A Review on the Side Effect of Weight Gain in Response to Selective Serotonin Reuptake Inhibitors, Monoamine Oxidase Inhibitors, and Benzodiazepines

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Introduction

Anxiety, depression, and other mood disorders can impact behavioral and physical elements of the body. Behaviorally patients can experience decreased mood, changes in circadian rhythm, and changes in appetite. These symptoms may lead to weight gain because there is a change in the body. While appetite changes manifest themselves differently for individuals that experience depression, the medication that the patients are placed on can further exacerbate the weight gain they may experience. Weight gain can occur because of appetite changes associated with depression. In order to treat mood disorders, drugs can be administered in order to reduce the symptoms. However, there are side effects that come with the use of drug treatment. One major side effect of these drugs is weight gain. The majority of patients experience weight gain when they start treatment. There is debate on whether or not the drugs themselves cause weight gain or if it is the leveling out of symptoms from the ailment that causes weight gain. This review examines the difference between selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors (MAOI), and benzodiazepines (BDZ) and how they impact weight gain. While each drug has the side effect of weight gain each drug impacts the body in a different way.

SSRIs are typically used to treat depression, anxiety, and other mood disorders. Some specific SSRIs that are commonly used are bupropion which is typically used to treat depression but can also be used as a potential treatment in order to help patients stop smoking. Amitriptyline and nortriptyline are used to treat depression but can also help to decrease nerve pain. Olanzapine is a specific SSRI that can be used to treat bipolar disorder, depression, anxiety, and

schizophrenia. While the drug can help with the symptoms of a lot of different disorders, it is not without its side effects. Some side effects include weight gain, metabolic disorders, and type 2 diabetes (Seretti et al., 2010). SSRIs are helpful in treating a multitude of disorders and ailments. However, there are always side effects to consider. Since SSRIs are a newer class of antipsychotics there are not as many side effects and they are not as drastic as older classes of antipsychotics, such as MAOIs.

Monoamine oxidase inhibitors (MAOI) are typically used to treat depression. While treatment is usually effective these drugs are not used as often recently. The reasoning behind the limited use of MAOIs is due to the fact that new classes of antipsychotics are safer and present less side effects. MAOIs can have considerable side effects which can commonly lead to a discontinuation of treatment because patients do not want the added burden of side effects. Weight gain is a common side effect of the use of MAOIs because of the way that the drug acts on creating fat deposits and impacts glucose processing. Since some food restriction occurs as a way to prevent weight gain while taking MAOIs there is a risk of having significant weight gain for the duration of treatment.

BDZs are antipsychotics that are typically used as a treatment for anxiety. Some commonly used BDZs are Valium and Xanax. However, this review considers the effects of diazepam. Diazepam is a specific BDZ that is typically used to treat anxiety, panic disorders, insomnia, and some symptoms of schizophrenia. Diazepam shows the least amount of weight gain out of the drugs discussed and the least amount of weight gain as compared to other BDZs. In some cases there is a weight decrease but then a slight weight increase as treatment continues. However, that is not nearly as common in individuals that take diazepam. Even when weight gain does occur it is not as drastic as it may be with other drugs.

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRI) are mostly commonly used to aid the treatment of depression, anxiety, and bipolar disorder. While SSRIs are a newer class of antipsychotics, which should indicate that there is a reduction of the side effects, there are still some side effects that are associated with the use of SSRIs. One of the side effects of SSRIs is weight gain during treatment, with around 48 percent of patients taking SSRIs experiencing weight gain (Azmeraw et al., 2019).

Shi and colleagues (2017) stated that there was an increase in depression and individuals on SSRIs may experience an increased risk of obesity. Looking to see if there was a correlation between the two started to provide insight about how SSRIs were impacting the body and if the new class of antipsychotics had the side effect of weight gain similar to the older classes of antipsychotics. Obesity and depression impact each other inversely because as there is an increase in weight gain there is an increase in depression, and individuals that have depression may experience a change in appetite where they consume more food which can lead to obesity.

