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Patients perception of self-administrated medication in the treatment of hereditary angioedema

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ABSTRACT

Background: Early therapy of hereditary angioedema (HAE) decreases morbidity, improves outcomes, decreases absenteeism, and possibly decreases mortality. This can be accomplished best with self-therapy. Previously, the authors examined barriers to self-therapy from the perspective of the nurse and the physician, but data are lacking on what patients perceive as major barriers to self-administered therapy for HAE.

Objective: To identify those barriers in a prospective fashion by patient interview.

Methods: After approval from the institutional review board, a telephone survey was performed of patients with HAE from a database of patients who were recently seen in the clinic. The survey focused on anxiety, depression, stress, concerns regarding method of administration, the ability to inject themselves, and what they perceived as barriers to providing self-care.

Results: Ninety-two patients were contacted and 59 agreed to participate. With 69% of those patients currently undergoing self-administered treatment, the results showed minimal depression and anxiety, a high satisfaction with treatment, and significant compliance with treatment. Most of those not yet on self-administered therapy wanted to start despite being satisfied with the care received in the emergency department. They also believed care at home would be optimal. The main concern of the 2 groups was not being able to treat themselves in the event of an HAE attack.

Conclusion: From these data, it is obvious that most patients are willing to self-treat. This suggests that physicians should encourage self-treatment of HAE to improve outcomes and quality of life of patients with HAE.

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Introduction

Hereditary angioedema (HAE) is an autosomal dominant condition that usually presents as acute attacks of nonpitting, nonpruritic swelling of the skin and subcutaneous tissue including the face, larynx, abdomen, and extremities.¹ In type 1 (HAE with deficient C1 inhibitor) and type 2 (HAE with dysfunctional C1 inhibitor), this results from a deficiency or impairment of function of the C1 esterase inhibitor (C1-INH).² C1-INH is a key regulator of the complement, fibrinolytic, contact, and coagulation systems.³ The prevalence of this disease is rare, with the estimated prevalence estimated to be 1:10,000 to 1:50,000.⁴ The less prevalent type 3 (HAE with normal C1-INH) presents with similar symptoms, but the etiology of the angioedema is not proved, although it is believed to be due to bradykinin.^{5,6}

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Therapeutic regimens include treatment of acute attacks or long- and short-term prophylactic therapy. In the past, most patients were treated in acute care centers, clinics, or emergency departments. Recently, however, self-administration of HAE treatment has been recognized as a treatment option in the most recent guidelines from the World Allergy Organization owing to safety, efficacy, and convenience.³

Treatment options for self-administered therapy consist of Berinert (C1-INH; CSL Behring, King of Prussia, Pennsylvania), Firazyr (icatibant, a bradykinin receptor blocker; Shire, Lexington, Massachusetts), Cinryze (C1-INH; Shire), and Reconst (recombinant C1-INH; Pharming, The Netherlands), with the World Allergy Organization advocating for self-care or home care of HAE through consensus and evidence-based medicine. It has been recommended that all therapy options be made available to all patients with HAE worldwide; however, self-administration is preferred because of improved quality of life through proven decreases in morbidity, absenteeism, cost, disease burden, and possibly mortality.^{7–10}

Previously the authors examined barriers to self-therapy from the perspective of the nurse¹¹ and the physician,¹¹ but data are lacking on what patients perceive as major barriers to self-administered therapy

for HAE. Also, patients' perception on how to perform self-therapy and how it has affected their emotional state has rarely been explored.¹² The present aim was to identify barriers to self-administration, with a focus on views of available therapy, disease severity, and patients' perceived capability to self-administer their medications subcutaneously or intravenously. The goal of this study was to demonstrate what these barriers to self-administered therapy are, the degree to which these affect patients' choices in choosing a treatment option, and the perceived or actual impact that self-administered therapy has on their lives.

