depression is acknowledged to be dead, and most SSRI advertising campaigns are now part of history. We look forward to a day when telling depressed patients they have a serotonin imbalance is as anachronistic as the miserable ovoid creature from the Zoloft advertisements of the past, and we believe that

day will come sooner than some might suppose. We encourage our colleagues in organized psychiatry to work towards this end by improving medical education and ongoing training, by endorsing shared decision-making, and by ensuring that informed consent is based on the scientific literature.

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neuroimaging biomarkers to achieve unprecedented levels of precision in predicting individual patient outcomes following CBT (Doehrmann et al., 2013; Siegle et al., 2012). These are just a few examples of an ongoing and iterative process of discovery in which neuroscience and clinical psychological science inform one another and create avenues for continuing to improve on the valuable tools psychologists already have at their disposal.

We enthusiastically welcome any of the contributors to the special issue, as well as any readers who find the topic engaging, to attend our SIG meeting which occurs annually at the ABCT convention. The meeting will serve as a useful launching point for ABCT members from all backgrounds to learn more about the possibilities our SIG members envision for translational and neurocognitive research and to engage in an open dialogue around these issues. We hope and expect that ABCT will continue to be a place where individuals utilizing diverse methodologies can learn from one another, united in the goal of relieving the suffering caused by psychological conditions.

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LETTER TO THE EDITOR

Response to Lacasse and Leo (2015)

Ronald W. Pies, *SUNY Upstate Medical University*

FOR THE PAST 33 YEARS as a psychiatrist, teacher, and writer, I have advocated a comprehensive, "biopsychosocial" model of mental illness and its treatment. Indeed, my 1994 textbook was titled *Clinical Manual of Psychiatric Diagnosis and Treatment: A Biopsychosocial Approach*. There is overwhelming evidence that biological and genetic factors contribute to the risk of developing some psychiatric disorders, including but not limited to major depressive disorder (MDD) (Gold et al., 2015); however, psychological, social, and cultural factors are also involved in the genesis of many psychiatric disorders, including MDD (Compton & Shim, 2015). Hence, a purely "chemical imbalance theory" of depression or any mental disorder is simplistic, incomplete, and unhelpful when it

implies that psychosocial factors are unimportant.

Unfortunately, in recent years, antipsychiatry bloggers have argued that "psychiatry"—in some broad, institutional sense—has promoted a "chemical imbalance theory" of mental illness in general. I have argued that there has been no such general "theory" propounded by academic psychiatrists, psychiatric textbooks, or official psychiatric organizations, such as the American Psychiatric Association. I stand by that claim. On the other hand, most psychiatrists would acknowledge that the biogenic amine *hypothesis* of affective disorders (Schildkraut & Kety, 2015) has indeed led many physicians to use the unfortunate, shorthand expression "chemical imbalance" to explain how antidepressants may work. I have repeatedly pointed out that

this expression, even if intended to reduce the stigma associated with psychiatric illness, is still misleading (Pies, 2011; Pies, 2014a). I have also acknowledged that in the 1990s, there was an overemphasis on the role of serotonin in the etiology of depression (Pies, 2015b).

Unfortunately, the article by Drs. Lacasse and Leo (2015) in the October special issue of *the Behavior Therapist* (Deacon & McKay, 2015) misrepresents my views in the matter of the so-called "chemical imbalance theory" (CIT) and insinuates that I have acted in bad faith, owing to alleged "conflicts of interest." These aspersions seem based, in part, on the false claim that I consider use of the chemical imbalance metaphor as merely "a little white lie"; and on the equally false claim that I was "paid to help [drug companies] promote their products." Specifically:

- Lacasse and Leo (2015) mistakenly imply that I either originated, or endorse, the phrase "little white lie" in reference to the CIT. In truth, I have never applied that expression to, for example, a clinician's telling a patient, "Your emotional problem is due simply

to a chemical imbalance.” I would regard such a statement as simplistic and reductionistic, and would never shrug it off—as Lacasse and Leo imply—as “a little white lie.” Lacasse and Leo may have made an innocent mistake in attributing this expression to me, owing to two online versions of my “Nuances” article (2014a, 2014b). However, had they investigated carefully, they would have seen that it was journalist Robert Whitaker who first employed the “little white lie” expression in the context of the CIT (Levine, 2014), and that my subsequent use of that phrase (Pies, 2014b) was in reference to Whitaker’s comments in his interview with Bruce E. Levine. Unfortunately, in the *Medscape* version of my “Nuances” paper—which originally appeared in *Psychiatric Times* (Pies, 2014a)—I did not put Whitaker’s phrase in quotes, for which omission I take responsibility. However, I could easily have cleared up any confusion on this point, had Drs. Lacasse and Leo discussed the matter with me, before writing their article.

