ABSTRACT

Prader-Willi Syndrome and a Potential Weight Loss Supplement

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Prader-Willi Syndrome (PWS) is a genetic disorder caused by a lack of the 11q-13q segment of the paternal chromosome 15. Although the cause of the lack of genetic information varies, the result is an extreme increase in appetite, hypogonadism, mental retardation, and behavioral problems. Often, the most prominent obstacle the individual with PWS faces is managing the excessive weight gain that comes with having constant, ravenous hunger. Since there currently is no cure, managing the symptoms is the focus for most doctors. If the issue of excessive weight gain can be mollified, then the disorder would become more manageable. Therefore, I am proposing a hypothetical research project that examines the effects of capsaicin, a potential weight loss supplement, on individuals with PWS. Since the experiment is hypothetical, a guideline for this potential project is explored, along with rubrics for interpreting possible results. Several potential data sets have been prepared, and are accompanied by an interpretation of what these results could mean for PWS patients in the future.

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PRADER-WILLI SYNDROME AND A POTENTIAL WEIGHT LOSS SUPPLEMENT

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By

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CHAPTER ONE

Literature Review

Prader-Willi syndrome (PWS) is a rare genetic disorder that is caused by a lack of the 11q-13q region of the paternal chromosome 15. It was the first human imprinting disorder to be discovered, and was also the first discovery of a disease caused by uniparental disomy. (Chen, et al., 2007) (Cassidy & Driscoll, 2009) The incidence is between 1 in 10,000 and 1 in 15,000 live births, and its occurrence does not vary between different ethnicities. (Nussbaum, et al., 2007)

Some common physical characteristics of PWS include almond-shaped eyes, hypopigmentation, and low muscle tone. (Chen, et al., 2007) The ratio of muscle to fat is low, and less dietary intake is needed to meet the body's daily needs. (Allen, 2011) This tends to be problematic when considered in combination with the increased appetite, because not as much of the food taken in is utilized by the body, leading to an even greater propensity toward obesity. Slight to moderate cognitive impairment is also common.

Behavioral habits characteristic of PWS typically begin around the age of four. Common tendencies are skin-picking, obsessive compulsive habits, and autistic-like behaviors. (Chen, et al., 2007) While hoarding, arranging and ordering objects, and self-injuring habits are present, the well-known germophobic habits seen commonly in those with OCD are not usually seen in PWS patients. There are also many patients with PWS that exhibit signs of attention deficit hyperactivity disorder (ADHD). Specific symptoms

vary from case to case. (Wigren & Hansen, 2003) Interestingly, it has been observed that many children with PWS are exceptionally good at jigsaw puzzles. (Chen, et al., 2007) As this combines organizational and arranging behaviors, the parents ought to encourage this activity as a creative outlet for these common obsessive habits.

Another significant physical characteristic of PWS is hypogonadism. This is linked to the hypothalamus, and is caused by a lack of androgens and gonadotropins. This begins prenatally and continues for the rest of the individual's life, almost always resulting in infertility. (Chen, et al., 2007) However, hormonal treatment can sometimes help with hypoplasia.

The earliest symptoms of PWS are very unlike the later manifestations of the disorder, which is why it is typically diagnosed at a year to five years of age. Affected fetuses and newborns usually have low muscle tone, decreased movement, poor suckling, and an abnormal heartbeat. These are all early characteristic of PWS, but they are usually misdiagnosed as other disorders due to the rarity of PWS combined with the frequency of these symptoms' appearance in other illnesses, such as fragile-X syndrome, spinal muscular atrophy, or simply failure to thrive. Once PWS is suspected, a doctor will typically perform a PWS methylation test, confirming whether the individual does or does not have PWS. If the methylation test comes back positive, then it is often followed up by fluorescent in-situ hybridization (FISH). (Chen, et al., 2007)

Between the ages of one and six, the characteristics seen in newborns begin to fade, and those commonly found in most PWS patients start to manifest. (Chen, et al., 2007) In this transition period, the parents often believe that the child is recovering, and

the emerging veracious appetite is encouraged. However, this increased appetite does not fade, and the child will often gain large amounts of weight in a short period of time. Additionally, a mild to moderate mental retardation becomes apparent, as well as other behavioral tendencies typical of PWS. (Chen, et al., 2007)

Located in the 11q-13q PWS critical region is a small nuclear ribonucleoprotein N gene (SNRPN), which encodes a ribosome-associated protein that assists in gene splicing and is only found in the paternal chromosome 15, SNRPN is expressed in its highest amounts in the brain and heart, though it can be found throughout the body. Additionally, a gene known as P can also be found in this critical region, and is the blueprint for tyrosinase positive albinism. Its deletion is thought to be tied to approximately a third to half of patients with hypopigmentation. (Chen, et al., 2007)

PWS can occur by different means, manifesting itself in varying amounts of severity. Seventy-five percent of cases are caused by a new mutation of 15q11 to 15q13, one that is not inherited from either parent. (Chen, et al., 2007) Because of both this and the commonplace nature of the initial symptoms, PWS is not typically the first disorder to be suspected when the initial symptoms occur in newborns.

Twenty percent of PWS cases are due to maternal uniparental disomy, meaning that the patient has two copies of maternal chromosome 15. This could be caused by an early case of trisomy 15, where the extra chromosome 15 (likely paternal in origin) was lost via trisomy rescue. These patients often do not have some of the otherwise common facial characteristics of PWS, such as thin upper lip and almond-shaped eyes. There is also a lower occurrence of hypopigmentation and skin-picking, and some tend to have a

higher IQ and less behavioral problems. (Chen, et al., 2007) However, autism and psychosis are more common in these cases. (Cassidy & Driscoll, 2009)

Five percent of all reported cases of PWS are caused by a structural issue, such as translocation. (Chen, et al., 2007) The insertion of a different gene into the critical PWS region causes a disruption in this region, causing it to be nonfunctional. One percent of cases are a result of a microdeletion in the imprinting center in the father. (Chen, et al., 2007) In unaffected individuals, the father's imprinting center changes the chromosome 15 he received from his mother into a paternal chromosome 15, so that he only passes on paternal chromosome 15s. However, if there is an error in his imprinting center, the maternal 15 will remain, and some of his sperm will contain this error. If the sperm with a maternal 15 joins with an egg, the fetus would have PWS.

It is relevant to note that Angelman syndrome is also a result of a lack of the 11q-13q region of chromosome 15, except that Angelman patients are lacking the maternal genetic information. The deletion of two similar areas in chromosomes of different parental origin results in two distinct disorders. Genetic information from both the mother and the father must be present to produce an unaffected individual.

The risk of inheriting PWS depends on the cause of the disorder. In cases where it resulted from a deletion or uniparental disomy, the risk of passing the genetic information on is less than one percent. However, for imprinting errors, the recurrence risk can be around fifty percent. (Nussbaum, et al., 2007) In cases where the error lies in the imprinting center of the father, the odds of the faulty gene creating more genes with more flaws is more likely than random mutations occurring or maternal uniparental disomy.

A survey was conducted in England to gain more information about how children with PWS are managed and how they interacted within the family unit. There were three factors considered when choosing samples: single-parent or both parents, the number of siblings, and socio-economic status. Of the selected families, all members participated in the study. The parents completed questionnaires and were involved in interviews, and the children were given the option of speaking with the interviewer, drawing as a method of expressing feelings or ideas, or a combination of the two. There were also a handful of whole family observations. (Allen, 2011)

There were several conclusions formed by this study. Four families completely restricted their child from food access, twelve used either intermittent restriction or partial restriction, and four did not restrict the kitchen. This likely was a result of a difference in each family's perspective on the situation. For those that chose to leave the kitchen unlocked, restriction meant that the child was lacking self-control. The child must learn how to control him or herself, so that they will be prepared for any situation that could arise later in life. (Allen, 2011) This would likely allow the child to be the most prepared for adulthood, and could increase the level of independence that he or she could enjoy.

The families that chose to lock their kitchens expressed the view that restriction meant freedom. The child knew that he or she would be unable to access the kitchen, allowing him or her freedom to focus on other things. (Allen, 2011) This may not be the best method for giving the child skills to take into adulthood, but it does allow more freedom and happiness, so the quality of life may arguably be better.

Some families chose to rely on alternating between methods, depending on the needs of the child at the time. If the child begins abusing the food supply, the parent(s) can lock the kitchen until the child gets better at controlling him/herself. (Allen, 2011) Finding the method that works best for each patient is the key.

In 2003, a survey was performed by Wigren and Hansen that had a focus on the symptoms of the disorder and the behaviors that stemmed from them. Some noteworthy results were:

81% mild-moderate intellectual disability
76% were either currently on growth hormone treatment or had completed it
30% were greater than 2 standard deviations above the average body mass index
71% diagnosed at or before the age of 4
48% showed compulsive behaviors
38% ADHD
38% conduct problems
71% show skin-picking behavior
83% current and future child needs and services

It was noted that the body mass index was positively associated with ADHD-related and repetitive compulsive behaviors (meaning that those with ADHD-related behaviors tended to have a higher BMI), though the reason for this correlation was not discovered. (Wigren & Hansen, 2003) Perhaps those with a higher degree of these behaviors are more difficult to manage, and therefore the parents spent more time trying to do this than concerning themselves with the child's eating habits.

