Deconstructing the Chemical Imbalance Theory:

A Strategic Starting Point for Counter-Campaigns

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Abstract

The biomedical model dominates lay perception of depression etiology, as evidenced by widespread endorsement of the chemical imbalance theory. However, research has never identified a biological cause of, or reliable biological marker for, any mental disorder. Attributing depressive symptoms to biological dysfunction has been found to increase preference for pharmaceutical treatment and decrease confidence in the efficacy of psychosocial interventions. Yet, evidence has suggested that psychosocial therapies may promote more positive treatment outcomes. It is argued that belief in the chemical imbalance theory compromises the ability of patients to exercise informed treatment consent, and that organized medicine has an ethical obligation to correct this misconception. A novel study is proposed to support corrective measures. Previous work has explored the relationship between (a) direct-to-consumer advertising and belief in the chemical imbalance theory, and (b) etiological beliefs and attitudes towards psychotherapy. The proposed study seeks to expand both lines of inquiry through a population-based survey designed to (a) investigate the effect of direct-to-consumer advertising on consumer beliefs, and (b) identify the effect of consumer beliefs on attitudes regarding five distinct psychosocial interventions. To the best of my knowledge, this would be the first study to examine the effect of the chemical imbalance theory on consumer attitudes regarding specific psychosocial interventions, besides psychotherapy. As earlier work has also supported the proposal of counter-pharmaceutical campaigns, findings from the present study may provide a useful starting point for campaign content development.

Keywords: chemical imbalance, serotonin hypothesis, counter-campaigns

Introduction

In 1987, the Food and Drug Administration (FDA) approved Prozac (fluoxetine), the first selective serotonin reuptake inhibitor (SSRI). During the two decades that followed, antidepressant use among American adults increased 400% (Pratt, Brody, & Qiuping, 2011), the United States developed the highest prevalence of depression among 14 countries (World Health Organization, 2004), and disability rates due to mental illness, as measured by Supplemental and Social Security eligibility, more than doubled (Whitaker, 2010). While antidepressant use and disability rates increased, use of non-pharmaceutical treatments, such as psychotherapy, decreased considerably during the same time period (Olfson et al., 2002). Today, in contrast to steadily decreasing mortality rates of cardiovascular disease, stroke, and cancer, there is no evidence for reduced morbidity or mortality from any mental illness (Insel, 2009).

While temporal proximity does not prove that increased use of pharmaceutical medication is responsible for rising disability rates, Deacon (2013) has suggested that the possibility is "sufficiently plausible" to warrant serious investigation (p. 853). Likewise, Miller (2010) has criticized biological reductionism – that is, ascribing mental illness to primarily biological causes – as hindering crucial scientific and clinical progress. While further research is needed to determine whether antidepressant use worsens the course of depression (Fava, 2003), its failure to improve morbidity and mortality is beyond debate (Insel, 2009).

This conclusion supports the need to explore alternative treatments that might be more effective (Breggin, 2015). As summarized by Thomas Insel (2009), Director of the National Institute of Mental Health, "While psychosocial interventions have received much less marketing attention than pharmacological treatments, the results are arguably more encouraging" (p. 129). Specifically addressing antidepressants, Insel (2011) has since added: "The bottom line is that

these medications appear to have a relatively small effect in patients broadly classified as having depression" (para. 15.) Yet, with patients advocating the false belief that antidepressants "increase whatever it is in my body that makes me happy and calm" (Cohen & Hughes, 2011, p. 181), the question then becomes: What would it take to change consumers' minds?

The following paper will support two claims: (a) that changing lay perception of depression treatment is necessary, to encourage critical thinking about psychoactive drug effects and increase acceptance of psychosocial interventions (Breggin, 2015; Cohen & Hughes, 2011), and (b) that changing lay perception of depression treatment is possible, through promotional campaigns similar in strategy to those executed by the pharmaceutical industry (Santucci, McHugh, & Barlow, 2012). I will seek to distinguish my argument from existing literature by (a) exploring the effect of etiological beliefs on *specific* psychosocial interventions, besides psychotherapy, and (b) proposing a strategic starting point for counter-campaign development.

While counter-pharmaceutical campaigns have been supported by recent literature (Gaudiano & Miller, 2013), there has been limited discussion regarding strategy (with the notable exception of Santucci et al., 2012) and, to the best of my knowledge, no dialog addressing practical, content development (i.e., what should the campaign say first?). With hypothesized support from the proposed study, I hope to suggest a useful starting point for future consideration: Before attempting any other communication goals (i.e., promoting the benefits of psychosocial interventions), I propose that successful counter-campaigns will need to begin, first and foremost, with a strategic deconstruction of the chemical imbalance theory.

Although widely rejected by the academic community (Lacasse & Leo, 2015), the idea that depression is caused by a chemical imbalance remains popular in lay discourse (Frank, Lysaker, & Robinson, 2007; Link, Phelan, Bresnahan, Stueve, & Pescosolido, 1999). Despite the

fact that a chemical imbalance (most commonly understood as a serotonin deficiency) has never been found for depression (Glenmullen, 2000), the lay public continues to draw on biological analogies to understand disorder treatment. While psychiatry attempts to distance itself from the "pseudoscientific" notion that depression is caused by a chemical imbalance (Deacon, 2013, p. 852), lay publications perpetuate the myth that "depression is an illness like any other, no different than… diabetes" (Consumer Reports, 2013, p. 5). (See: McMullen & Sigurdson, 2014 for full discussion of the depression/diabetes analogy.)

As noted by recent studies, additional research is needed to investigate the factors that shape lay beliefs about the chemical imbalance theory (Jin Seong & Ho-Young, 2013), how those beliefs then, in turn, affect symptom perception (Kemp, Lickel, & Deacon, 2014) and treatment expectancies (Deacon & Baird, 2009), and how personal understanding of the chemical imbalance theory connects with public forms of knowledge (Cohen & Hughes, 2011). Ethical considerations regarding how much information to share with patients also warrants review (France et al., 2007). The present paper is designed in support of these goals, as well as the following arguments:

Concern for patient welfare, as well as the credibility of the field of psychology, necessitates an "urgent, honest, and public conversation" about the validity and utility of the chemical imbalance theory and the biomedical model that it represents (Deacon, 2013, p. 858). Psychology, as a profession, has an obligation to separate science and industry influence in pursuit of this goal (Antonuccio, Danton, & McClanahan, 2003; Gallo, Comer, & Barlow, 2013). The medical community needs to respond "vigorously" to pharmaceutical promotion (Wilkes, Bell, & Kravitz, 2000, p. 125), as health professionals and the lay public require a more rational understanding of how psychiatric drugs work (Breggin, 2015). To this end, "tainted" drug

company education needs to be replaced with scientifically based, useful information (Wolfe, 2002, p. 526). Patients need to be educated regarding critical evaluation of promotional claims (Bell, Kravitz, & Wilkes, 1999), and physicians need to be assisted in facilitation of this process (Rosenthal, Berndt, Donohue, Frank, & Epstein, 2002).

In response to the National Institute of Mental Health's claim that "the problems of dissemination and implementation are no less complex than understanding the intracellular signaling pathways or the language of genetic transcription" (Insel, 2009, p. 132), I concur; it is my humble hope that the argument presented below will serve as a small step in addressing this complexity.

Background

Derived from drugs meant to treat infections and found only "serendipitously" to alter mental state (Angell, 2011, para. 9), antidepressants are the cornerstone of the chemical imbalance theory – a hypothesis that, to this day, remains unproven (Dubovsky, Davies, & Dubvosky, 2003). Criticized for ex juvantibus reasoning (Carlat, 2010; Kirsch, 2009), the theory was nonetheless promoted by the pharmaceutical industry (Lacasse & Leo, 2005) – which struck gold with the development of SSRIs. Representing the first "rationally designed" class of psychotropic medication (Masand & Gupta, 1999, p. 69), SSRIs were developed to correct the serotonin deficiency proposed by the chemical imbalance theory (Antonuccio, Danton, DeNelsky, Greenberg, & Gordon, 1999). As described by Spiegel (2012), "It is because of the popularity of Prozac that the low-serotonin theory took hold" (para. 23).

