Placebo vs. SSRIs in the Treatment of Major Depression

Psychology

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Introduction

With more than 300 million individuals affected globally, depression is quickly becoming the illness of the 21st century (World Health Organization, 2018). “Depression (major depressive disorder or clinical depression) is a common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working” (“Depression”, 2017, para. 1). Scientists believe that depression is caused by an imbalance of chemicals in the brain (“Depression: How effective are antidepressants?”, 2017). Antidepressants “aim to increase the availability of these chemicals” (“Depression: How effective…”, 2017, para. 9).

There are several treatments for major depression. One treatment is the prescription selective serotonin reuptake inhibitors (SSRIs) drugs. Selective serotonin reuptake inhibitors (SSRIs) are a type of antidepressant drug that increases the amount of serotonin in the brain (Jacobson, 2014). SSRIs bind to SERT, a protein which transports serotonin to nerve cells, and prevents it from reaching the nerve cell (Jacobson, 2014).

Antidepressants are not the only treatment available. There is increasing evidence that placebo medication can be used to successfully treat major depression. Placebo drugs are “a therapy independent of any specific clinical procedures that results in client improvement” (Zimbardo & Gerrig, 2002, para. 1). Patients are given inactive medication such as pills, injections or liquids, usually without knowing that the medication is inactive (“Placebo Effect”, 2015). This triggers the placebo effect where patients expect to feel a certain way, and in believing so, may fulfil said expectations (“Placebo Effect”, 2015). A common misconception about placebos is that if they work successfully, there is no “biological pathology for what the
individual is experiencing” (Hedges & Burfield, 2005, p. 162). This assumption has created stigma around placebo treatment. There are, in fact, observable changes in brain activities suggesting that there is a much more complex relationship between “disorders, placebo, and clinical response” (Hedges & Burfield, 2005, p. 162) including changes in thinking processes. A study by Peciña, Bohnert, Sikora, Avery, Langenecker, Mickey and Zubieta (2015), for instance, showed that the μ-opioid receptors, which regulate mood, had an increase in brain activity.

Thus, this paper will examine the question, **To what extent is placebo medication more effective in the treatment of major depression in comparison to pharmacological antidepressant drugs (SSRIs)?** This question is of importance because there is a heavy reliance on antidepressants. Patients need to receive the best treatment available to cure their illness. If SSRIs aren’t the most effective medication, more reliance should be placed in other treatments. The following essay uses Cipriani, Furukawa, Salanti, Chaimani, Atkinson, Ogawa and Geddes (2018) to show there is a significant difference between SSRIs and placebos, Hieronymus, Lisinski, Nilsson, and Eriksson (2017) to show SSRIs don’t consist of a placebo effect, and Hieronymus, Emilsson, Nilsson and Eriksson (2016) to evaluate the Hamilton scale. Studies by Kirsch, Deacon, Huedo-Medina, Scoboria, Moore and Johnson (2008), Leuchter, Cook, Witte, Morgan and Abrams (2002), Andrews, Thomsom, Amstatdter and Neale (2012), Ferguson (2011) and Mora, Nestoriuc and Rief (2011) will be used to demonstrate the efficacy of placebo medication in the treatment of major depression.

The essay argues that placebo medication can be just as effective or perhaps more in treating major depression because there are fewer side effects, less risk of relapse, and research has shown that antidepressants consist of a placebo effect because patients believe that
antidepressants will alleviate their depression thus triggering the placebo effect and becoming “cured.” Simultaneously, if placebo medication is more effective, it suggests that major depression also has a cognitive and social component hence other treatments (cognitive behavioural therapy and group therapy) will be discussed in this essay.

**Explanation of SSRIs**

To understand how SSRIs work in treating depression, the biological etiology of major depression must be understood. According to Rot, Matthew and Charney (2009), no specific gene has been identified to cause depression. Instead, the presence of polymorphisms, a set of genes that are different amongst individuals, may increase the likelihood for depression. Scientists believe the serotonin transporter gene may have a role in causing depression because it has a polymorphism that results in two types of alleles: long and short. The short allele has been found to “reduce the speed with which serotonin neurons can adapt to changes in their stimulation” (Rot et al., 2009, para. 7). Therefore, the polymorphism doesn’t produce a lot of serotonin. Thus, SSRIs work by targeting this transporter gene to stimulate them to produce more serotonin.

