

The Placebo Effect: Plugging the Nostrils of Unmet Needs

James N. Baraniuk, MD

Corresponding author

James N. Baraniuk, MD
Division of Rheumatology, Immunology and Allergy, Room B105,
Lower Level Kober-Cogan Building, Georgetown University, 3800
Reservoir Road, NW, Washington, DC 20007-2197, USA.
E-mail: baraniuj@georgetown.edu

Current Allergy and Asthma Reports 2009, 9:149–152

Current Medicine Group LLC ISSN 1529-7322

Copyright © 2009 by Current Medicine Group LLC

Many common treatments for rhinitis symptoms are inadequate or ineffective. This may be in part because the drug does not address the pathologically altered mechanism of the rhinopathy. Objective measures may not detect treatment effects, or the treatment end points may be only subjective in nature. In many cases, these issues have not arisen because of potent placebo effects. Understanding the psychological, pharmacologic, and physiologic components of placebos is important for separating true treatment effects from those of the excipients in the vehicle. Separating the wasteful and potentially harmful effects of those excipients from the harmless and often partially beneficial effects on temporary symptom control is an important issue in clinical pharmacology that can aid in effective clinical trial design, use of objective and subjective test measures, and development of drugs to treat rhinitis.

Introduction

Specific therapies for most rhinitis syndromes have inadequacies. Congestion is one major symptom that remains largely unaffected by most current medications. Many medications are ineffective but have not been suitably tested to expose their fruitless use. Many are placebos. This should not be considered totally negative, as the placebo effect is a complex experience that is the sum of nonspecific (no treatment), true placebo (psychological), and physiologic effects. Lessons learned from trials of placebos can greatly enhance our interpretations of the placebo-controlled studies that are the ethical standard in clinical research. Most of the focus of the pharmaceutical industry for the past two decades regarding allergic rhinitis has been on developing more efficacious and safe

antihistamines and glucocorticoids, as well as improved delivery systems. These have greatly improved the treatment of allergic rhinitis but have had minimal effects on other nonallergic and infectious syndromes. These shortcomings provide abundant opportunities for new therapeutic options and drug development that focus on more recent concepts of disease pathogenesis.

We live in a world of efficacious antihistamines, intranasal glucocorticoids, and anticholinergics for the treatment of allergic rhinitis. These drugs have been less effective for nonallergic, viral, and other rhinopathies. When our patients use these antiallergy drugs for nonallergic symptoms, they are bound to become dissatisfied with their lack of efficacy. This may have led to the widespread use of irrational faith-based homeopathic and naturopathic nasal remedies. A patient with a nasal need is more likely than ever to turn to potions based on savvy marketing rather than mechanistic research.

The Placebo

This comes as no surprise because a significant component of the perceived beneficial effects of many of the drugs used to treat cough, cold, catarrh, allergic and nonallergic rhinitis, and otitis media can be attributed to the vehicle and placebo effects. Most clinical research into these products has focused on cough because of its annoying, often prolonged, and intractable nature. Eccles [1] has performed much of the work in this area. He determined that the sweet, viscous vehicles of cough syrups were often as efficacious as the antitussive preparations themselves. There was no doubt that these treatments were effective. However, up to 85% of the beneficial effect on cough was attributable to the vehicle/placebo effects, leaving a pharmacologic benefit of only 15% [2,3].

Placebo originated from Catholic Latin vespers, where it meant “I shall please” [4]. The medical placebo is a sham treatment (sugar pills, inert tonic) used by a physician to please or placate a generally anxious patient. The intent is to provide the appearance of active, caring therapy without doing any harm. The physician may not have a diagnosis or may consider the patient’s complaints mundane.

The large numbers of alternative medicine options (eg, aromatherapy, naturopathy, homeopathy, and acupuncture) have been inspired by individual responses observed

or experienced by individual physicians. The self-treating consumer may endorse these treatments with the active belief in their efficacy and thought process of “mind over nasal matters” [5,6]. The benefits are driven by the concept of *distributed practice*, in which approximately one third of patients will gain a self-perceived benefit. However, the relief may have a random distribution that cannot be predicted based on the condition, therapy, or timing of their use. Cough is a classic case in point [7–9]. A role for endogenous opioids in genetically predisposed subpopulations has been proposed to explain these seemingly random effects [10]. Some populations meeting specific psychometric constructs, such as external locus of control, may respond better than others [11].

