

An Exploration of Placebo Effects and Their Use in the Treatment of Depression

Liv Spina

The State University of New York at New Paltz

Abstract

Large placebo effects have been measured in the treatment of depression with psychotherapies and psychopharmaceuticals. Antidepressant medication has been shown to be marginally better at treating depression than placebo antidepressants, however, flawed study designs may be contributing to this marginal difference. Psychotherapies have also been implicated in being largely placebo treatments for depression, based on the historical trends of placebo interventions, the current definition of placebos, and the results of component control trials. The emerging idea that our best treatments for depression are largely (if not entirely) placebos suggests that the act of receiving care is an effective treatment for depression.

Key Words: Psychobiology, Placebo, Depression, Antidepressants, Psychotherapy

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When you read the word *placebo* the first thing that likely comes to mind is a *sugar pill*. However, a placebo is anything that serves to simulate care (Benedetti, 2021). A common manifestation of a placebo effect is when a child runs to their parents with a boo-boo and asks them to “make it all better”. Some cuddling and kisses usually do the trick to make the pain of a scraped knee disappear. Receiving care for an illness (regardless of what that care is) can cause remarkable medical improvements.

I begin by summarizing how the use and conceptualization of placebos have changed over time. The measures, general effects, and mechanisms of placebos are introduced. I then narrow my scope to the placebo effect in the treatment of depression, specifically through antidepressant medication and psychotherapy.¹ Placebos have been shown to be remarkably effective at treating depression, so utilizing placebos to treat depression could be a time saving, cost effective, and safer option.

What are Placebos?

Before the adoption of evidence-based medical practices, the most effective tool at a doctor’s disposal for treating illnesses was the placebo effect (Benedetti, 2014). For millennia, doctors have used primarily ineffective (and often harmful) treatments. Shapiro and Shapiro (1997) provide an extensive list of medical treatments from antiquity, including: “blood, fat, bile, viscera, bones, bone marrow, claws, teeth, hoofs, horns, sexual organs, eggs, and excreta of all sorts” (p. 23), as well as “submersion of subjects in water for as long as possible... twirling of

¹ I will not discuss other treatments for depression, such as brain stimulation therapies (e.g., electroconvulsive therapy and transcranial magnetic stimulation), less conventional therapies (such as ketamine, atypical antidepressants, and other experimental drugs), or other pseudoscientific approaches that are used to treat depression.

patients in a human centrifuge” (p. 88) (for a more extensive list of the many treatments used throughout history, see Shapiro & Shapiro, 1997 and their references). Their historical analysis highlights two enduring themes of placebo treatments, the first being remedies that claim to treat all illnesses or, one size fits all treatments. Some examples include the use of unicorn horn, bezoar, mandrake, and powdered Egyptian mummy as historical “cure all’s” that grew and faded in popularity from century to century (Shapiro & Shapiro, 1997, pp. 14-15). The second theme is the uniformity in effectiveness across different substances. When substances were not harmful, the lack of specificity of placebo treatments meant that patients’ improvements were largely attributed to the natural course of an illness (spontaneous improvement) and the placebo effect (Shapiro & Shapiro, 1997).

Eventually, healers realized that sometimes patients would get better regardless of what treatment they were given. These healers then began purposefully exploiting the placebo effect by intentionally giving some patients inactive substances to see if the patients would get better. If a patient came in with an illness that the doctor did not know how to treat, or perhaps the patient appeared more worried than ill, the doctor might give an inactive substance, and claim that it was an effective medicine. These non-specific treatments were coined *placebos* (from the Latin *to please*) in the 18th century (Shapiro & Shapiro, 1997). Doctors would give troublesome patients something *to please them*, rather than waste (what they thought were) active treatments on these patients.

The realization that inactive substances could often elicit meaningful clinical improvements in ill patients led many scientists to start questioning the effectiveness of current treatments. Thus, placebos began being used in research designs to measure how effective a treatment was, rather than as a treatment itself. Scientists asserted that if a placebo treatment was

as effective as the current treatment doctors were using, then the treatment was spurious. This belief was instrumental in combatting the plethora of nefarious medical practitioners who emerged in the 18th and 19th century to exploit ill patients by charging them for pricey, ineffective treatments. Governments became involved and tasked scientists (including Benjamin Franklin) with testing the reliability of “miracle cure” claims. When scientists disproved the medical claims made by these charlatans, the practice of testing the efficacy of medical treatment against a placebo control group was born (Shapiro & Shapiro, 1997).

As the practice of using placebos as control groups to test the efficacy of medical treatments became more widespread in the 20th century, the placebo effect became viewed as a nuisance, rather than a scientific treatment option. Placebos were still used by doctors to please anxious patients (and by con men to exploit people), but, in scientific literature, the focus of placebos was to prove whether a treatment was effective or not. The first double-blind placebo-controlled trial (in which neither the clinician nor the patient knew who received active treatment or placebo) was conducted in 1911 (Benedetti, 2021). Today, the gold standard for testing the efficacy of medical treatments is integrally tied to comparing treatment groups with placebo control groups (the randomized double-blind placebo-controlled study).

In the last few decades, scientists have begun to conceptualize placebos with a less pragmatic lens. Instead of just using placebos as a tool to test the effectiveness of treatments, researchers have begun to wonder why “inactive treatments” can sometimes improve patient outcomes. By considering the therapeutic implications of placebos, scholars have revolutionized our conceptualization of what a placebo is. Previously, I have alluded to the definition of placebo as being an inert substance that is used in place of a real treatment. However, the placebo effect is now regarded as the effect that the simulation of a therapeutic intervention has on a patient

(Price et al., 2008), while placebos themselves are conceptualized as anything that serves to simulate care. Placebo researchers see the placebo effect not as something to minimize, but rather as something to utilize in the treatment of patients (Program in Placebo Studies and Therapeutic Encounter, 2021). Recent research has even eroded the notion that placebos require deception in order to be effective. A study testing the effectiveness of non-deceptive placebos to treat irritable bowel syndrome showed that they significantly improved patient's symptoms (Kaptchuk et al., 2010). Placebo research now centers on understanding the interaction between the healing environment and our bodies, and how to use those interactions to improve patient outcomes.

Methods for Studying the Placebo Effect

Next, I provide an overview of how researchers measure placebo effects. Placebo effects can be caused by a variety of different factors (from patient-doctor interaction to a patient's emotional state, etc); therefore, to understand the causes of patient improvements, the contributing variables must be isolated. These isolated variables can then be compared to provide a deeper understanding of what causes a particular placebo effect. Figure 1 shows how, just as placebo effects make up some of the effect seen in the treatment group, so do variables affecting the no treatment group affect the score of the placebo group. Measuring the natural course of an illness is essential because symptoms can change over time, regardless of treatment. Factors that play a role in the change seen in no treatment groups include regression to the mean, spontaneous remission (or worsening), positive life events, rater bias, and others (Rutherford, 2014).

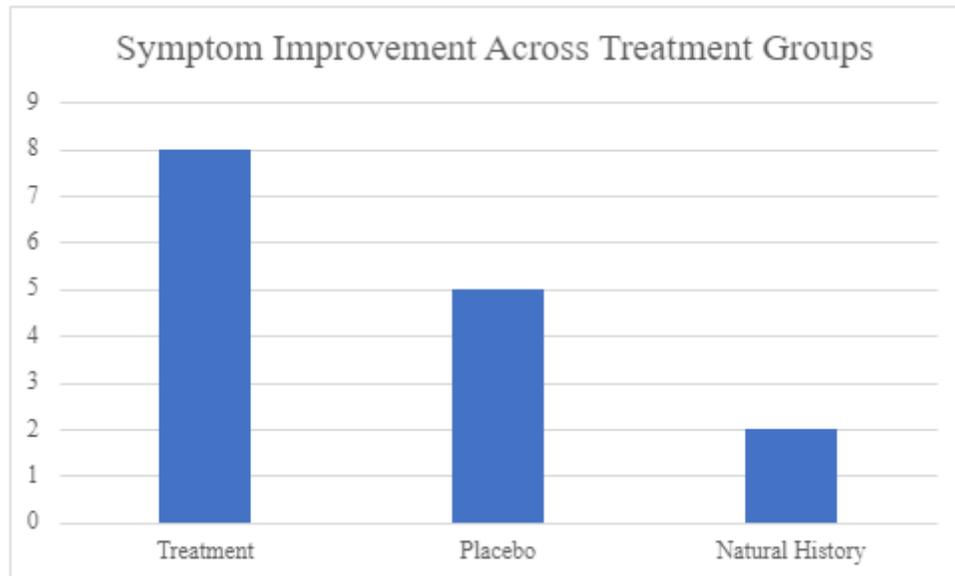


Figure 1: A representation of how different variables (such as placebo, treatment, and natural history of an illness) can add together to produce effects in patients. The effect seen in the treatment group can be found from subtracting the effect size of the placebo group (this assumes an additive model of placebo effects).

Study designs such as crossover designs and factorial designs are used to analyze placebo effects. Crossover designs attempt to eliminate noise created by between-group variations by comparing the placebo effect with treatment effects using within-subject designs (in within-subject designs, participants are given each treatment and their change in symptoms are compared for each treatment). However, these studies can be inaccurate if treatment effects are not quickly reversible (Benedetti, 2014). Factorial designs are used to study the interaction between different variables; in placebo research they can be used to study the interaction between treatment and expectation (Atlas, 2021). Researchers often assume an additive model of placebo treatment, that is, the placebo effect plus the active treatment equals the treatment effect. However, treatment and expectation effects might not be additive. Factorial designs help to distinguish the effects between different elements of care and test different combinations of

treatments on outcomes to give researchers a clearer picture on how combining variables impacts symptom outcomes.

Another technique used in placebo research is “The Open-Hidden Paradigm” (Price, 2008). When patients are given medication, they typically receive it from a caregiver. This is the “open” part of the paradigm since patients are aware that they are receiving treatment. In hidden treatment, patients are unaware that they are receiving medication. Hidden treatment can be conducted through an automated system in which patients are connected to a computer that administers treatment (perhaps on a schedule, or when a patient’s vitals hit a predetermined criteria). By measuring the effect of a treatment using the Open-Hidden Paradigm, researchers can isolate the effect of the simulation of care.

Factors That Influence Placebo Effects

Different variables that surround the active treatment (but are not the active treatment itself) can impact patient outcomes. Patients’ expectations, past experiences of learning, and therapeutic relationship with caregivers all contribute to placebo effects (Enck et al., 2013). Some of the research involving these variables and different illnesses are described below.