Growth hormone therapy was approved for children with PWS in July 2000. Many different studies have shown growth hormone treatment to be beneficial in most cases from newborns to adults. It stimulates growth, creating an adolescent growth spurt, which can help offset the fat accumulation by adding height that the fat can distribute to

and by increasing the mass of bone and muscle. It can also be used to create a more healthy body composition in adults. (Chen, et al., 2007)

Like any treatment, there is some amount of risk found in using growth hormone therapy. Between the time it was permitted and halfway through 2004, thirteen children worldwide died while using this treatment, but there was no solid connection between the treatment and their deaths. The overall risk is low, so most professionals recommend it, and most parents choose to use it for their children. (Chen, et al., 2007)

Another common treatment available to PWS patients is sex hormone replacement. In male patients, there is controversy between whether the patient should wait to see if they need the treatment, and can begin it around 17 or 18, if necessary, or if he should start on small doses at the age of 13 and increase the dosage slowly. (Chen, et al., 2007) This decision is likely one that is made on a case-by-case basis.

Sex hormone replacement therapy is not as common in girls, because the hypogonadism is not as evident. However, it can be used to begin menstrual cycle or to increase breast size. Additionally, estrogen treatments can be used to improve bone density, if necessary. (Chen, et al., 2007)

This treatment does have side effects. It has been known to increase the chance of stroke in females, and can sometimes worsen the behavioral side effects in males. (Nussbaum, et al., 2007) Patients with PWS and their parents should consult multiple specialists and take the time to find out what types of treatment will work best for their specific situation.

Bariatric surgery has been used in some cases with marginal benefits. It works for short-term weight loss, but overall has been observed to have more risks than benefits. Strict dieting and exercise are encouraged over the less-than-promising, more invasive surgery solutions. (Pereira, et al., 2009)

One of the best methods of dealing with the behavioral symptoms of PWS is distraction. Keeping the child occupied with other things can help them keep their mind off food. Getting him/her involved with sports or other physical activities can both help distract and improve physical well-being. Keeping a routine works well for some, because it brings security, but for some it can decrease quality of life. (Allen, 2011) However, due to the unique characteristics of each PWS individual, routines will typically work for the majority of cases.

Making a plan and establishing relationships between the family and specialists right after diagnosis can be helpful in improving the quality of life of the PWS patient. Since it has so many different aspects, it is advisable for the family to see multiple specialists, such as a cardiologist, a nutritionist, and a behavioral counselor. Many individuals with PWS are not able to live completely independent lives, so it is best for these connections to be formed early.

To date, no medicine has been discovered that is a long-term solution for controlling appetite, so the best that can be done at present is to control the dietary intake. (Chen, et al., 2007) Most PWS individuals have a strict reduced-calorie diet, between 600 and 800 calories per day for younger children and 800 to 1100 for older kids. (Pereira, et al., 2009) Weight and body mass index should be carefully monitored if possible, though

sometimes behavioral issues can make this problematic. Regular exercise is encouraged, as it improves both physical and mental well-being. (Chen, et al., 2007)

Detailed food logs are also very useful. Nutritionists can use this as a basis for keeping track of how the patient is doing, and as a way to keep accountability between the family and the specialist. (Pereira, et al., 2009) Creative solutions can be thought up to keep the child from feeling that their diet is monotonous, thereby improving his or her quality of life. Also, the patient must take vitamins to make up for the nutrients that are missed when living on such a low calorie diet. (Pereira, et al., 2009)

There are inherent problems when some of the behavioral aspects of PWS are compiled. As discussed, hoarding is a very common behavior, and when food is involved, the effects can be detrimental. Some of the PWS patients with a higher IQ are often clever about ways to get what they want. This tends to be problematic, as not only is it unhealthy behavior, it is also physically unhealthy. Methods of dealing with these issues include locking the kitchen, or seeking a behavioral specialist.

Tantrums are extremely common when PWS children are not given the food they want. However, there are some strategies to avoid or lessen the problem. Bargaining is acceptable and encouraged in these cases. The promise of a snack later in exchange for not eating a snack right then is a commonly used parental technique. However, using food to reward good behavior is not a good idea for those with this disorder, as it only compounds the problem. (Pereira, et al., 2009)

For many, a highly-structured eating schedule greatly improves the well-being of PWS children. Knowing exactly when to expect the next meal can provide piece of mind.

It is also good to occasionally allow “treats,” to break up the monotony. In addition, allowing the child to assist in the preparation of meals is encouraged, because it provides him or her with a feeling of control. (Pereira, et al., 2009)

Most adults with PWS are overweight, with a high prevalence of obesity. It is a difficult lifestyle to maintain. Death typically comes from complications associated with obesity, such as apnea or cardiorespiratory failure. Also, 2% to 8% of PWS deaths are caused by choking and gastric rupture. (Pereira, et al., 2009)

It is possible to live a happy, fulfilling life with PWS, though it is by no means an easy task. With a great deal of self-disciple, assistance from friends and family, or a combination thereof, it is certainly feasible that one could maintain a moderately healthy weight and lifestyle. Communal living is encouraged, as most adults with PWS are not able to live alone.

Nutrition is closely tied to successful and healthy living in every PWS case. In fact, nutrition is a crucial part of daily life for all individuals. The broad field of nutrition includes examination of cellular activities, immune system regulation, metabolism, and the interaction between genes and the environment. Associations between nutritional imbalance and many different types of disease have been established, such as various cardiovascular issues, cancer, and type 2 diabetes. A number of cases involving the unhealthy diet of a pregnant mother causing complications in the health of the baby have been noted. (Raqib & Cravioto, 2009)

The human body is relatively sensitive to chemical changes, and requires a certain amount of various types of chemicals each day. Vitamins, minerals, carbohydrates, and

protein are essential to a well-balanced diet. Since most PWS patients do not take in enough balanced nutrients (or at least they should not be, assuming they are following the strict diet set out for them), vitamins and other supplements are essential.

Given that weight and nutrition-related issues are so significant in the lives of PWS patients, this is a topic of research that would likely prove to be substantial. In the past, there has been a surprising lack of compiled nutrition-related data available, but new fields of study have grown and expanded to encompass these needs, such as nutrigenetics and nutrigenomics. These new disciplines have been used to manipulate foods in both quantity and quality. (Raqib & Cravioto, 2009)

An intriguing idea for a method of assisting PWS patients in keeping their weight within acceptable levels is the use of an appropriate, well-researched diet pill. It would have to be compatible with hormone therapy treatments, as many choose to place their children on growth hormones. Natural dietary supplements are preferred, if possible.

As of late, there has been an interest in a compound called capsaicin, found in cayenne pepper. A study was performed by researchers at Purdue University that involved twenty five adult male and female subjects, who each took a teaspoon of cayenne pepper in a meal. The addition of the cayenne pepper increased their body temperature and energy expenditure, which helped burn off calories. It has also been proposed that this supplement can help curb the appetite for the next meal. Scientists suspect that the capsaicin within the cayenne is the cause of these results. (“Eating spicy curry”, n.d.)

Dihydrocapsiate (DHC), a compound structurally similar to capsaicin and also found in chili peppers, is also being considered for possible weight loss assisting properties. It does not have the spicy flavor that capsaicin has, which may prove beneficial for those who have a low tolerance to spicy flavors. It also raises the metabolism, allowing the body to burn more energy. ("Can eating chillies", n.d.)

As of right now, there is no magic cure-all that can fix weight gain for the common man or for individuals with PWS. However, a natural compound such as capsaicin or DHC may be a step into finding a way to make our bodies more efficient in burning calories, which would prove extremely beneficial for PWS patients and other individuals who merely wish to lose a bit of weight. Perhaps the most positive aspect is that these compounds are natural, meaning that there is a lower chance of negative side effects that man-made medical remedies often cause.

Finding solutions to manage the weight gain of patients with PWS is crucial. Since natural dietary supplements are less likely to have adverse side effects and to interact with other medication, this would be an excellent place to search for answers until there is a cure. Therefore, I will discuss a hypothetical experiment that determines if the dietary supplement capsaicin would be effective as a weight loss aid for patients with PWS.

CHAPTER TWO

Methods and Materials

In the currently ongoing research being performed by Leutholtz and Willoughby, capsaicin and evodiamine are being studied for their effects on energy expenditure, hemodynamics, and markers of lipid oxidation both at rest and after a moderate amount of exercise. The weight loss epidemic and the desire to find natural substances that will function as effective weight loss supplements are the motivators behind this study.

The participants in the study are ten healthy men that lead active lifestyles, but were not on a routine exercise program for at least a year prior to the beginning of the research. Additionally, they are between the ages of eighteen and thirty, and at low risk for cardiovascular maladies. They had not consumed nutritional supplements for the three months prior to the study, excluding multi-vitamins.

The independent variables that are being used in this research are capsaicin, evodiamine, and a placebo. The dependent variables include the following: resting, exercise, and recovery energy expenditure, "heart rate, blood pressure, serum glycerol, free fatty acids, epinephrine, norepinephrine, and skeletal muscle levels of cyclic AMP, protein kinase A, and the vanilloid receptor." (Willoughby, et. al, 2011) As depicted in Figure 1, the samples will be taken at specific times before, during, and after exercise.

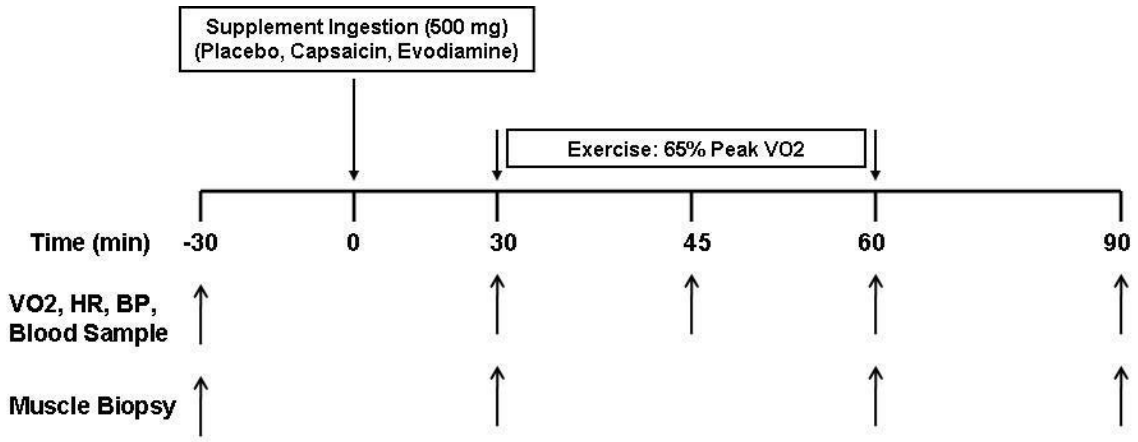


Figure 1. An illustration of the experimental protocol to be used in the study for each of the 3 testing sessions.

