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EFFECTIVENESS OF ACUPUNCTURE AS A NONPHARMACOLOGICAL INTERVENTION IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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DECLARATION OF COMPETING INTERESTS

The author declares no competing interests.

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PRESENTATION

This PhD, presented as a publication compendium, is the result of the combination of two of my greatest interests in recent years, acupuncture practice and research.

Since starting my studies in acupuncture, I have always been concerned about trying to learn the most appropriate way to treat patients. However, I soon realised that clinical practice was remarkably diverse among practitioners, even regarding aspects that seem essential for proper treatment such as diagnosis, acupuncture point location or the selection of therapeutic technique. Which one of those practices was the correct one? Which one could lead to a better therapeutic response? Was there any difference between them? Moreover, some people were even saying that acupuncture did not work at all, how could that be?

I first tried to answers these questions by observing the effect of therapeutic interventions in patients; however, this was a difficult task. There were many factors influencing patient responses, including natural changes from the disease, patient attitudes towards the disease and the treatment, the patient-therapist relationship and a large etcetera. I could not help having a feeling of uncertainty about what I was doing.

Some years later, I stared my studies in physical therapy with the idea of enhancing my knowledge and skills, but also hoping that I could somehow get rid of that feeling of uncertainty. I could not have been more wrong since during those years when I just faced the same questions and insecurities. However, during my degree, I was introduced 'evidence-based practice', a new approach to improving clinical practice decisions that seemed to be the answer to all my questions.

Although I soon realised that 'evidence-based practice' was not the ideal and perfect tool I thought it was at first, as it has several limitations and provides clear answers only on a small number of occasions, it really held my interest. I started to review the evidence on the use of acupuncture in several clinical situations, such as musculoskeletal conditions, neurologic disorders, digestive diseases, etc. It was during my third physiotherapy year, learning respiratory rehabilitation, that I stared to review the evidence for acupuncture in lung conditions; I found a recently published randomised control trial by Suzuki et al. on the treatment of chronic obstructive pulmonary disease (COPD). I remember talking about this paper with teachers and

being encouraged to continue researching the topic. That was a game changer for me since until then I had always thought that research was something out of my reach, something I could read about but not actively be part of.

It can be said that this PhD started with my physiotherapy dissertation, where I was encouraged by Dr Mercè Sitjà and tutored by Dr Jordi Vilaró to write a protocol for a systematic review about acupuncture treatment for COPD. Later, both would give me their support and become involved in the development of the systematic review, which resulted in two publications included in this thesis.

After finishing my physiotherapy degree, I decided to increase my knowledge in clinical research by doing a Master's degree in Applied Clinical Research in Health Sciences at the Universitat Autònoma de Barcelona, where I meet Dr Xavier Bonfill and Dr Gerard Úrrutia. That really helped me to improve my knowledge regarding research methodology and introduced me to several aspects that I had not taken into consideration until that moment, such as the completeness of reporting, which is the topic of the third publication of this thesis.

It was also during my Master's degree that I started to explore specific research methodology regarding acupuncture and made contact with researchers in the field. Those contacts would turn out to be essential later for the development of the projects of this thesis, as none of them would have been possible without Dr Jianping Liu and Dr Yutong Fei. Moreover, thanks to them I was also able to carry out a three-month research stay at the Centre for Evidence Based Chinese Medicine of the Beijing University of Chinese Medicine during my PhD.

Looking back, I must admit that after all these years, I have not been able to answer most of the questions that started this journey. However, I do not see these questions as a problem anymore, but rather as a pathway to creating new knowledge through future research.

RESUM

Antecedents: La malaltia pulmonar obstructiva crònica (MPOC) és una afecció d'alta prevalença que afecta el 12% de la població mundial, causada per una inflamació crònica de les vies respiratòries i els pulmons. Aquesta malaltia té un impacte important en la qualitat de vida del pacient provocant dispnea progressiva, tos crònica i producció d'esput, sibilàncies, opressió al pit i poca capacitat d'exercici. Encara que s'utilitzen diverses estratègies de tractament farmacològic i no farmacològic per a la MPOC, el maneig dels símptomes és insatisfactori en molts pacients i per tant, es necessiten noves estratègies. En els últims anys, s'han publicat diversos estudis que suggereixen que les tècniques d'acupuntura podrien ser beneficioses per als pacients amb MPOC; però l'evidència encara no és clara. A més, s'han trobat limitacions en la qualitat de la informació de les intervencions d'acupuntura en estudis anteriors en diferents afectacions com la artrosis de genoll, malalties neurològiques o càncer. Per tant, és important avaluar la qualitat de la informació dels assajos d'acupuntura sobre la MPOC per garantir una adequada avaluació, reproducció i implementació dels resultats dels assajos clínics.

Mètodes: Aquest treball costa de tres publicacions incloent dues revisions sistemàtiques, que avaluen l'efectivitat de les tècniques d'acupuntura més comunament utilitzades, i una avaluació de la qualitat de la informació de les intervencions d'acupuntura en assajos de MPOC.

Resultats: Les nostres dues revisions sistemàtiques van revelar beneficis d'algunes tècniques d'acupuntura en el maneig de el tractament de la MPOC. L'evidència suggereix beneficis de l'acupuntura amb agulla filiforme per a la dispnea, la capacitat d'exercici i la qualitat de vida i possiblement la acupressió per a la dispnea, la qualitat de vida i l'ansietat. No obstant això, l'evidència actual està limitada pel risc de biaix, l'heterogeneïtat i el baix nombre d'assaigs existents.

Pel que fa a la qualitat de la informació de les intervencions d'acupuntura, observem una informació subòptima en diversos elements de la llista de verificació STRICTA, inclosa la profunditat d'inserció de l'agulla, el tipus d'agulla, el nombre de sessions de tractament, el entorn i el context de el tractament, la descripció de l'acupuntura i la justificació del control.

Discussió: La investigació sobre les tècniques d'acupuntura comparteix algunes de les dificultats d'altres intervencions no farmacològiques, inclòs el reduït nombre de participants,

l'heterogeneïtat de la seva pràctica i les dificultats en el procés de cegament. Els investigadors han de ser conscients d'aquestes limitacions al dissenyar assajos futurs i triar els tipus d'intervenció i control més adequats d'acord amb la seva pregunta de recerca específica.

Les deficiències en la qualitat de la informació és un altre tema que s'ha de millorar, tant pel que fa a la metodologia dels assajos com a la descripció de la intervenció. Aquesta manca d'informació no només dificulta l'avaluació de el risc de biaix de l'assaig, sinó que també dificulta l'avaluació i reproducció adequades dels assajos.

Conclusions: Hi ha alguna evidència que l'acupuntura mitjançant agulla filiforme i la acupressió podrien ser útils en el tractament de la MPOC. Per altres intervencions l'evidència és incerta. Calen investigacions futures de més qualitat amb millores en la qualitat de la informació per tenir estimacions més fiables dels efectes de la tècnica d'acupuntura en pacients amb MPOC i permetre una recomanació sòlida pel que fa a l'ús de l'acupuntura.

RESUMEN

Antecedentes: La enfermedad pulmonar obstructiva crónica (EPOC) es una afección de alta prevalencia que afecta al 12% de la población mundial, causada por una inflamación crónica de las vías respiratorias y los pulmones. Esta enfermedad tiene un impacto importante en la calidad de vida del paciente al causar disnea progresiva, tos crónica y producción de esputo, sibilancias, opresión en el pecho y poca capacidad de ejercicio. Aunque se utilizan varias estrategias de tratamiento farmacológico y no farmacológico para la EPOC, el manejo de los síntomas es insatisfactorio en muchos pacientes , por lo que se necesitan nuevas estrategias de tratamiento. En los últimos años, se han publicado varios estudios que sugieren que las técnicas de acupuntura podrían ser beneficiosas para los pacientes con EPOC; sin embargo, la evidencia aún no es clara. Además, se han encontrado limitaciones en la calidad de la información de las intervenciones de acupuntura en estudios anteriores en afecciones como la artrosis de rodilla, enfermedades neurológicas o cáncer. Por lo tanto, es importante evaluar la calidad de la información de los ensayos de acupuntura sobre la EPOC para garantizar una adecuada evaluación, reproducción e implementación de los resultados de los ensayos clínicos.

Métodos: Este trabajo costa de tres publicaciones incluyendo dos revisiones sistemáticas que evalúan la efectividad de las técnicas de acupuntura más comúnmente utilizadas y una evaluación sobre la calidad de la información de intervenciones de acupuntura en ensayos de EPOC.

Resultados: Nuestras dos revisiones sistemáticas revelaron beneficios de algunas técnicas de acupuntura en el manejo del tratamiento de la EPOC. La evidencia sugiere beneficios de la acupuntura con aguja filiforme para la disnea, la capacidad de ejercicio y la calidad de vida y posiblemente la acupresión para la disnea, la calidad de vida y la ansiedad. Sin embargo, la evidencia actual está limitada por el riesgo de sesgo, la heterogeneidad y el bajo número de ensayos existentes.

Con respecto a la calidad de la información de las intervenciones de acupuntura, observamos una información subóptima en varios elementos de la lista de verificación STRICTA, incluida la profundidad de inserción de la aguja, el tipo de aguja, el número de sesiones de tratamiento, el

entorno y el contexto del tratamiento, la descripción del acupunturista y la justificación del control.

Discusión: La investigación sobre las técnicas de acupuntura comparte algunas de las dificultades de otras intervenciones no farmacológicas, incluido el bajo número de participantes, la heterogeneidad de su práctica y las dificultades en el proceso de cegamiento. Los investigadores deben ser conscientes de esas limitaciones al diseñar ensayos futuros y elegir los tipos de intervención y control más adecuados de acuerdo con su pregunta de investigación específica.
Las deficiencias en la calidad de la información es otro tema que debe mejorarse, tanto en lo que respecta a la metodología de los ensayos como a la descripción de la intervención. Esta falta de información no solo dificulta la evaluación del riesgo de sesgo del ensayo, sino que también dificulta la evaluación y reproducción adecuadas de la del ensayo.

Conclusiones: Existe alguna evidencia de que la acupuntura mediante aguja filiforme y la acupresión podrían ser útiles en el tratamiento de la EPOC. Para otras intervenciones la evidencia es incierta. Se necesitan investigaciones futuras de mayor calidad con mejoras en la calidad de la información para tener estimaciones más confiables de los efectos de la técnica de acupuntura en pacientes con EPOC y permitir una recomendación sólida con respecto al uso de la acupuntura.

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a highly prevalent condition, affecting 12% of the global population; it is caused by chronic airway and lung inflammation. This disease has an important impact on patient quality of life by causing progressive dyspnoea, chronic cough and sputum production, wheezing, chest tightness and poor exercise capacity. Although several pharmacological and non-pharmacological treatment strategies are used for COPD patients, they only aim to reduce the progression of the disease and control symptoms as much as possible. However, symptom management is till unsatisfactory in many patients and therefore new strategies are needed. Acupuncture is a therapeutic technique that originated from traditional Chinese medicine. It uses several stimulation methods, most of them non-pharmacologic, and has been traditionally used to treat multiple diseases, including respiratory conditions such as COPD. In recent years, several studies have been published suggesting that acupuncture techniques could be beneficial to COPD patients; however, the evidence is still not clear. Moreover, limitations on the completeness of reporting of acupuncture interventions have been found in past trials in different clinical health conditions, such as knee osteoarthritis, neurological diseases or cancer. Therefore, it is important to assess the current completeness of reporting of acupuncture trials on COPD to ensure the proper assessment, replication and implementation of the results of clinical trials.

Methods: This work resulted in three publications on this topic, including two systematic reviews assessing the effectiveness of the most common used acupuncture techniques and an assessment on the completeness of reporting of acupuncture interventions in COPD trials.

Results: Our two systematic reviews revealed benefits for some acupuncture techniques in the management of COPD treatment. Evidence suggests benefits of filiform needle acupuncture for dyspnoea exercise capacity and quality of life and possibly for acupressure for dyspnoea, quality of life and anxiety. However, the current evidence is limited by the risk of bias, heterogeneity and low number of existing trials.

Regarding the completeness of reporting of acupuncture interventions, we observed suboptimal reporting in several items of the STRICTA checklist, including needling insertion depth, needle

type, number of treatment sessions, setting and context of the treatment, description of the acupuncturist and control rationale.

Discussion: Although acupuncture techniques have been used for decades in China to treat lung diseases such as COPD, current evidence regarding its efficacy is still limited. Research into acupuncture techniques share some of the difficulties of other non-pharmacological interventions, including low number of participants, the heterogeneity of its practice and difficulties in the blinding process. Researchers must be aware of those limitations when designing future trials, and choose the most adequate intervention and control types according to their specific research question.

Deficiencies in acupuncture publications reporting is another issue that needs to be improved, both regarding the trials methodology and the intervention description. This lack of information does not only stifle the assessment of the trial's risk of bias, but also hinders the adequate assessment and reproduction of acupuncture research. Reporting guidelines such as CONSORT and STRICTA must be used to guarantee proper reporting in the published papers.

Conclusions: There is some evidence that filiform needle acupuncture and acupressure could be helpful in the treatment of COPD. For other interventions, i.e. moxibustion, acuTENS, ear acupuncture and cupping, the evidence is unclear. Future large high-quality research with better reporting is needed to have more reliable estimates of acupuncture technique effects in COPD patients to allow solid recommendation regarding acupuncture use.

INTRODUCTION

Acupuncture

Acupuncture is a therapeutic technique that originated from the principles of traditional Chinese medicine (TCM) about 2500 years ago. It is a complete medical system with its own specific human physiology, pathology, disease terminology, and diagnosis and therapeutic methods. This system has developed over its history and is closely linked to philosophical ideas and other aspects of Chinese culture (1).

The term 'acupuncture' originated from the Latin words 'acus', which means needle, and 'punctura', which means to needle or to stick needles (2). This might be the reason why in the West acupuncture is usually described as a therapeutic technique consisting of inserting fine needles in special locations on the body surface called 'acupuncture points', this idea can be seen in the current definition of the American Academy of Medical acupuncture which describes acupuncture as 'the stimulation of special points on the body, usually by the insertion of fine needles' (1).

However, the Chinese name for acupuncture is ZhenJiu (针灸), which incorporates two words or characters. The first character, Zhen (针), could be translated as metal or metal needle, while the second one, Jiu (灸), means heating or more accurately in this context moxibustion, a therapeutic technique consisting of applying heat using the combustion of *Artemisia vulgaris*. Thus, the original word in Chinese indicates that acupuncture is not only reduced to inserting needles, but other stimulations can be applied to acupuncture points (2). It is very common in clinical practice to stimulate acupuncture points with several methods such as pressure or massage (acupressure), heat (moxibustion), electricity (electroacupuncture) or even applying a mixture of plants (3).

According to the World Federation of Acupuncture-Moxibustion Societies, the lack of consensus on the basic definition of acupuncture has been an obstacle to clinical practice, research and legislation. Therefore, a project to develop its definition and basic scope has been proposed (4).

History

The first medical instruments found in China were sharpened stones and bones from around 6000 BCE; these instruments have sometimes been claimed to be the first primitive acupuncture needles. However, it is mostly believed that they were just instruments for common medical practices of the age, such as bloodletting or lancing abscesses. The first document that can be considered to unequivocally refer to acupuncture practice is Huang Di Nei Jing (The Yellow Emperor's Classic of Internal Medicine) written from 200 BCE to 200 CE. This text is a compilation of medical traditions and knowledge over several centuries and includes concepts such as the meridian system and Qi. This book is still considered a reference for many TCM practitioners today and is referenced in most modern TCM textbooks. Acupuncture continued to develop in the following centuries; for example, the specific locations of meridians and acupuncture points were more precisely described first using bronze statues in the 15th century and later through the work ZhenJiu Da Cheng (The Great Compendium of Acupuncture and Moxibustion) compiled from approximately 1522 to 1620 AD, which is the basis of modern acupuncture (5). Despite this, acupuncture has not always been a popular healing method in China, as in the 17th century this technique was excluded from the Imperial Medical Institute since it was claimed to be superstitious and irrational and mainly practiced by rural doctors. This situation worsened even further during the 20th century when the practice was banned in 1929, along with other forms of traditional medicine, due to the increasing acceptance of Western medicine. However, when the Communist government was installed in 1949, the practice of acupuncture was not only restored, but divergent practices and theories were standardised, and the first acupuncture research institutes were created. Since that period, acupuncture and TCM practice have coexisted with Western medicine in China (6).

Acupuncture arrived in Europe through merchant trading with China and Japan, especially from 1500 to 1700. French Jesuits spread this technique, using it to treat several pain disorders. During the following centuries, several clinical applications were developed by French, Portuguese, German, English and Italian physicians. All these clinical experiences shaped different opinions on the efficacy of acupuncture and led to the establishment of the International Society of Acupuncture in 1941 (7).

Traditional rationale

The main principles of TCM were defined before the second century BCE and second century CE and are based on the ideas and knowledge of the then-contemporary inhabitants of southeast Asia. Since these principles and nomenclatures have remained relatively unchanged until our day, they are not based on modern scientific theories.

The traditional vision of TCM states that all internal and external functions of the human body are produced by a vital energy called 'Qi'. This energy flows through the entire body through the meridian system and with other nutritious substances, like Xue (blood) and organic liquids; it regulates and nourishes all organs and tissues. In TCM, health is determined by the balance between the body functions and the environment; this idea of balance is mainly represented by the Yin and Yang theory. Therefore, any kind of disease is produced by an imbalance of Yin and Yang, which is manifested as an alteration of the normal flow of Qi. To restore the Qi flow, and therefore health, acupuncture techniques are used to stimulate acupuncture points located along the superficial path of the meridian system. Other classical theories used in TCM are the five elements (or movements) and the Zang/Fu theories, which are used to divide all physiologic processes of the human body in to five main groups, or elements, which are 'commanded' by the five Zang (organs) and the five Fu (viscera) (8–10). All these theories create a unique vision of human health that classifies illnesses into various exogenous and endogenous pathogenic factors, using terms such as 'kidney yang deficiency', 'water and fire imbalance' or 'heart blood insufficiency.'

Due to the expansion of acupuncture use and its adoption and implementation in different countries and cultures, various acupuncture styles have emerged. These differences are usually more related to diagnostic methods and theories regarding the selection of acupuncture points rather than the use of different acupoints or techniques.

TCM acupuncture is the most common acupuncture style. As previously explained, the communist government performed acupuncture standardisation in 1949 to systematise its practice in China. This standardised style is the one taught in TCM colleges and universities since the 1950s, and has become the mainstream style. However, other acupuncture practices and schools still exist within TCM, with differences in diagnostic and treatment methods (6). Korea and Japan, for example, have developed their own acupuncture styles by mixing traditional Chinese medicine theories with their own traditional medicines. This has led to the creation of different practices and approaches (11), such as the 'constitutional energy' concept, which is the main basis of Korean acupuncture (12).

Besides these different acupuncture styles based on traditional theories, in recent years, modern approaches to acupuncture have also been developed. Western medical acupuncture uses a scientific rationale based on human anatomy, physiology, and pathology instead of using traditional theories (e.g. Yin/Yang, Qi, Zang/Fu) (13).

Scientific rationale

The scientific study of acupuncture started during the modernisation period of this technique under the government of Mao Zedong; however, research at that time was unknown to many Western scientists since articles were mainly published in Chinese journals (14).

In the 1970s, several studies were published about the analgesic mechanism of acupuncture (15–18), and acupuncture was linked to the peripheral and central nervous system, leading to the endorphin theory (19,20). Interestingly, investigation in this field lead to the development of other pain control methods such as acupuncture-like transcutaneous nerve stimulation (AL-TENS) (21). Since those early studies, great progress has been made in the research field of acupuncture mechanisms, which has included research on meridians and acupuncture points, acupuncture neural pathways and its effects on several brain regions.

