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A study on symptom improvement and efficacy of formoterol plus budesonide in the asthma management in northern parts of Tamil Nadu

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ABSTRACT

The purpose is to study the asthma symptom improvement and efficacy of formoterol (LABA) and Budesonide (ICS) combination in the asthma management in northern districts of Tamilnadu. It is a multicentric, non-comparative, questionnaire and random sampling study was conducted in 145 mild to severe asthmatic patients. They were in Formoterol plus budesonide combination inhalation drugs available in DPI and pMDI. Among the 145 asthmatic patients, 45 patients, 6 patients and 94 patients were in DPI, nebuliser and pMDI devices respectively. During drug initiation, The Asthmatics were in mild (27%), Moderate (57%) and Severe (16%) stages. After one year of follow-up, the number of patients in the mild is 84%, moderate 14% and severe 2%. Among 45 DPI Asthmatic patients, 29 patients, 15 patients and 1 patient have reported the handling the devices as easy, medium and hard respectively. On the other hand, 94 pMDI asthmatic patients, 38 patients, 48 patients and 8 patients have reported the handling of devices as easy, medium and hard respectively. The treatment resulted in 77 patients as good, 65 as satisfactory and 3 as same. After one year, all the 145 asthmatic patients adhered with the treatment and experienced symptom improvement with 53% patients as good, 45% patients as satisfactory and 2% patients as same. The treatment of formoterol and budesonide combination in the northern districts of Tamilnadu have effectively controlled the asthmatic symptoms and improved the quality of life in asthmatics. Moreover, the patient's adherence to the treatment is good in the northern parts of Tamilnadu.

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INTRODUCTION

In India, in recent day's asthma has become more common in all categories of cities due to rapid industrialization and urbanization. Asthma, in simple term, it is defined as a chronic respiratory disease that is represented by chronic inflammation of the airways (Slejko *et al.*, 2014). It identified with airway hyperresponsiveness (a hyperbolic airway narrowing response to the trigger factors like animal dander, pollen, viruses, antigens, sprays/perfumes, etc.)

Which leads to the symptoms like wheezing, chest tightness, and breathlessness in recurrent episodes that can prolong time to time depending upon the

severity of inflammation. As per GINA (Global Initiative for Asthma), It affects 1-16% of the population globally (Price *et al.*, 2014). Approximately 12-15% of adults in India are reported to be asthmatics. Worldwide prevalence and incidence of asthma are increasing by 30% approximately over the past two decades.

According to the World Health Organization (WHO), in 2016, around 336 Million people were affected by asthma. It increases the burden for low and middle-income countries (Stallberg *et al.*, 2009). WHO created the strategy for prevention and control of asthma and their objectives are to improve the cost-effective medical treatment and guidance to asthma and to create awareness about asthma worldwide.

Thorough medical history and physical examination involve in the diagnosis of asthma, and the aim to assess the lung function of the asthmatics through the peak flow meter and spirometer (Haikarainen *et al.*, 2017). This provides complete data about the lung function and the severity of asthma (mild, moderate, and severe).

In asthma management, the primary aim is to minimize the exacerbation episodes and maintain control of the disease, reducing the risk of morbidity and mortality. The other goal of the therapy includes minimizing the asthma symptoms and frequency, the need for reliever medication to be controlled, normal physical activity and improve the pulmonary function and the asthmatics quality of life (Malmberg *et al.*, 2014). The criteria like number of exacerbations, number of nighttime symptoms, fewer than 3 doses/ week of $beta_2$ agonist bronchodilators, daytime symptoms< 3 days/week, normal physical activity, and no absenteeism from work or school must be assessed in each visit to achieve asthma control (Lähelmä *et al.*, 2016).

In asthma treatment, the pharmacological agents are classified as controllers (medication must be taken long-term to control the asthma symptoms) and relievers (medication gives quick relief of asthmatic symptoms) (Tamasi *et al.*, 2018)). The drugs like inhaled corticosteroids(ICS), long-acting $beta_2$ agonists (LABA), ICS+ LABA, leukotriene receptor antagonists(LTRAs), the long-acting muscarinic antagonist(LAMAs) includes in controller medications (Pirożyński *et al.*, 2017).