Methods

A 26-question survey was created to assess the barriers a patient might face when considering self-administered treatment or the current barriers patients face if they currently use self-administered therapy as their main form of treatment. In addition, those not on self-administered therapy were assessed to determine why they were not on self-therapy for HAE. First, the survey focused on patients' satisfaction with their current treatment regimen and their behaviors regarding the amount of prodromal symptoms and attacks that they actually treat. Second, the questions focused on their views regarding the barriers to switching to or currently using self-administered therapy. Furthermore, the potential and actual benefits of self-administered therapy were explored. Third, the survey asked the patients to describe their levels of anxiety and depression and the potential or experienced impact of using self-administered therapy.

Then, a database of patients with HAE recently seen in clinic was created and further subdivided into HAE types and current treatment regimens. Overall, the database consisted of 92 patients, and 59 patients participated in the study. Patients seen exclusively for research purposes and acquired angioedema were excluded and patients not seen recently were excluded. Some prospective participants also were lost because of contact information that was not updated. Patients of all ages were included. Institutional review board approval was obtained before the start of the study. Telephone survey data results were collected anonymously and were analyzed by an independent statistician. The self-treated and non-self-treated groups were compared by χ^2 test.

Results

Demographics

The mean age of the study participants was 34.92 years (SD 18.19), with the youngest participant being 4 years old and the oldest being 78 years old. Thirty-seven of the 59 participants were female, which made up 64.29% ($n = 27$) of the self-administered group and 58.82% ($n = 10$) of the non-self-administered group. When male and female participants were separated based on the current use of self-administered care, the results showed that the mean age of participants who self-administered treatment was older (39.74 years, SD 16.26, $P < .001$) than that of participants not currently on self-administered treatment (23.00 years, SD 17.58, $P < .001$). Of the 3 types of HAE, as expected, most participants had the more prevalent type 1 (72.73%, $n = 40$). The balance had type 2 HAE. There was no difference in the choice of care modality according to HAE type.

The current medications used by the participants ranged from using no treatment to danazol (8.47%, $n = 5$). However, 3 medications that were the most widely used were Berinert (20.34%, $n = 12$), Cinryze (8.47%, $n = 5$), and icatibant (Firazyr; 27.12%, $n = 16$). Icatibant also was commonly used in combination with other drugs, with a significant proportion using a combination of Berinert with Firazyr (16.95%, $n = 10$) and Cinryze with Firazyr (6.78%, $n = 4$; Table 1). Of interest is that none of the patients on ecallantide

Table 1

Current medications used as reported by study participants ($N = 59$)

Medication	Frequency	%	Cumulative Frequency	Cumulative %
Berinert	12	20.34	12	20.34
Berinert + Firazyr	10	16.95	22	37.29
Kalbitor	4	6.78	26	44.07
Cinryze	5	8.47	31	52.54
Cinryze + Firazyr	4	6.78	35	59.32
Danazol	5	8.47	40	67.79
Epinephrine	1	1.69	41	69.48
Firazyr	16	27.12	57	96.6
No medication	2	3.39	59	100.00

(Kalbitor; Dyax Corp, Burlington, Massachusetts) chose to participate in the study.

Participants were asked to categorize their current method of treatment. Of these, 71.19% ($n = 42$, $P < .001$) stated that they are currently self-administering their treatment, whereas the rest were stratified based on different health care providers. Of those participants, 8.47% ($n = 5$, $P < .001$) received care from a nurse at home, 16.95% ($n = 10$, $P < .001$) received their care in the emergency department, and 3.39% ($n = 2$, $P < .001$) received their care at a physician's office.

Frequency and Treatment of Attacks

Of the 59 study participants, all provided a ranking of the frequency of their HAE attacks and the severity of the attacks in interfering with their day-to-day lives. These frequencies were sorted to show the differences between the self-administered and non-self-administered groups using a χ^2 test. Overall, the frequency of attacks showed an even distribution for attacks per year, with 37.29% ($n = 22$) having fewer than 6, 20.34% ($n = 12$) having 6 to 12, 18.64% ($n = 11$) having 12 to 24, and 23.73% ($n = 14$) having more than 24 attacks per year. Although the disability associated with having HAE attacks showed that 32.20% ($n = 19$) rated the interference of the attacks on their lives as severe, 37.29% ($n = 22$) rated the interference as moderate.

