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CAG Repeat Length and Suicidality in Huntington's disease

Christen Kutz

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CAG Repeat Length and Suicidality in Huntington's disease

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A dissertation proposal presented in partial fulfillment

of the requirements for the

Degree of Doctor of Philosophy

March 2015

Signature (Approval) Page

We hereby certify that this dissertation, submitted by Christen Kutz, conforms to acceptable standards and is fully adequate in scope and quality to fulfill the dissertation requirement for degree of Doctor of Philosophy in Health Science.

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Abstract

The purpose of this study was to determine if a correlation exists between suicide and CAG repeat length in Huntington's disease.

Methodology:

A case-control study using the COHORT Study de-identified database was conducted. Responses were collected from 163 participants. Depression, substance abuse history and use of benzodiazepines were covariates. Responses to the UHDRS behavioral section pertaining to the frequency and severity of suicidal ideation ("feels life is not worth living", "has suicidal thoughts") were analyzed.

Results:

Despite taking depression, benzodiazepine use, and history of substance abuse into account, there was a predictive relationship between CAG repeat length and frequency of suicidal ideation ($p = .010$). When the effect of depression was taken into account, there was no significant relationship between CAG repeat length and the severity of suicidal ideation.

Recommendations:

The findings from this quantitative analysis supported using CAG length in a clinician's risk factor assessment to determine the frequency of suicidality.

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CAG Repeat Length and Suicidality in Huntington's disease

Chapter 1

Introduction

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, causing atrophy of the basal ganglia, specifically the caudate nucleus, putamen, and globus nucleus (Novak & Tabrizi, 2010; Roos, 2010; Ross & Tabrizi, 2011). The disease is characterized by choreiform movements, dystonia, mood and personality disorders, and cognitive impairment (Novak & Tabrizi, 2010; Ross & Tabrizi, 2011). The average age of HD symptom onset is approximately 39 years although pediatric cases have been reported (Huntington Study Group [HSG], 2011). Approximately 30,000 people in the United States (US) have clinical manifestations of HD, and an additional 150,000 healthy people are thought to be immediately at risk of developing HD (HSG, 2011). There is no gender or definite racial predispositions and the disease is found throughout the world (HSG, 2011). Prevalence rates are particularly high in selected genetically segregated areas, such as the Lake Maracaibo region of Venezuela (HSG, 2011). Huntington's disease is notably rare in Finland and Japan (HSG, 2011).

Overview

Huntington's disease has been traditionally diagnosed in individuals having 36 or more cytosine, adenine, and guanine (CAG) repeats on the short arm of chromosome 4 (Rosenblatt et al., 1996). As a result of this abnormality, a mutated huntingtin protein is produced. The number of CAG repeats on the huntingtin gene may cause variations in clinical presentation. HD research, involving genetics, has revealed variations in disease

presentation, severity of symptoms, and age of onset related to the number of CAG repeats on the huntingtin gene (Rosenblatt et al., 1996). Larger numbers of CAG repeats are associated with younger onset age, and CAG trinucleotide expansions in juvenile HD are usually in the range of 80 to 100 repeats (Brinkman, Mexei, Theilmann, Almquist, & Hayden, 2007). In addition, there may be differences in clinical presentation, including severity of movement disorder, psychiatric disease, cognitive dysfunction, and metabolism (Rosenblatt et al., 1996).

Huntington's disease patients progress to develop a combination of choreiform movements, dystonia, and parkinsonian features, including rigidity, postural instability and bradykinesia (Ross & Tabrizi, 2011). Abnormal eye movements can be one of the earliest motor signs of HD. Dysarthria, dysphagia, and hypermetabolism with subsequent weight loss are typical later manifestations of the illness (Aziz et al., 2008). The illness typically progresses over a period of 15 to 20 years after onset of symptoms. The initial decade of symptomatic HD is characterized by minimal functional disability and independence with activities of daily living (Roos, 2010). The last 5 to 10 years of HD can lead to profound physical and psychiatric debility (Roos, 2010). As a result, many affected individuals require 24-hour nursing care and/or extensive assistance with activities of daily living. The average age at death is 54 to 55 years of age (Harper, 2005).

In addition, different cognitive domains may be impaired, including attention, executive function, and sequencing (Roos, 2010). Cortical deficits, such as aphasia, agnosia, and apraxia, may also be present (Roos, 2010). Insight and central language function generally remain unaffected even in advanced stages (Roos, 2010). Psychiatric

disease is also common, typically manifesting as psychosis, affective disorders, suicidal ideation, and apathy. Individuals with HD develop significant personality changes, affective psychosis, or schizophrenic psychosis (Rosenblatt, 2007). Prior to the onset of clinically manifest disease, they tend to score high on measures of depression, hostility, obsessive-compulsiveness, anxiety, interpersonal sensitivity, phobic anxiety, and psychoticism (Duff et al, 2007). Behavioral disturbances, such as intermittent explosiveness, apathy, aggression, alcohol abuse, sexual dysfunction and deviations, and increased appetite, are common; delusion and paranoia are common, and hallucinations are less common (Anderson & Marder, 2001). Unlike motor and cognitive dysfunction, psychiatric changes tend not to progress with disease severity (Anderson & Marder, 2001).

Suicide. Individuals with Huntington's disease are more likely than the general population to commit suicide (Fiedorowicz, Mills, Ruggle, Langbehn, & Paulsen, 2011; Novak & Tabrizi, 2010). A survey of 4171 carriers of the Huntington's gene with pre-manifest and manifest disease found that 17.5% of suicidal thoughts occurred at or around the time of testing, and 10% of those had made at least one suicide attempt in the past (Novak & Tabrizi, 2010). Suicidal ideation was highest in gene carriers who were beginning to become symptomatic and in those who were beginning to lose independence and functional ability (Novak & Tabrizi, 2010). Risk factors for suicide are depression and impulsivity although some individuals with the disease have suicidal ideation in the absence of depression; for some, thoughts of suicide seem to be a rational response to their imminent loss of independence (Novak & Tabrizi, 2010). Other risk factors for

completed suicide in HD include male gender and lack of offspring; however, actual suicide attempts are greater in the female HD population (Fiedorowicz et al., 2011).

Problem Statement and Goal

The purpose of this quantitative analysis is to identify if there is a correlation between suicide and CAG repeat length in Huntington's disease. The goal of this research would be early identification, assessment, and treatment of suicidal behaviors to reduce the number of suicide attempts and completions in the HD patient population.

The research questions of this proposed research include the following:

1. What is the correlation between CAG repeat length and frequency of suicidal ideation?
2. What is the correlation between CAG repeat length and severity of suicidal ideation?
3. Does the Unified Huntington's Disease Rating Scale (UHDRS) behavioral assessment accurately represent suicidal behavior of Huntington's disease patients?

Significance and Need for Study

Death by suicide among individuals affected by HD is one of the serious consequences reported for this disease. In 1872, a physician, George Huntington, referred to a characteristic of the disease that would later acquire his name as "a form of insanity which leads to suicide" (Rubin, 2003, p. 8). The incidence of suicide and the conditions that predispose one to suicide is higher in HD than in the general population, including depression and isolation from the community, which occur commonly in HD (Rubin, 2003). Completed suicide rates have been reported to be as high as 13% in

Huntington's disease, reflecting a seven-to-12-fold increase from the general population (Paulsen et al., 2005). Comparison with other research suggested that suicide rates in HD remain higher than then those found in other medical conditions and neurodegenerative disorders (Paulsen et al., 2005).

Much of research on suicide risk in Huntington's disease has been centered on persons undergoing genetic testing. Less focus has been placed on suicidal ideation over the different stages of pre-manifest and manifest HD (Paulsen et al., 2005). The management of a suicidal HD patient potentially involves three components. The first component is the identification and treatment of existing psychiatric disorders (Mann, 2003). The second component is the assessment of suicide risk and limitation of access to lethal methods of suicide (Mann, 2003). The last component is the identification of the diathesis, which may in turn reduce the propensity to attempt suicide (Mann, 2003). There are currently no suicide prevention guidelines specific to Huntington's disease. If a predictive relationship is found to exist between CAG length and suicide, CAG repeat analysis may become a component when assessing suicide risk factors in a HD patient.

Research Hypothesis

There is consistent evidence suggesting that genetic factors play a role in the predisposition to suicidal behavior in the general population (Ozalp, 2009). Family, twin, and adoption studies have demonstrated that there is a genetic dimension to suicide (Ozalp, 2009). Although there is some overlap between suicide and mood disorders even among psychiatric groups with the highest risk, some patients never attempt suicide, indicating the importance of a diathesis or genetic link to suicide that is independent of the underlying psychiatric disorder (Ozalp, 2009). Among individuals with HD, suicide

is more common than in the general population and accounts for 5 to 7% of deaths. Over 25% of individuals with HD attempt suicide at least once (Ozalp, 2009). Some factors, which may contribute to suicide risk, have previously been identified, but no studies have investigated if there is a correlation between CAG length and suicide in Huntington's disease, which leads to the following hypotheses.

Hypothesis 1. CAG repeat length significantly predicts the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines

Hypothesis 2. CAG repeat length significantly predicts the severity of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

Hypothesis 3. The UHDRS behavioral assessment accurately represents suicidal behavior of Huntington's disease patients.

Definition of Terms

Adenine. Adenine (A) is one of four chemical bases in DNA with the other three being cytosine (C), guanine (G), and thymine (T). Within the DNA molecule, adenine bases located on one strand form chemical bonds with thymine bases on the opposite strand. The sequence of four DNA bases encodes the cell's genetic instructions. A form of adenine called adenosine triphosphate (ATP) serves as an energy storage molecule and is used to power many chemical reactions within the cell (National Institute of Neurological Disease and Stroke, 2014).

Allele. An allele is one of two or more versions of a gene. An individual inherits two alleles for each gene: one from each parent. If the two alleles are the same, the individual is homozygous for that gene. If the alleles are different, the individual is heterozygous. Although the term "allele" was originally used to describe variation among genes, it now also refers to variation among non-coding DNA sequences (National Institute of Neurological Disease and Stroke, 2014).

Agnosia. Agnosia is characterized by an inability to recognize and identify objects or persons. People with agnosia may have difficulty recognizing the geometric features of an object or face or may be able to perceive the geometric features, but not know what the object is used for or whether a face is familiar or not. Agnosia can be limited to one sensory modality, such as vision or hearing. For example, a person may have difficulty in recognizing an object as a cup or identifying a sound as a cough. Agnosia can result from strokes, dementia, developmental disorders, or other neurological conditions. It typically results from damage to specific brain areas in the

occipital or parietal lobes of the brain (National Institute of Neurological Disease and Stroke, 2014).

Aphasia. Aphasia is difficulty in expressing oneself when speaking, trouble understanding speech, and difficulty with reading and writing. Aphasia is not a disease, but a symptom of brain damage (National Institute of Neurological Disease and Stroke, 2014).

Apraxia. Apraxia is characterized by loss of the ability to execute or carry out skilled movements and gestures, despite having the desire and the physical ability to perform them. Apraxia results from dysfunction of the cerebral hemispheres of the brain, especially the parietal lobe, and it can arise from many diseases or damage to the brain (National Institute of Neurological Disease and Stroke, 2014).

Autosomal dominance. Autosomal dominance is a pattern of inheritance characteristic of some genetic diseases. "Autosomal" means that the gene in question is located on one of the numbered, or non-sex, chromosomes. "Dominant" means that a single copy of the disease-associated mutation is enough to cause the disease. This is in contrast to a recessive disorder in which two copies of the mutation are needed to cause the disease (National Institute of Neurological Disease and Stroke, 2014).

Bradykinesia. Bradykinesia is a decrease in spontaneity and movement. It is one of the features of extrapyramidal disorders (National Institute of Neurological Disease and Stroke, 2014).

Chorea. Chorea is comprised of involuntary, forcible, rapid, jerky movements that may be subtle or become confluent, markedly altering normal patterns of movement. Hypotonia and pendular reflexes are often associated. Conditions, which feature

recurrent or persistent episodes of chorea as a primary manifestation of disease, are referred to as choreatic disorders. Chorea is also a frequent manifestation of basal ganglia diseases (National Institute of Neurological Disease and Stroke, 2014).

Chronic. Chronic refers to a disease or condition that persists or progresses over a long period of time (National Institute of Neurological Disease and Stroke, 2014).

Cytosine. Cytosine is one of four chemical bases in DNA, the other three being adenine, guanine, and thymine. Within the DNA molecule, cytosine bases, located on one strand, form chemical bonds with guanine bases on the opposite strand. The sequence of four DNA bases encodes the cell's genetic instructions (National Institute of Neurological Disease and Stroke, 2014).

Cytosine adenine guanine or CAG. DNA repeats of cytosine, adenine, and guanine on the short arm of chromosome 4 are known as CAG (National Institute of Neurological Disease and Stroke, 2014).

Deoxyribonucleic acid. Deoxyribonucleic acid is the chemical name for the molecule that carries genetic instructions in all living things. The DNA molecule consists of two strands that wind around one another to form a shape known as a double helix. Each strand has a backbone made of alternating sugar (deoxyribose) and phosphate groups. Attached to each sugar is one of four bases: adenine, cytosine, guanine, and thymine. The two strands are held together by bonds between the bases: adenine bonds with thymine, and cytosine bonds with guanine. The sequence of the bases along the backbones serves as instructions for assembling protein and RNA molecules (National Institute of Neurological Disease and Stroke, 2014).

Dysarthria. Dysarthria is a disturbance of speech due to emotional stress, due to brain injury, or to paralysis, incoordination, or spasticity of the muscles used for speaking (National Institute of Neurological Disease and Stroke, 2014).

Dysphagia. Dysphagia is difficulty in swallowing (National Institute of Neurological Disease and Stroke, 2014).

Dystonia. Dystonia is involuntary, sustained or spasmodic, patterned, and repetitive muscle contractions, frequently causing twisting, flexing or extending, and squeezing movements or abnormal postures (National Institute of Neurological Disease and Stroke, 2014).

Gene. A gene is a functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA, and most genes contain the information for making a specific protein (National Institute of Neurological Disease and Stroke, 2014).

Guanine. Guanine is one of four chemical bases in DNA with the other three being adenine, cytosine, and thymine. Within the DNA molecule, guanine bases, located on one strand, form chemical bonds with cytosine bases on the opposite strand. The sequence of four DNA bases encodes the cell's genetic instructions (National Institute of Neurological Disease and Stroke, 2014).

Huntingtin gene. The huntingtin gene (HTT) has one region that contains a particular DNA segment known as a CAG trinucleotide repeat. This segment is made up of a series of three DNA building blocks (cytosine, adenine, and guanine) that appear multiple times in a row. Normally, the CAG segment is repeated 10 to 35 times within the gene. Although the exact function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain and is essential for normal

development before birth. Huntingtin is found in many of the body's tissues, with the highest levels of activity in the brain. Within cells, this protein may be involved in chemical signaling, transporting materials, attaching (binding) to proteins and other structures, and protecting the cell from self-destruction (apoptosis) (National Institute of Neurological Disease and Stroke, 2014).

