Does add-on halotherapy improve clinical outcomes of patients with a lung disease?

Author: Senna Diepeveen
Student number: 11217294
E-mail address: s.k.diepeveen@amsterdamumc.nl

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AMC senior tutor
Name: prof. dr. A.H. Maitland – van der Zee
E-mail address:
a.h.maitland@amsterdamumc.nl
Department: Respiratory Medicine
Institute: Amsterdam UMC location AMC
University: University of Amsterdam

Direct supervisor
Name: dr. Susanne Vijverberg
E-mail address:
s.vijverberg@amsterdamumc.nl
Department: Respiratory Medicine
Institute: Amsterdam UMC location AMC
University: University of Amsterdam

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This cover illustration is a Halotherapy room located in Spain. Cover illustration from Wikipedia. https://commons.wikimedia.org/wiki/File:Halotherapy_Spain_.jpg

Abbreviations

ABBREVIATION	MEANING
BHR	Broncho Hyperreactivity
CF	Cystic Fibrosis
COPD	Chronic Obstructive Pulmonary Disease
ECP	Eosinophilic Cationic Protein
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
FEF	Forced Expiratory Flow
HCT	Histamine Challenge Test
JBI	Joanna Brigs Institute
MCT	Methacholine Challenge Test
PAQLQ	Paediatric Asthma Quality of Life Questionnaire
PEF	Peak Expiratory Flow
QOL	Quality of Life
RCT	Randomized Controlled Trial
SF-36	Short Form Health Survey
VC	Vital Capacity

Abstract

Introduction: For a long period, mines and caves have been used to treat multiple diseases. Halotherapy is a form of therapy that tries to mimic the conditions in these salt caves to treat people with, amongst others, lung diseases.
Aim: The aim of this study was to 1) find out the mechanism of action of salt atomization in the lungs and 2) assess the effectiveness of halotherapy for the treatment of lung diseases.
Methods: A literature search was conducted using the PubMed database to find articles for both research questions. Included search terms were respectively “lung diseases” and “halotherapy” and “hypertonic saline/salt caves”. Inclusion criteria to assess effectiveness of halotherapy were studies performed in humans, patients with respiratory diseases, patients were treated with halotherapy and English/Dutch publication. Critical appraisal was done using JBI checklists.
Results: The search identified 9 eligible articles: 3 on the mechanism of action and 6 on the effectiveness of halotherapy. The mechanism of action is thought to depend on the increasing water flow to the airway surface because of the increasing Natrium Chloride gradient after inhaling Hypertonic Saline. In asthma induced rats halotherapy is thought to restore phagocytes levels. Six studies were found to assess effectiveness on halotherapy, three randomized-controlled trials (including 129 suffering asthma) and three (non-randomized) non-randomized experimental studies (including 178 patients suffering from asthma, bronchiectasis, bronchitis, and cystic fibrosis). The studies were assessed on their methodological quality using Joanna Brigs Institute (JBI) checklists. All the randomized controlled trials met at least 10 of the 13 criteria and in most studies it was unclear whether those delivering treatment were blinded. The non-randomized trials met at least four of the nine criteria. One study did not have a control group and most of the studies did not show whether appropriate statistical tools were used. The different types of halotherapy used in the studies used salt concentrations between 0,5 and 35 mg/m^3, 10-54 treatment sessions, a duration of 25-60 minutes, a humidity of 41-60% and a temperature of 18-24 degrees Celsius. Clinical outcomes measured that were assessed could be grouped into: lung function parameters, clinical symptoms, quality of life (QoL) and inflammatory parameters. One of the two studies that investigated QoL showed a significant increase in QoL. In the study of Bar-Yoseph et al. the weighted average of the PAQLQ increased from 6.29 to 6.71 (P=0.004). Only one of the two studies that investigated inflammatory parameters studies found a significant improvement in inflammatory parameters in some of the participants. Lazarescu et al. found an increase in the number of phagocytes in the blood and the activity of oxygen dependant granulocytes activity (p<0,1). Two of the two studies that investigated bronchial hyperreactivity (BHR) showed an improvement in BHR. Bar-Yoseph et al. showed that the BHR improved of 1/3 of their patients and Hedman et al. showed an improvement in 56% of their patients. Only one of four articles showed a significant improvement in spirometry values. Chervinskaya et al. showed an improvement of all the parameters of spirometry, with a difference of 14, in the group with severe obstruction (P<0.05). One of two articles showed an improvement in asthmatic symptoms. Chervinskaya et al. found that that the number of asthma attacks and respiratory discomfort had decreased from 81% to 52%. Overall, the randomized controlled trials show a less positive effect on the effectiveness of halotherapy than the (non-randomized) experimental trials.

Conclusion: Halotherapy seems to have a small positive influence on patients with lung diseases. Two of the four randomized controlled trials showed a positive effect of halotherapy on the BHR, even though one of them show only a short-term effect. The QoL is also improved using halotherapy.

