

Asthma as a Model for Placebo Effects in Modern Medicine

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Many a clinical intervention thrives on placebos. Lack of consensus—both definitional and methodological—however, contributes to general confusion and specious conclusions regarding the legitimacy and relevance of placebos in modern medicine. The apparent divergence between objective and subjective treatment outcomes, moreover, renders placebos clinically meaningless. Asthma provides a clinical model for studying placebos because it highlights how psychology works in concert with pharmacology. Here we examine placebos as valuable adjuncts to, rather than replacements for, pharmacological treatments.

INTRODUCTION

Wechsler et al. (2011) distinguish objective from subjective measures of lung function; their findings, however, fuel confusion about placebos, especially in the context of asthma (Gorski, 2011). The present piece highlights the role of placebos in asthma. Specifically, we argue for the value of subjective factors as well as the presence of objective placebo effects and responses in medicine.

MISNOMERS AND PLACEBOS

Discrepancies on what constitutes a “placebo” underlie much of the controversy surrounding the relevance of placebo effects to modern medicine. The word “placebo” surfaced in the early 1800’s as a medical term denoting treatment for ailments that doctors considered to be “all in the head” and were otherwise powerless to treat (Harrington, 2008). This definition instilled the widespread belief that placebos were mere “nothings”—tools to pacify the difficult and deluded.

Though this impression remains pervasive, what constitutes a “placebo” extends well beyond inert pills or injections. In fact, one may define placebo more broadly as that which confers a benefit explained by neither disease-specific pharmacologic activity nor natural phenomena such as spontaneous remission. Construed in this fashion, placebo could arguably represent the whole history of medicine prior to its shift to evidence-based intervention (Shapiro & Shapiro, 1997). Even contextual features of modern medical treatments contribute to healing. Seemingly simple cues such as pill-colour can mediate the patient response—blue placebo pills can act like

depressants, reducing heart rate amongst unsuspecting medical students (Blackwell, Bloomfield, & Buncher, 1972). Brand-name pills act more effectively than their no-name equivalent (Branthwaite & Cooper, 1981). Discounted prices can diminish the effectiveness of energy drinks (Shiv, Carmon, & Ariely, 2005) and a more expensive painkiller exerts greater analgesic power, increasing shock tolerance thresholds in healthy subjects (Waber, Shiv, Carmon, & Ariely, 2008). Dose perception also contributes to healing; patients who ingested four placebos a day showed a marked improvement over those who took two (De Craen et al., 1999). Such findings suggest that placebos are already active in current therapeutic interventions.

Evidently, placebos are not “nothings”, nor must one administer an actual inert substance to achieve a “placebo effect” (Miller & Kaptchuk, 2008). Dr. Gorski—a surgical oncologist, and panel-member at TAM—was thus correct in asserting “the term ‘placebo effect’ is a misnomer”, but not for the reasons he cites:

[The term “placebo effect”] implies that there is a true physiologic effect caused by an inert intervention. “Placebo response” or “placebo responses” seemed to us a better term because what we are observing with a placebo is in reality a patient’s subjective response to thinking that he is having something active done. In general, we do not see placebo responses [improving] objective outcomes; i.e., prolonged survival in cancer.

To begin with, the term “placebo effect” should not be singular. The diverse set of changes that accompany each individual treatment and

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TAM

The Amazing Meeting—an international conference on critical thinking dedicated to subjecting scientific advances to rigorous scrutiny. At TAM 2011 in Las Vegas, skeptics convened to discuss the merits and, moreso, the limitations of placebo. A summary of the discussion can be found at <http://www.sciencebased-medicine.org/index.php/spin-city-placebos-and-asthma/>.

PLACEBO RESPONSE

The change measured in the placebo group.

PLACEBO EFFECT

The difference between changes in the placebo and no-treatment groups.

disease escape the reaches of one explicable and reproducible “placebo effect” (Wampold, Minami, Tierney, Baskin, & Bhati, 2005). Certain diseases are more amenable to the effects of expectation and suggestion than others. For example, the placebo group comprises almost 100% of the drug effect in the antidepressant treatment for mild-to-moderate depression (Fournier et al., 2010; Khan, Leventhal, Khan, & Brown, 2002; Kirsch et al., 2008; Rief et al., 2009) but represents close to none of the improvement elicited by treating strep throat with penicillin (e.g. Zwart et al., 2000). Perceiving placebo effects as a unitary phenomenon spurs many individuals to misconstrue all placebo effects as illusory and merely subjective (Harrington, 2006). Acknowledging that the term “placebo effect” encompasses a multiplicity of manifestations according to disease and individual warrants a more nuanced analysis.