However, to this day, scientists have yet to identify a biological cause of, or even a reliable biological marker for, any mental disorder (Deacon, 2013) – leading some to question

whether interfering with serotonin reuptake may cause more harm than good (Breggin, 2015; Whitaker, 2010). According to Princeton neuroscientist, Barry Jacobs (1991):

> [SSRIs] alter the level of synaptic transmission beyond the physiologic range achieved under [normal] environmental/biological conditions. Thus, any behavioral or physiologic change produced under these conditions might more appropriately be considered pathologic, rather than reflective of the normal biological role of serotonin. (p. 22)

While a detailed discussion of the scientific intricacies framing the chemical imbalance theory is beyond the scope of this article, a brief summary of its evolution is provided for historical context. (For additional background, see: Deacon, 2013; France et al., 2007; Whitaker, 2010.)

Antidepressants

Thorazine, the nation's first antipsychotic, is widely credited with launching the psychopharmaceutical revolution (Whitaker, 2005). Following Thorazine's debut in the 1950s, the pharmaceutical industry soon introduced tricyclic antidepressants and monoamine oxidase inhibitors (France et al., 2007), followed in the late 1980s by SSRIs (Healy, 2015). However, the rise of psychopharmacology has been criticized as owing as much to chance as it does to science (Deacon, 2013) – a point well illustrated by the history of psychiatry's first "wonder" drug (Whitaker, 2010, p. 57).

In 1951, after observing the anesthetic properties of a new compound called chlorpromazine, French surgeon Henri Laborit began administering the drug to patients. Chlorpromazine was an immediate success, noted for its ability to induce "artificial hibernation" during surgical procedures (Ban, 2007, p. 495). Speaking at a conference in December 1951, Laborit suggested that the drug might even have a role in psychiatry, observing that

chlorpromazine produced a "veritable medicinal lobotomy" (Swazey, 1974, p. 104 as cited by Whitaker, 2010, p. 49). In 1955, chlorpromazine made its debut in the United States – marketed under a name new: Thorazine.

In the span of several years, iproniazid (a tuberculosis medication found to have energizing effects) and imipramine (a derivative of iminodibenzyl, a compound with molecular similarities to chlorpromazine) hit the market (France et al., 2007). Unlike Thorazine, which was considered a "major tranquilizer", iproniazid and impramine were termed "psychic energizers" (Moncrieff, 2008, p. 2349). In 1959, the *New York Times* began using a different name: antidepressants (Whitaker, 2010, p. 60). Yet, the antidepressant efficacy of both drugs was speculative, at best. As Marcia Angell, former editor-in-chief of the *New England Journal of Medicine* explained, "Instead of developing a drug to treat an abnormality, an abnormality was postulated to fit a drug" (2011, para. 11).

Speaking at a 1955 conference on chlorpromazine, psychiatrist E.H. Parsons warned, "We have to remember we are not treating diseases with this drug. We are using a neuropharmacologic agent to produce a specific effect" (*Chlorpromazine and Mental Health*, p. 132 as cited by Whitaker, 2010, p. 50). However, enthusiasm quickly blurred the line between evidence and expectation. The lay press began to suggest that iproniazid and impramine were "fixing" something in the brain (Olfman, 2015, p. 15). The introduction of second-generation antidepressants, which caused considerably less side effects than their predecessors (Olfson et al., 2002), tipped the scales. In 1987, Eli Lilly unveiled the nation's first SSRI. As described by Alan Frazer, Chair of Pharmacology at the University of Pennsylvania, "Prozac just blew everything else out of the water" (Spiegel, 2012, para. 19).

The Chemical Imbalance Theory

According to Healy (2015), the chemical imbalance theory took root in the public domain rather than in science. Encouraged by the recent discovery of "magic bullet" drugs (e.g., penicillin) which could effectively target specific diseases, the public enthusiastically welcomed antidepressants as a similar cure (Deacon, 2013, p. 847). However, as drug sales soared, researchers struggled to explain what antidepressants were actually fixing. Working backwards, scientists reasoned that since first-generation antidepressants raised norephinephrine and serotonin levels in the brain, depression might be caused by low levels of norephinephrine and serotonin (Coppen, 1967; Schildkraut, 1965). (For a more detailed review, including discussion of reserpine, see: Healy, 1987.) Unfortunately, the chemical imbalance theory never panned out (Whitaker, 2005). As Schildkraut (1981) concedes, "[T]he catecholamine hypothesis of affective disorders remains to be verified" (p. 336). The *American Psychiatric Press Textbook* concurs, stating, "Additional experience has not confirmed the monoamine depletion hypothesis" (Dubovsky et al., 2003, p. 479).

While no fully developed demonstration of a mechanism by which psychology or biology affects the other has ever been offered (Miller, 2010), a significant body of evidence contradicting the chemical imbalance theory exists (Whitaker, 2010). (See, for instance: Delgado, 2000, finding that monoamine depletion does not cause depression in healthy volunteers.) However, a summary of the theory's flaws is perhaps best captured by the "aspirin argument" – that is, the idea that fevers and headaches are helped by aspirin, does not mean that fevers and headaches are caused by low levels of aspirin in the brain (Angell, 2011; Lacasse & Leo, 2005; Valenstein, 1998).

By the 1990s, there was "no evidence that [SSRI] treatment corrected anything" (Healy, 2015, p. 1). Despite years of experimentation, there was no convincing, consistent proof for the chemical imbalance theory and, worse yet: the mechanism of action for antidepressants in treating depression had not been found (Antonuccio et al., 1999). Writing as recently as 2014, McMullen and Sigurdson concluded that, "how and even whether the regulation of levels of neurotransmitters in the brain works to relieve the symptoms of depression is unknown" (p. 310). Addressing implications to clinical practice, Moncrieff and Cohen (2009) have stated:

> [G]iven the paucity of the evidence, we suggest that prescribers should not present the drugs they prescribe for mental disorders as disease specific treatments. Psychiatric drugs might need renaming, to avoid the presumption of specificity built into labels like antidepressants…. (p. 2)

Pharmaceutical Promotion

Although attempts to construe psychological disorders as biological events have been criticized as "indefensible based on available theory and data, and… at least very suspect on logical grounds" (Miller, 2010, p. 716), the idea that depression is caused by a chemical imbalance was – until recently – vigorously promoted by the pharmaceutical industry (Lacasse & Leo, 2005; 2015). As spending on DTCA increased 212% between 1996 and 2000 (Rosenthal et al., 2002), it is perhaps not surprising that participants in a 2007 survey reported widespread exposure to the chemical imbalance theory, most often via television (France et al., 2007). Fueled by marketing claims that medication could correct neurotransmitter imbalances (Lacasse & Leo, 2005), antidepressant sales increased from $240 million to $11.2 billion in less than 20 years (1985-2004) (Whitaker, 2005).

While rapid expansion of the antidepressant market has been partially credited to DTCA campaigns (Donohue & Berndt, 2004), the World Health Organization (2015) notes that an "inherent conflict of interest" exists between the business goals of drug manufactures and the medical needs of patients (para. 2). Confusion arises when commercially driven information is represented as educational (Wolfe, 2002) – an issue of concern with both DTCA and physician detailing. Unfortunately, few health professionals and even fewer members of the general public understand the regulations surrounding pharmaceutical promotion (Wilkes et al., 2000).

For instance, although drug companies are not required to submit advertisements to the FDA for prior approval, approximately 50% of surveyed participants endorsed the view that they were (Bell et al., 1999). (While drug companies are required to submit all advertisements to the FDA, they are free to publish before approval.) Likewise, 43% thought that only "completely safe" prescription drugs could be advertised directly to the consumer, 21% believed that only "extremely effective" drugs could be marketed, and 22% believed that the advertising of prescription drugs with serious side effects had been banned (Bell et al., 1999). All of these statements are untrue.

While the FDA has no power to levy fines, proponents of DTCA point out that the agency may issue violation letters (Holmer, 2002). Unfortunately, only around 30 FDA employees are responsible for reviewing the roughly 30,000 submissions the agency receives each year – a figure that has led the General Accounting Office to conclude: "Misleading advertisements may have completed their broadcast life cycle before the FDA [has] issued the letters" ("Free Rein", 2003). Donohue, Cevasco, and Rosenthal (2007) noted that in 2004, only 32% of prescription drug advertisements went under FDA review before airing. Of further interest: Breggin (2015) has criticized FDA-required drug efficacy and safety studies as

"extremely flawed" (p. 7), with Bodenheimer (2000) noting that the pharmaceutical industry underwrites approximately 70% of all clinical drug trials in the United States. (For further discussion of this argument, see: Healy, Mangin, & Antonuccio, 2013; Kirsch, Moore, Scoboria, & Nicholls, 2002.)

