Original Article

Survey-Defined Patient Experiences With Aspirin-Exacerbated Respiratory Disease

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What is already known about this topic? Aspirin-exacerbated respiratory disease is a complex inflammatory airway syndrome that generally requires multiple medications to manage.

What does this article add to our knowledge? Aspirin therapy is reported to be effective in a majority of surveyed respondents, yet it continues to be underused for various reasons.

How does this study impact current management guidelines? Most patients with aspirin-exacerbated respiratory disease report significant burden of illness despite existing treatment options.

BACKGROUND: Aspirin-exacerbated respiratory disease (AERD) is a chronic illness of progressive recurrent sinus disease with nasal polyps and asthma. No population-based comprehensive surveys of patients with AERD have been carried out to assess specific quality-of-life impact or perceptions of treatment benefit.

OBJECTIVE: This survey analyzed perceptions and quality of life in those living with AERD and queried patient observations of treatment effectiveness. The survey assessed whether dietary and nutritional support was used to manage AERD, and if so, whether there was a perceived benefit.

METHODS: This survey was publicized through clinics that treat patients with AERD, Web sites, and online blogs.

RESULTS: Results are reported for 190 patients. Most subjects reported an adverse effect of AERD on quality of life. Chronic nasal symptoms followed by decreased sense of smell were reported to have the greatest impact on quality of life—in 81 (43%) and 74 (39%), respectively. Those who lost their ability to smell (n = 65; 34%) reported that they missed the enjoyment of food and eating the most. A minority indicated that a combination of medications (aspirin, leukotriene receptor antagonist, zileuton, or omalizumab) was more effective than 1 alone. Of those surveyed, 120 (63%) respondents felt that components of their diet contributed to their disease and 147 (77%) respondents reported having reactions after alcohol consumption.

CONCLUSIONS: Patients with AERD live with frustration and report a poor quality of life in spite of several pharmacologic treatments including aspirin desensitization followed by daily aspirin. Despite ongoing medical therapy, the burden of disease in AERD remains high. © **2015 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2015;3:711-8)**

Key words: *Aspirin-exacerbated respiratory disease; Aspirin-induced asthma; Desensitization; Survey; Quality of life*

Aspirin-exacerbated respiratory disease (AERD) is typified by adult-onset asthma, chronic rhinosinusitis, nasal polyposis, and upper and lower airway reactions to cyclooxygenase-1 (COX-1) inhibitors including nonsteroidal anti-inflammatory drugs.[1] Formal aspirin challenges are required for a definitive diagnosis of AERD, and daily aspirin administration after desensitization is a beneficial therapy in most patients.[2] A diagnosis of AERD is often life changing for patients. Yet, little is known about the perceived effectiveness of therapies that currently exist for patients with AERD. AERD is a complex inflammatory disorder, making it difficult to assess what constitutes "control" as would be sought for in a typical patient with asthma. In this survey, we assessed the quality of life in those with AERD and factors involved in the decision to use aspirin therapy, evaluated the perceived effectiveness of various established treatments in AERD, and gathered a census of foods or supplements implicated in the health of patients with AERD. Some of the questions used in this survey were prompted by patient reports in our AERD clinic. One purpose of the survey was to identify whether these anecdotal observations could be generalized to the AERD population.

METHODS

Study design

This cross-sectional survey questionnaire (in this article's Online Repository at www.jaci-inpractice.org), which is data collection from a specific point in time, was open to patients who identified themselves as having AERD. The Institutional Review Board and Human Subjects Committee at Scripps Clinic approved the study. Informed consent was waived. The survey was conducted from July 2014 to September 2014.

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Conflict of Interest: The authors declare that they have no relevant conflicts of interest.

Received for publication January 8, 2015; revised February 25, 2015; accepted for publication March 2, 2015.

Available online April 7, 2015.

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2213-2198

http://dx.doi.org/10.1016/j.jaip.2015.03.001

Abbreviations used
AERD- aspirin-exacerbated respiratory disease
COX-1- cyclooxygenase-1

Web Site development. The survey questions were converted into an online format and hosted by an external company. The survey was backed by an onsite-encrypted secure database that was moved to a secure system for analysis after the survey closure.

Survey population, recruitment, and data collection. Patients older than 18 years living in or outside the United States with AERD were invited to complete the survey. The survey was publicized on AERD blogs, support groups, and clinics. To be qualified for entry into the survey, respondents were required to meet the following criteria: (1) understand survey confidentiality, (2) be 18 years or older, (3) have a physician diagnosis of nasal polyps, (4) have a diagnosis of AERD, and (4) have had a reaction to nonsteroidal anti-inflammatory drugs. If responders did not meet these criteria, they were automatically disqualified and unable to access the survey further.