Huntington Study Group. The Huntington Study Group is a non-profit group of clinical investigators from medical centers in the United States, Canada, Europe, Australia, New Zealand, and South America, who are experienced in the care of Huntington patients and dedicated to clinical research of Huntington disease. The HSG was formed in 1993, prompted by the recognition that clinical research in HD required the participation of large numbers of research participants under the cooperative effort of skilled and experienced research physicians (Huntington Study Group, 2011).

Hypermetabolism. Hypermetabolism refers to a state of increased metabolism where by the body's rate of energy production rises above normal (National Institute of Neurological Disease and Stroke, 2014).

Mutation. A mutation is a change in a DNA sequence. Mutations can result from DNA copying mistakes made during cell division, exposure to ionizing radiation, exposure to chemicals called mutagens, or infection by viruses. Germ-line mutations occur in the eggs and sperm and can be passed on to offspring although somatic mutations occur in body cells and are not passed on (National Institute of Neurological Disease and Stroke, 2014).

Protein. A protein is a large molecule composed of one or more chains of amino acids in a specific order; the order is determined by the base sequence of nucleotides in

the gene that codes for the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs, and each protein has unique functions. Examples of proteins include hormones, enzymes, and antibodies (National Institute of Neurological Disease and Stroke, 2014).

Suicide. Suicide is a death caused by self-directed injurious behavior with any intent to die as a result of the behavior (National Institute of Neurological Disease and Stroke, 2014).

Suicide attempt. A suicide attempt is a non-fatal, self-directed, potentially injurious behavior with any intent to die as a result of the behavior. A suicide attempt may or may not result in injury (National Institute of Neurological Disease and Stroke, 2014).

Suicidal ideation. Suicidal ideation involves thinking about, considering, or planning for suicide (National Institute of Neurological Disease and Stroke, 2014).

Unified Huntington's disease Rating Scale. The UHDRS is a research tool developed by the Huntington Study Group to provide a uniform assessment of the clinical features and course of HD. The UHDRS has undergone extensive reliability and validity testing and has been used as a major outcome measure by the HSG in controlled clinical trials. The components of the UHDRS include the following:

1. Motor Assessment
2. Cognitive Assessment
3. Behavioral Assessment
4. Independence Scale
5. Functional Assessment

6. Total Functional Capacity (TFC) (HSG, 2011)

Unified Huntington's Disease Rating Scale behavioral assessment. Use the following keys to rate both severity and frequency:

Severity Frequency

0 = absent

1 = slight, questionable

2 = mild

3 = moderate

4 = severe

Sad mood. A sad mood is feeling sad, sad voice expression, tearfulness, inability to enjoy anything.

Low self-esteem/guilt. Low self-esteem/guilt includes self-blame, self-deprecation, feelings of being a bad or unworthy person, and feelings of failure.

Anxiety. Anxiety includes worries, anticipation of the worst, and fearful anticipation.

Suicidal thoughts. When one has suicidal thoughts, he or she feels life not worth living, may have suicidal intent, and/or be preparing for the act.

Disruptive behavior. Disruptive behavior includes being impatient, demanding, inflexible, physical violence, verbal outbursts, threatening, foul, or using abusive language.

Irritable behavior. Irritable behavior includes being impatient, demanding, inflexible, driven and impulsive, and uncooperative.

Obsessions. Obsessions are recurrent and persistent ideas, thoughts, or images.

Compulsions. Compulsions are repetitive, purposeful, and intentional behaviors.

Delusions. Delusions are fixed false beliefs, which are not culturally shared.

Hallucinations. Hallucinations are a perception without physical stimulus and can include the following: auditory, visual, tactile, gustatory, and olfactory hallucinations.

Example Questions:

1. Does the investigator believe the subject is confused?

Yes or No

2. Does the investigator believe the subject is demented?

Yes or No

3. Does the investigator believe the subject is depressed?

Yes or No

4. Does the subject require pharmacotherapy for depression?

Yes or No (HSG, 2011)

Summary

Huntington disease is an autosomal-dominant neurodegenerative disease, characterized by cognitive disturbances, motor abnormalities, and psychiatric symptoms, caused by an expanded CAG repeat on the short arm of chromosome 4. Suicidal ideation, suicide attempts, and completed suicides are frequent findings in individuals with Huntington's disease. The prevalence of suicide has been reported to be 20% in both pre-motor and motor-symptomatic mutation carriers (Hubers et al., 2012). Much of the research to date on suicide has involved critical periods of time during the course of the disease and possible risk factors, such as depression, impulsivity, and substance

abuse. The relationship between CAG length and suicide has not been previously studied. Suicide is one of the few potentially preventable causes of premature death in Huntington's disease and an improved understanding of potential risk factors for suicide, including CAG length, is worthy of attention and exploration.

Chapter 2

Review of Literature

Huntington Disease and Suicide

Suicidal behavior spans a spectrum that ranges from completed suicide, to suicide attempts, to suicidal ideation (Mann, 1998). Suicide can be defined as suicidal ideation, suicide attempt, or completed suicide (Crosby, Ortega, & Melanson, 2011, p. 23). To further clarify, suicide is a “death caused by self-directed injurious behavior with any intent to die as a result of the behavior” (Crosby et al., 2011, p. 23). A suicide attempt is “a non-fatal, self-directed potentially injurious behavior with an intent to die as a result of the behavior. The suicide attempt may or may not result in an injury” (Crosby et al., 2011, p. 23). Suicidal ideation is “thinking about, considering, or planning for suicide” (Crosby et al, 2011, p. 23).

Individuals with HD develop significant psychological disease, personality changes, affective psychosis, or schizophrenic psychosis (Rosenblatt et al., 2007). Prior to the onset of HD, they tend to have elevated scores on measures of depression, hostility, impulsivity, obsessive-compulsiveness, anxiety, interpersonal sensitivity, phobic anxiety, and psychoticism (Duff, Paulsen, Beglinger, Langbehn, & Stoudt, 2007). Behavioral disturbances, such as intermittent explosiveness, apathy, aggression, alcohol abuse, sexual dysfunction and deviations, and increased appetite, are frequently associated with the disease (Pagon, Adam, & Bird, 2010). In addition, paranoid delusions are common; whereas, visual and auditory hallucinations are not as likely (Pagon et al., 2010).

The incidence of depression and suicide in preclinical and symptomatic individuals is significantly more common in HD patients than the general population

(Paulsen et al., 2005). The etiology of depression in HD is unclear; it may be a pathologic, rather than a psychological, consequence of having the disease (Slaughter, Martens, & Slaughter, 2001). Suicide and suicidal ideation are common in persons with HD, but the incidence rate changes with disease course and predictive testing results (Almqvist, Bloch, Brinkman, Craufurd, & Hayden, 1999). Paulsen et al. (2005) suggested that suicide in patients with Huntington's disease occurs at a broad rate between seven and 200 times more often than in the general population (p. 725). Previous studies evaluating suicidal risk and actual completion in Huntington's disease vary greatly in methodology, making direct comparisons difficult (Paulsen et al., 2005). In one of the largest studies to date, Almqvist et al. (1999) evaluated the frequency of catastrophic events (CE), which include suicide, suicide attempts, and psychiatric hospitalizations, at predictive testing centers worldwide after collecting HD-predictive testing results through questionnaires (p. 1294). A total of 44 persons in a cohort of 4,527 (0.97%) test participants had a CE, which resulted in the following: five successful suicides, 21 suicide attempts, and 18 hospitalizations for psychiatric reasons (Almqvist et al. 1999, p. 1294). All persons committing suicide had signs of HD, whereas 11 of 21 (52.4%) persons attempting suicide and eight of 18 (44.4%) who had a psychiatric hospitalization were symptomatic. A total of 11 of 13 (84.6%) asymptomatic persons who experienced a CE during the first year after HD-predictive testing received an increased-risk result (p. 1295). Factors associated with an increased risk of a CE included a psychiatric history less than or equal to five years prior to testing and unemployed status (Almqvist et al., 1999, p. 1296).

Hubers et al. (2012) investigated the prevalence, clinical association, and predictors of suicide in Huntington's disease. Suicide was investigated in 152 HD mutation carriers and 56 non-carriers, and suicide was considered present if the score on the item "suicidal ideation" of the Problem Behaviours Assessment (PBA) was greater than one point. After 2 years, 100 mutation carriers who were free of suicide at baseline were re-assessed. Associations and predictors of suicide were analyzed using multivariate logistic regression analysis (Hubers et al., 2012). Associations and predictors of suicide were analyzed using multivariate logistic regression analysis (Hubers et al., 2012). The results indicated 11 (20%) pre-motor and 20 (20%) motor-symptomatic mutation carriers were considered suicidal compared to none of the non-carriers (Hubers et al., 2012). Suicidal mutation carriers were (a) more likely to use antidepressants (odds ratio [OR] = 5.3); (b) were more often apathetic (OR = 2.8); (c) more often had a depressed mood, according to the PBA (OR = 5.9); and (d) were more often diagnosed with a DSM-IV depression diagnosis (OR = 4.7; Hubers et al., 2012). Independent associations were more frequent use of antidepressants (OR = 4.0) and presence of a depressed mood (OR = 4.2; Hubers et al., 2012). Longitudinally, depressed mood (OR = 10.6) at baseline was the only independent predictor of suicide at follow-up (Hubers et al., 2012). Hubers et al. (2012) concluded it is important for health care providers to screen both pre-motor and motor-symptomatic HD mutation carriers for suicide.

Bird (1999) put these findings into perspective when he compared the suicide rate in Huntington's disease of 138 of 100,000 persons per year with that of the general population (12-13 per 100,000). Paulsen, Ferneyhough-Houth, & Nehl (2005) assessed

suicide along with suicide completion and report much higher rates. They indicated that suicidal ideation occurs in up to 50% of people with Huntington's disease (p. 725).

Several studies have suggested a greater risk of suicide in Huntington disease; however, unique risk factors for suicide in HD are not established. Fiedorowicz et al. (2011) sought to determine the risk factors for suicidal behavior in prodromal HD. Data was analyzed from the Neurobiological Predictors of Huntington's Disease Trial (PREDICT-HD) cohort study, which is a multi-site, longitudinal prospective study designed to identify and track markers of HD prior to the onset of classic motor symptoms. Individuals were recruited from 32 sites in the US, Canada, Europe, and Australia (Fiedorowicz et al., 2011). Prodromal HD can be defined as the presence of CAG repeat expansion prior to meeting the clinical criteria for a diagnosis of manifest HD (Fiedorowicz et al., 2011). Seven hundred thirty-five cases with HD gene expansion without manifest symptoms and 194 non-gene-expanded controls were included in this analysis (Fiedorowicz et al., 2011). A number of potential risk factors for suicidal behavior were assessed, including symptoms of depression, hopelessness, substance abuse, marital status, gender, and psychiatric history (Fiedorowicz et al., 2011). During a mean of 3.7 years of prospective follow-up, 12 cases (1.6%) attempted suicide and one completed suicide (0.1%). No suicides were observed among controls (Fiedorowicz et al., 2011). In univariate Cox proportional hazards regression models, a history of suicide attempts (HR 8.5, 95% CI [2.8–26.1], $p < 0.0002$) and a Beck Depression Inventory II score greater than 13 (HR 7.2, 95% CI [2.3–22.0], $p < 0.0006$) were associated with suicidal behavior (Fiedorowicz et al., 2011). These risk factors had independent effects in multivariate models. A history of incarceration in the past 2 years was also associated

(HR 12.5, 95% CI [2.7–56.6], $p < 0.002$), but uncommon (Fiedorowicz et al., 2011). No further risk factors were identified. Fiedorowicz et al. (2011) concluded a history of suicide attempt(s) and the presence of depression are strongly predictive of suicidal behavior in prodromal HD.

The majority of HD research has focused on cognitive and motor features of HD while the implications of psychiatric manifestations have received less consideration. A study by Wetzel et al. (2011) examined the presence of psychiatric comorbidity and its involvement in suicidal ideation. Research participants were recruited as part of an ongoing multi-site study at 43 Huntington Study Group sites across North America, Australia, and Europe (Wetzel et al., 2011). The Unified Huntington Disease Rating Scale (Huntington Study Group, 1996) is a standardized clinical rating scale that assesses four components of HD: motor, cognitive, psychiatric, and functional. The psychiatric portion of the UHDRS was primarily used in the current study (Wetzel et al., 2011). This section assesses the frequency and severity of 14 psychiatric symptoms associated with HD, using a semi-structured interview. The following symptoms were considered: sad mood, anxiety, suicidal thoughts, compulsive behavior, irritable behavior, apathy, delusions, and hallucinations (Wetzel et al., 2011). For each symptom, a total score was obtained by multiplying the severity score (rated from 0–4) by the frequency score (rated from 0–4), which results in a minimum score of zero and a maximum of 16 for each symptom (Wetzel et al., 2011). Five psychiatric factors, including depression/anxiety, suicidal thoughts, aggressivity, obsessive/compulsive behavior, and delusions, were also evaluated (Wetzel et al., 2011). Hallucinations were grouped into four distinct factors (audiovisual, tactile, gustatory, and olfactory; Wetzel et al., 2011). Suicidal ideation was

measured on the psychiatric portion of the UHDRS and was scored in terms of frequency and severity. Frequency scores were the following: 0 = almost never, 1 = seldom, 2 = sometimes, 3 = frequently, 4 = almost always (Wetzel et al., 2011). Severity scores were measured similarly: zero = absent, 1 = slight, 2 = mild, 3 = moderate, 4 = severe (Wetzel et al., 2011). A total suicidal ideation score was obtained by multiplying frequency by severity with ranges from 0 to 16 (Wetzel et al., 2011). In addition to the psychiatric symptoms, as measured by the UHDRS, (a) the total motor score; (b) the total cognitive score; and (c) past reports of alcohol, drug, and tobacco abuse were analyzed (Wetzel et al., 2011).

The Huntington Study Group collected data on over 4,000 patients with or at risk for HD worldwide; 18% of those reported suicidal ideation (Wetzel et al., 2011). Because the purpose of this study was to assess suicidal ideation in those with HD, only individuals with a current HD diagnosis score of 2 (probable HD) or 3 (definite HD) on the UHDRS were included in the current study. A total of 3,391 individuals in the database met these criteria. Of the 3,391 individuals with probable or definite Huntington disease, complete data was available for 1,941 individuals (Wetzel et al., 2011). Suicidal ideation was assessed as a categorical variable due to the skewed nature of the distribution. Suicidal ideation was scored as “present” or “absent” based on the suicide severity and frequency item of the UHDRS (Wetzel et al., 2011). Any endorsement of suicidal ideation (scores ≥ 1) was scored as present. This assessment of suicidal ideation serves as the dependent measure in further analyses. A bivariate logistic regression analysis was used to assess whether demographic (age, sex, years of education), motor symptoms, cognitive impairment (Symbol Digit Modalities Test),

and/or psychiatric symptoms (UHDRS Depression/Anxiety, Aggression, Obsession/Compulsion factors as well as alcohol, illicit drug, and tobacco use history) would predict the presence or absence of suicidal ideation Wetzel et al., 2011.