Additionally, the following chart shows the testing schedule.

Familiarization/ Entry (Visit 1)	Testing Session 1 (Visit 2)	Testing Session 2 (Visit 3)	Testing Session 3 (Visit 4)
Familiarization session	3-Day Dietary Intake Forms	3-Day Dietary Intake Forms	3-Day Dietary Intake Forms
Informed Consent Form.	Hemodynamic Measures.	Hemodynamic Measures.	Hemodynamic Measures.
Demographic Form	Muscle Biopsy	Muscle Biopsy	Muscle Biopsy
Health History Form	Blood Sampling	Blood Sampling	Blood Sampling
General Exam to Determine Qualifications to Participate in Study	Resting Energy Expenditure.	Resting Energy Expenditure.	Resting Energy Expenditure.
Determination of Height and Body Weight	Ingest 500 mg of Supplement	Ingest 500 mg of Supplement	Ingest 500 mg of Supplement
Assessment of Body Composition	Treadmill Exercise	Treadmill Exercise	Treadmill Exercise
Assessment of Peak Oxygen Consumption	Reported Side Effects From Supplement Questionnaire	Reported Side Effects From Supplement Questionnaire	Reported Side Effects From Supplement Questionnaire

An initial session and three testing sessions are currently in progress for each subject. The initial session is primarily to gather demographic information about each subject, and to get the preliminary measurement. The testing sessions are, of course, where the raw data is gathered.

Since treating the symptoms is the best that can be done at this time for PWS patients, finding new and better medical solutions to try to deal with the weight gaining that comes with having PWS is crucial. It would be beneficial to perform a study to determine if the use of a natural dietary supplement, such as capsaicin, is effective in the attempts at weight loss of individuals with PWS. Therefore, I am creating a theoretical study that could be performed to pursue these issues. From this point onward, for the sake of clarity, the project will be described in a sense that implied that the research is actually going to occur.

In this hypothetical, proposed study focusing on PWS patients, four test groups will be studied. A control group will be established, and members of this group will be given a placebo. The second group will be given a 500 mg dosage of capsaicin, and will only exercise the amount that they normally perform on a daily basis. The third will receive a placebo, and will exercise for an allotted amount of time that will be expounded upon later in this proposal, and the last group will receive 500 mg of capsaicin and will be asked to exercise as well. Having these four test groups will hopefully show if the capsaicin successfully leads to weight loss, and, if so, will also reveal if an increased amount of exercise leads to an even greater amount of weight lost.

A total of three testing sessions and two informational meetings per subject will be performed, with a seven to ten day gap between each session. The first meeting with

the PWS patient and his or her family will center on explaining the process to them, and making sure that all questions and concerns are addressed. The workout performed in the three testing sessions should entail a moderate amount of aerobic exercise. Thirty minutes of light jogging on a treadmill should suffice, followed by a fifteen minute cool down period. Finally, the last session will involve any concluding questions, the final weight will be taken, and the take-home survey, which will be discussed later, will be handed in.

The following will be measured at each testing session:

Initial weight,
Initial heart rate and blood pressure,
Weight after thirty minutes of exercise and fifteen minutes of cool down,
Blood pressure and heart rate after the cool down period.

Therefore, the research schedule would look something like this:

Initial Session	Testing Session 1	Testing Session 2	Testing Session 3	Final Session
Initial questions addressed and answered Participants are given the survey	Initial measurements taken 30 minutes of exercise performed 15 minutes of cool down Final measurements taken	Initial measurements taken 30 minutes of exercise performed 15 minutes of cool down Final measurements taken	Initial measurements taken 30 minutes of exercise performed 15 minutes of cool down Final measurements taken	Survey turned in Any remaining questions answered Final weight taken

Potential subjects for this study can be of any race, gender, or socioeconomic status. As a matter of fact, it would be ideal to have a diverse subject pool, because the data will be less likely to contain bias that would inherently come from a group of subjects with too many things in common. For example, it may be harder for women to lose weight than men. If this is true, and the majority of the subjects are women, then the

results could portray capsaicin to not work as well as it might have worked if more of the subjects had been men. Therefore, if possible, it would be best to have a variety of people for this study, with half of them being female and the other half male. Healthy subjects between eighteen and thirty years of age will be recruited, (Willoughby, Leutholtz, 2011) There will be five subjects from each group, making a total of twenty subjects. This should give enough to give variety, but not too much that the study becomes too expensive.

Application for this research must be strictly voluntary, and there will not be a monetary reward for participation. The best method of procuring subjects would be to post information about the study at dietary clinics, allowing the information to be viewed by potential subjects, but not forced upon them. Information could also be posted online. If subjects are not forthcoming, the decision to not include a monetary reward could be reconsidered, but the amount given to each participant should not be enough to create bias from any particular socioeconomic class.

There is always a possibility that there may be side effects from any type of medication. However, since the supplement being used is natural and is currently available as an over-the-counter nutritional supplement, the likelihood of an adverse reaction is fairly low. Additionally, the researchers overseeing the study will have already taken a training course in CPR, and there will be protocol set up in case there are any issues.

Another possible aspect of this research involves a questionnaire. This will be very loosely based off the research performed by Allen in 2011, as discussed in chapter one. (Allen, 2011) The PWS individuals and their families will be given the survey at the

first meeting, and it is to be completed and given back to the researchers at the last meeting. The survey will be a requirement, but answering individual questions on it will be optional. Essentially, the patients and their families are only required to put the information that they wish to include.

The first portion of this survey will focus on the medications the PWS patient is taking. This can be compared to the results from the study, so that if there are outliers in the results, they can compare them to the surveys to see if there are any correlations. The PWS patients, their family members, or a combination of these will be asked to create a list of how much medication he or she takes, and the dosage levels.

Also, the lifestyle and habits of the PWS patient will be investigated. Insight into a PWS patient's family life can give a personal and holistic perspective to the research. How the PWS individual and his or her family deals with the eating and behavioral issues could potentially affect his or her performance in the research. This section will include a number of questions about the patient's home life, as they will be asked to fill out a daily exercise and diet log. A subject with an active lifestyle and limited access to food is likely to lose more weight than one that does not exercise on a daily basis and has a higher calorie intake.

Finally, the last section of the survey will include a section where the patient and his or her family can write any additional information they feel will be useful in the study and can ask any further questions, which can be answered at the last meeting. This information can also help when studying the raw data received from the study done in the lab.

Analyzing the raw data will focus primarily on how much weight the subjects have lost, since that is the main objective of testing the supplement. If the group that took capsaicin and exercised loses the most weight, then there is most likely a strong correlation between weight loss and using capsaicin as a dietary supplement.

The null hypothesis would be that there is no correlation between weight changes in patients with PWS. On the other hand, the desired alternative hypothesis in this experiment that would allow us to reject the null hypothesis would be that capsaicin causes individuals with PWS to lose weight. Ideally, the group that takes capsaicin and does not exercise will lose more weight than the subjects that did not exercise and took the placebo. That will show the strongest relationship between capsaicin and weight loss. Also, the surveys will be analyzed and compared to the results, which can help when attempting to understand why anomalies and potential outliers may have occurred.

CHAPTER THREE

Results and Analysis

The most plausible method of analyzing the results of a hypothetical experiment is to investigate the possible outcomes. The results show a correlation between taking capsaicin and losing weight, thereby supporting the alternative hypothesis, or they might show the opposite (patients could perhaps gain weight from taking the supplement; another, less desirable alternative hypothesis), or the data may possibly show no correlation, which could not be used to reject the null hypothesis.

Since a full scale research project is not available to the author at this time, creation of hypothetical results becomes necessary. Additionally, due to the difficulty of ascertaining precisely what results there would be, it would be advantageous to examine the most likely possibilities. Since there is one primary source for data, the weight of the patients, a pool of hypothetical patients was devised, with the weight conjectured to demonstrate each scenario.

The three categories under investigation in relation to the supplement's effect on the patient's weight loss are: ineffective, effective, and adverse. The ineffective supplement would cause the subjects to generally maintain weight, meaning each participant's weight would remain fairly constant over the course of the study. The capsaicin would be considered effective if it causes the individuals to lose weight, to any

degree. Adverse would entail a weight gain, and therefore would be the least desired result of the study.

The following charts and descriptions elaborate on these different scenarios, and would serve as a rubric for the author should an actual study, rather than the hypothetical, be pursued.