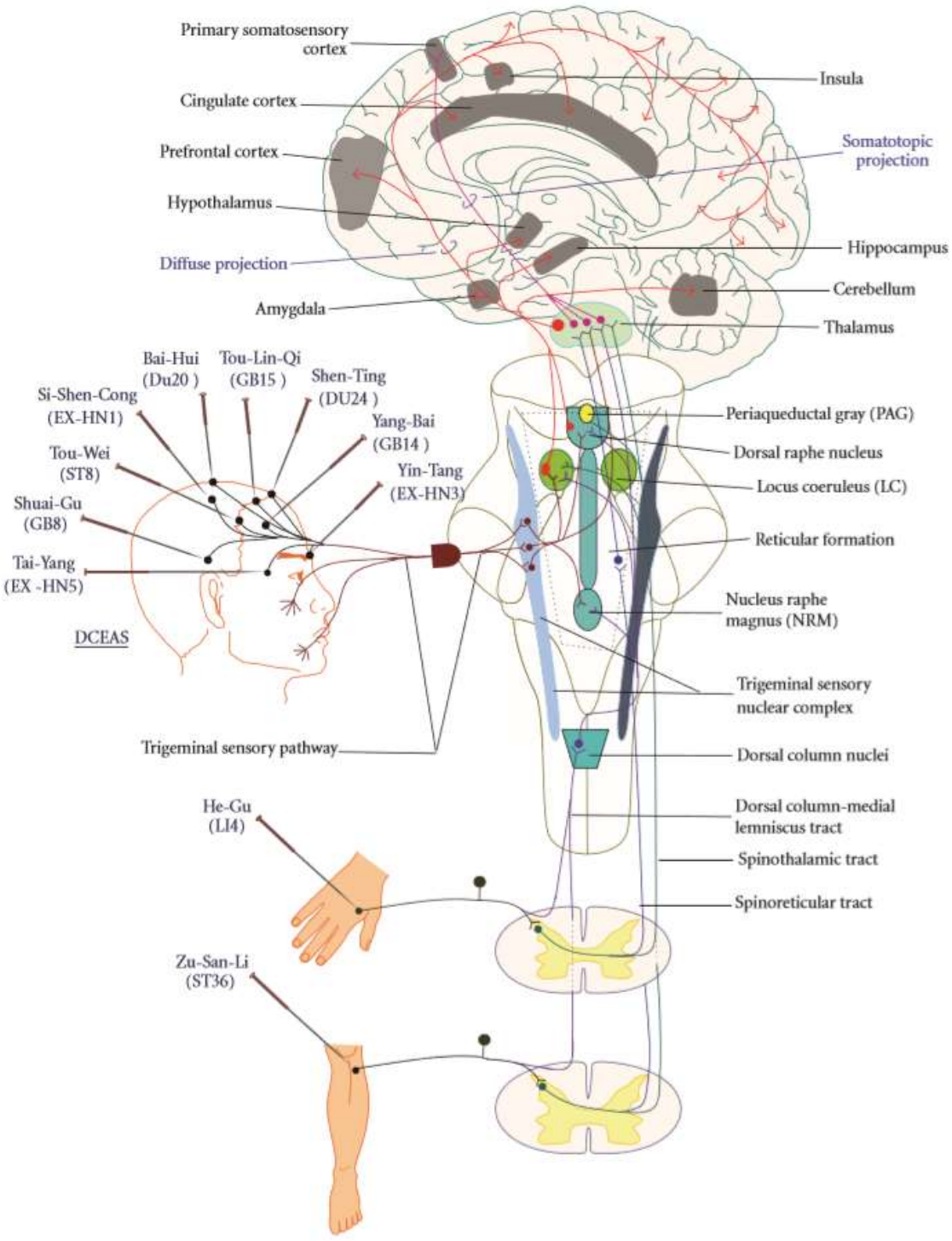
In recent years, meridians have been defined as anatomical structures by some researchers; for example, the primo vascular system (22) and the fascia system (23) have been proposed. The 'meridians phenomena', which refers to the propagated sensation along the path of meridians, has been studied using thermal and radioactive trace imaging techniques, but although results have partially showed the routes of some meridians, they have failed to identify the meridian system (24).

Researchers have tried to define acupuncture points define using electrode measurements of skin resistance, but this has not proven to be a method capable of discriminating between acupoints and non-acupoints (25,26). Many researchers have suggested that the meridian system is simply a functional but not anatomical concept, and includes a combination of many physiological systems, particularly the peripheral and central nervous system (27).

It has been proposed that acupuncture stimulation activates different receptors in the skin and deep tissue sensory afferent nerves. This stimulation usually triggers what is called the 'De Qi' or Qi sensation (27,28). The 'De Qi' is perceived in different ways depending on the afferent fibres stimulated and can include paraesthesia (β fibres), pressure or strain (Aγ fibres), shooting pain wind chill (Aδ), slow pain, pressure or temperature (C fibres) (29). After the stimulation of

these receptors, the stimulus is transmitted to the central nervous system through various afferent ascending pathways (dorsal column-medial lemniscus tract, spinothalamic tract, spinoreticular tract and trigeminal sensory pathway), reaching the brain stem and thalamus and stimulating different brain areas (Figure 1) (30).

Figure 1: Acupuncture neural pathways. Image from Zhang et al. (30)



The study of the changes to brain regions induced by acupuncture has been increasing in recent years and has targeted either acupoint specificity and acupuncture therapeutic mechanisms (31). Research in the field has been complex and heterogeneous; however, several systematic reviews have concluded that acupuncture may have specific effects on the central nervous system.

In the review by Huang et al., published in 2012 (32), the authors screened articles from English, Chinese, Korean and Japanese databases for studies applying functional magnetic resonance imaging to investigate brain responses to acupuncture. It was concluded that acupuncture stimulation modulates activity within specific brain areas, including the somatosensory cortices, limbic system, basal ganglia, brain stem and cerebellum.

More recently, Cai and colleges published a similar work in 2018 (33) with similar conclusions. In this paper, the authors screened all papers about brain functional connectivity networks in acupuncture research in humans published in PubMed in the English language. They concluded that acupuncture seemed to produce changes in several brain regions such pain, affective and memory-related brain areas. The review also found differences in brain connectivity when comparing acupuncture with sham acupuncture in the periaqueductal grey, the anterior cingulate cortex, left posterior cingulate cortex the insula, limbic/paralimbic areas and praecuneus. Moreover, the authors also stated that acupuncture could also regulate the limbic-paralimbic neocortical network, brainstem cerebellum, subcortical and hippocampus brain areas.

These findings were used to hypothesise a possible explanation to the potential effects of acupuncture in several clinical situations. Table 1 summarises the relation of several of the mentioned brain regions and their associated effects.

Table 1: Brain regions regulated by acupuncture and associated effects.

BRAIN REGION	FUNCTION (34)
Periaqueductal grey (PAG)	Pain, sleep, and consciousness
Anterior cingulate cortex	Pain, attention, memory, and emotion
Left posterior cingulate cortex	Cognition, attention, affect
Insula	Pain
Limbic/paralimbic areas	Emotions, memory, behabiour, motivation
Praecuneus	Conciousness, memory, space attention, executive fucntions
Brainstem	Cardiovascular system control, respiratory control, pain sensitivity control, alertness, awareness, and consciousness
Cerebellum	Locomotor coordination, higher-order cognitive and emotional function
Hypothalamus	Autonomic, neuroendocrine, visceral function and stress-processing center

Acupuncture techniques

Acupuncture is usually described in the West as a technique consisting of the insertion of fine needles; however, several other techniques are usually used alone or in combination. Some of the most commonly used acupuncture techniques are described below.

Filiform needle is the most well-known acupuncture technique and involves the insertion of very fine needles in the skin and muscle tissues. Needles are stainless steel, usually single use and have different lengths (commonly from 15 mm to 40 mm) and diameters (from 0.20 to 0.30 mm). Needles are inserted at different depths and using different angles depending on the selected point. In this technique, acupuncture stimulation is achieved not only by the insertion of the needle but also by its manipulation using rotation, lifting and thrusting movements until achieving the 'De Qi' sensation (35). Filiform needle acupuncture is considered a relatively safe treatment when provided by well-trained practitioners, since the most common side effects are minor events such as bleeding, haematoma, pain and vegetative symptoms. However, in some rare cases (less than 1 out of 10,000 treated people), severe events, including nerve lesions or internal organ injuries such as pneumothorax, can also occur (36,37).

Electroacupuncture (EA) consists of the percutaneous electrical stimulation of acupuncture points using an electronic device attached to acupuncture needles. Currently, EA is mostly used as an additive to manual acupuncture rather than a different technique (38). Most safety implications regarding EA are theoretical and based on research on the filiform needle technique. However, due to the electric stimulation delivered, it is not considered suitable for people with epilepsy, in the recovery phase of a stroke or with implanted medical devices (39).

AcuTENS is a modern acupuncture technique that consists of the stimulation of acupuncture points using transcutaneous electrical nerve stimulation (TENS). The main difference with electroacupuncture is its invasiveness, since the current is applied without piercing the skin. While electroacupuncture is applied through acupuncture needles, acuTENS uses transcutaneous electrodes (40). Due to its minimal invasiveness, acuTENS is considered safer than the filiform needle technique as it avoids the risk of bleeding, hematoma and tissue injuries; however, TENS is not recommended for patients with a pacemaker, epilepsy or heart problems, or in pregnant women (41).

Moxibustion consists of applying heat using the combustion of moxa (*Artemisia vulgaris*). The main moxibustion techniques include using a moxa stick, applying moxa cones to the skin surface or burning small pieces of moxa on top of acupuncture needles (42). Adverse events

related to moxibustion are rarely reported and therefore is considered a safe technique. However, this technique can cause irritation due to the moxibustion smoke and blisters or skin burns if it is not performed carefully (43).

Acupressure consists of the stimulation of acupuncture points and meridians using pressure with the therapist's or the patient's fingers. However, other devices such as elastic or inelastic bands, mats or different shaped objects designed for applying pressure to specific points can also be used (44).

Ear acupuncture, or auricular therapy, is a system of acupuncture with its own areas of stimulation on the surface of the auricle. This technique does not rely on the usual acupuncture points and meridians. Ear acupuncture includes several stimulation methods such as needling, using moxibustion, electroacupuncture, laser, acupressure seeds or even bloodletting (45). Possible side effects related to ear acupuncture depend on the stimulation method used (filiform needle, moxibustion, electroacupuncture, etc.), but they are all considered transient, mild and tolerable (46).

Besides the non-pharmacological acupuncture simulation methods mentioned above, several pharmacological methods are also used in TCM. Acupoint injection therapy and pharmacopuncture consists of the injection of different substances (medicines, self-blood, oxygen, and allergens or herbal extracts) into acupuncture points. These therapies are widely used in traditional East Asian medicine but very rare in the rest of the world (47). Another pharmacological technique is acupoint herbal patching, which is a TCM external therapy that combines the function of herbs on acupuncture points to maximise its therapeutic effect. This technique is commonly used for preventing acute attack of respiratory diseases such as asthma and chronic obstructive pulmonary disease, in many regions of mainland China (48).

Evidence-based practice in acupuncture

Evidence-based practice (EBP), or evidence-based medicine, was defined by Sackett in 1996 as 'the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients' (47). In EBP, clinical expertise, patient values and preferences and best research evidence are considered while making decisions about health care.

EBP is essential for health professionals and policy makers to reduce variations in clinical practice, enhance best practice, reduce costs, improve the quality of healthcare and increase patient satisfaction. For these reasons, in recent years, health professions have been seen the necessity of increasing the evidence of their therapeutic strategies, including acupuncture, which has translated in an exponential increase in research publications.

Evidence-based practice method

EBP uses a five steps process to find the best available evidence to guide clinical decisions (49).

The first step of the process is formulating a good research question, which is essential to identify research key concepts and stablish the appropriate sources for the research. To formulate precise and structured research questions, the PICO framework is usually used in EBP, defining the Problem/Population, Intervention, Comparison and Outcome of interest.

Once the research question is formulated, the second step consists of research to obtain information to answer the question. This is usually done by systematically reviewing the available evidence on the topic, using the most appropriate study designs depending on the nature of the research question. For example, to answer a therapeutic research question regarding efficacy and effectiveness, randomised controlled trials (RCTs) are screened, while for a prognosis research question, cohort and case-control studies are used. To do so, a search strategy is designed by combining search terms in multiple research databases and defining appropriate inclusion and exclusion criteria according to the research question.

The third step consists of examining the information found and assessing its validity and relevance. For this, not only is the relevance of the information to the question taken into consideration, but also the appropriateness of the methods and possible risk of bias.

Fourth, once the information has been obtained and assessed, it must be implemented into clinical practice. For this process, evidence must be integrated with clinical experience and patient preferences while taking into consideration its effectiveness, risks and adverse events, costs, applicability and implementation.

Finally, the fifth step of the process consists of the evaluation of the clinical results derived from the implementation of the intervention. This step may also lead to the formulation of a new research question for future improvement, turning the process in to a circle.

Randomised controlled trials and systematic reviews

As mentioned, RCTs and systematic reviews (SR) of RCTs, are the golden standard for assessing therapeutic interventions (50).

In RCT participants are usually divided into two groups or arms, the intervention group and the control group using a randomisation method to guarantee the equality and comparability between arms at the begging of the trial. This procedure minimises the variability of the groups by balancing possible confounding such as sex, age, health status etc., reducing the risk of systematic errors that might bias the results. Any randomisation method is considered valid in RCT, such as throwing a coin, picking a card or using random number tables, however, in large trials computer programming randomisation is used (51). In the intervention group participants receive the treatment that wants to be tested while depending on the aim of the trial, the control group may receive an active intervention, a sham intervention or even no treatment at all (waiting list) (52).

Due to the exponential increase of RCT publications, SR summarising the existence evidence are essential for health providers, researchers and policy makers to keep up with the literature. However, for these reviews to be useful, they need to be unbiased, so their conclusions can be reliable. SR involve a detailed and comprehensive plan and search strategy to identify, appraise and synthesise all relevant studies on a particular topic. To do so, a search strategy is developed to detect all relevant trials assessing the research question using several electronic data bases and may also include key journal or conference proceedings hand search. Once potential studies have been detected, study selection and data extraction is performed using the predefined inclusion and exclusion criteria. Regarding the analysis of the results, in a SR results can be analysed using descriptive and/or quantitative analysis. Descriptive analysis is used to inform about the number of trials screened and finally included in the review, the characteristics of participants, interventions, controls and outcomes used in the included trials. To analyse the effect of the interventions usually a quantitative analysis, called meta-analysis is used. Meta-analysis is a statistical method to pool data from different studies increasing statistical power of the individual trials and offering a more precise estimation of the real effect of the intervention (53). However, if it is not possible to perform a meta-analysis a descriptive analysis is used. Despite following all required steps to perform a good quality SR, the reliability of its conclusions

depends on the quality of the included trials since flaws in the design, conduct, analyses, and reporting can lead to underestimate or overestimate the effect of an intervention (54). To assess the risk of bias, SR use different tools such as the Cochrane Risk of Bias Tool (RoB) (55), and its most recent update RoB 2 (56), or the PEDro Scale (57).

Evidence on the effectiveness of acupuncture

Currently, there are more than and 4,300 RCT and 1,506 SR indexed in PubMed under the MeSH term 'acupuncture therapy' (58). Acupuncture research has had a high growth rate in the past two decades, increasing not only the number of RCT but also the impact factor of the journals in which they are published (59). Some examples of this are papers published in journals such as Nature Medicine (60), Journal of the American Medical Association (JAMA) (61), JAMA Internal Medicine (62) and Annals of Internal Medicine (63). As a result of this increase in the quantity and quality of acupuncture research, positive conclusions and recommendations are increasing in systematic reviews.

A summary of most recent systematic reviews with positive conclusions regarding acupuncture is presented in Table 2.

Table 2: Conditions with positive conclusions for acupuncture in recent SR.

CONDITION	SR (JOURNAL ABBREVIATION, YEAR)	CONCLUSION
Chronic pain	Acupuncture for chronic pain: update of an individual patient data meta-analysis (J Pain, 2018) (64)	Acupuncture is effective for the treatment of chronic musculoskeletal, headache, and osteoarthritis pain
	Non-invasive nonpharmacological treatment for chronic pain: a systematic review (Agency for Healthcare Research and Quality, 2018) (65)	Acupuncture can improve function and/or pain for at least one month after treatment
Low back pain	Evidence of efficacy of acupuncture in the management of low back pain: a systematic review and meta-analysis of randomised placebo- or sham-controlled trials (Acupunct. Med., 2019) (66)	There is moderate evidence of efficacy for acupuncture in terms of pain reduction immediately after treatment (sub)acute and chronic) when compared to sham or placebo acupuncture
	Cost-effectiveness of non-invasive and non-pharmacological interventions for low back pain: a systematic literature review (Appl. Health Econ. Health Policy, 2017) (67)	On the whole, the identified evidence on acupuncture interventions is supportive of the idea that provision of acupuncture, either on its own or in combination with usual care or other active treatments, improves low back pain and is a cost-effective option.

Migraine	Acupuncture for the prevention of episodic migraine (Cochrane Database Syst. Rev., 2016) (68)	Adding acupuncture to symptomatic treatment of attacks reduces the frequency of headaches
Tension-type headache	Acupuncture for the prevention of tension-type headache (Cochrane Database Syst. Rev., 2016) (69)	Acupuncture is effective for treating frequent episodic or chronic tension-type headaches
Knee osteoarthritis	Cost-effectiveness of adjunct non-pharmacological interventions for osteoarthritis of the knee (PLoS One, 2017) (67)	Acupuncture is cost-effective at this threshold, and thresholds down to £14,000 per quality adjusted life year.
Pelvic pain	Interventions for preventing and treating low-back and pelvic pain during pregnancy (Cochrane Database Syst. Rev., 2015) (70)	Evidence from single studies that acupuncture significantly improves evening pelvic pain better than stabilising exercises or usual prenatal care
Chronic prostatitis pain	Non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome: a Cochrane systematic review (BJU Int., 2019) (71)	Acupuncture is likely to result in a decrease in prostatitis symptoms
Fibromyalgia	Comparing verum and sham acupuncture in fibromyalgia syndrome: a systematic review and meta-Analysis (Evid Based Complement Alternat Med., 2019) (72)	Verum acupuncture is more effective than sham acupuncture for pain relief, improving sleep quality, and reforming general status in fibromyalgia syndrome posttreatment. However, evidence that it reduces fatigue was not found.

Moreover, several clinical guidelines have started to include acupuncture as a possible therapeutic option in condition such as osteoarthritis, low back pain, cervical pain, headache, depression, cancer care and allergic rhinitis.

A summary of current clinical guidelines with recommendations for acupuncture treatment is shown in Table 3.

Table 3: Conditions with positive recommendations for acupuncture in practice clinical guidelines.