- Citing papers I co-authored in 2003 and 2005—in which I disclosed having received occasional speaking honoraria from three pharmaceutical companies—as well as my consulting work with the medical communications company Apothecom (2001–2006), Lacasse and Leo assert that “. . . he [Pies] was paid to help [drug companies] promote their products at the time [their drug] advertisements were running” (p. 209). *Lacasse and Leo reach this conclusion without any direct knowledge of formal arrangements or agreements I may have negotiated in the years 2003–2005, or at any other time.*

Let me be clear: never, in any lecture I delivered that was underwritten by a pharmaceutical company, did I ever agree to “promote” a particular product; nor did I ever use slides or material provided by such companies, or have any personal contact with anyone representing the sponsoring company. I estimate that, in toto, I delivered 5 to 6 lectures, over a 30-year period, that were underwritten to some extent by pharmaceutical companies—with which I had no ongoing financial relationships.

As for my part-time consulting role with Apothecom, all stipends came solely from Apothecom and were paid to me on an ad hoc (hourly) basis. At no time did I

agree to “promote” any drug company’s product, nor was I induced or expected to do so by anyone at Apothecom. Of course, I am aware that “conflicts of interest” may sometimes arise inadvertently, even when physicians are not conscious of them, and I have written extensively on this issue (Pies, 2013). Furthermore, by 2007, when I became Editor-in-Chief of *Psychiatric Times* (2007–2010), I no longer accepted any lecture invitations (e.g., from various hospitals) that were supported by pharmaceutical companies.

As for Lacasse and Leo’s (2015) allegation that I “. . . didn’t speak out on the chemical imbalance issue decades ago” (p. 209)—for example, with an op-ed in the *New York Times*—there is a straightforward explanation for this. In my more than 30 years in psychiatry, I never once heard any of my colleagues or teachers propound a simplistic “chemical imbalance theory” of mental illness—or even of depression. I began addressing this issue in 2011, as I became increasingly aware of antipsychiatry bloggers using the “chemical imbalance” canard as a cudgel against psychiatry.

More substantively: Lacasse and Leo’s (2015) article ignores the critical distinction between a *hypothesis* and a *theory*—the latter being an integrated constellation of validated hypotheses (Understanding Science, 2015). Specifically, they fail to distinguish between the biogenic amine *hypothesis* of affective illness (which was indeed propounded by some psychiatrists, on good evidence) and a general, comprehensive *theory* that “mental illness is caused by a chemical imbalance”—which has never been the position of any professional psychiatric organization, or of most academic psychiatrists. Lacasse and Leo’s confusion is highlighted in their quite unconvincing Table 2 (p. 211), which cites precisely 9 psychiatrists (out of over 36,000 in the U.S.!) who refer in some fashion to a “chemical imbalance,” chiefly in the context of *depression*; or with respect to an antidepressant’s putative *mechanism of action*—not as a causal theory of “mental illness” in general.

Moreover, Lacasse and Leo’s (2015) paper obscures the difference between a putative *mechanism of action of a drug* (e.g., serotonin reuptake inhibition) and a *causal theory of mental illness* (the focus of my writings). To say that a drug “corrects a chemical imbalance”—as, indeed, some psychiatrists have stated—is not to claim that the illness being treated is caused by that imbalance. Many drugs work via mechanisms that are helpful for symptoms of a disease without addressing or revers-

ing the numerous (and often unknown) “causes” of that disease. For example, beta blockers are used to treat some cardiac arrhythmias, but nobody infers from this that the arrhythmia is *caused* by a deficiency of beta-receptor blockade. (Nor, for that matter, do cardiologists routinely explain to patients the mechanism of action of the medications they prescribe.) Of note: the most recent publicly available information from the American Psychiatric Association does not use the expression “chemical imbalance” in discussing risk factors for depression or the rationale for antidepressant treatment (What Is Depression, 2015).

Finally: If there is anything resembling an “official” psychiatric position on the causes of mental disorders, it is the 1978 statement from the American Psychiatric Association—which, unlike off-hand comments from one or another former APA president, was *approved by the APA Board of Trustees*, and is available online to this day:

“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.”