On the other hand, Short-acting inhaled $beta_2$ agonists (SABA) and inhaled anticholinergics are includes in reliever medications (Ekberg-Jansson *et al.*, 2015). The treatment algorithm of asthma is mentioned in Figure 1. The inhalation route of medication shows more efficacies in controlling asthma compared to oral medications with fewer side effects (Virchow *et al.*, 2008).

In the treatment of asthma symptoms (acute) and during the nocturnal awakening episodes, Inhaled SABA is preferred as reliever medications. ICS is recommended as first-line maintenance treatment in adults and children (Hantulik *et al.*, 2015). Besides, ICS+ LABA is highly effective in controlling and reduction of asthma symptoms. The present study was conducted in the northern parts of Tamil-Nadu. It aimed to evaluate the asthma symptom improvement and efficacy of formoterol (LABA) and Budesonide (ICS) combination in asthma management (Galffy *et al.*, 2013).

METHODS

Study Design and Participants

This study is a multicentric, non-comparative, randomized questionnaire survey conducted in the northern parts of Tamilnadu which comprise 8 districts, 145 Patients, with asthma were enrolled who had started their formoterol and budesonide for the treatment. During the time of enrolment, The Patients were questioned on socio-economic background, symptoms, and asthma management. After the treatment period of 1 year, we have surveyed the patients on symptoms control and management. This survey study was conducted between 11 December 2017 and 10 Jan 2019.

Sampling and Data Collection

We have surveyed the asthmatics in asthma camps conducted by Indian pharmaceutical companies. Primary data were collected as per the asthma questionnaire by the survey method and secondary data were compiled from published sources. The questionnaire includes asthma characteristics, symptom management, and socio-economic condition of the asthmatics (Bateman *et al.*, 2018).

Survey Questionnaire

Based on the Minnesota Department of Health for the asthmatic patients, we framed our questionnaire and modified as per the need of the study also suits the Indian asthmatics. We included symptoms related questions, as suggested by the top chest physicians in the surveyed region (Beasley *et al.*, 2019). The time taken for the enrollment survey was approximately 20 minutes per patient and the time taken for the follow-up survey was 15 minutes per patient.

Analysis of Primary and Secondary Endpoint

The primary endpoint was symptoms improvement in asthmatics and efficacy of the formoterol and budesonide combination. Symptom improvement