When divided based on current use of self-administered treatment, the self-administered group reported a higher frequency of having more than 24 attacks a year than the non-self-administered group (26.19%, $n = 11$, vs 17.65%, $n = 3$, $P = .004$). Most participants in the non-self-administered group reported fewer than 6 attacks a year (70.59%, $n = 12$, $P = .004$). Disability and interference in the lives of those who self-administered (severe, 42.86%, $n = 18$; moderate, 35.71%, $n = 15$; mild, 19.05%, $n = 8$; not at all, 2.38%, $n = 1$; $P < .001$) showed a higher degree of severity of interference compared with the non-self-administered group (severe, 5.88%, $n = 1$; moderate, 41.18%, $n = 7$; mild, 5.88%, $n = 1$; not at all, 47.06%, $n = 8$; $P < .001$).

Participants also quantified the number of attacks that they actually treated by self-administered and non-self-administered methods. They were asked to quantify these based on fewer than 10%, 25% to 50%, 50% to 75%, or 75% to 100% of attacks. Overall, 76.27% ($n = 45$) of participants were treating 75% to 100% of their attacks, with 69.05% ($n = 29$) of self-administering participants remaining in that stratification and 94.12% ($n = 16$) of non-self-administering participants remaining in that stratification.

Participants also were asked about prodromal symptoms, which were described as symptoms before swelling or attacks, and the frequency at which they treated those symptoms. The distribution of non-self-administering participants showed a bimodal pattern, with participants treating fewer than 10% (5.88%, $n = 1$) or 75% to 100% (94.12%, $n = 16$) of their prodromal symptoms. Most participants in the self-administered group (59.52%, $n = 25$) treated 75% to 100% of prodromal attacks; however, this group also had the