And this is precisely what most of my academic colleagues and I have been teaching—and telling our patients—for the past three decades (Pies, 2015a).

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Response to Lacasse and Leo (2015)

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IN THEIR RECENT ARTICLE, Drs. Lacasse and Leo (2015) continue an important discussion about the use of overly simplistic explanations of antidepressant actions. They argue that drug companies have used such explanations to market their drugs, and that psychiatrists have often been complicit—or at least silent—partners in this promotional technique.

In one section of the article, they accuse me of making deceptive statements to my patients about how antidepressants work. I deny this accusation. In talking to patients I simplify neurobiological concepts, using a shorthand to describe, in a simplistic way, some common theories of mental illness. I do this to enhance the placebo effect—which accounts for a significant portion of the overall effectiveness of antidepressants. Two of the most crucial components of the placebo effect are fostering positive expectations of success and reinforcing the medical ritual of pill-taking (Kaptchuk et al., 2010; Leuchter, 2014). In order to augment my patients' response to antidepressants, I will say something like, “This is a very effective medication, you should take this pill every morning, and you will begin to feel better within a couple of weeks.” If a patient asks me how the medication works, I will respond with, “We're not completely sure, but it has something to do with increasing levels of neurotransmitters like serotonin or norepinephrine—basically, these pills rebalance certain chemicals in the brain.”

There is nothing deceptive about such statements. While we don't understand exactly what serotonin's role is, we have some educated hypotheses. A recent review of serotonin and depression identifies 14 known serotonin receptor subtypes. When antidepressants bind to these receptors, a variety of chemical processes unfold, affecting levels of dopamine, norepinephrine, acetylcholine, cortisol—and yes, serotonin. While it isn't clear exactly how these chemical cascades alleviate depression or anxiety, it is clear that effective antidepressants exert their actions via shifts in the brain's biochemical milieu—and that serotonin is one of the central players in the drama (Kohler et al., 2015).

The authors, unfortunately, do not seem to be interested in scientific evidence.

In their role as the serotonin thought police, they brook no uncertainty: the serotonin theory is discredited, full stop. To support this conviction, they refer to a table entitled, “Evidence the Chemical Imbalance Theory of Depression Is Not Valid: Selected Quotations” (p. 210). But the table presents no “evidence” as we normally think of the term. Instead, it is a list of 12 statements made by various psychiatrists reflecting their personal opinions about the chemical imbalance theory. But just because smart people say something doesn't make it true. If it did, then their Table 2, “Promotion of the Chemical Imbalance Theory of Depression as Valid: Selected Quotations” (p. 211) would be an effective refutation of their entire article.

Lost in their polemic is the fact that as mental health clinicians, we are fortunate to be able to offer very effective treatments—both psychotherapeutic and psychopharmacologic—for our patients. There is much we don't understand, and we can do better. But mean-spirited attacks on colleagues are not going to help further the field.

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LETTER TO THE EDITOR

Response to Daniel Carlat (2015) and Ronald Pies (2015)

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Response to Daniel Carlat (2015)

In our recent article (Lacasse & Leo, 2015), we transcribed public statements made by Dr. Carlat on National Public Radio (NPR). Dr. Carlat disclosed that he used content similar to the Zoloft marketing campaign (Lacasse, 2005) to explain antidepressants to patients:

I'll often say something like the way Zoloft works, is, it increases the level of serotonin in your brain (or synapses, neurons), and, presumably, the reason you're depressed or anxious is that you have some sort of a deficiency. And I say that [chuckles] not because I really believe it . . . I think I say that because patients want to know something . . . They certainly don't want to know that a psychiatrist essentially has no idea how these medications work. (Davies, 2010)

Despite Dr. Carlat's allegation, we are not the serotonin thought police, ticketing offenders that violate our sensibilities. But, we don't believe we're alone in thinking it's objectionable to tell patients something you don't believe yourself. To say things like this publicly and not expect criticism seems naïve. We are not cherry-picking here, as Dr. Carlat has a history of such disclosures:

While it is true that most of our drugs affect neurotransmitters in various ways, when psychiatrists start using what I call neurobabble, beware, because we rarely know what we are talking about. I fall into this habit with patients all the time. When I find myself using phrases like "chemical imbalance" and "serotonin deficiency," it is usually because I'm trying to convince a reluctant patient to take a medication . . . (Carlat, 2010, p. 75; see pp. 74–83 for

published content similar to that reported in the NPR interview)

