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Challenging the Narrative of Chemical Imbalance: A Look at the Evidence

The idea of a "chemical imbalance" underlying mental disorder is pervasive in our society. In particular, the idea that clinical depression is caused by an imbalance of the neurotransmitter serotonin (which can be corrected through use of antidepressant medication) has been popularized since the introduction of the modern antidepressants in the late 1980s (Lacasse, 2005). This message has also been disseminated in the media, in direct-to-consumer advertising, and in educational materials for mental health clients (Lacasse & Leo, 2005; Leo & Lacasse, 2008; Hess, Gantt, Lacasse, & Vierling-Claasen, 2014). The serotonin theory of depression has been a crucial piece of the ascendance of biological psychiatry, the viewpoint which holds that DSM-defined mental disorders are diseases of the brain, no different than diabetes or cancer (Whitaker, 2010).

Clinical social workers who diagnose will often also play a psychoeducational role, informing clients about the cause, course and prognosis of their diagnosis. In this situation, the clinical social worker carries significant power in the clinician-client relationship. The social worker will be seen as the expert, and the client is likely to believe that what they are told is scientifically valid information. Thus, telling depressed clients that it is known that they have a chemical imbalance in their brain- that they have a brain disease- could have major effects regarding how clients see themselves, their condition, and their treatment needs (Hess et al., 2014). For instance, Kemp, Lickel & Deacon (2014) found that when participants with a history of depression who were told they had a serotonin imbalance, this had negative effects. Among them were a more pessimistic prognosis and the impression that drug treatment was more effective than psychotherapy (see also Deacon & Baird, 2009).

Thus, it is clear that bioreductionistic explanations have the potential to cause harm to clients, and that this issue should be carefully considered by practicing social workers. This raises two crucially important issues. First, do we know that social workers are in fact telling depressed clients that they suffer from serotonin imbalance? This research question has not received the extensive attention that it deserves, so far, but there is some evidence that this is taking place. In a small study, Acker (2013) found that 92% of clinical social workers at least "sometimes" explain to their clients that depression is caused by a chemical imbalance. Other research demonstrates that it is common for clients to be informed of this within mental health treatment more generally (Cohen & Hughes, 2011; Johnston et al., 2007) and there is little evidence that clinical social workers in general take a contrarian position as compared to psychiatry or psychology (Gomory, Cohen, Wong, & Lacasse, 2012).

The second and more important question is whether or not the serotonin theory of depression is *true*. Social workers have an ethical mandate to "critically examine and keep current with emerging knowledge relevant to social work" (National Association of Social Workers, 2008). Therefore, the scientific veracity of the serotonin theory is important. If social workers are informing clients of well-tested, accurate neuroscience research to help them better understand their condition, this makes good sense. However, if the serotonin theory has been scientifically falsified and social workers continue to use this explanation nonetheless, this would be deeply problematic.

Below, we make the case that the latter case is unfortunately true. The serotonin theory of depression was falsified many years ago. Its current popularity can be attributed to many potential factors: Relentless pharmaceutical marketing of antidepressant drugs, the influence of biological psychiatry on the field of social work, deficits in the education of aspiring mental

health professionals, and the intuitive appeal of reducing complex human behavior to simple explanations rather than the application of critical thinking (Kirk, Cohen & Gomory, 2013; Lacasse & Gomory, 2003; Valenstein, 1998). However, what is well established is that the serotonin theory of depression no longer holds the status of even a viable scientific theory – let alone information that should be passed on to social work clients. Given how easy it is (see below) to build the scientific case against the serotonin theory, its continuing popularity and use in clinical practice could be seen as astonishing.