Data evaluation. Completed surveys were analyzed, and incomplete surveys were discarded. Data evaluation was performed using Microsoft Excel (Microsoft Corp, Redmond, Wash) and Student *t*-test's online calculator (studentsttest.com).

RESULTS

Demographic characteristics

A total of 222 people entered the survey. Twenty-two did not complete the survey, and 10 were disqualified for not meeting the necessary criteria mentioned above. Eliminating these groups yielded 190 valid responders. The survey was anonymous and confidential. A total of 41% of the respondents were men and 59% were women. Most of the respondents were aged between 41 and 60 years (n = 111; 58%). Most of the respondents were white (n = 181; 95%). A total of 131 (69%) respondents had been living with AERD for more than 7 years, with most reporting 3 to 5 nasal polypectomies.

Quality of life

Mood. AERD adversely affects quality of life. On a scale of how badly AERD affected their lives, 1 (mild) to 9 (severe), most respondents (n = 43; 23%) ranked their quality of life a 7, with an average of 6 (Figure 1). These subjects also reported frustration (n = 118; 62%), fatigue (n = 128; 67%), irritability (n = 69; 36%), and depression (n = 59; 31%). Only 35 (18%) claimed having none of these emotions.

Sense of smell. By far, most of the respondents reported chronic nasal symptoms and decreased sense of smell—165 (87%) and 169 (89%), respectively—as the top 2 categories in which AERD diminished their quality of life (Figure 2). When respondents were asked to identify *one aspect* of AERD that decreased their quality of life the most, most identified chronic nasal symptoms (43%) followed by decreased sense of smell (39%). A majority (n = 184; 97%) had anosmia or hyposmia. Of those with impaired sense of smell, 65 (34%) reported that they miss the enjoyment of food and eating the most, 59 (31%) felt sadness at not being able to trigger pleasant memories through scent, and 41 (22%) felt unsafe because of the inability to smell smoke/fumes (Figure 3). Of the total patients with diminished sense of smell, 15 (8%) felt that that their sense of smell waned variably but was normal most of the time, 33 (17%) felt a decrease in their sense of smell randomly without any prediction when they would be able to smell again, 98 (52%) said that their sense of smell temporarily improved with either sinus surgery or steroids (intravenous or oral), and 36 (19%) felt that their sense of smell was completely gone and nothing seemed to temporarily improve it.

Urticaria and abdominal reactions. Fifty-four (28%) patients reported a history of urticaria diagnosed and confirmed by a physician. Of those with a history of urticaria, 33 (52%) stated that their hives resolved within an hour while 13 (20%) stated that their urticaria lasted weeks to months. Some patients reported urticaria on a monthly basis, whereas most patients with urticaria described episodes occurring 2 to 3 times per year. In this survey, 45 (24%) respondents reported severe abdominal pain as part of the AERD reaction.

AERD diagnoses

Of the 193 respondents reported to have AERD, 190 (98%) were diagnosed with nasal polyps by a physician, but only 52 (27%) respondents were diagnosed by an aspirin challenge, which is the criterion standard method of diagnosing AERD.[3,4] Alternatively, 93 (49%) had undergone aspirin desensitization, which serves as an aspirin challenge and could also confirm the diagnosis. It appears that allergists (n = 68; 36%) and otolaryngologists (n = 72; 37%) equally make the majority of the diagnoses compared with providers in other fields of medicine. However, when asked who primarily manages AERD, allergists had a greater influence (n = 96; 51%) than do otolaryngologists (n = 50; 26%), primary care physicians (n = 29; 15%), or pulmonologists (n = 15; 8%). Approximately a third of the subjects did not favorably rate their physicians' knowledge of AERD (giving a score of only 1-4 out of a range of 1-9). More individuals turned to social media sites (n = 149; 77%) and their own review of medical literature or medical news sites (n = 98; 52%) than discussing it with their own physician (n = 82; 42%).