We don't think scientific truth is so flexible, and disagree with shaping it for purposes convenient to the prescriber (e.g., to get patients to take medication, or to reassure the patient of the prescriber's expert knowledge). Dr. Carlat also writes that he boosts the placebo effect by telling patients that SSRIs are "a very effective medication" (Carlat, 2015; this issue, p. 262). Fournier et al. (2010) demonstrated a Number-Needed-to-Treat (NNT) of 11 for severely depressed patients. In other words, when prescribing to 11 severely depressed patients, a prescriber would expect 1 to have an impressive short-term response as compared to placebo. Given the existence of such data, we question the accuracy of claiming that antidepressants are "very effective" (see also Weitz et al., 2015).

Response to Ronald Pies (2015)

On the "Little White Lie" of Chemical Imbalance

In his reply, Dr. Pies (2015; this issue) states that he does not endorse calling the chemical imbalance a "little white lie," and that he was referencing Mr. Robert Whitaker when he used this phrase. We take his word on this, appreciate that he acknowledges his editorial error, and apol-

ogize for the confusion. We are glad that we and Dr. Pies have this opportunity to correct the record.¹ We note that a correction has been made to Dr. Pies' original article as of November 4, 2015 (Pies, 2014).

On Promotion of Psychiatric Drugs

Like many, we believe that academic psychiatrists have been too closely aligned with the pharmaceutical companies (e.g., Healy, 2004). In our article, we hypothesized, as we had before (Lacasse & Leo, 2009), that the flow of money from drug companies to academic psychiatry might be partially responsible for the resounding silence in academia regarding misleading advertising of psychiatric drugs. Dr. Pies had himself argued that pharmaceutical companies were responsible for spreading the chemical imbalance metaphor. While we agreed that this was part of the problem (Lacasse & Leo, 2005), we saw some irony in the fact that he had received funding from GlaxoSmithKline, among the worst offenders in our opinion when it came to misleading consumer advertising. We never accused Dr. Pies of acting in bad faith, and in fact wrote, "We want to be clear that we are not accusing Dr. Pies of anything" and that entanglements with drug companies aren't "uncommon among academic psychiatrists, and some would say it was par for the course in the 2000s" (Lacasse & Leo, 2015, p. 209). However, Dr. Pies strongly objects to our assertion that he has been involved in the promotion of psychiatric drugs, and so we will reluctantly respond.

How Psychiatric Drugs Are Promoted

As background, it is useful to understand the strategies that pharmaceutical companies use to promote² their products. They often contract with "medical communications companies," which specialize in "publication planning" and employ medical writers who contribute to (or even author or co-author) peer-reviewed articles (Lacasse & Leo, 2010), usually with academics listed as authors on the byline

¹In his 2014 article, Dr. Pies begins a paragraph by citing an interview of Mr. Robert Whitaker (Levine, 2014; Pies, 2014). Dr. Pies then writes about the "antipsychiatry movement." In these sentences there are no quotations and no citations; they consist of Dr. Pies' own interpretations. He mentions chemical imbalance, writing that "by promoting this little white lie..." Mr. Whitaker had used quotation marks around the phrase as editorial comment, but Dr. Pies did not. Without quotation marks or citation, we took this as we did his other writing in this section, as his opinion (we aren't the first to do so; see Hickey, 2014). We reproduced the entire quotation from Dr. Pies in a footnote, commenting on this exact issue (Lacasse & Leo, 2015, p. 209). A correction to the article (Pies, 2014) was made in November of 2015, after our article was published. Rather than clarifying where the phrase "little white lie" came from, Dr. Pies removed it and replaced it with "simplistic formulation." Interestingly, Mr. Whitaker did not characterize chemical imbalance as "simplistic" (Levine, 2014).