Physician detailing represents an arguably greater set of concerns. To ensure steady product demand, pharmaceutical manufacturers have traditionally deployed what Bell et al. (1999) refer to as "large armies" of sales representatives to market medications directly to physicians (p. 651). In fact, the majority of pharmaceutical promotional efforts focus on physicians (Donohue et al., 2007), with recent estimates suggesting that promotion to health care professionals accounts for more than 80% of all money spent on prescription drug promotion (Rosenthal et al., 2002). For perspective: While spending on DTCA increased by $1.7 billion between 1996 and 2000, spending on the promotion of prescription drugs to physicians increased by nearly $5 billion (Rosenthal et al., 2002).

Gallo et al. (2013) have rightfully concluded that matching the pharmaceutical industry's advertising dollars will not be feasible. In 2005 alone, SSRI/SNRI promotional spending exceeded $1 billion, with over $345 million attributed to DTCA (Donohue et al., 2007). However, as argued below, changing lay perception of depression treatment is both necessary and possible.

Changing Lay Perception of Depression Treatment is Necessary

As the potentially dominant cultural story of depression etiology, the chemical imbalance theory may exert significant influence on treatment-seeking behaviors (France et al., 2007) – a causal relationship that will be explored at greater length in the following sections. Although recent review suggests a decrease in pharmaceutical promotion of the serotonin hypothesis

(Lacasse & Leo, 2015) and an increasing openness to critical discourse about the biomedical model (Deacon, 2013), many members of the general public still believe that depression is caused by a chemical imbalance (Pescosolido et al., 2010). For these individuals, recovery is about "fixing that imbalance in the short term, usually with medication" (Ridge & Ziebland, 2006, p. 1043).

The notion that mental disorders are biologically based brain diseases pervades the American healthcare system (Deacon, 2013). And yet, no biological cause for any mental disorder has ever been found (Miller, 2010). Although psychiatrists have acknowledged a shift away from the chemical imbalance theory – see: "Serotonin: How Psychiatry Got Over Its High School Crush" (Pies, 2015) – two significant issues remain: (a) many members of the lay public still believe that depression is caused by a chemical imbalance (Link et al., 1999), and (b) even if specific belief in the chemical imbalance theory is waning, evidence suggests that 67% of the American public attributes depression to neurobiological causes (Pescosolido et al., 2010). While not problematic on its own, this unfounded belief (Miller 2010) increases the odds of treatment endorsement (Pescosolido et al., 2010) – which, most frequently, results in the prescription of antidepressants (Oflson et al., 2002). As summarized by Moncrieff and Cohen (2009), widespread use of psychiatric drugs is "justified" by the idea that antidepressants work by helping to correct underlying biological abnormalities (p. 1). However, there is no evidence that this is true (Breggin, 2015).

While biological therapies may one day prove effective in treating depression, antidepressants, in their current form, have provided no proof of lives saved or restored function (Healy, 2015; Insel, 2009). Further evidence, explored shortly, has even suggested that their use may result in active harm (Whitaker, 2010). On this foundation, I propose that changing lay

perception of depression treatment is necessary. I suggest that belief in the chemical imbalance theory, or a more generalized deferment to the biomedical model, promotes favoritism of pharmaceutical treatment (Kemp et al., 2014; Moncrieff & Cohen, 2009), which, in turn, results in patient harm. This argument is supported by three claims:

1. Belief in the chemical imbalance theory/deferment to the biomedical model results in patient confusion regarding depression etiology, prognosis, and treatment expectancy,
2. Favoring pharmaceutical treatment subjects patients to negative side effects that might otherwise be avoided through use of treatments not supported by the chemical imbalance theory/biomedical model, and
3. Favoring pharmaceutical treatment prevents potentially more positive outcomes by neglecting treatments not supported by the chemical imbalance theory/biomedical model.

Detailed discussion of each claim, as well as a more in-depth review of pharmaceutical promotion and its role in shaping patient and physician behavior, is provided below.

Lay Confusion Regarding Depression

A national survey found that 72.8% of respondents endorsed the view that depression was likely to be caused by a chemical imbalance (Link et al., 1999). Likewise, a 2007 study of 262 undergraduate psychology students revealed that 84.7% viewed chemical imbalance as a potential cause of depression (France et al., 2007). A 2011 survey of 22 adults taking psychiatric medication found a similar effect: two-thirds believed they had a chemical imbalance (Cohen & Hughes, 2011). This misconception is echoed by a depression patient named Matthew, observed by Ridge and Ziebland (2006):

> I mean it's chemical, you know I'm quite, you know I'm quite happy to admit there's something screwed up about my brain chemistry […] some people are diabetic, they take

> drugs, you know. And I know people say, "Oh, it's not the same." But I'm afraid it bloody well is. (p. 1043)

Unfortunately for patients like Matthew, this analogy is not true (McMullen & Sigurdson, 2014). And yet, belief in its premise – the idea that depression is a biological disease – has been found to guide treatment beliefs (Kemp et al., 2014).

In the first experimental study to examine the effect of the chemical imbalance theory on prognostic pessimism and treatment expectancies, Kemp et al. (2014) provided participants with bogus test results indicating that their depressive symptoms were either caused, or not caused, by a chemical imbalance. As hypothesized, those who received chemical imbalance feedback viewed pharmaceutical treatment as more credible and effective than psychotherapy. Participants who thought their depression was caused by a chemical imbalance also exhibited increased prognostic pessimism and lowered negative mood regulation expectancies – that is, believing depression was biologically based led participants to feel less hopeful about disorder prognosis and less confident in their ability to regulate their own moods.

As noted by Kemp et al. (2014), the clinical relevance of prognostic expectancy is well established. A 2010 review found that patient expectancy can "substantially" affect the results of clinical trials (Rutherford, Wager, & Roose, 2010, p.1). This conclusion is underscored by placebo studies, finding that drug-placebo differences in antidepressant efficacy are relatively small even for severely depressed patients (Kirsch et al., 2008). (For updated discourse on Kirsch et al.'s, 2008, findings, see: Huedo-Medina, Johnson, & Kirsch, 2011.) Yet, one of the most frequent explanations for accepting a biological view of depression is that medication seems to change or relieve distressing symptoms (Cohen & Hughes, 2011). Sources of this confusion, as well as other common concerns voiced by the lay public, are explored below.

If depression isn't caused by a chemical imbalance, why do antidepressants appear to work? SSRIs – the "treatment of choice" for most indications of depression (Masand & Gupta, 1999, p. 69) – selectively inhibit the presynaptic uptake of 5-hydroxytryptamine (5-HT), which leads to an increase of 5-HT (serotonin) concentration at the synaptic cleft (Wong, Bymaster, & Engleman, 1995). However, the efficacy of antidepressants does not appear to be related to this function (Antonuccio et al., 1999). A serotonin deficiency for depression has not been found (Glenmullen, 2000), which means that instead of correcting low levels of serotonin, SSRI blocking of 5-HT may actually foster a "pathologic" state of synaptic transmission (Jacobs, 1991, p. 22). As a result, researchers have suggested that claimed improvements produced by antidepressants may be best understood as side effects of drug-induced states (or a "partial disabling of the brain") that are of value to the patient (Breggin, 2015, p. 2; Moncrieff & Cohen, 2009).

For instance, Breggin (2015) has noted that while initial feelings of euphoria are often interpreted as improvement brought on by medication, the experience is actually a "very abnormal state" that precedes mania (p. 4). In a similar vein, Moncrieff and Cohen (2009) have stressed that psychiatric drugs are, first and foremost, psychoactive drugs. Rather than act against neurochemical substrates of depression, antidepressants appear to produce a drug-induced state of mind that may be viewed by the patient as beneficial (Breggin, 2015; Moncrieff & Cohen, 2009). As Antonuccio et al. (1999) observed: "One person's side effect (e.g., sedation, weight gain or loss, ejaculation difficulties) is another person's positive treatment outcome (e.g., longer sleep, improved appetite or weight control, prolonged sexual pleasure)" (p. 7). Medical spellbinding (that is, the use of a drug preventing the recipient from fully grasping its adverse effects) may further complicate patient perception (Breggin, 2015).