AERD treatment

Aspirin. Ninety-three (49%) respondents had undergone aspirin desensitization at some point in their life, but only 74 (39%) were still on aspirin treatment for their AERD. Of those who had been on aspirin, 85 (91%) found aspirin effective in controlling their symptoms. One (1%) was on aspirin 81 mg daily, 10 (13%) were on aspirin 82 to 325 mg daily, 31 (43%) were on aspirin 326 to 650 mg daily, and 32 (43%) were on aspirin 651 to 1300 mg daily. When offered aspirin desensitization, 88 (46%) were willing to go on aspirin while the others were reluctant. When asked why they were reluctant to undergo aspirin desensitization, 46 (45%) were concerned about taking aspirin long term, 28 (27%) were concerned about the safety, 19 (19%) said that their physician did not recommend it, and 9 (9%) claimed that the process was too expensive. For those respondents who discontinued the aspirin, reasons included the following: surgery and aspirin was never restarted (n = 18; 43%), ineffective (n = 7; 17%), stomach pains (n = 6; 14%), asthmatic or nasal symptoms (n = 4; 10%), other adverse effects (pancreatitis, esophageal spasms, could not remember the

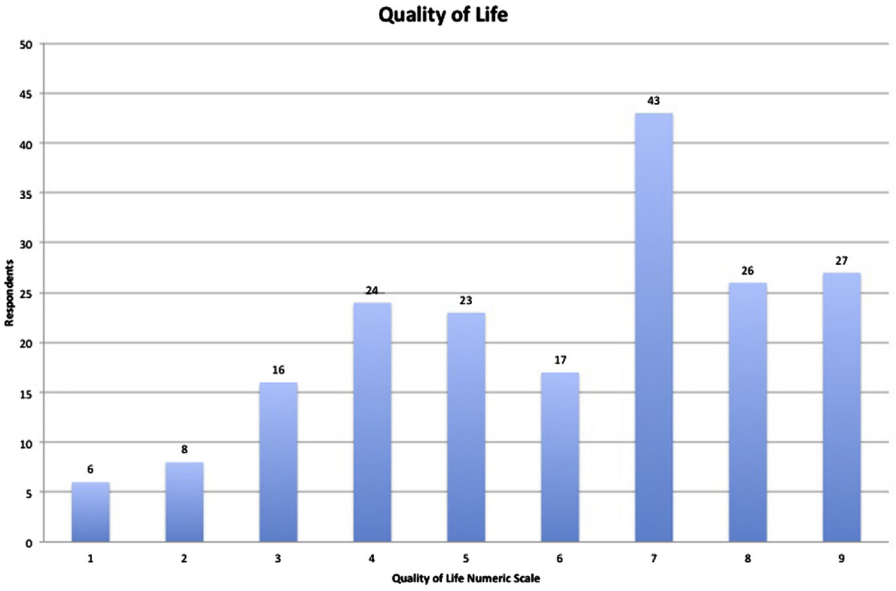

FIGURE 1. Quality of Life Scale. Respondents ranked how AERD affected their quality of life from 1 (mild) through 9 (severe). Mean, 6; median, 7.