The Serotonin Theory

In 1965, Joseph Schildkraut put forth the hypothesis that depression was associated with low levels of norepinephrine (Shildkraut, 1965), and later researchers theorized that serotonin was the neurotransmitter of interest (Coppen, 1967). In subsequent years, there were numerous attempts to identify reproducible neurochemical alterations in the nervous systems of patients diagnosed with depression. For instance, researchers compared levels of serotonin metabolites in the cerebrospinal fluid of clinically depressed suicidal patients to controls, but the primary literature is mixed and plagued with methodological difficulties such as very small sample sizes and uncontrolled confounding variables. In a review of these studies, the chairman of the German Medical Board and colleagues stated, "Reported associations of subgroups of suicidal behavior (e.g. violent suicide attempts) with low CSF–5HIAA [serotonin] concentrations are likely to represent somewhat premature translations of findings from studies that have flaws in methodology" (Roggenbach et al., 2002). Attempts were also made to induce depression by depleting serotonin levels, but these experiments reaped no consistent results (Heninger, Delgado, & Charney, 1996). Likewise, researchers found that huge increases in brain serotonin, arrived at by administering high-dose L-tryptophan, were ineffective at relieving depression

(Mendels, Stinnet, Burns, & Frazder, 1975). This and other research led many to conclude that the serotonin theory of depression was not a viable scientific theory- for instance, in 1990, Astra pharmaceutical company research scientist John Evenden stated, "The simplistic idea of 'the 5-HT [serotonin] neurone does not bear any relationship to reality" (Shorter, 2008).

Contemporary neuroscience research has also failed to confirm any serotonergic lesion in any mental disorder, and has in fact provided significant counterevidence to the explanation of a simple neurotransmitter deficiency. Modern neuroscience has instead shown that the brain is vastly complex and poorly understood (Horgan, 1999). While neuroscience is a rapidly advancing field, to propose that researchers can objectively identify a "chemical imbalance" at the molecular level is not compatible with the extant science. In fact, there is no scientifically established ideal "chemical balance" of serotonin, let alone an identifiable pathological imbalance. To equate the impressive recent achievements of neuroscience with support for the serotonin hypothesis is a mistake.

With direct proof of serotonin deficiency in any mental disorder lacking, the claimed efficacy of SSRIs is often cited as indirect support for the serotonin hypothesis. Yet, this *ex juvantibus* line of reasoning (i.e., reasoning "backwards" to make assumptions about disease *causation* based on the response of the disease to a *treatment*) is logically problematic—the fact that aspirin cures headaches does not prove that headaches are due to low levels of aspirin in the brain. Serotonin researchers from the US National Institute of Mental Health Laboratory of Clinical Science clearly state, "[T]he demonstrated efficacy of selective serotonin reuptake inhibitors…cannot be used as primary evidence for serotonergic dysfunction in the pathophysiology of these disorders" (Murphy et al., 1998).

Reasoning backwards, from SSRI efficacy to presumed serotonin deficiency, is thus highly contested. The validity of this reasoning becomes even more unlikely when one considers recent studies that call into question the efficacy of the SSRIs.

A series of studies finds only a small, clinically insignificant difference between the effectiveness of placebo and antidepressants (Kirsch et al, 2008). This modest efficacy and extremely high rate of placebo response are not seen in the treatment of well-studied imbalances such as insulin deficiency, and casts doubt on the serotonin hypothesis.

Also problematic for the serotonin hypothesis is the growing body of research comparing SSRIs to interventions that do not target serotonin specifically. For instance, a Cochrane systematic review found no major difference in efficacy between SSRIs and tricyclic antidepressants (Geddes et al., 2005) In addition, in randomized controlled trials, buproprion and reboxetine are just as effective as the SSRIs in the treatment of depression, yet neither affects serotonin to any significant degree. The over-the-counter supplement St. John's Wort (Szegedi, Kohnen, Dienel, & Kesser, 2005) and placebo (Hypericum Depression Trial Study Group, 2002) have both outperformed SSRIs in randomized controlled trials. Exercise was found to be as effective as the SSRI sertraline in a randomized controlled trial, and more effective at preventing relapse (Blumenthal et al., 1999). Perhaps most interestingly, tianeptine, an antidepressant which *lowers* serotonin levels of the brain (but which is not available in the United States) has comparable efficacy to the SSRI drugs (Kasper & Olie, 2002). This alone might be enough for some to dismiss the serotonin theory – since the theory is that lower serotonin causes depression and raising serotonin remedies depression.