With his account, Dr. Gorski dismisses the term placebo “effect” in favour of “response” when in fact the correct distinction between effect and response is of an entirely different ilk. In the context of a randomized controlled trial (RCT), “placebo response” encompasses the full change in the group receiving the inert pill. “Placebo effect” refers to the difference between the placebo response and the no-treatment group (Kirsch, 1997; Kirsch & Sapirstein, 1998; Raz, 2007). Without comparing the placebo group to a no-treatment group, factors such as natural disease progression and regression to the mean confound the placebo effect. Achieving definitional consensus is key to a coherent interpretation of past and future placebo research.

OBJECTIVE MEASURES OF PLACEBO EFFECTS

The recent study by Wechsler et al. demonstrates that self-reporting does not align with objective measures of lung function (FEV₁) in mild asthma. Sham bronchodilator and acupuncture conferred no measurable benefit over no-treatment, but were indistinguishable from active bronchodilator according to subjective reports. These seemingly clear observations may prompt the spurious conclusion that all placebo effects are purely “subjective”, with objective measures failing to corroborate self-reported change. As per Dr. Gorski:

Real medicine produces real, objectively measurable changes in physiology towards a more normally functioning state. Placebo medicine does not. In any rational, science-based discussion, this would be the end of the story.

The existing literature provides only tenuous support for this premature conclusion, particularly in light of budding research investigating the biological ramifications of the interaction between the nervous and immune systems—the “mind–body connection” (Sternberg 1997). Identifying how psychological processes such as stress, emotions and expectations may influence other bodily processes is central to establishing placebo effects as scientific phenomena beyond “magical thinking”. Extensive anatomical connections between nervous and immune systems (Goetzl, Chernov et al. 1985; Payan and Goetzl 1987; Felten and Felten 1991) motivated animal studies on the nature of their relationship. These efforts revealed endogenous chemicals such as certain proteins, hormones and neurotransmitters as mediators of this interaction (MacPhee, Antoni et al. 1989; Sternberg, Hill et al. 1989; Sternberg, Young et al. 1989; Edwards, Yungler et al. 1991; Misiewicz, Poltorak et al. 1997). Although these studies focused on animals, they relate to placebo effects in humans by demonstrating that the mammalian nervous system possesses the anatomical and functional connections necessary to exert profound effects on the rest of the body.

In human subjects, placebo scientists often distinguish between placebo effects resulting from expectation and those arising from conditioning. With classical conditioning, pairing contextual cues with drug administration can later permit these cues to elicit a response mimicking drug action; a process evident in both conscious afflictions such as pain and motor impairment, and unconscious processes such as hormone secretion (Ader and Cohen 1985; Benedetti, Pollo et al. 2003). In one particular immunology study, after pairing an intravenous immunosuppressant (US) with anise-flavored syrup (CS), leukocyte counts in 80% of multiple sclerosis patients dropped significantly in response to the administration of the CS alone (Giang, Goodman et al. 1996). Additional studies confirmed that inert substances enable robust and objective immunosuppression and immunostimulation via behavioral conditioning mechanisms (Pacheco-Lupez, Engler et al. 2006).

Beyond conditioned reactions, suggestion and expectation also exert physiological therapeutic effects. For instance, in patients with Parkinson’s disease, the expectation that an injection would ameliorate motor function objectively triggered increased dopamine levels in the brain (de la Fuente-Fernandez, Ruth et al. 2001). Preliminary studies show that verbal suggestion can also modulate processes such as blood pressure and gastric function (Meissner, 2011).

FEV₁

Forced Expiratory Volume in 1 second—a measure of lung function based on the amount of forced air exhaled over a one-second period.

Clearly, psychological processes such as expectation impact physiology over and above subjective experience, and yet Dr. Gorski asserts:

This issue of placebo responses being observed only in **subjective** patient-reported clinical outcomes (**pain**, anxiety, and the like) and not in objectively measured outcomes is an important one . . . as Mark Crislip so humorously pointed out, the placebo response is the beer goggles of medicine.

In reality, even the clinical manifestation of pain—as the ultimate subjective measure—has a physiological basis. Surreptitious inhibition of endogenous opioids, the body’s internal brand of morphine, leads to blockade of pain-relieving placebo effects (Amanzio & Benedetti, 1999; Levine, Gordon, & Fields, 1978). PET and functional magnetic resonance imaging (fMRI) studies corroborate these findings (Zubieta & Stohler 2009). Strikingly, naloxone, the opioid antagonist agent in these studies, also blocked a common secondary effect of these neurotransmitters: respiratory depression (Benedetti, Amanzio et al. 1999). The placebo-induced modulation by endogenous opioids on the respiratory system strengthens the notion that the brain instigates direct and objectively measurable effects on the rest of the body, and contradicting Dr. Gorski’s assertion that “Placebos don’t work in asthma.”