The expectation of improving one's symptoms plays a major role in placebo effects. From cardiac surgery to deep brain stimulation in Parkinson's disease to antidepressants, treatment outcomes are often predicted by patients’ expectations of improving prior to receiving treatment (Enck et al., 2013). Researchers have found that pain is significantly decreased in the open/ hidden paradigm for patients who receive open treatment, and that motor mobility is significantly increased in patients with Parkinson's who receive open treatment (Colloca, Lopiano, Lanotte, & Benedetti, 2004). Patients’ expectations of improving are influenced by

their past experiences with medical care, as well as their current environment. The therapeutic environment provides clues and cues to patients that are then interpreted to determine the effectiveness of treatment. For example, research has shown that receiving placebo shots of a pain analgesia results in greater pain relief than receiving a placebo pill (Kaptchuk et al., 2000). To patients, the intensity of a procedure provides clues as to how effective the procedure will be at improving their symptoms.

Learning also plays a large role in placebo effects, specifically classical conditioning. Classical conditioning is a process by which a previously neutral stimulus causes physiological changes in a patient after it has been paired with an active stimulus a certain number of times. This phenomenon has been shown in studies on pain analgesia (Jensen et al., 2015) and is promising for reducing the frequency of opiates used by patients. Pairing a placebo with treatment of a drug that increases growth hormones led to growth hormones being elevated later by placebos alone (Benedetti et al., 2003). Some physiological processes are impacted more by expectations (pain analgesia) while others show a greater response to conditioning placebos (hormone secretion) (Benedetti et al., 2003).

The last factor being discussed that plays a major role in placebo effects is the patient-caregiver relationship. Placebo effects in the treatment of chronic pain, irritable bowel syndrome, allergic reactions, and more have been shown to be more effective when patients are treated by a warm, empathetic provider, relative to a neutral doctor (Atlas, 2021). Atlas (2021) also reports that perceived similarity with a doctor can influence patient responses. This is especially prevalent in people with marginalized identities. The relationship between patient and caregiver has been termed the “therapeutic alliance” (Capuzzi & Stauffer, 2016), as researchers

have sought to emphasize the healing power from warm, compassionate, and competent healthcare providers.

Although much of placebo research has focused on pain amelioration, researchers have also noticed the large placebo effects seen in the treatment of depression. In the next section, I begin describing this prevalent mental illness before reporting on the placebo effects associated with the treatment of depression.

What is Depression?

Depression is generally defined as a mood disorder that elicits feelings of intense sadness and is accompanied by a wide range of psychological and physical symptoms (Raskin, 2019; Watson & Breedlove, 2016). Depression is unique in its prevalence, historically and cross-culturally; it is also one of the most common mental illnesses in the modern era. I begin my description of depression by discussing its conceptualization throughout history, followed by modern perspectives of what depression is and how it is measured. A comprehensive discussion of how depression is viewed and treated in non-western cultures, however, is beyond the scope of this thesis. To finish this section, I will discuss the prominent biological, psychological, and environmental perspectives of what causes depression.

Depression is one of the few medical conditions that has been described cross-culturally for millennia. Lawlor (2012) conceptualizes the history of depression as “a comparatively consistent disease phenomenon that is nevertheless endlessly reconceptualized and lived according to the experience of the particular culture and individual concerned” (Lawlor, 2012, p. 2). He argues that, although depression is a relatively common mental illness, it expresses itself uniquely with different symptoms in people across time and culture.

Parallel to the roots of western medicine, the roots of our modern conceptualization of depression begin in ancient Greece with a disease called “melancholia” (Lawlor, 2012). The core symptoms of melancholia as described by Lawlor were causeless sadness and fear. However, someone could also be diagnosed with melancholia if they had symptoms or “aggressive madness” or hallucinations (Lawlor, 2012, p. 25). Melancholia was thought to be caused by an excess of black bile (one of the notorious four humors from ancient Greek medicine, a system in which all illnesses were attributed to humoral imbalances).

Melancholia’s symptoms narrowed to only “fear and despondency” when western medicine was taken over by Galen in the second century CE. Some of Galen’s treatments, like a diet of warm and moist food, are now regarded as clearly placebo interventions; however, some of his recommended treatments are still used today to treat depression: exercise, massage, and active motions (Lawlor, 2012, p. 31).

During the Christian Era and the Renaissance, the conceptualization of the causes of depression shifted to outside (rather than from within) the human body. During the Christian Era, the term “acedia” was coined for monks who experienced low mood, boredom, and longing. This condition was attributed to the despair monks often felt from rigorously avoiding “temptations” in isolating conditions (Raskin, 2019). During the Renaissance, symptoms associated with melancholia broadened again to include a plethora of psychological symptoms that are now attributed to separate disorders. Believed causes of melancholia during the Renaissance were supernatural (religious or spiritual), natural (biological and astrological), and external (interpersonal relationships and difficult life circumstances) (Raskin, 2019).

The next reconceptualization of depression came during the Industrial Revolution, when the term “neurasthenia” was coined for the cooccurrence of sadness and anxiety. Following the

externalizing trend of the Renaissance, neurasthenia was thought to be caused by an “exhausted nervous system” that became overwhelmed through the oppressive consequences of life experienced during early industrialization (Raskin, 2019). This diagnostic category combines two modern illnesses that are highly co-morbid with each other: depression and anxiety. After neurasthenia comes our modern conceptualization of depression.

Modern Measures of Depression

To treat depression, researchers and clinicians have come up with ways to measure if someone has depression, as well as its severity. To do this, researchers have categorized the symptoms that usually accompany the feelings of intense, long-lasting sadness. In different contexts, different measures have been adopted to measure a patient's depression. The three main diagnostic tools used to measure depression are the *Diagnostic and Statistical Manual of Mental Disorders*, the Patient Health Questionnaire-9, and the Hamilton Depression Rating Scale.

Today in the United States, the American Psychiatric Association (APA) is responsible for the categorization of mental disorders, including depression. In the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013), there are eight distinct diagnoses for “depressive disorders.”² They include disruptive mood dysregulation disorder, major depressive disorder, persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. Nuances of patients' ages, duration of symptoms, symptom severity, and symptom onset distinguish these disorders from one another. Collectively though, the *DSM-5*

² The *DSM-5-TR* replaced the *DSM-5* in March 2022.

states that “the common feature of all of these disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual’s ability to function” (APA, 2013, p. 155). Going forward, I focus on major depressive disorder (MDD) diagnosis from the *DSM-5* because it is the most widely researched depressive disorder in placebo research. In general, study designs rarely distinguish between the *DSM-5*’s different diagnoses (because the differences are minor) when testing the efficacy of treatment for depression.

The *DSM-5* is used by doctors and clinicians to formally diagnose patients with a mental illness because it provides codes that are submitted to insurance companies for reimbursement purposes. However, in clinical practice, a rating scale called the Patient Health Questionnaire-9 (PHQ-9) is often used (Kroenke & Spitzer, 2002). Another rating scale that is commonly used to measure depression is the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). This 17-21 item scale is primarily used in research designs to rate the prevalence of symptoms of depression in clinical trials. The first two items of the HAM-D are shown in Figure 3. While the *DSM-5* is seen containing the cannon diagnostic criteria, in practice, researchers and clinicians often use rating scales like the PHQ-9 and the HAM-D to make diagnoses.

Hamilton Depression Rating Scale (HDRS)

PLEASE COMPLETE THE SCALE BASED ON A STRUCTURED INTERVIEW

Instructions: for each item select the one "cue" which best characterizes the patient. Be sure to record the answers in the appropriate spaces (positions 0 through 4).

<p>1 DEPRESSED MOOD (<i>sadness, hopeless, helpless, worthless</i>)</p> <p>0 <input type="checkbox"/> Absent.</p> <p>1 <input type="checkbox"/> These feeling states indicated only on questioning.</p> <p>2 <input type="checkbox"/> These feeling states spontaneously reported verbally.</p> <p>3 <input type="checkbox"/> Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.</p> <p>4 <input type="checkbox"/> Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.</p>	<p>2 FEELINGS OF GUILT</p> <p>0 <input type="checkbox"/> Absent.</p> <p>1 <input type="checkbox"/> Self reproach, feels he/she has let people down.</p> <p>2 <input type="checkbox"/> Ideas of guilt or rumination over past errors or sinful deeds.</p> <p>3 <input type="checkbox"/> Present illness is a punishment. Delusions of guilt.</p> <p>4 <input type="checkbox"/> Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.</p>
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Figure 3. Sample items from the Hamilton Depression Rating Scale.

Proposed Causes of Depression

To understand how to treat depression, we must understand what causes depression. This inquiry causes quite a stir among health care professionals and researchers who have different hypothesis about the underlying causes. The proposed causes can be broken down into three categories: biological, psychological, and social/environmental.

Many brain regions have been implicated in depression. A meta-analysis conducted by Palmer et al. (2015) looked at the differences in brain region activation between depressed patients and health controls across cognitively demanding tasks, emotionally valanced tasks, and in resting conditions. Their analysis found that people with depression showed greater activation in the right medial frontal, insula, and superior temporal regions during cognitively demanding tasks than healthy controls. During emotionally valanced tasks and resting-states, people with depression had greater activation in limbic areas, as well as the amygdala and subcallosal cingulate gyrus. This activation has been linked to the negative rumination associated

with depression, as there is similar activation during emotionally valanced tasks and under resting conditions.

The brain regions implicated in depression, along with the success of antidepressants, led to the most prominent biological theory of what causes depression: the chemical imbalance theory. The chemical imbalance theory (or more accurately, the monoamine theory of depression) hypothesizes that low levels of monoamine neurotransmitters (including serotonin, norepinephrine, and dopamine) in the synapses of the brain can cause depression (Kirsch, 2011). This theory was first hypothesized to explain why some patients reported improved "vitality and well-being" when taking MAOIs (MAOIs were first used to treat tuberculosis, and it was only through careful physician observation that its antidepressant qualities were noticed, and later exploited) (Kirsch, 2011).

One of the main criticisms of purely biological explanations for depression is that the diagnosis of depression is based primarily on self-reports rather than biological tests. Changes in brain activation can also only be viewed at a multi-cellular level (or higher), unless researchers use animal models (to measure the physiological effects of medications), or postmortem studies. Brain studies also are strictly correlational in nature- it is unclear whether changes in brain activation cause depression, or if depression leads to physiological brain changes. Until techniques are developed to track the progression of depression in the brain at a cellular and molecular level, we are unlikely to learn the physiological changes that cause, accompany, and/or follow depression.

