2013

Is Reduction of Caffeine Intake Effective in Reducing the Symptoms of Panic Attack in Panic Disorder Patients?

Elizabeth Wasson
Philadelphia College of Osteopathic Medicine, elizabethwas@pcom.edu

Is Reduction of Caffeine Intake Effective in Reducing the Symptoms of Panic Attack in Panic Disorder Patients?

Elizabeth Wasson, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences—Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 2, 2012

ABSTRACT

Objective: The objective for this selective EMB review is to determine whether or not the reduction of caffeine intake is effective in reducing the symptoms of panic attack in panic disorder patients.

Study Design: Review of three English language randomized control trials published in 2007, 2008, and 2009.

Data Sources: The double-blind placebo-controlled randomized control trials were obtained via PubMed.

Outcomes Measured: The prevalence of a clinical panic attack. Pre and post caffeine/placebo administration questionnaires were given to the participants. These surveys included the Subjective Units of Disturbance Scale (SUDS) and the Diagnostic Symptom Questionnaire (DSQ). These studies were modified for use with the DSM-IV definition of a panic attack.

Results: None of the patients who ingested the placebo showed evidence of a clinical panic attack. This was a consistent finding in all three studies. A panic attack was not experienced by any of the control subjects in the 2008 and 2009 studies. Two of the control subjects experienced a panic attack in the 2007 study after ingestion of caffeine. Finally, the panic disorder patients experienced a panic attack at frequencies of 60.7%, 52.0%, and 58.6%, in each of the studies, after administration of 480mg of caffeine.

Conclusions: All three studies showed sufficient association of ingestion of 480mg of caffeine with the induction of a clinical panic attack those afflicted with panic disorder. Although there is strong evidence showing that ingestion of caffeine in a patient with a panic induces a panic attack, there is no evidence showing that abstinence from this chemical reduces panic attack incidence. This is due to the fact that no credible scientific studies have yet been designed to show this information.

Key Words: Panic Disorder, Panic Attacks, Anxiety Disorder, Caffeine

INTRODUCTION

Panic Disorder is a condition defined by erratic episodes of profound anxiety, coupled with physical signs and symptoms, also known as panic attacks[1]. These signs and symptoms include chest pain, palpitations, profuse sweating, shaking, difficulty concentrating, shortness of breath, choking sensation, abdominal discomfort, fear of dying, and sensing a loss of control[2]. Not only can these symptoms be physically uncomfortable, they can also interfere with a person's daily activities. Oftentimes a patient afflicted with this spectrum of symptoms fears having a panic attack, especially in public, and will go to extreme lengths to avoid being in public when the attack comes on[1]. For this reason, these patients often develop a fear of being in public, let alone leaving their own homes. Because it is often difficult or impossible for this person to predict when they will have another "attack", there is a secondary development of agoraphobia, or the fear of being in public places[1]. In addition to the timing being unpredictable, the frequency of attack is also unpredictable. These panic attacks can come as frequently as multiple times per day, or as little as a few per year[1]. This all fuels the uncertainty and further anxiety surrounding panic disorder patients. The symptom profile and subsequent secondary illness attest to the severity of this mental illness and the patient's need to receive proper treatment.

Physician Assistants should be comfortable with the diagnosis and treatment of this anxiety disorder for multiple reasons. One of the reasons for concern is the epidemiology of this disease. Panic Disorder is estimated to affect 2.7% of adults in the United States, at an estimated 6 million people[3]. There is a lifetime prevalence of 1-3%, with a slight predominance in female patients[4]. These statistics attest to the importance of awareness by Physician Assistants, as well as the medical community. Patients often present first to their primary care provider seeking treatment for mental illness before reaching out to mental health specialists. This is one reason why Physician Assistants

need to be aware of current treatment recommendations. Another point of importance is the cost of care for this specific patient population. Exact numbers for the cost of panic disorder management worldwide are not available; however, the cost of mental health care for all Americans in 2006 was found to be 57.5 billion dollars[5], with a large percentage of those dollars being allotted for the treatment of anxiety disorders[5]. These staggering numbers also demonstrate the need for awareness and support of mental health amongst health care providers. A final rationale for support of this disease is the number of healthcare visits per year related to the spectrum of symptoms and secondary issues. Although there is no current data showing the number of health care visits per year for treatment of panic disorder, multiple studies have shown that patients affected by panic disorder present to their primary care physicians 3-5 times more than the average person, and to the emergency department 6 times as often[5]. This trend is thought to be due to the similarity of symptoms shared by panic attacks and other cardiovascular or respiratory conditions[7]. This data further supports the need for appreciation and knowledge of panic disorder amongst Physician Assistants.