Bivariate logistic regression was used with presence or absence of suicidal ideation as the dependent variable. The overall model was significant ($\chi = 377.12$, $df = 11$, $p < 0.01$; Wetzel et al., 2011). None of the demographic, motor, or cognitive variables was significant predictors of presence or absence of suicidal ideation (Wetzel et al., 2011). Higher UHDRS depression/anxiety (OR = 1.11, $p < 0.01$) and aggression (OR = 1.04, $p < 0.01$) factors were significant predictors of suicidal ideation, however (Wetzel et al., 2011).

Schoenfeld et al. (1984) presented data collected by the New England Huntington's Disease Center to evaluate the suicide patterns of patients with HD. Histories of 149 apparently unrelated families with Huntington's disease, involving 4,919 individuals were collected (Schoenfeld et al., 1984). Within the 149 family histories, there were 403 deceased individuals diagnosed with Huntington's disease and 103 individuals suspected of having HD. Cause of death was determined for 157 of these 506 individuals (Schoenfeld et al., 1984). Among the 403 deceased HD patients, there were nine documented suicides, all of whom were male. Of the 103 suspected HD patients, there were 11 documented suicides, seven males and four females (Schoenfeld et al., 1984). The method of suicide was ascertained for 14 of these individuals and included drowning (4), asphyxiation by poisonous gas (2), gunshot (1), hanging (2), jumping from a high place (3), drug overdose (1), and fire (1; Schoenfeld et al., 1984). Schoenfeld et al. (1984) concluded the prevalence of suicide appeared four times higher among

suspected HD patients than among the diagnosed and implied patients early in the course of their disease are particularly prone to suicide.

Hubers, van Duijn, Roos, van der Mast, and Giltay (2012) used data from the European Huntington Disease Network (EHDN) Registry Study to evaluate suicide in the European Huntington's disease population. Their study investigated the clinical associations and predictors of suicide in a large European cohort of HD mutation carriers (Hubers et al., 2012). The presence of suicide in the preceding month were assessed in 2106 mutation carriers from 15 European countries, all participating in the EHDN Registry. Mutation carriers were considered suicidal if the total score on the suicidal ideation assessment of the Unified Huntington's Disease Rating Scale was greater than 1 point (Hubers et al., 2012). Associations of suicide were analyzed using multi-variate logistic regression analysis, and Cox regression analysis was used to determine predictors of suicide (Hubers et al., 2012). Of the 1937 individuals characterized as free of suicide at baseline, 945 had one or more follow-up measurements. The results of the analysis indicated that at baseline, 169 (8%) mutation carriers were considered suicidal. Cross-sectionally, the presence of anxiety, aggression, a previous suicide attempt, and depression were independently associated to suicide (Hubers et al., 2012). During follow-up, 45 (5.5%) mutation carriers became suicidal (Hubers et al., 2012). The presence of depressed mood and the use of benzodiazepines at baseline were independent predictors of suicide at follow-up (Hubers et al., 2012). CAG repeat length was not a variable that was evaluated to determine if it were a predictor of suicide. Although suicidal ideation is commonly considered to be one index of suicidal risk, no studies have

previously examined if CAG repeat length may be a predictor of suicide. This proposed research will study if a correlation exists between suicide and CAG repeat length.

CAG Length and Clinical Presentation

Several articles were analyzed to identify if a predictive relationship exists between age of onset of Huntington's disease symptoms or clinical presentation of individuals based upon CAG repeat length. Zappacosta et al. (2006) conducted a study to determine if psychiatric disturbances in Huntington's disease are related to either the degree of cognitive or motor compromise or CAG repeat length (Zappacosta et al., 2006). The study included 17 male and 12 female subjects with genetically confirmed HD. The outcome measures were the following: (a) the Hamilton Psychiatric and Anxiety Rating Scales and Brief Psychiatric Rating Scale to assess psychiatric disturbances; (b) Folstein's Quantified Neurological Examination to evaluate motor status; and (c) the Mini-Mental State Examination, Raven Progressive Matrices, Phonemic Verbal Fluency Test, Short Tale Test, Visual Search Test, and Benton's Visual Orientation Line Test to evaluate cognitive function. The length of the CAG repeat sequence in the Huntington's gene was determined by quantitative polymerase chain reaction (PCR; Zappacosta et al., 2006). Results of the Folstein's Quantified Neurological Examination correlated with illness duration and length of CAG repeat (Zappacosta et al., 2006). Although psychiatric scores correlated significantly among themselves ($p < 0.01$), neither cognitive compromise, motor deterioration, nor CAG length were related to the extent of psychiatric compromise (Zappacosta et al., 2006). Zappacosta et al. (2006) concluded there was no correlation between disease severity and psychiatric disturbances, which may indicate that psychiatric disorders progress nonlinearly, possibly because of differential degeneration

of the striatal-cortical circuits. In addition, the lack of correlation between CAG length and cognitive and psychiatric variables need further investigation (Zappacosta et al., 2006).

Unintended weight loss. One of the hallmarks of Huntington's disease is unintended weight loss, the cause of which is relatively unknown (Aziz et al., 2008). Aziz et al. (2008) evaluated potential causes of weight loss, including motor, cognitive, behavioral disturbances, and CAG repeat length (Aziz et al., 2008). Five hundred eighteen patients with early Huntington's disease were included in this study (Aziz et al., 2008). Aziz et al. applied mixed-effects model analyses to correlate weight changes over three years to CAG length, body mass index (BMI), and Unified Huntington's Disease Rating Scale (UHDRS). Results indicated that mean body mass index decreased -0.15 units per year ($p < 0.001$), and subjects with higher CAG repeat numbers had a faster rate of weight loss (Aziz et al., 2008). However, no single UHDRS component, including motor, cognitive, and behavioral scores, was independently associated with the rate of weight loss (Aziz et al., 2008). Aziz et al. (2008) concluded weight loss in Huntington's disease is directly linked to CAG repeat length and is likely to result from a hyper-metabolic state.

CAG repeats. Ashizawa et al. (2008) evaluated parental versus maternal transmitted disease severity, atypical symptoms that may make initial diagnosis complicated, and the age of disease onset. The objective of this study was to determine if there is a relationship between CAG repeat size and clinical presentation (Ashizawa et al., 2008). The subjects included 36 patients with suspected HD and 12 patients with no relatives documented with HD (Ashizawa et al., 2008). Five of those failed to show the

expanded (> 37) CAG repeats and were therefore excluded from the study (Ashizawa et al., 2008). Incidentally, one of these patients was later diagnosed with neuroacanthocytosis (Ashizawa et al., 2008). The remaining 31 patients, including seven patients with atypical clinical features for HD (three without and four with family history of documented HD), were heterozygotes for the CAG repeat expansion (Ashizawa et al., 2008). The patients with atypical features presented with myopathy of unknown origin, low sperm count, action myoclonus, torticollis, Tourette syndrome, dystonia, and action tremor (Ashizawa et al., 2008). There were large CAG repeats (50 copies) in paternally transmitted HD cases with early onset of 30 years or younger (Ashizawa et al., 2008). Data was collected using PCR for DNA analysis (Ashizawa et al., 2008). The onset of Huntington's disease was defined as the "first realization of involuntary movements, dementia, or psychiatric manifestation by the patient, family, and/or physician" (Ashizawa et al., 2008, p. 1137). The Physical Disability Rating Scale was used to measure disease progression. The results of the study indicated the following conclusions: patients lacking a family history of Huntington's disease frequently showed no expansion of CAG repeats, the gender of the affected parent influences CAG repeat size, and the gender of the affected parent affects the phenotypic expression of offspring (Ashizawa et al., 2008). In addition, determination of CAG repeat size has a practical diagnostic value in patients who lack family history of HD or in those patients with an atypical clinical presentation (Ashizawa et al., 2008).

Andrew et al. (1993) conducted a study to determine if there were a relationship between CAG repeat length and clinical presentations of Huntington's disease. The subjects included 360 HD patients from 259 unrelated families (Andrew et al., 1993).

The methods of the study were not specified in the abstract and full-text article was not available in archives. The results of the study indicated there is a highly significant correlation between age of onset of symptoms and CAG repeat length (Andrew et al., 1993). In addition, there seems to be a correlation between age of death and the onset of other clinical features with CAG repeat number (Andrew et al., 1993).

Rosenblatt et al. (1996) investigated whether the rate of clinical progression in HD is influenced by the size of CAG expansion. The study included 512 subjects with a diagnosis of Huntington's disease (Rosenblatt et al., 1996). The outcome measures were Quantified Neurological Examination (QNE) with three sub-scales: (a) Motor Impairment Scale (MIS), chorea scale, and eye movement scale; (b) Mini-Mental Status Examination (MMSE); (c) activities of daily living (HD-ADL), and (d) CAG repeat length, using PCR (Rosenblatt et al., 1996). Included in the analysis were individuals with CAG lengths ranging from 36 to 97 repeats (Rosenblatt et al., 1996). The results of the study indicated that CAG length was significantly associated with the rate of progression with regard to motor impairment, eye movement, and cognition (Rosenblatt et al., 1996). There was not a significant correlation between CAG length and chorea and activities of daily living (Rosenblatt et al., 1996). In addition, it was presumed that the shortest CAG lengths had the latest ages of onset (Rosenblatt et al., 1996).

Theory Specific to Research Topic

The diathesis-stress model of suicidal behavior, a psychological theory that attempts to explain behavior as a pre-dispositional vulnerability, together with stress increases the risk of suicide (Ingram & Luxton, 2005). The diathesis, or predisposition, interacts with the subsequent stress response of an individual. Stress refers to a life event

or series of events that disrupt an individual's psychological equilibrium and potentially serves as a catalyst to the development of suicidal behavior (Ingram & Luxton, 2005). Thus, the diathesis-stress model of suicidal behavior serves to explore how non-biological or genetic traits (diatheses) interact with environmental influences (stressors) that lead to suicide (Ingram & Luxton, 2005). Mann (1998) proposed a stress-diathesis model of suicidal behavior based on his findings from a clinical study of a large sample of patients admitted to a university psychiatric hospital. When compared to patients without a history of suicide attempts, patients with a history of attempt had higher scores on subjective depression and suicidal ideation surveys and reported fewer reasons for living (Mann, 1998). In addition, suicide attempters showed higher rates of lifetime aggression, impulsivity, co-morbid borderline personality disorder, substance abuse and/or alcoholism, family history of suicidal acts, head injury, smoking, and history of child abuse (Mann, 1998). Mann concluded the risk for a suicidal act is thus determined not only by a psychiatric illness or stressor, but also by a diathesis exhibited by tendencies to experience more suicidal ideation and to be more impulsive, therefore, more likely to act on suicidal feelings (Mann, 1998). Simon, Swann, Powell, Potter, Kreshnow, and O'Carroll (2001) conducted a case-control study of nearly lethal suicide attempts among people 13 to 34 years of age. Subjects were asked, "How much time passed between the time you decided to complete suicide and when you actually attempted suicide?" (Simon et al., 2001, pp. 49-59). Attempts were considered impulsive if the respondent reported spending less than 5 minutes between the decision to attempt suicide and the actual attempt. Among the 153 case subjects, (a) 24% attempted impulsively (< 5 minutes), (b) 24% said 5 to 19 minutes, (c) 23% said 20 to 60 minutes,

(d) 16% said 2 to 8 hours, and (e) 13% said 1 or more days (Simon et al., 2001, pp. 49-59).

The purpose of this study was to determine if a correlation exists between suicide and CAG repeat length. Specifically, if CAG length is a diathesis or pre-disposition for suicidal behavior in Huntington's disease. Most stress-diathesis models presume that all people have some level of diathesis for any given psychiatric disorder (van Herrigan, 2012). The point at which the individual develops a disorder depends on the degree to which pre-dispositional risk factors exist and the severity of stress that is experienced (van Heeringen, 2012). This theory also assumes a dichotomous diathesis: either one has it (gene, brain pathology) or one does not have it (van Heeringen, 2012). If the diathesis is absent, stress has no effect, and there is no development of a psychiatric disorder. When the diathesis is present, the expression of the disorder will be conditional on the degree of stress (van Heeringen, 2012). The conceptualization of a diathesis as dynamic implies that such a diathesis is continuous rather than dichotomous. For example, schema models of depression were commonly regarded as dichotomous models; if an individual possessed a depressogenic schema, then he or she is at risk of depression when events that activate this schema occur (van Heeringen, 2012). More recent discussions of the schema model have, however, pointed at the possibility of a continuous character by describing the depressogenic nature of schemata as ranging from weak or mild to strong (van Heeringen, 2012). A continuous diathesis can involve interaction between a stress and a diathesis that might not be static, but may change over time (van Heeringen, 2012). The diathesis may increase or decrease so that the amount of stress needed for the

development of pathology may need to decrease or increase, which may explain differences in suicidal behavior among patients with HD (van Heeringen, 2012).

Summary of What is Known and Unknown about the Topic

Zappacosta et al. (1996) investigated the hypothesis that psychiatric disturbances in Huntington's disease are related to the degree of cognitive or motor compromise. In addition, the study was conducted to determine correlations between CAG repeat length and psychiatric disease severity in 17 men and 12 women from 24 families affected by Huntington's disease. The following evaluations were made: (a) the Hamilton Psychiatric and Anxiety Rating Scales and Brief Psychiatric Rating Scale were used to assess psychiatric disturbances; (b) Folstein's Quantified Neurological Examination was used to evaluate motor status; and (c) the Mini-Mental State Examination, Raven Progressive Matrices, Phonemic Verbal Fluency Test, Short Tale Test, Visual Search Test, and Benton's Visual Orientation Line Test were used to evaluate cognitive function. The length of the CAG repeat sequence in the Huntington's gene was determined by quantitative polymerase chain reaction (Zappacosta et al., 1996).

Cognitive test scores correlated significantly with each other; of these, results of the Visual Search and Short Tale tests correlated significantly with the Folstein's Quantified Neurological Examination score ($p = .05$ and $p = .03$, respectively). Results of the Folstein's Quantified Neurological Examination also correlated with the illness duration and the length of the CAG repeat. Although psychiatric scores correlated significantly among themselves ($p < .01$), neither cognitive compromise, motor deterioration, nor CAG length were related to the extent of psychiatric compromise. The lack of correlation between disease severity and psychiatric disturbances indicated that

psychiatric disorders progress nonlinearly, possibly because of differential degeneration of the striatal-cortical circuits (Zappacosta, 1996). According to Zappacosta et al., the lack of correlation between CAG length and cognitive and psychiatric variables needs further investigation.