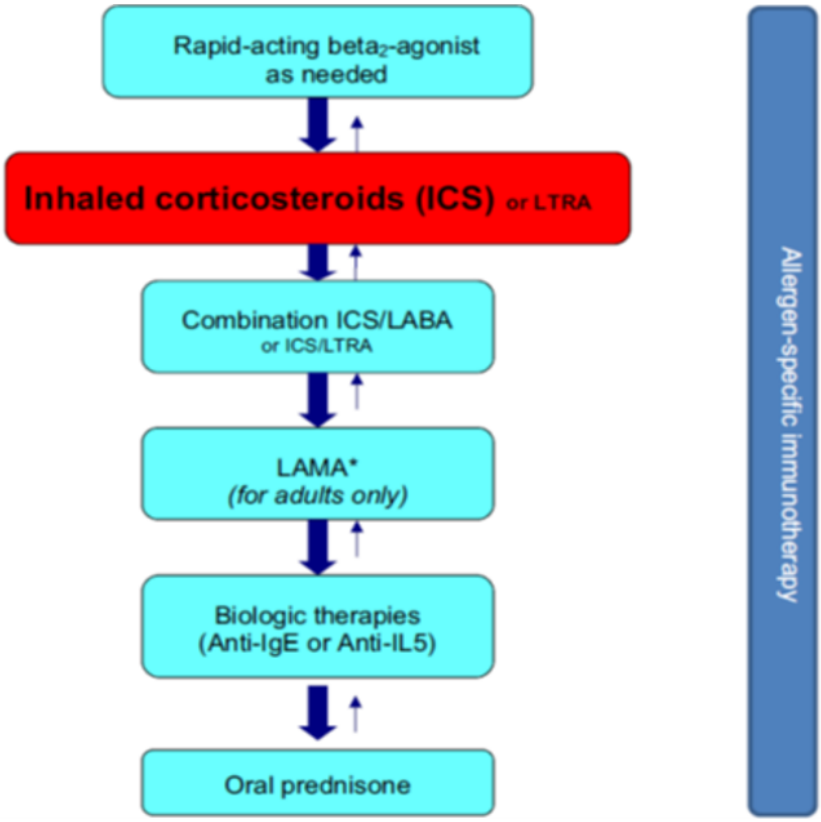

Figure 1: Treatment algorithm of asthma

Table 1: Baseline characteristics of the patients

Patients	n(%)
Sex, n (%)	
Male	78(53.7)
Female	67(46.2)
Residing in Polluted areas, n (%)	
Male	34(44.7)
Female	42(55.3)
Residing in Non-Polluted areas, n (%)	
Male	44(63.8)
Female	25(36.2)
Type of residing City, n (%)	
Rural	7(4.8)
Urban	79(54.5)
Mixed	59(40.7)

was comprised of several exacerbations during the Initiation and after one year, follow up with the inhaler medication. Thus, we have observed the switch over the number of exacerbations episodes in a positive manner and were analyzed and men tioned in Percentage. Similarly, the secondary endpoint was Inhaler used, Techniques involved in the inhalers, and pattern of drug usage (Husereau *et al.*, 2013).

All the secondary endpoints were analyzed and mentioned in Percentage. These endpoints will provide the role of formoterol and budesonide in the asthmatics.

RESULTS

Baseline Characteristics and Socio-Demographics of patients

Overall, 145 patients were surveyed in our study of whom all were surveyed after 1 year for the follow-

up of the asthma treatment. The majority of the patients were Male (n = 78; 53.7%) and were residing in the polluted areas (n= 76; 52%). The patients were resided in the Rural (n=7; 4.8%), Urban (n=79; 54.5%) and Mixed (n=59; 40.7%) types of cities in the northern districts of Tamilnadu. The baseline characteristics of the patients are shown in Table 1.

Formoterol and Budesonide treatment in Asthma stages

During the initiation of formoterol and budesonide for the management of asthmatics, the patients were in mild (n = 39; 27%), moderate (n = 83; 57%) and severe (n= 23; 16%) stages in the asthma. After 1 year, the Majority of the patients were adapted to the treatment and inhaler techniques. Thus, Shift of asthma stages were seen among the patients like in mild (n = 122; 84%), moderate (n= 20; 14%) and severe (n=3; 2%). Patients were surveyed during Initiation and after 1 year, follow up with asthma stages is shown in Figure 2.

Symptoms related

Exacerbation is a major symptom of asthma. Formoterol and budesonide combination was given to the asthmatics for management. Compare to the Initiation of formoterol and budesonide combination, after 1 year, 71(49%) patients were experienced 0 to 3 times exacerbation/week. The patients with 4 to 5 times exacerbation/week were 32(22%). 35(24%) patients were experienced 6- 7 times exacerbation/week and More than 8 times exacerbation were experienced by 7(5%) patients. The number of exacerbations/week experienced by patients during the drug initiation and after 1-year follow-up is shown in Figures 3 and 4.

Night awakenings and intervention in normal activity

Nighttime exacerbations result in night awakenings which disturbs the quality of life for asthmatics. 74 patients were suffered from night awakenings in between the period of 1 year.

Asthma symptoms intervene in the daily activity of the asthmatics. After Formoterol and budesonide treatment, only 23(16%) patients have reported the intervention of asthma symptoms in their normal activity. The intervention of asthma in normal activity is shown in Figure 5.

Type of inhalers used

Formoterol and budesonide are available in DPI and pMDI and Liquid form for nebulizers. Depend upon the patient's convenience and techniques adaption physicians have preferred a different type of Inhaler (Subramanian and Kumaresan, 2012). pMDI was used by 94 (65%) asthmatics for their symptom management. The types of inhalers used by the patients are shown in Figure 6.