If antidepressants don't correct depression, why do doctors prescribe them? The chemical imbalance theory has provided physicians with a convenient shorthand for communicating with patients (Healy, 2015). As explained by psychiatrist, David Carlat:

> 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, in your synapses, the neurons, and, presumably, the reason you're depressed or anxious is that you have some sort of a deficiency. And I say that not because I really believe it, because I know the evidence really isn't there for us to understand the mechanism – 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, para. 62)

Selective attention to antidepressant information promoted by the pharmaceutical industry can also make physicians unaware of opposing research that is worthy of clinical interest (Fava, 2002). Rather than coming as a surprise, Avorn, Chen, and Hartley (1982) have suggested that the predominance of non-scientific rather than scientific sources of drug information is consistent with what would be predicted from communications theory and marketing research data:

> Drug advertisements are simply more visually arresting and conceptually accessible than are papers in the medical literature, and physicians appear to respond to this difference. When the use of a product promoted in this way is also encouraged by patient demands and the desire of the physician to "do something medical," counter-arguments from empirical evidence may prove relatively weak and ultimately powerless. (p. 8)

Multiple studies examining the effect of pharmaceutical promotion on physician behavior have since confirmed this prediction. In a population-based survey of 1,050 physicians, Murray, Lo, Pollack, Donelan, and Lee (2003) found that of the 222 cases where a patient made a DTCA-prompted medication request, physicians deemed the request inappropriate in 108 cases; however, in 75 of those cases, the physician still did what the patient wanted, either partially or completely. In a randomized controlled trial focused specifically on depression, Kravitz et al. (2005) trained standardized patients (SPs) to portray symptoms of major depression and request antidepressants. In cases where SPs made general (i.e., not brand specific) requests, the rate of antidepressant prescription was 76%. Brand-specific requests were fulfilled 53% of the time, leading researchers to conclude that patients' requests have a "profound" effect on prescription practices in major depression (Kravitz et al., 2005).

Schwartz, Soumerai, and Avorn, (1989) found a similar effect, noting that of 110 responses, the most common reason offered by physicians for prescribing inappropriate medication was patient demand. However, the same study also found that over a quarter of the reasons given for non-scientific prescribing stemmed from a belief that clinical expertise, rather than scientific evidence, should govern clinical practice (Schwartz et al., 1989). In the context of depression, this belief may be partially shaped by clinical observation that antidepressants appear to "work" (see earlier discussion of drug-induced side effects, i.e., Breggin, 2015; Moncrieff & Cohen, 2009). Pharmaceutical promotion, in the form of physician detailing, may also exert significant influence on clinical expertise.

In an analysis of 538 studies between 1994-2000, interaction with pharmaceutical representatives was found to impact the prescribing practice of residents and physicians in terms of non-rational prescribing and preference/rapid prescribing of new drugs (Wazana, 2000).

Interestingly, receiving a gift and the number of gifts received correlated with the belief that pharmaceutical representatives have no impact on prescribing behavior (Wazana, 2000). However, while the majority of physicians perceive themselves as paying little attention to pharmaceutical promotion, compared to scientific literature, physician beliefs about the effectiveness of index drugs have revealed the opposite pattern (Avorn et al., 1982). After surveying 74 psychiatry residents, Hodges (1995) concluded, "The large number of trainees who agreed with the statement that they cannot be influenced by discussions (35%) or the receipt of gifts (57%) suggests some naïveté about the influence of the pharmaceutical industry on prescribing" (p. 558).

It has been estimated that the pharmaceutical industry spends up to $13,000 per physician per year promoting medications (Wazana, 2000). In the absence of mandatory postgraduate education, Avorn et al. (1982) have noted that pharmaceutical promotion becomes a major source of continuing education for physicians. The combination of this influence with DTCA-prompted patient demand (Kravitz et al., 2005), clinical observation of antidepressant effects (Breggin, 2015), and the convenience of biologically based explanations for depression (Davies, 2010) provides a general account for why physicians may prescribe antidepressants, in the absence of convincing evidence to do so.

Proposed Harm of Antidepressants

Pharmaceutical sales reflect the power of the biomedical model. In the decade following Prozac's debut, the proportion of treated individuals who used antidepressants increased from 37.3% to 74.5% (Olfson et al., 2002). Antidepressants are the most popular treatment for depression in the country (Antonuccio et al., 1999; Olfson et al., 2002), with 1 in 10 Americans, aged 12 and over, currently taking the medication (Pratt et al., 2011). And yet, depression – a

disorder that was once regarded as generally transient and self-correcting – is becoming increasingly chronic (Deacon, 2013), with patients voicing concern that pharmaceutical treatment "turns a period of crisis into a chronic mental illness" (Whitaker, 2010, p. 205). The following sections will support the argument that there are "infinitely" safer and more effective ways to treat depression, than pharmacotherapy (Breggin, 2015, p. 1).

Even when used alone at therapeutic levels, SSRIs produce fairly common side effects (i.e., those experienced by between 5% and 30% of patients), including: nervousness, tremor, anxiety, headache, insomnia, nausea, weight gain/loss, impaired memory, and sexual dysfunction (Antonuccio et al., 1999; Masand & Gupta, 1999). More severe effects have also been documented, with a recent review finding that SSRIs may double the relative risk of suicidality (Healy, 2003). Further, a survey of 661 outpatients who received at least one prescription during a four-week period found that SSRIs were the most frequently involved drug class in adverse medication events (Gandhi et al., 2003). Withdrawal symptoms also pose a serious concern, with Healy (2015) noting that most prescriptions are written for patients who face difficulties stopping medication. These patients are often advised to resume an antidepressant regimen because their difficulties indicate they need ongoing treatment (Healy, 2015) – a sentiment highlighted by the lay press:

> If you do not respond to the first drug tried – and studies suggest that about 30 to 40 percent of people don't – your doctor can (a) increase the dose of that drug or (b) switch you to another one. […] It's not uncommon to try as many as three or even four antidepressants before you find one that works. (Consumer Reports, 2013, p. 13)

Unfortunately, this perception reflects a fallacy. To date, no relationship has been demonstrated between therapeutic response and SSRI dosage (Antonuccio et al., 1999; Berney,

2005). In fact, although increasing dosage appears to be the preferred strategy of physicians when depressed patients have an insufficient response after four to eight weeks of SSRI treatment (Fredman, 2000), a review of eight clinical trials suggests that the dose-response curve is flat (Berney, 2005). Supporting this conclusion, three separate augmentation studies have found no advantage to tripling the dosage of Prozac, while additional studies have found no difference between administering the highest dosage of the antidepressant being tested and a placebo (Berney, 2005). Such results highlight the disproportionate cost-benefit paradigm of antidepressant use.

Deacon and Baird (2009) have suggested that the biomedical model makes pharmaceutical treatment more credible and acceptable to patients (a position firmly supported by this paper). Cohen and Hughes (2011) advanced this argument by proposing that such a process is likely bidirectional – that is, taking antidepressants, and experiencing positive effects, may influence belief in the chemical imbalance theory. In this sense, such a belief could be considered an additional "drug effect" (Cohen & Hughes, 2011, p. 183). Interestingly, belief in the chemical imbalance theory has not been found to reduce mental health stigma. In fact, ascribing biological explanations to depression has been found to reliably elicit *more* prejudice towards people with mental disorders than psychosocial explanations (Deacon & Baird, 2009).

An issue of final concern is the consistent finding that, while monoamine depletion in healthy volunteers does not cause depression (Delgado, 2000), patients who take SSRIs are more likely to experience a return of symptoms when serotonin is depleted (Salomon, Miller, Delgado, & Charney, 1993). There is also increasing awareness that, in some cases, long-term use of antidepressants may "enhance vulnerability to depression and worsen its long-term outcome and symptomatic expression" (Fava & Offidani, 2010, p. 1593).

Proposed Efficacy of Psychosocial Treatments

Although SSRIs have been hailed as having "revolutionized" the treatment of depression (Masand & Gupta, 1999, p. 71), Deacon (2013) highlighted a critical point: "If the biomedical paradigm has indeed revolutionized our understanding of the nature and treatment of mental disorder, tangible signs of its progress should be unequivocally evident by now" (p. 850). To the contrary, the last several decades have been characterized by a distinct lack of progress and improvement (Insel, 2009).

The primary aim of biomedical treatment research is to develop therapies that target underlying biological dysfunctions (Deacon, 2013). Such goals minimize the relevance of psychosocial contributions to mental health (Deacon, 2013), and foster pessimism about non-pharmaceutical treatments (Deacon & Baird, 2009; Kemp et al., 2014). However, the biopsychosocial model – the idea that depression is influenced by a complex interplay of biological, psychological, and social factors (Deacon & Baird, 2009) – encourages a more serious consideration of psychosocial interventions.

