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The Long-Term Effects of Using Placebo in Asthma Treatments

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Abstract: Asthma is a chronic respiratory disease characterized by hyperreactivity in the airways, which can lead to significant lung damage if not properly managed. While placebos—medications with no active therapeutic ingredients—are sometimes used in clinical trials to gauge the effectiveness of asthma treatments, their long-term use raises concerns. Placebos work primarily through psychological mechanisms by enhancing patients' expectations of treatment. However, prolonged reliance on placebo treatment in asthma could potentially mask symptoms, delay proper management, and lead to undetected lung damage or other adverse effects. This study explores the potential risks and consequences associated with long-term placebo use in asthma management.

Keywords: placebo; asthma; long-term effects; hyperreactivity; bronchial inflammation

Introduction

A mock treatment, known as placebo, meaning "I shall please" in the language of Latin, was first recognized and demonstrated by John Haygarth in 1799. (Perkins & Repper, 2021, p.213) Originated by using wooden rods instead of electromagnetic waves as a treatment for joint discomfort. Later, the inactive chemical treatment was widely utilized to treat a variety of disorders, including inflammation, Parkinson's disease, chronic pain, and insomnia. The mechanism of a placebo took advantage of expectation, mainly acting as a psychological treatment to cure those diseases. After the common usage of a placebo, Asthma also became an excellent model for using a placebo for treatment.

In the present day, Asthma is one of the most common illnesses, with a prevalence rate of 13.01% of patients in the world's population. (Jo, Lee, Kim, Park, & Kim, 2023, p.4) The disease is characterized by airway hyperresponsiveness, causing symptoms of shortness of breath, cough, and wheezing. Which can result in permanent lung damage. Many types of medications are utilized in lessening the severity of the symptoms, Beta2 agonists, corticosteroids, also including placebo.

The placebo trials were regarded as failures. Placebo is used in many clinical trials and medication studies to assess treatment efficacy. In trials, half the people in the trial group receive actual medication, and the other half receive an inactive drug or placebo, without acknowledging the type of medication they got. The result showed a significant rate of failure, with an inconclusive result of undistinguished performance between active and inactive medications. (Montgomery, 1999, p.275)

This paper will review the previous and current literature on placebo response with a focus on the outcome in asthma patients, the mechanism of placebo treatment, and the long-term effect on Asthma patients with a long duration period of placebo treatment in mitigating their symptoms.

Asthma

Asthma is a chronic immunological disorder, typically triggered by environmental allergens, which causes bronchial hyperreactivity. This leads to restricted, swollen airways and severe symptoms, such as coughing, wheezing, and shortness of breath (Sockrider & Fussner, 2020, p.26). In severe cases, asthma can rapidly progress to life-threatening conditions, even in well-managed

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patients (see Figure 1). Currently, asthma affects over 300 million people worldwide and is responsible for as many as 250,000 deaths annually.

Asthma is diagnosed using lung function tests, such as spirometry and peak flow tests, to measure how much air patients can breathe in and out. Determining the severity of asthma in each individual helps healthcare providers choose the most appropriate treatments (Mayo Clinic, 2024).

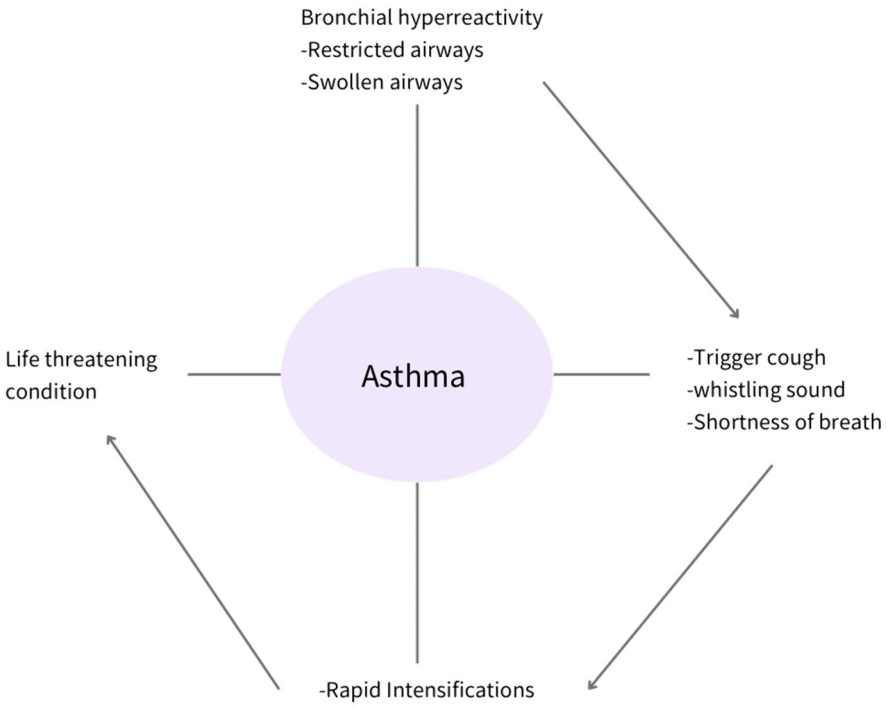

Figure 1. Flow chart of asthma symptoms intensifying through increased airway hyperreactivity, leading to life-threatening conditions.