In the Zappacosta study, the Hamilton Rating Scale for Depression (HRSD) was utilized to measure depression. The scale is a multiple item questionnaire designed for adults and is used to rate the severity of depression by probing mood, feelings of guilt, suicide ideation, insomnia, anxiety, weight loss, and somatic symptoms. Initially considered the gold standard for rating depression in clinical research, it is now criticized as a test instrument for clinical practice in part because it places more emphasis on insomnia than on suicidal ideas and gestures (Bagby, Ryder, Sculler, & Marshall, 2004). Rickards et al. (2011) used data from the European Huntington's Disease REGISTRY Study to examine the validity of the Beck Depression Inventory and the Hamilton Rating Scale for Depression in Huntington's disease. The outcome scores of the Hamilton rating Scale for Depression (Ham-D), Beck Depression Inventory (BDI), and Unified Huntington's Disease Rating Scale Behavioral Section were collected from the REGISTRY database (Rickards et al., 2011). All participants were divided into two groups (those experiencing depressed mood or no/minimal depressed mood) according to the item "depressed mood" of the UHDRS Behavioral section (Rickards et al., 2011). This item measured the frequency (score range: 0–4) and severity (score range: 0–4) of depressed mood that the person has been experiencing over the last month. Lower numbers represented less frequent and less severe depressed mood; whereas, participants were classified as depressed if they scored 6 or more (Rickards et al., 2011). Of all

patients with a BDI score, 180 patients (21.6%) were classified as endorsing depressed mood according to the criterion of a score of greater or equal to 6 on the depressed mood item of the UHDRS Behavioral section. Of all patients with a Ham-D score, 175 patients (22.8%) were classified as endorsing depressed mood, according to the criterion of a score of greater or equal to 6 on the depressed mood item of the UHDRS Behavioral section (Rickards et al., 2011). The concept of “depression” within the setting of a neurological disorder, such as HD, is problematic for two main reasons. The first reason is the symptoms of HD overlap with those of major depressive disorder. For instance, weight loss is a common symptom of HD regardless of mood status (Rickards et al., 2011). The second reason is that a depressive syndrome in patients with HD may be different from “major depressive disorder” because the etiology is different (Rickards et al., 2011). Rickards et al. discovered that apart from depressed mood, the best discriminators between HD patients endorsing depressed mood and those with no or minimal depressed mood were related to loss of interest, guilt, and suicide. Vegetative symptoms related to sleep and appetite were poor discriminators as were behaviors such as agitation and irritability (Rickards et al., 2011).

In contrast, the Unified Huntington’s Disease Rating Scale was developed by members of the Huntington Study Group in the early 1990s to provide a comprehensive and reliable instrument to assess the clinical features of HD. The UHDRS was tested by Kieburtz, Penney, Como, Ranen, and Schoulsson (1996) to determine reliability and consistency of the rating scale. Data from the final version of the UHDRS have been collected prospectively on 489 patients with manifest HD from 20 sites in North America and Europe (Kieburtz et al., 1996). Of this group, (a) 229 were men (46.8%), (b) 227

were women (46.4%), and (c) the gender of 33 (6.7%) was unknown. Four hundred and twenty-six patients were (a) White (87.1%), (b) 15 Black (3.1%), and (c) race was unknown in 48 (9.8%). In terms of inheritance, (a) 190 patients (38.9%) inherited HD from their mothers, (b) 211 inherited HD from their fathers (43.1%), and (c) the affected parent was unknown in 88 (18.0%; Kieburtz et al., 1996).

The final version of the UHDRS has four components, which assessed motor function, cognition, behavior, and functional capabilities. The motor section of the UHDRS assessed motor features of HD with standardized ratings of oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability (Kieburtz et al., 1996). The total motor impairment scores were the sum of all the individual motor ratings with higher scores indicating more severe motor impairment than lower scores (Kieburtz et al., 1996). The cognitive component was assessed by a phonetic verbal fluency test, Symbol Digit Modalities Test, and the Stroop Interference Test (Kieburtz et al., 1996). Higher scores indicated better cognitive performance. The behavioral assessment measured the frequency and severity of symptoms related to affect, thought content, and coping styles. The total behavior score was the sum of all responses; however, this score may have less usefulness than the individual subscale scores for mood, behavior, psychosis, and obsessiveness, which were created by summing the responses to the corresponding questions (Kieburtz et al., 1996). Higher scores on the behavior assessments indicated a more severe disturbance than lower scores (Kieburtz et al., 1996). The functional assessments included the Huntington's Disease Functional Capacity Scale (HDFCS), the Independence scale, and a checklist of common daily tasks (Kieburtz et al., 1996). The

independence scale was rated from 0 to 100. Higher scores on the function scales indicated better functioning than lower scores (Kieburtz et al., 1996).

Cronbach's alpha analyses were used to examine the internal consistency of the motor, cognitive, behavioral, and functional checklist components of the UHDRS (Kieburtz et al., 1996). In addition, Spearman rank order correlation coefficients were calculated to compare the total motor score, each cognitive test, the behavior score and each subscale, and the three functional scores (Kieburtz et al., 1996). The reliability of the motor component of the UHDRS was examined among three clinicians who were experienced with the evaluation of patients with HD (Kieburtz et al., 1996). Twenty-four patients were each rated by two of the three clinicians with the clinicians evaluating the patients independently. The inter-rater reliability of the total motor scores and of the chorea and dystonia scores was assessed by intra-class correlation (Kieburtz et al., 1996).

Kieburtz et al. found a high degree of internal consistency among the motor, behavioral, cognitive, and functional components of the UHDRS. Cronbach's alpha values were (a) 0.95 for the motor scale, (b) 0.90 for the cognitive tests, (c) 0.83 for the behavioral scale, and (d) 0.95 for the functional checklist (Kieburtz et al., 1996). In addition, the UHDRS assessed relevant clinical domains of HD and was designed for repeated administration during clinical research studies (Kieburtz et al., 1996).

Correlational analyses showed that four components of the UHDRS were highly inter-correlated with the exception of the total behavioral score, which did not correlate with any of the other assessments (Kieburtz et al., 1996). The 24 patients in the reliability study included 14 men and 10 women with an average age of 48.0 16.4 (mean SD) and duration of HD for 9.0 5.5 years (Kieburtz et al., 1996). TFC scores were 8.0 3.4 with a

range of 3 to 13. The intra-class correlation coefficient was (a) 0.94 for the total motor score, (b) 0.82 for the chorea score, and (c) 0.62 for the dystonia score (Kiebertz et al., 1996).

The UHDRS utilized several instruments and rating scales to assess various features of HD, including the quantitated neurological examination, HD functional capacity scale, HD motor rating scale, the physical disability and independence scales, Marsden and Quinn's chorea scale, HD activities of daily living scale, and behavioral assessment (Kiebertz et al., 1996). The UHDRS behavioral assessment included rating the severity and frequency of suicidal thoughts (life is not worth living, has suicidal thoughts, active suicidal intent, and preparation for the act; Kiebertz et al., 1996).

Two limitations were identified in the Zappacosta et al. study (1996) that should be addressed in order to determine if a predictive relationship exists among CAG repeat and suicide. The first limitation was the size of the study. A relatively small sample size of 17 men and 12 women from 24 families affected by Huntington's disease were included. In contrast, the COHORT database provided a larger sample size, including 2864 affected individuals and normal controls. The second limitation was the measurement tool used to assess mood. The Hamilton rating Scale for Depression was designed primarily for adults and is used to rate the severity of depression by probing mood, feelings of guilt, suicide ideation, insomnia, anxiety, weight loss, and somatic symptoms. The scale is used primarily as an assessment of depression severity rather than suicide risk. Whereas, the Unified Huntington's Disease Rating Scale Behavioral Assessment has been shown to be a reliable and consistent measure of mood and suicide (Kiebertz et al., 1996).

Contributions

The purpose of this study was to determine if CAG repeat length correlates with suicide in Huntington's disease. If a positive relationship exists, individuals with larger CAG length expansions may require additional testing, intervention, and psychotherapy for suicide prevention than an individual with a shorter CAG length. Individuals diagnosed or at risk for Huntington's disease have a greater suicide rate than the general population, but is this increased risk due to psychological and environmental factors alone, or can there be a genetic component that increases risk? Numerous studies have shown that there is an inverse relationship between age at onset of disease and CAG repeat length (Brinkman et al, 2007); however, there are no previous studies that have evaluated if CAG length can be associated with suicide specifically.

If a direct relationship between CAG length and suicide exists, individuals with greater CAG expansions should be monitored closely for suicidal ideation and changes in mood. Psychological support is critical when HD is complicated by depression and suicidal thoughts (Paulsen et al., 2005). Psychological help and social work planning can be adapted based upon the stage of the disease (Walker, 2007). Different phases of the disease require varying levels of assistance from psychiatrists, neurologists, social workers, dieticians, speech and occupational therapists, dental hygienists, and clinical psychologists (Paulsen et al, 2005). Several protective factors for suicide can be implemented by the patient, family, and health care provider, which may include (a) ensuring effective mental health care is offered to the individual; (b) establishing positive connections to family, peers, and community; and (c) establishing programs to teach individuals the skills to recognize and address stressors. Protective factors may reduce

suicide risk by helping individuals with HD to cope with negative life events and recognize when they need to reach out to others for help.

Summary

Suicidal behavior can include completed suicide, suicide attempts, and suicidal ideation. Individuals with Huntington's disease often develop significant psychological disease, including personality change, psychosis, depression, hostility, impulsivity, anxiety, aggression, and suicidality (Rosenblatt et al., 2007). Suicide and suicidal ideation are more common in persons with Huntington's disease than the general population, but the incidence rates may change with disease course and predictive testing results (Almqvist, Bloch, Brinkman, Craufurd, & Hayden, 1999). Several studies have investigated the prevalence, clinical association, and predictors of suicide in HD. To summarize, Almqvist et al. (1999) identified an increased risk of a suicidal event (ideation, attempt, or completion) occurred in individuals with a psychiatric history less than or equal to five years prior to testing and had an unemployed status. Hubers et al. (2012) studied the association and predictors of suicidal behavior and discovered that depressed mood was the only independent predictor of suicide after long-term follow-up. This theory was supported by Fiedorowicz et al. (2011) who concluded a history of suicide attempt(s) and the presence of depression were strongly predictive of suicidal behavior in prodromal Huntington's disease. No studies have been previously completed which evaluated the correlation between CAG repeat length and suicidality. If a predictive relationship exists, CAG length may be a future screening tool to assess suicidality and suicide risk.

Chapter 3

Methodology

Research Methods and Procedures

The Cooperative Huntington Observational Research Trial is an observational study designed to collect phenotypic data and biological samples from individuals with HD and their family members. A case-control study, using the COHORT Study de-identified database, will be conducted to determine if there is a correlation between suicide and CAG length. The COHORT database includes clinical assessments and genetic testing from 2,318 individuals collected by the Huntington Study Group over a 5-year period of time from 2005 to 2010 (HSG, 2011). The institutional review board of the University of Rochester and each site approved the protocol. All study participants were provided written informed consent or, if unable to consent, had an authorized representative provide consent on their behalf. Participants agreed to baseline and annual evaluations for an indefinite time period with no predetermined limit on the sample size. To protect the confidentiality and data of participants, all were assigned a unique identification number without identifying information (HSG, 2011).

Sample

Of the 2,318 individuals, 1,985 (85.6%) were classified into six analysis groups. Three groups had expanded CAG alleles (36 repeats or more): (a) individuals with clinically diagnosed HD ($n = 930$), (b) clinically unaffected first-degree relatives who had previously pursued ($n = 248$), or (c) not pursued ($n = 112$) predictive DNA testing. Three groups lacked expanded alleles: (a) first-degree relatives who had previously pursued ($n = 41$), or (b) not pursued ($n = 224$) genetic testing, and (c) spouses and caregivers ($n =$

430). The Huntingtin CAG repeat size was determined by polymerase chain reaction amplification, using genomic DNA extracted from blood and, if provided, lymphoblastoid cell lines. All genotyping was performed at a single site (Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts). Alleles with 36 or more repeats were considered expanded. Individual genotypes remained anonymous and were not communicated to any party (HSG, 2011).

The 1985 participants in this analysis were primarily female (56.3%), had completed at least 12 years of education at the time of enrollment (90.0%), but were not currently employed in the labor force (55.3%). At baseline, 94 (4.7%) of the 1,985 participants reported at least one prior suicide attempt. Individuals with clinically diagnosed HD were more likely to have attempted suicide (7.1%) than caregivers or spouses (1.2%; $p = 0.001$) and all other study participants (2.7%; $p = 0.001$). The most commonly used medications among those with clinically diagnosed HD were antidepressants (32.4%), multivitamins (27.4%), and anti-psychotics (24.5%). For all other groups, commonly used medications were multivitamins (27.4%), lipid-modifying agents (18.9%), and anti-depressants (11.5%; Dorsey, 2012).

The data collected included the following: demographics, family history, physical and psychological evaluations, UHDRS scores, genetic testing, and age of onset and death if applicable (HSG, 2011). COHORT participants completed a medical and neurological evaluation each year for up to 5 years. This evaluation included standardized assessments of movement, thinking, memory, ability to perform daily activities, and behavior (HSG, 2011). The COHORT study involved (a) a baseline visit, comprising an assessment with the Mini-Mental State Examination; (b) a neurological

and physical examination, including body mass index; and (c) the Unified Huntington's Disease Rating Scale 99 (UHDRS 99), conducted by trained study personnel. The UHDRS 99 evaluated four domains, consisting of motor function, cognition, behavior, and functional capacity. Further analysis compared individual items from the motor and behavioral sections of the UHDRS. These items are scored on a 0 to 4 point ordinal scale, with 0 representing no impairment and 1 to 4 representing increasing levels of impairment. The behavioral assessment evaluated the following components: sad/mood, low self-esteem/guilt, anxiety, suicidal thoughts, disruptive or aggressive behavior, irritable behavior, obsessions, compulsions, delusions, and hallucinations. Individuals reporting scores above a pre-specified threshold for depressed mood or suicidal ideation were referred to a mental health professional (Dorsey, 2012).

Through December 31, 2009, one completed suicide in an individual with clinically diagnosed HD and 11 suicide attempts (nine in individuals with clinically diagnosed HD) occurred. The individual who committed suicide had reported a prior history of depression and multiple previous suicide attempts. For the 11 participants who attempted suicide, nine (82%) were female, the mean age was 43.4 (range 26–55), seven (64%) had reported a prior history of depression, and four (36%) had reported a history of at least one previous suicide attempt. Suicides and suicide attempts were prospectively assessed and reported within three working days after a research site became aware of the event. To promote the safety of participants, a clinical monitor and an independent event monitoring committee evaluated reportable events, including suicides, suicide attempts, deaths other than suicides, and premature withdrawals.

