

Genetic versus Environmental Factors in the Etiology of Panic Disorder

Submitted by

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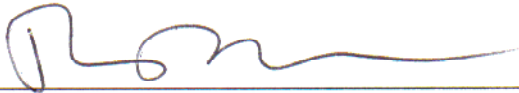
A project presented to the Department of
Physician Assistant of Wichita State University
in partial fulfillment of the
requirements for the degree
of Master of Physician Assistant

May, 2006

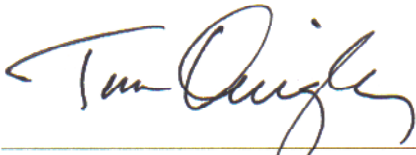
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We hereby recommend that the research project prepared under our supervision by Brian Zerger entitled Genetic versus Environmental Factors in the Etiology of Panic Disorder be accepted as partial fulfillment for the degree of Master of Physician Assistant.

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Abstract:

Introduction: The purpose of this study is to investigate the etiology of panic disorder. Specific objectives include comparing and contrasting the genetic versus environmental factors that contribute to the etiology of panic disorder. Currently, there are four main theories to explain the etiology of panic disorder: psychodynamic, behavioral, cognitive, and biological. *Methodology:* This is accomplished via a systematic review of evidence-based medicine. Search engines utilized included: MEDLINE FirstSearch, Medline PubMed, ProQuest Nursing, PsycINFO, Current Research and a bibliographic search of selected articles. *Results:* The best quality evidence indicates that between 40-60% of the etiology of panic disorder is due to genetics. Further, a body of good quality research states that environmental influences to the expression of panic disorder; such as CO² reactivity, learned anxiety, and fear conditioning; may also be heritable traits. Lifestyle choices, such as smoking, also play a role in the etiology of panic disorder. The evidence-based review does not support a role for the psychodynamic theory in the etiology of panic disorder. *Conclusion:* The majority of panic disorder is due to genetics. The minority of panic disorder etiology is best explained by the cognitive and behavioral theories on environmental factors. Such data suggest the best treatment for panic disorder patients should focus on medical therapy and cognitive-behavioral therapy.

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Acknowledgements:

I wanted to express my thanks to my professor and research advisor, Tim Quigley PA-C, for his guidance on this project. Thank you for your help and for your kind listening ear during my high-stress adventure through PA school. I also wanted to thank my wife Kristin for her patience, for believing in me, and for her love and support.

Introduction:

Anxiety disorders are the most common group of psychiatric disorders diagnosed in the United States today.¹ As many as one in four adults are affected by an anxiety disorder in their lifetime.¹ Most importantly, primary care providers diagnose and treat 90% of anxiety disorders.¹ With such a high prevalence, all primary care providers should be familiar with and recognize anxiety disorders. Typically, patients affected with anxiety disorders are between the ages of 20-45, female, and of lower socioeconomic status.¹

One of the anxiety disorders is panic disorder. The basic components of panic disorder are panic attacks. Panic attacks are defined as “[a] discrete period of intense fear accompanied by the abrupt onset of several cognitive and somatic symptoms.”² Some common symptoms of a panic attack include: “chest pain, pressure, or discomfort, hyperventilating, nausea or abdominal distress, trembling or shaking, excessive sweating, hot flashes or chills, and tingling or numbness in all parts of the body.”² Only those individuals, who experience repeated panic attacks, may be diagnosed with panic disorder.

In order to be diagnosed with panic disorder, according to the DSM-IV, a patient must have:

- A. recurrent, unexpected panic attacks;
- B. at least one of the attacks has been followed by one month or more of (1) persistent concern about having additional attacks, (2) worry about the implication of the attack or its consequences, or (3) a significant change in the behavior related to the attacks;

C. the panic attacks are not due to the direct physiologic effects of a substance or a general medical condition;

D. the panic attacks are not better accounted for by another mental disorder.¹

Once individuals have developed panic disorder, they are also very likely to try to avoid the situations that they associate with panic attacks. Agoraphobia is “a condition where the patient avoids situations in which escape may be difficult or embarrassing, or where help may not be available in case of another attack”.¹ Agoraphobia due to panic disorder can be very debilitating including avoidance of social and occupational settings.¹

Clearly, panic disorder has the capacity to disrupt the function of one’s life.

Background:

To date, the etiology of panic disorder remains unknown; however, several theories prevail which attempt to explain the cause of panic attacks or anxiety disorders in general. Psychoanalytic theorists, such as Freud, “originally argued that panic attacks occurred because threatening material was about to break through from the unconscious, so the individual panics.”³ Behavior theorists explain anxiety disorders as a classically conditioned response to an environmental stimuli; as faulty distorted thinking patterns; or as an imitation of the anxiety response of parents or other role models.² Cognitive theorists believe that individuals have a panic attack when they misinterpret an increase in arousal. For example, an abnormal heart rate would be seen as a life-threatening disorder, which causes individuals to panic.³ Finally, biological theorists believe anxiety disorders are due to neurotransmitters and hereditary transmission.² More specifically, biological theorists believe that the autonomic nervous system produces an excessive response, or overreacts, to only moderate stimuli.² Biological theorists have argued that

the neurotransmitters GABA, serotonin and norepinephrine all play a role in anxiety disorders due to the proven improvement in symptoms seen in patients who take benzodiazepines or selective serotonin reuptake inhibitors.² Another biological theory is that some individuals have inherited an overly sensitive respiratory control center. In these cases it is suggested that when a small increase in carbon dioxide occurs in one's blood, a signal is sent to the brain indicating that the body is suffocating; thus one panics.³ As is the case for so many other disorders, the true etiology of panic disorder is likely a combination of several factors.

The problem with not understanding the etiology of panic disorder is that it becomes tougher to treat. Practitioners need the best evidence available in order to efficiently address patients with panic disorder.

Purpose of Study:

The etiology of panic disorder is unknown. Although there are many theories as to its origin, no one has figured out how much of the burden of the disorder is due to genetics and how much is due to environmental factors. The purpose of this study is to investigate the literature of the etiology of panic disorder. Specifically, to comparing and contrasting the genetic versus environmental factors contributing to the etiology of panic disorder.