- **Spirometry** This test determines the narrowing of the bronchial tubes by measuring the amount of air each patient can breathe in after a deep breath and how fast they can breathe out.
- **Peak flow** A peak flow meter monitors how strongly the patient can breathe. Lower peak flow values may indicate a decrease in lung function and worsen asthma symptoms.

Determining individual asthma severity will assist professionals in selecting the most effective treatment. (Mayo Clinic, 2024)

Types of Treatments

Numerous medications are available to reduce the exacerbation in Asthma patients, such as Beta 2 agonists, Inhaled corticosteroids, and placebo. The adjustment of the types of medications corresponds with the severity of the patient's symptoms over time. (Sharma, Chakraborty & Hashmi, 2023)

Examining the first type of medication, Beta 2 agonists, Beta 2 agonists use the method of binding Beta-adrenergic receptors with bronchiole, along with stimulating G protein, to activate adenylyl cyclase which reduces airway smooth muscle contraction. Nevertheless, side effects from inhaling Beta 2 agonists in the long term, are that it can cause symptoms of nausea, and dizziness, and may lead to bronchitis, chronic obstructive pulmonary disease, or COPD.

Another common choice of medication is inhaled corticosteroids or ICS, controlling through suppressing the inflammatory response and lowering the exacerbation. The mechanism of switching off multiple activated inflammatory genes results in more appropriate long-term outcomes, and less severe side effects, including headache, throat irritation, and cough. Regardless of some side effects, inhaled corticosteroids became the first-line medication for asthma patients.

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Placebo inhaler is a novel choice of treatment, trials have been established in the past few decades. One of them is Dr. Michael Wechsler and Ted Kaptchuk from Harvard Medical School, saying Placebo treatment can help the patients feel better, but not lessen the disease. This means that no improvement in lung function was made from a placebo inhaler, however, improvements in the patient's feelings which are related to psychological factors are still in today's debate.(Dutile, Kaptchuk, & Wechsler, 2014)

The Mechanism of a Placebo

Placebo is a medication that plays with expectations. A psychological effect caused by placebo intake, alters brain chemistry, as a result of the activation of expectations that patients have for improvements after taking the placebo. Furthermore, the autonomic response is associated with placebo analgesia, also relating to verbal instruction. (Benedetti, Carlino, & Pollo, 2011, p.340-341) The outcome of the intake can be altered by many mechanisms in the human body (Benedetti & Amanzio, 2013, p.520), such as brain conditions of each patient, levels of expectation, and also genetic variation. As a result, patients receive various types of outcomes, depending on their emotional and physiological condition (Figure 2), giving placebos responses almost impossible to predict. Unpredictable responses from various patients' conditions can also lead to a Nocebo occurring, which is a contrast response of the placebo, which alternates with negative expectations which can exacerbate the symptoms of the patients in treatment. Another study found that the placebo effect can influence pain perception and involve brain areas such as the anterior cingulate cortex and the thalamus. (Benedetti, Pollo, Lopiano & Colloca, 2005, p.2274-2275)