Samenvatting

Introductie: Al jaren worden grotten en mijnen gebruikt voor het behandelen van verschillende soorten ziektes. Halotherapie is een vorm van therapie gebaseerd op de principes van de behandelingen in zulke grotten om hiermee, onder andere, longziekten te behandelen. Het doel van deze studie was 1) het uitzoeken van het effect van zout verneveling op de longen en 2) de effectiviteit van halotherapie als behandeling voor longziekten.
Methode: Een zoekactie in de PubMed database is uitgevoerd om artikelen te vinden voor beide onderzoeksvragen. Gebruikte termen waren respectievelijk longziekten en halotherapie en hypertonisch zout/zout grotten.
Resultaten: Uit de search kwamen negen goede artikelen: drie over het werkingsmechanisme van halotherapie en zes over de effectiviteit van halotherapie. Het wordt verondersteld dat het werkingsmechanisme berust op een toegenomen hoeveelheid water op het luchtweg oppervlakte. Dit komt door de toegenomen hoeveelheid natriumchloride na het inhaleren van hypertonisch zout. Ratten waarbij astma was geïnduceerd leek halotherapie de fagocyt aantal te herstellen. Zes studies over de effectiviteit van halotherapie zijn geïncludeerd, drie gerandomiseerde gecontroleerde studies (met 129 astmapatiënten) en drie niet-gerandomiseerde trials (met 139 patiënten met astma, bronchiëctasieën, bronchitis en cystische fibrose). De studies zijn beoordeeld op hun methodologische kwaliteit met behulp van checklists van het Joanna Brigs Institute. Van de gerandomiseerde studies voldeden de studies op zijn minst aan 10 van de 13 criteria. Het was bij de meesten onduidelijk of de persoon die de behandeling deed ook geblindeerd was. Van de niet gerandomiseerde studies voldeden de studies op zijn minst aan vier van de negen criteria. Eén studie had geen controlegroep en de meeste studies liet niet zien of ze gebruik hadden gemaakt van goede statistische analyse. Bij de verschillende soorten halotherapie werden concentraties zout gebruikt tussen de 0,5 en 35 mg/m3, 10 tot 54 therapiesessies, een duur van 25 tot 60 minuten per sessie, een luchtvochtigheid van 41-60% en een temperatuur van 18-24 graden Celsius. Eén van de twee studies die de kwaliteit van leven (QoL) onderzochten liet een significante verbetering van de QoL zien. In de studie van Bar-Yoseph et al. nam het gemiddelde van de PAQLQ toe van 6.29 tot 6.71 (P=0.004). Slechts één van de twee studies die de inflammatoire factoren onderzochten lieten een significante verbetering van inflammatoire factoren zien. Lazarescu et al. vonden een toename in het aantal fagocyten in het bloed en een toename van de activiteit van zuurstof afhankelijke granulocyten (P<0,01). Twee van de twee studies die de bronchiale hyperreactiviteit (BHR) onderzochten lieten een significante verbetering van de BHR zien. Bar-Yoseph et al. liet een verbetering van de BHR in 1/3 van de patiënten zien en Hedman et al. liet een verbetering in 56% van de patiënten zien. Eén van vier studies liet een verbetering in de spirometrie waarden zien. Chervinskaya et al. liet een verbetering in alle parameters van de spirometrie, met een verschil van 14, zien in de patiëntengroep met ernstige obstructie (P<0.05). Eén van twee studies liet een verbetering van astmasymptomen zien. Chervinskaya et al. vonden dat het aantal astma aanvallen en respiratoire discomfort hadden afgenomen van 81% tot 52%. De gerandomiseerde gecontroleerde studies lieten al met al minder positieve uitkomsten zien dan de niet-gerandomiseerde studies.

Conclusie: Halotherapie lijkt een klein positief effect te hebben op patiënten met longziekten. Twee van de vier gerandomiseerde gecontroleerd studies laten een positief effect van halotherapie op de BHR zien. Een van hen laat slechts een kortdurend effect zien. Ook de kwaliteit van leven wordt positief beïnvloed door halotherapie.

Introduction

Background

According to the WHO, respiratory diseases impose an immense health burden. About 65 million people worldwide suffer from Chronic Obstructive Pulmonary Disease (COPD) and about 334 million people worldwide suffer from asthma. COPD characteristics are destruction of the lung tissue and chronic bronchitis. The most important risk factor is smoking. Asthma is a chronic inflammation of the lungs mostly appearing in children. (Forum of International Respiratory Societies. 2017). Other lung diseases included in the rest of this paper are Cystic Fibrosis (CF), Bronchiectasis and bronchiolitis. The pathology of CF is based on a dysfunction in the CFTR protein that causes thickened secretion in multiple organ systems (Brennan et al., 2016). Bronchiectasis are caused by abnormal dilation of the airways of the lungs. This causes sputum production, cough and increased respiratory inflammation (Swenson et al., 2017). The mechanism of bronchiolitis is based on airway oedema and mucus plugging (Zhang et al., 2017)

Complementary and alternative medicine are extremely popular. Complementary medicine is used in addition to regular therapy. Alternative medicine is used instead of regular therapy. (Györik et al., 2004). In the United States 42% of the adults use a form of alternative medicine which costs about 27 billion dollars annually. (Eisenberg et al.,1998). Roughly 25-50% of the patients with asthma in America, Australia and the United Kingdom have used complementary therapy. The most used therapies were breathing techniques, homeopathy, and herbalism. Most patients found that the therapy improved their asthma “to some extent” or “to a slight extent” (Ernst, 2009). In the USA 26,7% of children with asthma have used complementary therapy. 75% of adult and child patients with Cystic Fibrosis in America have used complementary therapy (Mark et al., 2015).

The use of salt caves and subterranean environment to treat many different diseases including obstructive lung diseases is common in Central and East European countries (such as Poland, Ukraine, and Hungary). (Beamon et al., 2001). This kind of climatotherapy is called speleotherapy. (Lazarescu et al., 2014). Different kind of caves are being used in treating these diseases. Different sorts of caves and mines can be identified. There are Kars caves with high humidity, karst or granite bedrock caves with high radon radiation, potash mines with high pressure and salt mines with high or moderate temperature. Mines with a moderate temperature (13-20 degrees) have a humidity of 45-70% and are used for longer treatments from 8-10 hours. Mines with warm temperature (30-41 degrees) have a humidity of 70-100% and are used for treatment duration of about one hour (Beamon et al., 2001). Regarding to Beamon et al. a lot of parameters of the caves and mines can be of influence in the therapy. These include absence of normal biotic conditions, absence of temperature differences, higher radiation level, low mobility of air and large surface of interaction with the surrounding area, high relative humidity, high rate of air ionization, low levels of dust and pollen, low levels of bacteria, constancy of the climate and the presence of finest aerosol of vital elements. There is not enough evidence to support the effectiveness of speleotherapy

even though a Cochrane review shows some studies show little non-significant improvements after treatment. (Beamon et al., 2001).
Another clinical study about speleotherapy, done with COPD patients, suggests that the high vapour content, de negative electric charge and ionization and the high calcium and magnesium concentration contribute of a higher mucocillary clearance. Also, some climate factors in the cave, low allergen levels or other pollutants and even temperature attribute to the improvement of health. (Horvath, 1986).

Halotherapy is increasingly popular in Western countries. In halotherapy the conditions in Salt Caves are mimicked. Halotherapy is used as a complementary therapy for, amongst others, lung diseases. During a therapy session, patients sit in comfortable chairs in a specially designed room. Patients can wear their own clothes but are advised not to wear perfume. During the session music can be played to enhance the feeling of relaxation and rest and plaids are available if patients are feeling cold (Halotherapie-zoutkliniek Veenendaal). Exact numbers of the amount of halotherapy clinics in the Netherlands are not available, but when searching for these clinics online more than ten different clinics were found spread across the Netherlands.

Rationale and aim

The aim of this study was to assess the efficiency of halotherapy in the treatment of patients with lung diseases. First, the latest insights of the effect of salt atomization in the lungs was summarized and secondly, clinical studies that assessed the effectiveness of halotherapy were reviewed.

