The effects of using Plastic Dry Salt Inhaler (DSI) on adults with asthma and COPD

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Introduction

Asthma and COPD – general consideration
Asthma is a chronic inflammatory disease of the airways which causes recurrent episodes of wheezing, chest tightness and coughing. The inflammation which occurs in asthma is caused by many different cells and cellular elements including eosinophils, mast cells, T lymphocytes, macrophages, neutrophils, and epithelial cells. This inflammation is directly correlated to airway hyperresponsivenes. Control of airway inflammation will cause a decrease in hyper-responsiveness.
The four main components of airflow obstruction in asthma are:
Acute Broncho-constriction (allergen-induced broncho-constriction) results from IgE dependant mediator release from mast cells. Other causes of broncho-constriction include aspirin or NSAIDs, exercise, cold air, irritants or stress), **Airway Edema** (increased micro vascular permeability due to the release of inflammatory mediators causes increased thickening and swelling of the airway), **Chronic Mucus Plug Formation (i**n severe asthma, mucus secretion and the formation of mucus plugs can cause persistent airflow limitation) and **Airway Remodeling** (airflow limitation in some patients with asthma may be only partially reversible. This may be related to structural changes in the airway matrix which accompany longstanding airway inflammation)
Occurrence of Asthma: when asthma begins in childhood it is frequently associated with atopy, which is the genetic susceptibility to produce IgE to common environmental allergens. Mast cells and other airway cells are sensitized and become activated when they encounter specific antigens. In children with wheezing during a viral infection, allergy or a family history of allergy is the strongest associated factor with recurrent asthma throughout childhood.
Although asthma occurs most commonly in children, it can also occur later in life. Adult-onset asthma can be associated with atopy. However, there can be also other causes of asthma. Some adults develop asthma without IgE antibodies to allergens. These adults often have coexisting sinusitis, nasal polyps and aspirin or NSAID allergies. Occupational exposures to materials like plastic resins, biological enzymes, animal products and wood dusts can also cause asthma.
The physician usually looks for a history of wheezing, recurrent cough, particularly worse at night, recurrent shortness of breath, or recurrent chest tightness. These symptoms may occur or worsen with exercise, viral infection, animals, smoke, pollen, mold, strong emotional expression, menses, and airborne chemicals or dust. Physical exam should include a lung exam for wheezing, examination for nasal polyps or allergic rhinitis and skin exam for atopic dermatitis.

COPD is a disease that causes an irreversible limitation of the air flow, usually progressive, and is associated with an abnormal inflammatory response of the lungs to inhaled noxious particles or gases.
Pathological changes in chronic obstructive pulmonary disease (COPD) occur in the large (central) airways, the small (peripheral) bronchioles, and the lung parenchyma. The pathogenic mechanisms are not clear but most likely involve diverse mechanisms. The increased number of activated

polymorphonuclear leukocytes and macrophages release elastases in a manner that cannot be counteracted effectively by antiproteases, resulting in lung destruction. The primary offender has been human leukocyte elastase, with a possible synergistic role suggested for proteinase 3 and macrophage-derived matrix proteinases, cysteine proteinases, and a plasminogen activator. Additionally, increased oxidative stress caused by free radicals in cigarette smoke, the oxidants released by phagocytes, and polymorph nuclear leukocytes all may lead to apoptosis or necrosis of exposed cells. Accelerated aging and autoimmune mechanisms have also been proposed as having roles in the pathogenesis of COPD.
A clinical diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease. The diagnosis should be confirmed by spirometry. The presence of a post bronchodilator FEV1/FVC <0.70 and FEV1 <80% predicted confirms the presence of airflow limitation that is not fully reversible.
GOLD 2006 COPD staging:
Stage I: Mild COPD - Characterized by mild airflow limitation (FEV1/FVC < 0.70; FEV1 ≥ 80% predicted). Symptoms of chronic cough and sputum production may be present, but not always. At this stage, the individual is usually unaware that his or her lung function is abnormal.
Stage II: Moderate COPD - Characterized by worsening airflow limitation (FEV1/FVC < 0.70; 50% ≤ FEV1 < 80% predicted), with shortness of breath typically developing on exertion and cough and sputum production sometimes also present. This is the stage at which patients typically seek medical attention because of chronic respiratory symptoms or an exacerbation of their disease.
Stage III: Severe COPD - Characterized by further worsening of airflow limitation (FEV1/FVC < 0.70; 30% ≤ FEV1 < 50% predicted), greater shortness of breath, reduced exercise capacity, fatigue, and repeated exacerbations that almost always have an impact on patients' quality of life.
Stage IV: Very Severe COPD - Characterized by severe airflow limitation (FEV1/FVC < 0.70; FEV1 < 30% predicted *or* FEV1 < 50% predicted plus the presence of chronic respiratory failure). Respiratory failure is defined as an arterial partial pressure of O2 (PaO2) less than 8.0 kPa (60 mm Hg), with or without arterial partial pressure of CO2 (PaCO2) greater than 6.7 kPa (50 mm Hg) while breathing air at sea level. Respiratory failure may also lead to effects on the heart such as cor pulmonale (right heart failure). Clinical signs of cor pulmonale include elevation of the jugular venous pressure and pitting ankle edema. Patients may have *Stage IV: Very Severe COPD* even if the FEV1 is > 30% predicted, whenever these complications are present. At this stage, quality of life is very appreciably impaired and exacerba-tions may be life threatening. (*Excerpt from GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (2006)*)

Speleotherapy and halotherapy are relatively old therapeutic methods sometimes recommended for chronic obstructive disorders. However there is not enough available evidence to support the use of these methods.
Treatment in natural salt cave (speleotherapy) has been known for a long time. The efficacy of speleotherapy is associated with the unique cave microclimate. The natural dry sodium chloride aerosol is the major curative factor of the cave microclimate. It is formed by the convective diffusion from salt walls. Other factors such as comfortable temperature and humidity regime, the hypobacterial and allergen-free air environment saturated with aero ions enhance the therapeutic effect. The known mechanisms of action of Halotherapy are: mucolytic, antibacteriologic, anti-inflammatory, immunomodulating, hyposensibilizing.
The purpose of our study is to prove the efficacy of the Dry Salt Inhaler on adults diagnosed with asthma (both mild and severe) and COPD regarding the quality of life and the improvements of spirometry values

Study Type: Double-blind, randomized, bicentric, single-crossed, pilot and open.

Primary objective
Our aim was to evaluate the effects of inhaled dry salt in stage 2 and 3 COPD patients and also patients with asthma, in terms of ventilatory parameters – based on spirometry and the quality of life – based on our own design questionnaire.

Secondary Objective
We also aimed to achieve long-term improvements of life quality and decreased incidence of respiratory infections – mainly on patients that have persistent symptoms of asthma and COPD.