Methodology:

The design of this study will be a systematic review of evidenced-based medicine. A review of the literature was done using MEDLINE FirstSearch in which subjects of:

1. *panic AND disorder AND genetics AND full text*
2. *panic disorder AND genetics*
3. *panic disorder AND etiology*
4. *panic disorder AND genetics AND etiology*

5. *psychoanalytic theory*
6. *psychoanalytic theory AND panic disorder AND etiology*
7. *environment*
8. *panic disorder AND etiology AND environment*

A second search was done using Dissertation Abstracts Online using keywords:

1. *panic*
2. *panic AND disorder*
3. *panic AND disorder AND etiology*

and subjects:

1. *panic*
2. *leaning AND theory*
3. *psychoanalytic AND theory*
4. *cognitive AND behavioral AND theory*
5. *anxiety AND disorders*
6. *panic AND attacks*
7. *panic AND disorders*

A third advanced search of ProQuest was done using keywords *panic disorders AND genetics* and limits of scholarly journals, including peer reviewed. A fourth search was included using MEDLINE PubMed in which keywords *panic disorder AND genetic* were used with limits on English and randomized controlled trials. Fifth, a search of PsycINFO was done by first selecting search terms from PsycINFO index, then searching for those terms and then combining searches. Search terms identified in the PsycINFO index were *panic disorder* or *panic disorders* or *panic-generalized-agoraphobic*, *panic attack* or *panic attacks*, *environment*, *cognitive-behavioral* or *cognitive-behavior* or *cognitive-behavior-therapy* or *cognitive-behavioral*, *learning-theory*, *psychoanalytic-theory*, *etiology*. Combined searches included:

1. *panic disorder* or *panic disorders* or *panic-generalized-agoraphobic AND etiology*
2. *environment AND panic disorder* or *panic disorders* or *panic-generalized-agoraphobic AND etiology*
3. *learning-theory AND panic disorder* or *panic disorders* or *panic-generalized-agoraphobic*

4. *panic disorder* or *panic disorders* or *panic-generalized-agoraphobic* AND *psychoanalytic-theory*
5. *cognitive-behavioral* or *cognitive-behavior* or *cognitive-behavior-therapy* or *cognitive-behavioral* AND *panic disorder* or *panic disorders* or *panic-generalized-agoraphobic*
6. *environment* AND *panic attack* or *panic attacks* AND *etiology*
7. *cognitive-behavioral* or *cognitive-behavior* or *cognitive-behavior-therapy* or *cognitive-behavioral* AND *environment* AND *panic disorder* or *panic disorders* or *panic-generalized-agoraphobic*

Further, a bibliographic search of Battaglia and Ogliari⁴, Richborn-Kjennerud⁵, Kaplan and Sadock⁶ and the meta- analysis study by Hettema⁷ was also done. Lastly, a search of Current Research was done using the following keywords: *panic attack*, *panic disorder*, *anxiety disorder*, *cognitive behavioral theory*, *psychoanalytic theory*, *learning theory*, *panic disorders*, *panic attacks*.

MeSH terms utilized in this study include: panic disorder, etiology, genetics, environmental factors, and literature review.

Classification of studies is based on the three levels of evidence. Level 1 includes: high quality randomized controlled trials that consider all important outcomes and high quality meta-analysis using comprehensive search strategies. Level 2 includes: nonrandomized clinical trials, lower-quality randomized controlled trials, clinical cohort studies, and case-controlled studies with nonbiased selection of study participants and consistent findings. Also included in level 2 are high-quality, historical, uncontrolled studies or well designed epidemiologic studies with compelling findings. Level 3 includes: consensus viewpoint or expert opinion studies.

Literature Review:

Genetic Theories: Biological Data

Some of the most intriguing information we currently have about panic disorder data stems from twin studies. For example Kendler et al. (1993) performed a blind, structured, psychiatric interview of 2163 women from the population based Virginia Twin Registry, in which they investigated how important familial factors are in the etiology of panic disorders, to what extent panic disorder is due to genes versus shared family environment, and whether or not the presence or absence of panic disorder avoidance behavior is a index of the severity of liability to panic disorder.⁸ They addressed these questions by dividing the twins into three categories: concordant for non- affection (neither have panic disorder), discordant for affection (one has panic disorder and the other does not), and concordant for affection (both have panic disorder).⁸ Next they used a model of best fit to estimate the proportion of variance in liability to panic disorder due to individual specific environment, additive gene action, and common environment.⁸ They found that panic disorder as diagnosed in the general population sample is less familial than panic disorder seen in the clinical setting.⁸ They also found that the co-twin of an affected twin was at an increased risk for panic disorder compared to the general population.⁸ Further, they determined that panic disorder with a significant phobic avoidance represents a more severe form of panic disorder.⁸ Finally, they were unable to discriminate between the genetic and familial environmental transmission of panic disorder.⁸

A second twin study focused on the genetic transmission of an overly sensitive respiratory control center by having twin pairs inhale carbon dioxide. In this double

blind, random, crossover designed study by Bellodi et al. (1998), the genetic background of CO₂ induced panic attacks was investigated in 45 same sex pairs of twins randomly taken from Italy's national twins birth list.⁹ The researchers compared the concordance rates for CO₂ induced panic attacks in 20 monozygotic and 25 dizygotic twin pairs after inhalation of 35% CO₂.⁹ They found that the probandwise concordance rates for the 35% CO₂ induced panic attacks were significantly higher in monozygotic (55.6%) than dizygotic twins (12.5%) demonstrating heritability contributes substantially to the susceptibility to react to the gas with a panic like episode.⁹ They also found however, that one half of the monozygotic pairs of twins were discordant, suggesting that non-genetic factors also play an important role in the development of CO₂ induced panic attacks.⁹ Further, they also noted that the proband concordance rate for spontaneous panic attacks were higher in monozygotic twins (71%) than dizygotic twins (18%). Most interesting was the finding that the rates of families with secondary cases of panic disorder were 100% in pairs of twins concordant for panic disorder, 20% in those discordant for panic disorder, and 13.5% in those without panic disorder. Bellodi et al. (1998) conclude that there might not be a complete match between the genetic factors of panic attacks and the sensitivity of the respiratory control center and that other inherited factors may also play a key role in the development of panic disorder.⁹ Interestingly, Bellodi et al. (1998) results agree with an earlier study by Perna et al. (1996).¹⁰ This double-blind, random, crossover designed study also investigated the heritability of CO₂ induced panic attacks in patients with panic disorder. Further, they also measured the familial morbidity risk of those patients who had responded to the test with a panic attack in order to see if panic disorder had a genetic component.¹⁰ It was discovered that

