Evidence-based Strategies for Treatment of Allergic Rhinitis

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Current Allergy and Asthma Reports 2004, **4:**439–446
Current Science Inc. ISSN 1529-7322

In this review, an evidence-based medicine approach to diagnosis and treatment for allergic rhinitis is reviewed. We performed a search of the medical literature for randomized, placebo-controlled trials of nonsedating antihistamines, intranasal corticosteroids, montelukast, azelastine, allergen immunotherapy, and anti-IgE. The mean numbers needed to treat were: nonsedating antihistamines—15.2; nasal corticosteroids—4.4; montelukast—14.3; azelastine—5.0; allergen immunotherapy—4.6; and anti-IgE—12.4. Treatment thresholds for use were: antihistamines—23%; nasal corticosteroids—8%; azelastine—16%; montelukast—8%; anti-IgE—50%; and immunotherapy—25%. When used appropriately, this information could become very useful for clinicians, particularly if cost, convenience, and other indirect factors can be included.

Introduction

Evidence-based medicine (EBM) is the integration of best research evidence with clinical expertise and patient values [1••]. EBM techniques can help clinicians use the best evidence in the medical literature to make medical decisions. Although a great deal of information is available in the medical literature, the trick is to pull it all together so that rational decisions can be made about a clinical condition, such as allergic rhinitis (AR). The process that clinicians use to make a diagnosis, choose tests to increase or decrease the probability that the correct diagnosis has been made, and prescribe the most effective treatment is what clinical practice is all about. To make a diagnosis, most experienced clinicians use knowledge gained from that experience to gather information so that they can reduce the number of likely diagnoses from a large number of possibilities to a small number of most probable diagnoses. The process frequently involves the use of diagnostic tests to identify the most probable diagnosis leading to a treatment that is most likely to be effective.

Although this process might seem intuitive to the experienced clinician, intuition alone may lead to conclusions that result in less than optimal outcomes. For example, the learning process used to develop this experience may become corrupted by a variety factors leading to inefficient use of diagnostic tests or, at worst, incorrect interpretation of test results, the wrong diagnosis, and an ineffective or even harmful treatment.

To reduce the importance of nonscientific influences on the clinical decision-making process, it might help clinicians to use EBM procedures that have been developed for making clinical decisions. The purpose of this review is to illustrate the decision-making process as it pertains to one of the most common allergic conditions, AR. The procedure may seem counterintuitive in some respects, but, hopefully, the use of EBM practices will lead to consistently improved outcomes.

Probability of Diagnosis

The process of making a diagnosis and prescribing treatment begins with a determination of the probability for each diagnosis under consideration. To accomplish this, clinicians have been trained to develop a differential diagnosis consisting of a list of the most likely diagnoses and an estimate of their probabilities. This permits the selection of optimal diagnostic tests and treatments for each patient.

In the absence of data, the probability that a particular diagnosis is present can best be estimated from the prevalence of the disease in the underlying population. For persons randomly selected "off the street" from within a community, the prevalence of disease in their community would be the best initial estimate of disease probability. Patients seen in an allergist's office, on the other hand, have a different probability of having AR than randomly selected persons. These individuals generally have a clinical history that suggests (correctly or incorrectly) the presence of disease.

When faced with a patient who has a chief complaint of rhinitis, the usual approach is to ask a series of questions in an attempt to make a diagnosis. The chief complaint suggests a likely diagnosis or series of closely related diagnoses about which additional symptoms or signs can be inquired, to either increase or decrease the probability that the disease is present. In a sense, the clinician generates a

series of hypotheses about the likely diagnoses and tests them by asking questions. The answers either increase or decrease the probability that the diagnosis is present. Once the probability is either high or low enough to confirm the diagnosis, a treatment is recommended. If the diagnosis cannot be determined with sufficient certainty to justify an acceptable treatment, a diagnostic test is used to alter the disease probability.