Material and methods
The study was conducted on a patient pool of 30 individuals selected as following:
Inclusion criteria:
A subject was considered eligible for inclusion if all of the following applied:

- diagnosed with stage 2 or 3 COPD, more than 1 year in treatment
- diagnosed with asthma (mild, both persistent or intermittent, moderate or severe), more than 1 year in treatment.
- was able to understand and endorsed the written informed consent
- presented no other serious respiratory pathology (such as tuberculosis, lung cancer, pulmonary fibrosis, etc)

Exclusion criteria:

- had a current cardio-vascular diagnosis such as (arterial hypertension, heart failure, arrhythmias)
- had a life threatening diagnosis or one that could interfere with study procedures
- being pregnant or having the intention to remain pregnant
- being under 18-years old (as there is no data to sustain safety in child administration)
- sodium chloride intolerance
- psychiatric / severe neurologic condition
- patient discontinuation due to abandonment

The Study Design

Sample size: 21 patients concluded until abstract submission, 38 until present time.
We designed this study to be a double-blind, randomized trial, single crossed.
The initial pool of patients was divided in 2 arms of population:

1) The *PII* group was the group that initially took placebo for the first time and then continued to DSI inhaler for the next 2 periods
2) The *IPI* group was the group that took DSI inhaler device for the first time and at the second visit (V_1) they were crossed with the ones in *PII* group (figure 1).

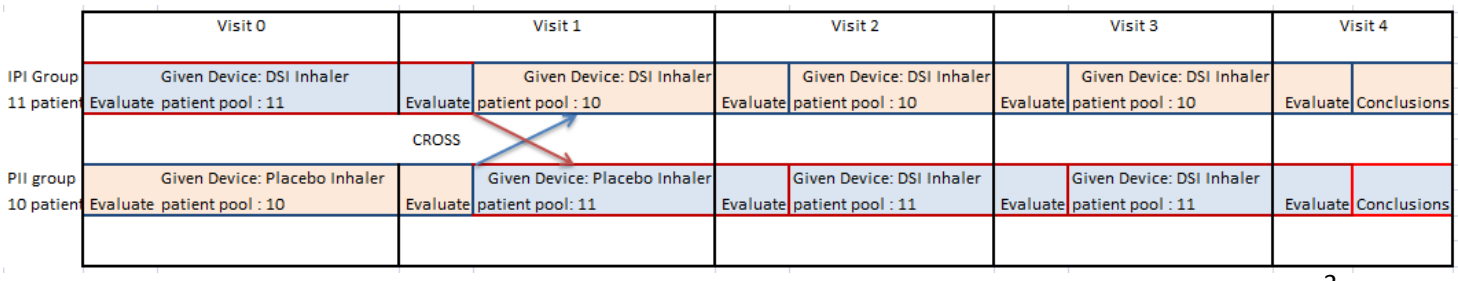

Figure 1 - Study Design

The randomization scheme was generated by using the Web site Randomization.com http://www.randomization.com. The scheme we applied was:

IPI_01: DSI Inhaler1
PII_01 DSI Inhaler2
PII_02 DSI Inhaler2
PII_03 DSI Inhaler2
PII_04 DSI Inhaler2
IPI_02 DSI Inhaler1
PII_05 DSI Inhaler2
IPI_03 DSI Inhaler1
IPI_04 DSI Inhaler1
PII_06 DSI Inhaler2
IPI_05 DSI Inhaler1

IPI_06 DSI Inhaler1
IPI_07 DSI Inhaler1
IPI_08 DSI Inhaler1
IPI_09 DSI Inhaler1
PII_07 DSI Inhaler2
PII_08 DSI Inhaler2
PII_09 DSI Inhaler2
PII_10 DSI Inhaler2
IPI_10 DSI Inhaler1
IPI_11 DSI Inhaler1

Figure 2 - The randomization scheme

IPI= Inhaler-Placebo-Inhaler
PII= Placebo-Inhaler-inhaler

As shown in the scheme, the two populations were all-together randomized, IPI group containing 11 patients and PII group containing 10 patients. This randomization scheme was only applied once, at visit V_0, and DSI Inhaler1 was the active-substance inhaler and DSI inhaler 2 was the placebo inhaler.

The treatment period was 6 weeks of standard asthma / COPD therapy according to GOLD 2005 guidelines, and one 15-20 minutes inhaling session, preferably during the evening, using the DSI device. For evaluation of patients we used 2 methods: **a quantitative evaluation** based on spirometry and pulmonary function report printed after the spirometry **and a qualitative evaluation** based on a life quality-improvement questionnaire that we design for this study (APPENDIX 3) – questionnaire meant to evaluate how patient felt while on treatment with DSI device in terms of ease of breath, relief of chronical symptoms, improvement of overall patient's functionality.
Spirometry testing:

- We used a certified and frequently calibrated spyrometer.
- Maximal patient effort was required.
- record the FVC, FEV1, and FEV1/FVC ratio

Methodology

- the patient effort should go on until a volume plateau is reached
- the recorded values should be the largest of three technical acceptable curves
- in order to be acceptable the recorded data should have a variation of less than 5% or 100 ml (whichever greater)
- the FEV1/FVC ratio will be calculated using the curve which has the largest FVC+FEV1 sum.

The patients were called for investigations on four clinical visits as following:
The first visit, $\mathbf{V_0}$ was the inclusion-visit when the patient was presented the study's protocol, the written consent and also was explained all the procedures of this clinical trial (APPENDIX 1).
During the V_0 the patient was reviewed and examined, if he haven't have done a chest x-ray recently, we instructed he would have one before starting the trial. We also checked the heart frequency, blood pressure and oxygen saturation and noted these values as initial values in the patient evolution page (**APPENDIX 2**). The patient was explored using a digital spirometer previously checked and calibrated

(calibration date: July 29Th, 2009), and the patient's pulmonary function report was also consented in the patient's evolution page.
At this point, if the patient was found suitable accordingly to inclusion criterions, he received a DSI inhaler device and was instructed to use it each day, in the evening, while sited, in a relaxed atmosphere (watching television or reading a book). She/he was instructed to inhale normally through the DSI device placed in the mouth and then exhale normally through the nose, for about 20 minutes. We also instructed patients that any unpleasant event should occur, even if it is about other pathology than the pulmonary condition she/he is aware of, they should stop the inhaling procedure immediately and contact the doctor as soon as possible.

The next visit, V_1 was made approximately 15 days after V_0 and the patient was scheduled for an interview of approximately 15 minutes.
During the interview, the patient was asked to rate each answer from the Quality of Life Improvement questionnaire (APPENDIX 3) with a number from 0 to 6, 0 meaning no symptom/never/no at all – which we rated as high improvement and 6 meaning very severe/very much restriction – which we rated as no improvement/worsen evolution.
After the interview the patients were examined and had their results of spirometry and blood pressure, cardiac frequency, oxygen saturation recorded in the patient's evolution page.
At this point, each pool of patients had already used an inhaler device, DSI_1 or DSI_2, so V_1 was the point where we did the cross-over, switching the ones using DSI_1 to DSI_2 and vice-versa.

V_2 and V_3 were visits alike, the patients were scheduled for their 15 minutes interview, having the Life Quality Improvement Questionnaire filled and being examined and investigated, accordingly to the procedures. During V_2 and V_3 we questioned the patients for eventual side-effects or abnormal effects presented during the study and we also checked that each patient has its basic medication properly administered. We also instructed the patients that the inhaler is an additional device and may under no circumstance replace any other inhaler she/he has to use in order to administer basic medication for asthma or COPD.
At the end of V_3 we automatically discontinued the patient and have him evaluated on a normal basis by his doctor. V_4 was a formal visit to discuss with the patients about their overall conclusions and the impact of DSI usage on their disease and their quality of life.