Techniques involved and cost factor

Techniques involved in the usage of the device plays a role in symptom management. The techniques involved in the inhalers were experienced hard by only 14(10%) asthmatics. Besides the cost spent on their treatment /month is quite expensive for around 50% of the asthmatics. It affects the intake of regular medication for economically weak patients.

Post-treatment effectiveness

Patients were in the treatment of formoterol and budesonide for a year show good response in controlling the asthma symptoms and improved the quality of life (Ferguson *et al.*, 2018). Overall, 142 (98%) patients were experienced good and satisfactory responses to the treatment. The patient's response after a year of treatment is shown in Figure 7.

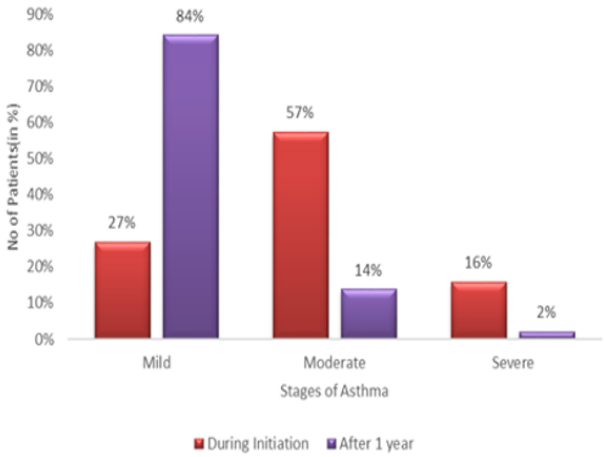

Figure 2: Treatment during Initiation and Follow-up

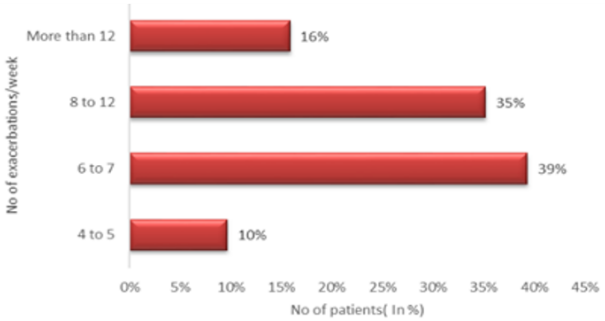

Figure 3: Exacerbation during the formoterol and budesonide initiation

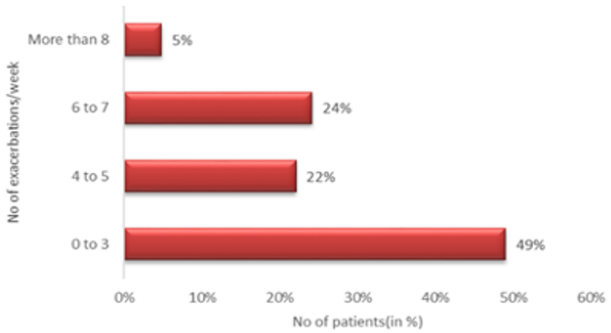

Figure 4: After 1-year treatment with formoterol and budesonide treatment

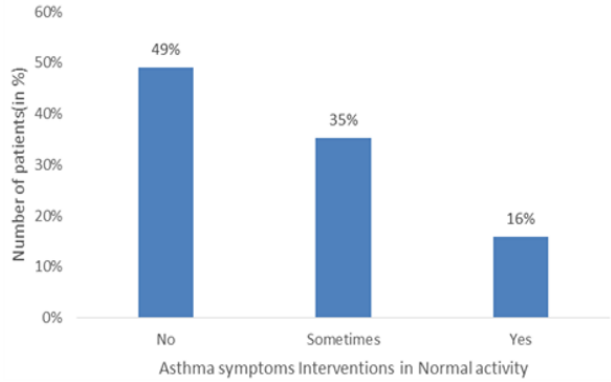

Figure 5: Intervention of asthma in normal activity

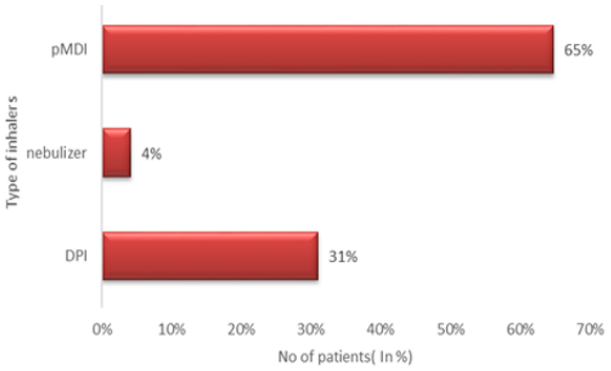

Figure 6: Types of inhalers used

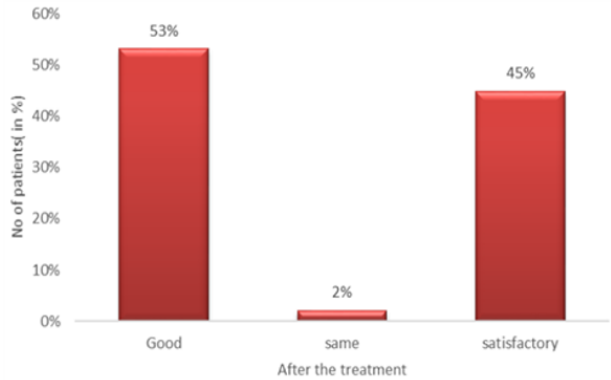

Figure 7: Patient response to the treatment

DISCUSSION

This Multicentric, Non-comparative, randomized questionnaire survey study conducted in the northern parts of Tamilnadu were demonstrated that the formoterol and budesonide combination shows that effective asthma symptoms management in the asthmatics. The patients had enrolled in this study were from both Polluted and Non- polluted regions and has been residing in the different types of city locations (Reddel *et al.*, 2017).