Like many other mental illnesses, the exact etiology of panic disorders is unknown; however, there have been multiple studies that link certain genetic abnormalities, as well as various environmental changes, to the root cause of panic disorder[1]. One theory proposes that lactate levels may somehow play a role, as a result of a study that showed induction of a panic attack in known panic disorder patients after the infusion of lactate[4]. Another possible etiology involves abnormally elevated noradrenergic impulses to the locus coeruleus[6]. Both etiologies can result in a type of malfunction of the nervous system in this patient population. There is also a known disruption of serotonin, norepinephrine, and/or γ-aminobutryic acid (GABA) levels in these patients, most demonstrated by a high positive response to drugs formulated to alleviate the dysfunctions in these neurotransmitter levels[1]. Furthermore, MRI studies have shown involvement of the temporal lobes

during panic attacks, most notably in the amygdala and hippocampus regions[1]. Because the etiology is still not entirely understood, there is continued room for research on treatments for this patient population.

There are a number of treatments designed to reduce the symptoms experienced by those afflicted with panic disorder. The mainstay of treatment as approved by the FDA for this disorder is either Xanax (Alprazolam) or Paxil (paroxetine)[1]. Though Xanax is a sufficient option, there is growing evidence to support of the use of selective serotonin re-uptake inhibitors (SSRIs), such as Paxil, for treatment of panic disorder[1]. Any of the SSRIs are a viable option for treatment, though Paxil is the one specifically approved by the FDA for this use and has the quickest onset of action of the SSRIs[1]. One down-side to the use of SSRIs for mono-therapy is that many of these drugs take time to build therapeutic doses in the patient's system[4]. For this reason, it may be indicted to use a drug such as Xanax as a supplemental therapy until sufficient doses of SSRIs can be achieved[4]. If a patient fails to respond to treatment with one of the first line agents, clinicians should try other SSRIs or benzodiazepines (Xanax)[1]. If the patient fails to respond to repeated attempts at treatment with mono-therapy, health care providers can do a trial of combination medications, such as an SSRI and a benzodiazepine[1].

Though there is no cure for panic disorder, effective control of the symptoms is a realistic goal[5]. Despite the existence of efficacious treatments for panic disorder symptoms, there continues to be an effort to find alternatives with a lower side-effect profiles and higher rates of symptom alleviation. Any medication will carry its own set of adverse reactions and intolerability for various reasons. Anytime a lifestyle modification can be suggested that helps alleviate symptoms or decrease severity of the disease, there is less of a burden on the patient. Because caffeine has long been known as a psychoactive chemical, resulting in alterations of mood and central nervous system functioning[7],

it is suggested as a possible etiology of anxiety disorders and panic disorder[1]. Caffeine has in fact been identified as a "panicogen", or a chemical believed to induce panic attacks, in a patient with an existing panic disorder[1]. Until recently, though, there has been insufficient evidence to show such relations between caffeine ingestion and induction of a clinical panic attack. Elimination of certain elements from one's diet has shown to make marked improvement in a patient's disease severity in several instances. For example, a patient's reduction of sodium intake has shown to decrease the intensity of a patient's hypertension[4]. If a chemical agent has been shown to induce panic attacks, it can be logically assumed that elimination of this panicogen from a panic disorder patient's diet may help improve the frequency of attacks and severity of symptoms. It is for this reason that several randomized control trials have been carried out in attempt to scientifically show a relationship between caffeine ingestion and induction of a clinical panic attack.

OBJECTIVE

The objective for this selective EMB review is to determine whether or not the reduction of caffeine intake is effective in reducing the symptoms of panic attack in panic disorder patients.

METHODS

Certain criteria were put in place for selection of the proper research to ascertain consistent, controlled results. The population used included adult patients between the ages of 18-55 with an existing diagnosis of panic disorder. The studies used for this systematic review were required to be double-blind, placebo controlled, randomized control trials. The intervention was a 480mg caffeine challenge, with the placebo being a visually matched decaffeinated coffee solution. The placebo was administered to a control group that was without the diagnosis of panic attack. The measured outcome was the incidence of a panic attack within 30 minutes of caffeine ingestion.