It is argued by this paper that neglect of non-pharmaceutical treatments, in favor of antidepressants, results in harm by preventing patients from experiencing more positive treatment outcomes afforded by psychosocial therapies. The proposed study, discussed shortly, will seek to evaluate the correlation between etiological beliefs and attitudes regarding antidepressants and five specific, psychosocial interventions. A brief review of current research, as well as the potential benefits of each psychosocial approach, is offered below.

Diet. Gastrointestinal (GI) distress has long been linked to psychological disturbance. (see: Ciacci, Iavarone, Mazzacca, & De Rosa, 1998, finding that one-third of celiac disease patients suffer from depression). While the mechanism of this relationship remains unclear

(Bushara, 2005), researchers have suggested that malabsorption of nutrients needed to manufacture serotonin may lead to psychological impairment (Hallert, Astrom, & Sedvall, 1982). However, more recent studies (Bercik, 2011; Bercik et. al, 2010) have found that in experiments resulting in increased GI inflammation, there are notable increases in anxiety-like behavior – and that treatment with a probiotic reduces anxiety symptoms. This evidence runs counter to the idea that depression may result from a serotonin deficiency, and instead suggests that bacteria may be decreasing the excitability of enteric neurons and signaling the central nervous system to reduce anxious behavior (Bercik, 2011). Illustrating just one of many ways in which the gut microbiome may influence the brain, research by Bercik et al. (2010) highlights the promising role of diet modification in addressing psychological distress.

Exercise. The efficacy of exercise in decreasing symptoms of depression has been well established (Craft & Perna, 2004). For instance, a review of research from 1976-1995 (Yeung, 1996) found that over 85% of studies showed at least some degree of improved mood following exercise. Overall, these effects appeared to occur regardless of age or gender (Yeung, 1996). In a particularly relevant study, Blumenthal et al. (1999) assigned 156 moderately depressed individuals to an exercise, medication, or exercise and medication group. Those in the exercise group walked or jogged on a treadmill for 30 minutes, three times per week for 16 weeks. Those in the medication group received an SSRI (sertraline/Zoloft). Those in the combination group received both medication and exercise. Results showed that while medication worked to reduce depression symptoms more quickly, there were no significant differences among treatment groups at 16 weeks. Of even greater interest: a 10-month follow-up revealed that exercise *only* group members had significantly lower rates of depression than those in the antidepressant or combination groups.

Meditation. Non-spiritual meditation has also been shown to have a therapeutic effect, with Hölzel et al. (2011) finding that participants who meditated for 30 minutes a day for eight weeks had measurable changes in gray matter density in parts of the brain associated with memory, sense of self, empathy, and stress. Benson (2001) has extensively documented the positive effects of a similar process, called the "relaxation response." A 2008 study (Dusek et al.) found that long-term practice of the relaxation response alters gene expression, while more recent work (Bhasin et al., 2013) has suggested that just one session of the relaxation response may induce rapid genetic changes.

Psychotherapy. Karon (2005) has claimed that even psychotic depression is best treated by psychotherapy without medication, noting, "Every affect, including depression, has meaning" (p. 45). In line with this view, multiple meta-analyses have found psychotherapy to be comparable (Hollon, Shelton, & Loosen, 1991) or more effective (Dobson, 1989) than pharmacotherapy (e.g., antidepressants). Likewise, the combined use psychotherapy and pharmaceutical drugs "does not appear to be clearly superior to either treatment" (Antonuccio et al., 1999, p. 10). Supporting this finding, even patients who endorse the chemical imbalance theory have claimed that therapy is "incredibly powerful" (Ridge & Ziebland, 2006, p. 1043). Representing a cost-effective (Antonuccio et al., 1999), side-effect-free alternative to antidepressants, psychotherapy is considered by some clinicians to be "the most effective [way] of helping people get over depression" (Breggin, 2015, p. 7).

Spiritual/Religious practices. Although intuitively suggestive of controversy, recent research (Ecklund, Park, & Sorrell, 2011) has found that scientists do not view religion and science as always being in conflict. This conclusion is promising, as a review of 444 studies, spanning 50 years, found that religious/spiritual involvement lessened the incidence of

depression and/or reduced depression severity in over 60% of studies (Bonelli, Dew, Koenig, Rosmarin, & Vasegh, 2012). Acknowledging the possibility of genetic influences, Miller et al. (2012) followed 114 adult offspring of depressed and non-depressed parents over the course of 20 years. Religious feelings were assessed at the 10-year mark. At the end of the study, those who had indicated that religion/spirituality was highly important to them were 73% less likely to be depressed. Even more encouraging: those at high risk of developing the disorder – due to prenatal depression – who indicated at the beginning of the study that religion/spirituality was highly important to them, were 90% less likely to have major depression.

The Role of Pharmaceutical Promotion

Patients. DTCA has a significant effect on patient demand for prescription drugs (Donohue et al., 2007) and, in turn, patient influence on physician prescribing behavior (Kravitz et al., 2005). Individuals diagnosed with depression during periods when DTCA spending was highest have shown 32% higher relative odds of initiating antidepressant treatment (Donohue et al., 2004). Supporting this conclusion, a survey of 148 online depression forum members revealed that DTCA led to requests for new prescriptions or a change in medications in 20% of respondents (Bell, Taylor, & Kravitz, 2010). Likewise, Murray et al. (2003) found that 80% of 1,050 surveyed physicians had experienced a patient asking about information from a drug advertisement during a visit in the past 12 months.

While patient behavior may be influenced by DTCA, only 4% of surveyed physicians felt that consumers were excellent or very good at evaluating the claims of pharmaceutical advertisements (Murray et al., 2003). This conclusion is especially alarming in light of recent criticism that DTCA portrays an “abhorrent” minimization of risks (Grow et al., 2006, p. 19). Of equal concern, Ingelfinger (1972) has noted that pharmaceutical advertising ignores other forms

of patient management, adding: “Advertisements should be overtly recognized for what they are – an unabashed attempt to get someone to buy something” (p. 1319).

Such criticism has led Wilkes et al. (2000) to suggest that organized medicine needs to “counter-advertise”:

> The public health community needs to create mechanisms for providing consumers with objective, independent information about available drug therapies, including their indications, risks, benefits, and alternatives. (p. 125)

This argument serves as a cornerstone of the present thesis and will be explored in greater detail, shortly.

Physicians. In a survey of 467 physicians, McKinney et al. (1990) found that only 10% of participants were satisfied with their previous training regarding professional interaction with pharmaceutical representatives. Psychiatry residents surveyed by Hodges (1995) expressed a similar sentiment: only 15% said they felt they had received enough education about interacting with pharmaceutical representatives. As physician detailing has been shown to exert significant influence on prescribing behaviors (Wazana, 2000), a need exists to both improve medical education and ongoing training (Lacasse & Leo, 2015) and develop an innovative means of communicating unbiased drug information to physicians (Avorn et al., 1982). As argued by Wolfe (2002): “The education of patients – or physicians – is too important to be left to the pharmaceutical industry, with its pseudoeducational campaigns designed, first and foremost, to promote drugs” (p. 526).

Although proponents suggest that pharmaceutical campaigns do, in fact, possess educational value (Calfee, 2002), Grow et al. (2006) characterize such claims as “erroneous” (p. 18). Ingelfinger (1972) concurs, writing:

> Information is a part of education, but the two processes are not the same… Pharmaceutical advertising, for example, is often said to be educational. It is not; such advertising is informational but almost never educational… It is all very helpful information, but information that is part of an advocacy operation. (p. 1319)

Unfortunately, more than 40% of psychiatry residents surveyed by Hodges (1995) felt that pharmaceutical representatives have an "important" teaching role. (Interestingly, less than a third felt that representatives provided useful and accurate information.)

Changing Lay Perception of Depression Treatment is Possible

It has so far been argued that the biomedical model of depression dominates the American health care system (Deacon, 2013), and that changing lay perception of depression treatment is necessary to (a) encourage critical thinking about psychoactive drug effects, and (b) increase acceptance of psychosocial interventions, so that patients may avoid unnecessary negative side effects and benefit from more positive treatment outcomes. The following sections will review evidence suggesting that such change is possible, and propose a novel starting point for future campaign development. I will conclude with the argument that, despite an inability to compete financially (Gallo et al., 2013), organized psychiatry may effectively counter misinformation presented by the pharmaceutical industry through strategic deconstruction of the chemical imbalance theory.