Research Questions

1) What is the working mechanism of salt atomisation in the lungs?

2) What is the effectiveness on halotherapy for lung diseases and under which circumstances is it effective?

Methods

Literature Search

The literature search was done in the PubMed database between November 2019 and January 2020. For both research questions a different search was performed. For the first research question included terms were Hypertonic Saline and Lung Diseases. Details of the search term can be found in Appendix 1. For the second research question included terms were Halotherapy and Lung Diseases. Details of the search term can be found in Appendix 2. For this search no distinguish was made between different lung diseases. Because halotherapy is also used for other diseases, such as eczema, the filter for lung diseases was necessary.

Screening and selection of studies

For research question 1 the most recent reviews about hypertonic saline use were selected. I looked at the extensiveness of the review and the journal the article was published in. Based on these criteria the reviews with the most strength were selected.
Beforehand we expected minimal research had been done about halotherapy. Because of this assumption few exclusion criteria were drafted for research question 2. Inclusion criteria for research question 2 were: studies performed in humans, patients with respiratory diseases, patients were treated with halotherapy and English/Dutch publication. No additional exclusion criteria were drafted for the screening of the entire text.

Critical appraisal

Articles found for research question 2 were all assessed on their methodological quality. Checklists from the Joanna Brigs Institute were used. The JBI checklist for randomized-controlled trials and the JBI checklist for quasi-experimental studies (non-randomized experimental studies) were used.

Data extraction

Data extraction was only used for research question regarding the effectiveness of halotherapy. To identify the effect of halotherapy firstly the study design characteristics were extracted. These included the name of the first author, the year in which the study was published, the country the study was executed and the design of the study. The patient's characteristics that were extracted were: the amount of patients included, the amount of patients that received treatment, the age of the patient population, the lung diseases the patients had and the severity of the lung diseases. To identify the effectiveness of halotherapy I looked at the characteristics of the room, the concentration of the salt, the size of the particle, the humidity in the air, the temperature, the duration of the treatment and the amount of treatments. To observe the outcomes, I looked at the tests used to measure the outcome, the results in the treatment group and the results in the placebo group when present. The tests used to measure the outcomes were divided in four different groups.

These four groups were: Quality of Life, inflammatory parameters, lung function parameters and clinical symptoms.

Results: the mechanism of action of Salt Atomization in the Lungs

Selected studies

234 articles were found that talked about the physiological effects of hypertonic saline inhalation on the lungs. After filtering the search for reviews, only 36 articles were left. Two reviews were selected that observed the effect of hypertonic saline in patients with CF (Tarran et al., 2007 & Elkins et al., 2006).
Also, a search including the search term “Salt Caves” was done. One study was found that did an experimental study with asthma induced in rats. (Lazarescu et al., 2014).

Mechanism of action

Hypertonic saline is used to treat patients with CF. Hypertonic saline in normal lung epithelia causes water to move to the airway surface. This is because of an increased Natrium Chloride gradient intracellular which causes water to move to the airway surface. In normal epithelia this results in only a modest amount of increased water flow. Tarran et al. explain the theoretical effect of hypertonic saline in lungs of CF patients. Under normal circumstances in lung epithelia of CF patients an increased Natrium and Chloride transport causes water to be absorbed from the airway lumen to the submucosa. When a hypertonic saline is added, the absorption of Natrium Chloride is much slower in CF patients than in patients with normal epithelia. Thus, the increased water flow to the airway lumen lasts a lot longer. These mechanisms should occur using 7% hypertonic saline. (Tarran et al., 2007). Elkins et al. also reviewed multiple possible mechanisms of action of hypertonic saline. They reviewed different hypothesis about the mechanism of action of 3-7% hypertonic saline in the lungs of humans. They suggest it firstly induces the viscosity of the sputum. Secondly, it induces restoration of the airway surface by increasing airway surface liquid. Thirdly, is stimulates cough. This cough is usually identified as a side-effect of hypertonic saline but can also be a beneficial mechanism as it accelerates the clearance of mucus (Elkins et al., 2006). Both studies show a positive effect on the use of hypertonic saline of the lung epithelial of CF patients. On the other hand, both studies only explained the hypothesis about the working mechanism of hypertonic saline on the lungs.

The effect of salt atomisation in the lungs can also be observed through Salt Mines. Lazarescu et al. performed a study on rats that were ovalbumin-sensitized to mimic the process of asthma in the lungs. These rats were treated in salt-mines of Turda, Cacica and Dej. The duration, and other factors, of the treatment was not said in this study. These rats showed an improvement of morphological parameters in the cells of the lungs compared to untreated rats. These morphological parameters included lung fibroblast. After treatment in the salt mines the total protein levels of these fibroblasts recovered to the original values of 80 mg compared to about 60 mg in rats with induced asthma and without treatment. Fibroblasts are thought to be important in remodelling the tissue structure of the lungs. (Lazarescu et al., 2014). Thus, this study suggests that salt inhalation had a positive effect on the damaged lung structures in lung diseases.

Results: Effectiveness of Halotherapy

Search and Study Selection

A total of 27 studies were found with this search. After screening on title and abstract four articles were removed. Three articles were excluded for treating patients with other diseases than lung diseases. The fourth article was excluded because this article was a review. The remaining 23 studies were searched and assessed on full text. 17 of these studies did not have an article available in English or Dutch. For this reason, they were excluded. Thus, I was left with six studies who met the inclusion criteria and were included in this review. Details of the study selection can be found in the flow chart in figure 1.

Critical appraisal

Three of the included studies were randomized controlled trials. These studies were assessed using the JBI checklist for Randomized Controlled Trials. The checklist consisted of thirteen criteria. Answer options were yes, no, unclear and not applicable. All the studies met at least ten criteria. In most studies it was unclear whether those delivering treatment were blind to treatment assignment or those delivering treatment were not blinded. Also, the allocation to the treatment groups was not always concealed or unclear. A complete overview of the critical appraisal can be found in Table 1.

Of the other three included studies, two were non-randomized clinical trials and one was an experimental study without a control group. These studies were assessed using the JBI checklist for Quasi-Experimental Studies (non-randomized experimental studies). This checklist consisted of nine criteria. The answer options were again yes, no, unclear and not applicable. Al of the studies met at least four of the criteria. None of them met all the criteria. In most studies it was unclear whether included participants were similar and received similar treatment other than the intervention of interest. In most studies it was also unclear whether appropriate statistical analysis was used. One study, Rabbani et al., did not have a control group. A complete overview of the critical appraisal can be found in Table 2.