Adverse events

Adverse events are defined as any untoward medical occurrence in a patient or clinical trial subject receiving a pharmaceutical product and which does not necessarily have a causal relationship with the treatment.
Serious adverse events are defined as any untoward medical occurrence that results in death or is life threatening, hospitalization or prolongation of hospitalization, significant or persistent disability, congenital anomalies.
Any adverse events that would have occurred had been evaluated by us, the investigators, in order to fit one of the three categories:

- mild: no limitations of usual activities
- moderate: some limitation of usual activities
- severe: inability to carry out usual activities

We also evaluated the likelihood to causation by the study procedure:

- unrelated – AE clearly not related to investigational agent
- unlikely - AE doubtfully related to investigational agent

- possible - AE may be related to investigational agent
- probable - AE likely related to investigational agent
- definite - AE clearly related to investigational agent

Any adverse event had been assessed and reported by the investigator using the provided forms (APPENDIX 4).
The site investigator ensured adequate clinical management of any AE until complete resolution to the best of his medical knowledge.
For this particular study a COPD or an asthma exacerbation will not be considered an adverse event unless it falls under the definition of a serious adverse event. However, no patient presented any exacerbation of asthma or COPD during the study.
As a particularity of the study there is a theoretical posibility of non-medical events linked to equipment malfunctions or liability issues – such as inhaler device stuffed, deteriorated, damaged by the patient, broken or lost.
Previous data published on various articles regarding halotherapy and speleotherapy have shown that using a device that contains sodium chloride or breathing in an environment with sodium chloride particles, may induce a sore throat sensation – this low intensity symptom usually resolves spontaneously or after temporarily discontinuation of use. Patients may also note some quantity and quality changes in sputum production (increased volume) – this should probably not be reported as an adverse event unless it is associated with other symptoms – the final decision belongs to the investigator. However an increased volume of sputum expectorated usually is associated with the sensation of relief – which is the aim of our study.

Ethical and legal aspects

The study will be conducted in conformity with the principles of the declaration of Helsinki and its amendments and local rules and regulations.
All study documentation was submitted by the investigator to an independent Ethics Committee; study procedures were conducted only after receiving approval.
Each potential study subject was given to read and sign an informed consent form prior to any study procedure. The informed consent form was provided in patient's native language – Romanian. For any explanation that was necessary, the investigator provided assistance throughout the study.
The informed consent form that was used can be found in Appendix 1.
In order to be recruited patients had a significant medical history of asthma or COPD documented by previous medical records.
All the patients must had a history of adequate standard COPD treatment for at least 2 months prior to inclusion. A quick remember on COPD staging and standard treatment according to GOLD 2006 was provided in the introduction part.
Although the DSI device only generates minute quantities of sodium chloride, it is prudent to assume that patients with co morbidities susceptible to be aggravated by Na intake should be excluded.
A recent COPD exacerbation (less than one month prior to V_0) and COPD treatment change are listed as exclusion criteria because of the effects they may entail on baseline parameters.
Technical data concerning DSI devices were provided and due to patent protection will not be listed.

Investigational product: DSI- **Dry Salt Inhaler** device made by INHALO DSI Hungary Kft., Hungary The probable action mechanism is that the osmotic effect of drawing fluid towards airway lumen determines a decrease of inflammatory edema and modifying the rheology of mucus promoting ciliary clearance.

The original **Dry-Salt-Inhaler**™ device is made of bio-compatible medical grade plastic (PC) and filled with rock salt crystals in natural form gathered from Transylvanian Praid salt mine.This 100% natural agent has as main component Sodium Chloride and Magnesium, Calcium in different forms.
The air circulates between the two porcelain filters and salt crystals, forming aerosolized micro particles of different sizes.

Results

Our results have shown an overall improvement of the quality of life, expressed both orally by the patients and observed after the gathering of data from the forms. Both asthma and COPD patients have spoken of a "feeling of breath relief" after only one day of use, and also they mentioned the improvement of their functionality. All the patients mentioned the increase production of expectorated sputum after 2 – 3 days of use and, differentiating from placebo groups, the ones using active-substance DSI did felt better overall at the end of the in-between-visits period.

We calculated the mean values of FVC, PEF and FEV1 as shown in the following charts:

Descriptives

	V4			Statistic	Std. Error
FVC-0	IPI		Mean	89.1429%	8.63666%
		95% Confidence Interval for Mean	Lower Bound	68.0097%	
			Upper Bound	110.2760%	
			5% Trimmed Mean	87.9921%	
			Median	79.0000%	
			Variance	522.143	
			Std. Deviation	22.85045%	
			Minimum	68.00%	
			Maximum	131.00%	
			Range	63.00%	
			Interquartile Range	38.00%	
			Skewness	1.160	.794
			Kurtosis	.688	1.587
	PII		Mean	81.4286%	3.89051%
		95% Confidence Interval for Mean	Lower Bound	71.9088%	
			Upper Bound	90.9483%	
			5% Trimmed Mean	81.1984%	
			Median	80.0000%	
			Variance	105.952	
			Std. Deviation	10.29332%	
			Minimum	67.00%	
			Maximum	100.00%	
			Range	33.00%	
			Interquartile Range	12.00%	
			Skewness	.660	.794
			Kurtosis	1.492	1.587
FVC-1	IPI		Mean	93.8571%	7.35957%

Descriptives

	V4			Statistic	Std. Error
FVC-1	IPI	95% Confidence Interval for Mean	Lower Bound	75.8489%	
			Upper Bound	111.8654%	
			5% Trimmed Mean	92.3968%	
			Median	86.0000%	
			Variance	379.143	
			Std. Deviation	19.47159%	
			Minimum	79.00%	
			Maximum	135.00%	
			Range	56.00%	
			Interquartile Range	18.00%	
			Skewness	1.996	.794
			Kurtosis	4.187	1.587
	PII		Mean	76.1429%	4.65694%
		95% Confidence Interval for Mean	Lower Bound	64.7477%	
			Upper Bound	87.5380%	
			5% Trimmed Mean	75.7698%	
			Median	78.0000%	
			Variance	151.810	
			Std. Deviation	12.32110%	
			Minimum	61.00%	
			Maximum	98.00%	
			Range	37.00%	
			Interquartile Range	16.00%	
			Skewness	.749	.794
			Kurtosis	.562	1.587
FVC-2	IPI		Mean	79.5714%	7.47331%
		95% Confidence Interval for Mean	Lower Bound	61.2849%	
			Upper Bound	97.8580%	