Arguments for a Counter-Campaign

Wilkes et al. (2000) are not alone in their suggestion that organized medicine needs to "counter-advertise" (p. 125). A number of researchers have voiced concern that current practice guidelines – which overstate the benefits of antidepressant use and understate the efficacy of alternative treatments – are inconsistent with scientific literature (Antonuccio et al., 1999;

Lacasse & Leo, 2005; Muñoz, Hollon, McGrath, Rehm, & Van den Bos, 1994; Pearsons, Thase, & Crits-Christoph, 1996). Wolfe (2002) has argued that public health agencies need to move "forcefully" to stimulate evidence-based conversations between doctors and patients (p. 526), while Rosenthal et al. (2002) have highlighted the importance of developing strategies to help patients evaluate DTCA. Addressing this "compelling need", Bell et al. (1999, p. 656) have offered support for a media literacy campaign. Likewise, Cohen and Hughes (2011) have argued that disseminating alternative hypotheses is "especially relevant" today (p. 183). This statement stands in support of Kemp et al.'s (2014) claim that clinicians, scientists, and mental health advocates need to promote a biopsychosocial perspective. As summarized by Deacon (2013): "We cannot afford the societal costs of failing to engage in open and honest discussion… of the biomedical paradigm" (p. 857).

Pharmaceutical Promotion as a Guide to Counter-Campaign Development

Numerous articles (Gallo et al., 2013; Gaudiano & Miller, 2013; Santucci et al., 2012) have noted the potential value of utilizing DTCA techniques, similar to those deployed by the pharmaceutical industry, as part of a counter-campaign. Extending this argument to anxiety disorders, Gallo et al. (2013) have written:

> Given the impressive results demonstrated in the pharmaceutical industry in regards to influencing attitudes, treatment-seeking behavior, and even provider behaviors, DTC marketing may be a promising vehicle for promoting evidence-based psychological treatment utilization rates…. (p. 796)

Likewise, researchers have suggested the benefit of counter-detailing (i.e., countering physician-focused pharmaceutical promotion). In an experimental controlled trial, Avorn and Soumerai (1982) provided physicians with "un-advertisements" and visits from "drug

information specialists" (trained by researchers in behavior change strategies and nuances of the drugs being de-marketed). Results showed a "clear divergence" of prescribing patterns between the detailed group and controls (Avorn & Soumerai, 1982, p. 383) – leading researchers to conclude that counter-detail campaigns may "effectively help to restore the balance between science and commerce in shaping physician drug choices" (Avorn et al., 1982, p. 8).

Deconstructing the Chemical Imbalance Theory

The pharmaceutical industry spent $32 million on DTCA and $985 million on physician detailing in 1999 (Rosenthal et al., 2002). That same year, drug companies spent over $197 million on political lobbying and campaign contributions (Wayne & Peterson, 2001). This stands in stark contrast to the limited funds and resources allocated to promote psychosocial interventions (Gaudiano & Miller, 2013). Yet, I propose that – owing to its unique appeal to authority – organized psychiatry is in a powerful position to counter pharmaceutical efforts through less financed means. I suggest that publicly deconstructing the chemical imbalance theory is an essential first step in this pursuit – and that doing so affords strategic value that will minimize the effectiveness of pharmaceutical dollars.

While a detailed discussion of counter-campaign goals, design, and execution is beyond the scope of this article, logic supporting the value of deconstructing the chemical imbalance theory is reviewed below. (For general campaign considerations, see: Santucci et al., 2012).

Revisiting the aspirin argument. Gaudiano & Miller (2013) have called upon allied psychological organizations to:

> …explore how we can effectively use counter-messaging to dispel the myths and misinformation that is in the public domain about the nature and treatment of mental

> health problems, as well as develop media campaigns that educate the public about psychosocial treatments as alternatives and options for consumers. (p. 821)

I suggest that deconstructing lay belief in the chemical imbalance theory is critical to accomplishing both goals – a point well illustrated by the aspirin argument.

Flaws in the chemical imbalance theory have been highlighted by the argument that just because aspirin helps headaches, doesn't mean that headaches are caused by a lack of aspirin in the brain (Angell, 2011; Lacasse & Leo, 2005; Valenstein, 1998). Examining this analogy from a different perspective: While aspirin sales are likely high due to aspirin's therapeutic effects, it stands to reason that sales would be significantly higher if patients actually believed that headaches were caused by a lack of aspirin in the brain. Such logic might even promote the belief that extended use of aspirin could prevent future headaches – a perception that would surely increase aspirin sales.

However, with so many similarities to the antidepressant/chemical imbalance paradigm, why is that aspirin sales aren't higher? It's safe to assume that even if aspirin manufactures devoted twice the promotional budget of antidepressants to convincing patients that headaches are caused to a lack of aspirin in the brain, this endeavor would be met with minimal success. Why?

Because the lay public has been exposed to enough evidence-based science to be able to confidently recognize this claim as false. Those harboring any doubt would likely ask their physician, who would quickly set the record straight: While aspirin may be beneficial in managing headaches, headaches do not have anything to do with aspirin. If aspirin manufacturers, nonetheless, decided to continue such a campaign, any opposing efforts to highlight scientific shortcomings would not represent an attack on the value of using aspirin in

certain cases – rather, efforts to elucidate scientific truth would support appropriate and ethically informed use of aspirin by both patients and physicians. Such counter-efforts would also safeguard the integrity and progress of future research, by ensuring that resources are not misappropriated to studies unduly focused on discovering the aspirin/brain connection.

In this same spirit, I propose that deconstructing the chemical imbalance theory is critical to countering misinformation propagated by the pharmaceutical industry. While financial competition may not be viable (Gallo et al., 2013), the organized efforts of leaders and clinicians within the medical profession – motivated by an ethical prerogative to facilitate *truly* informed patient consent and improve disorder prognosis through increased integration of treatments more aligned with current, scientific literature – represent an invaluable means for fundamentally altering lay perception of depression treatment. (See Cecchini et al., 2010, finding that physician counseling is one of the most effective intervention strategies for countering obesity.)

As illustrated by the aspirin argument, pharmaceutical dollars can't sell a theory that consumers confidently believe to be false. Antidepressants may produce desirable effects in certain cases (Breggin, 2015), but there is no convincingly evidence to suggest that they correct any neurobiological substrate of depression (Moncrieff & Cohen, 2009) or improve disorder morbidity or mortality (Insel, 2009). In fact, evidence suggests that antidepressant use may worsen long-term treatment outcomes (Fava, 2003; Whitaker, 2010).

And so, while logistical considerations may exceed the scope of the present paper, I propose a novel starting point for content and campaign development. Given widespread belief in the chemical imbalance theory (France et al., 2007; Link et al., 1999) and the demonstrated influence of pharmaceutical promotion on patient and physician behavior (Donohue et al., 2007; Wazana, 2000), I suggest that before promoting the benefits of psychosocial interventions, any

successful counter-pharmaceutical campaign will need to begin, first and foremost, with a strategic deconstruction of the chemical imbalance theory. To confirm the validity of this proposal, I have designed the following study protocol.

Proposed Research

Current research has focused on (a) gauging lay belief in the chemical imbalance theory (France et al., 2007; Link et al., 1999; Pescosolido, 2010), and (b) exploring whether acceptance of the chemical imbalance theory is correlated with consumer attitudes regarding pharmaceutical treatment and psychotherapy (Deacon & Baird, 2009; Kemp et al., 2014). I will seek to extend this work by identifying reliable ways in which acceptance of the chemical imbalance theory influences consumer attitudes regarding five specific types of psychosocial interventions, including: diet, exercise, meditation, psychotherapy, and spiritual/religious practices. I hypothesize that acceptance of the chemical imbalance theory will be positively related to: (a) DTCA exposure, (b) high confidence in the effectiveness of antidepressant treatment, and (c) low confidence in the effectiveness of psychosocial interventions. Analysis of attitudes regarding specific types of psychosocial therapy may prove useful in overcoming treatment-specific patient objections. Possible implications of this work include increased non-pharmaceutical treatment adherence, through informed design of counter-campaign strategy and content.

Study Design

Overview of the study. The prospective study will assess the association between etiological perception(s) and consumer attitudes regarding antidepressants and five psychosocial interventions. Questions will also measure source trust (e.g., doctors, magazines, commercials) to predict the potential effectiveness of various communication strategies (similar to the

obesity/public health strategies results produced by Cecchini et al., 2010). I propose a 27-question survey designed to meet the following objectives:

1. Determine whether participants have been exposed to antidepressant DTCA,
2. Identify causes that participants believe contribute to depression,
3. Evaluate whether these beliefs predict reliable attitudes towards antidepressants and/or specific psychosocial interventions, and
4. Suggest levels of trust for possible sources of mental health information.

