Published in final edited form as:
Curr Allergy Asthma Rep. 2009 March ; 9(2): 149–152.

The Placebo Effect – Plugging the Nostrils of Unmet Needs

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Abstract

Many common therapies of rhinitis symptoms are inadequate or ineffective. In part, this may be because the drug does not address the pathologically altered mechanism of the rhinopathy. Objective measures may not detect treatment effects, or the treatment endpoints may only be subjective in nature. In many cases, these issues have not arisen because of potent placebo effects. Understanding the psychological, pharmacological, and physiological 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, and can aid in effective clinical trials design, use of objective and subjective test measures, and drug development in rhinitis.

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 employment. Many are “placebos”. This should not be considered totally negative, since the placebo effect is a complex experience that is the sum of nonspecific (no treatment), true placebo (psychological) and physiological 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 has been on developing more efficacious and safe antihistamines and glucocorticoids, and improved delivery systems. These have greatly improved the treatment of allergic rhinitis, but have had minimal effects for 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 are now in a world of efficacious antihistamines, intranasal glucocorticoids, 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 by 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.

This comes as no surprise, since a significant component of the perceived beneficial effects of many of the drugs used for 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, intractable nature. Eccles has performed much of the work in this area [1]. 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 pharmacological 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 ranging from 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 of their efficacy and thought process of “mind over nasal matters” [5,6]. The benefits are driven by the concept of “distributed practice” where approximately one third of subjects 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 employ the excipients of the drug preparation (vehicle) in order 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 both general practitioners and the general public.

Four factors contribute to the benefits of drugs. Cough syrup will be used as the example since 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 towards the mean for the general population. This is the "tincture of time" effect that explains that "sick people get better" [16].

The "physiological" 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 mucous secretion in the pharyngeal to hypopharyngeal region. The viscous products may also 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 where capsaicin and other hot, spicy, piquante foods stimulated cholinergic glandular nasal secretions [18].

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

The sum of nonspecific (no treatment), true placebo (psychological) and physiological 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. demonstrated that the true "pharmacological" drug effect of 30 mg of dextromethorphan given as a hard gelatin capsule was virtually identical in magnitude and time course compared to the placebo response [20]. 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 in order to prepare the most effective therapeutic product.

An additional complication is that objective endpoints must be chosen that can, in fact, be changed by the treatment. 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, airflow resistance, and so 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 to 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. 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.

Better 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 may also add to our understanding of disease mechanisms in individuals, and the specific effects of individual therapies. Issues of cost and correlates with subject 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 where these sensory mechanisms may be impaired. Responses from healthy subjects may not be adequate. Symptom scores must assess the specific changes that are anticipated in an illness. Allergic rhinitis is an excellent example since histamine has overwhelming short – term effect on symptoms. Focused symptom scores such as the Total Nasal Symptom Score (TNSS) that assesses 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 to histamine, and so are likely to require different, more subtly phrased queries.

Congestion, the fourth component of TNSS, 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” should also be differentiated from mid – facial pain syndromes [25] that have a neurological 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 may also be confused with facial tenderness. Chronic fatigue syndrome (CFS) subjects have greater tenderness of their sinus regions than normal controls, allergic rhinitis, acute and chronic rhinosinusitis subjects [26]. This indicates systemic hyperalgesia due to spinal cord reprogramming that leads to chronic pain. Thus, the rhinitis of CFS may represent a variant of Chronic Regional Pain Syndrome (CRPS, aka reflex sympathetic dystrophy). This would be consistent with the heightened trigeminal chemosensitivity also found in subjects with sick – building syndrome and multiple chemical sensitivity [27]. These super – sensitive suffers may have survived natural selection by acting as vigilant

observers using their chemical sensitivity in the hunt for carion or avoidance of predators. There is also extensive evidence of autonomic dysfunction in nonallergic rhinitis [28]. Their rhinitis has been termed “dysautonomic rhinitis”. Finding appropriate subjective and objective methods of defining and measuring their cardinal symptoms and pathology may be as daunting as accepting this group’s functional disorders as “real” medical problems rather than figments of their doctors’ imaginations.

Acknowledgments

Supported by Public Health Service Awards 1 RO1 ES015382 and P50 DC006760, and Department of Defense Award W81XWH-07-1-0618.

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