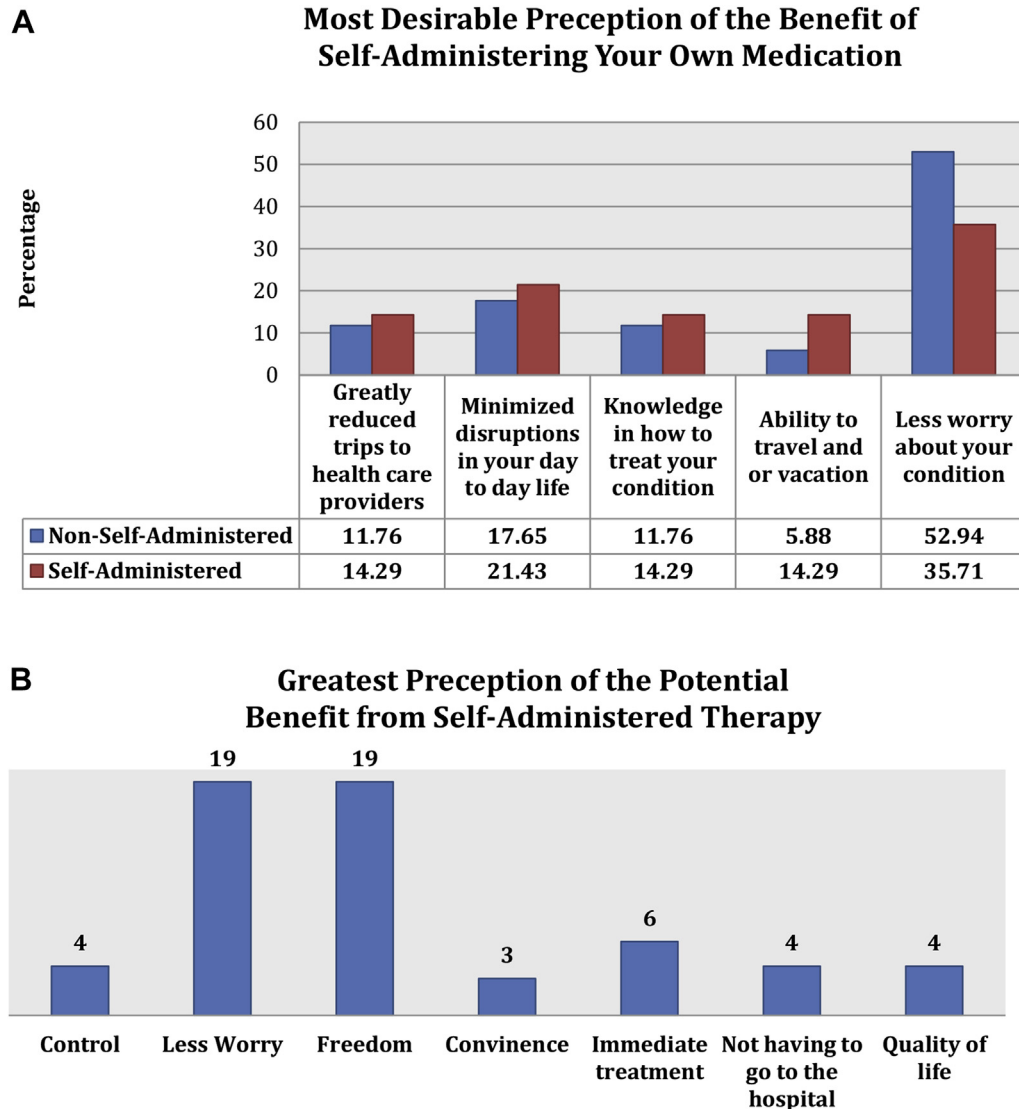


Figure 1. (A) Most desirable benefit in self-administering medication for hereditary angioedema. Numbers on the y axis represent percentages. (B) Greatest potential benefit to choosing self-administered therapy. Numbers represent frequencies of a response (N = 59 responses).

largest number of those treating fewer than 10% of their prodromal attacks (19.05%, n = 8).

Satisfaction, Perceptions, and Training Associated with Self-Administered Treatment

In the 2 groups, satisfaction with the current treatment regimen was high, with close to half of each group reporting complete satisfaction with the current treatment regimens (non-self-treated, 47.06%, n = 8; self-treated, 47.62%, n = 20).

Then, participants were asked about their perceptions of self-administered treatment and the ability of self-administering medications by subcutaneous and/or intravenous routes. Most participants (50.85%, n = 30) answered that they would be comfortable administering medications intravenously and subcutaneously, 18.64% (n = 11) responded the neither route would be comfortable, and 30.51% (n = 18) responded that they would be comfortable administering only subcutaneous injections.

When subsequently divided based on current use of self-administered care, there was a statistical significance in that 64.29% (n = 27, $P < .001$) of current self-administering users were comfortable

with subcutaneous and intravenous administrations, whereas only 17.65% (n = 3, $P < .001$) of those who were not currently using self-administered care were comfortable with subcutaneous and intravenous administrations. Overall, the non-self-administered group had the largest number (58.82%, n = 10, $P < .001$) of participants who said they were not comfortable giving themselves subcutaneous or intravenous injections.

Data on how many visits or training sessions to a health care provider it would take to learn how to competently self-administer HAE medication were collected from the self-administered and non-self-administered groups and showed that those in the non-self-administered group routinely overestimated the training sessions required, with 41.18% (n = 7) choosing more than 6 training sessions. In contrast, 75.61% (n = 31) of the self-administered group reported that it took 1 to 2 sessions to competently learn how to self-administer medications.

Data on preference for location of potential training sites were collected from the non-self-administered group and showed that most participants stated that being trained at home with a nurse (88.24%, n = 15) was preferable to being trained at a hospital (5.56%, n = 1) or a clinic (5.56%, n = 1). The self-administered group was asked

Table 2Greatest barrier to choosing self-administered therapy and the greatest worry or fear about self-administering therapy^a

Greatest barrier to choosing self-administered therapy		Greatest worry about self-administering therapy	
Performance	19 (32.20%)	Not being able to treat myself when I need it	35 (59.32%)
Expense	13 (22.03%)	Getting air into a vein	12 (20.34%)
Learning the technique	12 (20.32%)	Infection	6 (10.17%)
Safety	10 (16.95%)	Death	5 (8.47%)
Sterility	5 (8.47%)	Bleeding	1 (1.69%)

^aNumbers represent response frequencies (N = 59 responses).

where they were actually trained when learning self-administration of their medication. Most reported being trained at home with a nurse (90.25%, n = 35), and a small percentage reported being trained at work (4.88%, n = 2) or a hospital (4.88%, n = 2).

