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Depression and anxiety in patients with hereditary angioedema

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ABSTRACT

Background: Hereditary angioedema (HAE) is characterized by edematous swelling attacks of the face, extremities, abdomen, genitalia, and upper airway. The potential for laryngeal swelling makes the disease life-threatening, and the swelling elsewhere contributes to the significant burden of illness. The increased risk for mental health disorders in HAE is due to the burden of disease and possibly associated activation of the immune system.

Objective: To determine the prevalence of depression and anxiety in HAE patients and the most high-yield features of depression to target in a clinical encounter.

Methods: Depression and anxiety symptoms were evaluated using the 29 items of the Hamilton Depression Rating Scale along with the 14-item Hamilton Anxiety Rating Scale. The sample size was 26 participants with a diagnosis of type 1 or 2 HAE drawn from a cohort of 60 adult patients. In addition, a literature search was performed regarding how immune modulation affects depression and anxiety.

Results: A total of 39% of participants were identified as experiencing depression of mild (50%), moderate (40%), or severe (10%) levels. Fifteen percent of participants displayed prominent anxiety, half of whom had mild anxiety, 25% moderate anxiety, and 25% severe anxiety. The literature on inflammation and depression suggests a possible link between HAE and depression.

Conclusion: Our data and the literature support that depression and anxiety symptoms are common in patients with HAE and may be secondary to chronic disease burden, associated pathophysiologic features, or both. Treatment that addresses the psychosocial and mental health of HAE patients is critical for best practice.

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Introduction

Hereditary angioedema (HAE) is a rare but debilitating disease that affects 0.00002% of the population, and there is little knowledge currently available regarding the nature of how this illness affects people psychologically. We sought to add to the growing body of knowledge regarding the mental health implications of HAE. Symptoms of depression and anxiety were measured through use of clinician-driven rating scales; however, much of the insight gained through the interview experience transcends the numerical simplicity of a rating scale. This study aims to not only present the data from the scales but also to use the qualitative data from the interviews to identify the most significant features of this disease to drive research in the most productive direction and help physicians understand the nuances of the HAE patient experience.

The biological mechanism that drives symptom severity in HAE is a deficiency in C1 esterase inhibitor (C1INH) protein. The C1INH protein is a key regulator of early complement activation, including MASP2, C1r, and C1s.[1,2] The C1INH protein is also a regulator of factor XII, kallikrein, factor 11, and plasmin system.[1,2] Consequently, the C1INH protein plays a role in regulation of both the contact system and complement system. Specifically, the physical symptoms of this disease are mediated through increased activation of the contact system cascade, including factor 12 and kallikrein, resulting in the key mediator of bradykinin that results in markedly increased vessel permeability.[1,2] Recent literature exploring psychoneuroimmunology has illustrated the potential of the immune system and central nervous system to interact and bring about changes in mood and anxiety.[3,4]

Bradykinin is the key mediator for the symptoms associated with HAE swelling attacks, and the high levels are a result of inadequate C1 inhibitory function.[1,2,5] Bradykinin is metabolized by several different enzymes, one of which is carboxypeptidase M. The resulting metabolite of des-Arg9-bradykinin is a bradykinin B1 receptor agonist.[6] Bradykinin B1 receptors, which respond strongly to bradykinin breakdown product des-Arg9-bradykinin, have been reported to directly mediate depressive symptoms in mice treated with lipopolysaccharide.[7] The increased vessel permeability

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mediated by bradykinin has been reported to be amplified by interleukin (IL) 1β.[8] IL-1β is a proinflammatory cytokine that has been demonstrated to induce behavioral changes.[9] Increased activation of inflammatory mechanisms, particularly IL-1β, may be linked to both exacerbating symptoms associated with HAE swelling attacks and behavioral changes in animal models. It is from these data that we attempt to explain the depression and anxiety associated with HAE and how worsening depression and anxiety may modify the severity of the disease and the reverse. Although no human data have demonstrated this, we hope to initiate further research into the interplay between the neurocognitive system and contact system in HAE.