Modern placebo-controlled trials generally use the excipients of the drug preparation (vehicle) to separate the true drug effect from that of the preparation. Nasal saline sprays have been used as comparators. However, this lavage can have beneficial effects on its own [12–14]. The mechanism(s) for these effects may include the dilution and accelerated clearance of proinflammatory mediators; dissolution of mucoclots into less viscous, more lubricating mucus; desensitization of hyperresponsiveness nociceptive sensors on epithelial cells and neurons; or correction of dysregulated epithelial lining fluid osmolarity.

The value of placebo-controlled trials was demonstrated in a 1944 study of patulin, a penicillin antibiotic, for the treatment of the common cold [15]. The antibiotic was no more efficacious than placebo injections. Unfortunately, the critical lesson of this trial—that antibiotics have no effect on viral rhinitis—has been persistently ignored or disbelieved by some clinicians.

Placebo Mechanisms

Four factors contribute to the benefits of drugs. Cough syrup is used as the example because it has been evaluated most extensively. These factors can be applied in similar fashion to other treatments and ailments.

The absence of any treatment is associated with a nonspecific placebo benefit, as the underlying cause heals spontaneously or the level of symptoms regress toward the mean for the general population. This is the tincture of time effect that explains that “sick people get better” [16].

The physiologic placebo effect is due to physical properties of the excipients. In the case of cough syrups, these properties include the sweet or bitter taste; oral sensations produced by the sapid textures of sugar, honey, or treacle; and sharpness of capsaicin, lemon, or citric acid. The latter substances stimulate type C afferent nerves and recruit parasympathetic salivation and mucus secretion in the pharyngeal to hypopharyngeal region. The viscous products also may generate central opioid neuropeptide release by themselves [17]. This demulcent effect may lubricate pharyngeal and laryngeal mucosae and reduce stimulation of hypersensitive nociceptive cough receptors. This is analogous to gustatory rhinitis, in which capsaicin

and other hot, spicy, piquante foods stimulate cholinergic glandular nasal secretions [18].

Comparison of vehicle treatment with no treatment demonstrates the combination of pharmacologic and psychological “true” placebo effect. For example, the antitussive effects of no treatment were compared with those of a placebo capsule for cough associated with upper respiratory tract infections. No treatment produced a 7% decrease in cough frequency, compared with a 50% decrease after use of placebo [19]. Use of capsules avoided the pharmacologic benefits of syrups. The psychological therapeutic effect is related to the patient’s belief in the medicine’s efficacy [20]. Again, this effect may be related to the perceptions of locus of control, physician–patient interactions, expectations, the appeal of advertising, as well as other issues. Opioid neurotransmitter systems also may be involved, as naltrexone can reduce this psychological component [21].

The sum of nonspecific (no treatment), true placebo (psychological), and physiologic effects is the perceived placebo effect [3]. Perceived placebo responses to antitussives range from 56% to 105% of the active treatment (mean, 85%). For example, Lee et al. [19] demonstrated that the true pharmacologic effect of dextromethorphan, 30 mg, given as a hard gelatin capsule was virtually identical in magnitude and time course to the placebo response. The effects of different delivery vehicles, whether liquid, solid, or inhaled, have not been as well studied in specific illnesses such as nonallergic rhinitis but will be essential to the preparation of the most effective therapeutic product.

Unmet Needs

An additional complication is that objective end points that can be changed by the treatment must be chosen. This is problematic on several fronts. Objective methods such as acoustic rhinometry, rhinomanometry, peak nasal inspiratory flow, or flow-volume loops can assess nasal air space volume and airflow resistance and thus also the vascular changes that regulate deep venous sinusoidal filling and mucosal thickness. However, these changes may not be subjectively detectable by test participants. This is suggested for menthol, which had no effect on objective measures of nasal airflow but significantly increased the perception of nasal patency in 10- and 11-year-olds [22••]. Models for testing the sensation of nasal patency in younger age groups are inadequate. Dextromethorphan significantly elevated the dose of citric acid required to increase the rate of coughing in smokers [23]. However, this objective assessment was not supported by subjective observations from the coughers themselves. Instead, the subjective data indicated a strong placebo effect. This suggested that cortical perceptions and preconceptions may modify test outcomes without the implicit awareness of the test participant.

Measures of plasma flux across the mucosal membrane and glandular exocytosis are required to directly

assess the relative contributions of vascular permeability, cholinergic reflexes, and related mechanisms in clinical studies. These more specific tools may be more useful than weights of secretions for assessing long-term efficacy of treatments such as botulinum toxin for rhinorrhea in nonallergic rhinitis without eosinophilia [24]. Cytology, proteomic, and genomic (mRNA) assessments also may add to our understanding of disease mechanisms in individuals and the specific effects of individual therapies. Issues of cost and correlates with patient improvement must be considered with these methods.