After 1 year follow-up with the patients, the Majority of the moderate and severe asthmatics were shifted to mild stages of asthma (O'Byrne *et al.*, 2017). The shifted patients have regularly used the medication without missing a dose. This formoterol and budesonide combination helps patients to control the asthma symptoms and prevents from worsening of the asthma inflammation in day to day life. The number of exacerbation/ week was minimized gradually and improved their quality of life (Dhandayuthapani and Shivashankar, 2020).

Generally, exacerbation during night time affects the sleep and quality of life. In this study, patients have experienced the night time awakenings and gradually reduced compared to the time of Initiation (Byrne *et al.*, 2018). In asthmatics, the symptoms were found to be intervened with the normal activity were less and during the symptoms, they effectively used the reliever medications (Beasley *et al.*, 2016).

Physicians choose the type of inhalers based on the patient's adaptability to the techniques, drug deposition in the site, and cost-effectiveness (Mckeever *et al.*, 2018). Both the reliever and controller drugs have been available in the DPI and pMDI inhalers. pMDI was the most effective in drug deposition and quite convenient for the patients (Nunes *et al.*, 2017). Some patients felt difficult in adapting the inhaler handling techniques due to their age factor and missing hand and mouth coordination (Chen *et al.*, 2019). Certainly, the cost of the inhalers was concerned for economically weak patients. Due to the reasons, they were irregular in taking the medications and delaying in the repurchase of the inhalers (Wang *et al.*, 2018).

In this study, commonly all the patients in the mild to moderate stages of asthma were felt the treatment was good and satisfactory (Du *et al.*, 2017). Also, they have followed the proper techniques, regular usage of the drug without missing the dose, effective usage of reliever drugs during the symptoms.