To determine if there is a correlation between CAG length and suicide, focus would be placed on the suicidal thought assessment, which evaluated suicidal thoughts, suicidal intention, and preparation for the act of suicide. In a secondary analysis of COHORT, data pertaining to the Unified Huntington's Disease Rating Scale behavioral assessment and death records will be evaluated to determine if there is a predictive relationship between CAG repeat length and suicidality. A correlation analysis will be made to determine if a predictive relationship exists between these two variables.

Data Analysis Plan

Demographic Information

Data will be entered into SPSS version 22.0 for Windows. Descriptive statistics will be conducted to describe the sample demographics as well as any research variables to be used in the analyses. Frequencies and percentages will be calculated for any categorical variables of interest, such as gender or ethnicity. Means and standard deviations will be calculated for any continuous variables of interest, such as age (Howell, 2010).

Pre-Analysis Data Screening

Data will be screened for accuracy, missing data, and outliers or extreme cases. Descriptive statistics and frequency distributions will be conducted to determine that responses are within the possible range of values and data are not distorted by outliers. The presence of univariate outliers will be tested by examination of standardized values. Standardized values will be created for each scale level research variable and examined for values that fall above 3.29 and those which fall below -3.29, which indicate outliers (Tabachnick & Fidell, 2012). Cases with missing data will also

be examined for non-random patterns. Participants with large portions of non-random missing data will be excluded.

Research Question One

Does CAG repeat length significantly predict the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines?

H01: CAG repeat length does not significantly predict the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

Ha1: CAG repeat length does significantly predict the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

To address research question one, ordinal logistic regression will be conducted. Ordinal logistic regression is appropriate when the goal of research is to assess if a set of dichotomous or interval-level independent variables predict an ordinal dependent variable (Tabachnick & Fidell, 2012). In the proposed analysis, CAG repeat length of Huntington's disease sufferers will be the independent, or predictor variable. Depression, substance abuse history and use of benzodiazepines will be covariates, and responses to the UHDRS survey items pertaining to the frequency of suicidal ideation ("feels life is not worth living", "has suicidal thoughts") will form the dependent variable. CAG length will represent the amount of CAG repeats on the short arm of chromosome 4, and suicidal ideation frequency will be representative of responses to the UHDRS survey items pertaining to the frequency of a patient's suicidal ideation. Suicidal ideation

frequency will have possible scores between zero and four, and the number of CAG repeats does not have a definitive upper bound.

Standard multiple regression – the enter method – will be used. The standard method enters all independent variables (predictors) simultaneously into the model. Unless theory sufficiently supports the method of entry, the standard multiple regression is the appropriate method of entry. Variables will be evaluated based on what each add to the prediction of the dependent variable that is different from the predictability provided by the other predictors (Tabachnick & Fidell, 2012). The χ^2 test will be used to assess whether the set of independent variables collectively predicts the dependent variable. The pseudo R², will be reported and used to determine how well variations in the dependent variable can be accounted for by the set of independent variables. The Wald statistic will be used to determine the significance of each predictor.

Unlike non-logit linear regressions, the logistic regression does not have the same assumptions of normality and homoscedasticity. Instead, the logistic regression only requires an adequate sample size. The typical rule of thumb for a logistic regression is 20-30 total participants per predictor variable (Peduzzi et al. 1996; LeBlanc and Fitzgerald, 2000). Thus, at minimum, there should be at least 80-120 participants since there are at least 4 predictors (CAG, drug abuse, depression, benzodiazepine use). The other assumption of the ordinal regression is the assumption of parallel slopes. Parallel slopes assumes that the estimate for the slope is the same across all categories of the dependent variable. Thus as the predictor variable increases by one unit, the likelihood for the participant to be in one higher unit in the ordered dependent variable increases linearly. This assumption is tested via the chi square test of parallel slopes. If the

assumption of parallel slopes fails, then a multinomial logistic regression will be conducted instead.

Research Question Two

Does CAG repeat length significantly predict the severity of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines?

H02: CAG repeat length does not significantly predict the severity of suicide ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

Ha2: CAG repeat length does significantly predict the severity of social ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

To address research question two, ordinal logistic regression will be conducted. In the proposed analysis, CAG repeat length of Huntington's disease sufferers will be the independent, or predictor variable. Depression, substance abuse history and use of benzodiazepines will be covariates, and responses to the UHDRS survey items pertaining to the severity of suicidal ideation ("feels life is not worth living", "has suicidal thoughts") will form the dependent variable. CAG length will represent the amount of CAG repeats on the short arm of chromosome 4, and suicidal ideation severity will be representative of the responses to the UHDRS survey items pertaining to the severity of a patient's suicidal ideation. Suicidal ideation frequency will have possible scores between zero and four, and the number of CAG repeats does not have a definitive upper bound.

Standard multiple regression – the enter method – will be used. The standard method enters all independent variables (predictors) simultaneously into the model.

Unless theory sufficiently supports the method of entry, the standard multiple regression is the appropriate method of entry. Variables will be evaluated based on what each add to the prediction of the dependent variable that is different from the predictability provided by the other predictors (Tabachnick & Fidell, 2012). The χ^2 test will be used to assess whether the set of independent variables collectively predicts the dependent variable. The pseudo R², will be reported and used to determine how well variations in the dependent variable can be accounted for by the set of independent variables. The Wald statistic will be used to determine the significance of each predictor.

Prior to analysis, the assumption of parallel slopes will be assessed. This assumption will be tested via the chi square test of parallel slopes. If the assumption of parallel slopes fails, then a multinomial logistic regression will be conducted instead.

Research Question Three

Does the UHDRS behavioral assessment accurately represent suicidal behavior of Huntington's disease patients?

To address research question three, descriptive statistics will be conducted on responses to the UHDRS for the sample. Means and standard deviations will be calculated for the suicidal behavior subscales of the UHDRS assessment to provide average responses, while frequencies and percentages will indicate how many participants were ranked as "absent," "slight / questionable," "mild," "moderate," or "severe" for the severity and frequency of each suicidal behavior. These statistics will provide a summary of the responses for the sample which may then be compared to previous literature concerning suicidal behavior. If the sample matches roughly with

previous literature, the UHDRS can be said to accurately represent suicidal behavior for the subjects enrolled in the COHORT study.

Sample Size Justification

The proposed study will utilize two ordinal logistic regressions. Because these were the only inferential analyses, a minimum sample size to achieve empirical validity was calculated for these analyses. The typical rule of thumb for a logistic regression is 20-30 total participants per predictor variable (Peduzzi et al. 1996; LeBlanc and Fitzgerald, 2000). Thus, at minimum, there should be at least 80-120 participants since there are at least 4 predictors (CAG, drug abuse, depression, benzodiazepine use).

Resource Requirements

The COHORT database includes clinical assessments and genetic testing from 2,318 individuals collected by the Huntington Study Group over a 5-year period of time from 2005 to 2010 (HSG, 2011). All COHORT data to be shared among researchers had all identifying information removed. In order to gain access to the de-identified database, a research proposal was submitted and reviewed by the Huntington Study Group. Upon approval of the research proposal, a clinical data disclosure agreement was executed between the investigator and the Huntington Study Group. After the contract was finalized, a CD-ROM using a password-protected zip drive was shipped via Federal Express (HSG, 2011). Included in the CD-ROM were the de-identification plan, data dictionary, family history data dictionary, genotypic data, and family history data (HSG, 2011). The resources required for access to the COHORT de-identified database after approval from the Huntington's Study Group included a computer with WinZip installation and Excel software.

Reliability and Validity

The most common confounding variables of case-control studies are sampling bias and observation or recall bias (Hulley, 2007). The case (pre-manifest HD individuals) and the control groups may each be biased (Hulley, 2007). In this particular study, participants of COHORT were voluntarily enrolled at a specialized HD clinic or research center in North America or Australia. It is also important to evaluate if there were bias among the normal controls. In this instance, the control group of the COHORT study was primarily family members of Huntington's disease participants. Additionally, retrospective studies have a greater chance of recall errors or incomplete information (Blessing, 2006). Retrospective recall bias can be minimized by using archived data for other purposes before the studied outcome had occurred (Blessing, 2006). A limitation is the reliability or availability of previously collected data (Polit, 2008).

Sampling bias can be minimized by obtaining a random sample of the patients with the disease as well as the controls (Hulley, 2007). To enable the controls to accurately represent the same population as the cases, one of the following four techniques should be utilized: convenience sampling, matching, using more than one control group, and/or using a population-based sample (Hulley, 2007). A convenience sample occurs when the control and cases are sampled from the same population, such as the same health care clinic (Polit, 2008). A convenience sample is relatively easy to obtain, but may reduce the external validity of the study (Polit, 2008). Matching is another technique utilized to accurately represent the population (Hulley, 2007). The advantage of matching is that it allows for a smaller sample size for any given effect to be

statistically significant (Hulley, 2007). In contrast, “over-matching” may cause the true differences to be underestimated (Polit, 2008). A research conclusion may be more robust if more than one control group is utilized (Blessing, 2006). If the study demonstrates there is a significant difference between the cases and the controls, additional sampled control groups will enhance the final results (Hulley, 2007). Lastly, using a random sample of patients with disease and controls from the population can minimize sampling bias (Hulley, 2007).

Selection bias can occur when entry into a study is influenced by investigator knowledge of the exposure status of potential subjects (Blessing, 2006). This type of bias is more common in case-control study designs because the disease state is already known before entry into the study (Blessing, 2006). Observation or information bias is common when assessing disease outcomes in follow-up studies and exposure assessment in case-control studies (Polit, 2008). In case-control study designs, the disease state has already occurred at the initiation of the study and information is sought about exposures in the past (Hulley, 2007). Bias can occur from either the investigator’s or the subject’s attitude towards the study (Polit, 2008). Lastly, confounding exists when the relationship between the exposure and the disease is a result of a mixture of the effect of the exposure under evaluation and other extraneous factors (Polit, 2008).

Limitations

Although COHORT has tremendous value and potential, it has several limitations. The study population, overwhelmingly White, relatively highly educated, and currently centered in three countries, may not be representative of the broader HD population (Ha et al., 2012). Study participants were enrolled primarily at academic research centers,

which might limit the generalizability to individuals lacking access to these clinics, including those residing in nursing facilities (Ha et al., 2012).

Timeline

An estimate has been made for the timeline for this project. The proposed timeline for this study is 4 months for data analysis and interpretation.

Chapter 4

Results

Introduction

The Cooperative Huntington Observational Research Trial (COHORT) is an observational study designed to collect phenotypic data and biological samples from individuals with HD and their family members. A case-control study, using the COHORT Study de-identified database, was conducted to determine if a correlation between suicide and CAG length exists. The COHORT database includes clinical assessments and genetic testing from 2,318 individuals collected by the Huntington Study Group over a 5-year period of time from 2005 to 2010 (HSG, 2011). The institutional review board of the University of Rochester and each clinical research site approved the protocol. All study participants were provided written informed consent or, if unable to consent, had an authorized representative provide consent on their behalf. Participants agreed to baseline and annual evaluations for an indefinite time period with no predetermined limit on the sample size. Institutional Review Board approval from Nova Southeastern University was obtained prior to any study related procedures conducted.

Descriptive Statistics

Responses were collected from 163 participants. 142 participants (87%) recorded a response of 0 for drug abuse, two participants (1%) recorded a response of 1 for drug abuse, and 19 participants (12%) recorded a response of 2 for drug abuse. Forty-eight participants (29%) recorded a response of 0 for depression and 115 participants (71%) recorded a response of 1 for depression. One hundred and eighteen participants (72%) responded “No” to Benzodiazepine use and 45 participants (28%) responded “Yes” to

Benzodiazepine use. Results for the occurrence of each confounding variable can be found in Table 1.

Table 1

Frequencies for each Control Variable in the Sample

Response	<i>n</i>	%
Drug use		
No	142	87
Yes, active	2	1
Yes, not active	19	12
History of depression		
No depression	48	29
Depression	115	71
Benzodiazepine use		
No	118	72
Yes	45	28

The mean amount for CAG repeat length in the sample was 43.69 ($SD = 4.09$).

Results for the descriptive statistics for CAG repeat length can be found in Table 2.

Table 2

Descriptive Statistics for CAG Repeat Length

Variable	Minimum	Maximum	Mean	Std. Deviation
CAG Repeat Length	38	59	43.69	4.09

Research Question One

Does CAG repeat length significantly predict the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines?

H₀1: CAG repeat length does not significantly predict the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

H_{a1}: CAG repeat length does significantly predict the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

An ordinal logistic regression was conducted to assess if CAG repeat length predicted frequency of suicidal ideation. Prior to analysis, the assumption of proportional odds was assessed by using the test of parallel lines. Results of the test of parallel lines were not significant ($p = .993$) and the assumption was met. The results of the ordinal logistic regression showed significance, $\chi^2(4) = 14.17, p = .007$, suggesting that CAG predicted frequency of suicidal ideation. Since the model was significant, the individual predictors were examined. CAG repeat length was a significant predictor of frequency of suicidal ideation, $p = .010$, suggesting that as CAG repeat length increased, the likelihood of being in a higher category of frequency of suicidal ideation also tended to increase. Depression was also found to be a significant predictor of frequency of suicidal ideation, $p = .004$, suggesting that participants with depression had a higher likelihood of being in a higher category of frequency of suicidal ideation. Results of the ordinal logistic regression are presented in Table 3.

Table 3

Ordinal Logistic Regression for CAG Repeat Lengths, Drug Abuse, Depression, and Benzodiazepine Use Predicting Frequency of Suicidal Ideation

Variable	<i>B</i>	<i>SE</i>	<i>Z</i>	<i>p</i>	95% Confidence Interval	
					Lower Bound	Upper Bound
Drug Abuse	-.30	0.23	-1.28	.200	0.47	1.17
Depression	1.03	0.36	2.88	.004	1.39	5.69
Benzodiazepine Use	-0.03	0.34	-0.08	.934	0.50	1.89
CAG Repeat Length	0.09	0.04	2.59	.010	1.02	1.18

Research Question Two

Does CAG repeat length significantly predict the severity of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines?

H₀2: CAG repeat length does not significantly predict the severity of suicide ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

H_a2: CAG repeat length does significantly predict the severity of social ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

An ordinal logistic regression was conducted to assess if CAG repeat length predicted severity of suicidal ideation. Prior to analysis, the assumption of proportional odds was assessed by using the test of parallel lines. Results of the test of parallel lines were not significant ($p = .107$) and the assumption was met. The results of the ordinal logistic regression showed significance, $\chi^2(4) = 11.83$, $p = .019$, suggesting that CAG repeat length predicted severity of suicidal ideation. Since the model was significant, the individual predictors were examined. The covariate depression was a significant predictor of severity of suicidal ideation, $p = .003$, suggesting that as depression increased, the likelihood of being in a higher category of severity of suicidal ideation also tended to increase. Thus, when the effect of depression was taken into account, there was no significant relationship between CAG repeat length and the severity of suicidal ideation. Results of the ordinal logistic regression are presented in Table 4.