In order to conjure the studies included in this analysis, a thorough search of randomized control trials was carried out between December 2011 and February 2012 via PubMed. All articles were published in peer reviewed journals and published in the English language. The key words used in the search were “panic disorder”, “panic attacks”, “anxiety disorder”, and “caffeine.” The articles selected for this systematic review also had to fit the criteria of Patient Oriented Evidence that Matters (POEMs). The inclusion was that of randomized, controlled, double blind, and placebo controlled studies published after 1997. The exclusion criteria included studies using patients under the age 18 and those over the age 55, as well as disease-oriented evidence (DOE) studies. Any studies published before the year 1997 were excluded from consideration. Furthermore, any patients who reported taking anti-anxiety medication within the past 3 weeks were excluded from the study. Patients also had to agree to abstinence from caffeine for 1 week prior to the study. All studies used reported p-values, which were used to convert the data to Relative Risk Reduction (RRR), Absolute Risk Reduction (ARR), and Numbers Needed to Treat (NNT).

A summary of the demographics included in these studies is provided below in Table 1:

OUTCOMES MEASURED:

Outcomes were measured largely on the basis on patient reporting, as well as through physician reporting. Pre- and post-caffeine/placebo administration questionnaires were given to the participants. The pre-test questionnaire was administered just before the caffeine distribution. The post-test surveys were given at 15 minutes and again at 30 minutes after ingestions of the solutions. These surveys included the Subjective Units of Disturbance Scale (SUDS) and the Diagnostic Symptom Questionnaire (DSQ)[2,7,8]. These studies were modified for use with the DSM-IV definition of a panic attack.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age (years)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Nardi (2009)[8]	Double-blind RCT	98	18-55	Patients 18-55 years of age, occurrence of three panic attacks in two weeks before the first challenge test day for the panic disorder patients, no use of any antipsychotic, antidepressant, benzodiazapine, or nonbenzodiazepine anxiolytic medication for at least four weeks, or fluoxetine for 5 weeks, before the first test by any subject, and a negative urine test for benzodiazepines and other medications just before each challenge test.	Patients aged less than 18 or older than 55; Unstable medical condition, cognitive-behavior psychotherapy during the study, or the presence of suicidal risk, history of respiratory disease, and smokers.	0	A 480mg caffeine challenge
Nardi (2008)[7]	Double-blind RCT	74	18-55	(See above inclusion criteria)	(See above exclusion criteria)	0	A 480mg caffeine challenge
Nardi (2007)[2]	Double-blind RCT	109	18-55	(See above inclusion criteria)	(See above exclusion criteria)	0	A 480mg caffeine challenge

The SUDS required the patients to rate their level of anxiousness on a scale of 0-10, with 0 being no anxiety and a 10 being the worst anxiety imaginable. The DSQ required four or more of the following symptoms, identified through patient reporting: fear of dying, chest pain/discomfort, shortness of breath, paresthesias, feelings of choking, dizziness/lightheadedness, depersonalization/ derealization, losing control/going crazy, chills/hot flushes, nausea/abdominal distress, palpitations, sweating, and trembling/shaking. Furthermore, the test subjects had to show evidence of at least one of the following cognitive panic symptoms: fear of dying, losing control, or "going crazy.[2]" Patients also had to report their own sensation of "panic or fear" in order to be considered as a true panic

attack responder. All of these responses were rated on a scaled of 0-4 by the patients, with 0 being no symptoms experienced and a 4 being the most severe form of that symptom. In addition to the patient's own reporting, two medical doctors had to be in agreement that the patient was experiencing a true panic attack. The thorough questionnaires, as well as the input required by a medical doctor, helps to rule out any cases of malingering or false reporting on the part of the patient. Important to note was that the SUDS was not used to clinically diagnose a panic attack; however, the information obtained from the SUDS provided valuable information to support the validity of the patients own experience.

RESULTS:

All three randomized control trials evaluated in this systematic review compared the effect of caffeine administration on patients with existing diagnosis of panic disorder. None of the participants withdrew from the study in any of the three articles. All three studies found a positive correlation between caffeine administration and induction of a panic attack in patients previously diagnosed panic disorder.