The trends of both obesity and major depressive disorder (MDD) have been steadily increasing with obesity impacting thirty-four percent of the population in the United States, as of 2016 (Lee et al., 2016). While that may not seem like a large percentage of the population the obesity rate has doubled since the early 1960's. While there has been a steady increase of obesity there has also been an increase of MDD. MDD impacted more than 350 million people across the world, as of 2016. Lee and colleagues (2016) studied the pathways of MDD and obesity compared to antidepressants and weight gain. The hypothalamic-pituitary-adrenal axis (HPA axis) deals with stress, digestion, and regulating body processes. This shows how changes in the

HPA axis can play a role in obesity. When there is irregularity in the HPA axis it can cause a change in digestion and can lead to obesity. This change in the HPA axis is associated with MDD because it is associated with stress and body processes, such as emotions. Therefore it begs the question, if there is an irregularity in the HPA axis, and obesity occurs as a result, can it cause MDD. Some SSRIs such as fluoxetine and escitalopram may initiate cravings for specific foods, like carbohydrates that increase weight, or increase body mass index (BMI). Patients experienced a .12 BMI increase after they had been taking the drug for six months which is an increase from the initial measure of .05 increase in BMI in the first 12 weeks of treatment. While individuals may not experience weight gain initially there are long term effects that may lead to the increase in weight gain if the drug is administered over a long period of time (Lee et al., 2016).

Han and colleagues (2008) studied the relationship between histamine receptors and weight gain. They focused on the occupancy of the H1-histamine receptor. The H1- histamine receptor is located in the hypothalamus and helps to regulate appetite. The study administered one of three different drugs, aripiprazole, olanzapine, and haloperidol to rats and measured food intake and weight gain to determine if the drug altered fat accumulation. The group that was given olanzapine experienced an increase in weight gain in just 12 weeks of treatment as compared to the control group that was not treated with the drug. Overall the study shows that weight gain will increase when participants start treatment and that there is an increase in H1-histamine receptor binding in the brain which leads to weight gain. H1-histamine receptor binding was determined after the rats had been euthanized and their brains were examined in order to determine that there was an increase in binding, which can lead to weight gain. Other studies solidify the idea that weight gain occurs rapidly at the start of drug use. Olanzapine and a

placebo were administered to two groups and observed to determine if there was a change in weight gain between the control and experimental groups. Healthy individuals that were given olanzapine experienced 3.4 kg increase in weight gain as compared to the control group after taking the drug daily for 3 weeks. This shows that at the start of antipsychotic treatment that there will be an increase in weight gain (Silverman et al., 2018). Lord and colleagues (2017) also studied how olanzapine can increase food intake and decrease glucose tolerance as well as a decrease in activity levels in rats. This study looks at the effects of Htr2c, a receptor of serotonin, and determines if agonists can help to decrease the side effects. Rats were administered the drug and their food intake and activity level was recorded. When rats were given olanzapine there was a significant increase in food consumption leading to weight gain and there was a decrease in the amount of physical activity that the rats were participating in, showing that the drug decreased their energy level while increasing their desire for food consumption. However, agonists of the Htr2c receptor, can help to reduce the side effects of the drug when taken in conjunction. Overall, olanzapine can lead to hyperphagia and can decrease energy levels of patients and increase the chance that they will become obese.

Olanzapine is considered in the new class of antipsychotics and is used to treat a multitude of aliments. However it ends up binding to H1-histamine receptors, acting as an agonist. Which causes weight gain and causes hyperphagia and a decrease in activity which can lead to weight gain as well. While agonist can act on the receptors it can help to reduce some of the side effects when they are taken in conjunction, olanzapine still causes a significant increase in weight gain, especially at the start of treatment.

Obesity is more common in individuals that suffer from psychiatric illness. This can be for a few reasons. Research shows that depression can often alter sleeping and eating habits

which can lead to weight gain in individuals that are depressed. Another common trend with the use of some antidepressants is the fact that there will be an initial weight loss at the start of treatment followed by weight gain as treatment persists. Most SRRIs cause an increased desire for carbohydrates which can lead to weight gain when the desire is satisfied. FLX is a SSRI that causes an increase in desire to consume carbohydrates making it the leading SSRI to cause weight gain (Arndt, 2015). While there is an initial drop off of weight and many patients will lose weight initially there is ultimately an increase in weight over the duration of FLX treatment. Around week 50 of treatment weight gain is reported. This may be an indicator that the drug is going to cause weight gain in the long term (Serretti & Mandelli, 2010).