Table 4

Ordinal Logistic Regression for CAG Repeat Lengths, Drug Abuse, Depression, and Benzodiazepine Use Predicting Severity of Suicidal Ideation

Variable	<i>B</i>	<i>SE</i>	<i>Z</i>	<i>p</i>	95% Confidence Interval	
					Lower Bound	Upper Bound

Drug Abuse	-0.27	0.24	-1.16	.247	0.48	1.21
Depression	1.02	0.35	2.95	.003	1.41	5.46
Benzodiazepine Use	-0.38	0.34	-1.11	.267	0.35	1.34
CAG Repeat Length	0.06	0.04	1.73	.084	0.99	1.15

Research Question Three

Does the Unified Huntington's Disease Rating Scale (UHDRS) behavioral assessment accurately represent suicidal behavior of Huntington's disease patients?

H₀3: The Unified Huntington's Disease Rating Scale (UHDRS) behavioral assessment does not accurately represent suicidal behavior of Huntington's disease patients.

H_a3: The Unified Huntington's Disease Rating Scale (UHDRS) behavioral assessment does accurately represent suicidal behavior of Huntington's disease patients.

To address research question three, responses to the UHDRS behavioral assessment were examined. Suicidal ideation was measured on the psychiatric portion of the UHDRS and was scored in terms of frequency and severity. Frequency scores were: 0= almost never, 1= seldom, 3= sometimes, 4= almost always. Severity scores were measured similarly: 0= almost never, 1= slight, 2= mild, 3= moderate, 4= severe. Frequencies and percentages were calculated along with the proposed means and standard deviations to allow a comprehensive view of these responses. The most commonly cited frequency of suicidal ideation was *Seldom thinking about suicide – less than once a month*, with 88 (54%) patients reported as falling into this category. The least commonly cited frequency of suicidal ideation was *Not thinking about suicide or self-harm*, with 5 (3%) patients who were reported as falling into this category. The average frequency rating for the entire sample was 1.72 ($SD = 1.03$).

The most commonly cited severity of suicidal ideation was *No thoughts at current time, but person talks about suicide as a potential option*, with 88 (54%) of patients reported as falling into this category. The least commonly cited severity of suicidal ideation was *Has a plan and is actively preparing*, with 2 (1%) of patients reported as falling into this category. The average severity rating for the sample was 1.04 ($SD = 0.84$). Descriptive statistics for the frequencies of each response are presented in Table 5.

This analysis does not fully answer whether the Unified Huntington's Disease Rating Scale (UHDRS) behavioral assessment accurately represents suicidal behavior of Huntington's disease patients. Current literature cites the incidence and prevalence of suicide and the frequency of suicidality in Huntington's disease, but not specifically the severity of suicidal behavior. Wetzel et al. (2011) evaluated the role of co-morbidity in suicidal ideation in Huntington's disease. Suicidal ideation was examined in 1,941 HD patients enrolled in the Huntington Study Group (Wetzel, 2011). Of those, the frequency of suicidal ideation was 19% ($N= 369$). With regard to suicidality, greater than one-fourth of participants (26.5%) acknowledged a history of suicidal ideation, while 9.5% reported a history of at least one suicide attempt (Wetzel, 2011). Nineteen participants ($N=369$) endorsed current suicidal ideation (Wetzel, 2011). In comparison, 46% of the cohort used in this analysis reported suicidal ideation at least once a month. In addition, 75% of participants are either actively planning a suicide attempt or consider suicide to be an option in the future. Only 25% of participants admit to having no suicidal ideation.

Kieburtz et al. (1996) evaluated the reliability and consistency of the Unified Huntington's Disease Rating Scale (UHDRS). Neurologists, psychiatrists, neuropsychologists, and other healthcare professionals participated in drafting the final

version of the UHDRS (Kieburtz, 1996). Data from the final version of the UHDRS was prospectively collected on 489 patients with manifest HD from 20 sites in North America and Europe (Kieburtz, 1996). The final version of the UHDRS contained 4 components including motor function, cognition, behavioral, and functional abilities. Specifically, the behavioral assessment measures the frequency and severity of symptoms related to affect, thought content, and coping styles (Kieburtz, 1996). The total behavior score is the sum of all responses; however this total score may have less clinical applicability than the individual subscale scores for mood behavior, psychosis, and obsessiveness which are created by summing the corresponding questions (Kieburtz, 1996). The clinician is responsible for providing a clinical impression as to whether the patient, at the time of the evaluation, has clinical evidence of confusion, dementia, suicidality, or depression according to preset definitions in the examination guidelines (Kieburtz, 1996).

The results this analysis by Kieburtz et al. (1996) indicated there was a high degree of consistency in each of the four components of the UHDRS. Correlation analyses showed that four components of the UHDRS were highly inter-correlated, with the exception of the total behavioral score which did not correlate with any of the other assessments (Kieburtz, 1996). Additionally, higher psychosis and obsessive subscale scores correlated with lower functional scores and higher mood subscale scores correlated with better motor performance (Kieburtz, 1996). There was a high degree of reliability among the different UHDRS raters performing the motor assessment. The scores on the motor, cognitive, and functional components were highly inter-correlated, with the exception of the behavioral assessment which did not correlate well (Kieburtz, 1996). Kieburtz et al. concluded that behavioral abnormalities, unlike the slow and

steady deterioration of other domains, are heterogenous, episodic, and without clear progression. Also noted was behavioral dysfunction is one of the symptoms of HD most amenable to symptomatic intervention and is therefore, less likely to be consistently observed over time (Kiebertz, 1996).

Table 5

Frequencies and Percentages for Frequency and Severity of Suicidal Ideation from the UHDRS

Response	<i>n</i>	%
Frequency of suicidal ideation		
Not thinking about suicide or self-harm	5	3
Seldom thinking about suicide – less than once a month	88	54
Sometimes think about suicide – at least once a month	31	19
Frequently thinking about suicide – at least once a week	26	16
Often thinks about suicide – sometimes for days and week on end	13	8
Severity of suicidal ideation		
No suicidal thoughts	40	25
No thoughts at current time, but person talks about suicide as option	88	54
Seriously considered suicide but has no plan	25	15
Has a plan, but no active preparations	8	5
Has a plan and is actively preparing	2	1

Ancillary Analysis

It is possible that CAG repeat length has an effect on depression, and that this effect is carried over into suicidal ideation. An ordinal logistic regression was thus conducted to assess if depression mediates the relationship between CAG repeat length and suicidal ideation. A Baron and Kenny mediation analysis was conducted to assess this potential relationship. To assess for mediation, three regressions were conducted. For mediation to be supported, four items must be met: 1) the independent variable must

be related to the dependent variable, 2) the independent variable must be related to the mediator variable, 3) the mediator must be related to the dependent variable while in the presence of the independent variable, and 4) the independent variable should no longer be a significant predictor of the dependent variable in the presence of the mediator variable (Baron & Kenny, 1986).

The relationship between CAG repeat length and severity of suicidal ideation was not significant, and was not assessed any further. However, the relationship between CAG repeat length and the frequency of suicidal ideation was significant, and the mediating effect of depression was assessed further in regards to this relationship. Next, CAG repeat length was assessed for a relationship with depression (step 2) and did not relate to depression ($p = .213$). Thus, item 2 was not met, and the mediation analysis indicated no evidence of a mediating effect of depression on the relationship between CAG repeat length and suicidal ideation.

Summary

Data analysis of 163 COHORT study subjects was completed. The findings indicate CAG repeat length does significantly predict the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines. The results of the ordinal logistic regression showed significance, $\chi^2(4) = 14.17, p = .007$, suggesting that CAG length can predict the frequency of suicidal ideation. Since the model was significant, the individual predictors were examined. Despite taking depression, benzodiazepine use, and history of substance abuse into account, there is still a predictive relationship between CAG repeat length and frequency of suicidal ideation. CAG repeat length was a significant predictor of frequency of suicidal ideation, $p = .010$,

suggesting that as CAG repeat length increased, the likelihood of being in a higher category of frequency of suicidal ideation also tended to increase. In summary, for every CAG length increase, there is a 0.09 increase in suicidal frequency.

The results of the ordinal logistic regression did show significance, $\chi^2(4) = 11.83$, $p = .019$, suggesting that CAG repeat length predicted severity of suicidal ideation as well. Since the model was significant, the individual predictors were examined. The covariate depression was a significant predictor of severity of suicidal ideation, $p = .003$, suggesting that as depression increased, the likelihood of being in a higher category of severity of suicidal ideation also tended to increase. Thus, when the effect of depression was taken into account, there was no significant relationship between CAG repeat length and the severity of suicidal ideation.

Lastly, descriptive statistics were used to determine if the UHDRS behavioral assessment accurately represents the general Huntington's disease population. In this analysis, only 3% of patients did not think about suicide or self-harm at any time. The most commonly cited frequency of suicidal ideation was *Seldom thinking about suicide – less than once a month*, with 88 (54%) patients reported as falling into this category. The least commonly cited frequency of suicidal ideation was *Not thinking about suicide or self-harm*, with 5 (3%) patients who were reported as falling into this category. The average frequency rating for the entire sample was 1.72 ($SD = 1.03$). The most commonly cited severity of suicidal ideation was *No thoughts at current time, but person talks about suicide as a potential option*, with 88 (54%) of patients reported as falling into this category. The least commonly cited severity of suicidal ideation was *Has a plan*

and is actively preparing, with 2 (1%) of patients reported as falling into this category. The average severity rating for the sample was 1.04 ($SD = 0.84$).

This analysis does not fully answer whether the Unified Huntington's Disease Rating Scale (UHDRS) behavioral assessment accurately represents suicidal behavior of Huntington's disease patients. Current literature cites the incidence and prevalence of suicide and the frequency of suicidality in Huntington's disease, but not specifically the severity of suicidal behavior. A literature review was completed to provide a comparison of the prevalence of suicidal ideation and suicide attempts in other Huntington's disease studies. Wetzel et al. (2011) examined the presence of psychiatric comorbidity and its involvement in suicidal ideation in Huntington's disease. Suicidal ideation was evaluated in 1,941 HD patients enrolled in the Huntington Study Group. Findings included suicidal ideation of 26.5 % and self-reported history of suicide attempts of 9.5 %, which were consistent with current literature (Cummings, 1995; Kessler et al., 2005). The rates of suicidal ideation and history of attempted suicide in HD are significantly elevated compared with rates in the general population. Kessler and colleagues (2005) reported that 3.3 percent of individuals in the 2001–2003 National Comorbidity Survey Replication report current suicidal ideation, and less than 1 percent of participants reported a history of a suicide attempt. Paulsen et al (2005) conducted a survey of 4171 carriers of the Huntington's gene with pre-manifest and manifest disease found that 17.5% had suicidal thoughts at or around the time of assessment and 10% of those surveyed had made at least one suicide attempt in the past. Suicidal ideation was highest in gene carriers who were nearing the threshold of being diagnosed with manifest disease

(those with early motor signs of Huntington's disease), and in those who were beginning to lose their functional ability and independence (those with stage 2 disease).

Chapter 5

Discussion

Discussion

This chapter presents and summarizes the relationship between CAG length and suicidality in Huntington's disease. Huntington's disease is a fully penetrant, autosomal dominant, inherited, progressive neurodegenerative disease that causes dysfunction of motor and emotional control, cognitive ability, and involuntary choreiform movements (Ha et al, 2012). Huntington's disease has been traditionally diagnosed in individuals having 36 or more cytosine, adenine, and guanine (CAG) repeats on the short arm of chromosome 4 (Rosenblatt et al., 1996). As a result of this abnormality, a mutated huntingtin protein is produced. The number of CAG repeats on the huntingtin gene may cause variations in clinical presentation. HD research, involving genetics, has revealed variations in disease presentation, severity of symptoms, and age of onset related to the number of CAG repeats on the huntingtin gene (Rosenblatt et al., 1996). In addition, there may be differences in clinical presentation, including severity of movement disorder, psychiatric disease, cognitive dysfunction, and metabolism depending on CAG repeat length (Rosenblatt et al., 1996).

Individuals with Huntington's disease are more likely than the general population to commit suicide (Fiedorowicz, Mills, Ruggle, Langbehn, & Paulsen, 2011; Novak & Tabrizi, 2010). A survey of 4171 carriers of the Huntington's gene with pre-manifest and manifest disease found that 17.5% of suicidal thoughts occurred at or around the time of testing, and 10% of those had made at least one suicide attempt in the past (Novak & Tabrizi, 2010). Suicidal ideation was highest in gene carriers who were beginning to

become symptomatic and in those who were beginning to lose independence and functional ability (Novak & Tabrizi, 2010). Risk factors for suicide are depression and impulsivity although some individuals with the disease have suicidal ideation in the absence of depression; for some, thoughts of suicide seem to be a rational response to their imminent loss of independence (Novak & Tabrizi, 2010).

In the general population, approximately 90% of individuals who complete suicide have a diagnosable psychiatric disorder at the time of death, substance abuse, or affective disorder (Bertolote et al, 2003; Cheng, 1995). Other known risk factors for completed suicide include past suicide attempts, incarceration or arrest, access to suicidal means, family history of suicide, and current suicidal ideation (Druss & Pincus, 2000; Sher, 2006). Brezo, Paris, & Turecki (2006) suggested that personality features, such as hopelessness, neuroticism, perfectionism, aggression, and irritability are associated with suicidality.

Suicide is one of the few potentially preventable causes of premature death in Huntington's disease (Wetzel et al, 2011). Completed suicide in HD has been reported to be as high as 13% (Cummings, 1995), a seven to twelve fold increase above that of the general population's suicide rate of <1% (Farrer, 1986, Kessler et al, 2005). Among neurodegenerative disease, suicide rates in Huntington's disease remain the highest (Druss and Pincus, 2000). Farrer et al (1986) reported completed suicide rates in HD were 5.7% while 27.6% of individuals with HD admitted to at least one suicide attempt. The majority of research regarding suicide risk in HD has explored the relationship to genetic testing with less emphasis on suicidal ideation and risk over the course of the disease (Almqvist et al, 2003; Farrer, 1986). In order to assess which HD patients are at

increased risk to commit suicide, it is first important to identify the specific population that may be at highest risk to target counseling and additional precautions (Paulsen et al, 2005). Therefore, exploration and greater understanding of risk factors for suicide, such as CAG length, was worthy of further exploration.