Descriptives

	V4			Statistic	Std. Error
FVC-2	IPI		5% Trimmed Mean	79.2480%	
			Median	82.0000%	
			Variance	390.952	
			Std. Deviation	19.77252%	
			Minimum	50.00%	
			Maximum	115.00%	
			Range	65.00%	
			Interquartile Range	17.00%	
			Skewness	.489	.794
			Kurtosis	1.850	1.587
	PII		Mean	86.0000%	5.27347%
		95% Confidence Interval for Mean	Lower Bound	73.0963%	
			Upper Bound	98.9037%	
			5% Trimmed Mean	85.8889%	
			Median	93.0000%	
			Variance	194.667	
			Std. Deviation	13.95230%	
			Minimum	65.00%	
			Maximum	109.00%	
			Range	44.00%	
			Interquartile Range	18.00%	
			Skewness	.288	.794
			Kurtosis	.620	1.587
FVC-3	IPI		Mean	93.4286%	6.60035%
		95% Confidence Interval for Mean	Lower Bound	77.2781%	
			Upper Bound	109.5790%	
			5% Trimmed Mean	92.8095%	
			Median	94.0000%	
			Variance	304.952	
			Std. Deviation	17.46289%	
			Minimum	75.00%	
			Maximum	123.00%	
			Range	48.00%	
			Interquartile Range	26.00%	
			Skewness	.637	.794
			Kurtosis	-.403	1.587
	PII		Mean	78.7143%	2.27527%
		95% Confidence Interval for Mean	Lower Bound	73.1469%	
			Upper Bound	84.2817%	

Regarding the evolution of FVC parameter, as shown in the following graphics we found improvements within both populations (IPI and PII). Although all the patients mentioned improvements in breathing quality, our data showed that the population who received placebo at V_0 and then continued to active-substance inhaler showed a less-improvement than the ones that began with the DSI active-substance inhaler and then took the placebo-break.

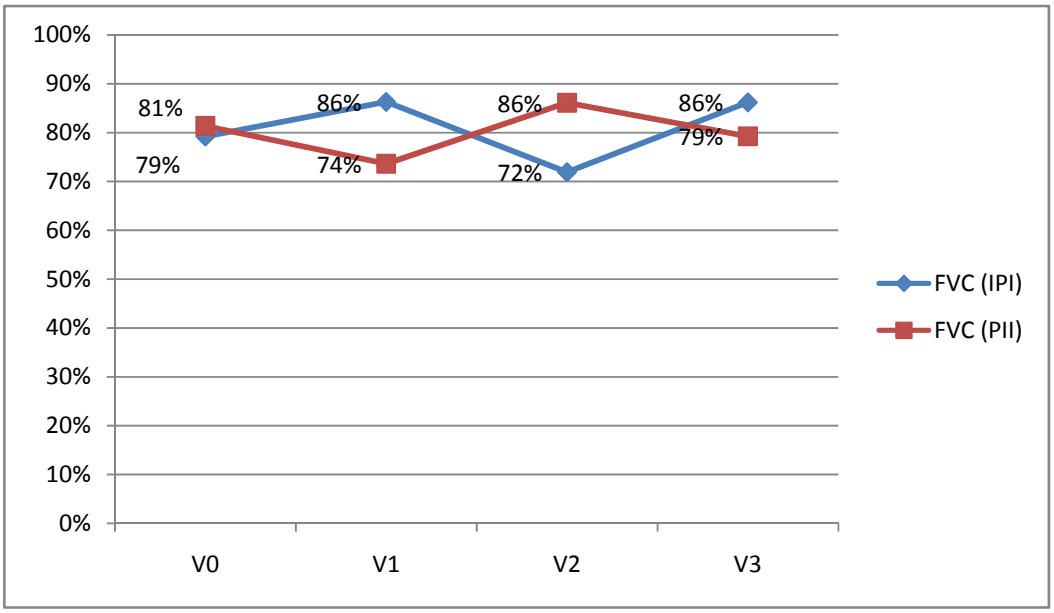

Figure 3 - Evolution of FVC

As shown in Figure 3, the FVC is improving with about 9% from the placebo use to active-substance use, proving the efficacy of the DSI device therapy and, correlating these results with the increased sputum expectoration, we can conclude that, in terms of air quantity, the DSI device increases the flow of air after use.

During the investigation of FEV1 parameter we have found that both populations (PII and IPI) improved their breathing parameter, as shown in figure 4, the best improvements being shown versus placebo periods both in IPI and PII populations.

PEF parameter also showed improvements (Figure 5 - The evolution of PEF) mostly on the population that started with the active-substance DSI device, fact that lead us further to the conclusion that, being used constantly and continually – without interruptions, for a long period of time, the DSI device may consistently contribute to improvements in overall functionality of patients. Since PEF is a high indicator of functionality from the larger airways, once again we can conclude that using the DSI device, additionally to sputum expectoration, the bronchial lumen is more relieved.

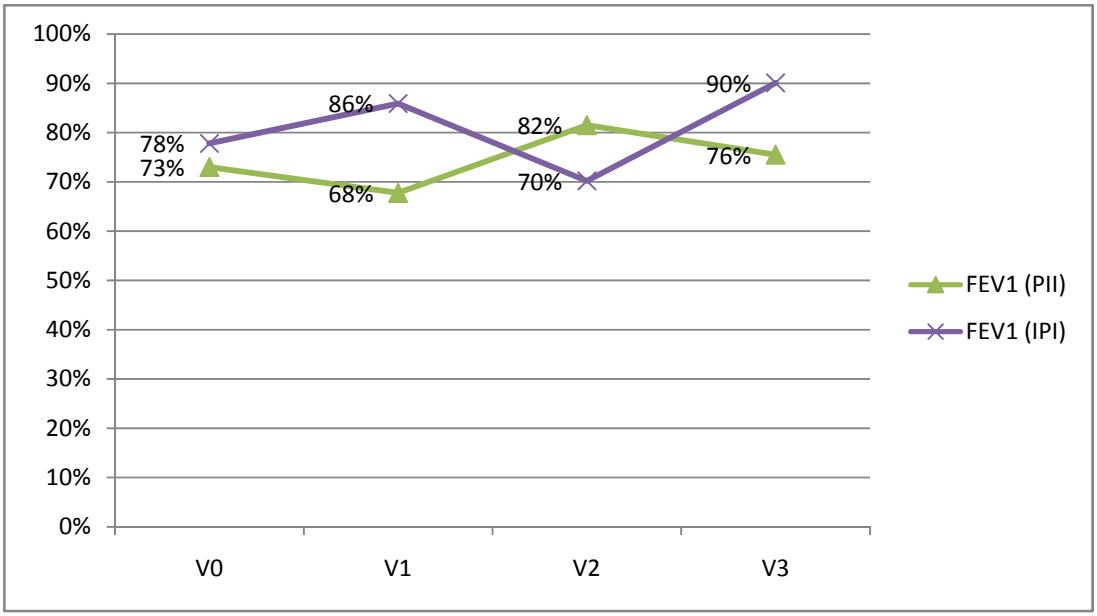

Figure 4 - The evolution of FEV1

V0= first patient visit schedule (considered Placebo) and V4= last visit

IPI= Inhaler-Placebo-Inhaler (At visit V1 patient received Inhaler, V2 received placebo, V3 received inhaler)
PII= Placebo-Inhaler-inhaler (At visit V1 patient received Placebo, V2 received Inhaler, V3 received Inhaler)