Aside from strictly biological hypotheses, there are many psychological explanations for the causes of depression. The prominent therapeutic psychological frameworks are psychoanalytic and cognitive behavioral, and they link different psychological experiences to

depression (Capuzzi & Stauffer, 2016). The psychoanalytic theory of depression is that depression is anger turned inward. Psychoanalysts believe that insecure attachments to caregivers in childhood can lead to developing depression in adulthood. The leading cognitive behavioral theory of depression, called the cognitive triad, comes from Aaron Beck. In this framework, Beck states that negative thought patterns lead to depression. In a nutshell, depression is caused by negative beliefs about oneself, negative beliefs about one's experiences, and negative beliefs about the future (Hollon & Beck, 1979; Raskin, 2018, p. 164). Psychological explanations for depression are often criticized for their lack of empirical testability, and thus lack of empirical support. These factors are often only measured through subjective measures.

Environmental stimuli are also believed to play a big role in depression (Raskin, 2018). Negative life events that often lead to normal sadness can also trigger depression, especially if these negative events happen over a long period of time. However, a fully environmental approach to depression ignores that some people do not experience depression in response to negative life events, while others do.

Although there is still much uncertainty about what exactly causes depression, most scholars agree that a combination of biological, psychological, and environmental factors can contribute to depression. Currently, there are also many treatments for depression. The three main treatment options recommended for depression on the National Institute of Mental Health's website are: medications, psychotherapies, and brain stimulation therapies (2018). Because of the bounds of my thesis, I will not be discussing brain stimulation therapies. Benedetti (2021) summarizes brain imaging data that show that, while there is some overlap, different brain regions are implicated in drug and psychotherapeutic treatment of depression (and thus, different brain regions are involved in placebo controls of these treatments). Research has also shown that

a large portion of the main treatments for depression can be associated to placebo treatment. In the next two sections, I describe current treatments of depression, and their associated placebo effects.

The Mechanisms of Antidepressants

The 20th century saw a rapid rise of evidence-based drug therapies, including for the treatment of depression. Shapiro and Shapiro (1997) briefly describe the evolution of psychotropic drugs specific for depression, from monoamine oxidase inhibitors (MAOIs) to tricyclic antidepressants (TCAs) to serotonin reuptake blockers (or selective serotonin reuptake inhibitors; SSRIs). Each successive drug had fewer adverse side effects, thus replacing its predecessor as the more preferred antidepressant. However, Davis et al. (as cited in Shapiro & Shapiro, 1997, p. 93) found that all antidepressant drugs were equally effective in treating depression, with similar effectiveness across the different depressive subcategories. These findings are surprising because the three classes of drugs affect a range of neural circuits and neurotransmitters in different ways. If drugs with different chemical effects cause the same type and amount of improvement of depressive symptoms, then are the active ingredients what causes clinical improvement?

MAOIs and TCAs are considered older antidepressant medications and are used less than newer treatments because of their more intense adverse side effects. MAOIs function by inhibiting the degradation of norepinephrine and serotonin, thus increasing their bioavailability in the synaptic cleft. TCAs also increase the bioavailability of neurotransmitters, specifically serotonin and noradrenaline, by blocking their reabsorption into presynaptic cells. They also block the extraneous neurotransmitter receptors, which has been hypothesized to be the cause of their unpleasant side effects.

The most common antidepressants today are selective serotonin reuptake inhibitors (SSRIs), and they have been shown to increase the amount of serotonin in the synaptic cleft. SSRIs block the reabsorption of serotonin into the presynaptic neuron by blocking the reuptake transporter of the presynaptic cell. Figure 4 depicts the neural mechanisms of SSRIs (Lundbeck Institute, 2016). SSRIs are used to treat a myriad of disorders, including obsessive compulsive disorder (OCD), childhood enuresis, major depressive disorder, severe anxiety disorder, bipolar disorder, post-traumatic stress disorder (PTSD), and social anxiety disorder (Wood, 2021). Polymorphisms in the serotonin reuptake transporter gene have been correlated with depression (as well as other mood disorders) (Best et al., 2010). Researchers have also observed that depressed people have less of a serotonin by-product in their blood, suggesting that serotonin levels are abnormally low (Visser et al., 2010). It is worth noting that 95% of the body's serotonin is produced in the intestine (Terry & Margolis, 2016). The proposed impact of changing the absorption pattern of serotonin is that it increases the likelihood of neuroplasticity in neurons associated with information processing in the brain, thus allowing those with depression greater ease to alter depressive thought patterns to non-depressive thought patterns (Harmer & Cowen, 2013).

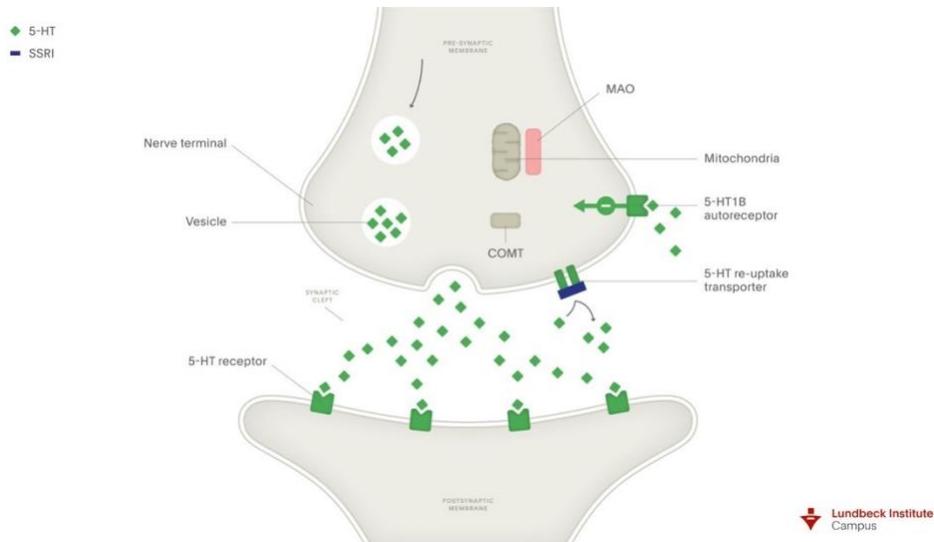


Figure 4. The neural mechanisms of Selective Serotonin Reuptake inhibitors. 5-HT is synonymous with the neurotransmitter serotonin for the purposes of this depiction. Open source from Lundbeck Institute.

A review article by Harmer and Cowen (2013) relays the cognitive and physiological effects of SSRIs. Short-term effects of SSRI intake by healthy participants included an increase in positive emotional processing (the opposite of the heightened negative emotional processing seen in depression). In neuroimaging studies, healthy volunteers also showed a decrease in amygdala activation in response to fearful facial expressions (an opposite activation pattern is seen in neuroimaging of the amygdala of depressed patients). Depression patients taking SSRIs showed a decrease in negative emotional biases in cognitive tests (another hallmark symptom of depression) after one week of taking SSRIs (although they did not yet show a clinically significant improvement in mood). The higher-than-average neural responses to negative facial expressions normally exhibited by depressed patients (as seen through neuroimaging of the amygdala and ventral striatum) were also shown to be diminished in these tasks (Harmer & Cowen, 2013).

Although the chemical imbalance theory is the most widely accepted theory for the biological mechanisms of depression, many scholars question its validity (Benedetti, 2021; Kirsch, 2011). Two damning pieces of evidence contradict it: 1. drugs that do the opposite of SSRIs have not been shown to cause depressive symptoms in healthy patients, and 2. these drugs have even exhibited antidepressant effects.

Kirsch references clinical reports that reserpine (a drug that decreases brain levels of serotonin, norepinephrine, and dopamine) was initially observed to increase depressive symptoms in some patients, but after more careful examination of the data, researchers found that only 6% of patients who were treated with reserpine (for other illnesses) developed clinical depression (Kirsch, 2011). It is worth emphasizing his point that 94% of patients who took a drug that decreased the number of available depression-associated neurotransmitters (the supposed biological cause of depression) did not develop depression. Additional studies have explored the impact of decreasing serotonin levels in humans with interesting results.

Delgado et al. (1990) looked at the effects of depleting tryptophan (an amino acid that is an essential ingredient in serotonin and other neurotransmitters) on depressive symptoms in patients whose depression had improved while taking SSRIs. They found that participants whose tryptophan levels were decreased had relapses in depressive symptoms that were reversed after tryptophan was reintroduced into their diet (as compared to placebo controls). A more recent review article (Young, 2013) relayed data showing that recently recovered depressed patients (who were currently taking SSRIs) had reappearances of depressed mood following acute tryptophan depletion (ATD). Interestingly, recovered depressed patients no longer on antidepressants (as well as healthy patients) did not show a lowering of mood accompanying ATD. Tryptophan depletion sometimes leading to depressed moods, but other times not, could be

an example of a conditioning response to elevated levels of serotonin. Harmer and Cowen (2013) bring up this point, wondering if repeatedly taking antidepressants could lead to a “serotonin dependence” that, when serotonin levels are lowered, could lead to people feeling depressed. Perhaps the elevated levels of serotonin have been associated with depression amelioration in patients currently taking SSRIs- so when serotonin levels are diminished, those recovering from depression experience depressed moods again. This could account for why people who are not taking an SSRI do not experience depressed mood, because their positive moods are not associated with an increase in serotonin.

Benedetti (2021) also calls into question the assumed antidepressant functions of SSRIs by referencing another drug- tianeptine- which acts as a selective serotonin reuptake enhancer (SSRE, the opposite function of SSRIs). These two drugs- which have opposite physiological effects on the neurotransmitter serotonin- were shown to have similar antidepressant properties. These findings call into question the current assumed model of how the bioavailability of serotonin in the synaptic cleft is connected to depression. However, an alternative explanation is possible for the effectiveness of both SSRIs and SSREs in the treatment of depression. These molecules, which have opposite effects, may both increase the amount of serotonin that is available to interact with postsynaptic receptors. Since neurons need a certain amount of neurotransmitter interaction with their receptors to fire, having high levels of serotonin in the synaptic cleft may help with this. However, the hastening of the active transport of serotonin back into the presynaptic cell (after it has been released into the synaptic cleft and interacted with the receptors of the postsynaptic neuron) may facilitate future firing events. Instead of just releasing a small amount of serotonin at a time (which may not be enough to initiate the action potential of a postsynaptic neuron), the expedited active transport of serotonin back into the

presynaptic cell may allow there to be adequate stores of serotonin ready to be released.

Upregulation through the development of more postsynaptic receptors because of the depletion of serotonin in the synaptic cleft could be another way that SSREs work. They could also function by dysregulating the negative feedback loop that occurs when neurotransmitters in the synaptic cleft interact with the presynaptic auto receptors. The activation of presynaptic auto receptors initiates a negative feedback loop, so increasing the speed of transport of serotonin back into the presynaptic neuron through SSREs could potentially increase the amount of serotonin produced overall.