The differential diagnosis of rhinitis includes (in no particular order) such conditions as infectious rhinitis (the common cold), anatomic obstructions (*eg*, nasal polyps, deviated nasal septum), nonallergic rhinitis, AR, and several others with lower probabilities. Because the benefit of specific treatments may differ for each of these diagnoses, it is important to determine which one is present. Because some treatments that may be considered for AR are effective only if IgE-mediated mechanisms exist (*eg*, immunotherapy, environmental control, anti-IgE), it is important to determine the probability for each of these diagnoses when such treatments are considered. Treatments that do not depend on the presence of allergic triggers (*eg*, nasal and oral corticosteroids, antihistamines, leukotriene modifiers) do not require proof of IgE-mediated allergy. However, these treatments may not be effective if the correct diagnosis is a viral infection or an anatomic or neurologic problem.

From an EBM perspective, the physician has identified diagnoses for which the probability is high enough to merit further consideration. In the absence of any information about a particular patient, the probability that he or she has a particular diagnosis depends on the prevalence of the condition in the population from which that individual arises. For AR, the prevalence has been estimated to be between 16% and 26% [2]. For the purpose of this discussion, we assume that the prevalence of AR is 21%, recognizing that this estimate will vary from one report to another.

Diagnostic Tests

Diagnostic tests are performed to obtain information that can alter the probability of disease. If we define the prevalence of disease in a population as the pretest probability, a diagnostic test can be used to convert that to a post-test probability. A particular test should be done only if there is uncertainty about the probability of the diagnosis or if the effectiveness of a treatment is dependent on the result of the test. If a "gold standard" test, such as a double-blind, placebo-controlled food challenge (DBPCFC) for food allergy, nasal, or bronchial challenge for rhinitis and asthma, respectively, or sting challenges for Hymenoptera sensitivity can safely and conveniently be performed, they should be done first to avoid the need for other tests. Because many of these gold-standard tests are time-consuming, not widely available, and associated with potential harm, should the patient have a severe reaction, alternative diagnostic tests usually are used instead. In addition, because the benefit of certain treatments, such as immunotherapy, depends on the immune mechanism of disease, determination of specific IgE antibodies is necessary when considering their use.

Likelihood ratios

To be useful, a diagnostic test should have defined performance characteristics relative to a gold standard. Most studies that define such characteristics express the results in terms of sensitivity, specificity, and both positive and negative predictive values. Although these descriptors are useful indicators of the ability of a test to rule a diagnosis either in or out, their interpretation suffers from limitations, including a strong influence by the underlying prevalence of the disease and an inability to use them to convert pretest to post-test probabilities. In addition, gold standards used to determine these are subject to question [3]. For these reasons, likelihood ratios (LR) have become increasingly useful. An LR is the ratio of the odds that the patient whose test results fall within a particular range has the disease divided by the odds that they do not. In other words, it is the ratio of the pretest to the post-test odds that a particular disease actually is present.

When the LR relates to a test with dichotomous (positive or negative) results, a convenient formula for LR when the test result is positive is

$$\text{LR+} = \text{Sensitivity} / (1 - \text{Specificity})$$

whereas, if the test result is negative, the formula for LR is

$$\text{LR-} = (1 - \text{Sensitivity}) / \text{Specificity}$$

When the test results can take on more than two levels, determination of LR is more complicated.

To use LRs to determine post-test probabilities, it is first necessary to convert the pretest probability to pretest odds using the formula:

$$\text{Pretest odds} = \text{Probability} / (1 - \text{Probability})$$

The post-test odds can be determined as

$$\text{Post-test odds} = \text{LR} \times \text{Pretest odds}$$

The odds can be converted back to probability using the formula:

$$\text{Probability} = \text{Odds} / (1 + \text{Odds})$$

Another way to express the formula is:

$$\text{Post-test probability} = \frac{\frac{p}{1-p} \times LR}{(1 + \frac{p}{1-p}) \times LR}$$

where p = pretest probability and LR = likelihood ratio.