Another study shows that FLX impacts and delays the reuptake of serotonin which helps with symptoms of depression. Ardent and colleagues (2015) performed a study in which rats that are forced into a swim test, experience symptoms of depression. Neurochemical changes can occur because of the environment in which the rats were reared in. Rats were raised in enriched, isolated, or standard environments. The goal is to determine if the environment changes the brain and if there is a change in body weight for the rats that were treated with FLX. The rats that were raised in the enriched and isolated environments experienced weight gain but the rats that were raised in the standard environment did not experience weight gain. This shows that not only is weight gain environmental but that the drug can also play a factor in weight gain (Arndt et al., 2015). Since there are different environmental factors for all people, the environment will play a role in their individual weight and weight gain. Individuals that are taking FLX may experience weight gain because of the drug's side effects but also because of the environment in which they live.

Scabia and colleagues (2018) studied how the leptin system and the brain derived neurotrophic factors (BDNF) are impacted by the use of FLX. Leptin is used to communicate between the brain and the organs in order to regulate body weight. Ideally, it is to indicate to the brain how much fat is stored so that there is a decrease in food intake and an increase in activity. Individuals that are obese experince a change in the set point for the amount of fat that is stored. Therefore the brain will think that they need more food when in reality they have enough fat stored and would be able to stop eating. While this changes, it can go back to a normal set point if the individual participates in lifestyle changes. BDNF is used in order to reach homeostasis and causes a decrease in appetite. BDNF is activated when FLX is present which ideally would help the individual to lose weight (Scabia et al., 2018). During this study 80 mice were used, with 25 of the mice having genetic mutations that impair the function of their BDNF. FLX was administered by being dissolved in water. They found that weight did decrease in the rats because their BDNF was activated by FLX initially indicating that there was a decrease in appetite. However, this trend did not last. Rats eventually experienced weight gain. This shows that the drug may be helpful initially in obesity treatment but would not be an effective treatment in the long run.

FLX is an effective antipsychotic treatment however individuals may discontinue treatment because of the weight gain side effect. In the short term weight loss occurs however, when treatment persists there is an increase in weight which is why people would stop treatment in the long term. Since weight loss occurs initially it may be a helpful short term treatment for obesity. Ensuring that the treatment does not last for a long period of time is critical because if not weight gain will occur. Finally, FLX is not the only factor when considering weight gain. The environment in which the individual lives helps to create a predisposition for weight gain. If

they live in an enriching or inversely isolated environment then they will experience weight gain. However, living in a standard or controlled environment would not lead to weight gain, but there will always be some environmental factors that impact whether or not an individual is at a higher predisposition to experience weight gain while taking FLX.

Fava (2000) solidifies the impact of treatment length in their meta-analysis. The study considered weight gain as a side effect of both depression and the use of antidepressants. Weight gain is typically a problem during both short term and long term use of a particular drug. However, when administering SSRIs there is the idea that treatment time impacts the potential side effects. The study found that SSRIs, in general, do not cause weight gain when they are used for a short amount of time. However, the meta-analysis shows that when treatment persists there is an increase in weight. This may be due to two factors. The first is that weight gain is a side effect of the SSRI itself whereas, the second is that the SSRI is treating the symptoms of depression and bringing the individuals appetite and sleeping habits back to a normal level. Therefore, patients would experience weight gain not solely as a side effect of the drug but because of the improvement in psychopathology. Another study shows the impact of treatment length by asking survey questions to determine which drugs the individuals were taking and recorded their weight before and after treatment. Out of the drugs reported SSRIs, in general, had the highest association with 55 percent of participants experiencing weight gain within the first six weeks. After three months of treatment, 80 percent of participants had experienced weight gain (Uguz et al, 2015). Blumenthal and colleagues (2014) expands on the idea that different drugs can impact the side effects when they looked at the long term use of SSRIs, specifically bupropion, nortriptyline, and amitriptyline. These drugs as compared to older tricyclics and monoamine oxidase inhibitors (MAOI) showed significant weight gain during treatment. Patients

that were on at least one drug experienced weight gain and when they terminated treatment they no longer experienced the side effect.