There may be other biological effects of these drugs, still unaccounted for, which function to decrease depression; however, Kirsch lays out a cognitive explanation for the effectiveness of antidepressants- specifically, the placebo effect.

The Placebo Component of Antidepressants

In the treatment of depression with SSRIs, the placebo effect has been found to be the major contributing factor in improving patient outcomes. Meta-analyses have estimated that the percentage of clinical improvement from antidepressants that can be attributed to the placebo effect is between 51%-68% (Kirch & Sapirstein, 1998; Reif et al., 2009). Kirch and Sapirstein (1998) detail that the natural course of depression accounts for 24% of improvements seen, while the active ingredient effect attributes 25% of the improvements. Expectations play a role in the success of antidepressant treatment, and a current theory postulates that an enhanced placebo effect from this expectation is what is leading to the physiological effects of SSRIs.

While arguably clinically insignificant (meaning that they do not reflect noticeable improvement by patients; Kirsch, 2011), clinical trials still sometimes find a statistically

significant difference in depressive symptoms between patients who take antidepressants versus those who take placebos (DeRubei, Siegle, & Hollon, 2008). If the bioavailability of serotonin is not what is causing improvements, then what is? Kirsch (2011) argues that the belief of improvement associated with psychiatric treatment (mediated by the presence of antidepressant-induced side effects) is what causes the statistically significant differences between the active-drug and placebo arm of studies on antidepressants.

As discussed, the gold standard of clinical trial study designs are double-blind, randomized control trials. This study design is used to minimize biases that might skew the results (through influencing participants expectations) and make a treatment seem more (or less) effective than it is. However, achieving a truly “blind” study is difficult, and requires the use of active placebos (these are placebos that mimic the side effects of the active treatment but do not contain the active ingredient being tested) (Shapiro & Shapiro, 1997). Because the study designs employed when testing the efficacy of SSRIs generally do not use active placebos, researchers have argued that these trials may be obscuring the full placebo effect of antidepressants (Kirsch, 2011). Like most medications, SSRIs have side effects, including anxiety, indigestion, diarrhea or constipation, changes in appetite, dizziness, blurred vision, dry mouth, etc. (for a more comprehensive list, see the NHS.uk website). Kirsch argues that patients who experience side effects are more likely to believe that they have been given the active treatment, causing them to “break blind.” This belief could be what causes the clinical improvement seen from taking antidepressants (Kirsch, 2019). Studies examining the effects of belief on depression treatment are described below.

In one of these studies, the researchers reanalyzed data of the effects of sertraline (an SSRI), Saint John’s wort (a dietary supplement implicated in the treatment of mood disorders),

and placebo in treating MDD (Chen et al., 2011). The authors found that there was no significant difference in symptom improvement across all three groups; however, patients who believed that they had received an active treatment (irrespective of actual treatment) showed greater improvements than those who believed that they had received a placebo. This finding suggests that the expectation of receiving an active treatment corresponds with symptom alleviation in those who suffer from MDD.

A study conducted by Rutherford et al. (2014) found that the expectation of receiving a placebo treatment can worsen treatment outcomes. In this crossover study, all participants started on fluoxetine (an SSRI), and after 12 weeks of open treatment, participants were randomly assigned to blind treatment of either continuing fluoxetine or switching to a placebo. Participants were told that they had a 50% chance of being switched to placebo, and this led to an average increase in MDD severity after the transition, regardless of whether they were switched to placebo or not. This data supports the hypothesis that expecting active treatment in antidepressant drug trials improves symptoms by showing that the uncertainty of being switched to a placebo can worsen symptoms.

Kirsch presents more data that supports the theory that treatment expectation impacts symptom outcomes, specifically regarding experiencing side effects. Kirsch reports data (from Rabkin et al., 1986) that 89% of participants in the active treatment group correctly guessed that they were in the treatment group, and doctors had 90% accuracy in guessing which participants were in the active treatment group (participants in the placebo group were just better than chance at guessing their group affiliation). The greater accuracy in predicting group affiliation by those in the active treatment group was explained based on the adverse side effects caused by SSRI's (it is worth noting that participants in placebo groups can also experience side effects, known as

nocebo effects, but generally less often). Patients' awareness of their assigned treatments has been shown to bias their reports of symptoms; raters in clinical trials have also shown bias in assessing symptoms when they know in which treatment group a participant is (Shapiro & Shapiro, 1997).

In fact, Kirsch has argued that controlling for the presence of side effects in participants of clinical trial could eliminate the significant difference in treatment effect between placebos and SSRIs (2011). Therefore, he has argued that the treatment benefits associated with taking antidepressants are caused by the expectation of healing that accompanies *the adverse side effects* of SSRI treatment. How can nausea, insomnia, and many other adverse side effects help treat depression? Kirsch argues that these symptoms signal to a patient that they are receiving a treatment that is working (since it is having a noticeable side effect) and that these signals elicit hope in patients (an emotion that is absent from many people who suffer from depression), and this hope leads to symptom improvement.

However, some studies have cast doubt on this interpretation. A study conducted by Hieronymus et al. (2018) sought to test Kirsch's hypothesis that the side effects of antidepressants can lead to a decrease in depression symptoms (rather than the active medication). They analyzed data from 15 clinical trials run by pharmaceutical companies testing the effects of two different SSRIs (citalopram and paroxetine) on patient's symptoms. Hieronymus et al. found a significant difference between the treatment and placebo group (of both drugs) on scores of the depressed mood item of the HAM-D (as depicted in figure 3). They found no significant difference between treatment groups that had adverse side effects versus participants in treatment groups who did not experience adverse side effects. In conclusion, they stated that "the placebo-breaking-the-blind theory has come to influence the current view on the

efficacy of antidepressants to a greater extent than can be justified by available data” (Hieronymus et al., 2018, p. 1735).

While Hieronymus et al. (2018) sought to challenge Kirsch’s assertion that the side effects of antidepressants improve patient outcomes through enhancing patient expectancy, their study methodology and data interpretations were flawed. Most egregiously, the study did not compare the outcome differences in participants in the placebo group who experienced symptoms versus those in the placebo group who did not experience symptoms. In the section on methods, I described the importance of factorial designs. The study analyzed the interaction between symptom severity in SSRI treatment groups and patient outcome; however, they did not look at the same interaction between symptoms and outcomes in placebo groups. As stated previously in this section, patients generally have fewer side effects when they receive placebo treatments. This could lead to the effect seen when comparing placebo groups to SSRI groups. To understand the interaction between treatment and side effects on depression symptoms, researchers must compare participants who develop side effects in both SSRI treatment and placebo treatment. However, an even more effective way of analyzing the effect of patient expectancy on depression scores would be to ask participants to what treatment group they believe they were assigned, and then assess whether a correlation between treatment expectation and outcome exists (as proposed by Rabkin et. al., 1986).

Another flaw in Hieronymus et al.’s study was the team’s decision to only use data from one item of the HAM-D to analyze depression symptoms because some of the items in the HAM-D overlap with SSRI side effects (such as fatigue, nervousness, somatic anxiety symptoms, gastrointestinal issues, somatic symptoms, genital symptoms, and weight fluctuations). However, 10 of the 17 items on the HAM-D include symptoms of depression that

are not listed as side effects to Paroxetine on the MedlinePlus Website (2022). To analyze the effect of a treatment on depression, it is essential to accurately measure depression symptoms by considering more than one factor that is involved with depression.

Aside from methodological problems, Hieronymus et al. (2018) failed to mention the lack of *clinical* significance in the difference in scores between placebo and SSRI treatment groups. Much of the criticism surrounding the efficacy of antidepressants is based on the assertion that, although SSRI effects are found to be statistically significant, they are not seen as clinically significant because of their small effect size (Cohen's $d = .3$, Hengartner & Ploderl, 2018). This is because a small effect can be counted as "meaningful" (statistically significant) if there are enough participants. In principle, statistical significance serves to require larger differences in data in smaller trials than in larger trials, thereby not letting smaller (and inherently less representative) trials have as much "weight" as larger (more representative) trials. But when studies have very large subject pools, even slight differences will become significant; therefore, it is essential to not only analyze statistical significance, but also effect size when making assumptions based on data sets. In the Hieronymus et al. (2018) study, the average symptom change ranged from a .31 to .49 difference. This is about an average 8-12% decrease in score on the depressed mood item. So, for every two to three participants, one of them would be rated as improving by one point more than a participant in the placebo group.

Another study cited previously also reports a statistically significant difference between placebo treatment and SSRI treatment (DeRubei, et al., 2008). A study conducted by DeRubeis et al. (2005) found participants responded equally as well to antidepressant medication and Cognitive Behavioral Therapy, but significantly worse to placebo pill treatment. However, patients who received antidepressant medication had their treatment augmented with lithium or

desipramine “as needed” (DeRubei et. Al., 2008, p. 790). There is no mention of those receiving placebo pills getting treatment augmentation with more placebo pills. This disparity in the amount of treatment across placebo and antidepressant groups means that the placebo treatment did not accurately control for the antidepressant medication, and thus could account for the significant difference between the two groups. This study also did not use active placebos that induced side effects in patients, like the antidepressant side effects.

A better study design that would test the effects of experiencing adverse side effects on depression treatment outcomes would be to compare an active treatment (an SSRI) to an active placebo (as proposed by Kirsch, 2011). An active placebo is a substance that mimics the side effects of a drug; this controls for the side effects of a drug when measuring drug efficacy. An active placebo for an SSRI would be a treatment that induces the common side effects of SSRIs (nausea, insomnia, loss of appetite, etc.) at about the same rate that SSRIs do, but that does not affect serotonin reuptake (since serotonin reuptake is proposed to be the active mechanism that treats depression in SSRIs). This study design would allow researchers to isolate the healing effects that are induced through the experience of adverse side effects.

In summary, while the placebo component has been shown to be a large contributor to the treatment effect of SSRIs, studies still sometimes find a significant difference between treatment with SSRIs and placebos. Some scholars argue that this difference is not due to the active effect of SSRIs, but rather the presence of side effects associated with SSRIs, leading to patients breaking blind in clinical trials. Breaking blind changes participants’ expectations of improving, and thus improves their depressive symptoms. To test this hypothesis, further research analyzing the effectiveness of SSRIs must compare SSRIs against active placebos. In the next section, I discuss the other most popular treatment for depression: psychotherapy.