77% (n=203) of patients with panic disorder had positive reactions to the 35% CO₂ challenge.¹⁰ Also, through 897 direct interviews and the use of the Family Research Diagnostic Criteria, familial morbidity risk of panic patients was 12%.¹⁰ Perna et al. (1996), concluded that CO₂ hypersensitivity was significantly related to familial genetic risk for panic disorder.¹⁰

A third twin study, by Stein et al. (1999), tried to explain the familial predisposition to panic disorder by exploring the possibility that a psychological characteristic that predisposes one to panic anxiety sensitivity might be inherited.¹¹ They further wanted to estimate the genetic versus environmental influences on anxiety sensitivity.¹¹ Fundamental to this study is the idea that the higher the anxiety level one has, the greater the chance that one is likely to experience anxiety symptoms as alarming, dangerous or threatening. This study recruited 337 volunteer general population twin pairs from newspaper ads, media stories and twin club registries.¹¹ Each twin was sent a questioner which allowed the researchers to measure their beliefs about the consequences of their anxiety symptoms on the Anxiety Sensitivity Index, a five-point Likert scale.¹¹ Therefore, the higher the score on the Anxiety Sensitivity Index, the more characteristics one has for panic disorder. Biometrical model fitting was used to address variance attributable to additive genetic factors, shared environmental factors, and non-shared environmental factors. They found that anxiety sensitivity has a strong heritable component, accounting for nearly half of the variance in total anxiety sensitivity scores.¹¹ They also found that there is no genetic discontinuity between normal and extreme scores on the Anxiety Sensitivity Index, which suggests that both levels are equally heritable.¹¹ In other words, Stein et al. (1999), suggest that the development of panic disorder is not

only due to the inheritance of a physiological trait, such as CO₂ reactivity, but also due to cognitive risk factors, including anxiety sensitivity, which are also heritable.

Further evidence for the genetic influence in the etiology of panic disorder comes from the cognitive-behavior theorists. Specifically, Beek and Griez (2002) studied whether first-degree relatives of panic disorder patients were more or less anxiety sensitive than controls.¹² Two questionnaires, the Anxiety Sensitivity Index and the Body Sensations Questionnaire, were self administered to 30 controls, 38 panic disorder patients, and 23 first degree relatives of panic disorder patients.¹² It was found that first-degree relatives of patients with panic disorder were more anxiety sensitive than controls.¹² This study however, did not find higher scores in first-degree relatives of patients with panic disorder on the Body Sensations Questionnaire.¹² Beek and Griez hypothesize that a larger sample may be needed to find such results on the BSQ.¹² Although a small sample size limits this study, it is significant to note that it supports the Stein et al. (1999) study that anxiety sensitivity is a heritable trait. Finally, Beek and Griez also assert that anxiety sensitivity alone is not sufficient to develop panic disorder, but rather it requires a variety of psychological and biological factors.¹²

Meta-analysis studies also are important for understanding the etiology of panic disorder. One such study by Hettema et al. (2001), looks at family and twin studies to try to assess the genetic and environmental factors in the etiology of panic disorder.⁷ This study further addresses the magnitude of familial aggregation of anxiety disorders.⁷ Methodological design included combining data from primary sources to provide estimates of familial risk and heritability.⁷ For family studies, odds ratios were used as a measure of association, and for twin studies proband wise concordance rates were used.⁷

This study indicated that five out of five studies of panic disorders supported the familial aggregation on panic disorder.⁷ In other words, there was a significant association between panic disorder in probands and panic disorder in first degree relatives across all five family studies.⁷ In regard to the 3 twin studies examined, it was found that they did not support a role for common family environment in the etiology of panic disorders.⁷ However, the twin studies did support that genes affect panic disorder similarly in men and women.⁷ Most interesting was the fact that a combined data of both twin studies and familial studies produced a best fit model which only required additive genetic and individual environment to account for liability to panic disorder. Hettema et al.(2001) attributed 30-40% of the variance in liability to additive genetics and the remaining percent to individual specific environment.⁷ However, when Hettema et al. (2001) reanalyzed their data taking in account measurement error, they estimated heritability in the 50-60% range.⁷ Further, the heritability estimate of the previous combined data were statistically significant.⁷

Another study supporting a significant genetic role in the etiology of panic disorder is by Scherrer et al (2000). These researchers used a bivariate twin design to quantify the amount of genetic, shared environmental, and unique environmental factors which influenced the risk for panic disorder in male twins.¹³ These researchers interviewed 8169 male-male twin pairs from the Vietnam Era Twin Registry and implemented the genetic modeling approach to account for individual differences in phenotypes. Their results indicated a 5.9% lifetime prevalence of panic disorder with a mean age of onset to be 20.1 years old.¹³ Most importantly, they found that genetic factors accounted for 43.4% of the variance in the risk for panic disorder with the

remainder of variance due to unique environmental factors (including measurement errors).¹³

One of the first studies to suggest a familial transmission of agoraphobia and panic disorder was conducted by Noyes et al. (1986).¹⁴ Specifically, the researchers were interested in figuring out if panic disorder and agoraphobia are separate disorders, or if they are a single illness. The researchers operationalized this question by measuring the morbidity risk that those with panic disorder and those with agoraphobia have relatives affected with the same disease as the probands.¹⁴ Conversely, it was also noted that if panic disorder and agoraphobia are linked, then the morbidity risk of both diseases appearing in the family members could be measured.¹⁴

They investigated this question by selecting 40 probands with agoraphobia from an agoraphobia self help group and matched them by age and sex to 40 probands with panic disorder identified in a previous study.¹⁴ In addition they included twenty randomly selected control probands and matched them by age and sex with the agoraphobic probands.¹⁴

Prospective probands were then given questionnaires and interviews designed to distinguish between panic disorder and agoraphobia.¹⁴ Next, all first-degree relatives over the age of eighteen were contacted and given the same interview as the probands.¹⁴ All relatives also completed the Symptom 90 checklist, Eysenck Personality Inventory, Fear Survey Schedule and Agoraphobia Symptom Rating Scale.¹⁴ Morbidity risks for panic disorder and agoraphobia were calculated using a single age of onset distribution for the panic disorder and agoraphobic probands.¹⁴ Cumulative proportions of probands affected were then age-adjusted.¹⁴