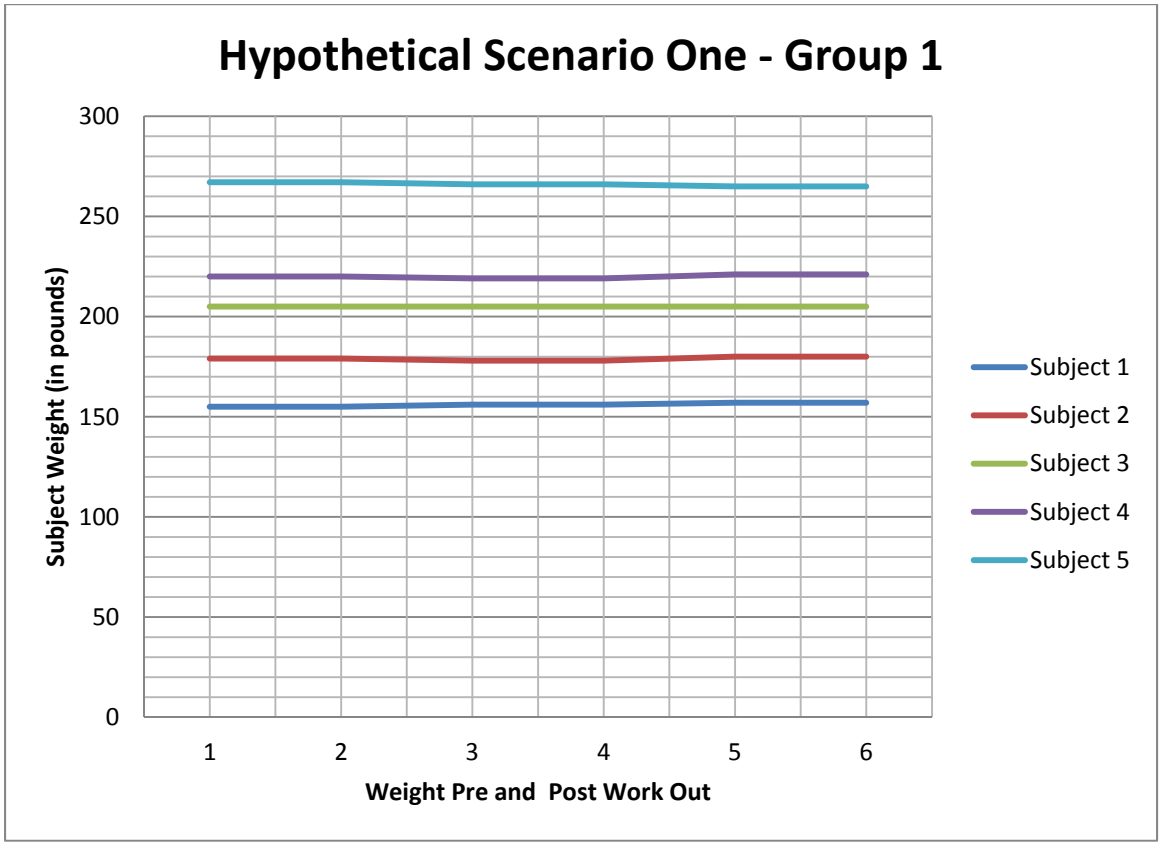
For the sake of clarification, the x-axis on each graph is delineated as follows:

1: weight at session one, pre-work out
2: weight at session one, post-work out
3: weight at session two, pre-work out
4: weight at session two, post-work out
5: weight at session three, pre-work out
6: weight at session three, post-work out

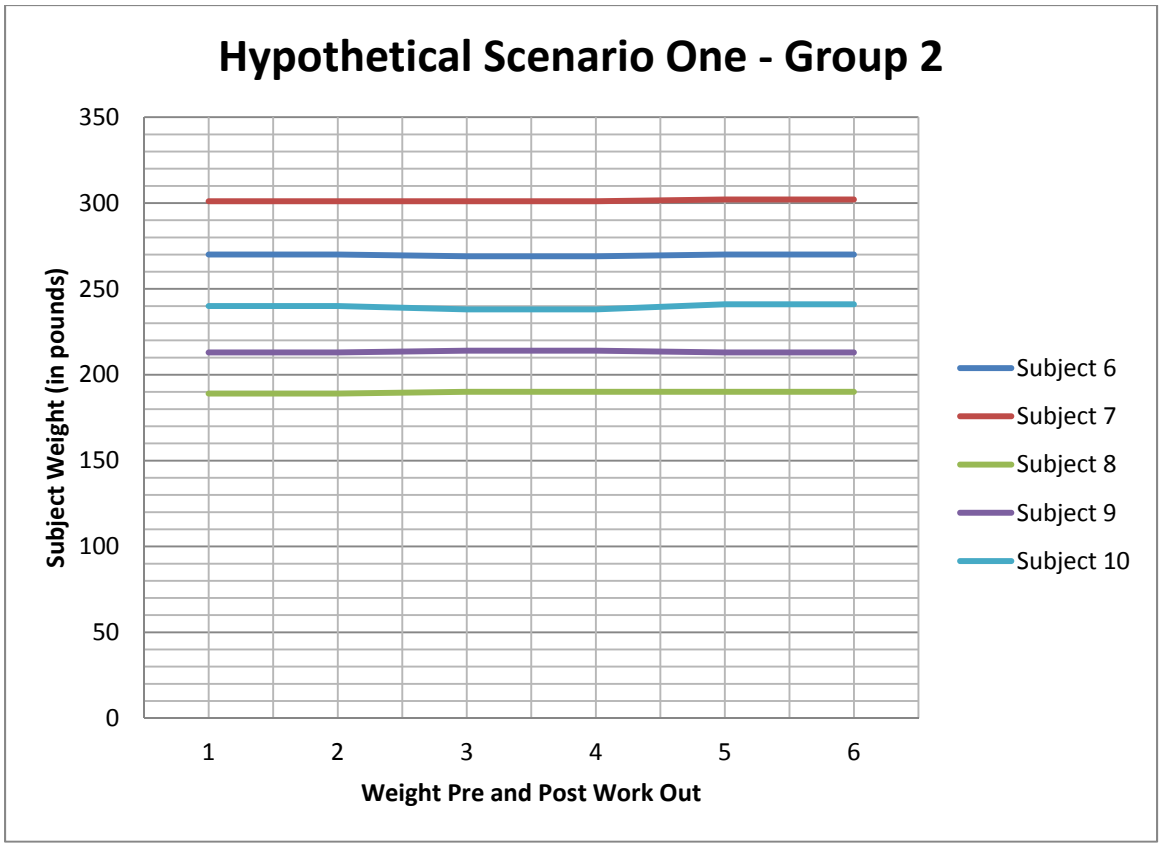
In groups where no work out was required at the research facility, there is no weight change between pre and post work out.

Hypothetical Scenario One

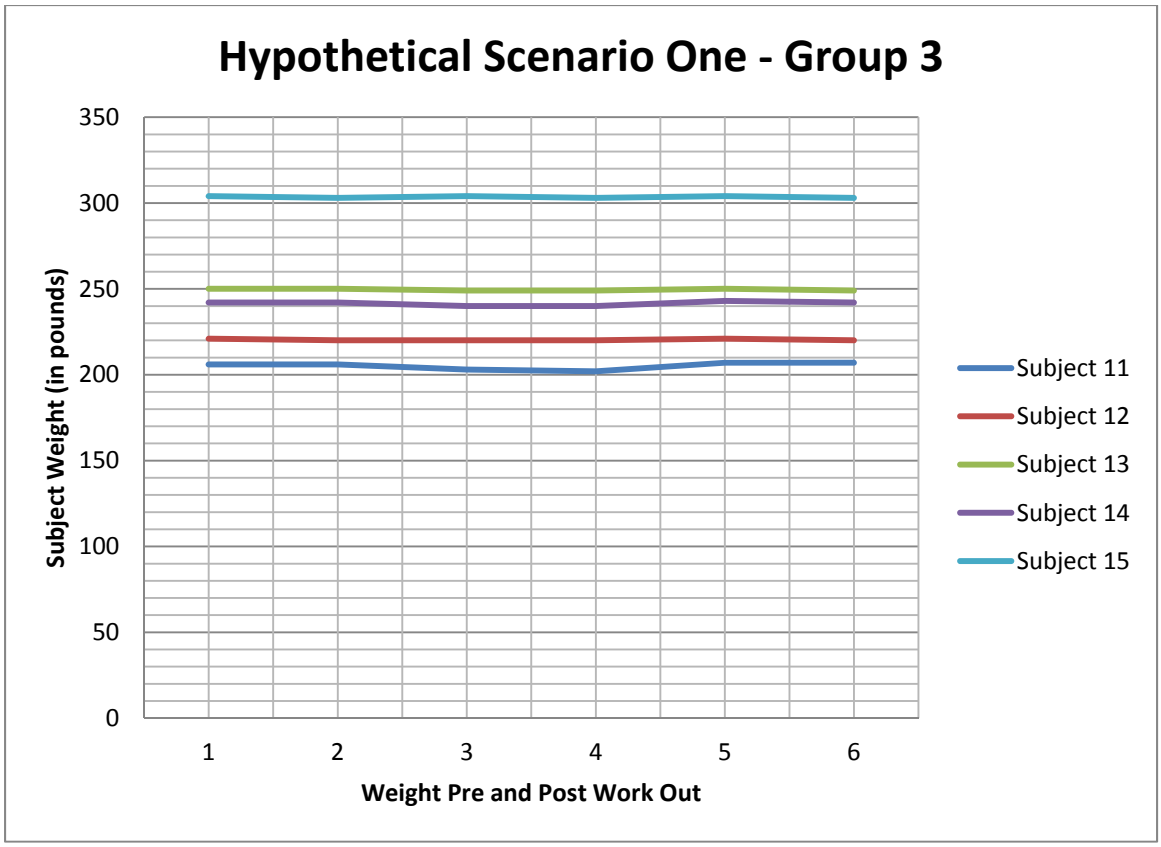
The supplement would be considered ineffective for use in these circumstances if the results came back in a manner similar to the following hypothetical results:



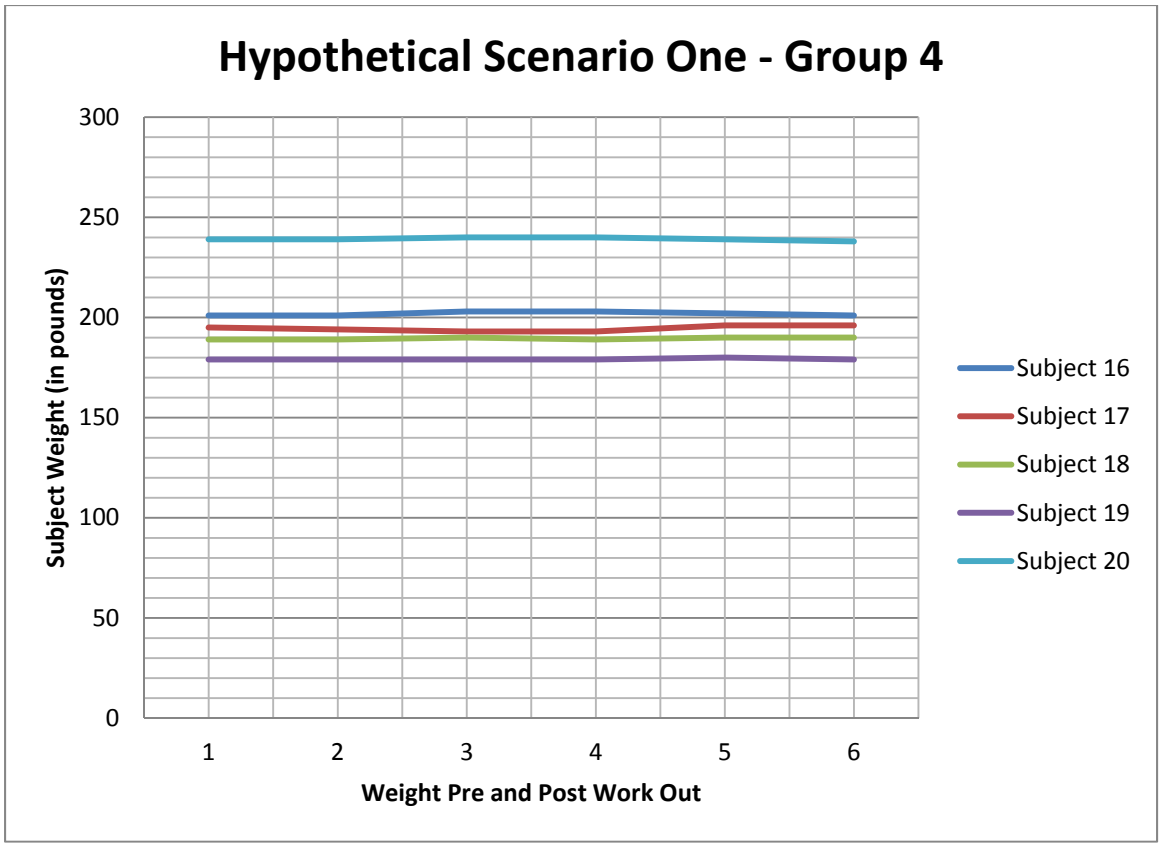
Group one in hypothetical scenario one was given a placebo, and did not perform additional exercise. Therefore, no noticeable trends in weight gain or loss are observed, because there is no difference in their behavior, chemically or physically. Maintenance of initial weight range would be noted by the lack of strong deviation of the lines on the graph.



Group two was given a 500 mg dose of capsaicin, but the participants were not asked to change their current level of daily exercise. If the supplement worked, it would depict a slight decrease in weight in a majority of participants. Since the supplement is ineffective in this hypothetical scenario, there is no substantial weight gain or loss on the graph. Again, the final weights are very close to the originals, with little change in between.



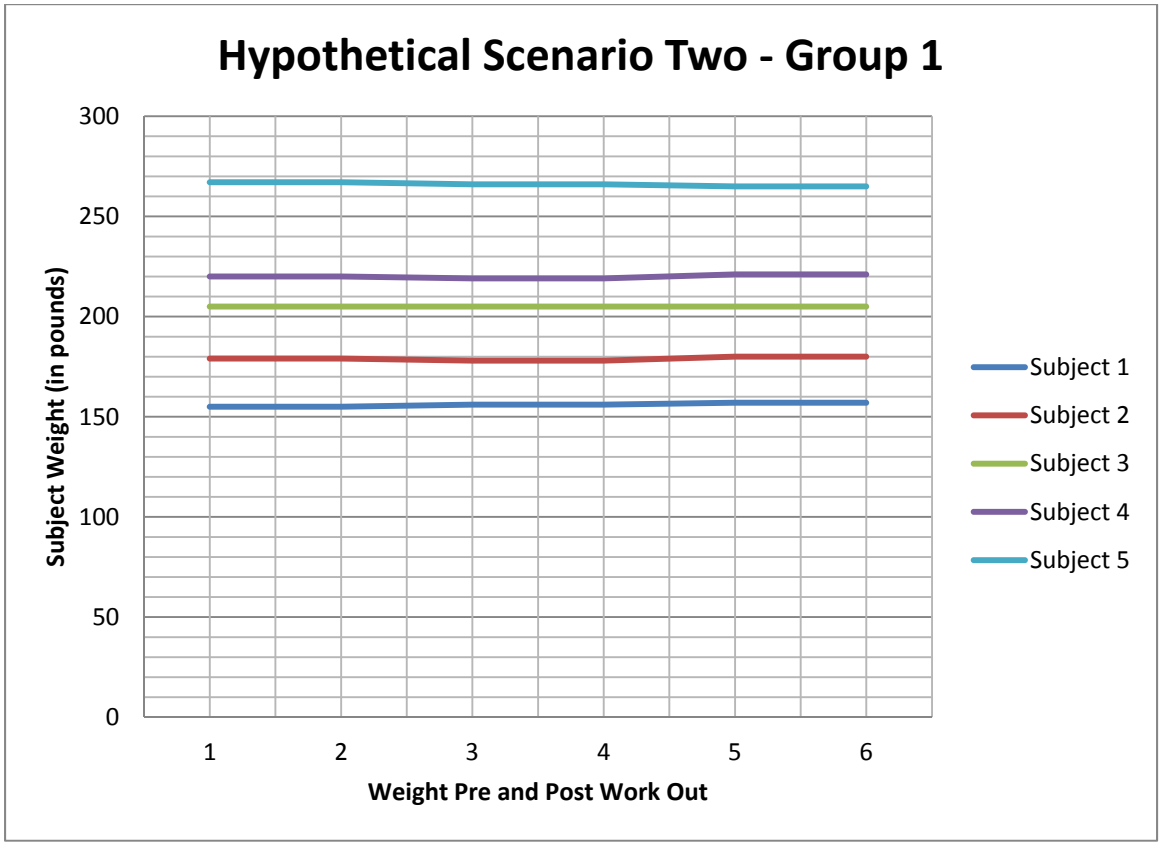
The potential data above is from a hypothetical subject pool that is given a placebo and asked to exercise the allotted amount for this study. The patients might show a slight amount of weight loss from the exercise, but they are unlikely to experience a sharp weight loss or gain. One variable that could affect the results of this group would be if the participant's general exercise level varied significantly from the level assigned to the group for the purpose of the study; i.e., if he or she decided to exercise more in his or her free time.



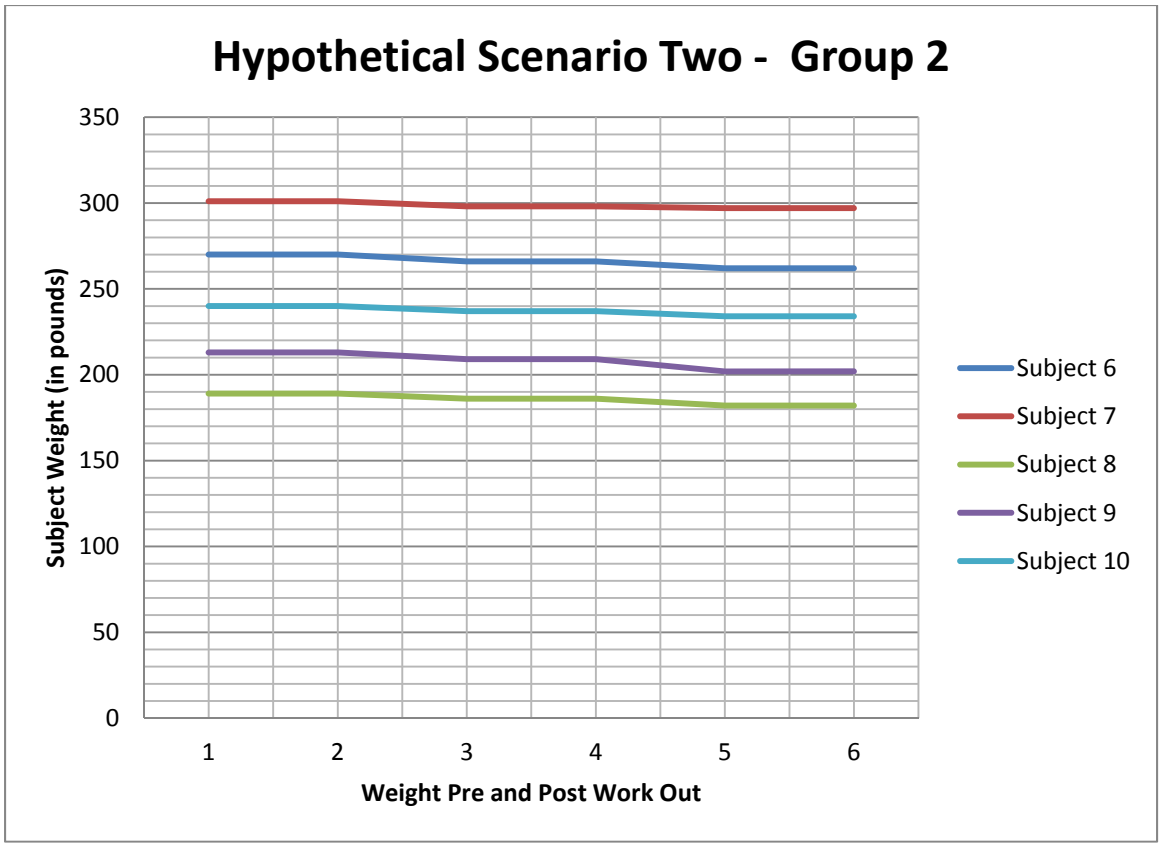
The last group in this scenario was given the supplement and asked to exercise with our researchers. This group, when compared to the others, should show the greatest amount of change, if the supplement is successful. In this scenario, there is not a substantial change in weight for this group, which would indicate that capsaicin likely does not significantly affect weight gain or loss. Whether this applies to the population as a whole, or if this merely applies to patients with PWS, would require further research.