CONDITION	CLINICAL GUIDELINE (COUNTRY, YEAR)	RECOMMENDATION
Osteoarthritis	2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee (EEUU, 2020) (73)	Acupuncture is conditionally recommended for patients with knee, hip, and/or hand osteoarthritis
Low back pain	Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline (EEUU, 2017) (74)	Evidence supports the effectiveness of acupuncture for chronic low back pain (low to moderate strength of evidence) Limited evidence shows that acupuncture is modestly effective for acute low back pain (low strength of evidence)

	Non-Specific Low Back Pain (Germany, 2017) (75)	Acupuncture can be used to treat chronic low back pain as part of an overall concept in combination with activating therapeutic measures
Cervical pain	The Global Spine Care Initiative: applying evidence-based guidelines on the non-invasive management of back and neck pain to low- and middle-income communities (International, 2018) (76)	For patients with chronic spinal disorders without serious pathology clinicians may also consider acupuncture.
	National Clinical Guidelines for non-surgical treatment of patients with recent onset neck pain or cervical radiculopathy (Denmark, 2017) (77)	Consider offering acupuncture in patients with recent onset neck pain in addition to other treatment
Headache	Diagnosis and management of headaches in young people and adults: summary of NICE guidance (UK, 2012) (78)	Consider a course of up to 10 sessions of acupuncture over five to eight weeks for the prophylactic treatment of chronic tension-type headache. Consider a course of up to 10 sessions of acupuncture over five to eight weeks according to the person's preference, comorbidities and risk of adverse events if both topiramate and propranolol are unsuitable or ineffective.
Major depression	Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder (Canada, 2016) (79)	Acupuncture is recommended as a third-line treatment, with Level 2 evidence in the adjunctive treatment of mild to moderate major depressive disorder
Cancer care	Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline (EEUU, 2016) (80)	Clinicians may prescribe directly or refer patients to other professionals to provide acupuncture. Evidence quality: low; strength of recommendation: weak
	Management of menopausal symptoms in women with a history of breast cancer-Clinical Practice Guideline (Australia, 2016) (81)	Acupuncture and electro-acupuncture can be considered for the management of moderate to severe vasomotor symptoms in women with a history of breast cancer. Grade D Acupuncture can be considered for the management of sleep disturbance in women with a history of breast cancer. Grade C
	Clinical practice guidelines on the evidence-based use of integrative	Acupressure and electroacupuncture are

	therapies during and after breast cancer treatment (EEUU-Canada, 2017) (82)	recommended for reducing chemotherapy-induced nausea and vomiting.
	Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline (EEUU, 2018) (83)	Acupressure and acupuncture are recommended for reducing chemotherapy-induced nausea and vomiting. Grade B
Allergic rhinitis	Clinical Practice Guideline: Allergic rhinitis (EEUU, 2015) (84)	Clinicians may offer acupuncture, or refer to a clinician who can offer acupuncture, for patients with allergic rhinitis who are interested in non-pharmacological therapy.

Despite all the research that has been done, the evidence for acupuncture is considered inconclusive for many disorders. Even in fields where systematic reviews have suggested acupuncture as a reasonable option, such as chronic pain, acupuncture remains underused in mainstream practice (85). Actually, acupuncture practice is quite controversial and has been claimed to be merely a placebo.

This situation is probably due to the existence of conflicting results. Several acupuncture trials have found positive effect when acupuncture is compared to usual care but not when comparing it with sham acupuncture. An excellent example of this phenomenon is a study performed by Haake et al. on chronic low back pain (86). In this large three-arm multicentre RCT with 1,162 participants performed in Germany, the effectiveness of real and sham acupuncture, with a response rate of 47.6% and 44.2% respectively, almost double that of the conventional therapy (a combination of drugs, physical therapy and exercise) with a response rate of 27.4%. However, the difference between the real and sham acupuncture groups was not statistically significant.

New studies have shown that a difference between real and sham acupuncture does exist, as shown in a meta-analysis by Vickers et al. (64), but it is small and a large sample size is needed to detect it. This review included 39 RCTs, with 20,827 participants with non-specific musculoskeletal pain, osteoarthritis, chronic headache or shoulder pain, and found superiority of acupuncture with effect sizes close to 0.5 in comparison to the no acupuncture control and 0.2 for the comparison with sham control.

Although critics still claim that this proves that acupuncture is only a placebo and the small differences found could be due to bias induced by the methodological flaws of the included studies, others find it questionable that a simple placebo can outperform usual care (87).

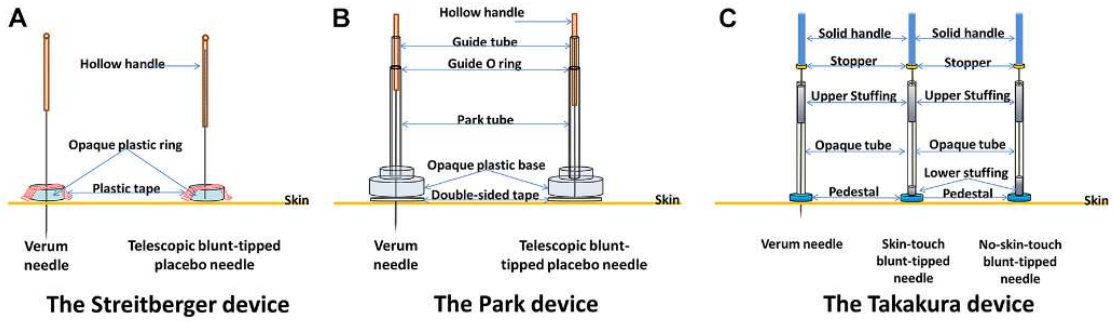
Risk of bias in acupuncture trials

Bias can be defined as 'a systematic error, or deviation from the truth, in results' and can lead to the over or under-estimation of the results of a clinical trial (88). Those errors are derived from problems in the methodology of a study, and should be taken into consideration when interpreting the conclusions of a trial. In fact, risk of bias is the most common reason in SR and clinical guidelines for lowering the strength of the conclusions and recommendations about acupuncture.

There are several sources of risk of bias in acupuncture trials; however, those presented here are those caused by intrinsic characteristics of the intervention and those caused by methodological flaws.

Risk of bias caused by the intrinsic characteristics of the technique include limitations such as the lack blinding of participants and practitioners. Lack of blinding of participants can lead to placebo or nocebo responses due to positive or negative expectations to the received intervention. Lack of blinding of the person delivering the intervention can also have an impact on the results due to differences in the interaction with participants in the intervention and control groups, which may include more attention or empathy. However, those limitations are difficult to avoid in non-pharmacological intervention trials. In the case of acupuncture, acupuncture-naïve patients can be blinded using needle-insertional and non-insertional sham controls. Needle-insertional sham controls include regular needling of non-acupuncture points or irrelevant acupuncture points (real but with an irrelevant action for the study) and shallow needling at non-acupuncture, irrelevant or real acupuncture points. Non-insertional sham controls use devices with a blunt retractile needle that simulate piercing into the skin. They are used in conjunction with real needle devices that are exactly the same except for the needle, which is non-retractile and actually pierces the skin (Figure 2). Despite these strategies, currently there are no methods that can blind the person performing the acupuncture treatment (89).

Figure 2: Non-Insertion Sham Controls. Image from Zhang et al. (89)



Risk of bias caused by methodological flaws is produced by avoidable sources of bias and include issues with the comparability of study participants due to deficiencies in the randomisation and allocation process (selection bias), problems with the measurement of the outcomes due to the lack of blinding of assessors (detection bias) and issues due to missing information regarding the study outcomes or participants dropout (reporting bias). However, many acupuncture trials do not report enough information to assess the mentioned sources of bias. For example, a recent cross-sectional study examined the risk of bias in acupuncture RCTs for knee osteoarthritis. The study found a lack of reporting in 39.9% of the trials regarding the randomisation process, 87.5% regarding allocation concealment and 87.6% regarding blinding of personnel and outcome assessors (90).

Completeness of reporting in acupuncture trials

To be able to adequately assess health research, complete and clear information on its methodology and findings must be adequately reported, but the completeness has been considered suboptimal in acupuncture trials (91,92). This problem has not only been reported in acupuncture trials since similar issues have been found in other medical specialities (93,94). To ensure transparency, reporting guidelines (RG) have been created to help authors to provide all relevant information of their research.

'Standard Protocol Items: Recommendations for Interventional Trials' (SPIRIT) and the 'CONsolidated Standards Of Reporting Trials' (CONSORT) statements are the two main guidelines for reporting intervention trials. The SPIRIT statement was designed to facilitate high quality reporting for clinical trials protocols and consists of a 33-item checklist of recommended items and a diagram focusing on study planning, conduct, reporting and appraisal (95), while the CONSORT statement focuses on the reporting of randomised trials and consists of a 25-item checklist focussing on the design, analysis and interpretation of the trial, and a flow diagram to

detail participant progress (96). In addition, the CONSORT statement has been expanded with multiple extensions to cover different variations of a standard two group parallel design such as cluster trials (97), non-inferiority trials (98), pragmatic trials (99), etc. Moreover, extensions have also been created for specific interventions such as herbal medicinal interventions (100) and non-pharmacological treatment interventions (101). One of these extensions is the 'Standards for Reporting Interventions in Clinical Trials of Acupuncture' (STRICTA) (96).

STRICTA guidelines were developed as an official extension to the CONSORT statement in 2010, to provide a detailed description of all acupuncture intervention components. As mentioned, incomplete description of interventions is a major problem affecting reproducibility in clinical practice and the interpretation of results in the research context, for example, for assessing acupuncture dose. Although this is not only an issue in acupuncture trials, as similar problems have been found in medical (102) or physiotherapeutic intervention studies (103), it may have a greater impact on acupuncture trials since acupuncture is practiced in many different modalities and styles that vary widely across practitioners.

STRICTA is composed of 16 subitems designed to offer a complete description of all acupuncture treatment characteristics including the acupuncture rationale, needling details, treatment regime, other treatment components used, practitioner background and details of the control or comparator intervention (see Table 4). The current endorsement of CONSORT and STRICTA guidelines by many journals has improved the completeness of reporting and risk of bias of recent acupuncture trials, although further improvements are needed (104).

The STRICTA guidelines have an important limitation, in that they are only focused on filiform needle interventions and not on other techniques such as moxibustion, acupressure or cupping. For this reason, other guidelines such as the 'Reporting Interventions in Clinical Trials Of Moxibustion' (STRICTOM) (105) and the 'Standards for Reporting Interventions in Clinical Trials of Cupping' (STRICTOC) (106) have been proposed, although they are not currently official CONSORT extensions.

Table 4: Checklist for items in Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) 2010 (96)

ITEM	DETAIL
1. Acupuncture rationale	1a) Style of acupuncture (e.g. Traditional Chinese Medicine, Japanese, Korean, Western medical, Five Element, ear acupuncture, etc)
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate
	1c) Extent to which treatment was varied
2. Details of needling	2a) Number of needle insertions per subject per session (mean and range where relevant)
	2b) Names (or location if no standard name) of points used (uni/bilateral)
	2c) Depth of insertion, based on a specified unit of measurement, or on a particular tissue level
	2d) Response sought (e.g. de qi or muscle twitch response)
	2e) Needle stimulation (e.g. manual, electrical)
	2f) Needle retention time
	2g) Needle type (diameter, length and manufacturer or material)
3. Treatment regimen	3a) Number of treatment sessions
	3b) Frequency and duration of treatment sessions
4. Other components of treatment	4a) Details of other interventions administered to the acupuncture group (e.g. moxibustion, cupping, herbs, exercises, lifestyle advice)
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients
5. Practitioner background	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience)
6. Control or comparator interventions	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice
	6b) Precise description of the control or comparator. If sham acupuncture or any other type of acupuncture-like control is used, provide details as for Items 1 to 3 above.

Chronic Obstructive Pulmonary Disease

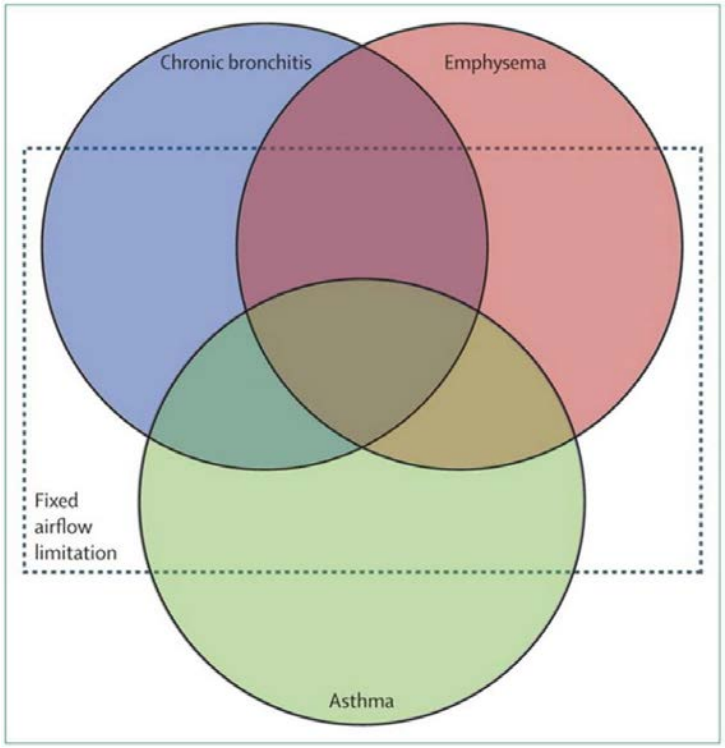
Chronic obstructive pulmonary disease (COPD) is a complex disease with different components that overlap with other similar clinical conditions (107). In the past, physicians have used the terms 'emphysema' and 'chronic bronchitis' to refer to what we now recognise as COPD. It was not until 1995 that the American Thoracic Society and the European Respiratory Society first defined COPD as 'a disease state characterised by the presence of airflow limitation due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive, may be accompanied by airway hyper-reactivity, and may be partially reversible' and 'reduced maximum expiratory flow and slow forced emptying of the lungs, which is slowly progressive and mostly irreversible to present medical treatment' (108,109).

Currently, COPD is defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as 'a common preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases' (110). Compared with previous definitions, in our days, more emphasis is put in the fact that COPD is usually preventable, its inflammatory nature and the importance of its exacerbations and comorbidities.

COPD belongs to a group of pulmonary conditions characterised by airflow limitation, such as asthma, bronchiectasis and airway obliteration (111). Airflow limitation is a condition where, due to different causes, the airways are narrowed, increasing airflow resistance and causing difficulties in lung ventilation. This condition is defined using a spirometric test, when the forced expiratory volume in 1 second (FEV_1) and the forced vital capacity (FVC) ratio is below a certain value, usually 70%, after taking bronchodilators. In COPD, airflow limitation is chronic, persistent and caused by airways and parenchymal damage due to chronic inflammation. This situation leads to the development of progressive dyspnoea, cough and sputum production that end up affecting the patient's physical activities, daily life activities and quality of life. Moreover, COPD is associated with other concomitant chronic diseases and comorbidities, increasing morbidity and mortality (112). These situations are accentuated by exacerbation periods with an acute worsening of respiratory symptoms (113).

COPD can include several airways diseases and parenchymal destruction, which can vary from person to person and may overlap with other conditions such as asthma, chronic bronchitis and emphysema (114). Moreover, those conditions can develop without airflow obstruction. This complex scenario is represented in Figure 3.

Figure 3: Subsets of chronic obstructive pulmonary disease. Image modified from Rennard et al, (115).



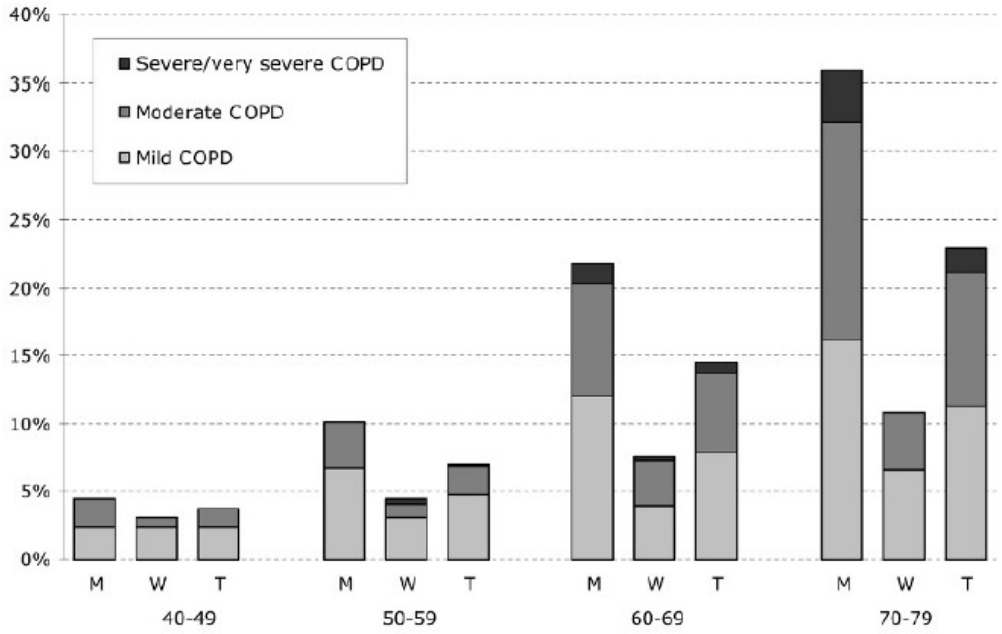
Epidemiology

As a chronic disease, COPD has an important prevalence, especially in the older population, and is also one of the leading causes of death and disability worldwide with high health care costs. It is estimated that more than 12% of the general population of the world suffers from COPD, with the highest prevalence in the American region (14.53%) and the lowest prevalence in southeast Asia/western Pacific region (8.80%) (116).

In Spain, the latest COPD prevalence study shows an overall prevalence of 10.2% in people between 40 and 80 years of age, affecting 15.1% of men and 5.6% of women (117). By age, the prevalence is higher in subjects aged ≥70 years (22.9%), also with more severe cases in this age group. According to severity, it has been estimated that 56.4% of patients have mild disease, 38.3% moderate, 4.6% severe and 0.5% very severe disease (117). Data regarding COPD severity depending on age and gender is summarised in Figure 4.

In relation to phenotypes, the ESPIRAL-ES study, a large observational cross-sectional multicentre study which included 1,610 Spanish patients, concluded that the most prevalent phenotype is the non-exacerbation type, with 46.7% of cases, followed by 22.4% exacerbators with chronic bronchitis, 16.4% exacerbators with emphysema and finally 14.5% of patients with asthma-COPD overlap syndrome (118).

Figure 4: COPD severity depending on age and gender. Image from Miravitlles M. et al. (117).



M: male; W: women; T: total

COPD is the fourth leading cause of death worldwide according to the World Health Organisation (WHO), causing the death of 3.17 million people in 2015 (119). This is projected to increase in coming years up to the third leading cause of death worldwide by 2030 (120), causing 27% of all deaths, only surpassed by 33% for cancer and 29% for cardiovascular disease (121). In Spain, it is estimated that 18,000 to 29,000 people die from COPD every year; it is the fourth leading cause of premature death (120). According to each autonomous community, in 2014, Murcia was the region with the most deaths caused by COPD with a rate of 18.94 for every 100,000 inhabitants, while Melilla was the region with fewest deaths with 10.06 for every 100,000 inhabitants. Catalonia was the seventh region with deaths due to COPD with a rate of 17.17 for every 100,000 inhabitants (122).

Beside its mortality, COPD is the seventh global cause of disability in the world, with a 2.7% overall disability-adjusted life year (DALY) loss (123). DALYs are calculated as the combination of years of life lost due to premature mortality and years lived with disability. COPD-related disability is directly associated with its symptoms, which have a considerable impact on the patient's quality of life and overall health status, compromising the patient's day-to-day activities, physical activity and sleep (124).

COPD has also high economic costs associated to health care resource usage. An economic analysis from 2003 on data from a large-scale international survey, assessing COPD in North

America and Europe, estimated a mean annual direct cost from 4,119 US dollars per patient in the United States to 522 US dollars in France, and a total societal cost, including lost productivity, per patient from over 5,646 US dollars in the United States to 1,023 US dollars in The Netherlands (125).

A more recent study in the Autonomous Community of Extremadura (Spain) estimated an average annual cost per patient of 3,077 €, with direct health care costs of 1,645 €, direct non-health care costs of 1,440 € and labour productivity losses of 672 €. The total annual cost of patients with COPD in Extremadura reached 36.2 million € in 2015 (126).

Risk factors

COPD development has been related to several risk factors, most of them related to chronic or acute airway inflammation episodes. Currently, most studied factors are smoking, exposure to other particles, genetic factors and other lung diseases.