**Explanation of placebo medication**

There are two main theories of the placebo effect: conditioning and expectation (Mora et al., 2011). Classic conditioning suggests that patients associate the placebo pill, based on prior experiences, with a positive effect which alleviates their symptoms (Mora et al., 2011). The
second theory is the expectation effect which suggests that patients form expectations about the positive effects of the drug. This results in the actualisation of their expectations (Mora et al., 2011). These expectations can be evoked by what doctors tell their patients about the drug or “general knowledge about the effectiveness of a certain drug” (Mora et al., 2011, p. 1880).

Although expectation and conditioning are separate mechanisms, they are very much linked. Expectations of how a drug works can be formed using conditioning techniques (Medoff & Colloca, 2015). For instance, pairing a pill with a less painful stimuli conditions individuals to associate that drug with getting better. Experiences that an individual has had intaking a placebo also affects their response to the drug i.e. a positive experience results in a positive response to the drug (Medoff & Colloca, 2015). Thus, the experience conditions individuals to think a certain way about the placebo drug and consequently, they form an expectation of its efficacy.

**Significant difference between SSRIs and placebo medication**

There is evidence to support that SSRIs do have a significant difference than placebo medication in treating patients with major depression. A meta-analysis was done by Cipriani et al. (2018) with the aim of investigating which antidepressants were most effective but the meta-analysis had greater implications than that. A range of antidepressants including various types of SSRIs was researched and each was compared to placebo medication. The researchers found that all the antidepressants were far more likely to work than the placebo drugs. Furthermore, half of the most effective antidepressants were SSRIs, specifically escitalopram, paroxetine and sertraline (Cipriani et al., 2018). Antidepressants, including SSRIs, affect the level of depression in participants, more so than the placebo medication.
There are several limitations to Cipriani et al.’s (2018) study. The data was only taken for eight weeks of the treatment. It is not guaranteed that antidepressants are suitable for long-term use. Furthermore, perhaps the extent of the effectiveness of the antidepressants has not been made clear because of the short time. It could be possible that antidepressants show benefits in long-term treatment. The study also did not analyse individual data, taking the patient’s age, gender etc. into account. This is a limitation because trends in data, such as whether patients in a certain demographic group respond better to antidepressants, weren’t identified. The study is a massive generalisation of all patients with major depression, assuming they are all the same when in reality, every patient responds differently to treatment.

The arguments Andrews et al. (2012) and Cipriani et al. (2018) make have their merits but can’t be taken at face value. Both studies were meta-analyses. Hence, further criticism is researchers can pick data that shows placebo drugs are more effective than antidepressants; they are more susceptible to researcher bias. It can be concluded that perhaps Andrews et al. (2012) was indeed reductionist in massively generalising that SSRIs are not effective at all because Cipriani et al. (2018) showed SSRIs are indeed effective. However, Cipriani et al.’s study only spanned eight weeks. It’s not clear whether SSRIs are effective in the long-run. Therefore, placebo medication may be more effective over long periods because it doesn’t affect homeostatic mechanisms the way SSRIs do.

**Side-effects of SSRIs**

SSRIs have many more side-effects than placebo medication. SSRIs can cause “diarrhoea, headaches, sleep problems and nausea” (“Depression: How effective…”, 2017, para.
Some studies even suggest that there is a correlation between the intake of SSRIs and the number of suicides in teenagers (“Depression: How effective…”, 2017). Andrews et al. (2012) believed that SSRIs had these side effects because homeostatic mechanisms were imbalanced throughout the body due to the increase in serotonin levels. This triggers mechanisms that depend on serotonin for regulation to go haywire and thus display those side effects.

Patients taking antidepressants have a higher chance of relapsing back into depression. The explanation behind this has to do with the role of serotonin. Andrews et al. (2012) explained that serotonin has evolved to regulate many of the body’s processes and is responsible for homeostasis. When patients intake SSRIs, they spread around the body. SSRIs work by increasing the amount of serotonin and so, Andrews et al. (2012) argue, this imbalances other homeostatic mechanisms which are functioning properly. When SSRIs are discontinued, an imbalance of serotonin is created once more. The researchers postulate that the stronger the SSRI, the more likely that patients will relapse into depression. Andrews et al. (2012) conducted a meta-analysis of studies investigating the effects of the discontinuation of antidepressants. They found “strong positive relationships between the risk of relapse after discontinuation and the degree to which the antidepressant used in the study increases serotonin” (Andrews et al., 2012, para. 37). This suggests that patients who don’t take antidepressants such as SSRIs have a lower chance of relapse.