In fact, the underlying physiology of asthma provides the biological model for mind–body effects. Immune and inflammatory pathways are major contributors to airway function in asthma, and are highly susceptible to conditioning and other psychological processes. Specifically, stress is a key component and mediator of the immune system (Chen & Miller, 2007). Studies of inflammatory diseases such as rheumatoid arthritis reveal that stress can, depending on duration and intensity, both enhance and depress immune function (Potter & Zautra, 1997; Straub, Dhabhar et al. 2005). More particular to asthma, research indicates that stress amplifies immune response (Chen & Miller, 2007; Liu et al., 2002). A study of asthmatic college students showed that stress during an exam period led to greater eosinophil counts in the blood and sputum of the students (Liu, et al., 2002). There are several possible pathways that mediate this interaction (Chen & Miller, 2007; Miller & Wood, 2003). Some posit that irregular HPA-axis activity responsible for the low, flat cortisol response to stress in asthmatic patients could underlie the symptoms triggered by intense emotions (Buske-Kirschbaum, von Auer et al. 2003; Liezmann, Klapp et al. 2011). The role of the immune system in asthma not only

paves the way to enhancing disease management through conditioned placebo effects (Pacheco-Lupez, Engler, Niemi, & Schedlowski, 2006), but also highlights the need to manage stress as a complement to pharmacological treatment.

In addition to the global immune pathways, the nervous system also appears to play a major role in asthma, regulating local immune response (Thayer & Sternberg, 2009). As part of the parasympathetic nervous system (PSNS), the vagus nerve monitors visceral organs and modulates immunological response through processes such as the cholinergic anti-inflammatory pathway (Tracey, 2002). Moreover, the sympathetic nervous system (SNS) modifies airway function through adrenergic activity due to fight-or-flight responses. Rather than exerting opposing effects, however, the SNS and PSNS may work synergistically to reverse inflammation. Addressing the impact of central nervous system (CNS) in immune responses, researchers have observed neural correlates of asthmatic symptoms. fMRI data demonstrates a significant correlation between the anterior cingulate cortex (ACC) and insula—areas involved in visceral perception, homeostasis and emotional regulation—and markers of inflammation and airway obstruction in asthma (Rosenkranz, Busse et al. 2005). PET data corroborates the fMRI findings (Ohira et al., 2006). These results reveal potential physiological pathways for psychological influences on asthma symptoms.

Currently, numerous studies demonstrate the role of verbal suggestion on bronchial tone (Meissner, 2011). Empirical inquiry into the effects of expectation in asthma dates back to the 19th century, when a fake rose induced cold-like symptoms, including pulmonary distress (Mackenzie, 1886). Later studies showed that administering saline while suggesting that it was a bronchoconstrictor could elicit bronchoconstriction. Conversely, pairing saline with the suggestion that it was actually a bronchodilator reversed the initial bronchoconstricting effects_(Butler & Steptoe, 1986; Luparello, Lyons, Bleecker, & McFadden, 1968; McFadden, Luparello, Lyons, & Bleecker, 1969). In one recent study by Kemeny et al. (2007), FEV1 measurements indicated that placebo bronchodilators suppressed airway response to subsequent methacholine administration. Moreover, placebo effects in asthma may be organ specific. One particular study reversed nocebo bronchoconstriction with a placebo bronchodilator, without alleviating the nocebo side-effects of increased heart rate and skin conductance (Butler & Steptoe 1986). These data denote the existence of truly objective physiological responses to suggestion.

EOSINOPHIL

A type of white blood cell associated with asthma and allergy.

HPA AXIS

The interaction between the Hypothalamic, Pituitary and Adrenal glands involved in mediating stress response.

METHACHOLINE

Synthetic molecule used in certain tests of airway hyperreactivity the results of which may be used to diagnose asthma.

NOCEBO

A term describing a placebo that has a detrimental effect on the patient

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While certain studies indicate that suggestion can indeed influence physiology, other studies found no significant contribution by suggestion to objective measures of lung function (Isenberg, Lehrer, & Hochron, 1992b), similar to the findings of Wechsler et al. in their recent paradigm. Due to highly variable methodologies, none of these studies, refuting or supporting the reality of placebo effects in asthma, is conclusive or broadly generalizable. In the fields of immunology and respirology, even clinical intuition is divided. Certain clinicians predict that placebos and subsequent expectations merely alter perception, while others acknowledge the potential for objective changes (R. Anbar, F. Noya, personal communication August 2011). These discordant reports nonetheless invite further investigation into the possibility of placebo effects in asthma, rather than grounds to dismiss it as Dr. Gorski does, on the basis of a single pilot study.