Home also was the first choice for the most comfortable location to receive therapy regardless of current route of treatment (non-self-treated, 82.35%, n = 14; self-treated, 100.00%, n = 41). In addition, 11.76% (n = 2) of participants in the non-self-administered group chose to receive their care at a hospital or a clinic.

Confidence and Benefits of Self-Administered Treatment

The 2 groups were asked about their confidence in self-administering their HAE medication in various situations. These situations included self-administering a subcutaneous treatment in an airplane, in a car, at home, at the workplace, and during a vacation. Participants in the non-self-administered group had close to an even split in responding that they had confidence in their ability to self-administer at all locations (58.82%, n = 10, $P < .001$) and that they did not believe they could perform the administration (41.18%, n = 7, $P < .001$), whereas 100% (n = 42, $P < .001$) of participants in the self-administered group responded that they would be able to administer their treatments at all these locations.

Participants also were queried on the prospect of a home therapy partner who was trained to administer therapy to provide support and advice. Most participants (59.32%, n = 35) stated that it would not affect them in any way, 32% (n = 19) stated that they would be more likely to try self-administered treatment, and 8.47% (n = 5) stated that it would not make them more willing to try self-administration.

A telephone helpline and a support Web site for the self-administered route of treatment were met with lukewarm opinions, with only 44.06% (n = 26) stating that a telephone helpline would be helpful, somewhat helpful, or extremely helpful and 55.93% (n = 25) stating the same about a Web site for support.

Participants also were asked about the perceived benefits of self-administration. When asked about the most desirable benefit, most chose having to worry less about their condition (Fig 1A). There also was a follow-up question for which participants were asked to respond in free form about the greatest potential or actual benefit of choosing self-administered therapy. Their responses are presented in Figure 1B.

Participants' views on the possibility for decreased medical expenses, risk of disability, and risk of death associated with self-treatment also were queried. Most (87.93%, n = 51) anticipated a decrease in medical expenses, and 79.66% (n = 47) anticipated a lower risk of disability and death associated with self-administered treatment.

Barriers and Fears Associated with Self-Administered Treatment

Participants' fears and prospective barriers to choosing or currently using self-administered treatment were queried by asking them to choose the greatest barrier to self-administered therapy, with most choosing that performance (ie, the process of injection) was their greatest barrier. Also, their greatest worry or

fear about self-administered therapy was not being able to treat themselves when needed for an attack (Table 2).

When dividing the 2 groups, the greatest barrier for participants in the non-self-administered group was learning the technique (58.82%, n = 10, $P < .001$), which was in contrast to those in the self-administered group who chose self-injection (40.48%, n = 17, $P < .001$) as the greatest barrier. For worries, most participants in the 2 groups (non-self-treated, 64.71%, n = 11; self-treated, 57.14%, n = 24) stated that not being able to treat themselves when they needed to was the greatest worry in administering their HAE medication.

Effects on Depression and Anxiety

Participants also were surveyed on their levels of depression and anxiety, which were categorized as always, more than half the day, less than half the day, rarely, and never. Most participants reported at least some level of depression, although the non-self-administered group had the most participants who reported no depression (70.59%, n = 12, $P = .014$) or anxiety (58.82%, n = 10, $P = .020$; Fig 2). Then, the groups were surveyed on whether they believed self-administered therapy could lower or had lowered their levels of depression or anxiety, with 78.05% (n = 32) of the current self-administered group reporting a decrease in depression or anxiety and only 22.22% (n = 4) of the non-self-administered group believing that it could decrease depression or anxiety (Fig 3).