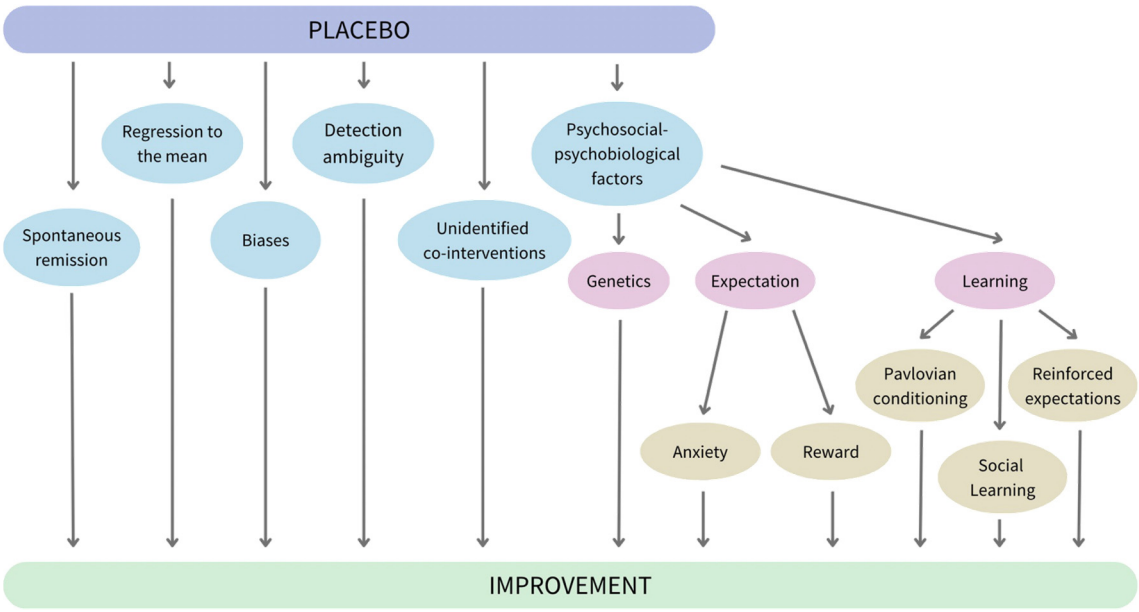

Figure 2. Variables influencing the placebo mechanism in controlling bronchial hyperreactivity (Benedetti, Carlino, Pollo, 2011).

Neural networks are the ones affected by the response of placebo (Benedetti, Carlino, & Pollo, 2011, p.340), several cortical areas were found to be activated by placebo examining the anterior cingulate cortex and dorsolateral prefrontal cortex (Petrovic, Kalso, Petersson, Andersson, Fransson, & Ingvar, 2002). The research shows that the activation-reducing pain-modulating system also reaches down toward the spinal cord and inhibits the occurrence of dorsal horn neurons. The brain-mind responses to the treatment also showed evidence of implications of multiple brain systems and neurochemical mediators, which include opioids; calming and anti-pain hormones, and dopamine; a pleasure hormone, that refers to the differentiation of brain activity.

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The Danger of Placebos

In conditions like asthma, where effective management is essential to control inflammation and prevent airway constriction. Relying on a placebo can lead to serious consequences, since a placebo is not an active medication, the placebo only works psychologically for the patients, causing only a sense of relief and comfort. The absence of appropriate medication means that asthma symptoms can worsen, leading to increased frequency and severity of exacerbations coordinating with their disease; in this case, Asthma which revolves around the respiratory system and lung function. This can cause significant risk to lung function, as the underlying asthma remains untreated. The decline in lung function with delayed acknowledgment and treatment can be deadly. (Kemeny, Rosenwasser, Panettieri, Rose, & Kline, 2007, p.1375) Delay treatment also leads to missing out on real effective care which can prevent long-term damage and reduce the severity of Asthma.

Physiological and Psychological Effects

It's well-documented that placebo responses in asthma can have real physiological effects, not just psychological ones. The study showed that patients who receive placebo treatments sometimes show measurable improvements in lung function, such as an increase in Forced Expiratory Volume in 1 second (FEV1). FEV1 is a key indicator of how well air is moving out of the lungs and is used to assess the severity of asthma. (Wechsler & Kelley, 2011, p.119) This physiological response could be attributed to several factors, including the brain's ability to modulate respiratory function through expectation, stress reduction, and even changes in airway inflammation. The positive expectation from receiving treatment can lead to real changes in how the body functions, at least temporarily. Nevertheless, while placebo responses can show improvement, they don't address the underlying causes of asthma. Asthma involves chronic inflammation and constriction of the airways, which requires targeted medical treatments to manage effectively. Using placebos in clinical practice or research might create a misleading picture of a treatment's effectiveness. If a placebo seems to improve symptoms, it might falsely suggest that a treatment is more effective than it is. (Bootsma & Dekhuijzen, 2009, p.233) This can lead to careless management of the disease, as it doesn't address the core causes of asthma. For patients, this means they might not receive the necessary therapies that could better control their condition and prevent long-term damage.

Discussion

Exacerbation from Placebo

"Placebo treatments in asthma can significantly improve subjective symptoms such as dyspnea and wheezing, demonstrating the powerful role of patient expectation and the brain's influence on respiratory function." (Beecher, 1955, p.1602) Placebos can lead to improvements in some symptoms of Asthma. This is largely due to the power of psychology (Kirsch, 2013, p.128). When patients believe they are receiving treatment, their brains can produce physiological changes that mimic relief. This is a result of the brain's ability to influence various body functions, including respiratory function. Furthermore, The placebo effect may involve the release of endorphins or other neurotransmitters that can temporarily ease symptoms or make the patient feel better.