This study characterizes and describes the depressive and anxiety symptoms of patients with HAE in 2012, despite considerable patient and physician education on this subject and4 (4 in the United States) new medications added during the past 5 years. We discuss the defining features of the HAE patient experience, including those features that could not be captured by the scale alone, to provide the most complete picture of what it is like to live with HAE.

Methods

This study was approved by the institutional review board of Penn State University. The primary investigator (A.S.F.) was trained by a psychiatrist (E.F.S.) to administer the Hamilton Depression Rating Scale (HDRS)[10] and the Hamilton Anxiety Scale (HAS)[11] effectively over the telephone.

Patients were contacted from a cohort of 84 individuals diagnosed with Type 1 or Type 2 HAE. All patients had laboratory proven HAE type 1 (HAE with C1INH deficiency) or HAE type 2 (HAE with C1-inhibitor deficiency dysfunction). Twenty-four of these individuals were younger than 18 years and therefore reduced the pool of contacts to 60 individuals of consenting age. Of 60 individuals contacted, 26 were enrolled in the study. Those who were not enrolled could either not be contacted or declined to participate. The study was administered over the telephone, after an oral informed consent was obtained, and the data were stored in a deidentified fashion on a secure database to ensure confidentiality.

In addition to administration of structured HDRS and HAI questions, data were gathered qualitatively on the patient experience. Questions on the HDRS and HAI that referred to physical symptoms were explored and scored if the participant expressed that the symptom was due to depression or anxiety and was not a result of HAE. The first 17 items of the HDRS were used to tabulate the total depression score for grading of their symptoms according to the scale. These items capture melancholic depression, characterized by depressed, anhedonic mood, and vegetative symptoms (eg, insomnia, decreased appetite, and restlessness). Atypical depression with reverse vegetative symptoms (eg, hypersomnia, increased appetite, and psychomotor slowing) was also captured. Descriptive statistics were calculated for the HDRS and HAE scales.

In addition, the literature on inflammation, depression, anxiety, and HAE was researched using the PubMed, Ovid, and Google search engines. Keywords included *hereditary angioedema, HAE, depression, anxiety, inflammation, bradykinin, IL-1, C1 inhibitor, complement, Hamilton Depression Rating Scale,* and *Hamilton Anxiety Rating Scale.*

Results

There were a total of 26 respondents with this survey, making the response rate 43.3%. Demographic characteristics of the study participants are listed in Table 1. Mean (SD) scores of the 17-item, 21-item, and 29-item HDRS were 7 (6.2), 8 (6.5), and 11 (8.9), respectively. The range of scores was 0 to 19, and the median was 5. The first 17 items of the HDRS were used to arrive at totals for separating the sample according to severity of symptoms. Thirty-nine percent of participants were experiencing mild, moderate, or severe depressive symptoms. The breakdown of severity as classified with the HDRS is found in Figure 1.

Table 1
Demographic characteristics of the study participants

Characteristic	Finding
Sex, %	
Male	54
Female	46
Mean age, y	
Male	41
Female	48
Hereditary angioedema type, %	
Type 1	84
Type 2	16

Each question was also analyzed to arrive at a mean score. This part included all 29 questions that explore mental health in the longest Hamilton form. The mean score for each question was then divided by the total of possible points for that question to arrive at a mean for that particular question regarding the proportion of possible points. The results of this analysis are represented in Figure 2. The questions of initial insomnia ("difficulty getting to sleep"), general somatic symptoms ("feels tired or exhausted, loss of energy, diffuse muscular aching in back or limbs, heavy, dragging feelings in arms or legs"), and delayed insomnia ("waking in early hours of the morning and unable to fall asleep again") were, respectively, the top 3 symptoms of the questionnaire that elicited the greatest response (Fig 2). Atypical depressive symptoms (hypersomnia, hyperphagia, carbohydrate craving, and social withdrawal) were less common in this population. The mean (SD) score for the 21-item HDRS was 8 (6.5), the median score was 6.5, and the range was 0 to 20. The 29-item HDRS had a mean score of 11 (8.9), a median score of 12, and a range of 0 to 27. Fifteen percent of participants displayed prominent anxiety, half of whom had mild anxiety, 25% moderate anxiety, and 25% severe anxiety. There is no lower classification available on this scale below mild severity. The 4 most notable symptoms explored in questions in terms of the proportion of possible points were the following: anxious mood ("worries, anticipation of the worst, fearful anticipation, irritability"), intellectual ("difficulty in concentration, poor memory"), depressed mood ("loss of interest, lack of pleasure in hobbies, depression, early waking"), and tension ("feeling of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax").