Table 1. Statistics in allergy to timothy grass

	History	95% CI	Prick test	95% CI	ID test	95% CI	In vitro
Sensitivity	1	0.96-1.00	0.83	0.66-1.00	0.89	0.74-1.00	0.94
Specificity	0.36	0.23-0.49	0.86	0.76-0.96	0.7	0.57-0.83	0.7
LR+	1.56	1.26-1.92	5.95	2.90-12.20	2.96	1.88-4.66	3.13
LR-	0	0	0.19	0.07-0.55	0.16	0.04-0.59	0.09
Pretest probability = 0.21							
Post-test prob+			0.61		0.51		0.45
Post-test prob-			0.05		0.04		0.02
If history positive, pretest probability = 0.29							
Post-test prob+			0.71		0.55		0.56
Post-test prob-			0.07		0.06		0.04

Sensitivity, specificity, and likelihood ratios (LR) with 95% confidence intervals (CI) for clinical history, prick, and intradermal skin tests with timothy grass. LR for in vitro tests came from another similar study. Post-test probabilities (prob) are shown, assuming 21% prevalence. In the presence of a positive history, the post-test probabilities shown result from a pretest probability of 29%.

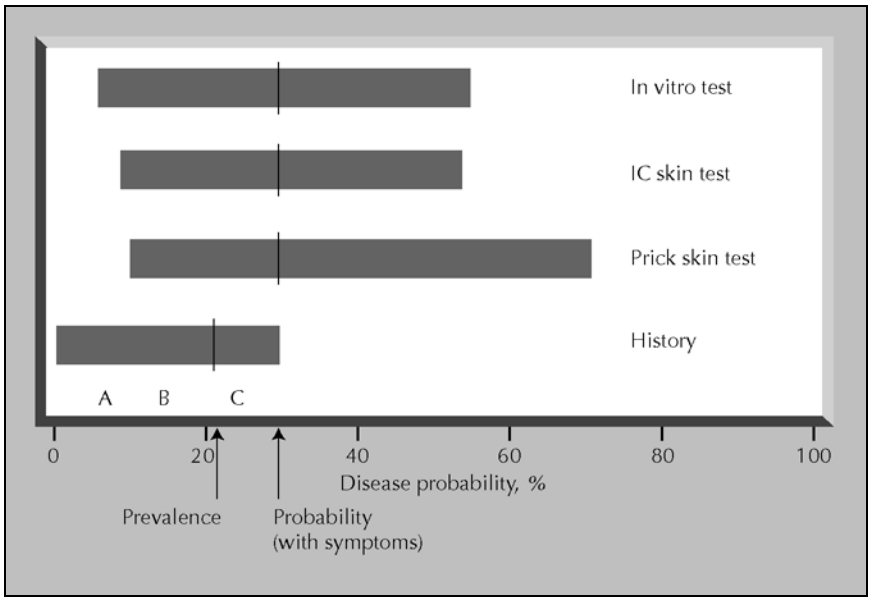

Figure 1. Probability of allergic rhinitis given positive and negative results for various diagnostic tests centered on the post-test probability given symptoms. Treatment thresholds: *A* = nasal steroids and montelukast; *B* = azelastine; *C* = antihistamines and immunotherapy. Note that immunotherapy is only effective if a test for specific IgE is positive. IC—intracutaneous.

The value of a diagnostic test, therefore, is its ability to increase or decrease the probability that a disease is present. The post-test probabilities resulting from LR+ and LR- for a given test define a range around the treatment threshold in which performance of the test is likely to change a treatment decision. These are referred to as the lower and upper test-treat thresholds between which there is an area of uncertainty that justifies the need for further testing. A test, therefore, should be performed if the pretest probability falls within the range of uncertainty. If not, the test is unlikely to change the treatment decision, and it should not be performed.

For AR triggered by grass pollen, we have used a study by Nelson *et al.* [4•] to determine LRs as shown in Table 1. If the prevalence of AR in the population is 21%, the post-test probability of disease is 29% if there is a positive history for rhinitis symptoms. In the absence of such a history, the probability of disease is zero, because people who have no symptoms do not have rhinitis. The post-test probability is higher with a positive percutaneous (prick) test (61%) than with a positive intracutaneous (IC) test (51%), reflecting the reduced specificity of the latter test. For in vitro tests, the post-test probability has been reported to be 45%, although this will vary from one study to another, depending on which antigen is tested and the type of in vitro test [5]. A negative result for prick, IC, and in vitro tests reduces the probability of disease to 7%, 6%, and 4%, respectively. In the presence of a positive history, the pretest probability for skin tests is 29%, leading to post-test probabilities of 71%, 55%, and 56% for prick, IC, and in vitro tests, respectively. This illustrates the importance of obtaining a positive history prior to performing these diagnostic tests.