Study characteristics

The included studies for research question 2 were published between 1995 and 2017. Of the six studies included three studies were randomized controlled trials and three studies were non-randomized clinical trials. All the randomized controlled trials were done with patient suffering from mild to moderate asthma (Bar-Yoseph et al., 2017, Sandell et al., 2012 & Hedman et al., 2006). One study was done with children between five and thirteen years of age (Bar-Yoseph et al., 2017). The other two studies were done with patients older than 18 years (Sandell et al., 2012 & Hedman et al., 2006). Bar-Yoseph et al. included 56 patients, Sandell et al. included 39 patients and Hedman et al. included 32 patients.

The other three studies were non-randomized clinical trials. Two of them were done with a control group (Chervinskaya et al., 1995 & Lazarescu et al., 2014). One study was done only with patients suffering from asthma (n=19). The patients in this study were seven to sixty

years old. (Lazarescu et al., 2014). One study was done with patients suffering from non-CF related bronchiectasis (n=20). The patients in this study were 20 to 53 years old. (Rabbani et al., 2013). The last study was done with patients suffering from Asthma, Chronical Bronchitis, Bronchiectasis and CF (n=139). Al patients were in a disease stadium of prolonged exacerbation. The patients in this study were 16 to 62 years old. (Chervinskaya et al., 1995). A complete overview of the study characteristics can be found in Table 3.

Differences in halotherapy characteristics

Most studies used halotherapy applied in a specifically designed room in which the walls were covered with a layer of salt. One study used European Salt Company certified-origin iodized rock salt (Bar-Yoseph et al., 2017). Comfortable chairs were available in all rooms for patients to relax on during their therapy.

Two studies used only 10 therapy sessions. These sessions took place in two weeks. (Sandell et al., 2012 & Hedman et al., 2006). The other studies used more treatment sessions. This differed from 12 to 56 sessions (Bar-Yoseph et al., 2017, Lazarescu et al., 2014 & Chervinskaya et al., 1995). These treatment sessions were scattered over two to eight weeks. The treatment duration differed a lot between the different studies. The shorted treatment duration was a duration of only 40 minutes (Hedman et al., 2006). The longest treatment duration was a duration of 60 minutes. (Chervinskaya et al., 1995).

Two studies did not report the concentration of the salt particles in the therapy chamber during therapy. (Bar-Yoseph et al. 2017 & Lazarescu et al. 2014). The other studies used concentrations between 0,5 mg/m^3 to 10,8 mg/m^3 (Sandell et al., 2012, Hedman et al., 2006 & Chervinskaya et al., 1995). Two studies did not report the size of the Salt particle. (Lazarescu et al., 2014 & Sandell et al. 2012). The other studies reported a particle size between 2 and 20 millimetres (Bar-Yoseph et al., 2017, Hedman et al., 2006 & Chervinskaya et al., 1995).

Two studies did not report the humidity in the treatment room. (Lazarescu et al., 2014 & Sandell et al., 2012). The other studies reported a humidity in the treatment room between 41% and 60% (Bar-Yoseph et al., 2017, Hedman et al., 2006 & Chervinskaya et al., 1995). The temperature in the rooms deferred from 18 to 24 degrees Celsius (Bar-Yoseph et al., 2017, Hedman et al., 2006 & Chervinskaya et al., 1995). Yet again two studies did not report the temperature in the treatment groups. (Lazarescu et al., 2014 & Sandell et al., 20120.)

One study stood out between the other studies. Instead of using a treatment room for the halotherapy, Rabbani et al. used inhalers. These inhalers were filed with 70 grams of salt. Patients were asked to use the inhalators daily for two months. They used the inhalers for 25 minutes each session. (Rabbani et al., 2013). The overall characteristics of the different types of halotherapy used in the different studies can be found in table 4.

Outcome measurements

Quality of Life

Quality of Life was assessed in two studies (1 RCT). QoL was measured using the Paediatric Asthma Quality of Life Questionnaire (PAQLQ) and the Short Form Health Survey (SF-36). (Bar-Yoseph et al., 2017 & Rabbani et al., 2013).

Inflammatory parameters

Inflammatory parameters were measured in two studies (1 RCT) through sputum samples. One study measured the number of phagocytes and neutrophils as an indicator for inflammation. (Lazarescu et al., 2014). One study measured the concentration of Eosinophilic Cationic Protein (ECP), the number of eosinophils and the number of neutrophils. (Sandell et al., 2012).

Lung function

In five studies lung function weas measured through spirometry (3 RCT's). Bar Yoseph et al. measured the forced expiratory volume in the first second (FEV_1), the forced vital capacity (FVC) and the forced expiratory flow at 25% and 75% (FEF_{25-75}). Rabbani et al. measured the FEV_1, the FVC and the $FEF_{25-75.}$ Sandell et al. measured the FEV_1, the FVC and the peak expiratory flow (PEF). Hedman et al. also measured the FEV_1, the FVC and the PEF. Chervinskaya et al. measured the vital capacity, the FVC, the FEV_1 and the FEF at 50% (FEF_{50}) (Bar-Yoseph et al. 2017, Rabbani et al. 2013, Sandell et al. 2012, Hedman et al. 2006, Chervinskaya et al. 1995). Two studies used bronchial hyperreactivity (BHR) to measure the lung functions. Methods used were the Methacholine Challenge Test (MCT) and the Histamine Challenge Test (HCT). (Bar-Yoseph et al., 2017 & Hedman et al., 2006). Rabbani et al. also used a six-minute walk challenge as a measurement of lung function. (Rabbani et al., 2013). Bar-Yoseph et al. measured the fractionally exhaled NO levels. (Bar-Yoseph et al., 2017).

Asthma symptoms

Three studies also looked at the self-reported asthma symptoms that occurred during the treatment period and the use of emergency bronchodilator medication (2 RCT's) (Sandell et al. 2012, Hedman et al., 2006 & Chervinskaya et al., 1995). An overview can be found in table 3.

Effect of halotherapy on outcomes

Firstly, the effect of halotherapy on the QoL was measured. The two studies that measured the quality of life both showed an increase in quality of life reported after the treatments. Only the results from Bar-Yoseph et al. the changes in most parameters of the PAQLQ were significant. The symptom score increased from 6.32 to 6.78 (P=0.016) and the emotional function increased from 6.5 to 6.85 (P=0.007). The weighted average increased from 6.29 to 6.71 (P=0.004). The placebo group in this study showed no significant increase in Quality of Life. Two parameters, activity limitation and emotional function, show a slight increase (Bar-Yoseph et al., 2017). In the study from Rabbani et al. little changes in the SF-36 parameters

were found. Al physical health parameters increased. Especially the physical functioning and the role limitations due to physical problems increased with respectively 4 and 9 points. Most of the metal and emotional health parameters also increased. Only vitality showed a mean decrease of 1 point. Overall, the physical health increased with 4 points (p=0.562) and the mental and emotional health also increased with 4 points (p=0.229) (Rabbani et al., 2014). The study of Bar-Yoseph et al. was a randomized controlled trial. The study of Bar-Yoseph et al. studied the effect of children. Concludingly, halotherapy shows a positive effect on the QoL in children and adults.