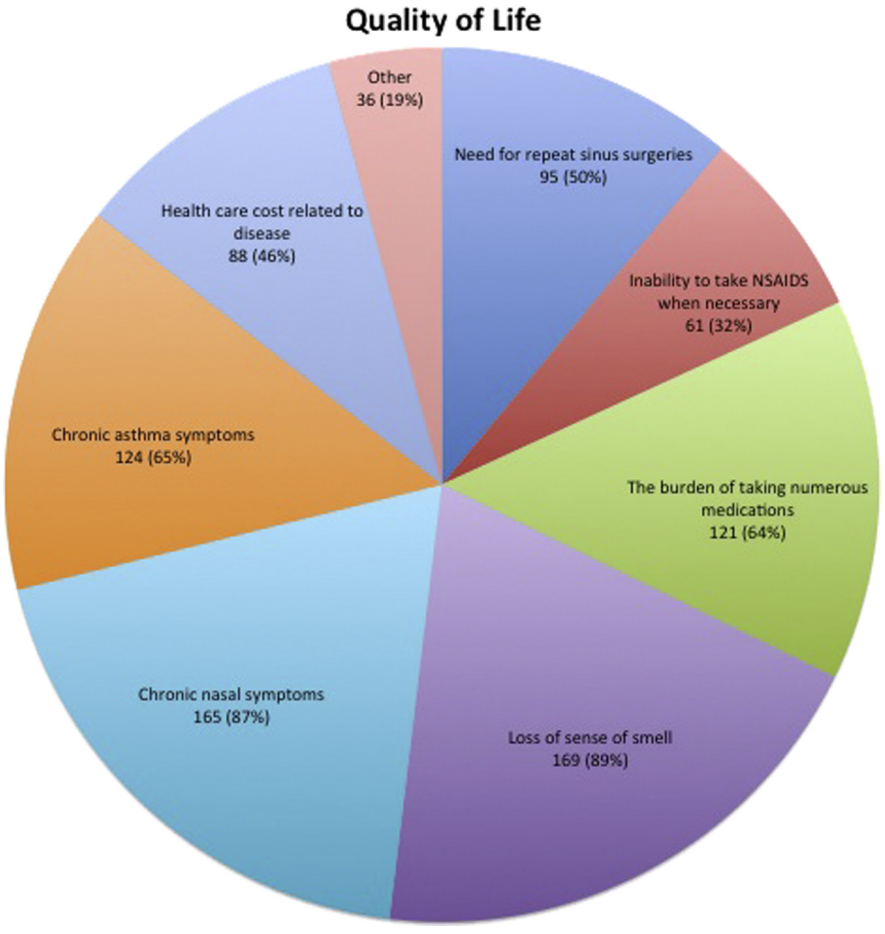

FIGURE 2. Aspects of AERD that affect quality of life. The category "Other" included rhinorrhea, frequent sinus infections, and facial pain.

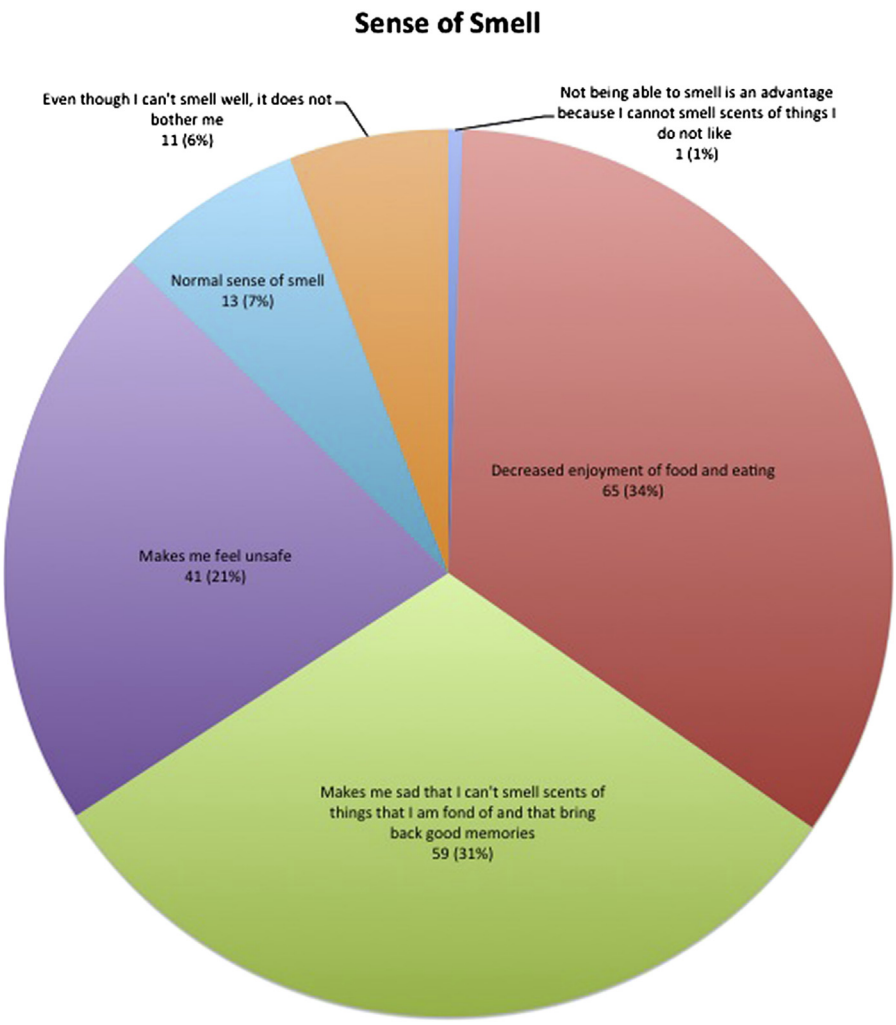

FIGURE 3. Effect of sense of smell on quality of life.

dosing) (n = 3; 7%), stomach ulcers (n = 3; 7%), or pregnancy (n = 1; 2%).

Effects of aspirin on quality of life. In the 74 patients who were currently taking aspirin at the time of the survey, AERD affected their quality of life on an average of 5.39 ± 2.27 compared with an average of 6.36 ± 2.14 in those not on aspirin, on the scale ranging from 1 (mildly affects quality of life) to 9 (severely decreases quality of life) ($P = .003$). Sense of smell was slightly improved (mean, 2.14 ± 1.16) in the group on aspirin compared with the group not on aspirin (mean, 1.83 ± 1.10) ($P = .082$).

Immunotherapy. Of those with AERD, 59 (31%) respondents had allergic rhinitis but decided never to undergo allergy immunotherapy, 86 (45%) had concurrent allergic rhinitis and were on immunotherapy, 53 (62%) on immunotherapy did not find it effective, 26 (30%) found it somewhat effective, and 7 (8%) found it extremely effective.