Hypothetical Scenario Two

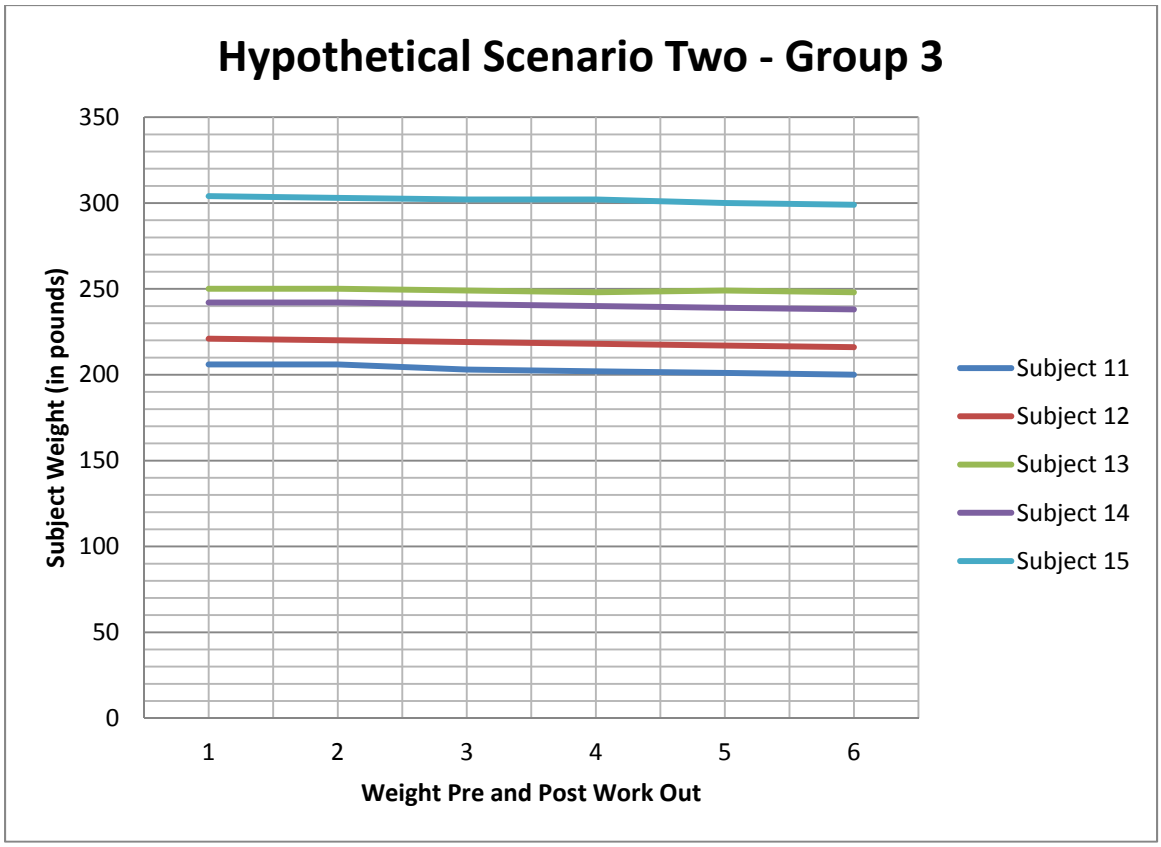
The following hypothetical results represent the desired outcome of the proposed study:



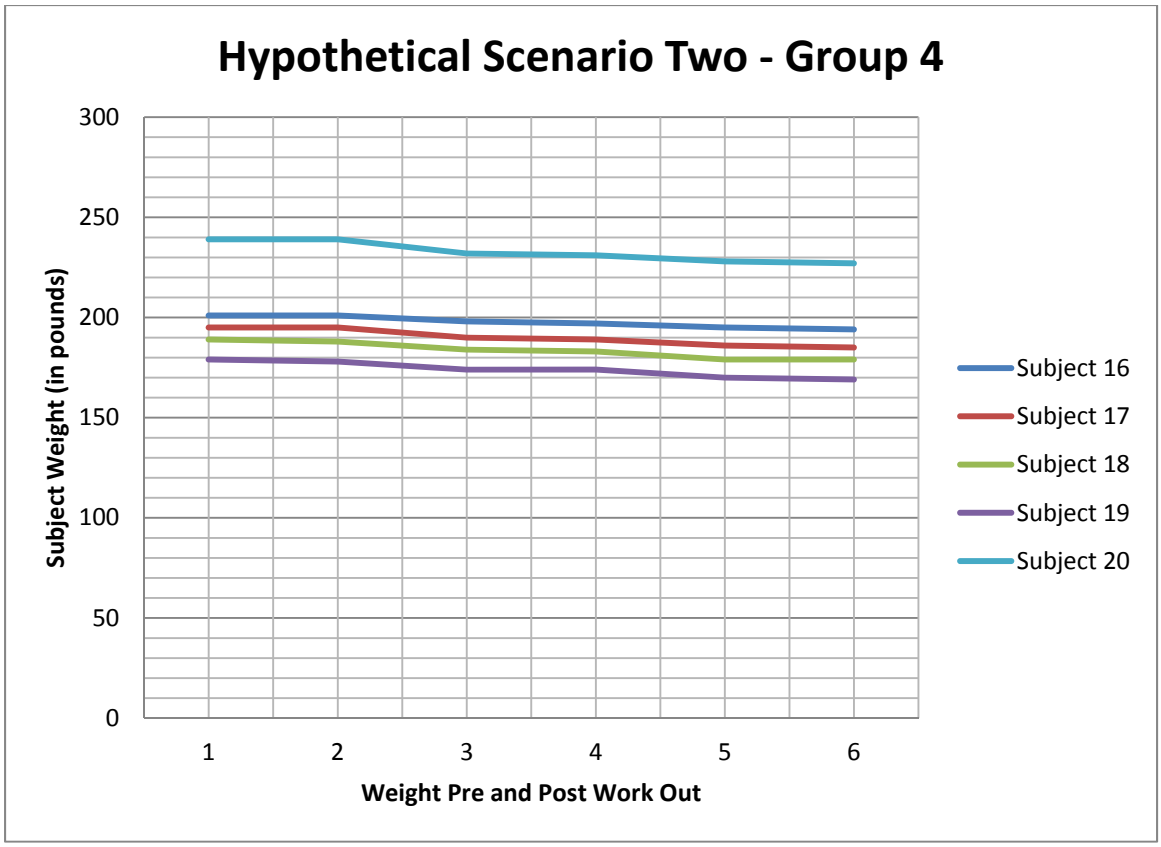
Group one of this scenario was the control group, and was therefore given a placebo and did not perform extra exercise. They did not show any significant change in weight. In fact, group one for all these hypothetical scenarios will have similar results, because the subjects do not take capsaicin. This is also true for group three.



Group two was given the supplement, but was not required to exercise in the lab. If the capsaicin is an effective weight loss supplement, the participants would ideally show at least some degree of weight loss. As the hypothetical data above shows, there is a slight downward trend, which would indicate a positive outcome and be beneficial for the individuals with PWS.



The third group was given the placebo and asked to exercise. This would potentially cause a slight decrease due to exercise, but the positive result could best be attributed to the increased exercise routine and is not related to the supplement.