Andrews et al.’s study (2012) had many criticisms as pointed out by Sareen and Enns (2012). First, the theory proposed by the researchers is reductionist. Andrews et al. (2012) claimed that antidepressants interfered with homeostatic mechanisms and even drew parallels to how Tylenol also affects homeostasis in the body. In doing so, the researchers seem to insinuate
that diseases and illnesses should not be treated with medicine as they ruin the chemical balance of the body. Second, Sareen and Enns (2012) claim that Andrews et al. were biased in presenting their findings. No information was presented as to how articles were chosen and only studies which supported their argument were used. No counter-evidence was used to offer a balanced view of placebo versus SSRIs.

**Side-effects of placebo—nocebo effect**

Clinical trials have shown that patients taking placebo drugs may still experience the side effects of antidepressants. This is termed as the nocebo effect. The nocebo effect is essentially the negative part of the placebo. It can also be explained using the conditioning and expectation theory. Patients may have side effects from taking placebo pills because of their former experiences with antidepressants or if they have been told that a certain drug tends to have side effects (Mora et al., 2011).

This brings in an evaluation of the term “placebo” which isn’t clearly defined or researched (Pies, 2012). A placebo in a clinical trial is far more than just giving participants a sugar pill; it’s more a comparison of “medication plus supportive care, versus placebo tablet plus supportive care” (Pies, 2012, para. 11). This is important to note because it is difficult to isolate the effect of the treatment to solely placebo or antidepressants if participants in a clinical trial are also given lots of support (Pies, 2012). This isn’t to say that participants should not be given any care but only to point out that “we cannot assume that the results reflect the inherent power of the sugar pill versus the active drug” (Pies, 2012, para. 11). Mora et al. (2011) claim that the nocebo effect prevents placebo medication from being effective is flawed. It is crucial not to blindly
attribute side effects that patients have to the placebo pill. The reported side effects may actually be part of the patient’s original symptoms, but they chose to connect it to the prescribed pill. It is also possible that “somatic symptoms” which are “extremely common in the general population” may have been misclassified as a side effect of the placebo drug (Mora et al., 2011, p. 1883). This shows that placebo medication is superior to SSRIs when accounting for side effects.

**Evidence suggesting SSRIs consist of a placebo effect**

Some researchers have suggested that antidepressants consist of a placebo effect which seems to place placebo medication higher up on an altar. Kirsch et al. (2008) conducted a meta-analysis of all clinical trials (of antidepressants) which were submitted to the US Food and Drug Administration (FDA). The researchers found that SSRIs didn’t show any significant difference in the treatment of mild to moderate depression from placebo drugs (Kirsch et al., 2008). There was only a “small and clinically insignificant difference” for patients who had severe depression (Kirsch et al., 2008, para. 6). For patients with scores of 28 and more on the HRSD questionnaire indicating very severe depression, there was a clinically significant difference between the antidepressants and placebo drugs (Kirsch et al., 2008). The data for this was further analysed and the researchers found that these severely depressed patients were, in fact, showing a “decreased responsiveness to placebo rather than an increased responsiveness to antidepressants” (Kirsch et al., 2008, para. 6). The researchers concluded that there wasn’t a significant difference between antidepressants (including SSRIs) and placebo drugs in patients with mild to severe depression. Patients with the most severe depression do show a better
responsiveness to the antidepressants but the researchers believe that this is due to a decrease in responsiveness to the placebo effect.

Kirsch et al.’s findings have been supported by other studies. Leuchter et al.’s study (2002) aimed to show “50%–75% of antidepressant drug effect consists of a placebo effect” (Leuchter et al., 2002, para. 24). Participants with major depression were given either placebo drugs or SSRIs (venlafaxine or fluoxetine) in a double-blind trial. The participants were then divided into four groups: “medication responders, placebo responders, medication non-responders, placebo non-responders” (Leuchter et al., 2002, para. 1). The findings were that 52% of the participants taking active SSRIs responded to it, while 38% of the placebo group responded to the placebo drug. It was difficult to tell who had taken which medication solely based on their initial and final depression score. This shows that placebo drugs may be just as effective as SSRIs.