Figure 1 shows disease probability for AR with the prevalence in the general population as an initial estimate. Once the history is known, the post-test probability either increases to 29%, if there are symptoms, or decreases to 0%, if not as shown on the bar labeled "History." The pretest probabilities and upper and lower post-test probabilities for prick, intracutaneous, and in vitro tests also

are shown, assuming a pretest probability of 29%. If the patient has no symptoms, there is no point in doing any diagnostic tests because the post-test probability would remain at 0%, regardless of the test results.

The advantage of using LRs over other measures of test performance, such as sensitivity, specificity, or predictive values, is that the pretest odds that the disease is present can be multiplied by the LR to get the post-test odds. In addition, the post-test odds from one test, such as in vitro measurement of specific IgE, can be used as the pretest odds for the next test—for example, a challenge test. In this way, a series of independent tests can be performed sequentially until the probability of disease either is high enough to confirm the diagnosis or low enough to rule it out. Because LRs depend on the performance characteristics of the test, they should be determined independently for each diagnostic test. The LRs for a number of allergy tests including history, percutaneous and intracutaneous tests, and in vitro tests for specific IgE antibodies for AR recently have been determined by Gendo and Larson [6••]. With the use of LRs, misleading concepts such as "false positives" and "false negatives," are eliminated because the actual purpose of a diagnostic test is to convert a pretest probability to a post-test probability.

Treatment Thresholds

Once the probability of a particular diagnosis is determined, the next step is to determine how probable that diagnosis needs to be to justify a particular treatment. Although it may seem that the diagnosis should either be ruled in or out with as much certainty as possible, in many situations a lower probability would suffice, possibly sparing the patient expensive and uncomfortable diagnostic testing. Therefore, it is necessary to determine what probability will be used to rule the diagnosis in or out. In other words, how low does the probability that a patient has a disease need to be to state confidently that the person does not have the diagnosis and, therefore, either no treatment is needed or a different diagnosis should be considered? Conversely, how high does the probability need to be to recommend treatment without any further diagnostic testing?

To answer these questions, we need to define the purpose of treatment as any intervention that maximizes wellness by reducing the elements that diminish it. These elements may include, but are not limited to, the burden of disease and harm from treatment. This can be accomplished by maximizing the benefits of treatment while simultaneously minimizing the burden or harms of that same treatment. We can define this as the wellness utility, which can range from 0, for maximum sickness, to 100%, for perfect health. The treatment threshold is the probability of disease below which no treatment is given and above which treatment is provided. This probability threshold depends on the relative harm and benefit of each treatment, and, therefore, differs depending on which treatment is being considered. A treatment that is highly beneficial with little harm could be prescribed when the disease probability is low, but another treatment with high harm and little benefit in the absence of disease could require a high probability. Although the probability of disease falls somewhere between zero and 100%, the treatment threshold justifying a particular treatment can best be determined by considering what happens to the wellness utility when the disease is either present (100% probability) or not (zero probability) (Fig. 2).

If a patient does not have the disease (disease probability = 0) and no treatment is provided, there is no harm. Thus, the patient's wellness is 100%. If treatment is given in the absence of disease, the reduction in wellness exclusively results from the harms of treatment. These harms may be either physiologic or nonphysiologic in nature. Physiologic harm may result from undesirable side effects, whereas nonphysiologic harms may include the cost of treatment, the complexity of the treatment, and the hassle of using the treatment. Although these nonphysiologic harms clearly are important, we focus on the physiologic harms here, because they can be most easily determined.

Conversely, if a patient has the disease, and treatment is not provided, the reduction in wellness is due to the untreated disease itself. The benefit of treatment is the reduction in disease burden that results from treatment compared with placebo. Because this can only occur if there are symptoms, it makes no sense to treat a patient when no symptoms are present because there cannot be any benefit. In other words, treatment of people selected randomly off the street without first getting a history of symptoms is not likely to result in benefit. Although disease burden is considered to be relatively constant, changes in disease severity in response to environmental changes (*eg*, seasons) tend to make allergic diseases different from other, more constant conditions, such as hypertension.