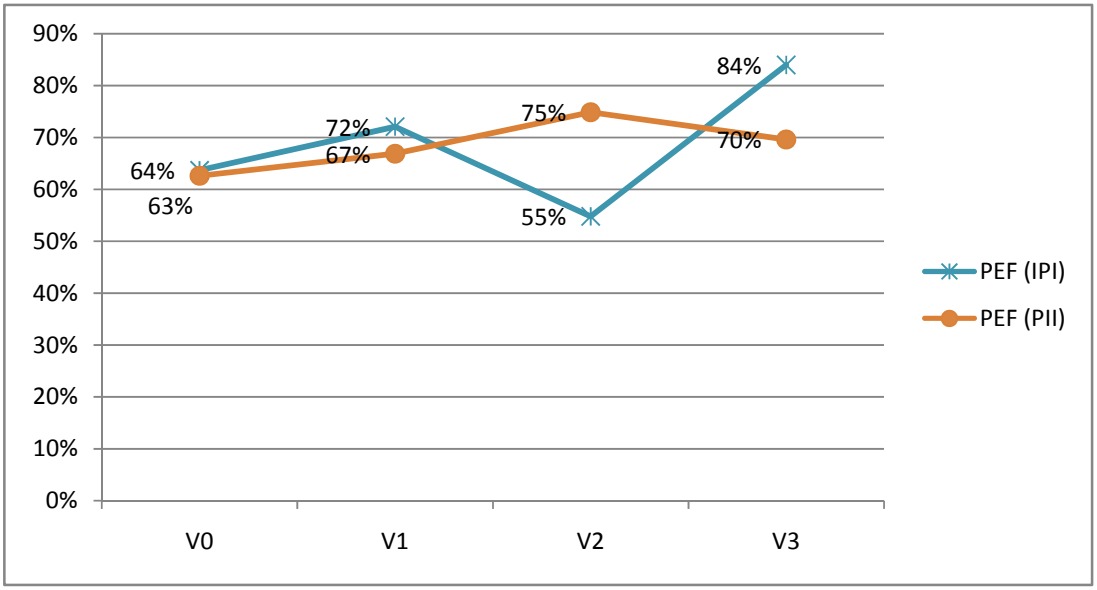

Figure 5 - The evolution of PEF

Since the ventilatory parameters of a patient with asthma or COPD cannot be spectacularly boost even with standard brochodilatators in such a short time, the differences between the average values obtained in FVC, FEV1 and PEF between V_0 and V_4 are clear signs of improvement and the differences between the two populations show that continuously usage of the DSI is better and indicated.

In terms of quality of life, our results showed definite improvements and the consented values come to strengthen the patients' stories about the sensation of relief and better breathing. The overall unanimous perception was that since they started to use the DSI device, the quality of breathing and their functionality improved as well as the relief of the resident symptoms. Analyzing this data we were surprised to notice that the two populations, both IPI and PII, had different initial scores – after the first use, since some of them used the Placebo-device and the others were using the active-substance DSI device.

The final average scores and the differences between them are shown in the following figure (lower values are better).

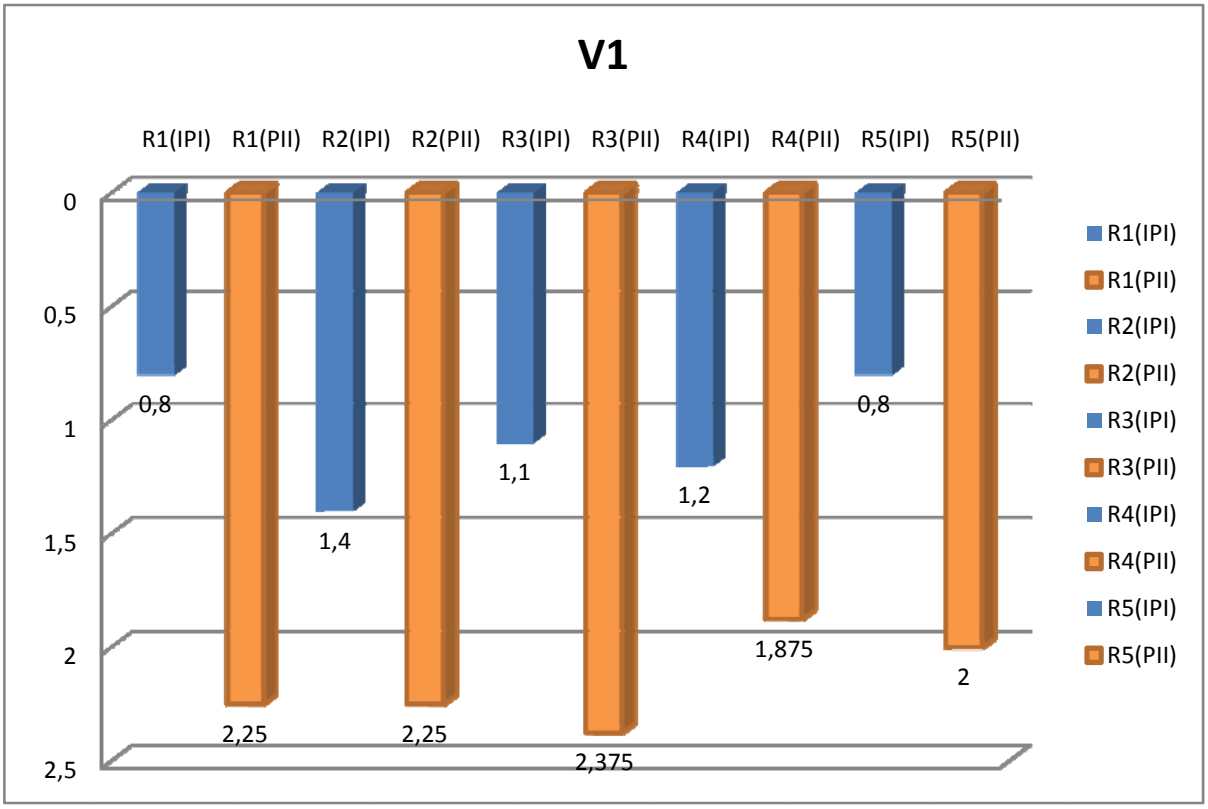

Figure 6 - The differences between the two populations answering the questions at V1 (visit 1)

This figure shows the clear differences in average scores from the two populations, registered from the entire questions (R1 – R5) .Conclusive example is at question 1 (answer R1):

The question was "During the last 7 days how often did you wake up in the night because of the symptoms of asthma/COPD?" 20% of the IPI patients responded "0" – meaning "Never" and 80% of the

patients answered “1” – meaning “rarely”. On the other hand, the PII population answered conclusively “no improvement” – this way showing that the DSI active substance device differentiates to the placebo device. 38% of the PII patients answered “3” for question 1 (V_1) – meaning “sometimes”, 50% answered “2” – meaning “a few times” and only 12% answered “1” – meaning “rarely”.