Psychotherapeutic Treatments for Depression

Shapiro estimates that the number of psychotherapies described in medical texts throughout history to be around 1,000 (Shapiro & Shapiro, 1997). Today, there are more than 400 different psychotherapies offered (Benedetti, 2021). The types of psychotherapies range from humanistic to psychodynamic to cognitive behavioral therapy. Because of the bounds of my thesis, I will describe only the two most common frameworks for psychotherapy: psychodynamic and cognitive behavioral therapy (CBT). Therapeutic intervention theories are often taught as distinct from each other; however, in practice clinicians often combine elements from different psychotherapies.

First conceptualized by Josef Breuer and Jean-Martin Charcot, psychoanalytic (now referred to as psychodynamic) therapy was further developed and popularized by Sigmund Freud in the 20th century. Proclaimed “the talking cure,” Freud popularized the first official western form of talk therapy after observing that patients’ psychological conditions improved when they talked about their trauma and emotions rather than receiving the popular cure of the day, hypnosis (Capuzzi & Stauffer, 2016).

To treat various mental disorders (including depression,) psychoanalysts employ techniques such as free association, transference, and dream analysis to understand the underlying factors influencing their client’s distress. Overall, these techniques involve therapists listening to what their clients say, and then analyzing what the client has said to uncover unconscious conflicts leading to their dysfunction. Psychoanalytic therapists use discussion-based therapy to treat their clients (i.e., it is a “talking cure”). Talking through a client’s dysfunction with a therapist is thought to bring self-awareness to the clients (bringing the unconscious to the conscious mind). The goals in psychoanalytic therapy are for clients to

understand how their past influenced their present functional and dysfunctional behavior.

Therapists aim to examine the unresolved conflicts in their clients' lives, connect how they relate to current maladaptive behaviors, and cultivate self-awareness to treat mental illness symptoms (Capuzzi & Stauffer, 2016).

One of the most cited limitations of psychoanalytic therapy is that there is a lack of empirical research and evidence-based support for its efficacy (Capuzzi & Stauffer, 2016, p. 100). There is no written set of standards for analyzing client's thoughts, so it is extremely difficult to study psychodynamic therapy empirically. In lieu of this major shortcoming, clinical psychologists created a therapy that could be systematized so that it could be studied empirically, and thus be evidence-based.

The most popular modern therapy is cognitive behavioral therapy (CBT). This therapy is the combination of behavioral theories and cognitive theories of treatments for mental illnesses. The core tenant of CBT is that thoughts mediate behavior. To accurately measure behavior throughout therapeutic interventions, CBT therapists developed strict definitions for thought processes and behaviors. CBT is the most widely studied therapy for all mental illnesses, including depression, and has been shown to be an effective treatment for alleviating depression (Capuzzi & Stauffer, 2016).

CBT interventions are a combination of behavioral and cognitive interventions. CBT is a structured therapy, driven by specific goals for the clients, and delivered in a time-limited manner (generally between 16-20 weeks of therapy; Capuzzi & Stauffer, 2016). Some of the behavioral interventions used to change maladaptive behaviors are reinforcement, extinction, shaping, stimulus control, and aversive control. Cognitive therapeutic interventions revolve around identifying cognitive distortions (thoughts that are not consistent with reality) and

changing these thought patterns. Some cognitive interventions include thought stopping, positive self-statements, cognitive restructuring, reframing, and roleplaying (for a more extensive list, see Capuzzi & Stauffer, 2016, p. 290). Cognitive and behavioral interventions are used for treatments of all mental illnesses, including depression.

The CBT conceptualization of depression is summarized best in Beck's cognitive therapy for depression (Hollon & Beck, 1979). CBT therapists believe that people develop depression if they have learned and internalized negative core beliefs about themselves, those around them, and the world. These negative core beliefs can be feeling incompetent, worthless, helpless, and unlovable. Other cognitive deficits, such as selective attention and memory biases towards negative events, are also implicated in the CBT model. To treat depression, CBT therapists teach clients cognitive and behavioral skills to help clients develop more accurate and positive beliefs. CBT for depression is generally 8-16 sessions and revolves around cognitive restructuring. In this process, clients learn to notice their automatic thoughts and evaluate them. They then identify the underlying assumptions to these thoughts (the negative core beliefs) and are encouraged to test the hypothesis generated by these thoughts (Capuzzi & Stauffer, 2016). For example, automatic thoughts that surround being unlovable are taught to be combated by recalling moments when the client felt loved, and by thinking about current loving relationships (German et al., 2019).

Unlike psychodynamic therapy, the design of CBT lends itself well to being studied empirically. This has led to a plethora of research supporting CBT's effectiveness as a treatment for depression. A 2013 meta-analysis comparing 115 studies that looked at the treatment of depression in adults found a medium effect size for patients treated with CBT (Cuijpers et al., 2013). Because of the well-established efficacy of CBT to treat depression, researchers have

tested the efficacy of treating depression across different populations. A quick search on Google Scholar shows that CBT has been shown to be effective in treating children with depression, perinatal depression, depression comorbid with diabetes, and many more populations (Arnberg & Ost, 2014; Sockol, 2015; and Tovote et al., 2014, respectively).

Clinical Trial Design for Psychotherapies

Before I describe the placebo effects implicated in psychotherapeutic treatment, understanding how psychotherapies are studied in clinical trials is crucial. Like other medical interventions, psychotherapies must be compared to active controls and a natural history group to test their effectiveness. However, unlike antidepressant medications, coming up with a placebo psychotherapy is incredibly difficult (Enck & Zipfel, 2019; Shapiro & Shapiro, 1997). This has led to many clinical trials comparing CBT to wait-list controls (a group that receives no treatment). This is problematic because wait-list controls are not an active placebo; comparing a treatment group to a wait-list control group is like comparing a treatment to the natural course of an illness (although Enck & Zipfel (2019) have argued that wait-list controls themselves can elicit placebo effects through the participant's expectations of receiving treatment at a nearby date). To isolate the "active ingredient" in psychotherapy, researchers have called for using component-control experimental designs (Lilienfeld et al., 2015; Shapiro & Shapiro, 1997). These study designs use additive and subtractive methods to distill the different components of psychotherapy from each other and compare the results to determine which elements are leading to symptom improvements. The obvious limitation here is that this study design is much more difficult than administering a placebo pill.

Other components of psychotherapy clinical trial design complicate the validity of assumptions that can be made from clinical trials. Unlike trials involving antidepressants,

blinding participants to the type of treatment they are receiving is nearly impossible. As described previously, blinding patients is crucial to separate noise from the effect of an intervention. Because of the impossibility of blinding, psychotherapeutic clinical trials also cannot employ a cross-over design (Enck & Zipfel, 2019). Even with these difficulties, researchers have found other ways to analyze the placebo effects implicated in psychotherapies.

Psychotherapy and its Placebo Effects

Like antidepressant medication, scholars have argued that much (if not all) of the treatment effects associated with psychotherapy are due to placebo effects. To follow, I describe how modern psychotherapies resemble the historical descriptions of placebo medical treatments given by Shapiro and Shapiro (1997). Research is also discussed on how what is controlled for in medical clinical trials as the placebo effect (like patient-doctor interaction, positive beliefs about treatment outcome, etc.) is often considered the active ingredient in psychotherapeutic interventions (Benedetti, 2021). Because of this, researchers have tried to compare psychotherapies against active controls, and when this has been done, psychotherapies are not significantly better than placebo therapies.

Psychotherapies resemble the different categories of placebos, as previously summarized (Shapiro & Shapiro, 1997). The first is a one-size-fits all approach. This is seen when one psychotherapy is used to treat many different disorders. Recall Shapiro and Shapiro's discussion of treatments such as theriac, unicorn horn, and mandrake. These fictitious substances were legendary treatments proclaimed to cure any type of ailment (Shapiro & Shapiro, 1997, p. 12). A quick Google search finds the claim that "psychotherapy can be helpful in treating most mental health problems" including, but not limited to, anxiety disorders, mood disorders (including depression), addictions, eating disorders, personality disorders, and psychotic disorders

(*Psychotherapy - Mayo Clinic*, 2016). Modern mental health professionals treat psychotherapies similarly to how past physicians treated cure-all substances.

The other pattern resembling historical placebo treatments is that many different treatments are used to treat the same illness. Recall descriptions from Shapiro and Shapiro indicating that doctors throughout history have given a myriad of different treatments to try and heal the same illness (Shapiro, 1997). This theme parallels the hundreds of psychotherapies today that are used to treat depression (Benedetti, 2021). Moreover, these psychotherapies, with supposedly different active ingredients (analyzing unconscious factors, eliminating cognitive distortions, changing behavior, mindfulness techniques, etc.), are equally as effective at treating depression. This phenomenon was first observed in 1936, and termed the Dodo Bird Verdict (Rosenzweig, 1936). Since then, the lack of a significant difference in treatment outcomes across different psychotherapeutic treatments has been shown empirically in many different studies (Cuijpers et al., 2013; Enck & Zipfel, 2019).

One of the explanations for the large placebo effect seen across psychotherapies is that psychotherapies share many common factors. These include the use of suggestion and persuasion by a therapist, the expectancy for improvement, as well as a therapist's credibility, attention, and allegiance (Lilienfeld, Lynn, & Lohr 2015, p. 171). Benedetti (2021) comments on this fact, remarking that these common factors are often controlled for by placebos in medical clinical trials. This suggests that the common factors across psychotherapies are what lead to symptom improvements, and that the common factors across psychotherapies are what lead to symptom improvements, and that these common factors are placebos.

In fact, in their seminal work, Shapiro and Shapiro (1997) proclaim that psychotherapies are in fact just placebos. Evidence for this claim (summarized in Wampold et al., 2005) is seen in

studies using subtractive designs to test for critical elements in psychotherapies. A study using a component control design focusing specifically on CBT found that taking out critical elements of CBT (as described in Beck et al., 1979) did not decrease its effectiveness in alleviating depression, even after a six month follow up of participants conditions (Jacobson et al., 1996). Ahn and Wampold (2001) conducted a meta-analysis of component control studies (those using subtractive designs) and found that taking out critical elements from different forms of psychotherapies (including CBT and other therapies) did not decrease their effectiveness. This suggests that the distinctive elements of psychotherapies are not the active elements. Indeed, even psychotherapists acknowledge and emphasize the importance of non-specific factors in treating illnesses. According to Capuzzi and Stauffer, “the helping relationship is the cornerstone on which all effective helping rests” (Capuzzi and Stauffer, 2016, p. xxix).

Comparing the Placebo Effects of Antidepressants and Psychotherapies

Now that placebo effects in antidepressant and psychotherapeutic treatment of depression have been discussed, it is time to compare their effects. These two treatments share a pattern of many different active ingredients being an effective treatment for the same disorder. However, the physiological changes observed differ between the two treatments. These physiological changes have been implicated in the enhanced treatment effect seen when antidepressants and psychotherapies are used in tandem to treat depression. Placebo effect mechanisms are also implicated when combining more than one treatment.