Smoking

Although non-smokers can also develop chronic airflow limitation (127,128), smoking is considered the most well-known risk factor for COPD (129). Smoking is mainly referred to cigarette smoking however, other types of tobacco such as pipe, cigar or water pipe and marijuana are also risk factors since they all contain irritants that trigger lung inflammation (130,131). It is also important to remark that smoking also has an impact on people around smokers, since passive smokers also have an increased risk of developing COPD (132). Moreover, smoking during pregnancy could also predispose to COPD since it has been related to deficiencies on lung function in newborns (133). Smoking is a dose-dependent risk factor; for this reason, smoking burden is a key factor for COPD development and although this is usually measured in pack-years, a product of smoking duration in years and the average number of packs of cigarettes smoked a day, recent studies have shown that smoking duration alone might provide a stronger risk estimation (134).

Exposure to other particles

Exposure to organic and inorganic dusts, chemical agents and fumes is also related to the development of COPD and can occur at the workplace (occupational exposure) and due to indoor or outdoor air pollution. Occupational exposure occurs in jobs with exposure to dust and fumes (135) and it has been estimated that 19.2% overall and 31.1% of non-smokers with COPD in the United States could be attributable to this cause (128). Indoor air pollution is related to

biomass cooking and heating in poorly ventilated rooms; it is estimated that almost three billion people use biomass and coal as their main source of energy (136). Finally, outdoor air pollution, especially in urban regions, could also contribute to the development of the disease, since high levels of particulate matter < 2.5 μm diameter and nitrogen dioxide can affect lung function especially in children by impairing lung growth. The role of air pollution seems to be relatively small compared with cigarette smoking; however, the effects of short-term high-peak exposures and long-term low level exposures are not known (137).

Genetic factors

The main genetic risk documented for COPD is a deficiency in alpha-1 antitrypsin, a hereditary disease associated lung but also liver diseases. Patients with this condition usually develop their first lung symptoms between ages 20 and 50 (138). Besides this condition, a significant family risk of airflow obstruction in smoking siblings of patients with severe COPD has been documented, suggesting that other genetic factors could play a role in COPD development (139).

Other lung diseases

Other chronic lung diseases such as asthma, chronic bronchitis or emphysema or even some acute conditions such as frequent lung infections also increase the risk of developing COPD (140–142). These conditions might have a greater impact during childhood, since the lungs are not fully developed. A recent observational study on a cohort of 8,583 participants found that asthma, bronchitis, pneumonia and allergic rhinitis are predictors of future COPD development (143).

Physiopathology

Chronic inflammation is the main cause of all histopathological COPD features; however, the mechanisms regarding the development of the disease are quite complex and occur simultaneously in several levels and structures.

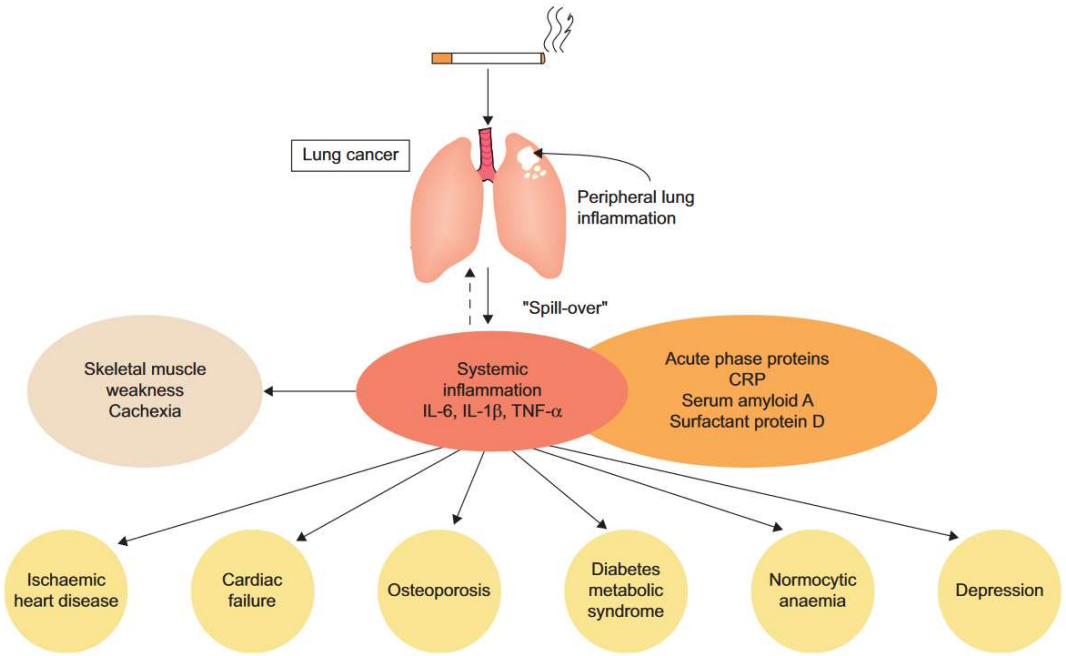
Exposure to irritating substances, such as those in tobacco smoke and polluted air, injures airway epithelial cells and stimulates inflammatory mediators such as NF-κB, growth factors, chemokines, IL-8 and TNF-α. This acute inflammation is a beneficial process that helps the cells of the immune system mobilise to the injured region and support epithelial cell wound healing. However, when the exposure to irritating substances is chronic, this process is amplified and persists even after the cessation of exposure to the irritating substance. In this situation, immune cells can destroy healthy tissues in a misdirected attempt at initiating the healing

process, leading to permanent damage and pathologic changes, especially in the lung parenchyma, proximal and peripheral small airways and pulmonary vasculature (144,145).

Lung structural alterations in COPD lead to changes in normal lung ventilation since the narrowing of the small airways due to inflammation and exudates increases airflow resistance. This is even greater during the exhalation phase since lung elastic recoil is diminished in COPD patients, leading the small airways to collapse and trapping air during exhalation. This creates an imbalance in the inhalation and exhalation phases, resulting in lung hyperinflation and elevated intrathoracic pressure. This situation does not only reduce inspiratory capacity but also reduces venous return and has been associated with reduced ventricular filling, stroke volume and cardiac output (146). In severe conditions, such as an exacerbation, this can result in respiratory insufficiency or even respiratory failure. In COPD, it is common to observe chronic gas blood alterations, hypoxemia and/or hypercapnia, which is compensated for by changing the breathing pattern and an increase in blood bicarbonates (147).

Smoking also contributes to systemic inflammation by activating the release of polymorphonuclear leukocytes, the generation of systemic oxidative stress, the activation of coagulation factors and a direct effect on the endothelial function of peripheral vessels (148). This state of chronic systemic inflammation has been proposed as a risk factor for developing cardiovascular and metabolic diseases, which could explain the high prevalence of these comorbidities in COPD patients (149).

Figure 5: Role of systemic inflammation in the development of CODP comorbidities. Image from Barnes et al. (149)



Symptoms and comorbidities

As previously explained, COPD is a complex disease that can include several clinical situations; however, several symptoms are common in this condition such as dyspnoea, cough and sputum production, wheezing and chest tightness, exercise limitation, anxiety and depression, exacerbations and other comorbidities.

Dyspnoea

Dyspnoea can be defined as 'a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity... [it] derives from interactions among multiple physiological, psychological, social, and environmental factors, and may induce secondary physiological and behavioural responses.' (150). Dyspnoea is one of the main symptoms of COPD and usually the most limiting one, and it appears COPD is already at a moderately advanced stage. Dyspnoea in COPD is usually progressive as a result of several mechanisms including hyperinflation, impaired lung capacity, hypoxemia, hypercapnia and neuromechanical dissociation (151). This symptom has a great impact on patient quality of life by decreasing exercise capacity and interfering with the patient's daily life activities (152); it is also associated with depression and anxiety (153). This creates a vicious circle of dyspnoea-inactivity-deconditioning, leading to more dyspnoea. Dyspnoea is not properly managed in many patients with current medications and there is a need for additional therapies (152).

Chronic cough and sputum production

Cough is often the first COPD symptoms and might be intermittent at first but it becomes chronic with time and is usually accompanied by sputum production, especially in those patients with a pattern of chronic bronchitis (154). Sputum is the result of an increase of mucus production and a decrease of cilia function, both caused by bronchial epithelial destruction due to chronic inflammation (155). Chronic cough and sputum have been suggested as a risk factor for exacerbations of COPD (156).

Wheezing and chest tightness

Wheezing is produced by the narrowing of small airways during inspiration or expiration and may be audible without any tool or with the help of a stethoscope (157). Wheezing is not present in all patients with COPD, but it is more common in asthma-COPD overlap syndrome (158). Chest tightness may be consequence of intercostal muscle contraction and often appears after exertion (124).

Exercise limitation

Regular physical activity has been associated with better outcomes on lung function however, symptoms such as dyspnoea and coughing progressively develop in COPD and eventually limit exercise capacity and increase physical inactivity and sedentary behaviours. It has been well-established that physical inactivity and sedentary behaviours are a risk factor for cardiovascular diseases, obesity, diabetes, cancer, dementia and physical disability (159).

Another factor for exercise limitation in COPD is limb muscle dysfunction. Limb muscle dysfunction is a systemic consequence of COPD, leading to morphological and functional changes that impair muscle function and performance (160). Muscle dysfunction, especially in the lower limbs, has an important impact on physical activity, exercise tolerance, quality of life, and even survival in this disease (161).

Anxiety and depression

Anxiety and depression are highly prevalent in COPD, although prevalence estimations vary greatly due to differences in the diagnosis tool used and disease severity. Most recent studies have estimated that up to 40% and 24% of COPD participants suffer from anxiety and depression, respectively. Moreover, both situations often co-occur with half of patients with depression also suffering from anxiety (162). Anxiety and depression are not only related to psychological and emotional distress, but also with increased morbidity and mortality (163) and a reduction in physical activity (164) and quality of life (165) in COPD patients. Anxiety and depression are challenging since there is a bidirectional relationship with other COPD symptoms.

Exacerbations

Acute exacerbations of COPD (EACOPD) can be defined as 'episodes of increasing respiratory symptoms, particularly dyspnoea, cough and sputum production, and increased sputum purulence' (166). EACOPD can be triggered by several factors however, most common causes are respiratory infections and air pollution. EACOPD are the most frequent cause of medical visits, hospital admissions and mortality among patients with COPD and are associated with quality of life impairment and accelerated lung function decline (167).

Comorbidities

COPD is also associated with other extrapulmonary disorders such as fatigue, weight loss and anorexia, cardiovascular disorders and cancer (149). In a recent prospective, multicentre, observational study with a cohort 1,582 COPD participants, only 28% of patients had no

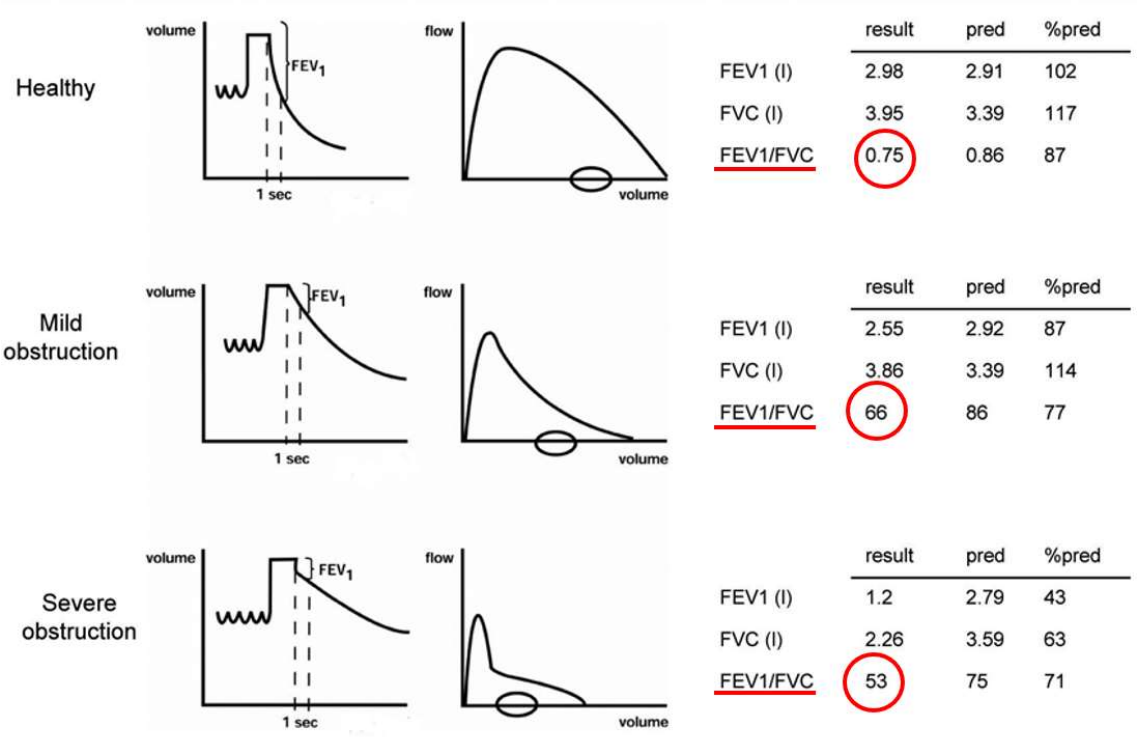
comorbidities associated with COPD, and the number of comorbidities increased with the severity of the disease (112). Cardiac comorbidities were more frequent in men and anxiety-depression and osteoporosis were more frequent in women. Comorbidities are a major cause of death, since COPD by itself is only considered the underlying cause in 59.8% of deaths. The most common causes of death among the comorbidities are acute myocardial infarction, other ischaemic heart disease and lung cancer (168).

Diagnosis

COPD diagnosis is considered in patients with dyspnoea, chronic cough or sputum production and/or a history of exposure to risk factors. For diagnosis, a spirometry test is required to assess the presence of persistent airflow limitation, defined by the ratio $FEV_1/FVC<0.70$ after the use of a bronchodilator (110,169). This is also the criterion used in the most recent Spanish guidelines for COPD diagnosis (170).

Figure 6 shows examples of volume-time and flow-volume curves in a spirometry test in healthy, mild obstructive and severe obstructive patients. Observe the reduction in FEV_1 and flow values in the obstructive cases during a forced spiration.

Figure 6: Simplified healthy, mild obstruction and sever obstruction examples of volume-time and flow-volume curves in a spirometry test. Image modified from Broekhuizen BD, et al. (171)



However, a fixed ratio of 0.70 for every patient may not be accurate in the youngest and oldest patients since important airflow changes occur due to aging (172). It has been stated that this only could not lead to potential overdiagnosis of COPD in elderly people (173) but also an underdiagnosis in adults under the age of 45 years (174). For this reason, some researchers have proposed to use another cut-off point using a FEV_1/FVC value below the lower fifth percentile of an aged-matched healthy reference group, which is called the lower limit of normal (LLN). However, it is not clear which criterion is better. Research seems to show that although the fixed ratio could be better to diagnose subjects with more severe airflow limitation, the LLN could be a better criterion for less severe airflow limitation patients (175). Also, a recent trial comparing both diagnoses in elderly patients showed that the fixed ratio of 0.70 seams to over-diagnose COPD, while LLN definitions may under-diagnose COPD as compared to an expert panel diagnosis (176). Since it is not clear which diagnostic criterion is better, most guidelines recommend the fixed ratio cut-off, arguing that it is simpler and more consistent than other methods.

Assessment

Determining the severity of COPD in each patient is key to providing the proper treatment and reducing the impact of the disease; however, due to the heterogeneity of the symptoms, this is a complex procedure that includes multiple assessments (177). These assessments include the severity of airflow limitation, the dyspnoea level, health status and quality of life, exercise tolerance, mortality and morbidity risk, the patient's risk level and the phenotype classification.

Airflow limitation severity

The level of airflow limitation is an important outcome for assessing lung function decline and is considered an important index for predicting clinical outcomes. The GOLD classification is the most used method for this purpose and uses several spirometry cut-off points of the theoretical predicted FEV_1 value to classify patients into four main groups (GOLD 1-4) (see Table 5). However, it is important to highlight that there is a weak correlation between airflow limitation and patient symptoms or health impairment, as a substantial proportion of subjects with severe airflow obstruction do not report symptoms, exacerbations or exercise limitation (178).

Table 5: GOLD classification of airflow limitation severity in COPD. Adapted from Agusti A. et al. (178)

In patients with $FEV_1/FVC<0.70$ and based on post-bronchodilator FEV_1		
GOLD 1	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4	Very Severe	$FEV_1 < 30\%$ predicted

Dyspnoea level

Several methods for assessing dyspnoea have been developed in recent years; however, the most common used ones are the modified Medical Research Council dyspnoea scale (mMRC), the modified Borg Scale (mBorg scale) and the numeric rating scale (NRS).

The mMRC is a quite simple self-administered tool used to assess dyspnoea severity during activities of the daily living. This scale classifies patients depending on the situation they experience dyspnoea. In the minimum grade (grade 0), dyspnoea only appears after considerable physical effort, while at the maximum grade (grade 4) the dyspnoea level prevents patients from leaving home or appears during light activities such as dressing (179). The mMRC it is also consistent with other measures of health status and can be used to predict lung function decline, mortality risk and to estimate physical activity level (180).

The mBorg scale was originated from the original Borg scale to specifically assess symptomatic dyspnoea. This scale is a category-ratio scale with numbers from 0 to 10 and expressions related to those numbers that progressively indicate a worsening from the dyspnoea intensity, such as ‘very slight’, ‘moderate’, ‘severe’, etc. For the assessment, patients are asked to look at the scale and pick a number that matches their dyspnoea perception. This scale has been found to be a valid, reliable and easy-to-use tool in COPD patients (181).

The NRS is another commonly used self-reported scale that, like the mBorg scale, goes from 0 to 10, with 0 indicating ‘not breathless at all’ and 10 indicating ‘as bad as you can imagine’. Although this scale was first developed for pain assessment, it is now also considered a valid tool for dyspnoea assessment (182).

Health status and quality of life

Health status and quality of life are assessed using several questionnaires such as the COPD Assessment Test (CAT), the St. George’s Respiratory Questionnaire (SGRQ), the Clinical COPD Questionnaire (CCQ) or the Chronic Respiratory Questionnaire (CRQ).

The CAT was developed as a short and simple instrument to simplify previous longer and more complex questionnaires. It consists of eight items covering cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitations at home, confidence leaving home, sleep, and energy. Each item is scores from 0 to 5 with a total score from 0 to 40 with higher scores indicating poorer health status. This instrument can help to predict COPD exacerbation, health status deterioration, depression, and mortality (183).

The SGRQ is a 50-item questionnaire regarding symptom components and impact on social activities with a score from 0 to 100, with higher score indication more limitations (184). The SGRQ has also been found to predict exacerbations, hospital admissions and mortality in COPD patients. However, this questionnaire has been claimed to be time-consuming and difficult to use and calculate scores (185).

The CCQ is a 10-item auto administered questionnaire scored from 0 to 6 and contains three domains: symptoms, mental and functional dysfunction. In this questionnaire, higher scores also indicate a worse quality of life. The CCQ is considered a valid and reliable tool with good sensitivity for exacerbations (186).

The CRQ is a 20-item interviewer-administered questionnaire with four domains assessing both physical and emotional status of chronic respiratory diseases. Contrary to the previously mentioned scales, in the CRQ, higher scores indicate better health-related quality of life (187).

Exercise tolerance

Exercise tolerance has been assessed in COPD patients using adapted physical tests such as the six-minute walk test (6mwt), the incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT).

The 6mwt is a reliable widely used test to assess exercise tolerance in COPD patients. In this test, patients are asked to walk on a flat track for as much distance they can in 6 minutes (188). The primary outcome of the test is the total distance walked in the 6-minute time period (6mwd), which has been found to be a predictor of an increased risk of hospitalisation and mortality for values lower than 350 meters (189). Other variables derived from the 6mwt such as mean walk speed, distance-saturation product, exercise-induced oxygen desaturation and unintended stops have also been found useful for mortality and hospitalisation prognosis (190).