Leukotriene receptor antagonists. Many patients with AERD have been treated with a leukotriene-modifier drug such as montelukast, zafirlukast, or pranlukast (n = 168; 88%). Of those who have been on a leukotriene-modifier drug, 64 (38%) stopped it because it was ineffective, 20 (12%) found it ineffective but stayed on it because their doctor wanted them on it, 58 (35%) felt that it was somewhat effective, and 26 (15%) found it extremely effective.

5-Lipoxygenase inhibitor. Some patients with AERD have also been treated with a 5-lipoxygenase inhibitor such as zileuton. Most of the 190 respondents had never been on zileuton (n = 144; 76%), but 46 (24%) had tried it. Of those on zileuton, 20 (43%) stopped it because it was ineffective, 2 (4%) found it ineffective but continued it because their physician kept them on it, 11 (24%) found it somewhat effective, and 13 (28%) found it extremely effective.

Omalizumab. Omalizumab is a humanized recombinant mAb that blocks the binding of immunoglobulin IgE to its high-affinity Fc receptor. Of those surveyed, 174 (92%) had never been on omalizumab while 16 (8%) had been on omalizumab. Of the 16, 5 (31%) found it ineffective and discontinued it, 2 (13%) found it ineffective but continued it per advice by their

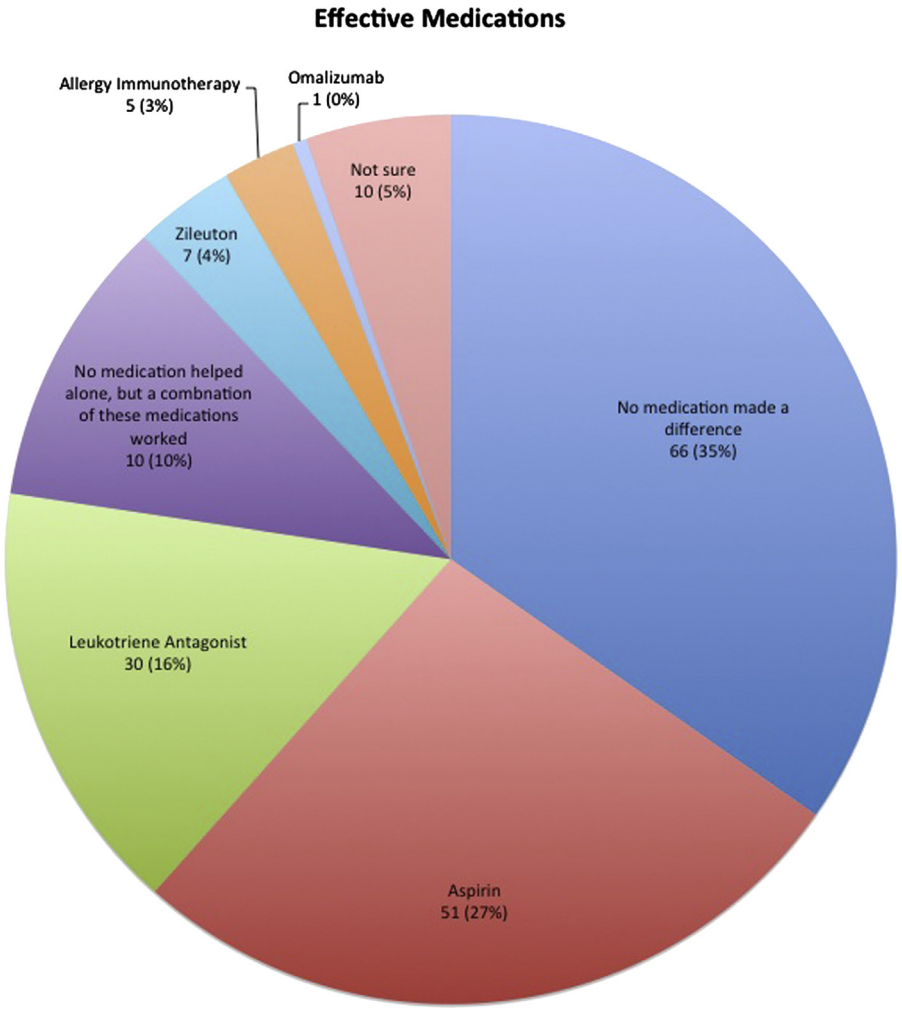

FIGURE 4. Effectiveness of various medications in AERD.

physician, 6 (38%) found it somewhat effective, and 3 (19%) found it extremely effective.