Furthermore, at V_3, after all the patients took both placebo and active substance, the answers have scores close to “0” meaning definite improvement in both functionality and quality of life, as shown in the following figure:

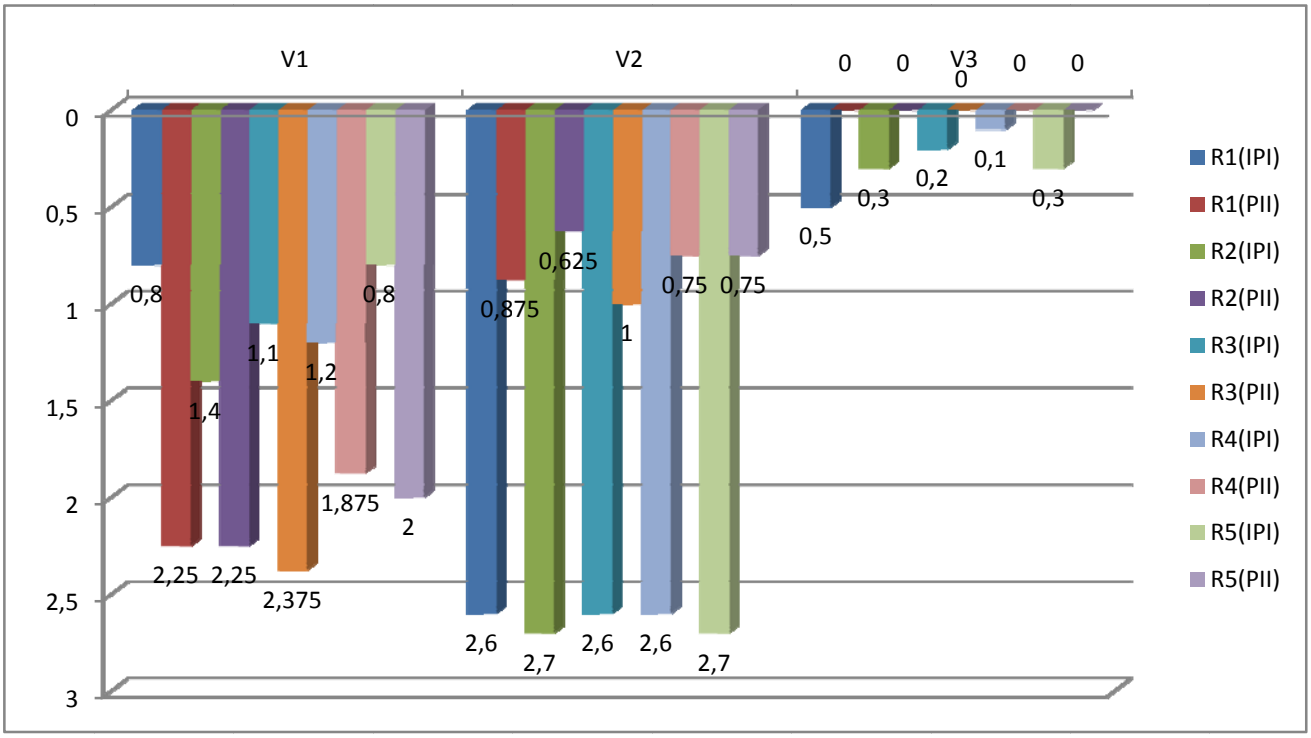

Figure 7 - The average answers from both PII and IPI

IPI= Inhaler-Placebo-Inhaler **PII= Placebo-Inhaler-Inhaler**

Looking separately at the two populations, we found that the IPI pool improved their scores with an average of 70% from V_1 to V_3 showing a decrease of their life quality by rating with higher grades (worse) the answers during the V_2 – which, for them, it was the visit after placebo.

Spectacular is the comeback of the scores towards below 1 during the V_3 interview, showing that the placebo interruption worsened the good evolution they had in terms of life quality.

IPI	Questions	V1	V2	V3	Improvement of score (v1 to V3)
Average scores	R1	0,8	2,6	0,5	-38%
	R2	1,4	2,7	0,3	-79%
	R3	1,1	2,6	0,2	-82%

	R4	1,2	2,6	0,1	-92%
	R5	0,8	2,7	0,3	-63%

Figure 8 - Average scores from IPI population and the improvement of score calculated based on the initial value

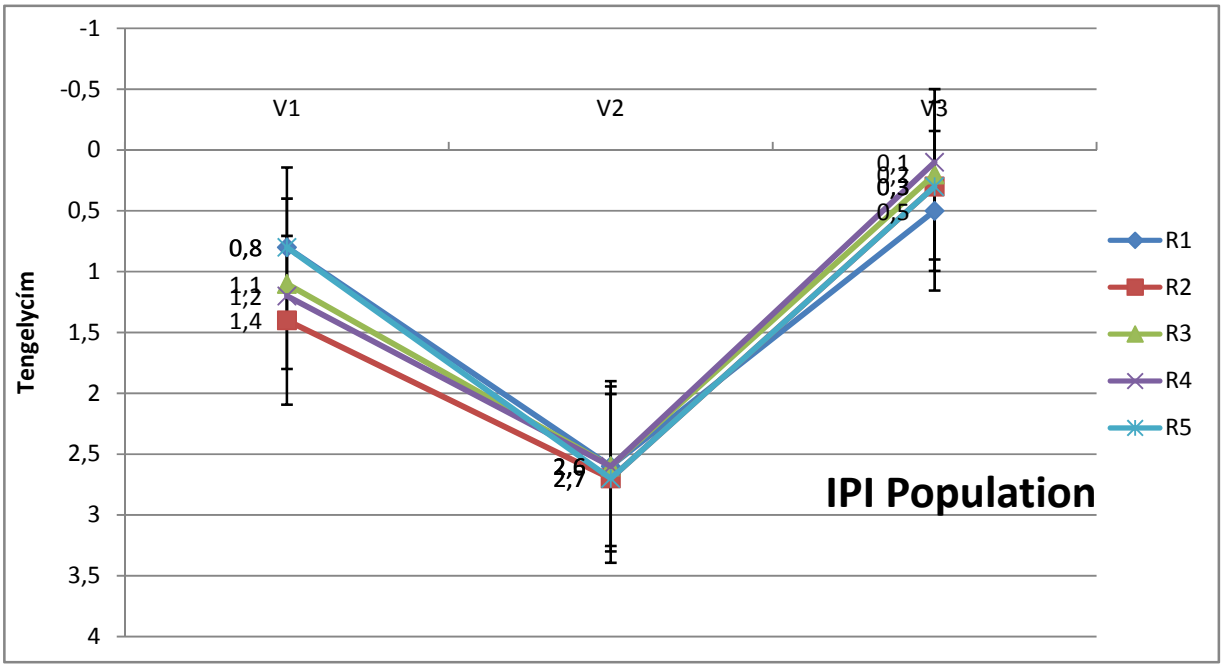

Figure 9 - the evolution of scores within IPI population (Inhaler-Placebo-Inhaler)

The PII population, as shown, had a better evolution, indicating that the usage in a constant manner of the DSI device, without interruptions, may produce definite life-improvement on a long-term period.

The PII group showed improvements from V_1 to V_2 on an average of 63% and total improvement from V_1 to V_3 – as no patient responded that their symptoms bothered them after using the DSI device for a 30 day period. This result translates in the mandatory conclusion that the DSI device is an enhancer in terms of improving the quality of life along with the standard medicines one patient has to take.