The ISWT and ESWT are commonly used methods for assessing exercise tolerance in COPD patients. These are symptom-limited exercise tests where patients walk on a 10-meter track at an incremental speed for the ISWT, and at a constant speed for the ESWT (85% of the ISWT

performance), determined by audio cues. The tests finish when the participant is unable to maintain the required speed. The primary outcomes are total distance walked for the ESWT and total time walked for the ESWT (191).

Patient risk level: risk stratification

Disease stratification aims to predict a patient's risk or exacerbations, disease progression, complications and mortality to adjust diagnostic and therapeutic intervention levels. According to a recent review of national guidelines in the European Union and Russia, there are several differences in the methods of stratification and prediction of future risk of COPD patients. For example, the Italian and Finnish guidelines only consider the airflow limitation severity to assess a patient's risk. However, most guidelines also consider symptom severity using several methods such as the mMRC, CAT, CCQ, episodic or daily symptoms, exercise capacity or oxygenation (192).

Spanish national guidelines (GesEPOC) propose a simplified risk stratification based only on two levels, low risk and high risk. For this classification, several factors are considered, such as the degree of obstruction, the grade of dyspnoea and the presence of exacerbations (193).

Treatment and management

Currently, there is no conclusive evidence that any existent medication modifies the long-term decline in lung function in COPD. Treatment objectives are to reduce disease symptoms, to reduce the frequency and severity of exacerbations and to improve the prognosis. Both short-term benefits (disease control) and mid- to long-term goals (reduction in risk) must be reached (177).

According to the most recent GOLD guidelines, COPD treatments can be divided into the following groups: smoking cessation, vaccinations, pharmacological treatment, pulmonary rehabilitation programs, supportive, palliative, end-of-life and hospital care, other treatments and interventional therapy (110).

Smoking cessation

Smoking cessation is considered the most effective way to influence COPD's natural history. Smoking cessation programs include several strategies that might be used in combination. The main recommended treatments are educational interventions, cognitive-behavioural therapy and pharmacologic products such as nicotine replacement products, bupropion and varenicline (194).

Vaccinations

As previously explained, acute exacerbations are the most common cause of hospital readmissions and mortality in COPD patients. For this reason, vaccinations are used to prevent exacerbations triggered by community-acquired respiratory infections. Currently, influenza and pneumococcal vaccines are recommended (195).

Pharmacological therapy

The basis of treatment of stable COPD is to reduce airflow obstruction using long-acting bronchodilators (LABD) that might be used alone or in combination. In the case of situations with a more severe inflammatory component, such as exacerbator phenotypes and asthma-COPD overlap, LABD are usually combined with inhaled corticosteroids. In the case of exacerbators with an emphysema component, theophylline can also be added. In case of exacerbators with a chronic bronchitis component, mucolytics, phosphodiesterase-4 inhibitors or antioxidants can be added to control the excess of mucus and according to severity antibiotics might be used to prevent respiratory infections. Finally, medication can be added to control patient comorbidities (193).

Pulmonary rehabilitation programs

Pulmonary rehabilitation programs (PRP) are comprehensive interventions and strategies that include exercise training, education, nutrition and psychological support. In these programs, several professionals such as pneumologists, physiotherapists, nurses, occupational therapists, nutritionists and psychologists work together to offer a multidisciplinary approach tailored to each patient's specific needs (196).

Exercise training is one of the most important components of PRP and includes several modalities. Strength training using progressive overload results in functional adaptations that have been found to improve muscular dysfunction. Aerobic resistance training, most commonly using treadmills and cycle ergometers, is used to improve muscular resistance and improve cardiovascular response. For patients with difficulties in maintaining submaximal efforts for long periods of time, interval training is used, since similar benefits to aerobic resistance training have been observed. Respiratory muscles can also be targeted such as in inspiratory muscle training; however, this is currently only recommended for patients with inspiratory muscle weakness (197).

Respiratory physiotherapy includes bronchial clearance techniques for patients with increased sputum production or difficulties in expectoration, re-education of the respiratory pattern and relaxation techniques to avoid hyperventilation and reduce anxiety (198).

Other components of PRP are: educational interventions regarding smoking cessation, the use of inhaler devices, recognition of exacerbations symptoms and instructions about how to proceed during symptom worsening. Nutritional support, including dietary recommendations and nutritional supplementation, aim to maintain a proper body composition, especially in patients with low body fat levels since this has been associated with increased mortality in COPD. Psychosocial support helps patients to deal with anxiety and depression and other psychosocial alterations in order to improve their confidence and self-esteem (199).

PRP have been found to be effective for improving dyspnoea, quality of life and exercise tolerance, although no statistically significant improvements have been found for pulmonary function and mortality (196).

Supportive, palliative, end-of-life and hospital care

Palliative care aims to improve symptom management and quality of life at the end of a COPD patient's life. However, several barriers have been identified such as the uncertain prognosis of COPD (200).

Other treatments

Depending on the patient's condition, other treatments can be used. For example, for patients with severe resting hypoxemia, long-term oxygen therapy has been found to improve survival (201). Also, ventilatory support is used in patients with obstructive sleep apnoea or chronic hypercapnia (202).

Interventional therapy

For participants at an advanced COPD stage and considerable destruction of the lung parenchyma, surgical interventions can be considered. Surgical or bronchoscopic volume reduction interventions are considered in participants with emphysema phenotypes. These interventions have been found to reduce mortality patients with both predominantly upper-lobe emphysema and low baseline exercise capacity (203). Lung transplantation has been shown to improve quality of life and lung function; however, it is not clear if it improves patient survival (204).

Acupuncture for COPD

Acupuncture has been traditionally used to treat all kind of health conditions, including COPD, since from a traditional rationale, acupuncture is able to treat any disease by regulating energetic imbalances. Besides this, recent research has also suggested possible physiological mechanisms to explain some of the positive effects of acupuncture in COPD seen in some RCTs.

Traditional acupuncture practice in COPD

From a traditional perspective, COPD is a condition thar primarily affects the organ called *Fei* (translated as lung but not to be mistaken by the actual lungs in western physiology). This organ is responsible of the respiratory function but also has an important role in Qi absorption and diffusion and liquid metabolism; therefore, its impairment may cause dyspnoea, wheezing, cough, accumulation of phlegm in the lungs and low exercise capacity. Once this has happened, and since in TCM all organs are connected, the disease may evolve to other functional systems leading to new symptoms. For example, if the disease affects the organ called *Pi* (usually translated as spleen), the functions of which are to absorb nutrients from food for Qi production and metabolism, symptoms such as fatigue and sputum production may increase and body weight and muscle mass loss or even malnutrition may develop. Another organ that is easily affected in COPD is *Shen* (translated as kidney), which is not only responsible for liquid metabolism in the lower body, but it also stores vital energy or essence and regulates aging. *Shen* impairment is related a more severe stage of the disease in which symptoms like dyspnoea, tiredness and lack of energy are increased; this leads to an overall deterioration of all vital systems.

These three organs, i.e. Fei, Pi and Shen, are the ones mainly considered in the mainstream TCM diagnosis of COPD. However, due to the diversity of styles and diagnostic systems, a variety of possible alternative diagnoses may be also used.

In any case, traditionally acupuncture is considered to be able to regulate organ functions affected by COPD and therefore improve patient symptoms and quality of life by regulating the Qi of these organs. This is done by different stimulation methods (acupuncture techniques) on the surface of the body (acupuncture points) that are linked to the functional organs through the acupuncture meridians.

Acupuncture physiological mechanisms in COPD

Besides the traditional explanation, recent research has also proposed several physiological mechanisms that could explain the possible benefits produced by acupuncture in COPD participants, such as improvements in dyspnoea perception, anti-inflammatory effects, effects on the tone of accessory respiratory muscles, effects on mood, anxiety and depression and autonomic nervous system regulation.

Dyspnoea perception

There is currently some evidence that acupuncture could improve dyspnoea perception. A recent SR on breathlessness in advance disease found a benefit of acupuncture in patients with several conditions (205).

This effect could be mediated by endogenous opioids. It is quite well-established that acupuncture stimulation triggers the diffuse noxious inhibitory control activating the parabrachial nucleus and the arcuate nucleus of the hypothalamus, thereby stimulating the periaqueductal grey matter and descending inhibitory pain pathways. This process is mediated by the release of several endogenous opioids in the central nervous system such as beta-endorphins, enkephalins and dynorphins (206–209). However, endogenous opioids do not only play a role in pain modulation but also can modify dyspnoea in COPD patients (210). Although these effects have usually been associated with invasive acupuncture techniques, AcuTENS stimulation has also been found to increase beta-endorphin levels in COPD participants, improving dyspnoea, reducing respiratory rate and improving FEV_1 (40).

The effect of acupuncture on dyspnoea could also be mediated by the regulation of the respiratory centre, since the decrease in pulmonary function in COPD has been associated with abnormal excitability of this centre (211). There is some evidence that electroacupuncture could have a role regulating the respiratory centre via the downregulation of orexins and orexin receptors in the hypothalamus and the medulla, according to research in rat COPD models (212,213).

Anti-inflammatory effects

Acupuncture has been found to reduce pulmonary inflammatory response in rat COPD models by regulating inflammatory cytokines (214–216). These effects may be related to the regulation of the cholinergic anti-inflammatory pathway favouring an important reduction in airway and lung parenchyma damage and delaying the progression of COPD (214).

Also, acupuncture and particularly electroacupuncture could regulate the neuroimmune system, leading to important anti-inflammatory systemic effects according to animal research on induced acute pancreatitis (217) and sepsis (218). These effects seem to be mediated by cholinergic anti-inflammatory pathways activated by the vagal nerve (219), which modulates the production of catecholamines by the adrenal glands (220). As mentioned above, systemic inflammation has been linked to COPD comorbidities such as cardiovascular and metabolic diseases; acupuncture could reduce the risk of developing those diseases by this mechanism.

The anti-inflammatory effect of acupuncture has been studied in similar diseases such as asthma. A recent systematic review, which included nine randomised control trials, observed a significant decrease in interleukin-6 levels when acupuncture was used in addition to usual treatment (221).

Effects on the tone of accessory respiratory muscles

Several authors have also suggested that acupuncture might have a role in the treatment of COPD by decreasing the tone and alleviating fatigue in accessory respiratory muscles, since many acupuncture points used for COPD are located on those muscles (222). This might be due a local enhanced blood flow effect produced by needling, leading to an improvement in respiratory muscle strength and oxygen supply. These improvements not only decrease dyspnoea but also improve exercise capacity by increasing the oxygen supply to the lower limb muscles (223,224).

Effects on mood, anxiety and depression

Acupuncture could also have positive effects in the management of anxiety and depression in COPD patients. A recent SR has suggested that the addition of acupuncture to regular treatment could improve depression and the therapeutic response rate compared with regular treatment alone (225). This antidepressant effect could be mediated by the limbic system, the amygdala and the anterior cingulate cortex (226) by modulating the corticostriatal reward/motivation circuitry (227).

Autonomic nervous system regulation

Acupuncture has been found to regulate the autonomic nervous system through two main pathways. The first one involves the stimulation of hetero-segmental points, located on the limbs; this has been found to regulate the vagal nerves through the stimulation of the supraspinal circuit. The second pathway involves homo-segmental points, located on the trunk, which activate sympathetic nerves located in the same dermatome by the medullar reflex. This

mechanism has been found to have an effect on arterial pressure (228), cardiac activity (229) and gastric motility (230,231). Although this mechanism has not been studied regarding pulmonary function, it seems plausible that it may play a role since it has recently been stated that individuals with COPD show a reduction in both sympathetic and parasympathetic activity, associated with decreased complexity of autonomic nervous system function (232).

Evidence for acupuncture in COPD

There has not been a lot of interest in western acupuncture research on COPD compared with other fields such as analgesia; however, the number of publications in the English language has been growing in recent years.

The first papers published in a western journal regarding the use of filiform needle acupuncture in the treatment of COPD was a pilot trial by Jobst et al. published in the Lancet in 1986 (233). In this trial, 12 matched pairs of participants with COPD were treated with acupuncture or placebo acupuncture (inserting needles at non-acupuncture points). After a three-week intervention, authors observed a significant improvement in breathlessness and exercise capacity in participants receiving traditional acupuncture, although no changes were seen in lung function measures. However, despite these first encouraging results, no further trials were published in the English language until 2011, when Deering et al. published a three-arm RCT (234). This trial, with 60 participants, compared the use of acupuncture plus pulmonary rehabilitation, pulmonary rehabilitation alone or a waiting group and found that acupuncture could lead to a reduction in dyspnoea for a longer period of time, although no differences were found in other outcomes compared with pulmonary rehabilitation alone. The largest trial on this topic was published in 2012 by Suzuki et al. (235). This trial, performed in Japan, included 111 COPD patients in a 12-week RCT with a sham acupuncture group using a non-penetrating needle device. The study concluded that acupuncture could be a useful adjunctive therapy for COPD by reducing dyspnoea and improving exercise capacity, airflow obstruction and health-related quality of life.

Regarding the use of acupressure, the first trial published in an international journal was the one by Maa et al in 1997 (236). In this trial, which enrolled 39 participants, researchers used a 12-weeks self-administered acupressure program in addition to pulmonary rehabilitation and observed a reduction in dyspnoea and decathexis (disinterest in life). Similar results were later found by Wu et al. in 2003 and 2005 were besides dyspnoea; benefits were also found for anxiety and depression although the sample sizes of both studies were rather small (237,238).

Later, between 2010 and 2017, several papers were published using AcuTENS. Most of these trials were published by the same research group in Hong Kong using the stimulation of a traditional acupuncture point used to treat dyspnoea and showing successful results after a single (40) or multiple session treatment (239). These improvements in dyspnoea were not seen in a later trial by Öncü et al., but in that trial AcuTENS seemed to improve exercise capacity (240).

To try to summarise all this evidence and include research published only in the Chinese language, Coyle et al. published in 2014 an SR that included all kinds of acupuncture techniques (pharmacological and non-pharmacological) (241). At that time, the authors found 16 RCT on the topic and concluded that acupuncture therapies may result in important clinical benefits regarding dyspnoea and quality of life. However, the authors were limited by the small number and risk of bias of the included trials. Also, a separate analysis for each acupuncture technique was not possible, except for acuTENS, and the authors had to plot all trials together. For these reasons, no firm conclusions could be drawn regarding the effect of each acupuncture technique.

It is also interesting to point out that there are no publications regarding the completeness of reporting of acupuncture interventions specific to COPD. The assessment of the completeness of reporting has been performed in other clinical situations, such as knee osteoarthritis (92), neurological diseases (242) and cancer (91), to highlight deficiencies affecting not only the proper evaluation of the trial results but also its reproducibility in clinical practice; this is lacking for COPD.

JUSTIFICATION

COPD is a highly prevalent chronic disease with a considerable impact on patient health and quality of life due to progressive dyspnoea and low exercise capacity.

Although there are currently several treatments for COPD, including pharmacological and non-pharmacological interventions, none of them are curative. Moreover, current treatments are not enough to control all symptoms in all patients, and some pharmacological interventions can produce important side effects in the long term. For those reasons, there is a need for new strategies for controlling COPD symptoms.

In recent years, some research has suggested that non-pharmacological acupuncture techniques, such as filiform needle acupuncture, acupressure or acuTENS, could be effective as add-on techniques in the treatment of dyspnoea to improve exercise capacity and quality of life in COPD patients. However, current evidence is still uncertain due to the small number of trials. Moreover, clinicians might not be able to access all the current evidence since many trials are published in Chinese journals.

For these reasons, a large spectrum review to identify trials on the subject is needed. This will not only allow the assessment of acupuncture efficacy and effectiveness in COPD, but also the assessment of important aspects regarding trial methodology such as the risk of bias of the trials and the completeness of reporting of acupuncture interventions in the published papers.

OBJECTIVES

General objective

The objectives of this thesis are both methodological and clinical:

1. To identify and summarise the available evidence on the effects of acupuncture for the treatment of COPD and assess the completeness of reporting of acupuncture interventions in existing trials according to systematic review methodology.

Specific objectives

1. To assess the available evidence of the effects of non-pharmacological acupuncture techniques on dyspnoea, quality of life, exercise capacity, anxiety and depression and lung function in COPD and their possible adverse events.

2. To evaluate the completeness of reporting of acupuncture interventions in COPD trials according to STRICTA guidelines.

MATERIAL AND METHODS

For the first specific objective, to assess the available evidence of the effects of non-pharmacological acupuncture techniques on dyspnoea, quality of life, exercise capacity, anxiety and depression and lung function in COPD and their possible adverse events, a systematic review was performed. The review included randomised and quasi-randomised control trials and was performed following the recommendations of the Cochrane handbook for systematic reviews of interventions (243). To be able to perform this systematic review, a collaboration was established between the School of Health Sciences Blanquerna and the Centre for Evidence-Based Chinese Medicine from the Beijing University of Chinese Medicine and Pharmacology. This was necessary since many publications were expected to be published in the Chinese language.

For the second specific objective, to evaluate the completeness of reporting of acupuncture interventions in in COPD trials, we performed a cross-sectional study assessing the adherence of acupuncture intervention description to STRICTA guidelines. For this objective, the collaboration between the School of Health Sciences Blanquerna and the Centre for Evidence-Based Chinese Medicine was extended to the Iberoamerican Cochrane Centre - Sant Pau Biomedical Research Institute.

Systematic review methods

To perform this SR the Cochrane Handbook for Systematic Reviews of Interventions (243) was followed and the protocol for the review was previously registered at PROSPERO database (Available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015074) (Annex 1).

Eligibility criteria

Study designs: Randomised controlled trials or quasi-randomised trials and crossover trials

Participants: COPD patients with different grades of obstruction (GOLD A to D) in exacerbation or stable periods.

Intervention: Non-pharmacological modalities of acupuncture (filiform needle, electroacupuncture, acupressure, moxibustion, ear acupuncture, etc.).

Control: Sham acupuncture or no acupuncture.

Outcomes: Dyspnoea, quality of life, adverse effects, exercise capacity, lung function or anxiety and depression.

Information sources

An electronic search was performed up to June 2019. The databases included were the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, CINAHL, AMED (Ovid), PEDro, PsycINFO, CNKI, VIP, Wanfang and Sino-Med.

The bibliographies of selected articles were also consulted in search of additional studies not detected in the initial searches.

Manual reviews were also performed on international respiratory diseases conferences (European Respiratory Society and American Association for Respiratory Care).

No language restriction was applied.

Search strategy

We conducted a comprehensive search using the following key words and their variations: “acupuncture”, “moxibustion”, “acupressure”, “electroacupuncture”, “AcuTENS”, “ear acupuncture”, “cupping”, “COPD”, “randomised control trial”. The search strategy was adjusted for each database.

Study selection

The reviewers worked in pairs and independently identified the articles that met the inclusion criteria, first through title and abstract and afterwards through full text paper.

Data collection process

Reviewers, both in pairs and independently, extracted data using a standardised data extraction form (Annex 2). A pilot test was performed prior to data extraction to check the suitability of the form, as well as its understanding by the reviewers. A third author was consulted in the case of discrepancies. Lack of data or inconsistent data were managed by contacting trial authors; if this was not possible the data was not included in the meta-analysis.

Risk of bias in individual studies

The Cochrane Risk of Bias Assessment Tool (55) was used to assess the risk of bias in the papers. Due to the nature of acupuncture techniques, the Cochrane risk of bias tool was modified to add "blinding of outcome assessment". "Blinding of personnel" was removed because a person providing acupuncture treatment cannot be blinded.

Synthesis of results

When possible, results were summarized in a meta-analysis using RevMan 5.3 software and applying a fixed effects model to summarise the results when heterogeneity was not relevant (I^2<30%), otherwise, a random effects model was used. If I^2 value was over 70%, a narrative synthesis of the available data was performed.