When comparing these data to values for a healthy population, the best reference value was from a review of 27 articles that determined the healthy population mean (SD) to be 3.2 (3.2) on the 17-item HDRS, with a total of 84% of the healthy controls scoring below the cutoff of 7 recognized by the HDRS.[10] Our study found the mean (SD) to be 7.1 (6.2) for our sample with the 17-item HDRS. These data are compared in Table 2. Table 3 includes the literature search consulted that specifically relate to depression and anxiety in HAE patients.

Discussion

Our report is the first report, to our knowledge, on the prevalence and symptoms of depression and anxiety in patients with HAE since approval of 4 medications uniquely designed and approved for HAE in the United States. We found that 39% of respondents were currently experiencing clinically significant depressive symptoms. Our results were very similar to a much larger study of nearly 500 participants that found that 42.5%[12] of participants were experiencing depression according to the highly comparable and valid 9-item Hamilton Short Form.[13] Depression is a major consequence

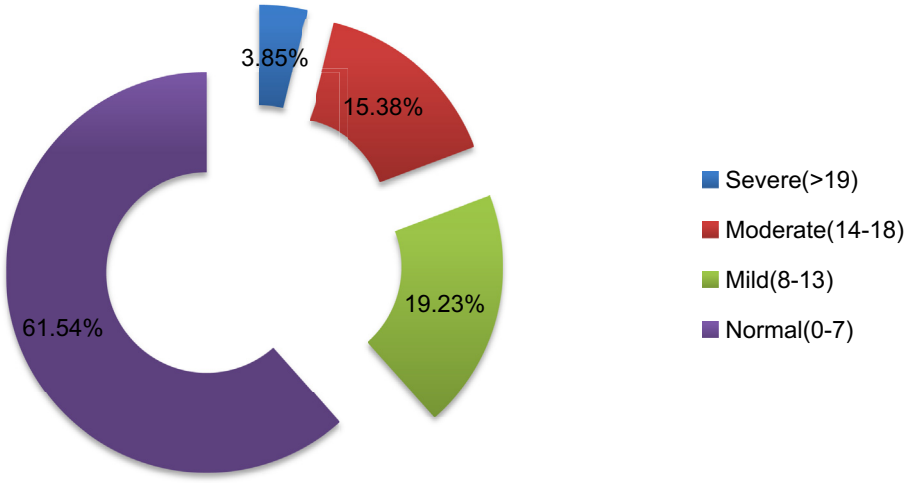

Figure 1. Depressive symptom severity as classified by the 17-item Hamilton Depression Inventory (score ranges)[10] in patients with hereditary angioedema.

of living with HAE. Depressive emotional distress appears to affect patients most significantly with regard to impaired sleep and fatigue; however, patients expressed a wide range of depressive symptoms. Rates of depression in our sample were slightly less than in the study by Lumry et al,[12] and differences in the 2 findings amounted to only 3.5%. This finding suggests that even with newly released medications depression is common and the health care professional should target depression during medical encounters and prescribe appropriate therapy when indicated.

Anxiety was noted in patients, but anxiety was regularly described as being much less bothersome after diagnosis and treatment. Patients also expressed a range of symptoms in terms of anxiety and found that anxious mood, depression, cognitive impairment, and tension were the most marked symptoms attributed to current feelings of anxiety in the sample. A Danish study found that the mean time to diagnosis after the patient's first noticeable attack was 16 years.[14] A much larger study by Lunn et al of 313 patients from the United States, Germany, United Kingdom, France, and the Netherlands found the mean time to diagnosis after the first experience of symptoms was 8.3 years, and this study pointed out numerous misdiagnoses, including some that involved unnecessary surgical procedures.[15] Clearly, the burden of illness can be notably worse preceding diagnosis.[16] Further prospective studies are needed to capture the temporal relationship between depressive and anxiety symptoms and diagnosis and treatment of HAE. One possibility to combat the depression and anxiety comorbidity seen in this disease may be raising awareness in the medical community to help patients receive a prompt diagnosis.