These two studies are not without their criticisms. A strength of Kirsch et al.’s (2008) study is the researchers explained how trials for their analysis were chosen. Only trials for which before and after data was presented were chosen in order to avoid researcher bias. Yet there is still the slight possibility of bias as they may have specifically chosen trials for which participants showed the same improvement from placebo drugs as SSRIs. A major criticism of Kirsch et al.’s study (2008) is that all the data only came from one dataset: the US Food and Drug Administration (FDA). This makes it difficult to generalise their findings because they may only be applicable to the FDA. As for Leuchter et al. (2002), a criticism is that the placebo responders had a tendency to have mild depression and had been depressed for a relatively short
time. It isn’t clear whether placebo medication will be effective for participants who have been severely depressed for a long time.

Evidence suggesting SSRIs don’t consist of a placebo effect

Hieronymus et al. (2017) did a meta-analysis of “patient-level data regarding item-wise symptom ratings and timing of adverse events for all industry-sponsored, Food and Drug Administration-registered, placebo-controlled trials regarding adult major depression” which tested the efficacy of SSRIs (Hieronymus et al., 2017, para. 4). They aimed to disprove a theory which claimed that SSRIs were only more effective than placebo drugs in clinical trials because the SSRIs would cause side-effects in the participants and so, the participants would know that they were taking active medication, thus “enhancing the expectation of improvement” in patients (Hieronymus et al., 2017, para. 1). In other words, the placebo effect was taking place. The SSRIs tested were fluoxetine, sertraline, paroxetine and citalopram. The researchers found that patients who had taken paroxetine or citalopram had “a larger reduction in depressed mood than those given placebo regardless of if they report adverse events or not” (Hieronymus et al., 2017, para. 17). This finding was reached by comparing, for example, the SSRI-treated participants who had reported early side effects to the drug to placebo-treated participants who also claimed to have side effects, and SSRI-treated participants who did not report side effects were compared to placebo-treated participants who also did not report side effects. The researchers concluded that for the SSRIs tested, the placebo effect did not have an impact on the reduction of depressive symptoms in the participants (Hieronymus et al., 2017).
**Issues with Hamilton Depression Scale (HRSD)**

This leads to a criticism of both placebo and antidepressants studies: the HRSD which is used in most studies to assess depression. Hedges and Burchfield (2005) argue that the HRSD is not an adequate measurement of depression for several reasons. First, in the whole questionnaire, only one question measures the mood of the patients. To make matters worse, that item is rated by the clinician or researcher—it’s not a self-assessment by the patient. This makes the results prone to researcher bias, causing them to increase the difference between antidepressants and placebo. Second, there are several items related to sleep and anxiety. If an antidepressant has sedative properties, then those questions alone will boost the difference between antidepressants and the placebo group in clinical trials. Hedges and Burchfield’s (2005) arguments are supported by research done by Hieronymus et al. (2016).

Hieronymus et al. (2016) conducted a meta-analysis to show that SSRIs were effective in treating depression but the scale used for measuring depression, the HRSD, was not representative of the participants’ depression. From solely looking at the sum, Hieronymous et al. found that 56% of clinical trials “failed to separate active drug from placebo” (Hieronymous et al., 2016, para. 1). Instead, the researchers used a depressed mood scale of 0-4 to assess depression because they argued depressed mood is a key symptom of the disorder. From this study, a key conclusion is that a better scale needs to be used to assess major depression—especially for use in clinical trials—which is not susceptible to researcher bias or skewed in a way to consistently present results that fulfil an agenda.
**Placebo drift**

Another criticism of both studies, as they compare placebo drugs to SSRIs, is placebo drift (Hedges & Burchfield, 2005). A placebo drift is an increase in response rate to placebo medication (Sonawalla & Rosenbaum, 2002). There has been a 7% increase every decade in the responsiveness to placebo medication. This is likely caused by researchers using less severely depressed participants in clinical trials. This may be done to better show the efficacy of SSRIs but several studies such as Leuchter et al. (2002) show that less severely depressed patients show a higher response to placebo drugs too. The implications of this are that the sample isn’t representative of the population so the findings are, to a certain extent, skewed creating less generalisability. Hieronymus et al. (2017) directly contradicts Kirsch et al. (2008) by showing that SSRIs don’t consist of a placebo effect but this may not be generalised to all SSRIs as only four types of SSRIs were tested. It is safe to conclude that for depressed patients with lower HRSD scores, placebo medication is as effective as SSRIs because patients may have more expectations from the drugs which translate into the placebo effect. If the placebo effect is triggered by SSRIs and is a cognitive process, is major depression solely caused by biological factors?