They found that agoraphobic and panic disorder probands had roughly the same number of first degree relatives (256 and 241 respectively) affected and these relatives had comparable sex ratios and age distributions.¹⁴ In other words, Noyes et al. (1986) found that these disorders are linked rather than separate disorders. Further, they found that the combined risk for panic disorder and agoraphobia was 19.9% among the agoraphobics' relatives and 19.2% among the relatives of panic disorder patients.¹⁴ They concluded that agoraphobia, like panic disorder, is familial in nature. Most interesting was the fact that Noyes et al. (1986) also found that all of the agoraphobic probands in the study gave a history of panic attacks; and, no agoraphobic proband or relative failed to report panic attacks.¹⁴

Thus, a second conclusion was that agoraphobia is a more severe disturbance than panic disorder. This finding is supported by the facts that probands and relatives with agoraphobia had an earlier onset of illness, more persistent and disabling symptoms, more frequent complications, and a less favorable outcome than probands and relatives with panic disorder.¹⁴ Although Noyes et al. (1986) have compelling data the method of sample collection may have accounted for their findings. However, this study is of particular importance because it was one of the first studies to include the idea that panic disorder may be genetic in origin.

It has further been postulated that panic disorder is largely due to environmental factors which cause an individual to learn to be fearful of a particular stimuli. Hettrema et al. (2003) challenged this claim with a twin study that suggested that fear conditioning could also be a hereditary trait. They began by exposing 173 same sex twin pairs (MZ= 90, DZ= 83) to either fear-relevant or fear-irrelevant pictures.¹⁵ These stimuli were also

paired with an electro-dermal shock which served as the unconditioned stimulus. The fear response was measured by the amount of electro-dermal skin conductance response.¹⁵ Structural equation modeling was then implemented to the 3 phases of conditioning: habituation, acquisition and extinction.¹⁵ They found that every phase of the fear conditioning process in humans demonstrated heritability in the 35-45% range.¹⁵ This finding is significant because this is approximately the same percentage found for the heritability of anxiety disorders.¹⁵ Hettema further suggests that two sets of genes may possibly underlie the trait of fear conditioning. One set of genes that would affect non-associative process of habituation that is also shared with acquisition and extinction, and a second set of genes which is associated to fear conditioning processes.¹⁵ Although Hettema et al. (2003) voice an intriguing possibility of inherited fear conditioning; unfortunately, most of the results lack either statistical power or variance, and thus their argument must be weighted accordingly.

Recent biological gene research may explain the etiology of panic disorder. Linkage and association are used to identify the approximate location of susceptible genes, according to Arnold et al.(2004)¹⁶ Linkage studies identify anonymous DNA markers across a family tree or affected relative pairs, in order to pick out possible locations of susceptible genes.¹⁶ Association studies identify candidate genes based on a researcher's hypothesized location of genes that may be involved in a disease process.¹⁶ Linkage studies by Hamilton et al. produced significant linkage to chromosome 13q and 22q and panic disorder probands.¹⁶ Moreover, Thorgeirsson et al. found a linkage for panic disorder and the 9q31 gene in the Icelandic population.¹⁶ A final linkage study

used Bayesian statistic methods and found strong evidence for a region of chromosome 7p and panic disorder.¹⁶

Association studies have implicated several candidate genes such as: adenosine 2A (ADOR2A), cholecystinin (CCK), serotonin (5HT1A and 5HT2A), catechol-O-methyltransferase (COMT), angiotensin (ACE) and cyclic adenosine monophosphate response modulator (CREM).¹⁶ All of the previous genes were studied because they are known to be involved in creating symptoms that are seen in panic disorder patients. However, all of the mentioned possible associated genes need further research in order to replicate results and increase sample size and power.

Pathophysiologists have also contributed to the search for the origin of panic disorder. They have implicated, through a series of studies, the amygdala as a possible location involved in panic disorder.¹⁷ They reason that the amygdala has neural connections to higher cortical, subcortical and brainstem structures which have been shown to be involved in the acquisition and retention of conditioned fear in animals.¹⁷ In humans these same connections are used to acquire and interpret data needed to select fear responses according to context.¹⁷ Further, these connections facilitate the expression of cognitive, affective, motor, and autonomic components of anxiety.¹⁷ Their research is supported by the known inhibitory activity of GABA and N-methyl-Daspartate receptors in the amygdala and the efficacy of benzodiazepine anxiolytics on panic disorder.¹⁷

Environmental theories:

While there is significant evidence to suggest genetic etiology for panic disorder, one must also consider other factors that may influence panic disorder. Several

researchers argue that genetics make patients susceptible to panic disorder, but an environmental trigger is still needed for the disorder to be expressed.

The Cognitive Theory:

One such study by Bouwer and Stein (1997) hypothesized that patients with panic disorder would have more history of traumatic suffocation as compared to controls; and, patients with a history of traumatic suffocation were more likely to have respiratory symptoms compared with those without such a history.¹⁸ Central to this study is the work of Klein, who showed that panic attacks can be triggered by CO₂ inhalation and lactate administration.¹⁸ Klein concluded that panic attacks occur when one's physiological monitor of CO₂ and lactate, falsely signals a lack of oxygen.¹⁸

Bouwer and Stein thus follow up Klein's work by first forming two research groups, one of 167 patients with panic disorder and the other of 60 psychiatric comparison subjects. Both groups were selected non-randomly from an anxiety disorders clinic and an outpatient psychiatric hospital. A history of traumatic suffocation was defined as shortness of breath due to near drowning, torture by suffocation, and choking during rape.¹⁸ Subjects were then interviewed by a single qualified psychiatrist, and the frequency to which patients answered positively to having had a traumatic suffocation event was measured. Their results indicated that 19.3% of panic disorder patients provided a history of a traumatic suffocation experience.¹⁸ Interestingly, those who had a traumatic suffocation experience were also more likely to report nocturnal panic attacks.¹⁸ This finding is significant because during sleep there is an increase in PCO₂.¹⁸ Statistical significance also indicated that respiratory symptoms were the most prominent symptoms found in those PD patients with a history of traumatic suffocation.