Of all the treatments offered, aspirin itself was reported to be the most beneficial (n = 51; 27%) followed by a leukotriene receptor antagonist (n = 30; 16%) and a combination of medications (n = 20; 10.5%) (Figure 4). Overshadowing these statistics were the 66 (35%) who reported "no medicine has made a difference for my symptoms." Of this group, 13 (19%) had been on aspirin or were currently taking aspirin while 54 (81%) had never been on aspirin. Systemic steroids continued to be required in most of the respondents. Eighty-eight (46%) reported 3 or more systemic steroids bursts in the past 12 months.

Dietary factors

Alcohol. Similar to previously reported rates, 147 (77%) reported some reaction to alcohol consumption.[5] These symptoms included worsening nasal symptoms, asthmatic symptoms (cough, wheeze, shortness of breath), and urticaria or flushing (Figure 5). A total of 120 (63%) felt that in addition to alcohol, some other component of their diet led to a reaction.

Toothpaste. Toothpaste, as well as spearmint or peppermint flavored chewing gum, has been reported to cause bronchospasm in AERD.[6,7] Anecdotally, in our practice, several patients with AERD specifically reported that they cannot tolerate minty toothpaste without causing some degree of immediate respiratory symptoms. In this survey, 51 (27%) reported some allergic symptoms from toothpaste, including nasal symptoms (n = 6; 12%), asthma symptoms (n = 33; 65%), nasal and asthmatic symptoms (n = 9; 18%), or urticaria and/or flushing (n = 3; 6%).

Cow's milk. Some patients with AERD (30%) feel that ingesting cow's milk worsens their symptoms. They reported that cow's milk caused worsening nasal (n = 29; 51%), asthma (n = 7; 12%), both nasal and asthma (n = 16; 28%), or urticaria/flushing symptoms (n = 5; 9%). A total of 133 (70%) patients reported no adverse reaction to milk.

Salicylate diet. Low-salicylate diets have been recommended by some to reduce symptoms. Of those surveyed, 71 (37%) had tried a salicylate-free diet compared with 119 (62%) who did not. Of those who tried a low-salicylate diet, 5 (7%) reported worsening symptoms, 24 (34%) reported no improvement, and 24 (34%) reported moderate to significant improvement. When asked how they heard about the low-salicylate diet, most said that

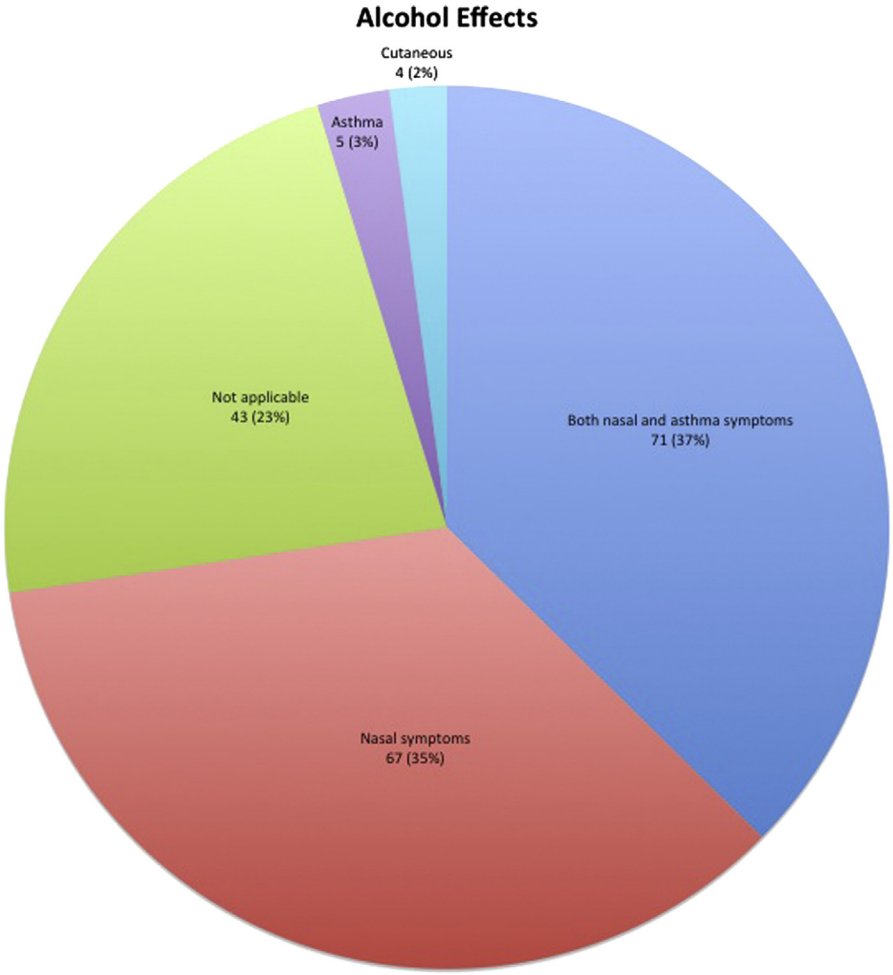

FIGURE 5. Effects of alcohol consumption in AERD.