Shi and colleagues (2017) suggests that there is a connection between the use of antidepressants and exercise levels, smoking or nonsmoking, and dietary habits. When comparing the listed drugs that participants were taking SSRIs, in general, showed the highest amount of weight gain. While SSRIs had the highest amount of weight gain they had especially high levels of weight gain when the individual had an unhealthy lifestyle, including decreased physical activity and high fat food consumption. There is a positive association between weight gain and the use of antidepressants but weight gain is heightened when the individual has an unhealthy lifestyle (Shi et al., 2017). The age of patients can also impact the way that they respond to the drug. Reekie and colleagues (2015) shows that 2.8 percent of children and 5.7 percent of adolescents suffer from depression. If children experience severe enough depression at such a young age and need medical treatment, they are most commonly treated with SSRIs as compared to other forms of antidepressants or anti anxieties. When studying the potential side effects of the drug on children a meta-analysis was conducted to examine weight gain in children and adolescents that were treated with SSRIs. Findings show that children that were treated with SSRI experienced an initial decrease in weight as compared to the placebo group. However, there was a spike in weight after children had been on the drug which is similar to how adults respond to treatment. Specifically, olanzapine, clozapine, and risperidone were the drugs that caused the most significant amount of weight gain in young people. The study also shows that there is a strong connection between children that are obsese and children that are on antipsychotics (Reekie et al., 2015). This may indicate that when a child takes antipsychotics for an extended period of time that there may be a potential for them to become obese. Since age and

length of treatment play a slight role in the side effects of drug use, it is important to consider that ethnicity could also play a role in weight gain. Research shows that there may be a weight gain difference between caucasians and people of color. A study recorded weight gain in adolescents from the time they were prescribed the drug and at the time that there was self reported weight gain. Results showed that there was a significant difference in weight gain for race, specifically African American, but that gender did not play a role. There was a significant difference in weight gain because African American participants experienced a higher amount of weight gain than white participants. There is a significantly higher weight gain for non white patients than white patients. This is an important note for prescribing physicians to consider when prescribing because there is a higher likelihood that non white patients may experience side effects at a higher level (Ramsey et al., 2019).

Understanding how demographics can impact side effects of SSRIs is important because it shows that not only is weight gain a significant side effect but that it can impact individuals in different ways and that it can impact groups of people in different ways. Individuals in groups that are impacted more greatly by side effects, such as non white individuals, may still experience the same symptoms and side effects as white individuals. However, non white individuals may experience weight gain caused by SSRIs in a more noticeable way.

As previous research has shown the length of treatment of SSRIs impacts the possibility for weight gain. Research shows that during short term treatment there is no weight gain in individuals taking SSRIs. However, when treatment persists there is an impact on weight gain and patients may experience this side effect. Demographics and genetics can also play a role in the way that SSRIs contribute to weight gain since some side effects will impact some patients but not others, or the side effects will impact different individuals at different levels of severity.

Differences in environment, lifestyle choices, and genetic predispositions can be contributing factors to overall weight gain during the course of treatment. Future research may be able to look at the relationship between demographics and the prevalence of diagnosis and the prescribing of SSRIs in minority groups. It is also something that is important for patients and physicians to consider when they are considering the best treatment options because there is the idea that patients may respond to drugs differently and increase their susceptibility to experience side effects based on their race, age, and other genetic factors.

Monoamine Oxidase Inhibitors

Studies have examined the way that MAOIs impact glucose transportation, fat deposits, the effect on white adipose tissue, and lipid inhibition. In order to determine the impact MAOIs can have on the body it is important to understand the side effects of MAOIs and the purpose of the drug. MAOIs are most recently seen as a last resort since there are so many side effects that can occur from use. Currently in the United States only four MAOIs have been approved for treatment by the Food and Drug Administration (FDA). The four MAOIs that have been approved are, phenelzine sulfate, isocarboxazid (ICX), tranylcypromine sulfate, and selegiline hydrochloride, which is only used for Parkinson's treatment. The side effects of the drugs may not be dependent on the dosage. When there is a higher dosage that does not indicate that there will be an increase in side effects. In addition to weight gain some of the most common side effects of the drug is dizziness, tremors, blurred vision, and dry mouth. However, weight gain is the most significant side effect and a meta analysis shows that there is not a connection between dosage and an increase in side effects. However, weight gain does occur during treatment and while there is also an effect of fat storage while taking MAOIs there is also an increase in food

cravings and food intake. This leads to a rise in discontinuation because patients do not want to experience significant weight gain (Thase et al., 1995).