However, physiological damage to the lungs and respiratory system is not cured and can create a serious respiratory condition in the long term. "Relying on placebos for asthma treatment can create a false sense of security, resulting in under-treatment of the condition and an increased risk of irreversible lung damage." (Wechsler & Lavoie, 2011, p.487) If patients rely on placebos instead of effective asthma treatments, they might believe their condition is under control when it is not. This can lead to a lack of adherence to necessary medical therapies, such as inhaled corticosteroids or bronchodilators, which are crucial for managing asthma. Asthma management typically involves medications that target inflammation and bronchoconstriction. Placebos do not address these underlying issues. Relying on placebos means missing out on these essential treatments. Altogether, without proper treatment, asthma can progress and lead to long-term damage to the lungs,

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examining chronic inflammation and structural changes in the airways, which are irreversible and will lead to diminished lung function over time. (Biller-Andorno & Lenk, 2007, p.5)

Conclusion

In conclusion, because a placebo can biologically lessen the hyperactivity of the airways, it is undoubtedly one of the best treatments for people with asthma. However, a placebo is unable to treat Asthma conditions, the long-term effects of placebo use in asthma patients can cause the disease to worsen and damage lung function. To ensure patients' safety, further research should be done to ascertain whether a placebo is safe over the long term. Furthermore, the use of a placebo should be conducted under expert supervision, to prevent inaccurate use of the medication.

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References

1. Beecher, H.K. (1955). The Powerful Placebo. Journal of the American Medical Association, 159(17), 1602-1606.
2. Benedetti, F., Pollo, A., Lopiano, L., & Colloca, L. (2005). "Consciousness and the placebo effect." *The Lancet*, 364(9441), 2274-2275.
3. Benedetti, F., Carlino, E., & Pollo, A. (2011). How placebos change the patient's brain. *Neuropsychopharmacology*, *36*(1), 339-354.
4. Benedetti, F., & Amanzio, M. (2013). Mechanisms of the placebo response. *Pulmonary pharmacology & therapeutics*, *26*(5), 520-523.
5. Bootsma, L.J., & Dekhuijzen, P.N.R. (2009). Ethical issues in placebo-controlled clinical trials in asthma. European Respiratory Journal, 34(1), 233-239.
6. Biller-Andorno, N., & Lenk, C. (2007). The use of placebo in clinical trials: ethical considerations. Philosophy, Ethics, and Humanities in Medicine, 2(1), 5.
7. Dutile S, Kaptchuk TJ, Wechsler ME. The placebo effect in asthma. Curr Allergy Asthma Rep. 2014 Aug;14(8):456. doi: 10.1007/s11882-014-0456-2. PMID: 24951239; PMCID: PMC4351653.
8. Harrison Wein, Ph.D., Vicki Contie and Brian Doctrow, Ph.D. Placebo Improves Asthma Symptoms, But Not Lung Function. [Published July 25, 2011], from https://www.nih.gov/news-events/nih-research-matters/placebo-improves-asthma-symptoms-not-lung-function
9. Jo, E. J., Lee, Y. U., Kim, A., Park, H. K., & Kim, C. (2023). The prevalence of multiple chronic conditions and medical burden in asthma patients. Plos one, 18(5), e0286004.
10. Kirsch, I. (2013). Antidepressants and the placebo effect. Zeitschrift für Psychologie, 221(3), 128-134.
11. Kemeny, M. E., Rosenwasser, L. J., Panettieri, R. A., Rose, R. M., Berg-Smith, S. M., & Kline, J. N. (2007). Placebo response in asthma: a robust and objective phenomenon. *Journal of Allergy and Clinical Immunology*, *119*(6), 1375-1381.
12. Mayo Clinic. (n.d.). *Asthma* [Diagnosis and treatment]. Mayo Clinic. Retrieved August 15, 2024, from https://www.mayoclinic.org/diseases-conditions/asthma/diagnosis-treatment/drc-20369660
13. Montgomery, S. A. (1999). The failure of placebo-controlled studies. *European Neuropsychopharmacology*, *9*(3), 271-276.
14. Petrovic, P., Kalso, E., Petersson, K. M., & Ingvar, M. (2002). Placebo and opioid analgesia--imaging a shared neuronal network. *Science*, *295*(5560), 1737-1740.
15. Perkins, R., & Repper, J. (2021). Reframing the placebo effect. The importance of meaning. Mental Health and Social Inclusion, 25(3), 213-217.
16. Sharma S, Hashmi MF, Chakraborty RK. Asthma Medications. [Updated 2023 Jun 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531455/
17. Sockrider, M., & Fussner, L. (2020). What is asthma?. *American journal of respiratory and critical care medicine*, *202*(9), P25-P26.

 doi:10.20944/preprints202409.1395.v

18. Wechsler, M.E., & Lavoie, K.L. (2011). Placebo effects in asthma. Current Allergy and Asthma Reports, 11(6), 487-494.
19. Wechsler, M.E., Kelley, J.M., Boyd, I.O.E., et al. (2011). Active Albuterol or Placebo, Sham Acupuncture, or No Intervention in Asthma. New England Journal of Medicine, 365(2), 119-126.