Note that a line drawn between each wellness utility as shown in Figure 2 defines the utility of treatment that occurs when the treatment either is or is not given. Because the goals of treatment are to maximize wellness while minimizing harm, no treatment is preferable when disease probability is very low, and treatment is preferred when disease probability is high. The intersection of these two lines defines the probability of disease at which the treatment and nontreatment utilities are equal. This treatment threshold can be calculated as

$$Rx = Harm / (Harm + Benefit) [7]$$

In deciding which treatments are most appropriate, the challenge is to determine the harms and benefits for each treatment option. If we ignore cost, hassle, and other nonphysiologic factors, measurable harm exists in the frequency of adverse effects. The benefits of treatment can be expressed as the percentage of patients who demonstrate a clinically important improvement in wellness compared with those who receive placebo.

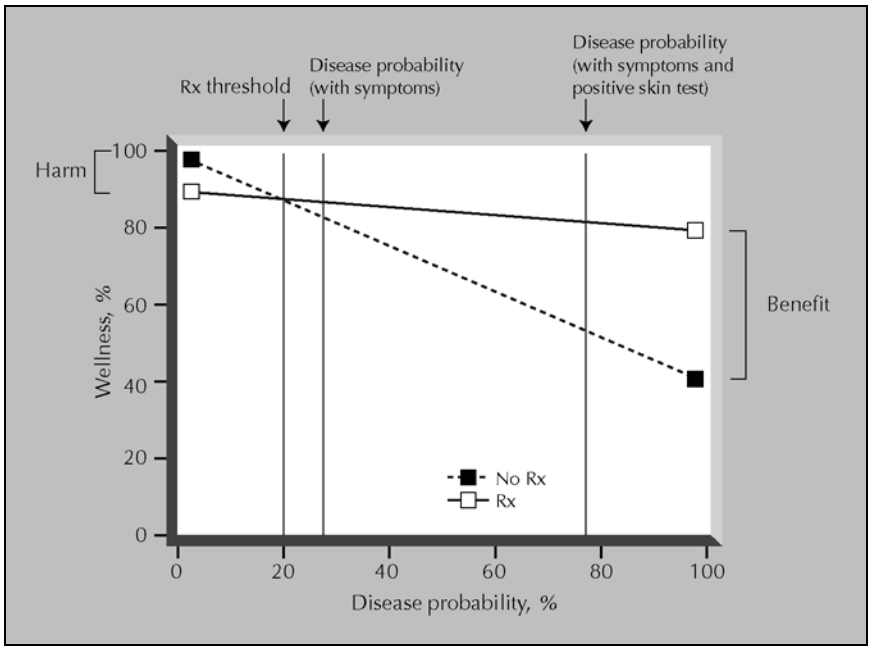

Figure 2. Wellness utility of treatment and no treatment for various disease probabilities. The intersection of the *two lines* is the treatment threshold. Note that if the disease probability is greater than the treatment threshold, the treatment is justified, but a residual harm of treatment persists. Rx—treatment.

Benefits and Harms of Treatment: Number Needed to Treat and Number Needed to Harm

The most consistent way to measure the direct benefit and harm of a treatment, ignoring cost and other nonphysiologic factors, is to determine the number needed to treat (NNT) and number needed to harm (NNH). NNT is the average number of persons who need to receive a treatment for one additional person to benefit from it. The lower the NNT, the more effective the treatment. Conversely, NNH is the average number of persons who must receive the treatment for one additional person to experience harm. To determine the magnitude of the benefit or harm when measuring NNT and NNH, investigators performing the research need to define a priori (in advance of performing the study) how much of a change in either benefit or harm they would consider to be clinically important. The result is a percentage of patients who receive either benefit or harm from the treatment relative to no treatment or to a placebo. This represents a measure of the absolute harm or benefit.