An example of the comments made by patients that emphasize their subjective concerns are below and were collected from the qualitative results of the interview. During the qualitative section of the interview, patients reported a high degree of satisfaction with their current care but significant emotional distress and disappointment in the past when they could not get an accurate diagnosis.

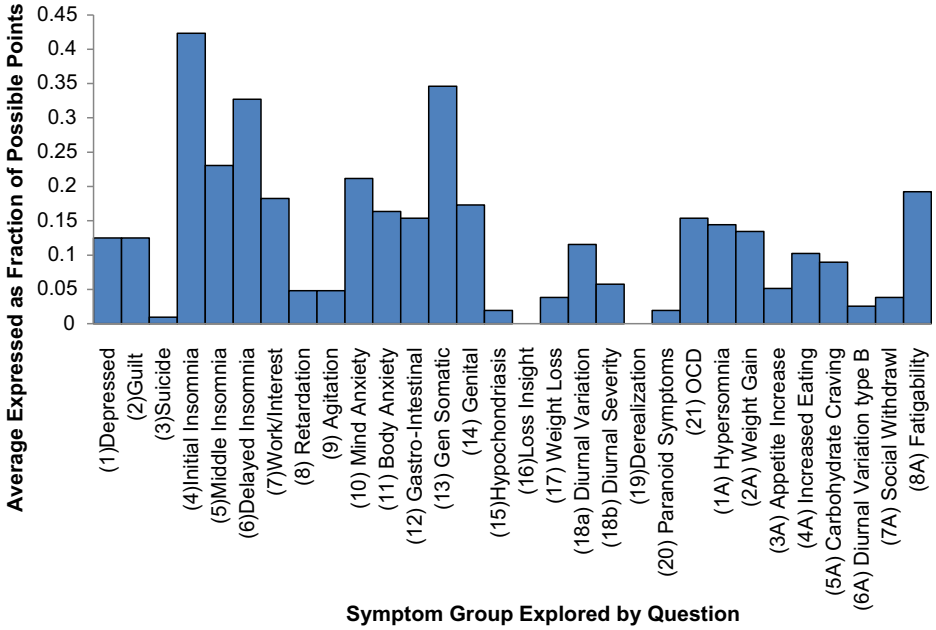

Figure 2. Mean score of individual Hamilton Depression Rating Scale items expressed as a fraction of possible points in patients with hereditary angioedema. OCD indicates obsessive-compulsive disorder.