Studies have also looked at how the significant side effect of weight gain occurs in the body during the duration of treatment. During the use of MAOIs there is an increase in the stimulation of glucose transport which means that glucose tolerance rises, this may lead to a potential in sugar and high carbohydrate diets. This can lead to increased challenges when treatment persists because there may be increased fat deposits potentially leading to obesity. In this study rats were used in order to determine if MAOIs increase fat deposits in the body. They also looked at the possibility of reducing weight gain by pairing MAOIs with semicarbazide sensitive amine oxidase (SSAO). The theory behind combining these drugs in order to limit weight gain is that they will inhibit the white adipose tissue in order to reduce potential weight gain. In experiment one, female rats were given MAOIs, pargyline, for three weeks. During experiment two, female rats were given MAOIs for an extended period of time, 9 weeks, to indicate chronic treatment. Finally in experiment three, seven-week old obese male rats were treated with MAOIs and SSAOs for four weeks. BMI measurements were taken on all rats during the course of treatments and for the duration of the experiment. The results indicated that there was an increase in weight gain for those that were treated with MAOIs. However, those that were treated with MAOIs and SSAOs experienced decreased BMI and a decrease in food intake. This was shown in fat accumulation in hyperphagic rats which shows that when the drugs are used in combination that there may be a significant weight loss (Carpene et al., 2007). Future research may be able to explore that as a further treatment for MAOIs.

Phenelzine is a specific MAOI that has been approved for use in the United States. It is one of the older MAOIs that is oftentimes prescribed with dietary restrictions. Since there is a

potential for significant weight gain dietary restrictions are recommended in order to avoid or limit weight gain. Wine, cheese, beer, and other fermented foods are some of the suggested foods to avoid because they can lead to weight gain and ultimately cardiovascular problems. The study looks at how phenelzine specifically impacts lipid accumulation in the body. They used two groups of 12 mice that were given phenelzine dissolved in water for 12 weeks. After sacrifice, the organs were weighed in order to determine if there was lipid accumulation in the organs, there was an increased lipid accumulation in rats that were given phenelzine. Results indicated that rats that were exposed to the drug had increased food intake, which contained 45 mg of tyramine. Since there was an increase in weight gain there may also be increased cardiovascular strain (Carpene et al., 2018). Possibilities for future research would be to look at the long term effects of treatment and the consumption of high tyramine foods to see if it would lead to heart complications in the rats. Carpene and colleagues (2018) advanced their research by looking at the relationship with sucrose to determine if there was weight loss. While it is unclear if potential weight loss is caused by the drug or by the improvement of symptoms of the mood disorder to cause a more normal appetite and activity level. In this study mice were exposed to high concentration sucrose solutions in order to see how phenelzine impacts the body. The results showed that there was weight gain when the drug was administered and that there was an accumulation of lipids and fat deposits in the liver. While this indicates that there was weight gain there is no way to differentiate between the source of the weight gain, it could be the side effect of the drug or the increased exposure to high concentration sucrose solutions.

While there is evidence of phenelzine leading to weight gain, other studies have also shown that phenelzine can be used to facilitate weight loss. Phenelzine can be used as a potential obesity treatment because of the way that it inhibits white adipose tissue and can impair fat

accumulation. In this study rats were treated with phenelzine for nine weeks. Researchers predicted that there would be a decrease in fat accumulation in order to create weight loss. After nine weeks of treatment there was a reduction in weight and there was also a reduction of fat accumulation in order to stimulate weight loss. However, weight gain may still occur. There were still some cases of fat accumulation which indicates that phenelzine is not completely effective in the treatment of obesity (Carpene et al., 2014). Another study shows evidence of there being a decrease in weight while taking phenelzine. This study used five male non obese rats and five obese female rats. The female rats were given phenelzine and the male rats were given saline in order to determine if the obese female rats would experince weight reduction. The results indicated that there was a decrease in weight and there was also a decrease in fat deposits throughout the body. While this is true for short term treatment it may not be true for long term treatment and weight gain may occur when treatment is extended (Carpene et al., 2008).