The purpose of this quantitative analysis was to identify if there is a correlation between suicidality and CAG length in Huntington's disease. The goal was to enable early identification, assessment, and treatment of suicidal behaviors to reduce the number of suicide attempts and suicide completions in the HD patient population. Some factors which may contribute to suicide risk have been identified, such as depression, history of substance abuse, and use of benzodiazepines, however no previous studies investigated the relationship between CAG repeat length and suicide in Huntington's disease. This lead to the following research hypotheses:

Hypothesis 1. CAG repeat length significantly predicts the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines

An ordinal logistic regression was conducted to assess if CAG repeat length predicted frequency of suicidal ideation. The results of the ordinal logistic regression showed significance, $\chi^2(4) = 14.17, p = .007$, suggesting that CAG predicted frequency of suicidal ideation. Since the model was significant, the individual predictors were examined. CAG repeat length was a significant predictor of frequency of suicidal ideation, $p = .010$, suggesting that as CAG repeat length increased, the likelihood of being in a higher category of frequency of suicidal ideation also tended to increase. Depression was also found to be a significant predictor of frequency of suicidal ideation,

$p = .004$, suggesting that participants with depression had a higher likelihood of being in a higher category of frequency of suicidal ideation. The relationship between CAG repeat length and the frequency of suicidal ideation was significant, and the mediating effect of depression was assessed further in regards to this relationship. CAG repeat length was assessed for a relationship with depression and did not relate to depression ($p = .213$).

Hypothesis 2. CAG repeat length significantly predicts the severity of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

An ordinal logistic regression was conducted to assess if CAG repeat length predicted severity of suicidal ideation. The results of the ordinal logistic regression showed significance, $\chi^2(4) = 11.83$, $p = .019$, suggesting that CAG repeat length predicted severity of suicidal ideation. Since the model was significant, the individual predictors were examined. The covariate depression was a significant predictor of severity of suicidal ideation, $p = .003$, suggesting that as depression increased, the likelihood of being in a higher category of severity of suicidal ideation also tended to increase. Thus, when the effect of depression was taken into account, there was no significant relationship between CAG repeat length and the severity of suicidal ideation.

Hypothesis 3. The UHDRS behavioral assessment accurately represents suicidal behavior of Huntington's disease patients.

This analysis does not fully answer whether the Unified Huntington's Disease Rating Scale (UHDRS) behavioral assessment accurately represents suicidal behavior of Huntington's disease patients. Current literature cites the incidence and prevalence of suicide and the frequency of suicidality in Huntington's disease, but not specifically the

severity of suicidal behavior. Further research is needed to determine if the UHDRS behavioral assessment is a true representation of suicidality in HD.

Implications

Assessing or treating a suicidal patient represents one of the most challenging tasks a clinician has to face in their professional life, both intellectually and emotionally. Currently, there is little guidance to help clinicians identify and treat an individual with HD who is contemplating a fatal act. CAG repeat length may be an important tool for clinicians to identify individuals with HD who have a greater risk for suicidal tendencies. The objective is to identify potential risk factors for suicidal behavior so that high risk patients may be prioritized. Research has shown that between 40-60% of individuals who commit suicide had seen a physician in the month prior to suicide; of these most had seen a general physician rather than a psychiatrist (Bertolote, 2000). The implications of this research for patient management is the recognition that CAG repeat length can be a predictor of suicide frequency. The ultimate goal is to provide clinicians with adequate education and resources to identify these high risk individuals so patients may receive appropriate and timely intervention.

Currently, there are no clinical guidelines for the management of a suicidal Huntington's disease patient. In 2014, the World Health Organization (WHO) published "Preventing Suicide: A Resource for General Physicians", which is a series of resources addressed to specific social and professional groups particularly relevant to the prevention of suicide in general. Although not specific to HD, the World Health Organization provided a list of high risk socio-demographic factors to help guide clinicians in the identification of suicidal patients:

HOW TO IDENTIFY PATIENTS AT HIGH RISK OF SUICIDAL BEHAVIOUR

A number of clinically useful individual and socio-demographic factors are associated with suicide. They include:

- Psychiatric disorders (generally depression, alcoholism and personality disorders);
- Physical illness (terminal, painful or debilitating illness, AIDS);
- Previous suicide attempts;
- Family history of suicide, alcoholism and/or other psychiatric disorders;
- Divorced, widowed or single status;
- Living alone (socially isolated);
- Unemployed or retired;
- Bereavement in childhood.

If the patient is under psychiatric treatment, the risk is higher in:

- Those who have recently been discharged from hospital;
- Those who have made previous suicide attempts. (WHO, 2014)

In addition, recent life stressors associated with increased risk of suicide include: (WHO, 2014)

- Marital separation;
- Bereavement;
- Family disturbances;
- Change in occupational or financial status;
- Rejection by a significant person;
- Shame and threat of being found guilty.

The following recommendations for the management of suicidal patients in general were made by the World Health Organization in 2014: (WHO, 2014)

MANAGEMENT OF SUICIDAL PATIENTS

If a patient is emotionally disturbed, with vague suicidal thoughts, the opportunity of ventilating thoughts and feelings to a physician who shows concern may be sufficient (WHO, 2014). Whatever the problem, the feelings of the suicidal person are usually a triad of helplessness, hopelessness and despair (WHO, 2014). The three most common states are:

1. Ambivalence. The majority of suicidal patients are ambivalent till the very end. There is a see-saw battle between the wish to live and the wish to die. If the ambivalence is used by the physician to increase the wish to live, the suicide risk may be reduced (WHO, 2014).
2. Impulsivity. Suicide is an impulsive phenomenon and impulse by its very nature is transient. If support is provided at the moment of impulse, the crisis may be defused (WHO, 2014).
3. Rigidity. Suicidal people are constricted in their thinking, mood and action and their reasoning is dichotomized in terms of either/or. By exploring several possible alternatives to death with the suicidal patient, the physician gently makes the patient realize that there are other options, even if they are not ideal (WHO, 2014).

Enlisting support

The physician should assess the available support systems, identify a relative, friend, acquaintance or other person who would be supportive to the patient, and solicit that person's help (WHO, 2014).

Contracting

Entering into a “no suicide” contract is a useful technique in suicide prevention. Other people close to the patient can be included in negotiating the contract. The negotiation of the contract can promote discussion of various relevant issues. In the majority of instances patients respect the promises they give to a physician. Contracting is appropriate only when patients have control over their actions (WHO, 2014). In the absence of severe psychiatric disorder or suicidal intent, the physician can initiate and arrange pharmacological treatment, generally with antidepressants, and psychological (cognitive behaviour) therapy (WHO, 2014). The majority of people benefit from continuing contacts; these should be structured to meet individual needs (WHO, 2014).

The recommendations for suicide prevention from the World Health Organization are a valuable resource for general physicians, however there are no current guidelines for clinicians who specifically treat Huntington’s disease patients. The Huntington’s disease Society of America (HDSA) is a national, voluntary health organization dedicated to improving the lives of people with Huntington's disease and their families. The mission statement of the HDSA emphasizes a desire to promote and support research and medical efforts to eradicate Huntington's disease, to assist people and families affected by Huntington's disease to cope with the problems presented by the disease, and to educate the public and health professionals about Huntington's disease (HDSA, 2014). In 2011, the Huntington’s disease Society of America released, “A Physician’s Guide to the Management of Huntington’s Disease, Third Edition”. Chapter 6, “The Psychiatric Disorder”, was authored by Adam Rosenblatt, M.D. Dr. Rosenblatt wrote in his preface, “Psychiatric symptoms have long been understood to be a common and inherent part of

Huntington's disease (HD). In the classic description of the condition which bears his name, George Huntington referred to "the tendency to insanity, and sometimes that form of insanity which leads to suicide..." (Nance, Paulsen, Rosenblatt, & Wheelock, 2011) Most physicians understand this in the abstract, yet people with HD with psychiatric problems suffer from under-diagnosis and under-treatment (Nance et al., 2011). This is regrettable, because psychiatric problems in HD are often the most disabling and yet the most treatable" (Nance et al., 2011). Chapter 6 included diagnostic and treatment recommendations for depression, obsessive and compulsive behavior, and delusions and hallucinations in the Huntington's disease patient. Also included was a small section on suicide in the Huntington's disease patient, which reads as follows (Nance et al., 2011):

"Suicide is alarmingly common in people with HD, possibly because of the frequent co-morbidity of depression and personality changes resulting in disinhibition and impulsive behavior, but that does not mean that suicide is not preventable. Depressed individuals should always be asked about suicide, and this should be regularly re-assessed. It is a misconception that suicidal individuals will not admit to these feelings. The question should be asked in a non-intimidating, matter-of-fact way, such as "Have you been feeling so bad that you sometimes think life isn't worth living?" Or, "Have you even thought about suicide?" If the person acknowledges these feelings, the clinician needs to ask more questions to evaluate the severity of the situation and decide on the best course of action. Are the feelings just a passive wish to die or has the person actually thought out a specific suicidal plan? Does the person have the means to commit suicide? Has she prepared for a suicide, such as by loading a gun or hoarding pills? Can the person identify any factors which are preventing her from killing herself? What social supports

are present? Some individuals, although having suicidal thoughts, may be at low risk if they have a good relationship with their doctor, have family support, and have no specific plans. Others may be so dangerous to themselves that they require emergency hospitalization. Although there are instances of non-depressed individuals with HD harboring chronic suicidal feelings, most, if not all, suicidal people with HD are suffering from major depression and can be treated successfully. In cases of completed suicide in HD of which there are first-hand knowledge, the person was usually well understood by his family to be suffering from depression and attempts at treatment had been initiated, but sadly proved insufficient. If the clinician is unsure, the person should be treated presumptively. This is not to say that a person with HD, particularly early in the course of the disease, may not express a fear of becoming helpless one day, or a desire not to live past a certain degree of impairment. A physician should listen supportively to these concerns, realizing that most individuals in this situation will be able to adapt if they are not suffering from depression” (Nance et al., 2011).

One of the clinical implications of this research would be the use of CAG repeat length in risk factor assessment for suicidality in the HD population. CAG repeat length may be used as a method to screen for individuals with a higher suicide risk so that preventative measures may be taken prophylactically. Individuals with high CAG repeat lengths can be assessed earlier and in more depth for suicidal behavior. As a result of early intervention, individuals can contract for safety and be offered psychotherapy, psychiatric consultation, support groups, and anti-depressant medication if indicated. Home evaluations can be conducted to evaluate if there are weapons or means of suicide

assessable to the patient. The development of suicide guidelines for Huntington's disease patients would be a valuable resource for clinicians in the future.

Recommendations

One of the important messages from Dr. Rosenblatt's recommendations was suicide is "preventable". Proper identification of the risk factors for suicide in Huntington's disease followed by aggressive intervention may allow suicide to be a "preventable" complication of HD. The findings from this quantitative analysis support using CAG length in a clinician's risk factor assessment to determine the frequency of suicidality. A future recommendation includes the development of suicide prevention guidelines for clinicians who care for Huntington's disease patients. Guidelines may include the use of CAG repeat length in the risk stratification analysis for suicidality in HD.

This analysis does not fully answer research question number three, "does the Unified Huntington's Disease Rating Scale (UHDRS) behavioral assessment accurately represent the suicidal behavior of Huntington's Disease patients?" Current literature cites the incidence and prevalence of suicide and the frequency of suicidality in Huntington's disease, but not specifically the severity of suicidal behavior. Future recommendations would also include further analysis particularly directed at evaluating the severity of suicidal behavior in the Huntington's disease population.

Lastly, the scores on the motor, cognitive, and functional components of the Unified Huntington's Disease Rating Scale were validated and highly inter-correlated among raters, with the exception of the behavioral section (Kiebertz, 1995). In the behavioral section, the rater must formulate a clinical impression of mood based upon

individual responses to questions. The total behavioral score did not correlate with any of the other assessments in the analysis by Kieburtz et al. in 1995, however, higher mood sub-scale scores correlated with better motor performance and higher psychosis and obsessive sub-scale scores correlated with lower functional scores (Kieburtz, 1995). These findings reflect that behavioral abnormalities, unlike the slow progression in other domains, are heterogeneous and episodic (Kieburtz, 1995). Also noted is the fact that behavioral disturbances in Huntington's disease are more likely to improve with symptomatic intervention compared to motor symptoms (Kieburtz, 1995). A final recommendation would be to future research to analyze the behavioral component of the UHDRS to determine if direct patient questioning would be more reliable than rater summation of responses.

Beyond this analysis, the COHORT database is a valuable resource to HD investigators and may lead to other research opportunities. The phenotypic and genotypic data can be assessed by potential investigators by submitting a brief research proposal to cohort.projectmanager@ctcc.rochester.edu (HSG, 2014).

Limitations and Delimitations

While the Huntington Study Group COHORT database used in this investigation has tremendous value and potential, it does have several limitations. This research population involves participants who are predominantly Caucasian and relatively highly educated, which may not be representative of the general HD population. Additionally, individuals in the COHORT study were primarily from only three countries which may limit certain ethnicities from participation. Study participants were enrolled at clinical research sites that are members of the Huntington Study Group (HSG). HSG research

sites, for the most part, are large academic institutions with dedicated movement disorder centers. This too may not be representative of the general Huntington's disease population as many individuals with HD do not live within close proximity to these type of specialized centers. The cohorts used in these analyses are out-patient, ambulatory participants, thus limiting conclusions with respect to individuals with advanced disease and/or higher severity of motor signs. Many patients with end-stage HD reside in nursing facilities which would limit access to research opportunities. Lastly, individuals who participate in clinical trials tend to be more compliant with keeping appointments and adhering to treatment plans. In addition, there is typically greater familial support and willingness to assist with transportation to research visits. As a result of these limitations, the data used from participants in the COHORT Study database may not be representative of the general HD population.

The Unified Huntington's Disease Rating Scale (UHDRS) is the current 'gold-standard' outcome measure used in HD research. The UHDRS is divided into multiple subscales, assessing motor and cognitive function, behavioral (i.e., psychiatric) symptoms, and functional capacity. The scale was developed and tested in gene expansion carriers who had manifest motor symptoms of HD, may not be sensitive to changes in the earlier stages of the disease. The UHDRS Behavioral Subscale includes 11 items that independently assess frequency and severity of psychiatric-related symptoms. The UHDRS Motor and Behavioral Subscales were administered to each patient at each visit by a qualified rater. A qualified rater for the COHORT Study is an experienced investigator that has been deemed competent to administer the UHDRS by the Huntington Study Group. In the behavioral section of the UHDRS, the investigator

asks the participant questions about sad/mood, low self-esteem/guilt, anxiety, suicidal thoughts, disruptive/aggressive behavior, irritable behavior, obsessions, compulsions, delusions, and hallucinations. The rater must then rate both the frequency and severity of the behavior on a scale from 0 (absent) to 4 (severe). In the behavioral section, the rater must formulate a clinical impression of mood based upon individual responses to questions. Rater errors can occur when an investigator observes and evaluates a participant. Personal perceptions and biases may influence how an individual's performance is scored. In addition, individuals with HD may not respond in the same way to investigator questioning than if the questions were given in the form of a questionnaire which could be completed privately. Lastly, due to the likelihood of cognitive dysfunction associated with HD, individuals may not have the self-awareness to acknowledge or express the degree of behavioral symptoms that are actually present.