Continuous outcomes were expressed as mean difference with 95% confidence interval or standardised mean difference when different scales were used. For trials with different arms using acupuncture, the results were combined before meta-analysis using the Cochrane Handbook.

Additional analyses

Since studies included patients with different conditions (stable and exacerbation) and this could lead to heterogeneity in our results, we decided to separate them into two subgroups in all meta-analyses. The results are therefore presented separately when heterogeneity was too big (I^2<70%) between subgroups or in one of the subgroups.

Cross-sectional study methods

Study selection

For this study we used the results of our previous systematic review, which included randomized or quasi-randomized trials using filiform needle acupuncture for COPD.

Data collection process

Reviewers extracted the data independently in pairs using a standardised data extraction form. A specific extraction document with instructions was created by the authors for evaluating STRICTA guidelines adherence. This extraction table was tested with a pilot data extraction to ensure its usability.

Since some STRICTA subitems refer to multiple aspects (e.g., “names of points used” subitem refers not only to the name or location of points but also to if they are used unilaterally or bilaterally), besides considering items just as reported or not reported, we also considered partially reported items and recorded the reasons for there being. This was done to provide more detailed information regarding the aspects that should be improved in the reporting of future trials. Partial reporting was also considered when the authors reported information in other sections, such as the introduction or the discussion.

Synthesis of results

A descriptive analysis was used to summarise the results using percentages and absolute numbers.

RESULTS

Publications presented as part of this thesis

First and second publications

Due to the large amount of data obtained in our systematic review, the results were published in two separate papers, one addressing trials using filiform needle acupuncture and the second summarising the evidence of all other non-pharmacological techniques.

> **Fernández-Jané C**, Vilaró J, Fei Y, Wang C, Liu J, Huang N, Xia R, Tian X, Hu R, Yu M, Gómara-Toldrà N, Solà-Madurell M, Sitjà-Rabert M. Filiform needle acupuncture for COPD: A systematic review and meta-analysis. Complement Ther Med. 2019 Dec;47:102182.
>
> Impact factor (SJR 2018): 0.65, Q1

> **Fernández-Jané C**, Vilaró J, Fei Y, Wang C, Liu J, Huang N, Xia R, Tian X, Hu R, Yu M, Gómara-Toldrà N, Solà-Madurell M, Sitjà-Rabert M. Acupuncture techniques for COPD: A systematic review. BMC Compl Altern Med. 2020 May 6;20(1):138.
>
> Impact factor (SJR 2018): 0.75, Q1

Third publication

In our third publication, we assessed the completeness of reporting of acupuncture interventions.

> **Fernández-Jané C**, Solà-Madurell M, Yu M, Liang C, Fei Y Sitjà-Rabert M, Úrrutia G. Completeness of reporting acupuncture interventions for COPD: Review of adherence to the STRICTA statement. F1000Res. 2020 Apr 2;9:226.
>
> Impact factor (SJR 2018): 1.24, Q1

Results summary

First publication

Background: This is the first part of a larger spectrum systematic review which aims to identify and evaluates the effectiveness of all different non-pharmacological acupuncture techniques used for COPD. In this first publication, we describe the results of filiform needle acupuncture

Methods: Randomised controlled trials up to May 2019 were searched in 11 databases. Data extraction and risk of bias assessment was conducted in pairs independently. RevMan 5.3 was used for the meta-analysis.

Results: 28 trials using filiform needle alone or in combination of other techniques were included. Compared with no acupuncture, no difference was seen for dyspnoea, but statistical benefits were found on quality of life (Std. MD: -0.62, 95%CI: -0.90, -0.34), exercise capacity (stable subgroup) (6MWT MD: 33.05m, 95%CI: 19.11, 46.99) and lung function (FEV_1% MD: 1.58, 95%CI: 0.51, 2.66). Compared with sham, statistical benefits were found on dyspnoea (Std. MD: -1.07, 95%CI: -1.58, -0.56), quality of life (Std. MD: -0.81, 95%CI: -1.12, -0.49), exercise capacity (6MWT MD: 76.68m, 95% CI: 39.93, 113.43) and lung function (FEV_1% MD: 5.40, 95%CI: 2.90, 7.91; FEV1/FVC MD: 6.64, 95%CI: 3.44, 9.83).

Conclusions: Results show that filiform needle acupuncture might be beneficial for COPD, but due to the low quality of the studies this should be confirmed by future well-designed trials.

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Filiform needle acupuncture for copd: A systematic review and meta-analysis

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ABSTRACT

Background: This is the first part of a larger spectrum systematic review which aims to identify and evaluates the effectiveness of all different non-pharmacological acupuncture techniques used for COPD. In this first publication, we describe the results of filiform needle acupuncture
Methods: Randomised controlled trials up to May 2019 were searched in 11 databases. Data extraction and risk of bias assessment was conducted in pairs independently. RevMan 5.3 was used for the meta-analysis.
Results: 28 trials using filiform needle alone or in combination of other techniques were included. Compared with no acupuncture, no difference was seen for dyspnoea, but statistical benefits were found on quality of life (Std. MD: -0.62, 95%CI: -0.90, -0.34), exercise capacity (stable subgroup) (6MWT MD: 33.05 m, 95%CI: 19.11, 46.99) and lung function (FEV_1% MD: 1.58, 95%CI: 0.51, 2.66). Compared with sham, statistical benefits were found on dyspnoea (Std. MD: -1.07, 95%CI: -1.58, -0.56), quality of life (Std. MD: -0.81, 95%CI: -1.12, -0.49), exercise capacity (6MWT MD: 76.68 m, 95% CI: 39.93, 113.43) and lung function (FEV_1% MD: 5.40, 95%CI: 2.90, 7.91; FEV1/FVC MD: 6.64, 95%CI: 3.44, 9.83).
Conclusions: Results show that filiform needle acupuncture might be beneficial for COPD, but due to the low quality of the studies this should be confirmed by future well-designed trials.
Protocol registration: PROSPERO (identifier: CRD42014015074).

1. Background

Chronic obstructive pulmonary disease (COPD) is defined as chronic and irreversible airflow obstruction, characterised by decreased forced expiratory volume in the first second (FEV_1) compared to forced vital capacity (FVC).[1] The main cause of this disease is considered to be smoking or exposure to other gases and harmful particles that cause an inflammatory reaction in the airways and lung parenchyma and structural abnormalities in the airways.[1,2] These alterations trigger the main symptoms of the disease: progressive dyspnoea, chronic cough, sputum production and recurrent respiratory infections that cause exacerbations of the disease.[1] An increase in the people affected by COPD is expected in the coming years, and it is estimated that COPD will be the fourth most prevalent disease worldwide in 2030.[3]

Treatment of COPD is symptomatic; there is no intervention able to modify the progressive decline in lung function in the long term.[2] Consequently, the aim of all interventions is to reduce its symptoms and improve quality of life as long as possible.

Acupuncture is a therapy that derives from the Traditional Chinese Medicine (TCM) based on the stimulation of specific areas of the body surface (acupuncture points) using different stimuli such as the insertion of acupuncture needles (filiform needles), application of pressure

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(acupressure), heat (moxibustion) or electricity (electroacupuncture).[4] Some studies have been published indicating that acupuncture may have beneficial effects on COPD patients with regard to dyspnoea, exercise capacity, quality of life and lung function.[5–8] Barring these results, at the time this review was designed, there was only one specific systematic review on the effect of acupuncture and its potential use in the treatment of COPD.[9] This review, which included 16 studies, concluded that acupuncture was beneficial in outcomes like dyspnoea, exercise capacity and quality of life but not on lung function. However, this review pooled together different acupuncture techniques like filiform needle, moxibustion and acupoint transcutaneous electrical nerve stimulation and acupressure as well as pharmacological modalities such as point application therapy. When authors tried to analyse each technique separately, they only had one study per subgroup (except for Acu-TENS).

The aim of our review was to identify and evaluate separately the efficacy of non-pharmacological acupuncture techniques in the treatment of COPD patients and, therefore, perform a large spectrum review. Due to the vast amount of data obtained and the impossibility of condensing all of it in one single paper, we finally decided to publish the results in two different papers.

In this first publication, we will only focus in filiform needle acupuncture, alone or in combination with other techniques, due to the fact that it is the most common acupuncture technique used around the world.

2. Methods

2.1. Protocol and registration

For this review we followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions.[10] The protocol was previously registered at PROSPERO (CRD42014015074) and is available on: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID = CRD42014015074

2.2. Eligibility criteria

We included randomised controlled trials or quasi-randomised trials and crossover studies, meeting all following criteria[1] performed in COPD patients with different grades of obstruction (GOLD A to D) in exacerbation or stable periods; [2] assessing non-pharmacological modalities of acupuncture (filiform needle, electroacupuncture, acupressure, moxibustion, ear acupuncture, etc.) compared with a control group (sham acupuncture or no acupuncture), in addition to usual care (medication, physiotherapy, pulmonary rehabilitation, etc.); and[3] reporting at least one of the following outcomes: dyspnoea, quality of life, adverse effects, exercise capacity, lung function or anxiety and depression.

Exclusion criteria were as follows[1] if acupuncture was compared with a different acupuncture technique or a therapy not used in usual care; and[2] randomised cluster studies.

Due to do the large amount of different acupuncture techniques found, we decided to exclude those that were mainly used only in China and therefore focus on the most known and practiced ones in the world. Trials about those techniques are listed in the results section but were not analyzed. This exclusion criteria was not contemplated in our original protocol.

No language restriction was applied.

2.3. Information sources

An electronic search was performed up until May 2019. Databases included were Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, CINAHL, AMED (Ovid), PEDro, PsycINFO, CNKI, VIP, Wanfang and Sino-Med.

In addition, the bibliographies of selected articles were consulted in search of additional studies not detected in the initial search. Manual reviews of international respiratory disease conferences (European Respiratory Society and American Association for Respiratory Care) were also performed from 2010 to 2019.

2.4. Search

We conducted a comprehensive search using the following key words and their variations: "acupuncture", "moxibustion", "acupressure", "electroacupuncture", "AcuTENS", "ear acupuncture", "cupping", "COPD", "randomised control trial". The searching strategy was adjusted for each database (see additional file 1).

2.5. Study selection

The reviewers (CFJ, MSR, JV, WC, HN, XRY, TX, HRX, MY, MS and NGT) worked in pairs and independently identified the articles that met the inclusion criteria, first through title and abstract and afterwards through full text paper.

2.6. Data collection process

The reviewers (CFJ, MSR, JV, WC, HN, XRY, TX, HRX, MY, MS and NGT) worked in pairs and independently extracted the data using a standardised data extraction form. A pilot test prior to the data extraction was performed to check suitability of the form, as well as its understanding by the reviewers. A third author was consulted in case of discrepancies. Lack of data or inconsistent data were managed by contacting the trial authors; if this was not possible, data was not included in the meta-analysis.

2.7. Risk of bias in individual studies

The Cochrane risk of bias assessment tool[11] was used to assess the papers' risk of bias.

2.8. Summary measures

Continuous outcomes were expressed as mean difference (MD) with 95% confidence interval (CI) or standardised mean difference (Std. MD) when different scales were used. For trials with different arms using acupuncture, results were combined before meta-analysis using the Cochrane Handbook.[17]

2.9. Synthesis of results

Heterogeneity of the study results was evaluated through the I^2 statistic. For the meta-analysis, post-treatment data from each group or post-treatment differences between groups were used. When this was not reported or large baseline differences between the groups were found, the differences from baseline data from each group were used. The results were combined in a meta-analysis using RevMan 5.3 software and applying a fixed effects model to summarise the results when heterogeneity was not relevant ($I^2 < 30\%$). Otherwise, a random effects model was used. If I^2value was over 70%, a narrative synthesis of the available data was performed.

2.10. Additional analyses

Since studies included patients with different conditions and this could lead to heterogeneity in our results, we decided to separate them in two subgroups in all meta-analysis, stable patients and exacerbated patients. Therefore, when heterogeneity was too big ($I^2 > 70\%$) between subgroups or in one of the subgroups, results are presented separately.

2.11. Publication bias

Publication bias was assessed for meta-analysis with more than 10 trials using a funnel plot.

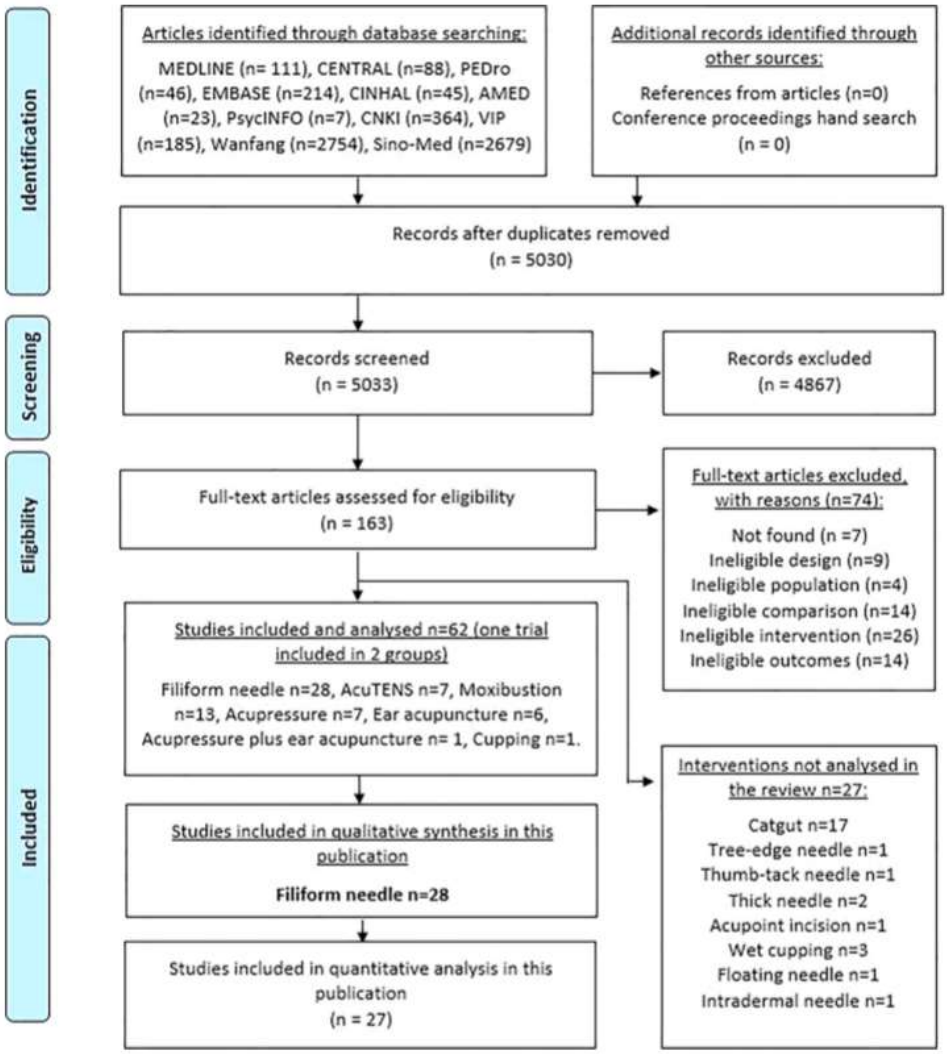

Fig. 1. Flowdiagram.

3. Results

3.1. Study selection

To identify potentially eligible studies, reviewers in pairs independently screened all 5030 unduplicated titles and abstracts retrieved, and full text of 166 articles were obtained for final inclusion decisions. Fifty-one articles were excluded for reasons shown in Fig. 1. As mentioned in the methods section, several acupuncture techniques used only in China—catgut implant (17 studies), three-edge nedlee (1 study), thumb-tack needle (1 study), thick needle (2 studies), acupoint incision (1 study), wet cupping (3 studies), floating needle (1 study), or intradermal needle (1 study) were not included in the analysis. Eighty-eight studies were included and analysed in the review; of those, 28 used filiform needles alone or in combination with another technique, 7 used only Acupoint transcutaneous electrical nerve stimulation (AcuTENS), 13 only moxibustion, 7 used acupressure, 6 only ear acupuncture, 1 combined acupressure with ear acupuncture and 1 used a cupping technique (one trial was included in 2 groups) (Fig. 1).

As previously explained, we only focused on filiform needle technique in this paper.

3.2. Study characteristics of filiform needle trials

Details from the 28 trials included in the filiform needle acupuncture group are summarised in Table 1.

Twenty-seven trials were classified as parallel randomised control trials since they all described that groups were generated randomly, however, 10 trials did not describe sufficient information about the sequence generation process.[5,12,21,27,28,30–32,34,35] 1 trial was classified as a parallel quasi-randomised control trial since sequence was generated by date of admission.[22]

Table 1
Details from filiform needle studies.

First author, year	Design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes and endpoints
Filiform needle vs. no acupuncture								
Stable condition								
Deering, 2011[18]	RCT	60 (31:29) Stable within the last 4-6 weeks	I: 65.1 (9.7) C: 67.7 (5.3)	LI11, LI10, SJ10, SJ6, LU5, LU7 + Pulmonary rehabilitation	Pulmonary rehabilitation + a recommendation of 3 additional days of unsupervised home exercise (30 min)	20 min	Once a week for 7 weeks	Dyspnoea (Borg, mMRC) QoL (SGRQ) Exercise capacity (ISWT) Lung Function (FEV_1-%, FVC-%, IVC-%, PiMax) Postintervention and 3 months follow up
Deng Y 2019[26]	RCT	86 (49:37)	64.28 (3.61) 64.96 (3.27)	BL12, Dingchuan (EX-B1), RN17, BL13, ST40, SP10, LU5 Warm needle acupuncture +Regular medication and aerobic treatment	Symptomatic treatment: anti-infection, oxygen inhalation, antispasmodic, antitussive, expectorant, cough and phlegm	Not mentioned	3 to 5 times per week for 4 weeks	Exercise capacity (6mwd) Lung function (FEV_1-L, FEV_1/FVC, PEF) Postintervention
Jia J, 2004[25]	RCT	44 Moderate and severe	I: 61.0 (33.2) C: 60.0 (34.8)	Major acupoints: BL13, BL43, BL23, ST36, KI3, LU9 + 1-2 matching acupoints: Dingchuan (EX-B1), CV17, LU5, LU7 Twisting, lifting and thrusting after the arrival of qi + Bronchodilators, anti-inflammatory and anticholinergic drugs + Pulmonary rehabilitation	Bronchodilators, anti-inflammatory and anticholinergic drugs +Pulmonary rehabilitation (Walking at 60 m/min 10 to 30 min and up to 80/min for 23-30 min, and diaphragmatic breathing)	I: 30 min C: 1 h	A: 50 sessions every 2 days for 100 days	Lung Function (FEV_1-%, FEV_1/FVC, TLC-%, RV-%, RV/TLC) Postintervention
Li L 2017[38]	RCT	90 (51:39)	I: 62.74 (2.15) C: 65.81 (2.75)	BL23, CV17, Dingchuan (EX-B1), BL43, ST36, LU5, ST40, SP10 Warm needle acupuncture +Regular medication and aerobic training + Pulmonary rehabilitation	Symptomatic treatment: anti-infection, oxygen inhalation, antispasmodic, antitussive, expectorant, cough and phlegm	Not mentioned	3 to 5 treatments per week for 4 weeks	Lung function (FEV_1-% and L, FEV_1/FVC) Postintervention
Liu XL, 2015[17]	RCT	59 (36:23) Mild and moderate	56.51 (6.96)	GV14, BL13, BL17, BL20, BL23 Warm needle acupuncture +Routine treatment	Routine treatment: tiotropium inhalation	30 min	Once every 2 days for one month (15 sessions)	QoL (CAT) Lung Function (FEV_1-%, FEV_1/FVC) Postintervention
Wang LL, 2013[28]	RCT	80 (68:12) Not mentioned	I: 67.21 (7.7) C: 66.5 (8.8	BL13, BL20, BL23, CV17, BL26, BL43, EX-B1, LU9, KI3, ST36, PO5, CV22, CV12, SP9, GV20, EX-HN1, HT7. + Pulmonary rehabilitation	Pulmonary rehabilitation (bronchodilators and breathing exercises)	Not mentioned	Once a day for 2 months	Dyspnoea (SGRQ, mMRC, Borg) Exercise capacity (6MWD) Lung function (FEV_1-%) Postintervention
Xie JH, 2014[15]	RCT	80 (40:40) Not mentioned	I: 68.9 (8.7) C: 68.5 (9.6)	Major acupoints: ST36, BL13, Dingchuan (EX-B1). + Matching acupoints: BL43, BL15, GV14, BL12 Warm needle acupuncture at back acupoints and ST36 + Bronchodilators and anti-inflammatory drugs	Bronchodilators and anti-inflammatory drugs	30 min	I: 24 sessions 3 times a week for 8 weeks Drugs: 2 a day for 8 weeks	Lung Function (FEV_1-%, FEV_1/FVC, PEF) Postintervention
Yang JG, 2016[16]	RCT	61 (37:24) Not mentioned	57.97 (8.09)	Warm needle acupuncture at GV14, BL13, BL17, BL20, BL23. + Drug treatment	Drug treatment	30 min	14 sessions, once every 2 days	QoL (CAT) Lung function (FEV_1-%, FEV_1/FVC) Postintervention
Yang P, 2009[14]	RCT	80 (54:26) Not mentioned		Major points: ST36, SP6, CV4, Dingchuan (EX-B1. For excessive accumulation of phlegm dampness type: ST40, BL13 For extravereted blood type: SP10	+ Body exercise and healthy education	30 min	40 sessions, once daily for 20 days, 10-day interval	QoL (QOLS) Exercise capacity (6MWD) Lung function (FEV_1-%, FEV_1/FVC) Postintervention