**Treatments that help depression**

Major depression isn’t only caused by biological factors and so, doesn’t have to only be cured by drugs affecting our biology. Sullivan, Neale and Kendler (2000) conducted a meta-analysis to investigate whether the etiology of major depression was solely genetic. The researchers analysed twin-studies and found that genetics did play a huge role in causing major
depression. However, they also found that the environment played a role in causing depression (Sullivan et al, 2000). Therefore, major depression isn’t only caused by genetic factors; rather it is caused by a combination of environmental and genetic etiologies. Environmental etiologies can be broken down into cognitive factors and social factors. One theory arguing as a cognitive factor is Beck’s cognitive theory of depression. Beck proposed that negative experiences carried on from childhood lead to the creation of negative beliefs and schemas (Reilly, Ciesla, Felton, Weitlauf and Anderson, 2011). “Beck described beliefs regarding the self, one’s personal world, and the future as the negative cognitive triad” (Reilly et al., 2011, p. 522). This increases the risk of getting depression because people’s own negative thoughts trap them into a vicious cycle of depression.

There are other treatments that have been successful in treating depression, hence showing that depression is caused by more than an imbalance of chemicals. One possible treatment in accordance with Beck’s theory is cognitive behavioural therapy (CBT) which aims to change the mindset of depressed patients. Chan (2006) conducted a meta-analysis comparing cognitive behavioural therapy (CBT), pharmacological drugs (PT) and a combined treatment (CT). He found that cognitive behavioural therapy was a “promising approach” to treating depression (Chan, 2006, para. 1). This shows major depression doesn’t have to be cured using a biological approach.

Social factors can also cause depression. Kendler, Karkowski and Prescott (1999) investigated whether stressful life events had a causal relationship with major depression by using twins. The researchers’ findings were stressful life events did cause major depression. Kendler, Hettema, Butera, Gardner and Prescott (2003) found, after interviewing twins, that loss
and humiliating events were likely to cause depression. A social therapy for depression is group therapy where several patients suffering from disorders come together and discuss. Bolton, Bass, Neugebauer, Verdeli, Clougherty, Wickramaratne (2003) investigated the effectiveness of group therapy in villages in Uganda. They found group therapy was very effective in reducing depression and more cost-effective (Thimm & Atonsen, 2014), thus, as demonstrated by Bolton et al. (2003), feasible to use in developing countries.

Conclusion

To conclude, there are numerous studies that have shown that placebo medication is a superior treatment to SSRIs. Ferguson (2011) found that SSRIs had many side effects including nausea, dizziness and weight gain. Andrews et al. (2012) justified this by postulating that homeostatic mechanisms were affected negatively due to the fluctuations in serotonin levels. Andrews et al. (2012) further argued that this increased the risk of relapse into depression with SSRIs. Kirsch et al. (2008) proposed that antidepressants were successful because they contained a placebo effect themselves. This evidence in support of placebo medication must be taken with a pinch of salt. Research (Hieronymous et al., 2016; Hieronymous et al., 2017; Cipriani et al., 2018) has shown antidepressants are more effective in treating major depression and that limitations such as the Hamilton scale and depressive level of participants are why there is evidence to support placebo medication. Several areas still need to be researched including the long-term effect of placebo medication and the efficacy of placebo medication on severe major depression.
Although more research is required to settle the debate of placebo versus SSRIs, there is no denying that placebo medication does exist and have the ability to help depressed patients. Evidence supporting placebo medication is effective demonstrates that major depression isn’t merely a biological disorder. There are social and cognitive factors that come into play as demonstrated by Kendler et al. (1999) and Beck’s cognitive triad. Therefore, treatments need to be adapted by taking these factors into consideration. Examples of treatments in accordance with these factors are CBT and group therapy. Perhaps isolating these factors and treatments isn’t the best treatment for depression. A more holistic approach to treating major depression may, ultimately, be more effective. Further study must be done regarding how effective a combination of all these treatments would be in alleviating depression.

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