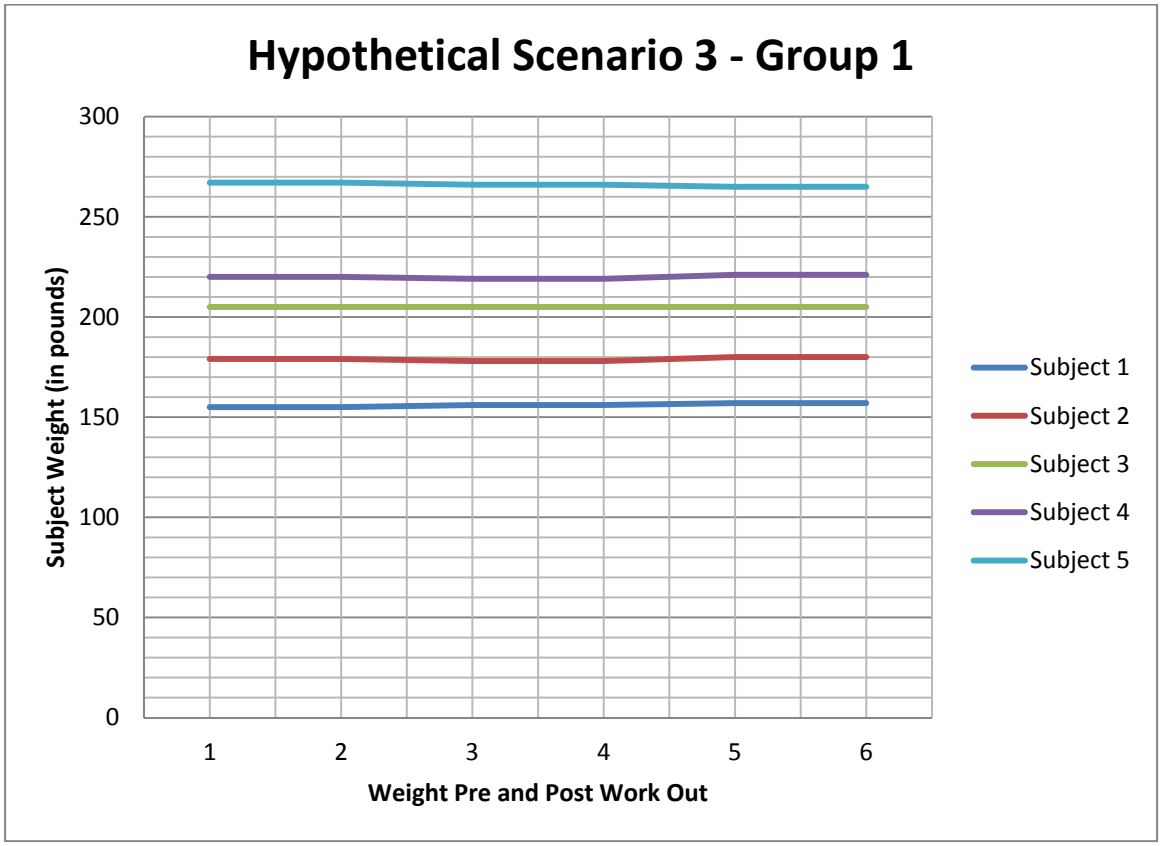


In these results, the control group performed as expected, in that there was a fairly constant weight level for each individual. Both the group taking the placebo with exercise and the group taking capsaicin without exercise collectively lost some weight, and the group with exercise and the supplement lost a respectable amount of weight. These results would demonstrate a fairly strong correlation between the supplement and weight loss in patients with PWS.

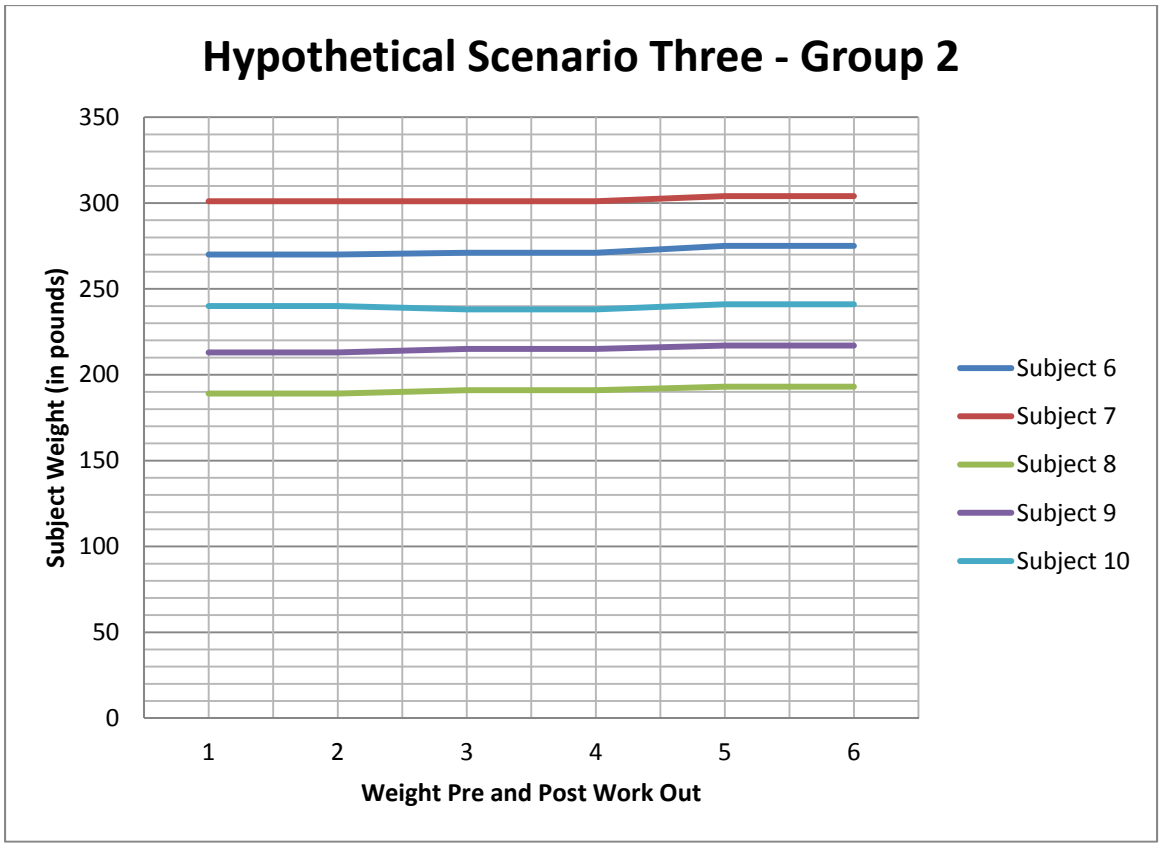
Overall, when compared to the control groups one and three, the subjects seemed to lose noticeable amounts of weight. This would be a strong indicator that capsaicin was the cause for this weight loss, and that this may be an effective weight loss supplement for individuals with PWS.

Hypothetical Scenario Three

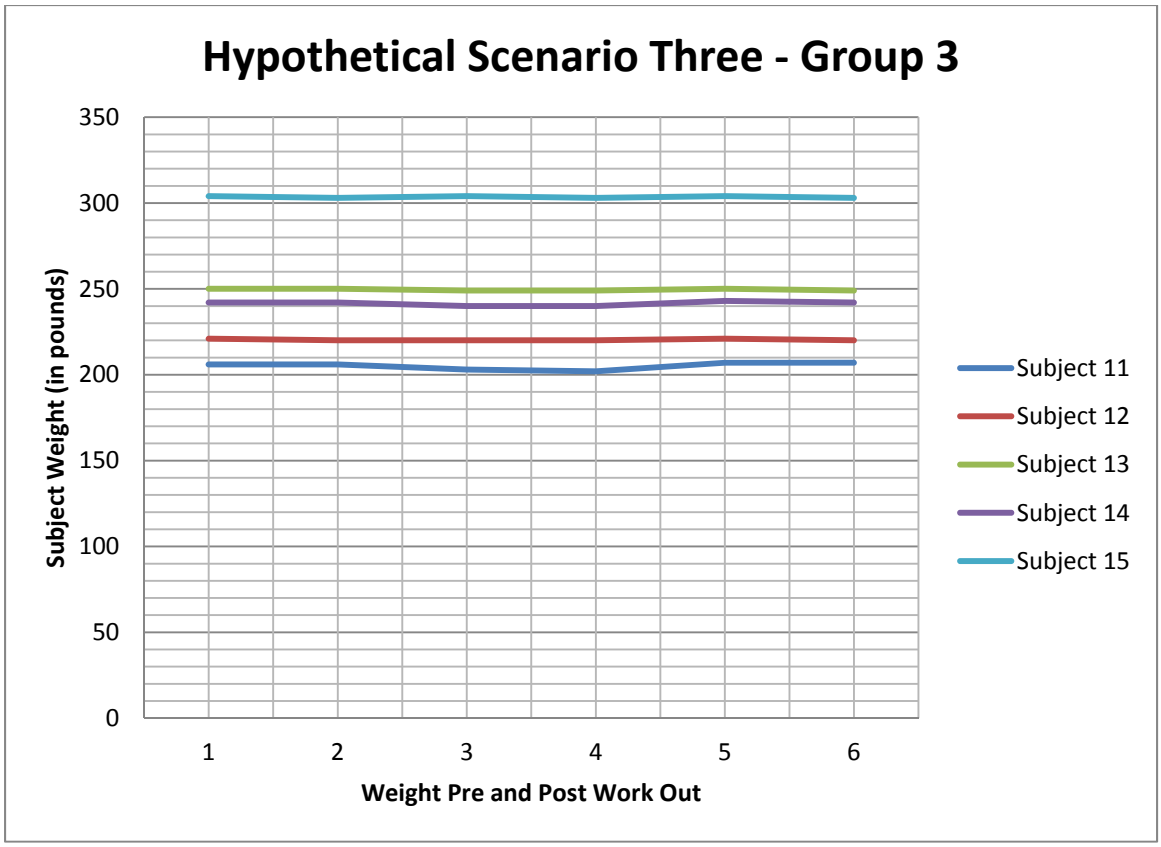
It is also possible to have the following results:



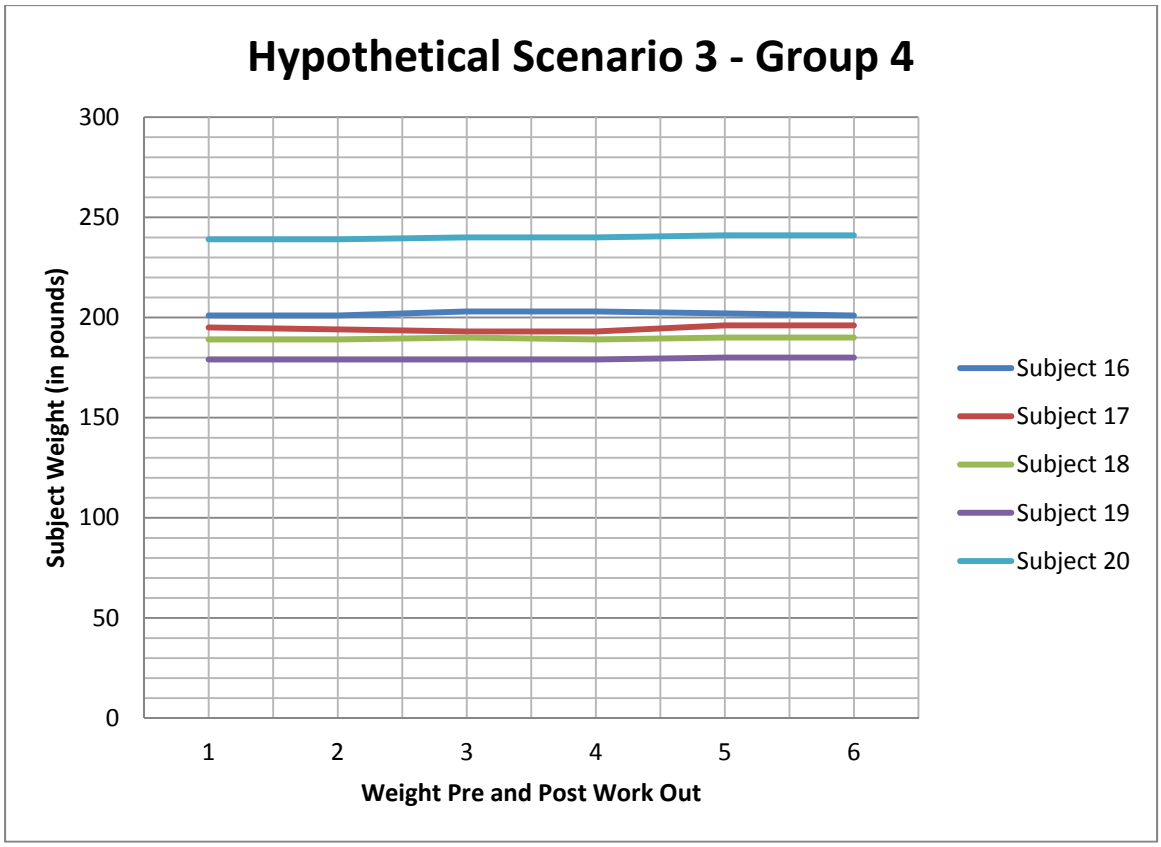
As before, group one is given a placebo and not required to exercise, and is used as the control group. These individuals should not show a considerable amount of weight loss or gain, and function similarly to the other two control groups.



The second group in scenario three is given the capsaicin, but is not asked to exercise. These results indicate an adverse effect; the participants seem to have gained weight. Obviously, this is not a desired result for individuals with PWS, since these patients already experience difficulty in trying to lose weight. A supplement that would cause them to gain weight would be less than desirable.



The third group received a placebo and exercised the required amount of time. These individuals will perform approximately the same as the ones from the previous group threes: mild, if any, weight loss.



The final group from scenario three took the supplement, exercised, and still gained weight. These results would lead to the plausible conclusion that the supplement would not be useful in PWS patients who are attempting to lose weight. This would be a good indication that capsaicin is not a good weight loss supplement for individuals with PWS, and alternative treatments should be studied instead.

There is an inherent amount of variability between each subject's results. Since the group of subjects is intended to be as diverse as possible, it is extremely unlikely that they will all have a similar reaction to the supplement, and they certainly will not have identical lifestyles. Some of the individuals might unintentionally increase their amount of daily exercise, since they know that they will be weighed at the testing sessions, and they wish to show progress.

There could also be a few patients that would place more confidence in the supplement, and therefore might not exercise as much because of it. These individuals could potentially gain weight, if they were taking the placebo. This is why there are multiple subjects for each category: so that their results can be compared to each other and outliers identified as such.

Additionally, the amount of weight lost by those who used capsaicin would vary between individuals. This would depend on each person's metabolism; each person's body interacts with the environment slightly differently, so some could potentially lose more weight than others. In fact, it is entirely possible for the supplement to cause one person out of the group to gain weight, while the rest lose weight. This outcome would also serve as cause for further research.

CHAPTER FOUR

Conclusions

Perhaps the most direct way to deal with Prader-Willi Syndrome (PWS) at the phenotypic level is to simply talk with the patients and their families one-on-one, and determine how they are coping with the disease, what modifications they have had to make in their daily activities, what successes they have experienced, and what has not worked. This is the first step in personalized care; since each patient will be unique, finding out how they cope with the disease is the best way to decide how to treat the individual.

This individualized approach lends itself to a survey methodology. In conducting research on a broad scale, it is logistically difficult to speak with each person at length about how they manage with PWS. Though in-person interviews would be the ideal, the surveys are a good second choice as they facilitate the collection of the information the researchers may not be able to gather otherwise, as well as giving the individuals with PWS a sense of privacy, since it is often difficult for patients to speak directly to others regarding their own personal struggles.

The survey included in the proposed research incorporates a section where the PWS individuals and their families could indicate which medicines he or she is taking, as well as what medicine they have taken in the past, and, if it was unsuccessful, why it did not work in their opinion. Knowing what medications the individual has taken in the past assists the research team in identifying whether there are hidden or masked patterns in the data.

For example, there could be a particular type of medicine that causes the patients to have more difficulty in losing weight, and this could be evident in the data collected. The research team would then know that the reason the subject did not lose as much weight had more to do with the medication, as opposed to thinking that the capsaicin did not work as well as it did in other patients. Conversely, the patients could be on other medications that result in weight loss, and could skew the results from the study, making the results appear more successful than they actually were. Identifying what medication each patient is on currently, or has taken in the past, can assist in avoiding these sorts of mistakes. This is generally accounted for in studies.

Part of the difficulty in finding a cure for PWS is that there are multiple methods of inheriting the disorder. Since the disorder can come from imprinting errors, deletion, or uniparental disomy, perhaps the best manner in which to find a cure that works efficiently for each type is to conduct research for each segment. However, since the manifestations have a great deal of overlap, the research for treating general symptoms could be related as well.

The conclusion of this research would undoubtedly be dependent upon the results of data collected. If capsaicin did not show a positive correlation to weight loss, then the next step would likely be to repeat the research using a different supplement. However, if the supplement did appear to aid in weight loss, then it could prove extremely beneficial for PWS patients. Medicine that would help them lose weight would be welcomed, because it is so hard for those who suffer from PWS to keep their weight at a healthy level.

It is relevant to point out that it is possible for the patients to gain or lose weight, even if they are a member of the control group, because some variability is both possible and probable, particularly in studies with human subjects. They might subconsciously decide to work harder at eating better and exercising more since they know that they will be weighed at their next session, causing them to lose weight, even though they might be in the placebo group. On the other hand, the patient might not work as hard to live healthier, thinking that the supplement would take care of the weight loss for them, which could lead to unexpected weight gain.

Since each patient is different, finding a "cure-all" that works for everyone is virtually impossible. Therefore, doctors must do the best they can to find out as much as possible about the individual's specific needs, and identify a way to treat him or her that suits the patient best. Thus, even if the capsaicin is found to aid in weight loss for the majority of the research group, further research would be needed to determine the potential for replication to a much larger population of PWS patient.

Since capsaicin is found in chili peppers, it would be acceptable to sell over the counter as a dietary supplement, because it is unlikely that it would interact negatively with other medications. The only concern would be for those that are allergic to chili powder. It would be unwise to allow them to take capsaicin supplements, though it would depend on the exact component in the powder that they were allergic to. Regardless, it would likely be advantageous for these individuals to investigate other weight loss supplements.

The layout of this research is fairly straight forward, and could be modified for any number of uses. The data collected could be changed to consider specific variables and how they affect a small group of individuals, which is the method the author used to modify the research by Willoughby, et. al. Additionally, a different supplement could be exchanged for capsaicin, and the same parameters applied to determine if it showed a positive correlation to the desired outcome for either a specific group of people, or for the general public. This is ideal, because if capsaicin does not work, the head of this research may decide to try something else to see if it works better or worse than capsaicin. It would simply be a matter of identifying an alternate supplement, locating new subjects and re-starting the experiment.

Ideally, the ultimate goal for those working with PWS would be to cure the disease. There are inherent issues to determining out how to cure this disease, because by the time one discovers that the individual has this disorder, it would be difficult to make a treatment that could work backwards and fully cure the patient. The only authentic way to ensure that the genetic information is all there would be through genetic engineering, and that contains an entirely different set of challenges ethically, financially, and more. This is an open field of research that needs to be undertaken, because if an uncomplicated, efficient, and inexpensive method of eliminating this disease can be discovered, then this would of course be the most desirable course of action.

The survey is a central component to this research, as mentioned previously. In the case of the PWS patient, it would be important to include a section where dietary habits are discussed. Since the PWS individual's interaction with food is so essential, investigating how each individuals deal with the disorder is very important, because it

can determine areas needing further research. Knowing what the patients struggle with can show researchers what needs to be studied, and finding out areas where a majority of patients are doing well can keep scientists from studying areas that may not need their attention as much as others.

A good example of this scenario would be hypopigmentation. There would be little reason to extensively research a method to correct this aspect of PWS, because that is likely not the major concern for most patients and their families. Time would be better spent examining ways to fix weight gain problems, to deal with the autism-related side effects, or the behavioral issues.

Knowing that they are not alone is perhaps the most encouraging information that can be given to PWS patients and families. Any research group or physician should invest time identifying a short list of support groups and online resources, and have them available to the participants, should they want them. While this is not necessarily a component of the research, it is essential to provide holistic support to those suffering from PWS. The Prader-Willi Syndrome Association (USA) would be an excellent place to direct patients to, as the association has general information about the disease, information about other research that is currently being conducted, and resources that the families can use to get in contact with others living with PWS.

If a test could be established that identified the disorder early, and if the disorder was reversible in an inexpensive, effective way, then a large portion of time and resources would be shifted over to researching these methods. However, the research to treat the disease is most effective at this time, and studies such as the one that was

described previously are extremely helpful in determining what can be used to help individuals with PWS live as comfortably and well as they possibly can.

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