Most psychotherapies and antidepressant medication have shown similar symptom improvement across different types of treatment. As mentioned previously, many meta-analyses of the effectiveness of different types of psychotherapies have found that none are significantly better at treating depression (Cuijpers et al., 2013; Enck & Zipfel, 2019). Antidepressants also

exhibit this pattern; different antidepressants affecting different cellular mechanisms and neurotransmitters have not been shown to be significantly better at treating depression than one another (Davis et al., as cited in Shapiro & Shapiro, 1997, p. 93). When compared to each other, antidepressants and psychotherapies are equally as effective at treating depression. A 1999 mega-analysis comparing the outcomes of CBT therapy versus antidepressant medication for treatment of severe depression across four different studies found that there was no significant difference between groups within each of the individual studies, and across the four studies (DeRubeis et al., 1999). These observations are consistent with the historical perspective of placebo treatments being equally as effective as each other (Shapiro & Shapiro, 1997). In the treatment of depression, research has shown that there is no significant difference in the outcomes of patients who receive different forms of psychotherapy or those who receive different types of antidepressants.

Although antidepressants and psychotherapies show similar effectiveness in treating depression, they affect different regions of the brain. Recall that the brain regions implicated in depression are the amygdala, the frontal lobes, the parietal and posterior temporal cortex, the anterior cingulate cortex, and the hippocampus (Watson & Breedlove, 2016). Hypermetabolism in the basal ganglia and the insula has also been correlated with major depression (Boccia, Piccardi, & Guariglia, 2015). A meta-analysis conducted by Boccia et al. (2015) compared 58 neuroimaging studies to assess the neural differences across treatments for depression. These researchers compared fMRI images of patients treated with SSRIs and patients given psychotherapy. They found that participants who received psychotherapeutic treatment (including CBT, interpersonal therapy, or psychodynamic therapy) showed greater activation in the left superior and inferior frontal gyri, middle temporal gyrus, lingual gyrus, and middle

cingulate cortex, as well as the right middle frontal gyrus and precentral gyrus. In contrast, participants who received an SSRI showed higher modification in the right posterior insula, as well as increased activation in the prefrontal cortex, and decreased activation in the hippocampus and subgenual cingulate cortex. While some changes in brain regions overlap, most of the neural changes seen from antidepressant and psychotherapeutic treatment were reported to be distinct from each other.

How can two treatments with equal effectiveness on depression cause different physiological changes? One of the proposed explanations for this is that psychotherapies and antidepressants treat depression through top-down and bottom-up processes, respectively. Boccia et al. (2015) proposed that the bottom-up treatment of antidepressants works by disengaging ventral and frontal cortex and limbic regions. The regulation of the neural networks of the anterior cingulate cortex (implicated in processing hedonic stimuli) and the insula (implicated in interoception, or feeling sensations within the body, like your heartbeat) may also be a treatment mechanism of antidepressants. Boccia et al. (2015) also suggests that the changes in cortical networks seen with psychotherapeutic treatment reflects the high-level cognitive processes targeted to treat depression by psychotherapies. Harmer and Cowen (2013) also argue that antidepressants work in a bottom-up process; however, they point to the evidence that antidepressants decrease negative emotional biases seen in depression before clinically significant symptom improvement occurs.

The changes seen in different areas of the brain have been a proposed reason for the enhanced treatment effect of combining psychotherapy and antidepressants to treat depression (however, it is worth noting that these brain changes have only been observed as correlational changes, so causal attributions are yet unsupported). This theory has been proposed multiple

times and is summarized in Boccia et al. (2015): “the existence of complementary neural substrates for pharmacological and psychological therapies could account for the enhancing effect of psychotherapy on pharmacological therapy” (p. 620). In their meta-analysis, Cuijpers et al. (2013) found that the combined treatment of psychotherapy and pharmacotherapy was better than pharmacotherapy alone. A network meta-analysis also found that combining treatments was found to be more effective than psychotherapy alone and pharmacotherapy alone (Cuijpers et al., 2020).

However, a placebo explanation is also offered for the significantly better treatment outcomes seen when combining psychotherapy and antidepressants. The increased symptom improvement could be caused by a dosage effect. Recall that a placebo response can be enhanced by taking a larger dose of a placebo medication (Benedetti, 2021). The increased effectiveness of taking a larger dose could relate to the increased effectiveness seen from receiving two interventions for depression (psychotherapeutic and antidepressant) instead of just one. To test this hypothesis, a design comparing the effects of placebo psychotherapy and placebo antidepressant to typical psychotherapies and antidepressants could be employed.

A meta-analysis conducted by Cuijpers et al. (2010) examined studies combining psychotherapy with antidepressants versus psychotherapies with placebo antidepressants. They found a small but significant difference between the two groups. The standardized mean difference between the two groups was found to be 0.25. This corresponded to a numbers-needed-to-be-treated of 7.14 (or the number of patients needed to be treated to prevent an additional negative outcome), suggesting that active medication plays a minor part in the efficacy of combining treatments (Cuijpers et al., 2010). However, none of the studies included in the

meta-analysis used active placebos, so breaking-blind through experiencing symptoms could have played a role in the significant differences seen in treatment outcomes.

To better understand the interactions between psychotherapeutic treatment and antidepressant treatment, it is crucial that researchers study the improvement not of depression overall, but of the discrete symptoms that make up the illness. This would allow a more accurate understanding of what physiological changes correlate with which symptom abatement. It is also crucial that study designs start using active placebos to control for the side effects experienced by participants taking antidepressants.

Implications

A large placebo component has been attributed to both psychotherapeutic and antidepressant treatment of depression. This data calls into question the assumed reasons for these treatments' effectiveness, as well as the continued use of these treatments (specifically regarding cost, side effects, and time commitment). Economic interests play a large role in the proliferation of these treatments, as well as the bias of reporters offering recommendations. Current perspectives on the future of depression treatment are described before I offer my own recommendations for future treatment implementation and research of depression.

Implications for Antidepressants

Antidepressants are the first line of treatments for depression by physicians (Bauer et al., 2013). Considering the massive placebo effects reported in the use of antidepressants, why are pharmacological interventions so well regarded as the frontline treatment for depression? Some scholars have pointed out the economic interests of pharmaceutical companies to explain the continued proliferation of antidepressants (Kirsch, 2011). However, other interests such as time,

cost, availability of other treatments, and the ethical dilemma of prescribing deceptive placebos also play a role.

Depression has been reported as the 6th most costly health condition, and the costliest mental illness, with an estimated \$71 billion spent on its treatment a year (Dieleman & Birger, 2016). The National Health and Nutrition Examination Survey reported that from 2015-2018, 13.2% of adults used antidepressant drugs in the past 30 days (Brody & Gu, 2020). The global antidepressant market was expected to increase from \$14.3 billion in 2019 to \$28.6 billion in 2020 in response to the mental health issues brought about by the COVID-19 pandemic (Wood, 2020). With this amount of money being poured into antidepressants, pharmaceutical companies have major incentives to promote their products. Kirsch (2011) provides an exposé into the nefarious actions of pharmaceutical companies and the FDA to boost the appearance of the effectiveness of SSRIs. He includes examples of companies intentionally withholding studies that do not show a significant difference between antidepressants and placebos, as well as manipulating statistical analyses (for a detailed account of his investigation, see Kirsch, 2011).

Aside from the economic incentives proliferating antidepressant medication, the ease of access to antidepressants, as opposed to other treatments like psychotherapy, has contributed to the breadth of antidepressant usage. The average thirty-day supply for generic antidepressants costs between \$4 and \$20 (Cherney, 2020). However, these prices can change significantly based on insurance coverage, dosage, type of antidepressant, and augmentation with additional medications. Antidepressants are often the most convenient option for patients. Antidepressants are most often prescribed by primary care doctors, so they do not require patients to see a specialist. It is worth noting that taking a pill takes up almost no time in a person's day. Availability of other treatments plays a role in the extensive prescription and use of

antidepressants. Those without a car, living in rural communities, and/ or with long work hours have a more difficult time employing time intensive treatments for depression. Antidepressants are often used as a low cost, low time commitment treatment for depression.

Some scholars, however, argue that prescribing antidepressants is unethical (Jakobsen et al., 2020). They cite that the small effect sizes as compared to placebo antidepressants do not outweigh the potentially harmful side effects of antidepressants. As stated previously, researchers generally find a significant difference in treatment outcomes when comparing SSRIs to placebos; however, some researchers have claimed that the differences are clinically insignificant. A meta-analysis of 131 trials analyzing the effects of SSRIs versus placebos to treat MDD found that on average, those taking antidepressants scored 1.94 points lower on the HAM-D (recall that a higher score reflects more severe depressive symptoms) (Jakobsen et al., 2017). It is worth noting, as stated by the authors, that none of the placebo-controlled trials included active placebos, so these studies did not control for the effects of experiencing symptoms on patient outcomes. This improvement did not meet the authors' predetermined threshold of a 3-point improvement (out of the 52-point scale) as being a marker of clinically significant improvement. They also present data showing that those treated with SSRIs have a significantly increased risk of serious adverse effects, with 31/1000 SSRI patients experiencing serious adverse effects, versus 22/1000 control patients experiencing adverse effects.

Considering the high placebo effect in antidepressant treatment, and the additional adverse side effects when taking SSRIs, physicians should consider prescribing placebo medication to patients as a treatment for depression. As referenced previously, Kaptchuk et al. (2010) showed that treating patients with irritable bowel syndrome (IBS) with non-deceptive placebos (telling participants that they were receiving "inert substance, like sugar pills, that have

been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes”) significantly improved their symptoms over no treatment groups (p. 1). Like depression, the treatment of IBS has a large placebo component. Testing the efficacy of non-deceptive placebo treatment on patients with depression would provide guidance to physicians in prescribing open-label placebos to patients as a first line of defense to treat depression. Prescribing placebos would decrease the cost for patients and health care systems and, more importantly, decrease the risk of adverse side effects on vulnerable populations.

Implications for Psychotherapy

As mentioned previously, different psychotherapies have been shown to be equally effective in treating depression. This large placebo effect calls into question the “active ingredient” in therapy, and how minimum psychotherapy can be before it becomes ineffective. The economics of psychotherapy, like antidepressants, has been argued to play a role in the continued proliferation and exaltation of psychotherapies. However, the large variety of psychotherapies can be beneficial for patients (even though overall they are seen as equally effective).