Although SSRIs are considered “antidepressants,” they are FDA-approved treatments for many different psychiatric diagnoses, ranging from social anxiety disorder to obsessive-

compulsive disorder to premenstrual dysphoric disorder. Some consumer advertisements (such as the Zoloft and Paxil Web sites) have in the past promoted the serotonin hypothesis, not just for depression, but also for some of these other diagnostic categories . Thus, for the serotonin hypothesis to be correct as presented, serotonin regulation would need to be the cause (and remedy) of each of these disorders (Healy, 2002). This is improbable, and no one has yet proposed a cogent theory explaining how a singular putative neurochemical abnormality could result in so many wildly differing behavioral manifestations.

However, in addition to these critiques, it is also important to look at what is *not* said in the scientific literature. To our knowledge, there is not a single peer-reviewed article that can be accurately cited to directly support claims of serotonin deficiency in any mental disorder, while there are many articles that present counterevidence. Furthermore, the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, which is published by the American Psychiatric Association and contains the definitions of all psychiatric diagnoses, does not list serotonin as a cause of any mental disorder. The *American Psychiatric Press Textbook of Clinical Psychiatry* addresses serotonin deficiency as an unconfirmed hypothesis, stating, “Additional experience has not confirmed the monoamine depletion hypothesis” (Dubovsky, Davies, & Dubvosky, 2003).

In conclusion, there exists no rigorous corroboration of the serotonin theory, and a significant body of contradictory evidence. Far from being a radical line of thought, doubts about the serotonin hypothesis are well acknowledged by many researchers, including frank statements from prominent psychiatrists, some of whom are even enthusiastic proponents of SSRI medications. For instance, in 2006, Wayne Goodman, chair of the FDA Psychopharmacological Advisory Committee, admitted that the serotonin theory of depression is but “a useful

metaphor"- and one that he never uses within his own psychiatric practice (Lacasse & Leo, 2006). And in 2011, psychiatrist Ronald Pies, editor of *Psychiatric Times*, wrote: "In truth, the "chemical imbalance" notion was always kind of an urban legend – never a theory seriously propounded by well-informed psychiatrists" (Pies, 2011).

It seems clear, then, that informing clients that their depression is due to a serotonin imbalance is a serious empirical error. The psychiatric textbooks do not make this claim, and drug companies no longer run advertisements claiming that serotonin imbalance causes depression (Lacasse & Leo, 2005). Prominent psychiatrists have in fact abandoned this theory in response to the data which contradicts it, which is what good science looks like. It has been decades since huge doubts emerged over the serotonin theory and arguably, psychiatry gave up on this theory a decade ago. As social workers, we need to respond to empirical evidence and tell our clients the best-tested information that is out there- and this means jettisoning the chemical imbalance/serotonin theory.

Other Mental Disorders

We have focused here on the serotonin theory of depression because it is clearly the most popular bioreductionistic theory of mental disorder. However, a similar case could be made for claimed chemical imbalances in other mental disorders. Advertisements for psychostimulants have made claims that Attention-Deficit Hyperactivity-Disorder is due to a chemical imbalance of dopamine remedied by medication (Leo & Lacasse, 2009). An advertisement for aripirazole claimed that the drug would adjust the level of neurotransmitters in the patient's brain like a thermostat (Lacasse & Leo, 2006). So while we have focused here on depression and serotonin, a similar case can be made for many other mental disorders and treatments.

ADHD provides another clear example of the widely held assumption that mental disorders are due to one or another kind of chemical imbalance. Medications have been given to children diagnosed with ADHD for more than half a century, beginning with Ritalin, first licensed by the FDA in 1955 for treating what was known as hyperactivity. At present, 11 percent of American children have been diagnosed with ADHD (http://www.cdc.gov/ncbddd/adhd/data.html), a 41 percent increase in the past decade, with two-thirds receiving prescriptions for psychostimulants (http://www.nytimes.com/2013/04/01/health/more-diagnoses-of-hyperactivity-causing-concern.html?pagewanted=all). These stimulants target the neurotransmitters dopamine and norepinephrine, purportedly to increase focus and self-control by increasing the availability of these chemical messengers. Many parents have been concerned about the effects of these powerful drugs on developing brains, fearing that there maybe unforeseen harmful consequences. On the contrary, some researchers now assert. Not only are these drugs *not* neurotoxic, nor simply neurochemically neutral, but they are actually "neuroprotective."