THE IMPORTANCE OF SUBJECTIVITY

Despite the inconsistency of the asthma literature, many physicians dismiss subjective and psychological factors entirely, as Dr. Gorski does, in singular favour of pharmacological agents:

Asthma can and does kill, some 250 000 deaths per year worldwide. Choosing alternative medicine over effective asthma treatment because placebo responses lead to feeling better without altering the underlying illness, could very well lead to preventable asthma deaths.

While recognizing that asthma accounts for a sizable portion of disease burden on society (Morgan & Khan, 2003), psychosocial factors contribute greatly to its morbidity and mortality (Leigh, MacQueen, Tougas, Hargreave, & Bienenstock, 2003; Sodergren & Hyland, 1999; Strunk, Mrazek, Fuhrmann, & LaBrecque, 1985). For example, in a study where structured interviews compared children who died of asthma attacks with those who survived, identifiable factors such as family turmoil and emotional distress were significantly greater in those who subsequently died (Miller & Strunk, 1989; Mrazek, Klinnert, Mrazek, & Macey, 1991). Importantly, each patient presents with a unique profile of triggers—from intrinsic (i.e., emotional) in addition to extrinsic (i.e., pollen, animal dander, etc.) factors (Isenberg, Lehrer, & Hochron, 1992a), and accordingly requires differential treatment. For example, extant research demonstrates that parents can exert a considerable impact on childhood asthma (Madrid & Monte Rio, 2005; Mrazek,

Klinnert, Mrazek, & Macey, 1991; Weinstein, Chenkin, & Faust, 1997) specifically in cases with a strong emotional component to symptom onset. In some studies, children experienced symptom relief when they remained at home with a surrogate (Purcell et al., 1969), whereas others demonstrated exacerbation in response to separation (Miller & Wood, 2003). Psychological factors play an apparent role in asthma symptomatology and deserve clinical attention accordingly.

Dr. Gorski disputes the clinical validity of quality-of-life metrics, and minimizes the impact of subjective factors by equating asthma to an epidural hematoma, where feeling symptom-free erroneously masks a potentially lethal condition. This analogy falls short, however, because the symptoms for mild-to-moderate asthma such as coughing and wheezing do not correlate with underlying hypoxia—a condition that arises only in cases of extreme severity. Dr. Francisco Noya, a pediatric immunologist at the Montreal Children's Hospital, highlights that at this stage of asthma, “obstruction of airways does not affect oxygenation” but rather impairs regular breathing loops (personal communication, August 2011). Concerns other than hypoxia, however, arise from this disruption. Dr. Ran Anbar, a pediatric pulmonologist at SUNY Upstate Medical University, clarifies that “these asthma symptoms can be disruptive to life: they can cause nighttime awakening, which prevents good quality sleep, which can lead to many problems such as poor school or job performance, or even obesity” (personal communication, August 2011). Thus, while hypoxia is the most dire and life-threatening consequence, it may not be the most pressing concern in the cases of mild-to-moderate asthma.

Though symptoms can serve as a warning sign in severe asthma exacerbations, an often under-appreciated component requires direct mention. In certain instances, symptoms of coughing and wheezing may dissociate from objectively reduced lung function, even when these symptoms lead to hospitalization. Where hospitalization appears as a routine component of asthma management, Dr. Ran Anbar asserts that: “Asthma *can* be managed—any time a patient with asthma has been hospitalized has either been mismanaged or didn't take their medicine.” Dr. Anbar specializes in the most intractable forms of pediatric asthma, and must often couple psychological interventions with pharmacology to effectively manage his patients. Recently published, self-hypnosis successfully managed a boy's crippling external symptoms—previously unresponsive to medication—where lung function remained below average (Anbar & Sachdeva, 2011). Here, Dr. Anbar rectified low lung function with appropriate

bronchodilators, while implementing psychological management to supplement pharmacology's deficits. Evidently, psychology and subjectivity as adjuncts to pharmacology are key to disease management, the symptoms of which exert a profound and immediate handicap on quality of life.

Asthma provides a clinical forum for psychology to work in concert with pharmacology to affect stronger treatment outcomes. Its prevalence continues to rise in the face of modern pharmacological treatments (Morgan & Khan, 2003) that, alone, are clearly inadequate to curb the rise in disease. Harnessing psychological—or top-down—processes may serve to boost therapeutic efficacy and also reduce dependence on medication. As one case study illustrates, self-hypnosis allowed a patient with severe asthma to reduce systemic steroid intake (Anbar, 2003). Larger studies would no doubt be necessary to investigate the exact conditions under which these types of treatment are optimal, but such reports raise the potential for top-down processes to complement current pharmacology and bolster long-term treatment outcomes.