Just like psychopharmacology, psychotherapy is also influenced by the revenue it brings in from patients. When writing their argument for psychotherapy as the ultimate placebo, Shapiro and Shapiro (1997) reported that in 1994, there were 80 million visits to psychotherapists, for a total of \$4.2 billion in fees. Depending on the level of experience, therapy today generally costs between \$100- \$200 per session before insurance (Lauretta, 2022). Since the beginning of the COVID-19 pandemic, telehealth companies such as Better-Help have extensively promoted therapy as a treatment for mental disorders.

Shapiro and Shapiro (1997) level an impactful exposé into the proposed effectiveness of psychotherapies. They argue that the across-the-board effectiveness of different psychotherapies reflects historical patterns of placebos, and the lack of component-control clinical trials of psychotherapies is a major shortcoming in the science supporting psychotherapies. Since the turn of the century, randomized controlled trials employing component-control designs have yet to find an active ingredient distinct in one therapy from another. To Shapiro and Shapiro, “psychotherapy is useful, beneficial, and effective for many patients [... which] is true of many notable placebo treatments. Additional studies are needed before we can say with certainty that psychotherapy is more than a placebo” (Shapiro & Shapiro, 1997, p. 231).

Some criticisms of Shapiro and Shapiro’s (1997) perspective on psychotherapy as a placebo exist. These critics assert that Shapiro and Shapiro attempt to view psychotherapy through a medical lens (like antidepressants) rather than understanding psychotherapy as an interaction between people that can potentially provoke change. These researchers view the active ingredients in therapy as the common factors described earlier, and do not consider these common factors to be placebos. For more information on these viewpoints, see work by Wampold and others (Imel & Wampold, 2008; Wampold, 2015).

If psychotherapy is just a placebo, to what extent can the simulation of care be distilled down so that the non-active components of psychotherapy can be discarded? How much training is required for a counselor to administer effective therapy? A radical approach to the large placebo component of psychotherapy would be to purge psychotherapies of all non-essential factors, and to find the minimum amount of training needed for a clinician to evoke the therapeutic alliance with patients. However, this view does not consider patient population variation in treatment options. Because of the broadness of the diagnosis for depression, there is

a lack of understanding of why some people respond to some forms of therapy, and others do not. It is beneficial to have a variety of different psychotherapies offered, because patient choice in treatment is correlated with better patient outcome than when patients are randomly assigned to a treatment group (Enck & Zipfel, 2019).

Just like for antidepressants, examining improvements across individual symptoms and across different populations for different forms of psychotherapy could help establish whether these treatments have more specific effects that are obscured by the variation seen in the population of people diagnosed with depression. Psychotherapy provides a side-effect free treatment for depression, so its continued use does not pose risks to patients. This, however, does not mean that researchers should not continue to critically evaluate the effectiveness of psychotherapies, as suggested by some researchers (Kirsch, 2016). A danger of not critically evaluating psychotherapies as described by Shapiro and Shapiro is that “The placebo effect, [...] causes ineffective remedies to appear effective and thus obscures the recognition of new effective drugs” (Shapiro & Shapiro, 1997, p. 22). The future of placebo research should focus on maximizing placebo effects in clinical populations while not stalling progress in improving medical treatments in research setting.

Concluding Remarks

The large placebo component implicated in the treatment of depression can seem discouraging because it implies that our current treatments for depression have not advanced similarly to other medical interventions for other illnesses which have active, specific ingredients. However, another perspective on the literature is that the placebo effect is a crucial component for treating depression- the mere act of receiving care and expecting to get better is an effective treatment for depression.

It is important to note that many people who suffer from depression find immense relief from taking antidepressants, attending psychotherapy, and/ or receiving the other treatments currently available. Antidepressants provide a relatively cheap and easy treatment for depression, and psychotherapies provide a side-effect-free alternative. The continued celebration of the effectiveness of these treatments, however, could stunt further research, so acknowledging these treatments' large placebo components is imperative.

In the future, researchers must compare antidepressants to active placebos to clarify if there is any active component to antidepressants. The continued advancement of neuroimaging technologies will likely also aid in these discoveries. Another important consideration for future research is to measure treatment effects across the specific symptoms of depression. Since depression has a variety of adverse symptoms associated with it, looking at all the symptoms together could be obscuring specific treatment effects.

I hope that my work serves to encourage anyone experiencing depression to seek treatment. The continued research of placebo effects in depression is paramount to understanding how to improve treatment, and how to prevent depression through understanding its causes.

References

- Ahn, H. N., & Wampold, B. E. (2001). Where oh where are the specific ingredients? A meta-analysis of component studies in counseling and psychotherapy. *Journal of counseling psychology, 48*(3), 251.
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). <https://doi.org/10.1176/appi.books.9780890425596>
- Arnberg, A., & Ost, L. G. (2014). CBT for children with depressive symptoms: a meta-analysis. *Cognitive behaviour therapy, 43*(4), 275–288.
<https://doi.org/10.1080/16506073.2014.947316>
- Atlas, Y. L. (2021) A social affective neuroscience lens on placebo analgesia. *Trends in Cognitive Sciences 7*, 11. <https://doi.org/10.1016/j.tics.2021.07.016>.
- Bauer, Pfennig, A., Severus, E., Whybrow, P. C., Angst, J., & Möller, H.-J. (2013). World federation of societies of biological psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: Update 2013 on the acute and continuation treatment of unipolar depressive disorders. *The World Journal of Biological Psychiatry, 14*(5), 334–385. <https://doi.org/10.3109/15622975.2013.804195>
- Benedetti, F. (2014). *Placebo Effects: Understanding the mechanisms in health and disease* (2nd ed.). Oxford University Press.
- Benedetti, F. (2021). *Placebo effects: Understanding the other side of medical care* (3rd ed.). Oxford University Press

- Best, J., Nijhout, F. H., & Reed, M. (2012). Serotonin synthesis, release and reuptake in terminals: a mathematical model. *Theor Biol Med Model* **7**, 34 (2010).
<https://doi.org/10.1186/1742-4682-7-34>
- Boccia, Piccardi, L., & Guariglia, P. (2015). How treatment affects the brain: meta-analysis evidence of neural substrates underpinning drug therapy and psychotherapy in major depression. *Brain Imaging and Behavior*, *10*(2), 619–627.
<https://doi.org/10.1007/s11682-015-9429-x>
- Brody, D. J., & Gu, Q. (2020). *Antidepressant use among adults: United states, 2015-2018*. National Center for Health Statistics. <https://www.cdc.gov/nchs/data/databriefs/db377-H.pdf>
- Capuzzi, & Stauffer, M. D. (2016). *Counseling and psychotherapy: theories and interventions / edited by David Capuzzi and Mark D. Stauffer*. (Sixth edition.). American Counseling Association.
- Centers for Disease Control and Prevention. (2022, February 16). *Mental health - household pulse survey - covid-19*. Centers for Disease Control and Prevention. Retrieved March 2, 2022, from <https://www.cdc.gov/nchs/covid19/pulse/mental-health.htm>
- Chen, J. A., Papakostas, G. I., & Youn, S. J. (2011). J Clin Psychiatry: Association between patient beliefs regarding assigned treatment and clinical response: reanalysis of data from the Hypericum Depression Trial Study Group. *Alternative Medicine Review*, *16*(4), 370. <https://link.gale.com/apps/doc/A277520379/AONE?u=newpaltz&sid=bookmark-AONE&xid=fa7bae6a>

Cherney, K. (2020, July 24). *The cost of depression: Medications, therapy, and more*. Healthline.

Retrieved April 24, 2022, from <https://www.healthline.com/health/depression/how-much-does-depression-cost>

Colloca, L., Lopiano, L., Lanotte, M. & Benedetti, F. (2004). Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol.* 3, 679–684

Cramer. (2000). Defense mechanisms in psychology today. Further processes for adaptation. *The American Psychologist*, 55(6), 637–646. <https://doi.org/10.1037//0003-066X.55.6.637>

Cuijpers, P., van Straten, A., Hollon, S. D., & Andersson, G. (2010). The contribution of active medication to combined treatments of psychotherapy and pharmacotherapy for adult depression: a meta-analysis. *Acta psychiatrica Scandinavica*, 121(6), 415–423.

<https://doi.org/10.1111/j.1600-0447.2009.01513.x>

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K. S. (2013). A meta-analysis of cognitive-behavioural therapy for adult depression, alone and in comparison with other treatments. *The Canadian Journal of Psychiatry*, 58(7), 376–385.

<https://doi.org/10.1177/070674371305800702>

Cuijpers, P., Noma, H., Karyotaki, E., Vinkers, C. H., Cipriani, A., & Furukawa, T. A. (2020). A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World psychiatry: official journal of the World Psychiatric Association (WPA)*, 19(1), 92–107. <https://doi.org/10.1002/wps.20701>

Delgado, P. L., Charney, D. S., Price, L. H., Aghajanian, G. K., Landis, H., & Heninger, G.R. (1990). Serotonin Function and the Mechanism of Antidepressant Action: Reversal of

- Antidepressant-Induced Remission by Rapid Depletion of Plasma Tryptophan. *Arch Gen Psychiatry*. 1990;47(5):411–418. doi:10.1001/archpsyc.1990.01810170011002
- DeRubeis, R. J., Gelfand, L. A., Tang, T. Z., & Simons, A. D. (1999). Medications versus cognitive behavior therapy for severely depressed outpatients: Mega-analysis of four randomized comparisons. *The American Journal of Psychiatry*, 156(7), 1007–1013. <https://doi.org/10.1176/ajp.156.7.1007>
- DeRubeis, R. J., Siegle, G. J., & Hollon, S. D. (2008). Cognitive therapy versus medication for depression: treatment outcomes and neural mechanisms. *Nature reviews. Neuroscience*, 9(10), 788–796. <https://doi.org/10.1038/nrn2345>
- Dieleman, J.L., Baral, R., & Birger, M. (2016). U.S. Spending on Personal Health Care and Public Health, 1996–2013. *JAMA*. doi:10.1001/jama.2016.16885
- Enck, P., Bingel, U., Schedlowski, M., & Rief, W. (2013). The placebo response in medicine: Minimize, maximize, or personalize? *Drug Discovery*, 12.
- Enck, & Zipfel, S. (2019). Placebo effects in psychotherapy: A framework. *Frontiers in Psychiatry*, 10, 456–456. <https://doi.org/10.3389/fpsyt.2019.00456>
- German, R. E., Williston, M., & Hershenberg, R. (Eds.) (2019). Cognitive therapy for depression. *Society of Clinical Psychology | Division 12 of the American Psychological Association*. Retrieved April 7, 2022, from <https://div12.org/treatment/cognitive-therapy-for-depression/>
- Harmer, C. J., & Cowen, P. J. (2013). ‘it’s the way that you look at it’—a cognitive neuropsychological account of SSRI action in depression. *Philosophical Transactions of*

the Royal Society B: Biological Sciences, 368(1615), 20120407.