Unfortunately, many authors of clinical reports do not state their results in terms of percent of study subjects who respond to treatment. When analog data such as symptom or quality of life scores are presented instead of percentage of treatment responders, it is possible to estimate NNT, provided that sufficient information is presented in the clinical trial report. Necessary information consists of the analog results (*eg*, symptom scores) for both active and placebo groups; an estimate of sample variation, such as standard deviation; standard error of the mean or 95% confidence interval; the number of subjects in each group; and, ideally, the change that the investigators would consider to be clinically important. If the latter is not provided, a reasonable estimate of clinically important response would be 10% of the total range, although this may not be valid if the response is nonlinear. Unfortunately, most studies do not provide sufficient information to estimate NNT, making the determination of thresholds for various treatments very difficult [8].

If sufficient information is provided, the way to determine the percentage of responders in placebo and active groups is to calculate the Z score. If the mean change in symptom score in a treatment group is μ, a clinically important difference is C, and the standard deviation of the sample is σ, the Z score for the difference between the two is

$$Z = (C - \mu)/\sigma$$

Assuming a normal distribution, the percentage of subjects who would be expected to have this Z score is given by the formula

$$f(z, \mu, \sigma) = 1 - \frac{1}{\sqrt{2\pi\mu}} e^{-\left(\frac{(z-\mu)^2}{1\sigma^2}\right)}$$

The difference between this value for the active and placebo treatment groups is the percentage of subjects who respond to the treatment, which can be used to determine NNT. To simplify this calculation, we used the "normdist" function in Microsoft Excel to calculate the response frequencies.

Table 2. Benefit and harm in treatments for allergic rhinitis

Treatment	Benefit	NNT	Harm	NNH	Rx threshold, %	Study
Antihistamine						
Cetirizine	0.112	8.9	0.03	33	21	Day *et al.* [10]
Fexofenadine	0.066	15.2	0.013	77	16	Wahn *et al.* [11]
Desloratadine	0.056	17.9	0.021	48	27	Berger and White [12]
Loratadine	0.029	34.5	0.015	67	34	Day *et al.* [10]
Class mean	0.066	15.2	0.02	51	23	
Nasal sprays						
Triamcinolone	0.211	4.7	0.019	53	8	Munk *et al.* [13]
Fluticasone	0.168	6	0.015	67	8	Ratner *et al.* [14]
Budesonide	0.207	4.8	0.03	33	13	Fokkens *et al.* [15]
Mometasone	0.33	3	0.019	53	5	Lumry [16]
Class mean	0.229	4.4	0.021	48	8	
Nasal antihistamines						
Azelastine (daily)	0.16	6.3	0.031	32	16	LaForce *et al.* [17]
Azelastine (twice daily)	0.2	5	0.046	22	19	LaForce *et al.* [17]
Other						
Montelukast	0.07	14.3	0.006	167	8	Ratner *et al.* [14]
Omalizumab	0.081	12.3	0.08	13	50	Chervinsky *et al.* [18]
Immunotherapy	0.218	4.6	0.072	14	25	Walker *et al.* [19] Karaayvaz *et al.* [20]

Percentage of patients with benefit and number needed to treat (NNT) and percent of patients with harm and number needed to harm (NNH) for various treatments of allergic rhinitis. For antihistamines and nasal sprays, a class mean also is shown. The treatment threshold was determined as described in the text. The package insert was used to determine harms for all treatments, except immunotherapy. The harms used for this determination were: antihistamines—sedation; nasal sprays—epistaxis; azelastine—sedation (taste was much higher); montelukast and omalizumab—headache; and immunotherapy—sysemic reactions per course of treatment.

Evidence-based Medicine for Allergic Rhinitis

Now, we have determined the probability of AR using its prevalence and LRs for history and various relevant diagnostic tests. We also know how to determine the treatment threshold for various treatments. The next strategy is to identify treatments with thresholds that fall below the disease probability. For treatments that require certain tests to be positive, such as the presence of specific IgE antibodies and immunotherapy, disease probability for rhinitis and AR need to be determined separately.

Table 2 shows NNTs, NNHs, and treatment thresholds for various antihistamines and nasal corticosteroids, as well as values for montelukast, azelastine, anti-IgE, and immunotherapy. When determining these values, we did not attempt to perform an exhaustive search of the medical literature. Instead, we identified at least one controlled trial for each agent that provided sufficient information for us to determine NNT. We used the package inserts for the various agents to determine NNH. Whenever feasible, the same harms were used for each agent in a class, as shown in the table legend. The harms used in determining NNH were sedation for the antihistamines (including azelastine), epistaxis for the intranasal corticosteroids, headache for montelukast and anti-IgE, and systemic reactions for immunotherapy.