Questionnaires are likely to require more queries about gustatory, olfactory, textural, viscous, and perceived taste qualities in ill individuals in whom these sensory mechanisms may be impaired. Responses from healthy individuals may not be adequate. Symptom scores must assess the specific changes that are anticipated in an illness. Allergic rhinitis is an excellent example, as histamine has an overwhelming short-term effect on symptoms. Focused symptom scores, such as the Total Nasal Symptom Score, that assess complaints of histamine-related itch, sneeze, and rhinorrhea may be inappropriate in other rhinopathies. Other mediators and mechanisms that are important in viral rhinitis, bacterial sinusitis and otitis, and nonallergic rhinitis may induce different symptom complexes compared with histamine and therefore are likely to require different, more subtly phrased queries.

Unplugging Congestion

Congestion, the fourth component of the Total Nasal Symptom Score, is generally subjectively defined as the perceived sensation of nasal discomfort, “fullness” felt within the periorbital “sinus” regions, or obstruction to nasal airflow. Congestion is often used to refer to a patient’s symptom as well as the obstruction of nasal airflow. The nomenclature for the symptom and sign should be clarified by consensus. Congestion may be distinct from objectively measured reductions in nasal minimum cross-sectional area, nasal cavity volume, and increased nasal airflow resistance.

Congestion also should be differentiated from mid-facial pain syndromes [25] that have a neurologic basis. These issues will be essential for definitions of symptoms characteristic of unique nonallergic rhinopathies; the identification of specific mechanisms responsible for these symptoms; and development of mechanistically targeted, efficacious treatments.

Congestion also may be confused with facial tenderness. Individuals with chronic fatigue syndrome have greater tenderness of their sinus regions than normal controls and individuals with allergic rhinitis and acute and chronic rhinosinusitis [26]. This indicates systemic hyperalgesia due to spinal cord reprogramming that leads to chronic pain. Thus, the rhinitis of chronic fatigue syndrome may represent a variant of chronic regional pain syndrome, also known as reflex sympathetic dystrophy. This would be con-

sistent with the heightened trigeminal chemosensitivity also found in patients with sick building syndrome and multiple chemical sensitivities [27]. These supersensitive sufferers may have survived natural selection by acting as vigilant observers using their chemical sensitivity in the hunt for carrion or avoidance of predators. There is also extensive evidence of autonomic dysfunction in nonallergic rhinitis [28••]. This type of rhinitis has been termed *dysautonomic rhinitis*. Finding appropriate subjective and objective methods of defining and measuring the cardinal symptoms and pathology may be as daunting as accepting this group’s functional disorders as real medical problems rather than figments of their physicians’ imaginations.

Conclusions

Current antihistamines, glucocorticoids, and anticholinergic drugs have significantly improved the quality of life of allergic rhinitis patients. However, these and nonallergic rhinitis patients may have residual symptoms, such as congestion. Until therapy for this symptom improves, we can anticipate increased use of alternative products. Many of these may be beneficial in subsets of rhinitis patients. It will be our lot to determine whether the effects are pharmacologic or related to placebo effects. New subjective and objective tools will have to be developed to investigate the mechanisms involved. Newer concepts such as autonomic dysfunction and chronic nasal pain syndromes may offer novel models for approaching the issues of mechanisms and therapeutic assessments. Although the placebo-controlled clinical study is likely to remain central to proving drug efficacy, it may be necessary to carefully consider the mechanisms of placebo pharmacology to design the most effective investigations.

Acknowledgment

This work was supported by Public Health Service Awards 1 RO1 ES015382 and P50 DC006760 and Department of Defense Award W81XWH-07-1-0618.

Disclosure

No potential conflict of interest relevant to this article was reported.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
 - Of major importance
1. Eccles R: Mechanisms of the placebo effect of sweet cough syrups. *Respir Physiol Neurobiol* 2006, 152:340–348.
 2. Pavesi L, Subburaj S, Porter-Shaw K: Application and validation of a computerized cough acquisition system for objective monitoring of acute cough—a meta-analysis. *Chest* 2001, 120:1121–1128.