(Sismondo, 2009; Sismondo & Doucet, 2010). Unrestricted educational grants are another strategy used by pharmaceutical companies, as they are “. . . a well-established tool that all of the major pharmaceutical manufacturers use to disseminate information to the medical community. . . . The off-label promotion risk of educational grants appears to pose the greatest threat to the Federal health care programs and beneficiaries, but it is also the most difficult to demonstrate conclusively”³ (U.S. Senate Committee on Finance, 2007). Nonetheless, the legal complaint against GlaxoSmithKline for illegal marketing of drugs like Paxil and Lamictal (which was eventually settled for 3 billion dollars; Department of Justice, 2012) described the following:

GSK’s [GlaxoSmithKline’s] extremely aggressive off-label marketing campaigns for Lamictal included spending large sums of money in the form of unrestricted grants, membership on advisory boards and speaker’s fees on physicians and researchers who served as “national thought leaders.” (*United States of America v. GlaxoSmithKline*, 2012)

Certainly many professors believe they are being hired to share their expert opinion, but in the eyes of pharmaceutical and medical communications companies, academics are clearly being paid because their opinions are helpful in the promotion of the drug company’s product.⁴ At the risk of stating the obvious, from the companies’ point of view, it would make no sense to pay psychiatrists or medical writers if they didn’t have positive things to say about the product. From their point of view, the ideal

academic would be someone who believes that grants, payments, or the assistance of medical writers have no effect on their objectivity. In fact, academics receiving funding from drug companies or proxies may be genuinely unaware that they have been retained because their opinions have promotional value (e.g., Carlat, 2007). We do not believe that academics agree to just say anything the companies want in return for compensation, and we never asserted that Dr. Pies was a “hired gun.” We share the views of Dr. David Healy (2012), who argues that pharmaceutical companies seek out academics who already share their views.

Our Clarification

First of all, our statements were not based on any direct or firsthand knowledge of any verbal or written agreement that Dr. Pies had with Apothecom, or any other corporate entity. We were trying to be brief, and so we wrote that Dr. Pies “fails to mention that he was paid to help them [drug companies] promote their products” (Lacasse & Leo, 2015, p. 209). In retrospect, we could have written more clearly and specifically, and we therefore correct this section to read as follows:

Dr. Pies blames the drug companies for running misleading advertisements about chemical imbalance, belatedly admits he should have done something sooner, but fails to mention his involvement with the pharmaceutical industry. In 2005, he disclosed that “he has consulted for an independent medical education company that involves work with pharmaceutical company clients” (Pies & Rogers, 2005).⁵ As of 2003, Dr. Pies disclosed that he was a recipient of “ad hoc stipends from Abbott,

Janssen, GlaxoSmithKline, and other pharmaceutical or related corporate entities” (Chaudron & Pies, 2003, p. 1284). In this same 2003 article, Dr. Pies disclosed that he was a consultant for Apothecom (Chaudron & Pies, 2003), a medical communications agency listed in the Top-100 agencies by Medical Marketing and Media (Frank, 2015). The Apothecom website boasts that they are a “communications powerhouse” employing “130 scientific storytellers” and that they do “scientific branding . . . publications planning, delivery and maximizing . . .” (Apothecom.com, 2015). Dr. Pies reports working with Apothecom from 2001–2006 (Pies, 2015). As of 2003, Apothecom listed the pharmaceutical companies Abbott, Sepracor, and GlaxoSmithKline among their clients (Lieberman, 2003).

From 2002–2006, Dr. Pies was author or co-author of articles funded through unrestricted educational grants from GlaxoSmithKline (makers of the anticonvulsant drug Lamictal). These include an article entitled “The ‘Softer’ End of the Bipolar Spectrum” (Pies, 2002a); a 2002 article on combining lithium with anticonvulsants such as Lamictal in bipolar disorder (Pies, 2002b); a review article on “Matching the Bipolar Patient and the Mood Stabilizer” (Gelenberg & Pies, 2003); a 2003 article on postpartum psychosis and bipolar disorder stating that Lamictal “. . . also not FDA-approved for treatment of bipolar disorder, does appear especially useful for bipolar depression” (Chaudron & Pies, 2003, p. 1289);⁶ a review article focused on treatment of bipolar disorder with co-occurring substance use (Albenese & Pies, 2004); and a 2006 article recommending Lamictal for use in maintenance treatment of bipolar disorder (Marken & Pies, 2006). Another 2006 article funded by GlaxoSmithKline stated that “lamotrigine [Lamictal] may also have benefits in borderline personality disorder” (MacKinnon & Pies, 2006, p. 8), with the co-authors disclosing that “The authors of this paper do not have any commercial associations that might pose a conflict of interest in connection with this manuscript” (MacKinnon & Pies, 2006, p. 1). Dr. Pies was also co-author of a review article on treatments for insomnia which highlights the potential benefits of Lunesta, and acknowledges the assistance of Sepracor, Inc. (makers of Lunesta) in the preparation of the manuscript (Winkelman & Pies, 2005);⁷ and co-author of a 2007 article on insomnia in which the authors acknowledge “that they received compensation from Sepracor for services they pro-