Conversely, in those patients without such a history of traumatic suffocation, their main symptoms were cardiovascular in origin.¹⁸

Bouwer and Stein thus conclude that environmental triggering of panic disorder may reflect the importance of cues related to suffocation or may reflect physiological changes in one's suffocation alarm.¹⁸ One should note that Bouwer and Stein's results may lack generalizability due to a regional sample. Also the use of only one psychiatrist to assess patients may not allow their study to be reproduced. Finally, the non-random nature of their sample may raise several questions as to the validity of their results.

Friedman et al. (2002) also studied the incidence and influence of early traumatic life events in outpatients with panic disorder.¹⁹ Subjects taken from a general psychiatry outpatient clinic were divided into four groups: panic disorder (n=101), other anxiety disorders (n=59), chronic schizophrenia (n=22) and major depression (n=19).¹⁹ Patients then completed a Life History Questionnaire which asked for the occurrence of the following events: death or separation from either parent, separation or divorce of parents, substance abuse in either parents or siblings, childhood sexual or physical abuse, other traumatic events, age of onset of current psychiatric illness, previous psychiatric treatment or hospitalizations, presence of school phobias and/or separation anxiety, parental psychiatric histories, and the patient's description of the early family environment.¹⁹ In addition, the patients with panic disorder also completed the Agoraphobic Cognitions Questionnaire (which measures the degree to which a patient is afraid of various thoughts while experiencing anxiety), the Body Sensations Questionnaire, (which measures autonomic nervous arousal when anxious), and the Mobility Inventory for Agoraphobia, (a scaled measurement of 26 situations that

agoraphobic patients typically avoid).¹⁹ This data allowed Friedman et al. (2002) to measure the incidence that each group reported having had early traumatic life events and see if they correlated with an increased risk for the development of panic disorder.

Results indicated 39% of patients with panic disorder reported anxiety symptoms displayed in their parents compared to only 5% of schizophrenic patients and 0% of depressed patients.¹⁹ Investigators also found that both childhood physical and sexual abuse were associated with greater clinical severity in panic disorder patients. However, there was no significant difference in incidence of adverse early childhood events between panic disorder patients and psychiatric disorders in general.¹⁹ Thus, although there was a high rate of adverse childhood events in all groups, Friedman et al. (2002) concluded that these events were not risk factors specific to the development of panic disorder.¹⁹ Also there was a positive correlation between panic frequency and current depression.¹⁹ Finally, although Friedman et al. (2002) presents interesting results, one should realize that their questionnaires may have been affected by subject recall bias.

Influential Lifestyle Factors:

Although high quality research on the environmental etiology of panic disorder seems to be scarce, a recent study of the Japanese population addresses this issue with large, randomized, controlled trials. Kaiya et al. (2005) interviewed 4000 subjects taken randomly from the general population focusing on the role of factors related to lifestyle and living environment in the development of panic attacks and panic disorder.²⁰ Specifically, groups were manipulated according to age, sex, marital status, lifestyle issues (drinking, smoking, coping skills to stressors, dietary habits, like/dislike of exercise, ambient temperature), and number of days of winter per year experienced in

living areas.²⁰ These groups were then measured for the amount of people diagnosed with PA and PD within them. Statistical analyses were done using logistic regression with stepwise selection of variables.

Results indicated that female gender was the largest factor in the development of panic attacks/disorder.²⁰ Once again it seems that genetics play a large role in the etiology of panic disorder. However, several lifestyle factors, such as dislike of physical exercise and ability to cope with stressors also had associations with PA/PD.²⁰ Also, chronic avoidance of exercise could lead to a build up of lactate in one's system and thus predispose one to panic attacks.²⁰ When analysis focused only on female subjects, an association was found not only between poor stress coping ability, but also to marital status (not currently married) and panic attacks.²⁰ Analysis focused on male subjects found, though maybe due to chance, that male subjects who lived in areas with more winter days were also associated with panic attacks and panic disorder.²⁰

Kaiya et al. (2005) conclude that though it is unknown if dislike of exercise or poor-stress-coping ability cause panic disorder/attacks or are a result of panic disorder/attacks they are nevertheless related.²⁰ Thus, it should be clear that the etiology of panic disorder also relies upon an individual's environment.

Smoking is another environmental factor which has been associated with panic disorder. Richborn-Kyennerud et al. (2004) performed a longitudinal twin study using structural equation modeling to see whether or not panic attacks and cigarette smoking share genetic or environmental liability factors.⁵ The sample included 3172 female-female twin pairs (764=MZ, 645=DZ) taken from a population-based Norwegian twin registry.⁵ They found the correlation between monozygotic and dizygotic twins to be

very small, thus due to shared family environment.⁵ Further, results indicated that shared environmental factors accounted for 75% of the covariance between smoking and panic attacks; and, shared environmental factors were perfectly correlated accounting for 61% of the correlation between the phenotypes.⁵ Richborn-Kyennerud et al. (2004) conclude that the same shared environmental factors directly influence both panic and smoking.⁵ One can see that environmental factors definitely affect panic attacks; however, the researchers are also careful to point out that smoking may only increase the risk for panic attacks in genetically sensitive individuals.⁵ Lastly, although panic attacks and panic disorder are intricately related, realize this study only focuses on panic attacks.

A second study focusing on smoking was able to show an association to the development of panic disorder. Johnson et al. (2000) performed a community-based longitudinal study of 688 randomly selected youth to examine whether or not there was an association between cigarette smoking and anxiety disorders among adolescents and young adults.²¹ Groups were manipulated into age groups and then interviewed over time, implementing the Diagnostic Interview Schedule for Children, in order to measure the percentage of young smokers who developed anxiety disorders.²¹ Children were also divided into groups of heavy smokers (>20 cigarettes/day) and non-heavy smokers (<20 cigarettes/day). They found, after controlling for covariates, adolescence who smoked ≥ 20 cigarettes a day were at elevated risk for agoraphobia, generalized anxiety disorder, and panic disorder.²¹ Furthermore, they also found that quantity and frequency of cigarette smoking during adolescence were also associated with an elevated risk for agoraphobia, GAD, and PD.²¹ These associations remained significant after logistic regression analysis removed factors such as: age, sex, difficult childhood temperament,

alcohol/drug use and anxiety and depressive disorders during adolescence, parental smoking, education and psychopathology. Results were significant due to sufficient statistical power.