(continued on next page)

Table 1 (*continued*)

First author, year	Design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes and endpoints
				For deficiency of kidney-yang: KI1 For deficiency of yin: LR3 Moxibustion therapy for bilateral ST36 + Body exercise, healthy education			
Zhan WX, 2013[23]	QRCT	60 Moderate to very severe	I: 67.13 (7.88) C: 66.03 (8.45)	CV17 and CV19 + Usual treatment	Usual treatment (anti-inflammatory, eliminating phlegm drugs, symptomatic treatment)	3h	Once a day for 10 days	QoL (SGRQ) Exercise capacity (6MWD), Lung function (FEV_1-%) Postintervention
Zhu J 2017[24]	RCT	68 (42:26)	62.94 (7.56) 63.18 (6.73)	ST36, BL23, BL43, BL12, CV17, Dingchuan (EX-B1 Warm needle acupuncture + Regular treatment	Symptomatic treatment: anti-infection, oxygen inhalation, antispasmodic, antitussive, expectorant, cough and phlegm	Not mentioned	Once a day 5 times per week for 3 months	Lung function (FEV1-L, FVC-L, FEV1/FVC) Postintervention
Exacerbated condition								
Chen ZY 2013[26]	RCT	47 (51:5) * Not mentioned	72.43 (6.53)	General points: GV20, EX-HN1, ST9, LI18, SJ17, GB21, Zhike, Wei, Qi (Ex-CA), LU9, PC6, ST36, GB34, ST37, SP9, Shen (EX-HN1) Special points: Cough asthma: Zhike Bosom frowsty and flustered: CV22, ST18 ST16. Tonifying five Zang organs: LR13. Tonifying six hollow organs: CV12. Tonifying Qi: CV17, CV6. Enriching the blood: SP10, BL17. + Usual treatment	Usual treatment	40 min	7 sessions for 14 days (once every 2 days)	QoL (CAT) Lung Function (FEV_1-%, FEV_1/FVC) Postintervention
Dai L 2018[32]	RCT	68 (65:3)	66.46 (5.41) 66.79 (5.59)	Bilateral BL13, BL15, BL18, BL20, BL23, SP6, ST40, HE7 and DU20, +Symptomatic treatment	Symptomatic treatment: anti-infection, oxygen inhalation, antispasmodic, antitussive, expectorant, cough and phlegm	30min	Once a day for 14 days (14 sessions)	Lung function (FEV_1-%, FVC-%, FEV1/FVC) Postintervention
Gao YM 2014[20]	RCT	62 (35:27) Moderate and sever	I: 67.5 C: 68.2	Dingchuan (EX-B1) with electroacupuncture stimulation (20 times/min, maximum tolerance) + Basic treatment	Basic treatment (anti-infection treatment, continuous low flow oxygen therapy, reducing phlegm and spasmolytic drugs)	30-35 min	20 sessions, once a day first 10 days. Once every 2 days last 10 days	Dyspnoea (mMRC) QoL (CAT) Exercise capacity (6MWD) Lung function (FEV_1-L) Postintervention
Liu L, 2015[27]	RCT	80 (50:30) Not mentioned	60.75 (1.55)	BL13, BL23, CV6, CV4, CV17, ST36, Dingchuan (EX-B1) +Basic treatment	Basic treatment (Bronchodilator and anti-inflammatory drugs)	10 min	24 sessions, twice a week for 3 months	Exercise Capacity (6MWD) Lung Function (FEV_1-%, FEV_1/FVC) Postintervention
Wang JY, 2015[12]	RCT	63 (35:28) Not mentioned	64.00 (4.80)	ST36, ST40, SP6, SP15, CV12, CV13, CV6, CV4, LU9, LU5, LU6, Dingchuan (EX-B1) + Ginger moxibustion with cones at CV17 and ST36 + Basic treatment	Basic treatment: bronchodilators and anti-inflammatory drugs, vitamin and oxygen uptake as adjuvant therapy and mechanical ventilation applied in very sever patients	30 min	Once a day for 40 days	Lung function (FEV_1-%, FVC-%, MVV, MIP) Postintervention
Zhang YM, 2013[23]	RCT	63 Not mentioned	I 1: 68.53 (7.58) I 2: 72.21 (7.53) I 3: 71.47 (7.48) C: 69.76 (7.21)	I1: bilateral BL13 I2: bilateral TE6 I3: bilateral BL13 and TE6 Reinforcing-reducing method + Regular treatment	Regular treatment (Oxygen 2-3 L/min; antibiotherapy, bronchodilators and mucolytic drugs)	30 min	Twice daily for 14 days	Lung Function (FEV_1/FVC) Postintervention
		Filiform needle vs. sham acupuncture Stable condition						

(*continued on next page*)

Table 1 (*continued*)

First author, year	Design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes and endpoints
Cao L, 2012[21]	RCT	29 Not mentioned	I 1: 76.6 (6.50) I 2: 72.9 (8.33) C: 77.6 (5.70)	I1 : CV17, LU5, LU7, ST36, SP9, ST40, SP6, KI3 +Ear A (Shen Men, Fei, Qi Guan, Yan Hou, Dui Er Pin Jian) I2: CV17, LU5, LU7, ST36, SP9, ST40, SP6, KI3 +Sham Ear A + Regular treatment	Sham superficial acupuncture in same points slightly offset + Sham auricular points + Basic treatment (bronchodilator, anti-inflammatory, anti-cholinergics)	30 min	Acup: once a day, 20 sessions Ear Acup.: 3-5 times a day, 20 days	Dyspnoea (mMRC) QoL (CAT) Lung function (FEV_1-%, FEV_1/FVC) Postintervention
Feng J, 2016[29]	RCT	72 (64:8) Moderate to very severe	I: 67.8 (5.4) C: 67.1 (6.1)	Bilateral: LU1, LU9, LI18, ST36, GB12, BL13, BL20, and BL23 with manual stimulation and De qi response + Regular drug treatment	Sham acupuncture using Park sham device at same real acupuncture points. + Regular drug treatment	30 min	24 sessions, 3 times a week for 8 weeks	Dyspnoea (Borg) QoL (SGRQ) Exercise capacity (6mwd), Lung function (FEV_1-%, FVC-L) Postintervention
Ge Y 2017[30]	RCT	44 (38:6)	65 (6) 65 (7)	Acupuncture CV17, ST18, CV4, CV12, ST25 + electroacupuncture Regular medication and aerobic training	Sham acupuncture + sham electroacupuncture Regular medication and aerobic training	Not mentioned	14 treatments, 2 to 3 times per week	Exercise capacity (6mwd). Lung function (FEV_1-%, FVC-%, FEV_1/FVC) Postintervention
Guo YM, 2013[28]	RCT	33 (30:3) Not mentioned	I: 65.28 (5.73) C: 66.60 (6.06)	CV17, BL26, CV12, bilateral ST18, ST25, ST16. Manual + electrical stimulation + Aerobic exercise	Sham acupuncture with placebo needle same points + Aerobic exercise	I: 30 min	I: 14 sessions every 2 days	QoL (QOLS) Lung function (FEV_1-%, FEV_1/FVC, FVC-%, MVV) Postintervention
Jobst, 1986[5]	RCT	24 Not mentioned	I: 67.4 (11.3) C: 61.5 (17.6)	Points according to the principles of traditional Chinese medicine + Moxibustion if indicated	Needles inserted into non-acupuncture points	Not mentioned	13 sessions over 3 weeks	Dyspnoea (Borg, SOB) Exercise capacity (6MWD) Postintervention
Kuhlemann H, 1997[31]	RCT	10 (7:3) Not mentioned	64.3 (10.4)	LU1, LU9, BL13, KI3, BL23, ST36, ST40, SP6, CV17, CV6 With De Qi sensation + Corticosteroids, long and sort beta 2 adrenergic	Superficial acupuncture needling with no de Qi, 3 cm from real points + Corticosteroids, long and short beta 2 adrenergic	Not mentioned	7 sessions in 14 days. Once every 2 days	Dyspnoea (CRQ) QoL (CRQ) Lung function (FEV_1-%, VR/TLC, MOIP) Postintervention
Suzuki, 2012[6]	RCT	68 (63:5) Stable over 3 months Moderate n = 19 Sever n = 24 Very severe n = 25	I: 72.7 (6.8) C: 72.5 (7.4)	LU1, LU9, LI18, CV4, CV12, ST36, KI3, GB12, BL13, BL20 and BL23 Manual rotation + Daily medication	Park sham device over same points as experimental group + Daily medication	50 min	Once a week for 12 weeks	Dyspnoea (Borg, mMRC) QoL (SGRQ) Exercise capacity (6MWD) Lung function (FEV_1-%, FVC-%, RV/TLC, DLCO, MIP, MEP) Adverse events Postintervention
Tong J, 2014[18]	RCT	30 (27:3) Not mentioned	I: 64 (6) C: 67 (6)	CV17, ST18, CV4, CV12, ST25, ST16 Unilateral LI4, ST40 Manual and electrical stimulation + Aerobic exercise	Sham acupuncture at same points + Aerobic exercise	30 min	10-15 sessions. 2 to 3 times a week for 5 weeks	QoL (SGRQ) Exercise capacity (6MWD) Lung function (FEV_1-%, FEV_1/FVC, FVC-%, MVV) Postintervention
	Exacerbated condition							
Whale CA, 2009[24]	RCT	9 (5:4) Not mentioned	68 (range 53-78)	Bilateral LI4 + two upper sternal points (2 cm apart in the midline, advanced to the periosteum) no manual or electrical stimulation and no attempt to elicit de qi	Park sham Device over the kneecaps bilaterally and ST25 bilaterally	20 min	3 sessions (baseline, 24 h and 48 h)	Dyspnoea (VAS, Borg scale) Anxiety (VAS) Adverse events Postintervention
	Filiform needle vs drugs							
	Stable condition							
Gao J, 2011[13]	RCT	60 (25:35) Not mentioned	I: 64.87 (8.73)	Major acupoints: Dingchuan, BL13, ST36. + 2-3 matching acupoints: CV17, CV22,	Bronchodilators and anti-inflammatory drugs	30 min	I: 3 times a week for 8 weeks	QoL (SGRQ) Lung function (FEV_1-%,

(*continued on next page*)

Table 1 (*continued*)

First author, year	Design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes and endpoints
Yang J 2018[33]	RCT	61 0	C: 65.25 (10.66)	BL20, BL23, BL12, DU14, BL43, BL15. Warm acupuncture, two sticks for every point Dingchuan (EX-B1), BL13, ST36	Inhaled Seretide	Not metioned	C: twice daily for 8 weeks 3 times a week for 8 weeks	FEV_1/FVC, PEF) Postintervention QoL (SGRQ) Lung function (FEV_1-% and L, FEV_1/FVC, PEF) Postintervention

RCT: randomised control trial; QRCT: quasi-randomised control trial mMRC: modified medical research council; SGRQ: St George's respiratory questionnaire; ISWT: Incremental Shuttle Walking Test; QoL: quality of life; CAT: COPD assessment test; FEV_1 : forced expiratory volume in one second; FVC: forced vital capacity; QOLS: quality of life scale; MVV: maximal voluntary ventilation; TLC: total lung capacity; RV: residual volume; SOB: shortness of breath; 6MWD: 6-minute walking distance; CRQ: chronic respiratory questionnaire; MOP: mouth occlusive inspiratory pressure; MEP: mouth expiratory pressure; IVC: inspiratory vital capacity; PiMAX: maximal inspiratory muscle pressure.

Age of participants ranged from 56 to 77 years. Patient's severity was poorly reported, but it ranged from mild to very severe in the trials that did report it. After reading each paper carefully, 21 trials were classified as treating stable patients,[5,6,8,13–19,21,23,25,28–31,33–36] and 7 trials were classified as treating exacerbated patients.[12,20,23,24,26,27,32]

We found great heterogeneity in the filiform acupuncture protocols used in every trial. These differences included combining filiform needle with other techniques, the number of acupuncture points used, the length of the stimulation time and the duration of the study.

Filiform needle technique was used in combination with other techniques in 15 trials: combined with moxibustion in 10 trials,[5,11–16,34–36] with electroacupuncture in 4 trials[18–20,30] and with ear acupuncture in 1 trial.[21] Study duration ranged from 3 to 12 weeks with a treatment regime from once a day to once a week. Stimulation time was 20 to 40 min for most studies, and only 2 studies reported longer stimulation periods: Suzuki (50 min)[6] and Zhan (3 h).[22] Most of the trials used 6 to 12 points in their treatments, and only 3 studies[22–24] used fewer than 4 points. Acupuncture points were described as a fixed protocol in most trials, and only 5 used flexible protocols.[13–15,25,26] Most frequently used acupuncture points were ST36 (15 trials), BL13 (14 trials) and Dingchuan (EX-B1) and BL23 (12 trials).

In 17 trials, filiform needle acupuncture was added to usual treatment and compared with usual treatment alone.[8,12,14–17,20,22,23,25–28,32–36] Sham intervention was used in 9 trials using diverse procedures: non-penetrating needles at real points,[6,18,19,29,30] slightly offset points,[21] irrelevant points,[24] superficial needling at real points [31] or needling at non-acupuncture points.[5] Finally, regular drugs were chosen as a comparator in 2 papers.[13,33]

All trials assessed all outcomes at the end of the intervention and only one had 3 months follow up.[8]

3.3. Risk of bias within studies

Assessment of risk of bias of the included filiform needle trials is summarised in Fig. 2. Due the nature of filiform needle intervention, the Cochrane risk of bias tool was modified to add "blinding of outcome assessment". "Blinding of personnel" was removed due the fact that the person performing the acupuncture treatment cannot be blinded. In general, most of the studies had an unclear risk of bias due to the lack of information reported. Allocation concealment was one of the most critical aspects with only 4 trials (14.2%) classified with a low risk of bias. Blinding of outcome assessment was poorly described in most trials, only 6 (21.4%) were classified with a low risk of bias. Detailed risk of bias information of each trial is reported in additional file 2.

3.4. Synthesis of results of filiform needle acupuncture

Of the 28 trials included in the synthesis of the results, only 27were in the quantitative analysis, one trial was excluded for all meta-analysis due to important inconsistencies in the reported results.[29] To assess filiform needle acupuncture efficacy, 3 different comparison groups were formed: filiform needle vs. no acupuncture, filiform needle vs. sham and filiform needle vs. drugs. In each meta-analysis, patients in stable and exacerbated conditions were separated in subgroups to identify if those patient's characteristics could generate heterogeneity in our results. When possible, results combining the two subgroups are given; otherwise, results for the subgroups are presented.

3.4.1. Filiform needle vs. no acupuncture

Seventeen trials compared the efficacy of filiform needle with a group not receiving any acupuncture intervention.[8,12,14–17,20,22,23,25–27,32,34–36]

3.4.1.1. Dyspnoea. Three trials assessed dyspnoea in this comparison—2 including stable patients[8,26] and 1 including exacerbated patients.[20] The Borg scale was used in 2 trials, while the modified Medical Research Council (mMRC) scale was used in all 3 trials. According to the American

thoracic society/European respiratory society (ATS/ERS) Task Force, we analysed separately short term (Borg, Visual analogue scale (VAS), Short of breath (SOB)) and situational (mMRC) dyspnoea.[31]

Meta-analysis did not show statistical differences on the Borg scale (2 trials, 121 stable participants) (MD: -0.38; 95% CI: -0.8, 0.04; I^2 = 0%) (Fig. 3.a) nor for the mMRC scale pooling stable and exacerbates subgroups (3 trials, 183 patients) (MD: 0.12; 95% CI: -0.20, 0.43; I^2 = 58%) or analysing the two subgroups separately (Stable condition, 2 trials, MD: 0.07; 95% CI: -0.48, 0.62; I^2 = 67%) (Exacerbated condition, 1 trials, MD: 0.22; 95% CI: -0.02, 0.46) (Fig. 3.b).

3.4.1.2. Quality of life. Eight trials studied filiform needle effect plus regular treatment on quality of life compared with regular treatment alone. Six trials included stable patients,[8,14,16,17,22,27] while 2 trials included exacerbated patients.[20,26] Of the 8 trials, 3 used the St. George's Respiratory Questionnaire (SGRQ),[8,17,22] 4 trials used the COPD Assessment Test (CAT)[16,20,26,27] and 1 trial used the Quality of Life Scale (QoLS).[14]

For this comparison, a standardised mean difference was used, but we found great heterogeneity (I^2 = 94%). When exploring it, it was found to be due to one single trial (which results seemed to overestimate acupuncture's benefits compared with other trials). [14] After removing this trial, results showed a significant improvement on QoL (7 trials, 421 patients) (Std. MD: -0.62; 95% CI: -0.90, -0.34; I^2 = 50%), this result was seen for the stable subgroup (5 trials) (Std. MD: -0.64; 95% CI: -1.03, -0.26; I^2 = 62%) and the exacerbated subgroup (2 trials) (Std. MD: -0.54; 95% CI: -0.94, -0.15; I^2 = 15%) (Fig. 3.c).

3.4.1.3. Exercise capacity. Seven trials assessed exercise capacity, with 5 trials including stable patients [8,14,22,28,36] and 2 trials including exacerbated patients.[20,27] Exercise capacity was measured with the 6-minute walking test (6MWT) in 5 trials,[14,20,22,27,28] while the incremental shuttle walking test (ISWT) was used in only 1 trial,[8] for the meta-analysis this last paper was not included because tests measure different physiological responses.

Meta-analysis of trials using 6MWT showed high heterogeneity (I^2 = 88.6%). For stable patients subgroup (4 trials, 306 participants) heterogeneity was still too high (I^2 = 73%), but was reduced when removing trial from Zhan W,[23] which seamed to be outperforming, and results remained statistically significant (6MWT MD: 33.05 m; 95%CI: 19.11,46.99; I^2 = 67%).No statistical difference was seen in exacerbated patients (2 trials, 142 participants) (6MWT MD: 0.65 m; 95% CI: -20.74, 22.04; I^2 = 20%) (Fig. 3.d).