Table 2
Manuscripts focused on depression and anxiety in hereditary angioedema

Primary author	Anxiety	Depression	Citation
Dantzer		Yes	Dantzer R. Depression and inflammation: an intricate relationship. *Biol Psychiatry* 2012;71:4–5. doi:10.1016/j.biopsych.2011.10.025.
Haroon	Yes	Yes	Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*. 2011;37:137–162. doi:10.1038/npp.2011.205.
Viana	Yes	Yes	Viana AF, Izaque MS, Fabiana DN, et al. Kinin B1 receptors mediate depression-like behavior response in stressed mice treated with systemic *E coli* lipopolysaccharide. *J Neuroinflammation.* 2010;7:98. doi:10.1186/1742-2094-7-98.
Zimmerman		Yes	Zimmerman M, Chelminski I, Posternak M. A review of studies of the Hamilton Depression Rating Scale in healthy controls: implications for the definition of remission in treatment studies of depression. *J Nerv Ment Dis.* 2004;192:595–601.
Blalock	Yes	Yes	Blalock JE, Smith EM. Conceptual development of the immune system as a sixth sense. *Brain Behav Immun.* 2007;21:23–33. doi:10.1016/j.bbi.2006.09.004.
Bluthé	Yes	Yes	Bluthé RM, Pawlowski M, Suarez S, Parnet P, Pittman Q, Kelley KW, Dantzer R. Synergy between tumor necrosis factor α and interleukin-1 in the induction of sickness behavior in mice. *Psychoneuroendocrinology.* 1994;19:197–207. doi:10.1016/0306-4530(94)90009-4.
Bygum	Yes	Yes	Bygum A, Andersen KE, Mikkelsen CS. Self-administration of intravenous C1-inhibitor therapy for hereditary angioedema and associated quality of life benefits. *Eur J Dermatol.* 2009;19:147–151.
Dantzer	Yes	Yes	Dantzer R. Cytokine-induced sickness behavior: where do we stand? *Brain Behav Immun.* 2001;15:7–24. doi:10.1006/brbi.2000.0613.
Dantzer	Yes	Yes	Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci.* 2008;9:46-56.
Fields		Yes	Fields J, Ghorpade A. C/EBPβ regulates multiple IL-1β-induced human astrocyte inflammatory genes. *J Neuroinflammation.* 2012;9:177. doi:10.1186/1742-2094-9-177.
Huang	Yes	Yes	Huang S-W. Results of an on-line survey of patients with hereditary angioedema. April 2004. http://medjournal.hmc.psu.edu:2198/content/ocean/aap/2004/00000025/00000002/art00010?token=0049116687e442f2067217d766a77703a2b467b3134687627502b333e3568263c2b0923ca.
Lumry	Yes	Yes	Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc.* 2010;31:407–414. doi:10.2500/aap.2010.31.3394.
Mejia		Yes	Mejia P, Davis AE. C1 inhibitor suppresses the endotoxic activity of a wide range of lipopolysaccharides and interacts with live gram-negative bacteria. *Shock.* 2012;38:220–225. doi:10.1097/SHK.0b013e31825bf40e.
Rethorst		Yes	Rethorst CD, Toups MS, Greer TL, et al. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder. *Mol Psychiatry.* 2012). doi:10.1038/mp.2012.125.
Reynolds		Yes	Rethorst CD, Toups MS, Greer TL, et al. Pro-inflammatory cytokines as predictors of antidepressant effects of exercise in major depressive disorder [published online August 28, 2012]. *Mol Psychiatry.* doi: 10.1038/mp.2012.125.
Sorensen		Yes	Sorensen B, Streib JE, Strand M, Make B, Giclas PC, Fleshner M, Jones JF. Complement activation in a model of chronic fatigue syndrome. *J Allergy Clin Immunol.* 2003;112:397–403. doi:10.1067/mai.2003.1615.
Bygum	Yes	Yes	Bygum A, Aygören-Pürsün E, Caballero T, Beusterien K, Gholizadeh S, Musingarimi P, Wait S, Boysen H. The hereditary angioedema burden of illness study in Europe (HAE-BOIS-Europe): background and methodology. *BMC Dermatol.* 2012;12:4. doi: 10.1186/1471-5945-12-4.
Gower		Yes	Gower RG, Lumry WR, Davis-Lorton MA, Johnston DT, Busse PJ. Current options for prophylactic treatment of hereditary angioedema in the united states: patient-based considerations. *Allergy Asthma Proc.* 2012;33:235–240. doi:10.2500/aap.2012.33.3573.
Lumry	Yes	Yes	Lumry WR, Castaldo AJ, Vernon MK, Blaustein MB, Wilson DA, Horn PT. The humanistic burden of hereditary angioedema: impact on health-related quality of life, productivity, and depression. *Allergy Asthma Proc.* 2010;31:407–414. doi:10.2500/aap.2010.31.3394.
Prematta	Yes		Prematta MJ, Kemp JB, Gibbs JG, Mende C, Rhoads C, Craig TJ. Frequency, timing, and type of prodromal symptoms associated with hereditary angioedema attacks. *Allergy Asthma Proc.* 2009;30:506–511. doi:10.2500/aap.2009.30.3279.
Prior	Yes	Yes	Prior N, Remor E, Gómez-Traseira C, et al. Development of a disease-specific quality of life questionnaire for adult patients with hereditary angioedema due to C1 inhibitor deficiency (HAE-QOL): Spanish Multi-centre Research Project. *Health Quality Life Outcomes.* 2012;10:82. doi:10.1186/1477-7525-10-82.