Discussion

The World Allergy Organization has agreed that self-administration for attacks and prophylaxis of HAE is the preferred method of treatment because of its proven decrease in morbidity, absenteeism, cost, disease burden, and potential mortality, and it provides an increase in the quality of life.⁷ In addition, other consensus documents and guidelines support self-administration.^{13,14} What the guidelines do not address are the patients' wishes, worries, and perceptions of self-administration.

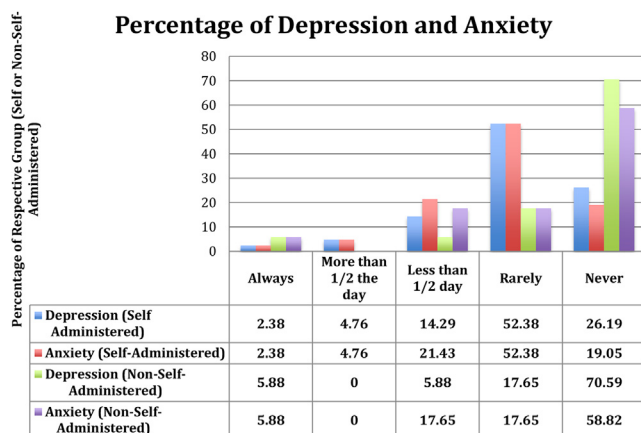


Figure 2. Percentage of participants with depression and anxiety sorted by self-administered and non-self-administered treatment.

Potential or Actual Effect of Self-Administered Therapy on Depression and Anxiety

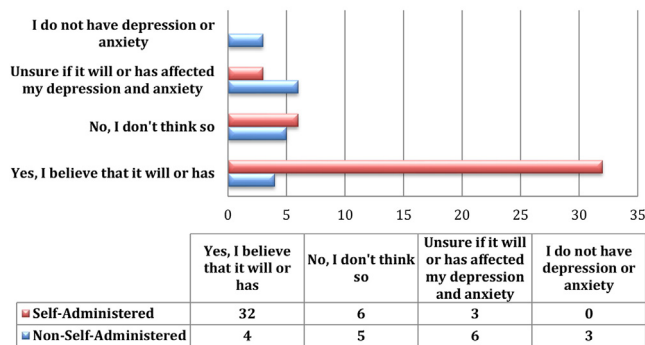


Figure 3. Potential perceived or actual effect of self-administered therapy on depression and anxiety (self-treated, $n = 41$; non-self-treated, $n = 18$).

In the present study, those who self-administered treatment were older than those who did not self-administer treatment. This was unexpected because the authors presumed that older patients would be less likely to learn new techniques. Because the present cohort included children and some were as young as 4 years, this could have affected age and self-treatment. There were no statistical differences between sex and HAE type in choosing self-administered treatments.

The reported frequency and severity of HAE attacks demonstrated that those who were using self-administered treatment were more likely to have frequent attacks and more morbidity from their attacks. The treatment rate for prodromal symptoms showed that most treated 75% to 100% of their attacks at the start of prodromal symptoms. This was possibly due to the increased awareness of patients and education from health care providers. It should be noted that the authors educate patients to treat at the first symptom of an attack, which could be prodromal symptoms; however, they do not emphasize treating prodromal symptoms during education.

As for satisfaction, close to half the participants in each group were completely satisfied with their current treatment regimens. This emphasizes that self-administration is not necessary for all patients. Regarding training and confidence, the non-self-administered group appeared to overestimate the training and difficulty in becoming proficient in self-administering. The self-administered group was more confident in their training and ability to perform subcutaneous and intravenous injections (64.29%, $n = 27$), and most (75.61%, $n = 31$) reported that their training took only 1 to 2 sessions for them to feel competent enough to self-administer. This is in contrast to physician assessment of needs to train patients. Most believed multiple appointments were necessary.⁹

The desire for comfort also was equal between the 2 groups, with the 2 groups preferring to be trained at home with a nurse and receive their treatment at home. This location preference matches that of nurses who also prefer that self-infusion teaching to be done at home.¹¹

Confidence also is a large factor in patients' adherence to treatment and comfort. One of the many benefits of self-administered therapy is the greater freedom to travel.⁴ The present study focused on being able to self-administer a subcutaneous treatment in an airplane, in a car, at home, at work, or on vacation. The non-self-administered group had a significant number of participants who stated they would not feel comfortable administering their medications in at least 1 of these situations, whereas 100% ($n = 42$, $P < .001$) of the current self-administered group indicated that they would be confident administering their treatment in these situations. These data support the notion that self-administration creates an additional sense of independence.