CONCLUSIONS

In this Multicentric, non-comparative, randomized questionnaire study in asthmatics who were in the treatment of formoterol and budesonide combination in the northern districts of Tamilnadu have effectively controlled the asthmatic symptoms and improved the quality of life in asthmatics. Dry powder inhalers and pressurized metered-dose inhalers were extensively used by all age groups of asthmatics. In some cases like geriatric/ children, asthmatics felt slightly difficult in using the pressurized metered-dose inhalers. Spacers were used in those patients and ensured the drug deposition in the pharmacological site. Governments must take several actions to provide free of cost inhalers or cost-effective prices which will help more asthmatics to adhere to the treatment and will improve their quality of life.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

REFERENCES

Bateman, E. D., Reddel, H. K., O'Byrne, P. M., Barnes, P. J., Zhong, N., Keen, C., Jorup, C., Lamarca, R., Siwek-Posluszna, A., FitzGerald, J. M. 2018. As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma. *New England Journal of Medicine*, 378(20):1877–1887.

Beasley, R., Holliday, M., Reddel, H. K., Braithwaite, I., Ebmeier, S., Hancox, R. J., Harrison, T., Houghton, C., Oldfield, K., Papi, A., Pavord, I. D., Williams, M., Weatherall, M. 2019. Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma. *New England Journal of Medicine*, 380(21):2020–2030.

Beasley, R., Pavord, I., Papi, A., Reddel, H. K., Harrison, T., Marks, G. B., Hancox, R. J., Weatherall, M. 2016. Description of a randomised controlled trial of inhaled corticosteroid/fast-onset LABA reliever therapy in mild asthma. *European Respiratory Journal*, 47(3):981–984.

Byrne, P. M. O., Fitzgerald, J. M., Bateman, E. D. 2018. Inhaled combined budesonide - formoterol as needed in mild asthma. *N Engl J Med*, 378(20):1865–1876.

Chen, Q., Hu, C., Yu, H., Shen, K., Assam, P. N., Gillen, M., Liu, Y., Dorinsky, P. 2019. Pharmacokinetics and Tolerability of Budesonide/Glycopyrronium/Formoterol Fumarate Dihydrate and Glycopyrronium/Formoterol Fumarate Dihydrate Metered Dose Inhalers in Healthy Chinese Adults: A Randomized, Double-blind, Parallel-group Study. *Clinical Therapeutics*, 41(5):897–909.e1.

Dhandayuthapani, M., Shivashankar, M. 2020. Asthmatics Treatment Updation and Compliance in the Asthma Management in Northern Districts of Tamilnadu. *International Journal of Research in Pharmaceutical Sciences*, 11(3):4990–4997.

Du, W., Zhou, L., Ni, Y., Yu, Y., Wu, F., Sh, G. 2017. Inhaled corticosteroids improve lung function, airway hyperresponsiveness and airway inflammation but not symptom control in patients with mild intermittent asthma: A meta-analysis. *Exp. Ther. Med*, 14(2):1594–1608.

Ekberg-Jansson, A., Svenningsson, I., Rågdell, P., Stratelis, G., Telg, G., Thuresson, M., Nilsson, F. 2015. Budesonide inhaler device switch patterns in an asthma population in Swedish clinical practice (ASSURE). *International Journal of Clinical Practice*, 69(10):1171–1178.

Ferguson, G. T., Papi, A., Anzueto, A., Kerwin, E. M., Cappelletti, C., Duncan, E. A., Nyberg, J., Dorinsky, P. 2018. Budesonide/formoterol MDI with co-suspension delivery technology in COPD: the TELOS study. *European Respiratory Journal*, 52(3):1801334–1801334.

Galffy, G., Mezei, G., Nemeth, G., Tamasi, L., Muller, V., Selroos, O. 2013. Inhaler competence and patient satisfaction with Easyhaler: results of two real-life multicentre studies in asthma and COPD. *Drugs RD*, 13(3):215–237.

Haikarainen, J., Selroos, O., Löytänä, T., Metsärinne, S., Happonen, A., Rytilä, P. 2017. Budesonide/Formoterol Easyhaler®: Performance Under Simulated Real-Life Conditions. *Pulmonary Therapy*, 3(1):125–138.