Dr. Gorski takes exception to Wechsler et al.'s discussion, as an assault by “quackademics” on Western medicine, interpreting that their claims of subjective improvement are “being sold to the public as evidence of “powerful” placebo effects and as evidence that we physicians should be doing more placebo medicine.” Dr. Moerman fuelled this outlook by over-generalizing the subjective component of disease. Granted, in specific instances, perception contributes significantly to the effectiveness of pharmacological treatment. For example, diazepam administered unbeknownst to anxious patients produced no clinically meaningful decrease in symptoms (Colloca, Lopiano, Lanotte, & Benedetti, 2004), and covertly withdrawing the medication did not precipitate rebound anxiety. More broadly, a pessimistic view on personal health contributes to heightened incidences of disease and mortality (Idler & Benyamini, 1997; Mossey & Shapiro, 1982). Suggestion does play a role in human health, but the specific contexts in which these effects are most salient remains a subject for further inquiry.

Crucially, we must acknowledge that those who claim the omnipotence of subjectivity are just as misguided as those who discount its power. There are limits to what psychological factors can achieve and in certain instances responses can be illusory. As an example, the idea that hypnotic suggestion can improve visual acuity is a pseudo-scientific myth. The suggestion itself cannot change the optics of the eye, but only influences how effective the patient believes his eyesight to

be (Raz, Marinoff, Zephrani, Schweizer, & Posner, 2004). Interpreting the import of subjective factors in disease requires moderation. Rather than eschewing western medical techniques, we emphasize harnessing the mind, as adjunctive therapy to complement current medical treatments.

FUTURE DIRECTIONS

Certain scholars deem the whole placebo evidence-base methodologically unsound—largely attributing the “placebo effect” to research artifact. With two controversial meta-analyses, Hrobjartsson and Gotzsche (2001, 2004) evaluated RCTs for treatments of ailments such as pain, nausea and hypertension for valid placebo effects, and found that they only institute a small subjective benefit; however, several methodological issues arise when relying on RCTs to observe placebo effects. Some trials specifically screen subjects to include only those who are least likely to respond to an inert substance (Busse & Lemanske, 2009). Moreover, because the processes of informed consent diminish patient expectation for “active treatment”, the RCT design should display the weakest placebo effects in medicine (Foddy, 2009). Such methodological considerations emphasize the need for prospective study designs to examine placebo effects directly rather than relying on a-posteriori observations.

Understanding which characteristics comprise a good placebo reactor constitutes a solid aim of future study designs. Front-runners of placebo research, however, acknowledge that responses to placebo are highly unreliable (Whalley, Hyland, & Kirsch, 2008) and that the search for predictive markers of susceptibility to placebo remains largely unsuccessful (Kaptchuk et al., 2008). One important factor that the literature in general, including the paper by Wechsler et al., neglects to explore is the role of age in placebo effects, as youth is emerging as a potential factor associated with susceptibility to suggestion. For example, children who suffer from migraine headaches also experience greater placebo effects than adults (Fernandes, Ferreira, & Sampaio, 2008; Lewis, Winner, & Wasiewski, 2005). A recent meta-analysis of anti-epileptic medications objectively verifies the elevated placebo effects in pediatric subjects; children in the placebo group were twice as likely as adults to achieve a 50% reduction in convulsive activity (Rheims, Cucherat, Arzimanoglou, & Ryvlin, 2008). The literature suggests, but does not conclude, that children may demonstrate heightened placebo effects in general, and thus be more amenable to psychological interventions.

Currently, our lab is designing and implementing a study to directly address the role of placebo effects in pediatric asthma. We complement the design of Wechsler et al. by controlling for factors such as age and verbal suggestion. Specifically in asthma, heightened placebo effects may accompany younger age (Kemeny et al., 2007). Our data should effectively contextualize the findings from Wechsler et al., and shed light on the relevance and role of suggestion in asthma management.

CONCLUSION

Recent critiques of Wechsler et al. disparage attempts to address placebo as the omnipresent silent partner in the care of asthma patients.

Although pharmacological treatments are the proven cornerstone of management, psychosocial factors may influence symptoms and improve disease outcomes. Rather than endorsing placebos as panaceas, we advocate the need to further explore its potential as an adjunct to traditional therapies. Embracing placebos, albeit judiciously, as a viable tool of the clinical armamentarium paves the road to a more scientific understanding of mind–body regulation.

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