PII	V1 (visit)	V2 (visit)	V3 (visit)	improvement V1 to V2	Improvement V1 to V3
R1	2,25	0,875	0	-61%	-100%
R2	2,25	0,625	0	-72%	-100%
R3	2,375	1	0	-58%	-100%
R4	1,875	0,75	0	-60%	-100%
R5	2	0,75	0	-63%	-100%
			Overall	-63%	

Figure 10 - Average scores from IPI (Inhaler-Placebo-Inhaler) population and the improvement of score calculated based on the initial value

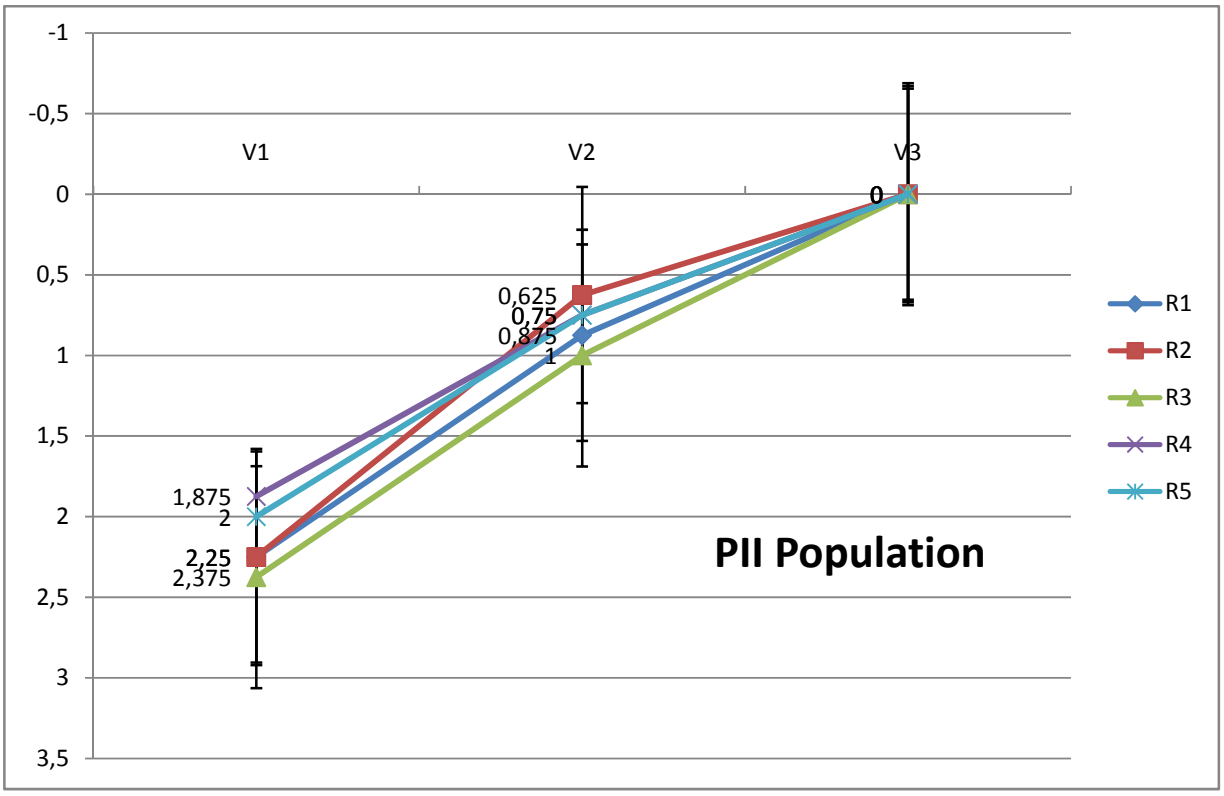

Figure 11 - The Evolution of Scores within PII population (Placebo-Inhaler-inhaler)

Conclusions

As we studied both the quantitative and the qualitative parameters on a significant pool of patients, we were able to draw conclusions regarding the use of the DSI device on patients with asthma/COPD. Although we found improvements of FVC, FEV1 and PEF parameters on spirometry, the average improvement of these parameters doesn't impress but it cannot be ignored. It is well known the fact that an asthmatic or COPD patient's spirometry values are in dependency with the atmospheric conditions, his life environment, exposure to pollution, etc – these factors being able to change the results of the evaluation. But correlating with the qualitative results, we found that the DSI inhaler has proved its efficacy versus placebo – improving the life quality and the breathing quality of all patients.

Due to the fact that patients have been breathing better and they all were on regular asthma/COPD medicines, the added DSI device increased the sputum expectoration and additionally helped to the relief of respiratory airways. This fact has a major importance in both prevention and speeding up the healing of respiratory infectious diseases that, in some cases, may be life-threatening to a COPD patient. Nevertheless, the DSI device usage on a regular basis and for a long period of time improves the patients' global functioning along with the quality of his life – making them able to do a better job in

daily activities and at home, as shown in reading the results from the Life-Quality Improvement Questionnaire found in APPENDIX 3. Additional statistical data can be found in APPENDIX 5.

Author:

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Radu CRISAN – MD,

Coordinator:

……

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Appendix 1

THE INFORMED WRITTEN CONSENT FOR PARTICIPATION TO A CLINICAL TRIAL FOR TESTING THE EFFICACY OF A MEDICINE

Name of the Investigator: Radu CRISAN, MD

Trial Title: The effects of using INHALO DSI´s Plastic Dry Salt Inhaler (DSI) on adults with asthma and COPD

INFORMATIONS:

This fact sheet may contain words and medical terms you do not understand. Please ask your doctor or nurse to explain any terms you do not understand.

1. **Description and Study's Objective**

You are invited to participate in the study of medical research, which has the following objectives:
Primary objective: to assess the efficiency of DSI inhaler device on patients with asthma and COPD in terms of quality of life.
Secondary objectives:

- to estimate of therapy effectiveness of DSI inhaler device in the frequency of infectious exacerbations.
- To estimate of the effect of DSI inhaler device therapy on symptoms of COPD

The study will involve the following procedure:
If you agree to participate in the study, you will be asked a few questions about your general health status and any symptoms of asthma or COPD that you have. A doctor will review and take blood

pressure, pulse, temperature and will make a clinical examination. If you were not yet made a chest x-ray, your doctor will send you to have one made before entering the study. These initial tests will determine if you are eligible for the study.
If you are a women with the probability of pregnancy, you will do a pregnancy test of urine and you will be harvested a blood sample for laboratory confirmation.

After beginning the study procedures, you will be asked to attend the clinic 3 times as follows:

I. Visit 1: date:
II. Visit 2: date:
III. Visit 3: date:

During the visits at the clinic, you will be again asked a few questions about your general health status and any symptoms of asthma and COPD that you have. The total participation in the study is up to 30 - 45 days.

This study was reviewed and approved by an independent medical ethics commission.

2. The Risks Associated With This Study

All medicines can have side effects on patients even if halotherapy (salt therapy) is a well-known alternative method of treating respiratory pathology since the nineteenth century.
There is always possibility of unexpected side effect of medication.
Monitoring development during your participation in this study will allow the doctor and nurses to observe and treat such an event immediately from his appearance. You should tell your doctor if a change in your health status while you are in this study. You should inform your doctor of any other medications you are taking and you will refrain from any activities, as your doctor advises.
You will not be allowed to enter into this study if you are a pregnant woman. If you entered this study and there is any possibility to get pregnant, you should use one of the permitted methods of contraception while participating in the study until at least the next menstruation. If you become pregnant you should tell your doctor immediately and he will do a follow-up check on you. You will be withdrawn from the study and you will prescribe another medicine, if necessary.