Secondly, the effect of halotherapy on inflammatory parameters has been studied. Two studies investigated the inflammatory processes after halotherapy. Lazarescu et al. found that halotherapy increases phagocytosis processes and non-specific anti-inflammatory resistance. This means an increase in the number of phagocytes in the blood and the activity of oxygen dependant granulocytes activity (p<0,1). Only a few patients with chronic bronchitis and chronic obstructive bronchial pneumopathy showed a significant positive change (Lazarescu et al., 2014). Sandell et al. did not found any significant changes in the anti-inflammatory processes. Patients showed an increase in the ECP values directly after treatment and showed and the ECP values almost doubled four weeks after treatment in the group with low concentrations of salt. The group with high concentrations of salt showed a decrease in the ECP values directly after treatment and it continued to decrease to four weeks after treatment. The placebo group showed only a little increase in ECP values (Sandell et al., 2012). Concludingly, high concentrations of salt seem to have a negative effect on the ECP values while low concentrations of salt seen to increase it a lot more than in the placebo group. Other inflammatory parameters in adults do not seem to be infected by halotherapy as found in the randomized controlled trial from Sandell et al.

Thirdly, the effect of halotherapy on lung function was investigated. Five studies investigated the effect of halotherapy on lung functions. Two of these studies look at the BHR after Halotherapy. Bar-Yoseph et al. found that BHR improved significantly as regard to the baseline characteristics (p=0.044) and the placebo group (P=0.012). After treatment, the amount of histamine necessary to decrease the FEV_1 with 20% became more than 1 mg in 1/3 of the patients. Less than 1 mg histamine needed to decrease the FEV_1 with 20% stand for a moderate impaired function. No significant changes were reported in the placebo group. Almost no improvement is seen in these patients. (Bar-Yoseph et al., 2017). Hedman et al. found that after treatment with halotherapy 56% of the patients had a decrease in BHR as regard to only 17% in the placebo group (P=0.040). 36% were nonresponsive to histamine after treatment as regard to 0% in the placebo group (p=0.017). After two months no more significant differences were measured within the groups and between the groups. Four of the thirteen patients left in the treatment group were non-responsive to histamine and one in the placebo group (p > 0.05) (Hedman et al., 2006). It seems that in both RCT's halotherapy had a positive effect on the BHR in adults and children. This effect did not seem to last for a long period and seemed to be bigger in adults.

All five studies used spirometry tests to measure the lung functions. Bar-Yoseph et al. found no improvement in spirometry levels after treatment in the treatment or placebo group. Two spiromatic parameters, FEV_1 & FEF_{25-75}, showed a decrease in the treatment group after

treatment comparing to baseline characteristics (p=0.03 & p=0.046) (Bar-Yoseph et al., 2017) No significant changes were found in spirometry levels by Rabbani et al. Only a small increase in $FEV_{1,}$ and FVC is seen (P>0.05) (Rabbani et al., 2013). No significant changes in spirometry parameters were found by Sandell et al. (P>0.05). Higher concentrations of salt used during the halotherapy show a minimal decrease in lung functions after treatment. These results were not significant. (Sandell et al., 2012). Hedman et al. found no between groups differences in spirometry parameters. Within the treatment group evening PEF significantly in increased (P<0.01). Compared with the placebo group the morning PEF increased with 2.7 and the evening PEF increased with 5.5 (Hedman et al., 2006). Chervinskaya et al. found that after seven days of treatment al parameters, VC, FVC, FEV, PEF, FEF50, significantly improved (P<0.05). The FEF_{50} increased the most with a difference of seven. At the end of the treatment sessions most parameters of spirometry, VC, FVC and PEF, showed a significant improvement (P<0.05). PEF increased the most with a difference of two. After dividing patients in four different groups depending on the extent of obstruction only the group with severe obstruction showed significantly improvement on all the parameters of spirometry (P<0.05).All the parameters increased with at least a difference of 14 and PEF increased the most. No significant improvement was found in the control group. (Chervinskaya et al., 1995). Concludingly, most studies did not find a significant increase in spirometry levels after halotherapy. The least results were found in the three randomized controlled trials. Higher concentrations of salt seem to even have a negative effect on patients. In the study that was done with children no positive effect has been found. It even seemed to worsen the spirometry levels in children, which means that halotherapy could be more effective in adults.

Bar-Yoseph et al. also looked at the FeNO levels after treatment. A slight increase in FeNO levels can be found in the placebo and treatment group. In the placebo group the FeNO levels increased from 22.01 to 28.97. In the treatment group the FeNO levels increased from 35.49 to 38.16. But these changes are all not significant. (Bar-Yoseph et al., 2017).

Rabbani et al. also used a six-minute walk test to evaluate the lung function. No significant changes were found after the halotherapy treatment. The saturation after the test after intervention even seemed to be decreased by 2% (Rabbani et al., 2013).

Asthma symptoms did not decrease as regard to the placebo group in the study of Sandell et al. Also, the use of bronchodilators did not differ (Sandell et al., 2012). Hedman et al. found nocturnal awakenings decreased significantly within the treatment group (P<0.05). There were no significant decreases in the asthma symptom score reported (Hedman et al., 2006). Chervinskaya et al. found that that the number of asthma attacks and respiratory discomfort had decreased from 81% to 52% (P<0.001). The amount of asthma attacks that were controlled by medication also decreased from 32% to 2% after treatment (P<0.001). Patients also reported a decreased occurrence of cough (P<0.001) and a more productive cough. The average duration of this remission was 7,6-0,9 months (Chervinskaya et al., 1995).

Three studies reported side-effects of the treatments. Two studies reported an increased irritative cough during the first part of the treatments. This cough mostly vanished during the

rest of the treatments. In the study of Chervinskaya et al. 35 patients (27%) presented with cough and in the study of Lazarescu et al. 7 patients presented with cough (36%) (Lazarescu et al., 2014 & Chervinskaya et al., 1995). One study reported xerostomia in six patients. The xerostomia in one patient was so severe the patient had to stop with the treatments (Rabbani et al., 2013).