<https://doi.org/10.1098/rstb.2012.0407>

Hengartner, M. P., & Plöderl, M. (2018). Statistically significant antidepressant-placebo differences on subjective symptom-rating scales do not prove that the drugs work: effect size and method bias matter!. *Frontiers in psychiatry*, 9, 517.

<https://doi.org/10.3389/fpsyt.2018.00517>

Hieronymus, F., Lisinski, A., Nilsson, S., & Eriksson, E. (2018). Efficacy of selective serotonin reuptake inhibitors in the absence of side effects: a mega-analysis of citalopram and paroxetine in adult depression. *Molecular psychiatry*, 23(8), 1731–1736.

<https://doi.org/10.1038/mp.2017.147>

Hollon, S. D., & Beck, A. T. (1979). Cognitive therapy of depression. *Cognitive-behavioral interventions: Theory, research, and procedures*, 153-203.

Jacobson, N. S., Dobson, K. S., Truax, P. A., Addis, M. E., Koerner, K., Gollan, J. K., ... & Prince, S. E. (1996). A component analysis of cognitive-behavioral treatment for depression. *Journal of consulting and clinical psychology*, 64(2), 295.

Jakobsen, J. C., Gluud, C., & Kirsch, I. (2020) Should antidepressants be used for major depressive disorder? *BMJ Evidence-Based Medicine*.

Jakobsen, J.C., Katakam, K.K., Schou, A. et al. (2017). Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. *BMC Psychiatry*.

<https://doi.org/10.1186/s12888-016-1173-2>

Jensen, K., Kirsch, I., Odmalm, S., Kaptchuk, T. J., & Ingvar, M. (2015). Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness. *Proceedings of the National Academy of Sciences*, *112*(25), 7863–7867.

<https://doi.org/10.1073/pnas.1504567112>

Kaptchuk, T. J., Goldman, P., Stone, D. A., & Stason, W. B. (2000). DO medical devices have enhanced placebo effects? *Journal of Clinical Epidemiology*, *53*(8), 786–792.

[https://doi.org/10.1016/s0895-4356\(00\)00206-7](https://doi.org/10.1016/s0895-4356(00)00206-7)

Kaptchuk, T. J., Friedlander, E., Kelley, J. M., Sanchez, M. N., Kokkotou, E., Singer, J. P., Kowalczykowski, M., Miller, F. G., Kirsch, I., & Lembo, A. J. (2010). Placebos without deception: A randomized controlled trial in irritable bowel syndrome. *PLoS ONE*, *5*(12).

<https://doi.org/10.1371/journal.pone.0015591>

Kirsch, I., & Sapirstein, G. (1998). Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention & Treatment*, *1*(2), Article 2a.

<https://doi.org/10.1037/1522-3736.1.1.12a>

Kirsch, I. (2011). *The emperor's new drugs: Exploding the antidepressant myth*. Basic Books.

Kirsch, I., Wampold, B., & Kelley, J. M. (2016). Controlling for the placebo effect in psychotherapy: noble quest or tilting at windmills?. *Psychology of Consciousness: Theory, Research, and Practice*, *3*(2), 121.

Kirsch, I. (2019). Placebo Effect in the Treatment of Depression and Anxiety. *Frontiers in Psychiatry*, *10*, 407. <https://doi.org/10.3389/fpsy.2019.00407>

- Kroenke, K & Spitzer, R. L. (2002). The PHQ-9: A new depression diagnostic and severity measure. *Depression in Primary Care*. <https://doi.org/10.3928/0048-5713-20020901-06>
- Lauretta, A. (2022, March 29). *How much does therapy cost?* Forbes. Retrieved April 24, 2022, from <https://www.forbes.com/health/mind/how-much-does-therapy-cost/>
- Lawlor, C. (2012). *From melancholia to Prozac: A history of depression*. Oxford University Press.
- Lilienfeld, S. O., Lynn, S. J., & Lohr, J. M. (2015). *Science and pseudoscience in clinical psychology*. Guilford Press.
- Lundbeck Institute Campus. (2016). [Infographic of the mechanism of action of selective serotonin re-uptake inhibitors]. <https://institute.progress.im/en/content/mechanism-action-selective-serotonin-re-uptake-inhibitors-ssris>
- Mayo Clinic Staff. (2018, February 3). *Depression (major depressive disorder)*. Mayo Clinic. Retrieved March 2, 2022, from <https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007>
- Placebo studies*. BIDMC of Boston. (n.d.). Retrieved April 15, 2022, from <https://www.bidmc.org/research/research-by-department/medicine/general-medicine-research/program-in-placebo-studies>
- Palmer, M. Susan., Crewther, G. Shelia., Carey, M. Leanne., and The SMART project team. A meta-analysis of changes in brain activity in clinical depression. *Frontiers in Human Neuroscience*, 8. <https://doi.org/10.3389/fnhum.2014.01045>

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A Comprehensive Review of the Placebo Effect: Recent Advances and Current Thought. *Annual Review of Psychology*, 59(1), 565–590. <https://doi.org/10.1146/annurev.psych.59.113006.095941>

Psychotherapy - Mayo Clinic. (2016, March 17). Mayo Clinic. <https://www.mayoclinic.org/tests-procedures/psychotherapy/about/pac-20384616>

Purves, D., Augustine, G. J., Fitzpatrick, D., Hall, W. C., LaMantia, A-S., McNamara, J. O., & Williams, S. M. (Eds.). (2004). *Neuroscience*. Sinauer. (Third).

Raskin, J. D. (2019). *Abnormal Psychology: Contrasting Perspectives* (1 ed). Red Globe Press

Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A. J., & Hofmann, S. G. (2009). Meta-analysis of the placebo response in antidepressant trials. *Journal of affective disorders*, 118(1-3), 1-8.

Rosenzweig. (1936). Some implicit common factors in diverse methods of psychotherapy.

American Journal of Orthopsychiatry, 6(3), 412–415. <https://doi.org/10.1111/j.1939-0025.1936.tb05248.x>

Rutherford, B. R., Wall, M. M., Glass, A., & Stewart, J. W. (2014). The role of patient expectancy in placebo and nocebo effects in antidepressant trials. *The Journal of clinical psychiatry*, 75(10), 1040–1046. <https://doi.org/10.4088/JCP.13m08797>

Shapiro, A. K., & Shapiro, E. (1997). *The powerful placebo: From ancient priest to modern physician*. Johns Hopkins University Press.

- Sockol, L. E. (2015). A systematic review of the efficacy of cognitive behavioral therapy for treating and preventing perinatal depression. *Journal of Affective Disorders*, 177, 7–21.
<https://doi.org/10.1016/j.jad.2015.01.052>
- Sun, Y., Fu, Z., Bo, Q. *et al.* The reliability and validity of PHQ-9 in patients with major depressive disorder in psychiatric hospital. *BMC Psychiatry* **20**, 474 (2020).
<https://doi.org/10.1186/s12888-020-02885-6>
- Terry, N., & Margolis, K. G. (2016). Serotonergic mechanisms regulating the GI tract: Experimental evidence and therapeutic relevance. *Gastrointestinal Pharmacology*, 319–342. https://doi.org/10.1007/164_2016_103
- Torres, F. (Ed.). (2020). *What Is Depression?* What is depression? Retrieved March 2, 2022, from <https://www.psychiatry.org/patients-families/depression/what-is-depression>
- Tovote, K. A., Fler, J., Snippe, E., Peeters, A. C. T. M., Emmelkamp, P. M. G., Sanderman, R., Links, T. P., & Schroevers, M. J. (2014). Individual mindfulness-based cognitive therapy and cognitive behavior therapy for treating depressive symptoms in patients with diabetes: Results of a randomized controlled trial. *Diabetes Care*, 37(9), 2427–2434.
<https://doi.org/10.2337/dc13-2918>
- U.S. Department of Health and Human Services. (n.d.). *Depression*. National Institute of Mental Health. Retrieved April 18, 2022, from <https://www.nimh.nih.gov/health/topics/depression>
- U.S. National Library of Medicine. (2022). *Paroxetine: Medlineplus drug information*. MedlinePlus. Retrieved April 20, 2022, from <https://medlineplus.gov/druginfo/meds/a698032.html>

- Visser, A. K., van Waarde, A., Willemsen, A. T., Bosker, F. J., Luiten, P. G., den Boer, J. A., Kema, I. P., & Dierckx, R. A. (2011). Measuring serotonin synthesis: from conventional methods to PET tracers and their (pre)clinical implications. *European journal of nuclear medicine and molecular imaging*, 38(3), 576–591.
<https://doi.org/10.1007/s00259-010-1663-2>
- Wampold, Minami, T., Tierney, S. C., Baskin, T. W., & Bhati, K. S. (2005). The placebo is powerful: Estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *Journal of Clinical Psychology*, 4(4), 835–854.
<https://doi.org/10.1002/jclp.20129>
- Imel, Z. E., & Wampold, B. E. (2008). The importance of treatment and the science of common factors in psychotherapy. *Handbook of counseling psychology*, 4, 249-266.
- Wampold, B. E. (2015). How important are the common factors in psychotherapy? An update. *World Psychiatry*, 14(3), 270-277.
- Watson, N. V., & Breedlove, S. M. (2016). *The Mind's Machine* (Second). Sinauer Associates, Inc.
- Wood, L. (2020, April 21). *Global antidepressants market (2020 to 2030) - covid-19 implications and growth*. GlobeNewswire News Room. Retrieved April 24, 2022, from <https://www.globenewswire.com/news-release/2020/04/21/2019282/0/en/Global-Antidepressants-Market-2020-to-2030-COVID-19-Implications-and-Growth.html#:~:text=The%20global%20antidepressants%20market%20is,impact%20on%20the%20global%20economy>.

Wood, L. (2021, April 26). *Global antidepressants market report 2021: Covid-19 causes a surge in demand for antidepressant drugs as mental health problems rise - researchandmarkets.com*. Business Wire. Retrieved April 25, 2022, from <https://www.businesswire.com/news/home/20210426005303/en/Global-Antidepressants-Market-Report-2021-COVID-19-Causes-a-Surge-in-Demand-for-Antidepressant-Drugs-as-Mental-Health-Problems-Rise---ResearchAndMarkets.com>

World Health Organization (2019). *International Statistical Classification of Diseases and Related Health Problems* (11th ed.). <https://icd.who.int/>

Young, S. N. (2013). The effect of raising and lowering tryptophan levels on human mood and social behaviour *Phil. Trans. R. Soc.*