discovered it on their own (n = 35; 45%) and a minority said that they heard about it from their ENT practitioner (n = 12; 16%), allergist (n = 8; 10%), primary care physician (n = 2; 3%), or a nonmedical source (n = 17; 22%).

Other diet interventions. A total of 67 (35%) patients stated that fish oil supplements or increasing fish intake improved their AERD symptoms, and 55 (29%) reported improvement with vitamin D intake. In terms of a low-histamine diet, only 4 (2%) had tried a low-histamine diet. Of those who tried a low-histamine diet, 1 (25%) found that it provided benefit.

DISCUSSION

The survey exposes many issues in the current treatment and management of AERD. Patients do not appear to be satisfied with current treatment options as evidenced by persistent symptoms, adverse effect on quality of life, and pursuit of various alternative treatment options.

Most of those on aspirin found it beneficial, and most of them were taking 325 mg or more aspirin daily, a dose most likely to be associated with symptom improvement.[8,9] Similar to previous studies, gastrointestinal adverse effects, need for surgery, and ineffectiveness were the most common reasons to discontinue aspirin.[10] Approximately half of our respondents were reluctant to go on aspirin therapy. Although various reasons were offered, this may be a missed opportunity for some patients because more than 80% of the subjects who reported "nothing worked for them" had never been on aspirin. It is not surprising that although aspirin was the most effective treatment for our respondents with AERD, a minority indicated that a combination of medications (aspirin, leukotriene receptor antagonist, zileuton, or omalizumab) was more effective than any one alone.

In addition to aspirin, other drugs that have been evaluated in the treatment of AERD include leukotriene receptor antagonist, zileuton, and omalizumab.[11] Little is known about how commonly these medications are used and other than a few small trials, little is known of the relative effectiveness of these medications in AERD. Given the upregulated leukotriene production in AERD, many patients are started on leukotriene-modifier drugs.

In this survey, half of the respondents on a leukotriene receptor antagonist found it to be helpful. There is generalized upregulation of cysteinyl leukotriene production in AERD with parallel increase in cysteinyl leukotriene receptor density on inflammatory cells.[12] Previous studies have demonstrated the role of montelukast in the treatment of AERD as well as showed a significant effect on the outcome of aspirin desensitization with a

shift in the reaction from the lower airways to more upper airway symptoms with lower asthma reactivity.[13-17]

Zileuton, a 5-lipoxygenase inhibitor, is another drug evaluated in the treatment of AERD. Of those surveyed, only a few (24%) had tried zileuton and approximately half found it effective. Double-blinded, placebo-controlled trials showed that zileuton improved pulmonary function, diminished nasal dysfunction, and inhibited aspirin-induced bronchoconstriction.[18,19] The finding that zileuton provides both upper and lower respiratory tract effects is promising.[20,21] Although we are unable to generalize worldwide, in our practice, cost and insurance coverage is a major limiting factor in the accessibility to zileuton.

Last, omalizumab is another drug used in asthma and allergic disease treatment. Although not specifically indicated for AERD, the diseases that make up AERD, specifically severe asthma, made us suspect that patients with AERD may have had experience with this drug. Although only 8% were taking omalizumab, more than half of them found it somewhat helpful. Several reports have suggested that it might be effective in treating chronic rhinosinusitis and recurrence of nasal polyps AERD.[22-25] Further double-blinded, placebo-controlled studies would be helpful to evaluate the effectiveness of omalizumab in the treatment of AERD.

Living with AERD is frustrating, as most of the survey respondents expressed. One of the most frustrating symptoms appeared to be loss of sense of smell and inability to enjoy eating. Unfortunately, almost 20% of our respondents appeared to have developed permanent ansomia as a result of AERD. Studies have shown that loss of sense of smell correlates with significantly lower quality of life, depression, bodily pain, and mental health.[26,27] This further emphasizes the need to diagnose and offer treatment to those with AERD.