3. Eccles R: The powerful placebo in cough studies. *Pulm Pharmacol Ther* 2002, 15:303–308.
 4. Harrington A: *The Placebo Effect: An Interdisciplinary Approach*. Cambridge, MA: Harvard University Press; 1999.
 5. Mills SY: The House of Lords report on complementary medicine: a summary. *Complement Ther Med* 2001, 9:34–39.
 6. Astin JA, Harkness E, Ernst E: The efficacy of “distant healing”: a systematic review of randomized trials. *Ann Intern Med* 2000, 132:903–910.
 7. Beecher H: The powerful placebo. *JAMA* 1955, 159:1602–1606.
 8. Kienle G, Kiene H: Placebo effect and placebo concept: a critical methodological and conceptual analysis of reports on the magnitude of the placebo effect. *Altern Ther Health Med* 1996, 2:39–54.
 9. Kienle GS, Kiene H: The powerful placebo effect: fact or fiction? *J Clin Epidemiol* 1997, 50:1311–1318.
 10. Sauro MD, Greenberg RP: Endogenous opiates and the placebo effect. A meta-analytic review. *J Psychosom Res* 2005, 58:115–120.
 11. Giesecke T, Williams DA, Harris RE, et al.: Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors. *Arthritis Rheum* 2003, 48:2916–2922.
 12. Spector SL: The placebo effect is nothing to sneeze at. *J Allergy Clin Immunol* 1992, 90:1042–1043.
 13. Spector SL, Toshner D, Gay I, Rosenman E: Beneficial effects of propylene and polyethylene glycol and saline in the treatment of perennial rhinitis. *Clin Allergy* 1982, 12:187–196.
 14. Vozeh S: Is the increasing use of evidence-based pharmacotherapy causing the renaissance of complementary medicine? *Br J Clin Pharmacol* 2003, 56:292–296.
 15. Patulin Clinical Trials Committee, Medical Research Council: Clinical trial of patulin in the common cold. 1944. *Int J Epidemiol* 2004, 33:243–246.
 16. Ernst E, Resch KL: Concept of true and perceived placebo effects. *BMJ* 1995, 311:551–553.
 17. Jain R, Mukherjee K, Singh R: Influence of sweet tasting solutions on opioid withdrawal. *Brain Res Bull* 2004, 64:319–322.
 18. Raphael G, Raphael MH, Kaliner M: Gustatory rhinitis: a syndrome of food-induced rhinorrhea. *J Allergy Clin Immunol* 1989, 83:110–115.
 19. Lee PC, Jawad MS, Hull JD, et al.: The antitussive effect of placebo treatment on cough associated with upper respiratory infection. *Psychosom Med* 2005, 67:314–317.
 20. Evans D: *Placebo. The Belief Effect*. London: Harper Collins; 2003.
 21. Benedetti FAM: The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. *Prog Neurobiol* 1997, 52:109.
 - 22.●● Kenia P, Houghton T, Beardsmore C: Does inhaling menthol affect nasal patency or cough? *Pediatr Pulmonol* 2008, 43:532–537.
- This study demonstrates an effect on a patient end point with failure to show objective changes in nasal airflow. It demonstrates the difficulties of developing alternative objective measures, especially when assessing neurosensory end points.
23. Ramsay J, Wright C, Thompson R, et al.: Assessment of antitussive efficacy of dextromethorphan in smoking related cough: objective vs. subjective measures. *Br J Clin Pharmacol* 2008, 65:737–741.
 24. Sapci T, Yazici S, Evcimik MF, et al.: Investigation of the effects of intranasal botulinum toxin type A and ipratropium bromide nasal spray on nasal hypersecretion in idiopathic rhinitis without eosinophilia. *Rhinology* 2008, 46:45–51.
 25. Jones NS: Midfacial segment pain: implications for rhinitis and sinusitis. *Curr Allergy Asthma Rep* 2004, 4:187–192.
 26. Naranch K, Park Y-J, Repka-Ramirez SM, et al.: A tender sinus does not always mean sinusitis. *Otolaryngol Head Neck Surg* 2002, 127:387–397.
 27. Shusterman D, Murphy MA: Nasal hyperreactivity in allergic and non-allergic rhinitis: a potential risk factor for non-specific building-related illness. *Indoor Air* 2007, 17:328–333.
 - 28.●● Elsheikh MN, Badran HM: Dysautonomia rhinitis: associated otolaryngologic manifestations and characterization based on autonomic function tests. *Acta Otolaryngol* 2006, 126:1206–1212.
- This analysis of the high prevalence of autonomic dysfunction syndromes in nonallergic, noninfectious rhinitis patients should yield a reappraisal of the systemic aspects of nonallergic rhinitis.