Discussion

In this study the working mechanism and effectiveness of halotherapy have been investigated. Salt nebulizers have been used in the treatment of patients with CF. The salt seems to increase the water flow to the airway surface. In rats with induced asthma salt cave therapy seems to increase the amounts of fibroblasts. These fibroblasts could potentially restructure damaged lung sites, but this needs further investigation.
Halotherapy seems to have the most positive effect on BHR. In two RCT's the BHR was reduced in the intervention group compared to the placebo group and this effect seemed bigger in adults. One study that looked at the long-term effects showed that the results did not last long after the treatments ended (2 months). One RCT also reported that the QoL improved after halotherapy. Spirometry levels minimally increased is some studies. In children and patients that underwent halotherapy with a higher salt concentration the spirometry parameters even seemed to worsen. In most studies no significant improvement in the placebo groups have been mentioned. The most important side effects were xerostomia and irritative cough. Overall, the RCT's reported less positive effect of the halotherapy compared to the non-randomized experimental trials.

The studies found for the research question regarding halotherapy effectiveness had their strengths and limitations. From the studies found that observed the effect of halotherapy only three studies were RCT's, which means the effect of the intervention compared to a control group can be assessed. In these randomized controlled trials not all of those who delivered treatment were blinded to treatment allocation. Two of the randomized controlled trials, Sandell et al. & Hedman et al., were done by the same research group in Finland. This means they used the same techniques for halotherapy and will not help us investigate optimal conditions for Halotherapy. Most studies were done with a small patient size. This means the chance of finding a significant effect is much lower. Three studies, Bar-Yoseph et al., Sandell et al. & Hedman et al., used certified European Salt Company (ESCO) salt in their halotherapy chamber. This makes it easier to repeat the trial using a similar compound and could mean the results are more reliable. Because of the small amount of studies found that investigated the effectiveness of halotherapy, the studies differed al lot on their design. This made it harder to compare the studies.

Noticeable is the fact that more than half of the study's needed to be excluded because they were not available in English of Dutch. These studies were mostly done in Russia (n=13) and one study was done in Hungary. When searching for the mechanism of action of salt aerosol therapy, again most studies were not available in English or Dutch. Also noticeable is the fact that a big part of the Russian studies was done by partly the same investigators. Some studies had an abstract available in English. Almost all these studies reported a positive effect of halotherapy.

More studies need to be done in the future to find out whether halotherapy can be useful in treating patients with lung diseases. These studies need to be done with bigger patient populations. I would recommend to only investigate one lung diseases. This is because in researches that has been done with patients with different lung diseases included no clear difference was made between the outcomes for the different diseases. Most researches I

included in this review investigated asthma. These studies showed many differences in the outcomes and patient population. Therefor further investigation of the effect of halotherapy on patients with asthma would be useful. Both the QoL and BHR showed promising improvements. The recommended outcomes would be a QoL questionnaire, a BHR test, spirometry functions and Inflammatory parameters in sputum. Many studies have been done with patient population with a huge diversity in age. To be able to make a decent recommendation, the age of the patient population should differ les. Bar-Yoseph et al. was to only study that used children as a patient population. In this population halotherapy even seemed to worsen lung function. Therefore, the recommended patient population for further studies are adults.

As for the halotherapy itself there is less evidence for the concentration of the salt in the room, the amount and duration of the treatments and the conditions in the halotherapy chamber. In most studies a treatment period of two weeks was used. Chervinskaya et al. had the most positive results and used a slightly longer treatment period of two to three weeks. Even though this study was a non-randomized trial, using a longer treatment period seems to be more effective and would be recommended for further studies. In most studies the temperature was around 20 degrees Celsius and a humidity of 40-60 percent were used. Therefore, using the same circumstances would be recommended. There is less evidence about the concentrations of salt that need to be used for halotherapy to be effective. Only one study used a concentration above $10mg/m^3$. Using different concentrations of salt to observe the effect of the different concentrations would be recommended in further studies. It is important that in this first study the actual mechanism of action of the salt particles becomes clear, which concentration is the most effective and whether it works best on severe or mild diseases. After this more studies can be done altering the humidity and temperature, the duration, and the amount of treatments. An overview of this future study can be found in table 5.

Furthermore, the cost effectiveness of halotherapy as an ad-on therapy should also be taken into consideration. None of the studies I found reported the cost of the halotherapy treatment. Because Halotherapy is alternative medicine it is not compensated by the insurance companies. The costs of the treatment for patients need to be evaluated compared to the effectiveness of the treatment. The costs of halotherapy should also be compared to other alternative/regular treatments of lung diseases and their effectiveness.

Based on the available information about halotherapy I would not recommend halotherapy as add-on treatment for patients with respiratory diseases. Simply because the available articles show contradictory outcomes and especially in children the effect of halotherapy is not clear enough. I would also not discourage patients who are desperate for a better treatment to try halotherapy. This because most of all nonharmful side effects of halotherapy were reported.

Conclusion

Based on the articles included in this paper halotherapy show promising results as a treatment for patients with lung diseases. Based on the effect of salt nebulisers in the treatment of CF, salt improves the water flow to the airway surface which increases Halotherapy could have a positive effect on QoL and BHR. High concentration of salt used in the treatment could possibly have negative effects on the lung functions. The treatment seemed to have less effect in children. Still, more research needs to be done to investigate the ideal circumstances for halotherapy and the specific mechanism of action in the lungs.