Health care providers use different tools to support patients with HAE. These so-called support tools include a home therapy partner, a telephone helpline, and a Web site for support. However, consistently among participants, the prospect of a home therapy partner did not affect their views on choosing self-administered care, and a telephone helpline and Web site were found to be only moderately helpful. This might be due to an increased confidence in the self-administered group, thus requiring minimal support mechanisms. The authors were surprised that a trained partner was rarely found to be an attractive option, especially if that patient's main fear was not being able to self-administer treatment during an attack.

Hereditary angioedema is disruptive to a patient's life and this is increased with the constant uncertainty of how or when to treat the condition.^{15,16} These concerns are central to what patients with HAE identify as the most desirable benefit in choosing self-administered therapy. The 2 groups' most desired benefit was less worry about HAE. This was especially apparent in the non-self-administered group because more than half the group chose this as the most desired benefit. This was further emphasized by participants' free text responses regarding the greatest potential benefit of self-administering therapy. Most stated "less worry and freedom" as the key reason to self-administer. This supports previous studies demonstrating that patients' most desired outcomes were time saved, independence, and convenience.⁴

Most participants in each group believed that self-administering HAE treatment would decrease medical expenses and lower the risk of disability and death. Despite these benefits, patients often experienced barriers and/or fears to switching to or using self-administered therapy. Among self-treating participants, most chose performance as their main barrier. For worries and fears, participants in each group chose not being able to self-treat as their greatest worry in switching to or using self-administered therapy to treat their HAE. This emphasizes the importance of having an action plan and a backup system for therapy when self-administration is not possible. Surprisingly few patients were concerned about air emboli, bleeding, death, or infection secondary to self-administration. This emphasizes that patients are more afraid of not being able to treat an attack than of the possible consequences of self-medication. This was found in the self-treating and non-self-treating participants. The authors anticipated that fear of adverse events was the barrier that prevented most non-self-treating participants from self-treatment. They also were surprised that intravenous therapy was not a major perceived barrier to self-administration.

The effects of HAE on depression and anxiety were noteworthy and previously noted in the literature¹²; however, a large percentage of non-self-treating participants reported never being depressed and only rarely anxious. This finding was surprising in a population of patients with HAE, and in comparison most self-administering participants reported being at least mildly depressed. The authors' interpretation of this finding is that patients with few attacks are less likely to experience significant morbidity and less likely to self-administer for this reason.

Contrary to expectation, most self-treating patients replied that they were only rarely depressed or anxious, despite frequent attacks. They were asked a follow-up question regarding the degree to which their depression or anxiety had been alleviated by switching to self-administered treatment. An overwhelming majority stated decreases in their depression and/or anxiety. This could explain the lower reported levels of depression and anxiety in those who are currently undergoing self-administered treatment, further showing the benefits of self-administered therapy as the main modality of treatment. The non-self-administered group was asked a similar question, but the question focused on the perception of potential benefits regarding depression and anxiety. Contrary to expectation,

some did not expect a benefit from self-therapy. Education by providers regarding the benefits of self-therapy could help patients have more control and freedom by providing self-care.

Limitations of this study mostly concern sample size, because only 59 of the 92 total patients who qualified participated. Those who participated compared with those who did not could have influenced the outcomes, but this is always a concern when enrolling subjects in a study such as this. In ideal conditions a larger sample of those currently using self-administered treatment and non-self-administered treatment would be optimal, but for a rare disease, this sample size seems appropriate. In addition, many of the queries demonstrated significant benefit for the self-treated group over the “dependent group,” suggesting the sample size was adequate. Another limitation is that this is a single-center study; however, 4 to 6 fellows and 8 faculty members make up the authors’ group and thus these data reflect more than just 1 physician’s approach to treating patients with HAE. Moreover, standardized instruments were not used to collect data and results before and after therapy were not compared; rather, self-treating participants were compared with non-self-treating participants.