We were interested in a large sample of subjects and their reports on dietary reactions. Anecdotally, patients in our clinic have reported immediate reactions to various foods including alcohol, tea, and toothpaste. Similar to a previous study looking specifically at alcoholic reactions in AERD,[5] we again find that approximately 77% of the subjects reported reactions to alcoholic beverages. Although red wine may be the most potent trigger, reactions occur with any alcohol. It is unclear how alcohol induces these symptoms. One theory has been the polyphenols found in many alcoholic beverages. Polyphenols, such as aspirin, may be inhibitors of COX-1.[28] Yet many patients report symptoms immediately after several sips of alcohol, which would not be expected if the mechanism were COX-1 mediated.[5] Furthermore, patients continue to report alcohol reactions even after aspirin desensitization. This suggests that COX-1—mediated reactions cannot explain all reactions to alcohol.

Patients report a wide variety of reactivity in their daily lives. Much of this reactivity is likely explained by the aggressive inflammatory nature of the disease and the waxing and waning nature of exacerbations secondary to viral illness, stress, and other environmental factors that could be falsely attributed to specific foods and diet. Nonetheless, there are consistent themes that many patients with AERD report that may be worth investigating further. For instance, patients with AERD report acute respiratory symptoms experienced to toothpaste.[7,29,30] Yet, this does not appear to occur in most of the patients with AERD. It is possible that spice, mint (ie, mint toothpaste), and alcohol acting through thermoreceptor transient receptor potential ion channels activate mast cells, which harbor various receptors for these triggers.[31-36]

Dairy products have been implicated as a cause of asthma exacerbation but with little scientific evidence to support this hypothesis.[37,38] Despite the lack of evidence, a brief Internet keyword search will demonstrate that the nonscientific community feels strongly that a connection between sinus health and dairy ingestion exists. In our questionnaire, nearly a third of the patients with AERD reported that dairy worsened respiratory symptoms. It is possible that in an already highly inflamed condition, the additional stimulus on mucus production from dairy could be perceived as having a serious adverse effect. This hypothesis merits further study given the prevalent belief that milk ingestion is connected to sinus health.

Aspirin is a salicylate, a compound also found naturally in foods. Consequently, some believe that a low-salicylate diet could potentially reduce their symptoms, but this diet is challenging to adhere to and consist of reducing fruits and vegetables consumption, which are a major source of dietary salicylates.[39] Although a low-salicylate diet is a logical assumption, salicylates do not inhibit COX-1 and a challenge study proved that patients with AERD tolerate ingestion of sodium salicylate.[40] Therefore, there is no compelling biochemical reason why a low-salicylate diet would be of any value to a patient with AERD even though 34% of the respondents who tried this diet reported improvement. This is a higher percentage reporting improvement than would have been anticipated. A small study by Sommer et al[41] also suggests that this dietary intervention could be beneficial. Further evaluation is needed to determine the mechanism of action and to confirm the reported benefit in this study. True double-blinded studies of diet interventions will likely be exceedingly difficult.

Patients are also interested in positive changes to their diet or supplements that could benefit their underlying inflammation. Currently, no studies support the relationship between fish oils and AERD. Regardless, 35% in this survey reported improvement in AERD symptoms with fish oil supplements, which suggests that there may be possible hypothetical benefits of fish oils unique to arachidonic acid metabolism disturbances in AERD.[42]

There are several limitations to this study. This is a cross-sectional questionnaire, and results are subject to response bias. Many patients cycle through trials of various treatments and thus patients may have been questioned at various stages of their illness, confounding perceptions of benefit. For example, a newly diagnosed patient might be more overwhelmed and rate quality of life lower than would a patient who has "learned to live" with a decade of symptoms. In addition, some patients in this survey may not have AERD. Although approximately half had an aspirin challenge or desensitization, the other half were diagnosed only by clinical history. This limitation was addressed with our screening questions, which have approximately 80% to 90% specificity for the disease.[10,43] Other limitations include the perception that these interventions are beneficial when they may be no better than placebo and then there is also the issue of recall bias. A solution to avoiding recall bias would be to verify the respondents' results with their medical records, but this was not possible nor the intent of the study. Furthermore, this study was advertised primarily through social media, which is a selective group typically more active in online discussions and may have more severe symptoms. It was not the intent of this survey to

assess medication treatment effectiveness, rather patient perception of treatment effectiveness.

CONCLUSIONS

This study will help physicians gain an understanding of questions being asked by the AERD community and avenues worthy of further exploration. Doing so will also guide patients with AERD to the best treatment, recognizing that multiple medications may be necessary to control their disease. The single most effective treatment option at this point continues to be aspirin therapy, yet it still seems to be underutilized for various reasons. AERD is still very much an underexplored area, and future studies are necessary to offer better treatment options to these patients.

Acknowledgments

We thank all the survey respondents and those who helped with publicity.

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