Survey questions will be administered securely through Research Electronic Data Capture (REDCap). REDCap is a secure web application for building and managing online surveys, specifically designed to support data capture for research studies. Study participants will be comprised of a nationally representative sample, recruited online through public sharing of the survey's REDCap link. Qualified participants will include adults (aged 18 years and older) who do not hold an advanced medical degree (defined as a M.D., Ph.D., and/or Psy.D.).

The questionnaire will be made available for a period of 30 days, with individual participant involvement lasting approximately 15-25 minutes. Analysis will include review of Likert-scaled items and collaborative assignment, between the study's investigators, of participant-generated responses into agreed-upon categories.

Research team. The study team will be composed of Dr. Stephanie Peabody and myself. The study team will be charged with implementing research procedures as approved by Harvard's Institutional Review Board (IRB).

Recruitment and consent procedures. Prior to the start of each survey, participants will read an electronic version of the Committee on the Use of Human Subjects (CUHS) Adult Consent Form (see: Appendix C).

Materials and measures. The self-administered questionnaire is composed of scales that have been validated for use by adult participants in previous research. The full text of the survey is located in Appendix A. A complete list of question references is available in Appendix B. Survey answers will be kept confidential and without personal identifiers in the REDCap system and will be accessed via a secure computer by the research team. Principal components analysis (PCA) will be used to determine the extent to which knowledge and endorsement of various psychosocial interventions form factors for chemical imbalance and non-chemical imbalance explanations for depression (methodology modeled on: Deacon & Baird, 2009).

Demographic data. Demographic data will be collected from the questionnaire including age, gender, and profession. The study team will use email and social media postings to encourage participants to complete the questionnaire. After completing the survey, all participants will be encouraged to email the study team with questions or concerns.

Possible benefits. Individuals may benefit from knowing they are participating in a study designed to inform the literature and medical community about lay perceptions regarding depression etiology and treatment.

Possible risks. Every attempt will be made to keep survey results confidential, although there is some risk that electronic data will be breached. All electronic survey data will be secured in the REDCap system on a password-protected computer.

Rights and privacy. All data and records generated during the study will be kept confidential in accordance with Health Insurance Portability and Accountability Act (HIPAA) policies on subject privacy. Such data and records will not be used for any purpose other than conducting the study. Consent forms and raw data will be stored in electronic form for six years

following the completion of the study. Following this six-year period, raw data and all associated files will be destroyed.

All key study personnel will complete Human Subjects Protection Training. This mandatory training in human subject protection provides formal, comprehensive education in order to protect participants from the risks associated with participating in research, and to reduce the risks to Harvard and investigators associated with non-compliance. Training covers institutional policies and procedures, federal regulations, and critical aspects of study implementation. A key component of this training is a review of HIPPA privacy measures.

Incentives/Remuneration. Incentives and remuneration will not be offered.

Conclusion

The present paper has argued that lay perception of depression etiology is shaped by the biomedical model (France et al., 2007; Pescosolido et al., 2010) – most commonly expressed via the chemical imbalance theory – and that deferment to this paradigm promotes favoritism of pharmaceutical treatment (Deacon & Baird, 2009) and discourages use of psychosocial interventions (Kemp et al., 2014). I've suggested that this set of attitudes, in turn, results in patient harm by (a) subjecting patients to negative side effects (i.e., Antonuccio et al., 1999; Healy, 2003) that might otherwise be avoided through use of non-pharmaceutical treatments, and (b) preventing patients from experiencing potentially more positive treatment outcomes afforded by alternative, psychosocial interventions (Blumenthal et al., 1999; Bonelli et al., 2012). I've suggested that faith in the chemical imbalance theory promotes further harm by encouraging patients to base beliefs regarding depression etiology, prognosis, and treatment expectancy on unsubstantiated claims.

Arguments for a pharmaceutical counter-campaign (Gallo et al., 2013; Gaudiano & Miller, 2013) – including DTCA (Santucci et al., 2012) and counter-detailing (Avorn & Soumerai, 1982) – have been supported as a viable solution to this problem. I have proposed a novel starting point for practical application (i.e., campaign strategy/content development): deconstruction of the chemical imbalance theory – and have argued that overcoming better financed pharmaceutical campaigns (Donohue et al., 2007) is possible if this strategy is executed by organized efforts within the medical community. To support this claim, I have proposed a nationally representative survey to extend the work of Kemp et al. (2014) and France et al. (2007). The proposed study seeks to gauge lay belief in the chemical imbalance theory and correlate this perception with attitudes regarding five specific psychosocial interventions (including: diet, exercise, meditation, psychotherapy, and spiritual/religious practices). It is hypothesized that results will support the present argument – finding that belief in the chemical imbalance theory is key to shaping lay perception of depression treatment. This evidence will, hopefully, provide researchers with a strengthened foundation for developing future counter-campaigns.

As a point of clarity, the value of antidepressant use, in certain cases, has not been disputed. However, this value is argued to be best understood through frameworks presented by Breggin (2015) and Moncrieff and Cohen (2009) – that is, perceived therapeutic benefits are the result of a drug-induced, altered state of mind; antidepressants do not "work" by addressing neurochemical substrates of depression. This distinction highlights an ethical claim propelling the present thesis: Patients have a right to base treatment decisions on truly informed consent.

Consumers are empowered to take control of their lives when they are "knowledgeable about what works to solve a problem" (Sanders & Kirby, 2012, p. 240). Patients are likely to

respond differently to an offer of a drug intended to produce an altered state of mind than a drug said to act on the underlying biological cause of depression (Moncrieff & Cohen, 2009). However, most patients are never given this choice. A significant part of recovery involves telling stories about depression and the self that "allow one to go on living" (Ridge & Ziebland, 2006, p. 1050) – yet, a majority of today's stories are based on false truths (Cohen & Hughes, 2011).

If, after developing a more rational understanding of psychopharmaceutical drugs, patients still choose to take antidepressants, then it is the position of this paper that they should be free to do so. However, if just one patient – out of the estimated 60 million Americans who take psychotropic medication (Medco Health Solutions, 2011 as cited by Deacon, 2013) – would change their mind based on the evidence presented today, then it is firmly argued that organized psychiatry has an ethical obligation to communicate this information. As warned by France et al. (2007): "Any unitary understanding of human suffering asserted in isolation of its nuances, may mislead those in need of treatment and confound self-understanding" (p. 411). We do not know how psychology/biology causation works – and there are serious costs to pretending that we do (Miller, 2010).

Critiquing the chemical imbalance theory – and the biomedical model that it represents – is no more an affront to disorder management than criticizing a campaign that claims headaches are caused by a lack of aspirin in the brain. To the contrary, advocating for an evidence-based understanding of depression supports ethically informed treatment decisions and appropriate use of therapies that might otherwise be avoided. It relaxes blinders placed on research, that may neglect promising but anti-theory evidence, and encourages a rightfully curious approach to scientific inquiry.

Cohen and Hughes (2011) have noted that, “it remains completely unclear who will expose laypersons and professionals to messages that encourage critical thinking about psychoactive drug effects and the origin and relief of psychological distress” (p. 183). To this point, I direct attention to Healy (1987):

> Change is likely to come from those new to a field, who by virtue of youth, or transfer from another discipline or by some other method have escaped the usual moulding (sic) pressure and who are more struck by what is not explained by the dominant view than by its improvements on previous views. (p. 350)

The present paper has attempted to highlight the brave work of researchers who have challenged the biomedical model of depression. It is my hope that the proposed study will contribute, in some small way, to this literature. There is currently no known biological cause of, or biological marker for, any mental disorder (Deacon, 2013) – yet, the majority of Americans believe depression is a confirmed, neurobiological disease (Link et al., 1999). It is the ethical responsibility of the medical community to correct this misconception. As argued by Miller (2010): “Intellectual modesty is in order” (p. 717).