Another common MAOI that is used is ICX. Research shows that there is an increase in effectiveness of the drug when side effects are present. Patients that experience side effects of weight gain, increased appetite, and increased sleep experience noticeably more significant improvements. This study looks at women ages 18-65. Forty-one participants were randomly assigned to ICX or placebo groups. The drug or the placebo were administered on a double blind basis. The results indicate that ICX was an effective treatment method. However, there was an increase in side effects. Patients experienced an increase in dizziness, blood pressure, and weight gain. When there are more significant side effects then there is a higher likelihood that the drug is more effective (Davidson and Turnbill, 1983). Riise and Holm (1984) looked at the relationship between ICX and weight loss. ICX typically causes weight gain however this study looks at the combination of ICX and mianserin (MIA). The rationale is that the combination of

the drugs will limit the side effects. There were 60 participants, 40 women and 20 men. During the first few weeks of treatment there was significant weight gain when participants were taking ICX. Individuals that were taking ICX and MIA still experienced significant weight gain. This shows that even when there is a combination of two drugs it did not decrease symptoms.

Overall, MAOIs are typically an effective treatment even though they are not used very often compared to newer antipsychotics. MAOIs can cause a significant number of side effects and while they can be an effective treatment method the side effects can decrease the continuation of the treatment. If there was a way to mitigate some of the side effects, whether it being a co-prescription of taking a drug that would combat the side effects or changing the way that the body responds to MAOIs may be helpful in continuing use. Since many people do not want to experience the side effects they are more likely to stop taking the drug which can become problematic because they are not being treated in an effective way. While there may be some circumstances in which MAOIs may decrease weight, the most common side effect is weight gain and can lead to more significant problems such as obesity and cardiovascular problems. More research could be conducted to look at how MAOIs could have a reduced number of side effects and also if there are particular circumstances or instances that would be beneficial in creating a way for people to maintain treatment while maintaining a healthy lifestyle without the side effects.

Benzodiazepines

Benzodiazepines (BDZ) are used to treat anxiety, schizophrenia, and a wide range of other affective disorders. Similar to SSRIs and MAOIs a potential side effect of BDZs is weight gain. Weight gain can be caused because of the way that BDZs impacts GABA receptors and there is an increased desire to consume fatty foods while being treated with BDZs.

The effects of GABA are critical in understanding how the drug causes weight gain. GABA receptors play a key role in hunger and satiety (Blasi, 2000) and when that system is disrupted it can cause imbalances in weight. Since BDZ can impact the GABAergic system it can cause individuals to consume more than normal because they feel as though they are hungry. Researchers have tried to examine the way that the side effect of weight gain can be mitigated. The use of tetrahydrocannabinol (THC) was suggested as a way to reduce the impact that BDZ has on the GABAergic system. The results did not support the hypothesis that THC would decrease food intake that was stimulated by BDZ. Since THC did not impact food intake it may indicate that THC and BDZs impact different pathways. BDZs have a greater impact in the ventromedial hypothalamus whereas THC impacts dopamine receptors which would cause an increase in appetite (Puttegowda et al., 2016).

GABA can impact weight gain and since BDZ impacts GABA it can lead to hyperphagia. When GABA receptors are acted on then it creates an increased sense of hunger. Research shows that there is a connection between anxiety and food intake. Establishing the idea that high fat foods are linked with symptoms of anxiety and an increase in weight gain can also be caused because of the way that BDZs impact GABA. This study considers if there truly is a relationship between anxiety and high fat foods and how that impacts the side effect of weight gain during BDZ treatment. Hamsters were given the drug and anxiety was induced, during this time they were presented with graham crackers, as their high fat food. The results indicated that there is a relationship between high fat food and increased intake during times of anxiety. Since there is an increase in food intake during times of anxiety, that indicates that there will be weight gain over an extended period of time. In the short term it would not have a drastic effect. However, when increased consumption occurs over an extended period of time there is going to be weight gain.

It is also important to note that there is a significant gender difference between the high fat intake of men and women. Women have a tendency to consume high fat foods during anxiety more than men, which may be an indicator of eating disorder predominance in women (Shannonhouse et al., 2015). This shows that not only do the symptoms of anxiety cause an increase in cravings and food intake but that there is an increased effect of weight gain when BDZs are used. Since BDZs would cause some weight gain in general and consuming high fat foods also causes weight gain then individuals that crave high fat foods during times of anxiety and are being treated with BDZs then they have a weight gain predisposition.