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References

1. Bar-Yoseph R, Kugelman N, Livnat G, Gur M, Hakim F, Nir V, et al. Halotherapy as asthma treatment in children: A randomized, controlled, prospective pilot study. Pediatr Pulmonol. 2017;52(5):580-7.
2. Beamon S, Falkenbach A, Fainburg G, Linde K. Speleotherapy for asthma. Cochrane Database Syst Rev. 2001(2):Cd001741.
3. Brennan ML, Schrijver I. Cystic Fibrosis: A Review of Associated Phenotypes, Use of Molecular Diagnostic Approaches, Genetic Characteristics, Progress, and Dilemmas. J Mol Diagn. 2016;18(1):3-14.
4. Chervinskaya AV, Zilber NA. Halotherapy for treatment of respiratory diseases. J Aerosol Med. 1995;8(3):221-32.
5. Eisenberg D, Davis R, Ettner S, Appel S, Wilkey S, Van Rompay M, Kessler R. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. Jama, 1998;280(18), 1569-1575.
6. Elkins M, Bye P. Inhaled hypertonic saline as a therapy for cystic fibrosis. Current opinion in pulmonary medicine, 2006;12(6), 445-452.
7. Ernst E. Complementary therapies for asthma: what patients use. J Asthma. 1998;35(8):667-71.
8. Forum of International Respiratory Societies. The Global Impact of Respiratory Disease – Second Edition. Sheffi eld, European Respiratory Society, 2017.
9. Györik S, & Brutsche M. Complementary and alternative medicine for bronchial asthma: is there new evidence?. Current opinion in pulmonary medicine, 2004;10(1), 37-43.
10. Halotherapie-zoutkliniek Veenendaal.
11. Hedman J, Hugg T, Sandell J, Haahtela T. The effect of salt chamber treatment on bronchial hyperresponsiveness in asthmatics. Allergy. 2006;61(5):605-10.
12. Horvath T. Speleotherapy: a special kind of climatotherapy, its role in respiratory rehabilitation. Int Rehabil Med. 1986;8(2):90-2.
13. Lazarescu H, Simionca I, Hoteteu M, Mirescu L. Speleotherapy - modern bio-medical perspectives. J Med Life. 2014;7 Spec No. 2:76-9.
14. Lazarescu H, Simionca I, Hoteteu M, Munteanu A, Rizea I, Iliuta A, et al. Surveys on therapeutic effects of "halotherapy chamber with artificial salt-mine environment" on patients with certain chronic allergenic respiratory pathologies and infectious-inflammatory pathologies. J Med Life. 2014;7 Spec No. 2:83-7.
15. Mark, J, & Chung Y. Complementary and alternative medicine in pulmonology. Current opinion in pediatrics, 2015;27(3), 334-340.
16. Rabbani B, Makki SS, Najafizadeh K, Vishteh HR, Shafaghi S, Karimi S, et al. Efficacy of Halotherapy for Improvement of Pulmonary function Tests and Quality of Life of Non-Cystic Fibrosis Bronchiectatic Patients. Tanaffos. 2013;12(2):22-7.
17. Sandell J, Hedman J, Saarinen K, Haahtela T. Salt chamber treatment is ineffective in treating eosinophilic inflammation in asthma. Allergy. 2013;68(1):125-7.
18. Swenson C, Schraufnagel D, Sadikot R. What is Bronchiectasis? Am J Respir Crit Care Med. 2017;195(8):P15-p6.
19. Tarran R, Donaldson S, Boucher RC. Rationale for hypertonic saline therapy for cystic fibrosis lung disease. Semin Respir Crit Care Med. 2007;28(3):295-302.
20. Zhang L, Mendoza-Sassi R, Wainwright, C, Klassen T. Nebulised hypertonic saline solution for acute bronchiolitis in infants. Cochrane database of systematic reviews, 2017;(12).

Figure 1: Flowchart study selection for research question 2

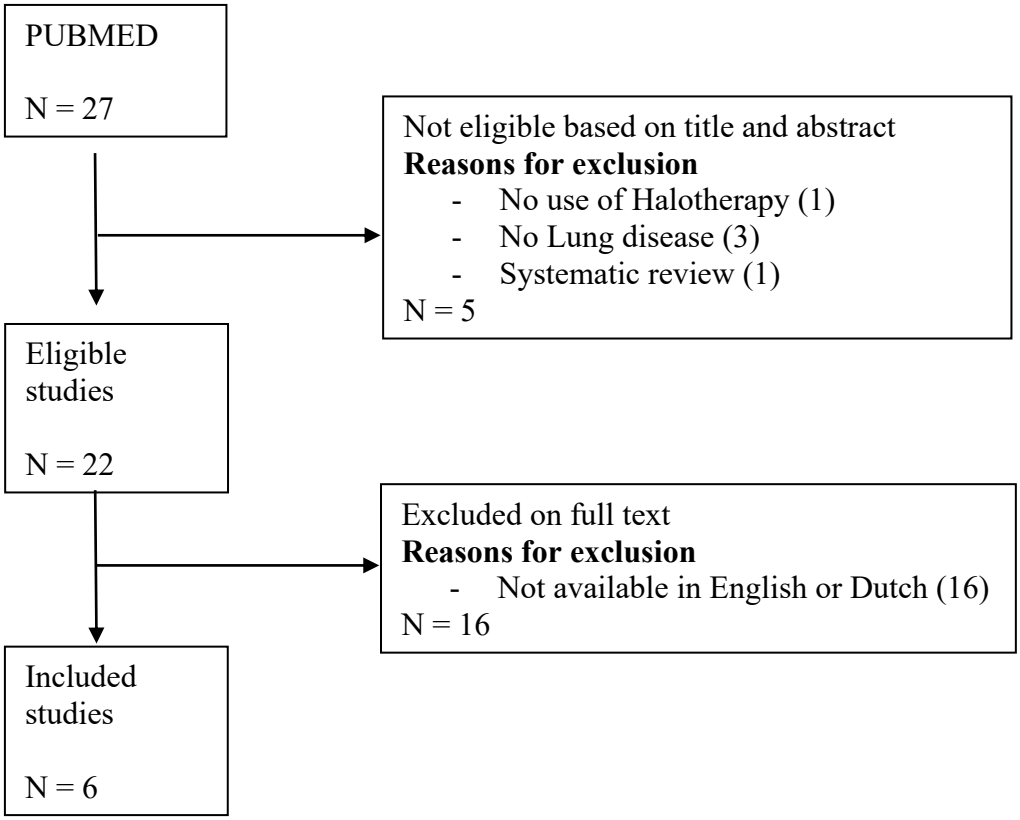

Table 1: Study characteristics of included studies on the effect of halotherapy.

Study	Country	Study Design	Lung disease	Age	Outcome measurements	Results
Bar-Yoseph et al. (2017)	America	Randomized controlled trial	Mild Asthma (n=56)	5-13	QoL: PAQLQ Lung function: Spirometry, BHR, FeNO	Improvement of QoL. Improvement BHR.
Lazarescu et al. (2014)	Romania	Clinical trial	Asthma (n=19)	7-60	Immune indicators: Phagocytes & neutrophils	Stimulation phagocytic processes and non-specific anti-inflammatory resistance.
Rabbani et al. (2013)	Iran	Clinical trial	Non-CF Bronchiectasis (n=20)	20-53	QoL: SF-36 Long function: Spirometry, 6-min walk test	Non-significant improvement of QoL.
Sandell et al. (2012)	Finland	Randomized controlled trial	Asthma (n=39)	18+	Immune indicators: ECP, eosinophils Lung functions: Spirometry, symptoms & medicine use	Non-significant improvement anti-inflammatory indicators. Improvement lung function and asthma symptoms with low-concentration salt.
Hedman et al. (2006)	Finland	Randomized controlled trial	Asthma (n=32)	18+	Lung functions: BHR, spirometry Clinical symptoms: Asthma symptoms, medicine use	Decrease of BHR. Not significant after two months. Increase FEV_1.
Chervinskaya et al. (1995)	Russia	Experimental trial	Asthma, Chronic bronchitis, Bronchiectasis, CF (n=124)	16-62	Lung functions: Spirometry Clinical symptoms: Asthma symptoms	Improvement clinical symptoms. Significant improvement in patients with severe obstruction.