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APPENDIX A: SURVEY QUESTIONS

#	Item
1	In your opinion, what are some likely causes of depression? Please provide up to five answers. For multiple responses, please rank in order of most likely to cause depression (1) to least likely (5).
2	The "chemical imbalance theory" refers to the idea that depression is caused by an imbalance of chemicals in the brain. Have you seen and/or heard of this theory before? Yes No
3	If you answered "Yes" to Question 2, please indicate where and/or how you have seen or heard depression described in this manner (please select all that apply): ☐ Books ☐ Friend/Family member/Other acquaintance ☐ Magazines ☐ Newspapers ☐ Online articles/Blogs ☐ Psychologist/Mental health professional ☐ Physician or other medical professional ☐ Social media ☐ TV
In general, how effective do you feel the following treatments are at fighting depression?	
4	Antidepressants Not at all effective 1 2 3 4 5 Extremely effective
5	Counseling/Talk therapy Not at all effective 1 2 3 4 5 Extremely effective
6	Diet Not at all effective 1 2 3 4 5 Extremely effective
7	Exercise Not at all effective 1 2 3 4 5 Extremely effective
8	Meditation Not at all effective 1 2 3 4 5 Extremely effective
9	Spiritual/Religious practices Not at all effective 1 2 3 4 5 Extremely effective
Please indicate your level of agreement with each of the following statements:	
10	Depression is primarily caused by an imbalance of chemicals in the brain. Strongly disagree 1 2 3 4 5 Strongly agree
11	Antidepressants treat depression by correcting a chemical imbalance in the brain. Strongly disagree 1 2 3 4 5 Strongly agree
12	Antidepressants are the best available treatment option for depression. Strongly disagree 1 2 3 4 5 Strongly agree
13	Doctors can fix depression by adding or subtracting brain chemicals until properly balanced.

	Strongly disagree 1 2 3 4 5 Strongly agree
14	Scientific studies have confirmed that depression can be caused by a chemical imbalance. Strongly disagree 1 2 3 4 5 Strongly agree
In general, how likely are you to try and/or encourage others to try the following treatments for depression?	
15	Antidepressants Very unlikely 1 2 3 4 5 Very likely
16	Counseling/Talk therapy Very unlikely 1 2 3 4 5 Very likely
17	Diet Very unlikely 1 2 3 4 5 Very likely
18	Exercise Very unlikely 1 2 3 4 5 Very likely
19	Meditation Very unlikely 1 2 3 4 5 Very likely
20	Spiritual/Religious practices Very unlikely 1 2 3 4 5 Very likely
21	What source(s) do you trust the most to communicate accurate information about depression? For multiple responses, please rank in order from most trustworthy (1) to least trustworthy (5).
In general, how knowledgeable do you feel regarding the following treatment options for depression? Please indicate your level of knowledge below.	
22	Antidepressants Very poor 1 2 3 4 5 6 7 Exceptional
23	Treatments other than antidepressants Very poor 1 2 3 4 5 6 7 Exceptional
24	Have you ever been diagnosed with or sought treatment for depression? Yes No
25	Has a family member, relative, or close friend of yours ever been diagnosed with and/or treated for depression? Yes No/Not that I'm aware of
If your doctor told you that the chemical imbalance theory is an unconfirmed hypothesis – in other words, that scientific studies could not confirm that depression is caused by a chemical imbalance – how likely would you be to:	
26	Try and/or encourage others to try non-pharmaceutical treatments for depression? Very unlikely 1 2 3 4 5 Very likely
27	Stop and/or encourage others to stop taking antidepressants? Very unlikely 1 2 3 4 5 Very likely

APPENDIX B: SURVEY OUTLINE AND REFERENCES

#s	Instrument	# Items	Reference
1	**Depression Etiology Question** The participant generates up to five likely causes of depression, ranked from "most likely" to "least likely" to cause depression.	1	France, C.M., Lysaker, P.H., & Robinson, R.P. (2007). The "chemical imbalance" explanation for depression: Origins, lay endorsement, and clinical implications. *Professional Psychology: Research and Practice, 38*(4), 411-420.
2-3	**DTCA Questions** After indicating whether the participant has seen and/or heard of the "chemical imbalance theory", the participant selects where and/or how they have heard depression described in this manner from a list of options. Possible answers are modeled on France, Lysaker, & Robinson's (2007) original list, with the addition of: *online articles/blogs* and *social media*.	2	France et al. (2007). The "chemical imbalance" explanation for depression: Origins, lay endorsement, and clinical implications. *Professional Psychology: Research and Practice, 38*(4), 411-420.
4-9	**Treatment Effectiveness Questions** The participant ranks the effectiveness of various depression treatments on a 5-point scale.	6	Original phrasing (to address specific psychosocial interventions), based on: Deacon, B. J. & Baird, G.L. (2009). The chemical imbalance explanation of depression: Reducing blame at what cost? *Journal of Clinical and Social Psychology, 28*(4), 415-435.
10-14	**Chemical Imbalance Questions** The participant indicates on a 5-point scale how much they agree with various statements relating to the chemical imbalance theory. Two questions were previously studied by France et al. (2007).	5	France et al. (2007). The "chemical imbalance" explanation for depression: Origins, lay endorsement, and clinical implications. *Professional Psychology: Research and Practice, 38*(4), 411-420.

15-20	**Likelihood to Try and/or Encourage Treatment Questions** The participant indicates on a 5-point scale how likely they are to try and/or encourage others to try various depression treatments.	6	Original line of questioning
21	**Source Trust Question** The participant generates up to five sources that they trust to communicate accurate information about depression. Multiple responses are ranked from "most trustworthy" to "least trustworthy".	1	Designed to assess potential intervention effectiveness, similar to the results produced by: Cecchini, M., Sassi, F., Lauer, J.A., Lee, Y.Y., Guajardo-Barron, V., & Chisholm, D. (2010).Tackling of unhealthy diets, physical inactivity, and obesity: Health effects and cost-effectiveness. *Lancet, 376*, 1175-1184.
22-23	**Treatment Knowledge Questions** The participant indicates on a 7-point scale how knowledgeable they feel regarding treatment options for depression.	2	Original line of questioning
24-25	**Personal Experience with Depression Questions** The participant indicates whether they or their family members/friends have ever sought treatment for/been diagnosed with depression.	2	France et al. (2007). The "chemical imbalance" explanation for depression: Origins, lay endorsement, and clinical implications. *Professional Psychology: Research and Practice, 38*(4), 411-420.
26-27	**Implications of Education Questions** The participant indicates on a 5-point scale how likely they would be to alter various behaviors based on a provided scenario.	2	Original line of questioning

Total # items = 27

Total time = Under 25 minutes

APPENDIX C: CONSENT FORM

Study Title: Antidepressants, Direct-to-Consumer Advertising, and the Mediating Role of the Chemical Imbalance Theory

Researchers: Jessica Walters, Dr. Stephanie Peabody

Participation is voluntary

It is your choice whether or not to participate in this research. If you choose to participate, you may change your mind and leave the study at any time. Refusal to participate or stopping your participation will involve no penalty or loss of benefits to which you are otherwise entitled.

What is the purpose of this research?

The purpose of this research is to assess the association between perception(s) regarding the chemical imbalance theory and attitudes towards various types of depression treatment.

How long will I take part in this research?

Your participation will involve one 15-25 minute survey.

What can I expect if I take part in this research?

As a participant, you will complete a private, online survey.

What are the risks and possible discomforts?

If you choose to participate, every attempt will be made to keep survey results confidential, although there is some risk that electronic data will be breached.

Are there any benefits from being in this research study?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include knowing that you are participating in a study designed to inform the literature and medical community about public perceptions regarding depression etiology and treatment.

If I take part in this research, how will my privacy be protected? What happens to the information you collect?

The data we collect will be recorded using REDCap (Research Electronic Data Capture), a secure web application in compliance with HIPAA standards.

The information with your name on it will be analyzed by the researcher(s) and may be reviewed by people checking to see that the research is done properly.

If I have any questions, concerns or complaints about this research study, who can I talk to?

The researcher for this study is Jessica Walters who can be reached at [phone number redacted]; [address redacted]; jwalters@fas.harvard.edu. The faculty sponsor is Dr. Stephanie Peabody who can be reached at [address to be determined]:

- If you have questions, concerns, or complaints,
- If you would like to talk to the research team,
- If you think the research has harmed you, or
- If you wish to withdraw from the study.

This research has been reviewed by the Committee on the Use of Human Subjects in Research at Harvard University. They can be reached at 617-496-2847, 1414 Massachusetts Avenue, Second Floor, Cambridge, MA 02138, or cuhs@fas.harvard.edu for any of the following:

- If your questions, concerns, or complaints are not being answered by the research team,
- If you cannot reach the research team,
- If you want to talk to someone besides the research team, or
- If you have questions about your rights as a research participant.