²The Oxford Dictionary defines promote as “...Further the progress of (something, especially a cause, venture or aim); support or actively encourage... Give publicity to (a product, organization, or venture) so as to increase sales or public awareness...”. The word “promotion” by itself does not imply that the information is biased, inaccurate or deceptive, nor is it intrinsically negative. Products can be honestly and enthusiastically promoted. This point may have been overlooked by some readers of our original article. Sismondo (2009) describes a balance between marketing and science among publication planners.

³One reason that it so difficult to demonstrate this conclusively, as the Senate notes, is because in many cases the money trail is complicated and difficult to sort out from the outside.

⁴Like our original article and the rest of this response, this paragraph reports our academic opinion on these issues.

⁵This is seemingly Apothecom, but Dr. Pies did not disclose the name of the company.

⁶Ghaemi, Shirzadi, and Filkowski (2008) examined GlaxoSmithKline’s unpublished negative studies and wrote: “[Lamictal] has very limited, if any, efficacy in acute bipolar depression and rapid-cycling bipolar disorder, areas in which practicing clinicians, as well as some academic leaders, have supported its use.”

⁷In an Op-Ed in the *New York Times*, Dr. Daniel Carlat critiqued an arguably similar article as a form of pharmaceutical company marketing (Carlat, 2006).

vided in support of the development of this manuscript” (Roth, Roehers, & Pies, 2007, p. 77). Several of the above-listed articles acknowledge editorial assistance and/or content contribution from medical writers without listing their company affiliation or who paid them for their work; the online resume of one such medical writer lists Apothecom as her employer at the time. Dr. Pies wrote that his relationship with Apothecom took place from 2001–2006 (Pies, 2015). In 7 of the 8 journal publications discussed above, Dr. Pies does not disclose a relationship with Apothecom.

Discussion

While we are pleased to make these clarifications, we think the primary issue remains the use of the chemical imbalance metaphor in clinical interactions with vulnerable patients. We find Dr. Pies’ arguments unconvincing, and it is obvious to us that the chemical imbalance theory was indeed embraced by the field of psychiatry (Whitaker, 2015), and that the explanation is still used by prescribers to this day. We have wondered what has motivated Dr. Pies’ shifting positions and arguments on this topic (Lacasse & Leo, 2015; Whitaker, 2015), and in his reply, we think he gave an answer. Dr. Pies writes, “I began addressing this issue in 2011, as I became increasingly aware of antipsychiatry bloggers using the ‘chemical imbalance’ canard as a cudgel against psychiatry” (Pies, 2015, this issue, p. 261). We think this is useful context to guide interpretation of his arguments. Dr. Pies is apparently defending his guild against outside attack (Whitaker, 2015; Whitaker & Cosgrove, 2015). Read as a sustained, political defense of his profession, we think his writings on chemical imbalance make perfect sense.

We are not part of this guild, so we have a different point of view. We think these issues are deeply important, not because psychiatry is under attack, but because we believe many depressed and anxious patients have been hurt by being told that they have a chemical imbalance in their brain that is corrected by psychiatric medication. We think calling this “misleading” is an understatement—and that learning now that chemical imbalance is only a metaphor (Lacasse & Leo, 2006) could well be traumatic. This is true both for the prescribers who were taught to use this metaphor, as well as for the patients who heard it from their physicians and believed it to be a scientific fact. As anyone who has dealt with trauma knows, the first step is to acknowledge what happened. Insisting that

it never occurred, or was less severe than perceived, or was unsanctioned by authorities, will inevitably cause negative reactions—especially so when these claims are not quite true.

We think it is in the best interests of the psychiatric profession to look closely at how the chemical imbalance metaphor has been used over the last 25 years. This is no easy task (Tavris & Aronson, 2008). It requires putting ego aside, listening carefully rather than lecturing, and a willingness to be open-minded and nondefensive. Rather than obfuscating the issue, or demonizing those delivering the bad news as “antipsychiatry,” the profession will eventually need to admit that patients were misinformed and harm was done. Once this step is taken, perhaps psychiatry can recapture the public’s trust and move forward.

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