In summary, there have been studies performed on health care providers’ views on self-administered treatment of HAE from the perspective of physicians¹ and nurses¹¹; however, research on the barriers, concerns, and benefits from the patient’s point of view had not been performed until this publication. The authors’ hope this research has provided stimulation for providers to further emphasize self-administered treatment as the standard of care for HAE and highlighted areas that are a concern for patients so these concerns can be addressed when educating patients about self-care.

References

- [1] Craig TJ. Recent advances in hereditary angioedema self-administration treatment: summary of an international hereditary angioedema expert meeting. *Int Arch Allergy Immunol*. 2013;161(suppl 1):26–27.
- [2] Dispenza MC, Gutierrez M, Bajaj P, Craig TJ. The need for individualized hereditary angioedema acute action plans: two case studies of misdiagnosed attacks and unnecessary surgeries. *Ann Allergy Asthma Immunol*. 2012;109:A66–A67.
- [3] Hemperly SE, Agarwal NS, Xu YY, Zhi YX, Craig TJ. Recent advances in the management of hereditary angioedema. *J Am Osteopath Assoc*. 2013;113:546–555.
- [4] Caballero T, Sala-Cunill A, Cancian M, et al. Current status of implementation of self-administration training in various regions of Europe, Canada and the USA in the management of hereditary angioedema. *Int Arch Allergy Immunol*. 2013;161:10–16.
- [5] Craig TJ, Berstein JA, Farkas H, Bouillet L, Boccon-Gibod I. Diagnosis and treatment of bradykinin-mediated angioedema: outcomes from an angioedema expert consensus meeting. *Int Arch Allergy Immunol*. 2014;165:119–127.
- [6] Bork K. An evidence based therapeutic approach to hereditary and acquired angioedema. *Curr Opin Allergy Clin Immunol*. 2014;14:354–362.
- [7] Cicardi M, Craig TJ, Martinez-Saguer I, Hébert J, Longhurst HJ. Review of recent guidelines and consensus statements on hereditary angioedema therapy with focus on self-administration. *Int Arch Allergy Immunol*. 2013;161(suppl 1):3–9.
- [8] Riedl M. Hereditary angioedema therapies in the United States: movement toward an international treatment consensus. *Clin Ther*. 2012;34:623–630.
- [9] Aygören-Pürsün E, Bygum A, Beusterien K, et al. Socioeconomic burden of hereditary angioedema: results from the Hereditary Angioedema Burden of Illness study in Europe. *Orphanet J Rare Dis*. 2014;9:99.
- [10] Longhurst HJ, Farkas H, Craig TJ, et al. HAE international home therapy consensus document. *Allergy Asthma Clin Immunol*. 2010;6:22.
- [11] Tuong LC, Olivieri K, Craig TJ. Barriers to self-administered therapy for hereditary angioedema. *Allergy Asthma Proc*. 2014;35:250–254.
- [12] Fouche AS, Saunders EF, Craig TJ. Depression and anxiety in patients with hereditary angioedema. *Ann Allergy Asthma Immunol*. 2014;112:371–375.
- [13] Betschel S, Badiou J, Binkley K, et al. Canadian hereditary angioedema guideline. *Allergy Asthma Clin Immunol*. 2014;10:50.
- [14] Zuraw BL, Banerji A, Bernstein JA, et al. US hereditary angioedema association medical advisory board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol Pract*. 2013;1:458–467.
- [15] Zilberg MD, Nathanson BH, Jacobsen T, Tillotson G. Descriptive epidemiology of hereditary angioedema emergency department visits in the United States, 2006–2007. *Allergy Asthma Proc*. 2011;32:390–394.
- [16] Wilson DA, Bork K, Shea EP, Rentz AM, Blaustein MB, Pullman WE. Economic costs associated with acute attacks and long-term management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;104:314–320.