CF = Cystic Fibrosis
QoL = Quality of Life
PAQLQ = Paediatric Asthma Quality of Life Questionnaire
BHR = Broncho hyperreactivity
ECP = Eosinophilic Cationic Protein
FEV_1 = Forces Expiratory Volume in the first minute

Table 2: Characteristics of halotherapy used in the different clinical studies.

Study	Concentration	Particle Size	Humidity	Temperature	Treatment Duration	Amount of treatments
Bar-Yoseph et al.	x	20 mm	44-60%	20-24 ℃	45 min.	14 (7 weeks, 2 times per week)
Lazarescu et al.	x	x	x	x	x	15 (daily)
Rabbani et al.	x (70 grams)	x	x	x	25 min.	56 (2 months, daily)
Sandell et al.	* 1. 6,6 mg/m3 2. 10,8 mg/m3	x	x	x	x	10 (2 weeks, 5 times per week)
Hedman et al.	7,1-7,6 mg/m3	<20 mm	41%	23 ℃	40 min.	10 (2 weeks, 5 times per week)
Chervinskaya et al.	* * 1. 0,5-2 mg/m3 2. 0,5-5 mg/m3 3. 1-9 mg/m3 4. 3-5 mg/m3	2-5 mm	45-55%	18-22 ℃	60 min.	12-25 (daily)

* = Concentration 1 was a low-salt concentration and concentration 2 was a high-salt concentration.
** = Concentration 1 was used for patients with asthma. Concentration 2 was used for patients with chronic bronchitis. Concentration 3 was used for patients with bronchiectasis. Concentration 3 was used for patients with CF.

Table 3: Critical Appraisal of Randomized Controlled Trials

Assessment criteria	Bar-Yoseph et al.	Sandell et al.	Hedman et al.
Was true randomization used for assignment of participants to treatment groups?	Y	Y	Y
Was allocation to treatment groups concealed?	N	U	Y
Were treatment groups similar at the baseline?	Y	Y	Y
Were participants blind to treatment assignment?	Y	Y	Y
Were those delivering treatment blind to treatment assignment?	N	U	U
Were outcomes assessors blind to treatment assignment?	Y	Y	Y
Were treatment groups treated identically other than the intervention of interest?	Y	Y	Y
Was follow up complete and if not, were differences between groups in terms of their follow up adequately describes and analysed?	Y	Y	Y
Were participants analysed in the groups to which they were randomized?	Y	Y	Y
Were outcomes measured in the same way for treatment groups?	Y	Y	Y
Were outcomes measured in a reliable way?	Y	Y	Y
Was appropriate statistical analysis used?	Y	U	Y
Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Y	Y	Y

Y = Yes N = No
U = Unclear NA = Not applicable

Table 4: Critical Appraisal of Quasi-Experimental Studies.

Assessment criteria	Rabbani et al.	Chervinskaya et al.	Lazarescu et al.
Is it clear in the study what is the cause' and what is the 'effect'?	Y	Y	Y
Were the participants included in any comparisons similar?	Y	U	U
Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest?	U	Y	U
Was there a control group?	N	Y	Y
Where there multiple measurements of the outcome both pre and post the intervention/exposure?	Y	Y	Y
Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analysed?	Y	U	Y
Were the outcomes of participants included in any comparisons measured in the same way?	Y	Y	Y
Were outcomes measured in a reliable way?	Y	Y	U
Was appropriate statistical analysis used?	U	Y	U

Y = Yes
N = No
U = Unclear
NA = Not applicable

Table 5: Study design for proposed future studies

Group	Disease	Group size	Treatment	Concentration	Humidity	Temperature	Duration	Amount of treatments
1	Asthma (Mild)	20	Halotherapy	5 mg/m^3	50-70%	15-20 ℃	60 minutes	21 (daily)
2	Asthma (Mild)	20	Halotherapy	10 mg/m^3	50-70%	15-20 ℃	60 minutes	21 (daily)
3	Asthma (Mild)	20	Halotherapy	15 mg/m^3	50-70%	15-20 ℃	60 minutes	21 (daily)
4	Asthma (Mild)	20	Placebo	0 mg/m^3	50-70%	15-20 ℃	60 minutes	21 (daily)
5	Asthma (Severe)	20	Halotherapy	5 mg/m^3	50-70%	15-20 ℃	60 minutes	21 (daily)
6	Asthma (Severe)	20	Halotherapy	10 mg/m^3	50-70%	15-20 ℃	60 minutes	21 (daily)
7	Asthma (Severe)	20	Halotherapy	15 mg/m^3	50-70%	15-20 ℃	60 minutes	21 (daily)
8	Asthma (Severe)	20	Placebo	0 mg/m^3	50-70%	15-20 ℃	60 minutes	21 (daily)

Appendix 1: Search for research question 1 (mechanism of action).

Subject	Search Terms
Lung Diseases	Lung Diseases [Mesh]
	Respiratory Tract Diseases [Mesh]
	Lung Diseases [tiab]
	Pulmonary Diseases [tiab]
	Respiratory Tract Diseases [tiab]
Halotherapy	Halotherapy [tiab]
	Halo-aerosol therapy [tiab]
	Dry salt inhalation therapy [tiab]
	Salt chamber therapy [tiab]

Appendix 2: search for research question 2 (effectiveness of halotherapy).

Subject	Search Terms
Salt Caves	Salt Caves [tiab]
Inhalation	Inhalation [Mesh]
	Inhalation [tiab]
	Inhalating [tiab]
Hypertonic Saline	Saline Solution Hypertonic [Mesh]
	Hypertonic Saline [tiab]
Lung Diseases	Lung Diseases [Mesh]
	Respiratory Tract Diseases [Mesh]
	Lung Diseases [tiab]
	Pulmonary Diseases [tiab]
	Respiratory Tract Diseases [tiab]