When patients were told by medical professionals that significant abdominal discomfort was "in their head," they were particularly distressed. Patients recounted how much more significant their sense of depression and anxiety had been when they were living with a rare disease that they could not get properly diagnosed. Anxiety seemed to be the most noted issue as patients struggled to cope with not knowing when their next attack would be, where it would affect them, what was wrong with them, and how their disease would progress throughout their lifetime.

After diagnosis, patients also experienced distress and felt rejected when physicians would not believe their direct and accurate diagnosis, especially when they would go into an emergency department setting. These experiences reduced their confidence in the ability of the medical community to help them should they experience a life-threatening laryngeal attack, where they would not have the ability to argue with physicians regarding the nature of their disease. Patients reported that the development of new treatment options with fewer adverse effects than older treatments had improved their quality of life.

The most potentially interesting theme noticed in the interviews was the potential relationship with mood and anxiety and likelihood of an attack. Several patients felt that not only did an attack cause feelings of depression and anxiety but also feelings of depression and anxiety have played a causative role in the initiation of an attack. Several noted significantly distressing life events as preceding their most significant attacks.

Table 3
The 17-Item HDRS findings compared with the general population values[a]

Variable	HAE cohort	General population cohort (n = 16)
Mean (SD) HDRS score	7.1 (6.2)	3.2 (3.2)
Individuals scoring >7, %	39	16
Individuals scoring >10, %	35	2.5

Abbreviations: HAE, hereditary angioedema; HDRS, Hamilton Depression Rating Scale.
[a]Higher values correlate with more severe depressive symptoms, and a score above 7 indicates clinically significant depressive symptoms.

In addition to the chronic burden of disease and delayed diagnosis, which increase stress, the inflammatory process that is etiologically responsible for HAE may in itself be a risk factor for depression.[1–9] The C1INH protein is a key component of the inflammatory cascade from a regulatory standpoint. IL-1β is one of the most well-studied inflammatory mediators relating to depressive symptoms in animal models, and it has recently been found to have a strong correlation for predicting the antidepressant effects of exercise in patients with major depressive disorder.[17] Furthermore, IL-1β in animal models increases the increased vessel permeability mediated by bradykinin.[8] Bradykinin circulates at higher levels in HAE patients, even between attacks, and significant increases mediate the notable symptoms of HAE.[1,2,5] The breakdown product of bradykinin (broken down by carboxypeptidase M), des-arg-9-bradykinin, is a strong agonist for bradykinin B1 receptors, which have been reported to directly mediate depressive symptoms in animal models.[6,7] Although the chronic disease burden is a key factor contributing to depression in the HAE patient population, there are several mechanistic links that may account in part for the elevated rates of depression seen in this population. Studying the relationship between disorders with distinct immunologic pathologic features, such as HAE, and depression and anxiety could prove to be pivotal as we continue to explore the immensely integrated nature of the human form.

A concern of any survey is selection bias. Unfortunately, all opportunities for volunteering adds bias. The number of responders to a request to be incorporated into the study was small but much greater than expected for most random surveys. Another concern with our data is the small number of patients who were surveyed. However, our data are similar to other larger studies, confirming it is valid. In addition, the timing of our study is key because it was accomplished after approval of 4 new medications, and this makes our data unique. Lastly, our literature search and discussion of the influence of cytokines on anxiety and depression in HAE add to the literature, and we hope this will direct future research.

In summary, depression and anxiety are important considerations in any serious chronic disease. Depression and anxiety appear to be an important concern in HAE in 2012, despite extensive education of patients, the public, and physicians about the disease, many recent publications addressing this issue, and 5 new medical therapies added during the past 5 years. The experience of living with a rare disease that has unique characteristics with significant implications, including death, especially when physicians often lack familiarity and the specialized knowledge to arrive at a diagnosis, contributes to the development of anxiety and depressive symptoms. In addition, inflammatory mediators may contribute to the depression and anxiety. Although the lives of HAE patients seem to have improved slightly with increased awareness and better treatment options, depression and anxiety are still important considerations for physicians when trying to care for patients with HAE. Screening for depression and anxiety and treatment or referral for treatment are critical needs in this population.

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