In a 2014 interview with Psych Congress Network, Timothy Wilens, professor of psychiatry at Harvard Medical School, stated that meta-analysis of 30 studies of children who have taken ADHD medication show that, over the years, the brains of these children turn out to look more like the brains of non-ADHD youngsters, thus indicating that there is a normalization in both function and structure of the brain following prolonged use of medication (http://www.psychcongress.com/video/are-adhd-medications-neurotoxic-or-neuroprotective-16223). A *New York Times* report from 2015 (http://well.blogs.nytimes.com/2015/02/02/can-attention-deficit-drugs-normalize-a-childs-

brain/?hpw&rref=health&action=click&pgtype=Homepage&module=well-region&region=bottom-well&WT.nav=bottom-well) includes a further argument from Dr. Wilens that these medications "normalize" children's brains, rewiring neural connections over time so the child feels more focused and in control.

It's not quite so simple, of course. When asked by the interviewer if these changes occur because the medication is directly altering the brain or because it allows these youngsters to have more normal interactions with the world, which in turn rewires the brain through the reciprocal action of neuroplasticity, Wilens admits that we really don't know. That's a significant gap in the causal chain. If it's *experience* that leads to changes in the brain, there's no inherent reason that pharmaceuticals are the sole or necessary agent for a child to have different experiences. How about changing the environment? (There's a novel idea.) Why assume that medication is the link between experience and brain? Not surprisingly, Wilens and other authors of the 2013 report he cites have received financial support over the years from pharmaceutical firms. In an email to the *Times* reporter, Dr. Wilens said he had not received "any personal income" from the pharmaceutical industry since 2009.

That aside, the ADHD-dopamine link is far from proven. Just because stimulant medication "works" to make children calmer does not mean that hyperactivity is caused by a lack of the neurotransmitter that the medication activates - no matter how comforting or convenient it might be to think so.

Thus, it is critical for social work students, clients and prescribers alike to realize what psychiatry diagnosis and treatment represents. Currently, by definition, almost every mental disorder in the DSM-5 is listed there because we do not know the etiology of the mental disorder. That is, conditions are listed in the DSM because we do not know the pathology of the mental

disorder- and this is true whether it is ADHD, depression, schizophrenia or Generalized Anxiety Disorder. Medical tests and examinations should be performed to ensure that the client's mental distress is not a downstream effect of a known medical disease (e.g., thyroid disease causing depression). But the reason that clinical assessment and person-in-environment approaches are so important- the entire reason that social workers and psychiatrists are dealing with mental health clients rather than neurologists- is that these conditions are somewhat mysterious (Lacasse, 2014)- and that includes the fact that we are ignorant of the pathophysiology.

This uncertainty may be disturbing, but social workers should think twice about solving this uncertainty by telling clients that they have a chemical imbalance. This is particularly true in modern age of the World Wide Web, where any client can simply Google "serotonin imbalance" and find many resources explaining that chemical imbalances are lay myths largely disseminated by pharmaceutical companies. Telling clients that they have a chemical imbalance when there isn't scientific evidence or tests to confirm this is troubling on an ethical level, but given the wide array of information available to clients, it could also create deep problems in therapeutic alliance.

Conclusion

The question of what to tell clients in lieu of the outdated chemical imbalance theory is a good one, if difficult to answer. It is important to point out that while there has been a huge problem in information dissemination, we have noted accurate portrayals of the chemical imbalance theory. The following statement, previously published on the website of the Mental Health Service at McGill University, is perhaps a good place to start:

> The term 'chemical imbalance is thrown around a lot these days. True conditions caused by chemical imbalances are relatively rare. All thoughts, feelings and motions in the

brain are mediated by the release of chemicals in brain pathways. Every person's brain is unique, leading each of us to have different traits and abilities. Just because your brain works in a particular way does not mean that you have a chemical imbalance. A certain amount of sadness, anxiety or other emotional upset is normal, and though we may be able to block these feelings by chemicals, this would tend to dehumanize us. Even when we use medication to help an individual with overwhelming emotions, most of the time this is not to repair a ‘chemical imbalance’ but simply to help contain symptoms.

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