Research examines the realtionship between obese and lean rats and weight fluctuation in the rats that are treated with diazepam. The results show that after initial treatment rats did not experience weight gain. Rather, both lean and obsese rats experienced a decrease in weight gain. While this did not persist there was only a slight increase in weight when long term treatment occurred. This shows that while there is a slight weight gain it is not the most predominant symptoms and that there is a more significant weight loss (Blasi, 2000). Diazepam indicates that there is greater evidence to indicate weight loss rather than weight gain.

Even when there is not a significant weight gain for diazepam there are other potentially dangerous side effects that are involved with the administration of diazepam. Puttegowda and colleagues (2016) studied how weight gain and side effects of insulin resistance can lead to heart problems in individuals. It is important to note that while weight gain is not as significant of a side effect for diazepam as it is in other drug treatments, it can still occur based on individual predispositions and other factors that play a role in the symptoms of anxiety and depression. There is an increased risk of cardiomyopathy in individuals that are taking diazepam and there may also be a side effect of insulin resistance. In this study they observed diazepam impacting

and reducing negative symptoms of schizophrenia but that there was an increase in side effects. There was an increase in weight gain for individuals that were taking the drug and since they are gaining weight there is increased strain placed on their heart which can lead to long term heart problems. While this may be true for this study and the individuals that were monitored it may not be the case for all patients. The patients in this study may have a history of heart problems or they may have a predisposition of heart disease which may indicate that there are more factors to consider than just side effects.

In order to mitigate side effects, studies show that there may be a connection between the use of diazepam and imipramine hydrochloride, used as an antidepressant and for nerve pain. The study used rats that were given 50 mg/kg of imipramine hydrochloride in conjunction with 5mg/kg of diazepam and rats that were given solely imipramine hydrochloride. The goal of the study was to determine if there was correlation between the two drugs and if administering imipramine hydrochloride with diazepam would decrease side effects that are caused by the use of diazepam. Rats were weighed initially and then periodically throughout the course of the study. Both treatment groups experienced a decrease in weight gain after the first few days. Imipramine hydrochloride reduced the rats appetite, this occurred because imipramine hydrochloride binds to receptors so that diazepam cannot increase appetite. Therefore, those that were being treated with diazepam and imipramine hydrochloride did not experience as much weight gain. These results follow the idea that diazepam might cause an increase in food intake and in order to reduce food intake then imipramine hydrochloride can be administered in order to reduce the individuals appetite (Okiyama et al., 1986).

Research has also considered how different BDZs, like Haloperidol. Haloperidol is an antipsychotic drug that increases food intake when treatment persists for a longer period of time.

However, researchers compared haloperidol to diazepam to determine if there is a relationship between the two. They predicted that there would be an increase in weight gain because people experience hunger and increased food intake. In order to determine if there is a difference in food intake between diazepam and haloperidol, male rats were divided into two groups. The first group was given haloperidol and the second group was given diazepam. They found that both drugs caused a reduction in food intake at first but then there was an increase in food intake when the treatment persisted. However, haloperidol caused hyperphagia and overall weight gain (Keranen and Sivenius, 1983). This study highlights the fact that while weight gain is a side effect of the use of diazepam it is not as significant of a side effect as it is in other BDZs.

The use of BDZs can cause obesity as demonstrated in the previously discussed studies. There is a distinct correlation between mental health and obesity. There is a strong increase in obesity for individuals that experience symptoms of anxiety and depression. However, medication has an effect on obesity as well and can lead to an increase in weight gain (Grundy et al., 2014).. While there is an increased risk of obesity while taking BDZs, since there is a decrease in weight gain initially it may be helpful in treating other disorders, such as a short term treatment of obesity and a secondary treatment for seasonal affective disorder (SAD).