The Nardi, et al 2007 study[2] found statistically significant data showing the correlation between caffeine ingestion and the resulting clinically determined panic attack. This study involved 29 patients with panic disorder, 27 patients with panic disorder accompanied by major depressive disorder, 25 patients with major depressive disorder (without panic disorder), and 28 control patients without any psychological diagnosis. For the purposes of this review, no information is being reported concerning the patients with major depressive disorder with or without panic disorder. In the panic disorder group, 17 of the 29 patients, or 56.6%, experienced a clinical panic attack within 30 minutes of ingestion of the caffeine solution. This study was the only one of the three articles to

report 7.1% (2 patients) of the control subjects experiencing a panic attack after ingestion of the 480mg of caffeine. None of the patients who were given the caffeine-free solution experienced a panic attack. This study also showed, therefore, that for every two persons treated with this intervention, one would benefit.

Table 2: Nardi, et al 2007 study[2] showing incidence of panic attack in panic disorder patients after administration of 480mg of caffeine:

CER	EER	RRR	ARR	NNT	p-value
0.07	0.58	7.25	0.51	2	<0.001

The Nardi, et al 2008 study[7] also found statistically significant data showing the correlation between caffeine ingestion and a subsequent clinically determined panic attack. This study involved 25 patients with panic disorder, 27 health patients that were first-degree relatives of the each panic disorder patient, and 22 control patients without any psychological diagnosis. For the purposes of this review, no information is being reported concerning the first degree relatives. This study found that 13 of the 25, or 52.0%, panic disorder patients experienced a panic attack after ingestion of the caffeine solution. None of the control subjects experienced a panic attack after ingestion of the caffeine solution. None of the subjects experienced a panic attack after ingestion of the placebo solution. This study also showed that approximately 1 in 2 patients would benefit this treatment type.

Table 3: Nardi, et al 2008 study[7] showing the incidence of panic attack in panic disorder patients after *administration of 480mg of caffeine*

CER	EER	RRR	ARR	NNT	p-value
0.00	0.52	____	0.52	2	<0.001

The Nardi, et al 2009 study[8] again found statistically significant data showing the correlation between caffeine ingestion and the resulting clinically determined panic attack. This study involved 28 patients with panic disorder, 25generalized social anxiety patients, 19 patients with performance social anxiety disorder, and 26 control patients without any psychological diagnosis. For the purposes of this review, no information is being reported concerning the patients with generalized social anxiety or performance social anxiety. In the panic disorder group 17 of the 28, or 60.7%, panic disorder patients experienced a panic attack after administration of the 480mg caffeine solution. None of the control subjects experienced a panic attack after ingestion of the caffeine solution. None of the patients, control or PD, experienced a panic attack after ingestion of the placebo solution. This study again showed that approximately 1 in 2 patients would benefit from this treatment.

Table 4: Nardi 2008 study showing the incidence of panic attack in panic disorder patients after *administration of 480mg of caffeine*

CER	**EER**	**RRR**	**ARR**	**NNT**	**p-value**
0.00	0.61	____	0.61	2	<0.001

The data in all three studies was collected on two different occasions, seven days apart from the preceding study. There was no follow up reporting to be collected from the participants. No harm can be found in patients withdrawing from caffeine ingestion, as caffeine is an unnecessary component in one's diet.

DISCUSSION:

This systematic review comprised of three double blind, placebo controlled, randomized control trials on the effect of caffeine ingestion and induction of a panic attack in those with panic disorder. Panic disorder is a serious mental illness that affects millions of people in the United States; therefore, a safe and effective treatment for symptom management is indispensable. All of the studies

conducted between 2007 and 2009 by the Laboratory of Panic and Respiration Institute of Psychiatry in Rio de Janeiro, Brazil revealed of numbers needed to treat of 2, which attests to the impact of caffeine on panic disorder patients' symptoms.

There are a limited number of studies concerning the direct administration of caffeine to panic disorder patients, perhaps due to the ethical implications of the intervention. Because of this, the Nardi trials were three of the most outstanding and relevant studies to this topic. The downside to all three of these articles being produced by the same research facility is that the data is subject to perhaps a larger degree of bias. For example, since the study was conducted in Brazil, only those of Brazilian ethnicity were considered in all three studies. This is perhaps one of the greatest limitations of this review, under the argument that certain ethnic groups are more subject to certain diseases than others and may therefore react differently to certain interventions or treatments. Along these same lines, the authors of these articles mention that coffee is a very important beverage to the culture of the Brazilians, implying perhaps a greater dependence on caffeine than may exist for other patient ethnicities.