Smoking seems to be correlated with panic attacks and panic disorder; however, other environmental factors, such as miscarriage, are not according to Geller et al. (2001). This cohort study consisted of a miscarriage cohort at a New York City hospital and a comparison cohort from the general population.²² The study specifically focused on the incidence and relative risk for panic disorder following six months after miscarriage.²² Risk of panic disorder following miscarriage was measured by use of a structured interview, the Diagnostic Interview Schedule, and comparing the incidence of panic disorder between groups. Results indicated that there was no evidence for increased risk of panic disorder or agoraphobia in the six months following miscarriage.²² These are important findings not only because other non-comparison group studies have indicated the opposite,²² but also because such evidence may be used to justify the role conditioning plays in traumatic life events that lead to the development of panic disorder.

Agoraphobia has been shown to play a role in the development of panic disorder.¹⁴ Thus, one may reason that if the etiology of phobias can be understood, one can also gain insight into the etiology of panic disorder. Kendler et al. (2002) attempts to understand the environmental etiology of panic disorder by applying the stress-diathesis model in a twin study. The stress-diathesis model proposes that most psychiatric disorders arise due to environmental adversity experienced by susceptible individuals.²³ Further, it predicts that among affected individuals, an inverse relationship exists between diathesis, or liability, and the level of onset-related environmental trauma.²³ Stated

differently, the more likely one is to get a phobia the less environmental trauma needed to express that phobia. Kendler et al. (2002) tests the validity of using the stress-diathesis model to report the etiology of phobias by hypothesizing that individuals with no memory of a traumatic event will have higher levels of endogenous liability.²³ Conversely, those who report the onset of their phobia related to a major self-trauma will have a lower average likelihood of endogenous origin to their phobia.²³ These hypotheses were tested using blind interviews of 7500 twins from a population based twin registry. Neuroticism was used as an index of phobia proneness.²³ Interviews were conducted, by qualified interviewers, using the Diagnostic Interviewer's Schedule. Neuroticism was measured using the Eysenck Personality Questionnaire.²³ The sample was divided into 5 categories: trauma to self, observed fear by others, taught by others to be afraid, and no memory of how or why fear developed. Analysis between groups for level of neuroticism was completed using logistic regression and analysis of co-variance. Results indicated that levels of neuroticism strongly predicted all 5 phobic subtypes.²³ Further, there was no significant risk of phobia in the co-twin seen when groups of twins with no memory of how they got their phobia were compared to those groups who did report an incident related to their phobia. Kendler et al. (2002) concluded that all tests to verify the validity of the stress diathesis model failed.²³ These findings indicate either that the stress diathesis model is not applicable to phobias or that most phobias are acquired innately.²³ One might speculate, then, that panic attacks that appear out of the blue are genetically programmed.

Behavior Theory:

Although research with well-constructed trials has uncovered many factors that are related to the etiology of panic disorder, some psychologists feel that panic disorder is still best explained by current theories. For instance, behavior theorists assert that panic attacks and panic disorder can be explained by classical conditioning.

Bouton et al. (2001) explains that when a conditioned stimulus, be it an event or situation, is paired with a panic attack and all of the associated physiological symptoms, learning occurs.²⁴ Further, the learning that takes place allows the conditioned stimulus to trigger panic and anxiety when they are encountered again.²⁴ The current learning theory explains anxiety and panic as two separate entities. Anxiety functions to prepare one's system for an anticipated trauma and panic functions to deal with a trauma in progress.²⁴ Anxiety and panic interact in order to develop panic disorder. Panic disorder develops when interoceptive and exteroceptive cues create a conditioned anxiety which in turn exacerbates panic attacks.²⁴ Interestingly, Bouton et al. (2001) also asserts that panic attacks can occur to conditioned stimuli through unconscious processing in an attempt to silence critics of the learning theory stating that nocturnal panic attacks falsify the theory.

Bouton et al. (2001) concludes that the best treatment of panic disorder involves extinction of all the stimuli, or situation, which cause a panic attack and not just a single trigger. The modern learning theory may explain how panic disorder is triggered in those patients who have a genetic predisposition to the disorder; however, the crucial points of the theory stated above are only supported by animal research and small sample trials.

Psychodynamic Theory:

Another theory addressing the environmental etiology of panic disorder is the psychodynamic theory. The psychodynamic theory originated with the works of Sigmund Freud and continues today to be applied to panic disorder by a few psychologists. Central to this theory is the idea of all mental life existing on two levels: the conscious and unconscious.

Busch et al. (1999) explain that panic disorder patients are unaware of angry feelings in their unconscious.²⁵ “Out of the blue” panic attacks are explained as a lack of conscious awareness to stressors which cause intrapsychic reactions that lead to panic.²⁵ Further, unconscious fantasy is seen as the organizer of mental life, and in panic disorder unconscious fantasies about separation and independence cause intrapsychic conflict.²⁵ In order to deal with these intrapsychic conflicts one then sets up a compromise formation. A compromise formation is a compromise between a forbidden wish, such as acting out angry thoughts toward someone, and the defense against such a wish.²⁵ Psychodynamists believe that panic attacks are the defense mechanism one has against acting out angry unconscious fantasies. Stated differently, patients with panic disorder have panic attacks because of an intrapsychic conflict between violence and fear of abandonment.²⁵ These patients would rather have a panic attack than have fantasies about fears of loss or violence.²⁵

Busch et al. (1999) conclude that panic disorder patients have difficulty controlling and tolerating angry feelings and thoughts.²⁵ Although the psychodynamic theory of panic disorder has been used successfully in case reports to treat panic disorder, it has not been proven by any randomized, controlled trials. The role of the

psychodynamic theory in the etiology of panic disorder therefore is highly questionable. The role of psychoanalysis in the etiology and treatment of panic disorder may be best explained by Gassner (2004) “[It is] widely considered by other clinicians to be inappropriate treatment . . . for patients with symptoms of agoraphobia and panic attack. (222)”²⁶

Integration of Theories:

The truth of the etiology of panic disorder is likely that genetic and environmental factors combine to produce the disorder. Battaglia and Ogliari (2005) present this perspective in a review of evidence based medicine. First, they point out that in the context of fear conditioning, learning is in itself a heritable trait.⁴ Second, twin studies report the heritability of anxiety and panic to be between 30-62%.⁴ Thirdly, the modern learning theory on panic disorder explains panic attacks as fundamental emotions to unconditioned fear occurring at an inappropriate time based on genetic vulnerability.⁴ Fourth, induced hypercapnia, via CO₂ challenge, has been shown to cause behavioral and physical responses in mammals, including humans.⁴ More specifically, hypercapnia originates in the ventral medulla, then extends to the pons, midbrain, limbic and paralimbic areas, the parahippocampal and fusiform gyrus, and the anterior insula.⁴ Activation of the limbic area is responsible for the feeling of being anxious and the rest of the neural network is responsible for the conditioning of “air hunger to fear”.⁴

Lastly, environment plays a significant role in the expression of panic disorder. Specifically, stress, in the form of suffocation, child abuse, child separation anxiety, or separation from caregivers can trigger panic disorder by changing gene expression.⁴ Battaglia and Ogliari assert that stress causes an upregulation of muscarinic cholinergic

receptors which “primes” the respiratory system for an increased response to a hypercapnic situation.⁴ Further, stress also causes upregulation of muscarinic receptors in the neocortex, amygdala, hippocampus and other brain areas which promote learning and avoidance of conditioned stimuli.⁴ Support for these conclusions includes identification of stress induced changes of genes at the 7q22 locus and the paraoxonase promoter gene.⁴ Lastly, these genes have an inverse relationship with anxiety measures.⁴ Certainly, Battaglia presents a thorough and interesting view on the etiology of panic disorder.

The majority of research on the etiology of panic disorder indicates that it has a strong genetic component. What is not known about panic disorder is what exactly makes up the rest of its etiology. Several studies indicate that possible environmental influences of smoking, anxiety sensitivity, or conditioning may play a role in the etiology of panic disorder.

In descending order the best evidence to explain the etiology of panic disorder currently is genetics, lifestyle choices, the cognitive theory, the behavior theory, and the psychodynamic theory. Eleven studies support a largely genetic etiology of panic disorder. Six of the eleven studies mentioned are level 1 studies, and the remaining five are level 2 studies. Five studies do not dispute the large role of genetics in the etiology of panic disorder, but explain the rest of the origin of panic disorder by lifestyle choices. Of those five studies, four are level 1 and one is level 2 research. Two studies explain the etiology of panic disorder with the cognitive theory. Both of these studies are level 2 research. One level 3 study explains PD etiology with the behavior theory. Two level 3 studies explain the etiology of panic disorder with the psychodynamic theory. One level

2 study explains PD etiology by molding together all of the best supported theories.

Stated differently, the quality and quantity of the evidence-based medicine to support each theory are summarized in Appendix 1.

Discussion:

Evidence in the Literature:

The above studies suggest that panic disorder has a largely genetic etiology. In fact, all of the high quality studies do not refute the large role that genetics play in the origin of panic disorder. Pure genetics, according to the evidenced-based medicine, are responsible for roughly 40-60% of the etiology of panic disorder. However, the role of environmental factors should not be pushed aside because several studies show how environmental factors may influence genetic expression of panic disorder. These studies included environmental factors such as smoking, learning anxiety, increased CO₂ sensitivity, and fear conditioning. Interestingly, the majority of the environmental factors suggest heritable traits. Thus, although the studies of the cognitive and behavioral theories were of lesser quality, they contribute to the etiology of panic disorder. Finally, there is very low quality evidenced-based medicine to support a role for the psychodynamic theory in the etiology of panic disorder.

Weaknesses in the Literature:

More large sample, randomized, controlled trials need to be done on the exact role environmental factors play in panic disorder. These studies should focus on the cognitive and behavioral theories.

Gaps in the Literature:

Research continues to explore exactly which gene or neurotransmitter is the source for panic disorder. Further, randomized, controlled trials are needed to legitimize any role for the psychodynamic theory in the etiology of panic disorder.

Conclusions:

To date the level 1 evidence-based medicine supports genetics as the primary contributor to the origin of panic disorder. Further, several good quality studies also show that key environmental factors, such as learned anxiety and fear conditioning, may also in themselves be heritable traits. Also indicated to be important is one's lifestyle choices. For example, smoking is key to developing hypercapnea, a trait known to exist in panic disorder patients. Only the worst quality research makes any attempt to correlate the etiology of panic disorder with the psychodynamic theory.

Overall, the research statement that the preponderance of level 1 evidence, in the etiology of panic disorder, supports genetics has been upheld. Further, also upheld is that the minority of the etiology of panic disorder is due to environmental factors.

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Appendix 1

Level 1: Includes high quality randomized controlled trials that consider all important outcomes and high quality meta-analysis using comprehensive search strategies.				
Author	N	Title of Study	Study Quality	Results
Bellodi	n=132	CO2- Induced Panic Attacks : A Twin Study (1998)	1	CO2 induced PA found in monozygotic (55.6%) and dizygotic twins (12.5%). Sensitive respiratory control center plays a role in etiology.
Hettema	5 family studies, 3 twin studies	A Review and Meta-Analysis of the Genetic Epidemiology of Anxiety Disorders. (2001)	1	They estimated heritability of PD in the 50-60% range.
Johnson	n=688	Association between cigarette smoking and anxiety disorders during adolescence and early adulthood (2000)	1	Adolescence who smoked ≥ 20 cigarettes a day were at elevated risk for agoraphobia, generalized anxiety disorder and panic disorder. ¹⁹ Furthermore, they also found that quantity and frequency of cigarette smoking during adolescence was also associated with an elevated risk for agoraphobia, GAD, and PD.
Kaiya	n=4000	Factors associated with the development of panic attack and panic disorder: Survey in the Japanese population (2005)	1	Though it is unknown if dislike of exercise or poor-stress-coping ability cause panic disorder/attacks or are a result of panic disorder/attacks they are nevertheless related.
Kendler	n=2163	Panic Disorder in Women: A Population - Based Twin Study (1993)	1	They also found that the co-twin of an affected twin was at an increased risk for panic disorder compared to the general population. Further, they determined that panic disorder with a significant phobic avoidance represents a more severe form of panic disorder.
Kendler	n=7500	The Etiology of Phobias: An evaluation of the Stress-Diathesis model (2002)	1	All tests to verify the validity of the stress diathesis model failed
Perna	n=203 PD pts, n=897 first degree relatives.	Family history of panic disorder and hypersensitivity to CO2 in patients with panic disorder (1996)	1	CO2 hypersensitivity was significantly related to familial genetic risk for panic disorder.
Richborn-Kjennerud	n=3172	Genetic and environmental influences on the association between smoking and panic attacks in females: a population based twin study (2004)	1	The same shared environmental factors directly influence both panic and smoking. Results indicated that shared environmental factors accounted for 75% of the covariance between smoking and panic attacks; and, shared environmental factors were perfectly correlated accounting for 61% of the correlation between the phenotypes
Scherrer	n=8169	Evidence for genetic influences common and specific to symptoms for generalized anxiety and panic. (2000)	1	They found that genetic factors accounted for 43.4% of the variance in the risk for panic disorder with the remainder of variance due to unique environmental factors