Summary

Overview

Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, causing atrophy of the basal ganglia, specifically the caudate nucleus, putamen, and globus nucleus (Novak & Tabrizi, 2010; Roos, 2010; Ross & Tabrizi, 2011). The disease is characterized by choreiform movements, dystonia, mood and personality disorders, and cognitive impairment (Novak & Tabrizi, 2010; Ross & Tabrizi, 2011). Approximately 30,000 people in the United States (US) have clinical manifestations of HD, and an additional 150,000 healthy people are thought to be immediately at risk of developing HD (HSG, 2011). Huntington's disease has been traditionally diagnosed in individuals having 36 or more cytosine, adenine, and guanine

(CAG) repeats on the short arm of chromosome 4 (Rosenblatt et al., 1996). As a result of this abnormality, a mutated huntingtin protein is produced. The number of CAG repeats on the huntingtin gene may cause variations in clinical presentation. In addition, there may be differences in clinical presentation, including severity of movement disorder, psychiatric disease, cognitive dysfunction, and metabolism (Rosenblatt et al., 1996). Individuals with Huntington's disease are more likely than the general population to commit suicide (Fiedorowicz, Mills, Ruggle, Langbehn, & Paulsen, 2011; Novak & Tabrizi, 2010).

Research Hypotheses

The purpose of this study was to determine if a correlation exists between suicide and CAG repeat length. Specifically, if CAG length is a diathesis or pre-disposition for suicidal behavior in Huntington's disease. Some factors, which may contribute to suicide risk, have previously been identified, but no studies have investigated if there is a correlation between CAG length and suicide in Huntington's disease, which leads to the following hypotheses.

Hypothesis 1. CAG repeat length significantly predicts the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines

Hypothesis 2. CAG repeat length significantly predicts the severity of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines.

Hypothesis 3. The UHDRS behavioral assessment accurately represents suicidal behavior of Huntington's disease patients.

Methodology

Research Methods and Procedures

The Cooperative Huntington Observational Research Trial is an observational study designed to collect phenotypic data and biological samples from individuals with HD and their family members. A case-control study, using the COHORT Study de-identified database, will be conducted to determine if there is a correlation between suicide and CAG length. The COHORT database includes clinical assessments and genetic testing from 2,318 individuals collected by the Huntington Study Group over a 5-year period of time from 2005 to 2010 (HSG, 2011). The institutional review board of the University of Rochester and each site approved the protocol. To protect the confidentiality and data of participants, all were assigned a unique identification number without identifying information (HSG, 2011). The COHORT study involved (a) a baseline visit, comprising an assessment with the Mini-Mental State Examination; (b) a neurological and physical examination, including body mass index; and (c) the Unified Huntington's Disease Rating Scale 99 (UHDRS 99), conducted by trained study personnel. The UHDRS 99 evaluated four domains, consisting of motor function, cognition, behavior, and functional capacity. To determine if there is a correlation between CAG length and suicide, focus would be placed on the suicidal thought assessment, which evaluated suicidal thoughts, suicidal intention, and preparation for the act of suicide. In a secondary analysis of COHORT, data pertaining to the Unified Huntington's Disease Rating Scale behavioral assessment and death records will be evaluated to determine if there is a predictive relationship between CAG repeat length

and suicidality. A correlation analysis will be made to determine if a predictive relationship exists between these two variables.

Sample

Of the 2,318 individuals, one completed suicide in an individual with clinically diagnosed HD and 11 suicide attempts (nine in individuals with clinically diagnosed HD) occurred. The individual who committed suicide had reported a prior history of depression and multiple previous suicide attempts. For the 11 participants who attempted suicide, nine (82%) were female, the mean age was 43.4 (range 26–55), seven (64%) had reported a prior history of depression, and four (36%) had reported a history of at least one previous suicide attempt. Suicides and suicide attempts were prospectively assessed and reported within three working days after a research site became aware of the event.

Data Analysis

Research Question One

Does CAG repeat length significantly predict the frequency of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines?

To address research question one, ordinal logistic regression was conducted. CAG repeat length was the independent, or predictor variable. Depression, substance abuse history and use of benzodiazepines was covariates, and responses to the UHDRS survey items pertaining to the frequency of suicidal ideation (“feels life is not worth living”, “has suicidal thoughts”) formed the dependent variable. CAG length represented the amount of CAG repeats on the short arm of chromosome 4, and suicidal ideation frequency was representative of responses to the UHDRS survey items pertaining to the frequency of a patient’s suicidal ideation. The χ^2 test was used to assess whether the set of independent

variables collectively predicts the dependent variable. The pseudo R², was reported and used to determine how well variations in the dependent variable can be accounted for by the set of independent variables. The Wald statistic was used to determine the significance of each predictor.

Research Question Two

Does CAG repeat length significantly predict the severity of suicidal ideation, when controlling for depression, substance abuse history, and use of benzodiazepines?

To address research question two, ordinal logistic regression was conducted. In the proposed analysis, CAG repeat length of Huntington's disease sufferers was the independent, or predictor variable. Depression, substance abuse history and use of benzodiazepines were the covariates, and responses to the UHDRS survey items pertaining to the severity of suicidal ideation ("feels life is not worth living", "has suicidal thoughts") were the dependent variable. CAG length represented the amount of CAG repeats on the short arm of chromosome 4, and suicidal ideation severity will be representative of the responses to the UHDRS survey items pertaining to the severity of a patient's suicidal ideation. The standard method entered all independent variables (predictors) simultaneously into the model. The χ^2 test was used to assess whether the set of independent variables collectively predicts the dependent variable. The pseudo R², was reported and used to determine how well variations in the dependent variable can be accounted for by the set of independent variables. The Wald statistic was used to determine the significance of each predictor.

Research Question Three

Does the UHDRS behavioral assessment accurately represent suicidal behavior of Huntington’s disease patients?

To address research question three, descriptive statistics were conducted on responses to the UHDRS for the sample. Means and standard deviations were calculated for the suicidal behavior subscales of the UHDRS assessment to provide average responses, while frequencies and percentages will indicate how many participants were ranked as “absent,” “slight / questionable,” “mild,” “moderate,” or “severe” for the severity and frequency of each suicidal behavior.

Results

Responses were collected from 163 participants. 142 participants (87%) recorded a response of 0 for drug abuse, two participants (1%) recorded a response of 1 for drug abuse, and 19 participants (12%) recorded a response of 2 for drug abuse. Forty-eight participants (29%) recorded a response of 0 for depression and 115 participants (71%) recorded a response of 1 for depression. One hundred and eighteen participants (72%) responded “No” to Benzodiazepine use and 45 participants (28%) responded “Yes” to Benzodiazepine use. Results for the occurrence of each confounding variable can be found in Table 1.

Table 1

Frequencies for each Control Variable in the Sample

Response	<i>N</i>	%
Drug use		
No	142	87
Yes, active	2	1
Yes, not active	19	12
History of depression		
No depression	48	29

Depression	115	71
Benzodiazepine use		
No	118	72
Yes	45	28

The mean amount for CAG repeat length in the sample was 43.69 ($SD = 4.09$).

Results for the descriptive statistics for CAG repeat length can be found in Table 2.

Table 2

Descriptive Statistics for CAG Repeat Length

Variable	Minimum	Maximum	Mean	Std. Deviation
CAG Repeat Length	38	59	43.69	4.09

An ordinal logistic regression was conducted to assess if CAG repeat length predicted frequency of suicidal ideation. Prior to analysis, the assumption of proportional odds was assessed by using the test of parallel lines. Results of the test of parallel lines were not significant ($p = .993$) and the assumption was met. The results of the ordinal logistic regression showed significance, $\chi^2(4) = 14.17, p = .007$, suggesting that CAG predicted frequency of suicidal ideation. Since the model was significant, the individual predictors were examined. CAG repeat length was a significant predictor of frequency of suicidal ideation, $p = .010$, suggesting that as CAG repeat length increased, the likelihood of being in a higher category of frequency of suicidal ideation also tended to increase. Depression was also found to be a significant predictor of frequency of suicidal ideation, $p = .004$, suggesting that participants with depression had a higher likelihood of being in a higher category of frequency of suicidal ideation. Results of the ordinal logistic regression are presented in Table 3.

Table 3

Ordinal Logistic Regression for CAG Repeat Lengths, Drug Abuse, Depression, and Benzodiazepine Use Predicting Frequency of Suicidal Ideation

Variable	<i>B</i>	<i>SE</i>	<i>Z</i>	<i>p</i>	95% Confidence Interval	
					Lower Bound	Upper Bound
Drug Abuse	-.30	0.23	-1.28	.200	0.47	1.17
Depression	1.03	0.36	2.88	.004	1.39	5.69
Benzodiazepine Use	-	0.34	-0.08	.934	0.50	1.89
	0.03					
CAG Repeat Length	0.09	0.04	2.59	.010	1.02	1.18

An ordinal logistic regression was conducted to assess if CAG repeat length predicted severity of suicidal ideation. Prior to analysis, the assumption of proportional odds was assessed by using the test of parallel lines. Results of the test of parallel lines were not significant ($p = .107$) and the assumption was met. The results of the ordinal logistic regression showed significance, $\chi^2(4) = 11.83$, $p = .019$, suggesting that CAG repeat length predicted severity of suicidal ideation. Since the model was significant, the individual predictors were examined. The covariate depression was a significant predictor of severity of suicidal ideation, $p = .003$, suggesting that as depression increased, the likelihood of being in a higher category of severity of suicidal ideation also tended to increase. Thus, when the effect of depression was taken into account, there was no significant relationship between CAG repeat length and the severity of suicidal ideation. Results of the ordinal logistic regression are presented in Table 4.

Table 4

Ordinal Logistic Regression for CAG Repeat Lengths, Drug Abuse, Depression, and Benzodiazepine Use Predicting Severity of Suicidal Ideation

Variable	<i>B</i>	<i>SE</i>	<i>Z</i>	<i>p</i>	95% Confidence Interval	
					Lower Bound	Upper Bound

Drug Abuse	-0.27	0.24	-1.16	.247	0.48	1.21
Depression	1.02	0.35	2.95	.003	1.41	5.46
Benzodiazepine Use	-0.38	0.34	-1.11	.267	0.35	1.34
CAG Repeat Length	0.06	0.04	1.73	.084	0.99	1.15

Suicidal ideation was measured on the psychiatric portion of the UHDRS and was scored in terms of frequency and severity. Frequency scores were: 0= almost never, 1= seldom, 3= sometimes, 4= almost always. Severity scores were measured similarly: 0= almost never, 1= slight, 2= mild, 3= moderate, 4= severe. Frequencies and percentages were calculated along with the proposed means and standard deviations to allow a comprehensive view of these responses. The most commonly cited frequency of suicidal ideation was *Seldom thinking about suicide – less than once a month*, with 88 (54%) patients reported as falling into this category. The least commonly cited frequency of suicidal ideation was *Not thinking about suicide or self-harm*, with 5 (3%) patients who were reported as falling into this category. The average frequency rating for the entire sample was 1.72 ($SD = 1.03$).

The most commonly cited severity of suicidal ideation was *No thoughts at current time, but person talks about suicide as a potential option*, with 88 (54%) of patients reported as falling into this category. The least commonly cited severity of suicidal ideation was *Has a plan and is actively preparing*, with 2 (1%) of patients reported as falling into this category. The average severity rating for the sample was 1.04 ($SD = 0.84$). Descriptive statistics for the frequencies of each response are presented in Table 5.

This analysis does not fully answer whether the Unified Huntington’s Disease Rating Scale (UHDRS) behavioral assessment accurately represents suicidal behavior of

Huntington's disease patients. Current literature cites the incidence and prevalence of suicide and the frequency of suicidality in Huntington's disease, but not specifically the severity of suicidal behavior. Wetzel et al. (2011) evaluated the role of co-morbidity in suicidal ideation in Huntington's disease.

Table 5

Frequencies and Percentages for Frequency and Severity of Suicidal Ideation from the UHDRS

Response	<i>n</i>	%
Frequency of suicidal ideation		
Not thinking about suicide or self-harm	5	3
Seldom thinking about suicide – less than once a month	88	54
Sometimes think about suicide – at least once a month	31	19
Frequently thinking about suicide – at least once a week	26	16
Often thinks about suicide – sometimes for days and week on end	13	8
Severity of suicidal ideation		
No suicidal thoughts	40	25
No thoughts at current time, but person talks about suicide as option	88	54
Seriously considered suicide but has no plan	25	15
Has a plan, but no active preparations	8	5
Has a plan and is actively preparing	2	1

Ancillary Analysis

It is possible that CAG repeat length has an effect on depression, and that this effect is carried over into suicidal ideation. An ordinal logistic regression was thus conducted to assess if depression mediates the relationship between CAG repeat length and suicidal ideation. A Baron and Kenny mediation analysis was conducted to assess this potential relationship. To assess for mediation, three regressions were conducted. For mediation to be supported, four items must be met: 1) the independent variable must

be related to the dependent variable, 2) the independent variable must be related to the mediator variable, 3) the mediator must be related to the dependent variable while in the presence of the independent variable, and 4) the independent variable should no longer be a significant predictor of the dependent variable in the presence of the mediator variable (Baron & Kenny, 1986). The relationship between CAG repeat length and severity of suicidal ideation was not significant, and was not assessed any further. However, the relationship between CAG repeat length and the frequency of suicidal ideation was significant, and the mediating effect of depression was assessed further in regards to this relationship. Next, CAG repeat length was assessed for a relationship with depression (step 2) and did not relate to depression ($p = .213$). Thus, item 2 was not met, and the mediation analysis indicated no evidence of a mediating effect of depression on the relationship between CAG repeat length and suicidal ideation.

Limitations and Delimitations

While the Huntington Study Group COHORT database used in this investigation has tremendous value and potential, it does have several limitations. This research population involves participants who are predominantly Caucasian and have relatively high educational levels. Study participants were enrolled at clinical research sites that are members of the Huntington Study Group (HSG). HSG research sites, for the most part, are large academic institutions with dedicated movement disorder centers. This too may not be representative of the general Huntington's disease population as many individuals with HD do not live within close proximity to these type of specialized centers. As a result of these limitations, the data used from participants in the COHORT Study database may not be representative of the general HD population.

The Unified Huntington's Disease Rating Scale (UHDRS) is the current 'gold-standard' outcome measure used in HD research. The UHDRS Motor and Behavioral Subscales were administered to each patient at each visit by a qualified rater. A qualified rater for the COHORT Study is an experienced investigator that has been deemed competent to administer the UHDRS by the Huntington Study Group. In the behavioral section, the rater must formulate a clinical impression of mood based upon individual responses to questions. Rater errors can occur when an investigator observes and evaluates a participant. Personal perceptions and biases may influence how an individual's performance is scored. Lastly, individuals with HD may not respond in the same way to investigator questioning than if the questions were given in the form of a questionnaire which could be completed privately.

Recommendation

The findings from this quantitative analysis support using CAG length in a clinician's risk factor assessment to determine the frequency of suicidality. A future recommendation includes the development of suicide prevention guidelines for clinicians who care for Huntington's disease patients. Guidelines may include the use of CAG repeat length in the risk stratification analysis for suicidality in HD.

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