The device used in this study may involve other risks that are not currently known.

3. Rewards of this study

By participating in this study, you partake in the evolution of Romanian medicine, the study of new directions to better treat and with best results, the pulmonary diseases.
You will also be watched carefully and you will be tested in different ways to monitor you health status.

You and other patients will benefit in the future of any product derived from this medical research. These benefits may include the possibility to improve your health status and that this study will help to establish an effective treatment for others who suffer from the same disease..

4. Alternative Therapy

If you wish to participate in this study, your doctor will prescribe you the standard treatment. He is able to answer any questions and discuss with you the risks and benefits of alternative treatments.

5. Privacy and review source documents

All medical records and related materials research that would identify you will be made secret. If you consent to participate in this study, you consent that medical information will be made available for the concern of representatives of National Medicines Agency of Romania and of the National Commission of Ethics, or other government agencies. It will also give permission for such medical information to be available to the sponsor, to the monitor of the study, other doctors, nurses, the Commission of Information Evaluation in the health unit that evaluates the safety and ethics of doing this study, to ensure that patients' rights are not violated, and staff involved in the study can assess the medication. These authorities will have access to your medical records without violating confidentiality, to the extent permitted by law or regulations. Investigator, regulators and trial sponsor can keep documents related to this trial indefinitely. If the results of this study will be published in the medical literature, your name will NOT be mentioned in them. Your family doctor can be informed of your participation in this study if you so wish.

6. The Right to ask questions and / or withdrawing from study

You are entitled to ask questions at any time any of the possible and / or known dangers that can present in this study. You will be informed on any significant information regardin you or your safety.

If you have any questions regarding this study or your rights as a subject of study, please contact:

Name: Dr. Radu Crisan
Phone: 0747113426

You have the right to withdraw from the study at any time. Your doctor may withdraw you from the study at any time if he feels that this is in your interest. Also the sponsor, ethics committee that approved this research study and regulating authorities in Romania can stop this study at any time.
If you retire voluntarily from the study or your doctor will ask you to do so, you must surrender all the medicines you have not used. You will ask questions about how you supported the studied drug. Also, you may be asked to cooperate by submitting to some laboratory and clinical tests that the doctor deems necessary.

7. **Payments**

You will not be given direct financial compensation for participation in this study.

8. **New discoveries**

You will be informed if new discoveries related to or are likely to affect your decision to participate or continue to participate in this study.

9. **Voluntary Participation**

Your participation in this study is voluntary. Your refusal to participate in this study by itself will not attract any penalty or loss of benefits to which you would have also the right. You may terminate participation in this study at any time, without losing the benefits to which you would have also the right.

You are entitled to receive a signed copy of this form.

STATEMENT OF CONSENT

The undersigned (full name - written in block letters) _____ have read and understand the above information describing this study and have received satisfactory answers to all my questions. I agree voluntarily to participate in this study.

Patient

Signature: _____

Date: _____

Investigator's STATEMENT

The undersigned (full name - written in block letters) _____ certify that to my knowledge, the patient signed the consent forms, was carefully and fully explained what this study is about, and that he understood the nature, risks and benefits involved participation in this research study.

Investigator's Signature: _____

Date: _____

APPENDIX 2 – Patient Monitoring Page and Adverse Reactions Page

Patient's Monitoring Page

Name of The Site: **Patient's ID:**

Patients's initials: _____ _____([N]ame, [S]urname)

Date:_____ (DD/MM/YY)

Age: ___ (years)

Sex: □ M □ F

Year of diagnosis of asthma: _____

Asthma severity: _____

Year of diagnosis of COPD: _____

COPD Stadium: _____

Is this patient receiving LTOT or Home Oxygen Therapy?

□YES □NO

Dry Sslt Inhaler Dose	Visit 1 (w1) Date: (DD/MM/YY)	Visit 1 (w1) Date: (DD/MM/YY)	Visit 1 (w1) Date: (DD/MM/YY)
	/ /	/ /	/ /
DSI DEVICE Daily use . 20 minutes (consent „YES" if used for 20 minutes or the actual amount of time)			

Concomitant medication

Medicine (ICN)	*Daily dose*	*Beginning date DD/MM?YY*	*Stop date DD/MM/YY*

Has this patient been hospitalized in between the visits? □YES □NO

If YES, consent date and duration of hospitalization_____

Patient's Evolution

Visit 0 (V_0). Date _____

TA	SaO_2	AV	FVC	FEV1	PEF

Other observations

……

……

Visit 1 (V_1). Date _____

TA	SaO_2	AV	FVC	FEV1	PEF

Other observations

……

……

Visit 2 (V_2). Date _____

TA	SaO_2	AV	FVC	FEV1	PEF

Other observations

……

……

Visit 3 (V_3). Date _____

TA	SaO_2	AV	FVC	FEV1	PEF

Other observations

……

……

APPENDIX 3 – Questionnaire for Quality of Life

Patient's Initials:

Visit _____ Date: / /

This is a questionnaire for the assessment of symptoms. Please answer questions **1** -5.

Circle the response number that best describes how you felt in the last 7 days.

1. In the last 7 days, how often **have you awakened on** average at night **because of your pulmonary disease?**	0 Never **1** Rarely 2 The few times 3 Several times 4 Often 5 Numerous times 6 I could not sleep because of my pulmonary condition
2. In the last 7 days, how **serious they were,** on average, **your pulmonary disease symptoms when you woke up** in the morning?	0 I had no symptoms **1** Symptoms very weak 2 mild symptoms 3 moderate symptoms 4 pretty severe symptoms 5 severe symptoms 6 very severe symptoms
3. In the last 7 days, how limited have you been, in general, in **your activities** because of your pulmonary disease?	0 Not limited **1** Very little limited 2 Slightly limited 3 Moderately limited 4 Very limited 5 Extremely limited 6 Total restricted
4. In the last 7 days, how much **lack of air** did you felt, in general, because of your pulmonary disease?	0 Not at all **1** Very little 2 Few times 3 Moderate 4 Quite a lot 5 Pretty much 6 Very much
5. For the last 7 days, how long did you had, in general, **a growl or a wheez in the chest?**	0 Never **1** Rarely 2 For a little while 3 Moderate period of time 4 Long period of time 5 Most of the time 6 All the time

APPENDIX 4 – Adverse Reaction Form

Adverse Events

Have there been any adverse events during the use of the DSI device?

□ YES

□ NO

IF YES, the adverse events were consensed as following:

The Date Adverse event occured	Did the patient's condition required hospitalization? YES/NO	The description of the adverse event	Treatment

If the treatment with the DSI device has been interrupted, please conent the date of the interruption:

____/_____/_____ (DD/MM/YYYY)

Please specify the reason for the interruption:

- □ Lost from evidence (never returned)
- □ Death
- □ Adverse events
- □ Patient discontinuation
- □ Investigator/sponsor/other authority's decision for discontinuation

Name of the Investigator:

_____

Signature: Date:_____(DD/MM/YY)

_____

APPENDIX 5. Additional statistical Data


Adobe Acrobat Document


Adobe Acrobat Document

(SPSS source)