Stein	n=337	Heritability of anxiety sensitivity: A twin study. (1999)	1	The development of panic disorder is not only due to the inheritance of a physiological trait, such as CO ₂ reactivity, but also due to cognitive risk factors, such as anxiety sensitivity, which are also heritable
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Level 2 includes nonrandomized clinical trials, lower-quality randomized controlled trials, clinical cohort studies, and case-controlled studies with nonbiased selection of study participants and consistent findings. Also included are high quality, historical, uncontrolled studies or well designed epidemiologic studies with compelling findings.

Arnold	review of EBM	Genetics of Anxiety Disorders (2004)	2	Linkage studies showed association to chromosome 13q and 22q and panic disorder probands, as well as the 9q31 gene, and a region of chromosome 7p.
Battaglia	review of EBM	Anxiety and Panic: from human studies to animal research and back (2005)	2	Learning is in itself a heritable trait. Twin studies report the heritability of anxiety and panic to be between 30-62%. Modern learning theory on panic disorder explains panic attacks as fundamental emotions to unconditioned fear occurring at an inappropriate time based on genetic vulnerability. Hypercapnia has been shown to cause behavioral and physical responses in mammals, including man. Stress, in the form of suffocation, child abuse, child separation anxiety, or separation from caregivers, can trigger panic disorder by changing gene expression.
Beek	n= 23 1 st degree relatives. n=38 PD pts. n=30 controls.	Anxiety sensitivity in first-degree relative of patients with panic disorder (2002)	2	First-degree relatives of patients with panic disorder were more anxiety sensitive than controls.
Bouwer	n= 167 PD pts. n= 60 controls	Association of panic disorder with a history of traumatic suffocation (1997)	2	19.3% of panic disorder patients provided a history of a traumatic suffocation experience.
Friedman	n= 101 PD pts. n= 22 schizophrenia pts. n= 19 major depression. n= 58 other anxiety disorders.	The Incidence and influence of early traumatic life events in patients with panic disorder: A comparison with other psychiatric outpatients. (2002)	2	These events were not risk factors specific to the development of panic disorder. There was also a positive correlation between panic frequency and current depression.
Geller	n= 230 gen. population. n=229 cohort.	Anxiety disorders following miscarriage (2001).	2	There was no evidence for increased risk of panic disorder or agoraphobia in the six months following miscarriage.
Hettema	n=173	A twin study of the genetics of fear conditioning (2003)	2	They found that every phase of the fear conditioning process in humans demonstrated heritability in the 35-45% range
Noyes	n=40, n=20 controls.	Relationship Between Panic Disorder and Agoraphobia. (1986)	2	They concluded that the results of the study confirm that agoraphobia, like panic disorder, is familial in nature. Agoraphobia is a more severe disturbance than panic disorder.
Roy-Byrne	Historical article on EBM	Search for the pathophysiology of panic disorder (1998)	2	The amygdala as a possible location involved in panic disorder. Their research is supported by the known inhibitory activity of GABA and N-methyl-D-aspartate receptors in the amygdala and the efficacy of benzodiazepine anxiolytics on panic disorder.

Level 3 includes consensus viewpoint or expert opinion studies.				
Bouton	position paper based on EBM	A modern learning theory on the etiology of panic disorder (2001)	3	Panic attacks occur due to the learning of conditioned stimuli.
Busch	Expert's position paper	Theory and technique in psychodynamic treatment of panic disorder (1999)	3	Panic disorder patients have panic attacks because of an intrapsychic conflict between violence and fear of abandonment. Panic disorder patients have difficulty controlling and tolerating angry feelings and thoughts.
Gassner	Expert's position paper	The Role of traumatic experience in panic disorder and agoraphobia (2004)	C	Using psychoanalysis in the etiology and treatment of panic disorder is widely considered by other clinicians to be inappropriate treatment . . . for patients with symptoms of agoraphobia and panic attack.

Appendix 2

Studies Excluded

Author	n	Title of Study	Reason for exclusion
Norton	n=125	Hierarchical Model of Vulnerabilities for Anxiety: Replication and Extension with a Clinical Sample. (2005)	1. Other studies have found their results degraded by combining data from anxiety and depression databases. 2. They only measure each construct once. 3. Their hierarchy of anxiety sensitivity and intolerance of uncertainty is questionable. 4. The cross-sectional correlational design of the study cannot rule out other potential explanations, like a comorbid diagnosis, to account for negative affectivity. 5. Overall, article focuses on anxiety disorders generally, not specifically PD.
Busch	position paper	Neurophysiological, Cognitive-Behavioral, and Psychoanalytical Approaches to Panic Disorder: Toward an Integration. (1991).	1. No RCT's. 2. Most statements only backed by case reports with small sample sizes. 3. It is a position paper arguing for the psychodynamic theory to explain PD, but offers little concrete evidence to do so.
Asnis	review of a study, N=153	Environmental Factors in Panic Disorder. (1999).	1. It is a review of a primary source.
Larsen	n=48	Analysis of Startle Responses in Patients with Panic disorder and Social Phobia. (2002)	1. Small sample size. 2. Non-random.
Yasushi Inada	n=63	Positive Association between panic disorder and polymorphism of the serotonin 2A receptor gene. (2003).	1. Small sample size. 2. Their choice of "super-normal" control subjects may have increased the difference between the groups.
Maier	n=40	A controlled Family Study in Panic Disorder. (1993)	1. The information presented is valid, yet relatively old and presented as well and better correlated in other trials. 2. Small sample size.
Bisaga	n=6	Cerebral glucose metabolism in women with Panic Disorder. (1998)	1. Small sample size.

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