Note that although antihistamines and montelukast have similar NNTs, the low frequency of side effects for the latter agent results in a lower treatment threshold. Immunotherapy has an NNT that is similar to that of nasal steroids, yet it has a substantially greater frequency of side effects, resulting in a higher treatment threshold that is dependent on the presence of specific IgE.

The values for immunotherapy were particularly difficult to determine. For harms, most immunotherapy studies describe the frequency of systemic reactions (SRs) per injection. This would be similar to describing the frequency of sedation per tablet of an antihistamine. NNH is measured per course of treatment and not per administration event. Another study of ragweed immunotherapy [9] showed the number of systemic reactions per course of immunotherapy, but the follow-up time was only 7 months. Because immunotherapy usually is given for 3 to 5 years, this could potentially underestimate the eventual rate of SRs by up to 10-fold.

It is important to note that the use of any treatment with a threshold below the disease probability can be justified. If an agent has a lower treatment threshold, it is not necessarily more effective than another with a higher treatment threshold. If the treatment threshold is lower than the disease probability, the wellness utility is maximally improved by the treatment benefit.

Dynamic Treatment Thresholds

Consider what happens as the disease severity of AR decreases—maybe, due to a fall in the pollen count. The

benefit of a particular treatment remains somewhat constant until the treatment completely eliminates all disease symptoms. At that point, if the amount of treatment remains constant, perhaps because of the way it has been prescribed, the benefit of the treatment decreases because less disease remains to be treated. Because the harm from the treatment remains constant in the presence of declining benefit, the treatment threshold will increase. If the disease burden decreases sufficiently, the treatment threshold will increase until it reaches the disease probability. Should the disease burden decrease further, that particular treatment would no longer be justified. In other words, the patient improved sufficiently that he or she may no longer need the treatment.

Because recommendations to take treatment may persist beyond the time that it is needed, patients may decide to reduce the harm of treatment intentionally by decreasing either the frequency or dose of treatment without first obtaining instructions from their physicians. When this occurs successfully, the treatment eventually is discontinued, and wellness is maximized. Unfortunately, if the symptoms recur, the patient may be labeled as "nonadherent." The problem with this situation is not necessarily in undertreatment by the patient but rather in overprescribing by the physician. Therefore, both the physician and patient need to recognize that the treatment threshold varies with disease severity, and that the treatment will need to be adjusted to account for this.

Conclusions

It is important for clinicians to use the most reliable data available so that patients receive the best treatment possible. By using the systematic approach described earlier, it should be possible for patients to consistently receive an accurate diagnosis and treatment that is justified by the diagnosis. This approach relies on evidence rather than on anecdotal experience that may become corrupted, and, therefore, its use may reduce the likelihood that an incorrect diagnosis will be made, leading to ineffective or even harmful treatments.

As we strive to practice EBM, there is a need to make its tools easier to use. Although we found it difficult to tease useful information out of published studies, as many studies do not report sufficient information to determine NNT, we believe that this information eventually will prove useful to clinicians and beneficial to their patients. We anticipate that some pharmaceutical manufacturers may prefer not see their products described in terms of NNT or NNH. Furthermore, AR is not a static disease, and as the disease severity decreases, the treatment threshold increases. Our patients are well aware of this, at least on an unconscious level, leading many to adjust their medication regimens to maximize their wellness with or without guidance from a physician.

It is important to recognize that we did not attempt to perform an exhaustive search of the literature when determining the thresholds listed in this review and that most studies we reviewed provided insufficient information, leading us to estimation. We also did not include indirect benefits and harms, such as cost, inconvenience, and psychological factors. Our intent with this review is that it will motivate others to perform more extensive analysis and, ideally, that pharmaceutical companies will provide this type of information in their product labeling. Once that occurs, evidence-based clinical practice will be closer to becoming a reality.

Acknowledgments

The authors received no financial support for this manuscript from any of the pharmaceutical companies whose products are described.

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- •• Of major importance

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