Hantulik, P., Wittig, K., Henschel, Y., Ochse, J., Vahteristo, M., Rytila, P. 2015. Usage and usability of one dry powder inhaler compared to other inhalers at therapy start: an open, non-interventional observational study in Poland and Germany. *Pneumonologia i Alergologia Polska*, 83(5):365–377.

Husereau, D., Drummond, M., Petrou, S., Carswell, C., Moher, D., Greenberg, D., Augustovski, F., Briggs,

A. H., Mauskopf, J., Loder, E. 2013. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *BMJ*, 346(mar25 1):f1049–f1049.

Lähelmä, S., Vahteristo, M., Metev, H., Taseva, M., Stamatova, N., Bartha, A., Schlezák, J., Sairanen, U. 2016. Equivalent bronchodilation with budesonide/formoterol combination via Easyhaler and Turbuhaler in patients with asthma. *Respiratory Medicine*, 120:31–35.

Malmberg, L. P., Everard, M. L., Haikarainen, J., Lähelmä, S. 2014. Evaluation of In Vitro and In Vivo Flow Rate Dependency of Budesonide/Formoterol Easyhaler®. *Journal of Aerosol Medicine and Pulmonary Drug Delivery*, 27(5):329–340.

Mckeever, T., Mortimer, K., Wilson, A. 2018. Quadrupling the inhaled glucocorticoid dose to abort asthma exacerbations. *N Engl J Med*, 378(10):902–912.

Nunes, C., Pereira, A. M., Morais-Almeida, M. 2017. Asthma costs and social impact. *Asthma Research and Practice*, 3(1):3–3.

O'Byrne, P. M., Jenkins, C., Bateman, E. D. 2017. The paradoxes of asthma management: time for a new approach? *European Respiratory Journal*, 50(3):1701103–1701103.

Pirożyński, M., Hantulik, P., Almgren-Rachtan, A., Chudek, J. 2017. Evaluation of the Efficiency of Single-Inhaler Combination Therapy with Budesonide/Formoterol Fumarate in Patients with Bronchial Asthma in Daily Clinical Practice. *Advances in Therapy*, 34(12):2648–2660.

Price, D., Fletcher, M., van der Molen, T. 2014. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *Primary Care Respiratory Medicine*, 24(1):14009–14009.

Reddel, H. K., Busse, W. W., Pedersen, S., Tan, W. C., Chen, Y.-Z., Jorup, C., Lythgoe, D., O'Byrne, P. M. 2017. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *The Lancet*, 389(10065):157–166.

Slejko, J. F., Ghushchyan, V. H., Sucher, B., Globe, D. R., Lin, S.-L., Globe, G., Sullivan, P. W. 2014. Asthma control in the United States, 2008-2010: Indicators of poor asthma control. *Journal of Allergy and Clinical Immunology*, 133(6):1579–1587.

Stallberg, B., Lisspers, K., Hasselgren, M., Janson, C., Johansson, G., Svardsudd, K. 2009. Asthma control in primary care in Sweden: a comparison between 2001 and 2005. *Prim Care Respir journal*, 18(4):279–286.

Subramanian, N., Kumaresan, C. 2012. Dry powder inhaler- formulation aspects. *Pharma times*, 44:14–18.

Tamasi, L., Szilasi, M., Galffy, G. 2018. Clinical Effectiveness of budesonide/formoterol fumarate Easyhaler for patients with poorly controlled obstructive airway disease: a real-world study of patient-reported outcomes. *Adv Ther*, 35(8):1140–52.

Virchow, J. C., Crompton, G. K., Negro, R. D., Pedersen, S., Magnan, A., Seidenberg, J., Barnes, P. J. 2008. Importance of inhaler devices in the management of airway disease. *Respiratory Medicine*, 102(1):10–19.

Wang, X., Li, Q., Liu, R., He, J., Wu, D., Wang, Y., Zhang, J. 2018. ADRB2 Arg16Gly polymorphism and pulmonary function response of inhaled corticosteroids plus long-acting beta-agonists for Asthma treatment: A Systematic review and meta-analysis. *Can. Respir. J*, pages 5712805–5712805.