Since there is an increase in obesity it is typical for anti anxiety medication to cause additional weight gain, the drug can cause obesity because of the combination of the appetite increase for anxiety and depression on top of weight gain side effect of the medication. Research shows that BDZs were administered to both male and female rats while monitoring food intake. The results showed that the rats initially lost weight and when they started to gain weight after a longer period of treatment, about three weeks, then there is a plateau in weight gain (Rahminiwati and Nishimura, 1999). This shows how in the short term it can be effective

treatment in weight loss because there is an initial weight reduction, even when there is an increase in weight after an extended period of time then the weight plateaus. This is helpful because it levels out appetites for some individuals potentially decreasing continuous and drastic weight gain. While it can facilitate the treatment of obesity in the short term it can also help with the treatment of SAD. SAD occurs during one season in particular and when the season is over, the symptoms dissipate. SAD is typically treated with bright light therapy however it is not always fully effective. Yamadera and colleagues (2001) looked at the use of BDZs as a method of treating SAD. Patients were given alprazolam, a specific BDZ, when light therapy was not effective. Each patient experienced improvement with the use of alprazolam. While improvement varied for each participant, all of the participants experienced overall benefits from taking alprazolam. This shows how BDZs can help to regulate sleep wake cycles and that they can increase appetite. While BDZs are an effective treatment for SAD there is also an increase in weight gain. This can also lead to a discontinuation of treatment, especially since individuals may only be treated seasonally (Yamadera et al., 2001).

BDZs are effective in treating symptoms of anxiety, depression, and other psychopathologies. However, the side effects of BDZs can lead to weight gain and potentially obesity. When there is an increase in weight gain it can cause an increase in cardiovascular strain which can lead to heart problems. It is important to consider this side effect and monitor patients that are being treated with BDZs so that they do not develop heart problems, specifically if they are experiencing weight gain as a side effect. If an individual is previously dealing with obesity then there may be a way to use BDZ as a tool in order to reduce obesity in a short term treatment. Further research would need to be studied or conducted in order to determine how effective it would be to treat obesity by using BDZs in the short term. Overall, BDZs in short term

treatments are an effective treatment method and do not cause weight gain, inversely during long term treatment there is a significant side effect of weight gain.

Discussion

The research above shows the relationship between drug treatments and the side effect of weight gain. While there are a multitude of side effects associated with any kind of medication, when comparing SSRIs, MAOIs, and BDZs weight gain is a significant side effect that is drastic enough to cause the suspension of treatment.

SSRIs exhibit significant weight gain because they increase the desire for high fat foods, similar to the use of MAOIs where foods that are high in tyramine are more appealing during treatment. The research shows that there is a link between SSRIs and obesity as well as a link between MDD and obesity. This shows that not only do SSRIs cause weight gain but that there is also an element of MDD causing weight gain, highlighting the fact that individuals that are being treated with SSRIs may be experiencing both symptoms of MDD as well as a side effect of SSRIs.

MAOIs impact lipid storage and fat deposits which can lead to weight gain. Since MAOIs have such high consequences of side effects they are not prescribed as often. When individuals are treated with MAOIs they are oftentimes told to regulate their diet and to avoid certain food because of the way that the drug impacts the body. The fact that MAOIs can impact fat deposits and can place unnecessary strain on the heart shows that the use of the drug leading to weight gain can also lead to cardiovascular problems associated with obesity.

BDZs impact the GABA system which causes patients to experience an increase in hunger since there is always binding to the receptors. When patients are always hungry they are going to consume more food which leads to weight gain. Overall, each drug impacts the body in

a different way but each drug has a common side effect of weight gain. Future research may be able to consider which drug has the highest rate of weight gain. Another effective future research method would be to create a study that would compare each class of drug to the other in order to determine which process of the body impacts weight gain the most.

After reviewing the research, SSRIs seem as though they have the least drastic side effects. SSRIs are the antipsychotic that is most commonly used due to the fact that MAOIs and BDZs have a greater number of side effects. However, based on the research the weight gain that is prevalent in SSRI use is not extreme enough for treatment to be fully terminated whereas the others have significant enough weight gain to cause discontinuation of treatment. It is important to note that each drug is going to respond to each patient in a unique way however there is a higher likelihood of weight gain when MAOIs and BDZs are not used. It also important to consider that each patient has a unique lifestyle and they are going to need a drug that compliments their lifestyle in the best possible way. Based on the research, weight gain is a side effect for each class of drugs, SSRIs, MAOIs, and BDZs, with each acting on a different part of the body to create a difference in the prevalence of the weight gain.

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