Another limiting factor in this analysis is that only the ingestion of 480mg was studied. Because patients naturally consume varying amounts of caffeine, we do not know how lower amounts of caffeine may impact a patient with panic disorder.

Further limitation includes the age restrictions of the three studies. The research team only included patients over the age of 18 years old and under the age of 55. Although patients younger than the selection criteria are not as known for their caffeine dependency, people younger than 18 do ingest caffeine and could perhaps benefit from this intervention. Subsequently, patients over the age of 55 consume caffeine in various forms and can still be afflicted by panic attacks. For this reason, the age selection from these studies can be considered a limiting factor to the use of this information.

Another argument can be made for the size of the patient populations. Each of the studies only involved 22-28 panic disorder patients. Although it can be difficult to obtain willing, consented patients for this study, a larger sample size may have resulted in higher or lower percentages of effect.

CONCLUSION:

Although there is strong evidence showing that ingestion of caffeine in a patient with a panic induces a clinical panic attack, there is no evidence showing that abstinence from this chemical reduces panic attack incidence. The evidence is inconclusive concerning the reduction of caffeine intake as an effective treatment for the reduction of the symptoms of panic attack in panic disorder patients. In order to obtain results to satisfy this question, a study should perhaps be designed involving existing caffeine consuming panic disorder patients who are then withdrawn from caffeine for a period of time and monitored for incidence of panic attacks. Additionally, further studies should be set up to involve patients of varying ethnicity and age to ensure that this is an effective treatment for any caffeine-consuming person. Because there is relatively no harm in having a patient withdraw from caffeine, clinicians should have no hesitation in recommending this as a part of a treatment plan to patients; they must be informed, however, that there has yet to be clinical evidence showing the efficacy of this as a treatment. Furthermore, if a patient did not already consume caffeine before his diagnosis with panic disorder, this treatment becomes irrelevant. Further research is warranted to confirm caffeine withdrawal an effective treatment for panic disorder patients.

REFERENCES:

1. Sadock BJ, Sadock VA. *Concise Textbook of Clinical Psychiatry*. 3rd ed. New York, NY: Lippincott Williams and Wilkins; 2008.
2. Nardi AE, Lopes FL, Valença AM, Freire RC, Veras AB, de-Melo-Neto VL, Nascimento I, King AL, Mezzasalma MA, Soares-Filho GL, Zin WA. Caffeine challenge test in panic disorder and depression with panic attacks. *Compr Psychiatry*. 2007 May-Jun;48(3):257-63.
3. Mental Illness and Panic Disorder statistics sheet. National Institute of Mental Health website. http://www.nimh.nih.gov/statistics/index.shtml. Accessed on October 1, 2012.
4. Reus VI. Chapter 391. Mental Disorders. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012. http://www.accessmedicine.com/content.aspx?aID=9112222. Accessed October 1, 2012.
5. Anxiety Disorder fact and statistics sheet. Anxiety and Depression Association of America website. http://www.adaa.org/about-adaa/press-room/facts-statistics. Accessed on October 1, 2012.
6. Nurcombe B. Chapter 41. Anxiety Disorders in Children and Adolescents. In: Ebert MH, Loosen PT, Nurcombe B, Leckman JF, eds. *Current Diagnosis & Treatment: Psychiatry*. 2nd ed. New York: McGraw-Hill; 2008. http://www.accessmedicine.com/content.aspx?aID=3291132. Accessed October 1, 2012
7. Nardi AE, Valença AM, Nascimento I, Freire RC, Veras AB, de-Melo-Neto VL, Lopes FL, King AL, Soares-Filho GL, Mezzasalma MA, Rassi A, Zin WA. A caffeine challenge test in panic disorder patients, their healthy first-degree relatives, and healthy controls. *Depress Anxiety*. 2008;25(10):847-53.
8. Nardi AE, Lopes FL, Freire RC, Veras AB, Nascimento I, Valença AM, de-Melo-Neto VL, Soares-Filho GL, King AL, Araújo DM, Mezzasalma MA, Rassi A, Zin WA. Panic disorder and social anxiety disorder subtypes in a caffeine challenge test. *Psychiatry Res.* 2009 Sep 30;169(2):149-53.