3.4.1.4. Lung function. Lung function was assessed in 15 trials using the forced expiratory volume in one second (FEV_1) and/or FEV_1 and forced vital capacity ratio (FEV_1/FVC). All 15 trials assessed FEV1: 11 trials including stable patients[8,14–16,22,25,27,28,34–36] and 4 including exacerbated patients.[12,26,27,32] Eleven trials also assessed FEV_1/FVC: 7 trials including stable patients[14–16,25,27,34,36] and 4 including exacerbated patients.[23,26,27,32]

The study by Jia et al[25] was not pooled in the FEV_1 and FEV_1/FVC meta-analysis due to the fact that the SD reported was drastically smaller than in the other trials. Contact with the author to solve this issue was not possible.

For FEV_1, 12 trials reported FEV_1 in % while 2 of them only reported litres (L).[34,36] Pooled results from trials reporting FEV_1 in % showed great heterogeneity due to the trial from Li et al,[35] outperforming the rest of the trials. When removing this trial meta-analysis did show a small but statistical significant improvement of 1.58 perceptual points on FEV_1% (11 trials, 729 participants) (95% CI: 0.51, 2.66; I^2 = 0%), this improvement was seen in the exacerbated subgroup (4 trials, 237 participants) (MD: 3.09; 95%CI: 1.00, 5.18, I^2 = 0%) but not in the stable subgroup (7 trials, 472 participants) (MD: 1.04; 95%CI: -0.21, 2.29, I^2 = 0%) (Fig. 3.e).

For FEV_1/FVC, the 10 trials were not meta-analysed due to high heterogeneity between the stable and exacerbated subgroups (I^2 = 77%). For the stable patients subgroup,[14–17,25,34,36] results showed no statistical difference between groups but heterogeneity was too high (I^2 = 83%), removing trial from Deng et al[36] reduced heterogeneity but results remained non-significant (5 trials, 349 participants) (FEV1/FVC MD: 1.33; 95% CI: -1.19, 3.85; I^2 = 38%). In the exacerbated subgroup, differences were found based in 4 trials[23,26,27,32] (330 participants) (MD: 3.42; 95% CI: 1.55, 5.29) (Fig. 3.f).

3.4.2. Anxiety and depression

No trial assessed anxiety or depression.

3.4.3. Filiform needle vs. Sham

Nine trials compared filiform needle with a sham intervention, with 8 trials including stable patients[5,6,18,19,21,29–31] and only 1 including exacerbated patients.[24]

3.4.3.1. Dyspnoea. Six trials studied the effect of filiform needle compared with sham acupuncture, with 5 trials including stable patients[5,6,21,29,30] and only 1 including exacerbated patients.[24] The Borg scale was used in 4 trials,[5,6,24,29] mMRC in 2 trials,[6,21] and SOB,[5] chronic respiratory questionnaire (CRQ)[31] and VAS[24] in one trial each.

Three trials measured short-term dyspnoea, two including stable participants[6,30] and one with exacerbated participants.[24] Heterogeneity was too great to plot all 3 studies (I^2 = 77%). For stable participants standardised

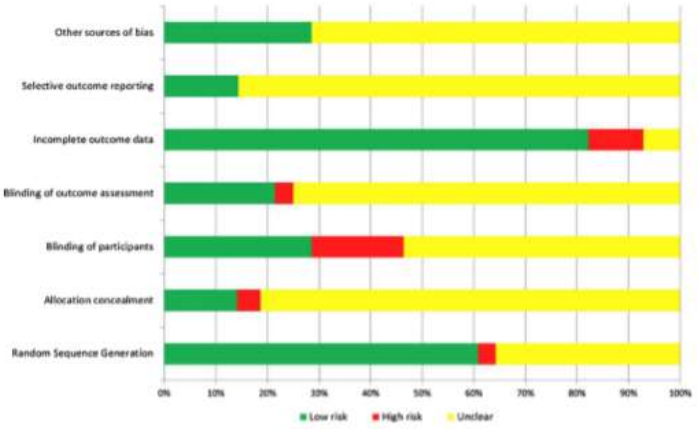

Fig. 2. Risk of bias of included studies.

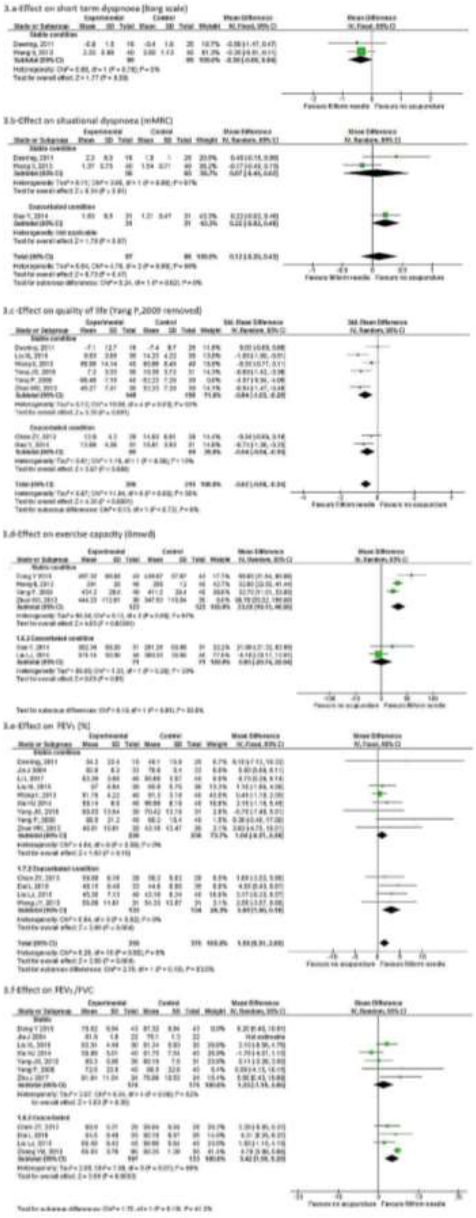

Fig. 3. Meta-analysis of filiform needle vs. no acupuncture.

mean difference showed a statistical benefit of real acupuncture using Borg and SOB measures (Std MD: -1.07; 95% CI: -1.58, -0.56; I^2 = 11%; 70 participants) (Fig. 4.a). For exacerbated participants no statistical differences where observed in a small pilot trial of only 7 patients.

Two trials reported situational dyspnoea both in stable patients (6,21,). Results showed a statistical reduction of 0.77 points on the mMRC scale (95% CI: -1.14, -0.41; I^2 = 26%) (Fig. 4.b).

Two trials were not included in the meta-analysis—Feng[29] as previously explained and Jobst, [5] since data was presented as median and range instead of mean and standard deviation.

3.4.3.2. Quality of life. Quality of life was assessed in 6 trials, all including stable participants.[6,18,19,21,29,31] The SGRQ was used in 3 trials,[6,18,29] and the CAT,[21] QoLS[19] and CRQ[31] were used in one trial each. Meta-analysis of 5 trials (176 participants)[6,18,19,21,30] shows an overall improvement in the real filiform acupuncture group (Std. MD: -0.81; 95% CI:-1.12, -0.49; I^2 = 24%) compared with sham intervention (Fig. 4.c).

3.4.3.3. Exercise capacity. Five trials assessed exercise capacity, all with stable patients and using the 6MWT.[5,6,18,29,30] Four trials that underwent meta-analysis showed a clinically significant increase of 76.68 m in the 6MWT in the real filiform acupuncture group compared with sham acupuncture (158 participants; 95% CI: 39.93, 113.43; I^2 = 0%) (Fig. 4.d). Feng's trial was not included.[29]

3.4.3.4. Lung function. Seven trials assessed lung function, all including stable participants.[6,18,19,21,29–31] Of those, all 7 trials reported FEV_1[6,18,19,21,29–31] and 5 reported FEV_1/FVC.[18,19,21,29,30] Pooled results for FEV_1 showed an improvement of 5.40 percentage points in the real acupuncture group compared with sham acupuncture (6 trials, 267 participants) (95% CI: 2.90, 7.91; I^2 = 0%) (Fig. 3.e). This improvement was also observed in FEV_1/FVC [18,19,21,31] (4 trials, 140 participants) (MD: 6.64; 95% CI: 3.44, 9.83; I^2 = 10%) (Fig. 4f[29].

3.4.3.5. Anxiety and depression. Only one small pilot trial with only 9 participants assessed depression using the VAS,[24] sample was too low to draw any conclusion. Depression was not assessed in any trial.

3.4.4. Filiform needle vs. conventional drugs

Only 2 papers compared filiform needle technique with conventional drugs (Seretide), both of them with stable participants.[13,33]

3.4.4.1. Exercise capacity. Two trials, both with stable participants analysed QoL using the SGRQ. Meta-analysis showed a statistical reduction of 4.77 points (120 participants) (95% CI: -8.50, -1.03; I^2 = 60%) (Fig. 5a)

3.4.4.2. Lung function. Two trials with stable participants assessed lung function, both using FEV_1% and FEV_1/FVC (13.33). Pooled results from FEV_1 and FV_1/FVC showed no significant difference compared with Seretide inhalation (120 participants) (FEV_1% MD: 0.00; 95% CI: -2.36, 2.35; I^2 = 0%) (Fig. 5b) (FEV_1/FVC MD: -1.70; 95% CI: -3.90, 0.50; I^2 = 0%) (Fig. 5c)

3.5. Adverse events

Adverse events of filiform needle technique were only assessed in 2 trials. For stable patients, Suzuki et al[6] reported 5 cases of subcutaneous haemorrhage and 5 cases of pain in the puncture site out of 30 participants in the real filiform needle acupuncture group. Other minor reactions like fatigue or dizziness were equally reported in the real and sham acupuncture group. For exacerbated patients, Whale et al[24] reported no side effects in the 4 participants receiving real filiform needle acupuncture. Not enough data was reported to calculate risks for each event.

3.6. Publication bias

Only one meta-analysis included more than 10 trials (Filiform needle vs no acupuncture for FEV_1). Funnel plot did not show evidence of publication bias (Additional file 3).

4. Discussion

4.1. Main results

From our knowledge, this is the first systematic review that evaluates specifically the effectiveness of filiform needle acupuncture for

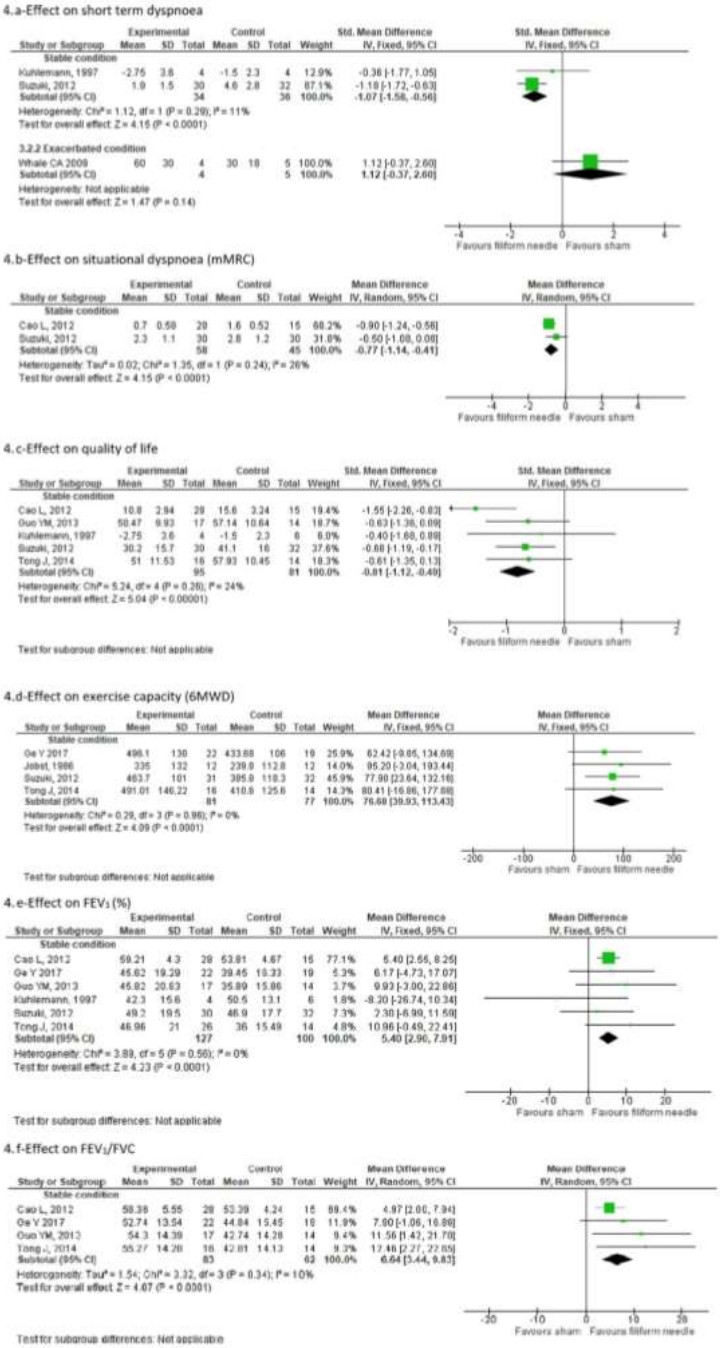

Fig. 4. Meta-analysis of filiform needle vs. sham.

COPD. Benefits were observed for stable patients with regard to dyspnoea, QoL and exercise capacity compared with sham. Those benefits were also seen in QoL and exercise capacity when the comparator was no acupuncture. For lung function, mixed results were obtained, but results that were statistically significant were not clinically relevant. Anxiety was only assessed in one small pilot trial and no conclusions could be drawn while depression was not studied in any trail.

Twenty-eight trials assessing the efficacy of filiform needle

acupuncture were included in this systematic review. Participants were adults and older adults with stable and exacerbated conditions. Comparison groups were no acupuncture, sham acupuncture and drug treatments. Treatment protocols were very heterogeneous and included different types and numbers of acupuncture points, different treatment regimens and different durations.

4.2. Implications for clinical practice

First, there is remarkable clinical diversity coming from acupuncture interventions. However, this reflects the common heterogeneity that exists in acupuncture's clinical practice and the lack of consensus about the best treatment for COPD, especially regarding duration and regime. From this observation, it should be strongly considered to create consensus about interventions and measures for future studies.

Second, dyspnoea results show that filiform needle acupuncture could have a beneficial effect especially in stable COPD patients when compared with sham acupuncture. This effect could be produced through the enhancement of the endogenous opioid system produced by acupuncture,[37] as endogenous opioids modulate dyspnoea in patients with COPD.[38] However, we observed better results in trials that evaluated dyspnoea at short term (Borg, VAS and SOB) than others evaluating situational dyspnoea (mMRC). We believe this could be due the fact that the mMRC is relatively insensitive to change due to therapeutic interventions such as acupuncture.[39,40] This difference between scales is also observed when acupuncture is compared with no acupuncture, where better results were also observed on the Borg scale compared to mMRC even though none of them was statistically significant.

ConceCVing QoL, both comparisons show a positive effect of acupuncture in COPD patients, independent of the instrument used (SGRQ, CAT, or QoLS). According to dyspnoea effects, a better perception of breathlessness perceived by patients could be a strong explanation of the improved QoL.[41] This effect is also perceived for the exacerbated patients and could confirm the role of dyspnoea in relation to QoL.

For exercise capacity, most of the studies used the 6MWT. This is a submaximal test that reflects the capacity to maintain daily physical activity.[42] Surprisingly, in stable patients the observed increase in walking distance is very high, 76 m (vs. sham comparison) and 33 m (vs. no acupuncture comparison), surpassing the minimum clinically important difference (30 m)[43] in both cases. Suzuki and co-workers demonstrated in different studies that acupuncture could reduce respiratory accessory muscle tension and increase oxygen saturation,[6,44] both circumstances could produce an important relief of the respiratory symptoms during walking favouring the improvements in distance.

Finally, the analysis of filiform needle acupuncture in pulmonary function (FEV_1 and FVC), even though statistically significant in some comparisons, does not show clinically relevant benefits. Those effects could be related to an activation of the autonomic nervous system when acupuncture is applied (decreasing bronchospasm) (6) but wouldn't be enough to be perceived as an improvement by patients.

It is of note that more outcomes had positive results when compared with a sham intervention than compared with no intervention. Even outcomes that were positive in both comparisons, like QoL and FEV_1, were greater in the sham comparison than in the no intervention comparison. Usually trials not using sham procedures tend to overestimate the real effect of the intervention due to patients' expectations, especially for self-reporting outcomes like dyspnoea and QoL. A possible explanation for this could be the small size of the trials, the heterogeneity of the intervention, the different characteristics of the included participants and the baseline treatments received. Those differences may lead to the different efficacies obtained for each trial. Higher quality trials (trials using sham) might have been better designed, and those factors had less of an impact on the results; therefore, results could be meta-analysed and CIs were smaller. Acupuncture seems safe for COPD patients, since only minor adverse events were described; however, the reporting of this outcome was really poor.

4.3. Relation with prior works

During the review process, two other similar works on this topic had been published by Coyle et al[9] and Wang et al[45]

In the first review 16 trials were included and concluded (that compared with placebo) acupuncture therapies could result in clinically significant improvements in dyspnoea, QoL and distance walked, but no benefit was observed in measures of lung function. When comparing our analysis with this review, similar results are observed confirming the acupuncture benefits in COPD. However, there are several differences between both reviews. Firstly, because Coyle et al included all kinds of acupoint stimulation interventions (even pharmacological ones) and only 5 of the 16 included trials used filiform needle acupuncture, all 5 trials have been included in our review.[5,6,13,24,31] Secondly, even pooling all the interventions together, Coyle's meta-analysis included a maximum of 5 trials, which decreased the statistical power and introduced an important confusion factor on the results. In the present review, we focused exclusively on filiform needle technique and the number of included trials of this technique was huge (28 vs. 5). These differences could be attributed to the fact that 19 of the included trials were published after 2013, when Coyle et al finished their database search. Finally, to try to avoid possible heterogeneity due to the different effect that acupuncture could have depending on a patient's state, we decided to do subgroup analyses for stable and exacerbated COPD patients.

In the second review Wang et al included 19 trials using filiform needle acupuncture techniques, such as manual acupuncture, electroacupuncture, warm acupuncture and ear acupuncture. In this review meta-analysis showed an improvement in the exercise capacity but not on quality of life using the overall score of the SGRQ. We believe these differences could be due to several factors. First, we included trials using filiform needle alone or in combination with other techniques such as any kind of moxibustion, which is very common in clinical practice, Wang et al however, only included warm acupuncture technique. Second, Wang et al plotted together body acupuncture and ear acupuncture whereas we examined ear acupuncture techniques separately. Finally, Wang's review only included trials with participants in stable condition.

4.4. Strengths and limitations

This is the most complete and extended systematic review on this topic to date. We included 7 international and 4 Chinese databases and no language restriction was applied. We strictly followed the review protocol during the study selection process and data extraction and analysis, even though we finally decided to publish the results in two separate papers due to the great amount of information obtained. This is the first review that separately analyses different acupuncture techniques and patient's conditions (stable and exacerbated). We decided not to plot all interventions together, because they may have different action mechanisms and, therefore, different effects in different clinical conditions. Regarding this, since in clinical practice most practitioners use filiform needle technique alone or in combination of other interventions, we plotted together trials following this practice.

For the limitations, we could not find any extra papers through hand searching, probably because we only explored American and European international congresses but not Chinese. However, the CNKI database includes Chinese conference proceedings and unpublished academic theses. We also could not review 7 trials, because it was impossible to obtain full text articles. We also could only asses publication bias based on one meta-analysis due to the small number of trials included in each comparison. Finally, important heterogeneity was found in many comparisons, this could be due differences in the treatment protocols and lack of trials quality, reducing the confidence in the results, for this reason we did not perform meta-analysis when heterogeneity was too high (over 70%).

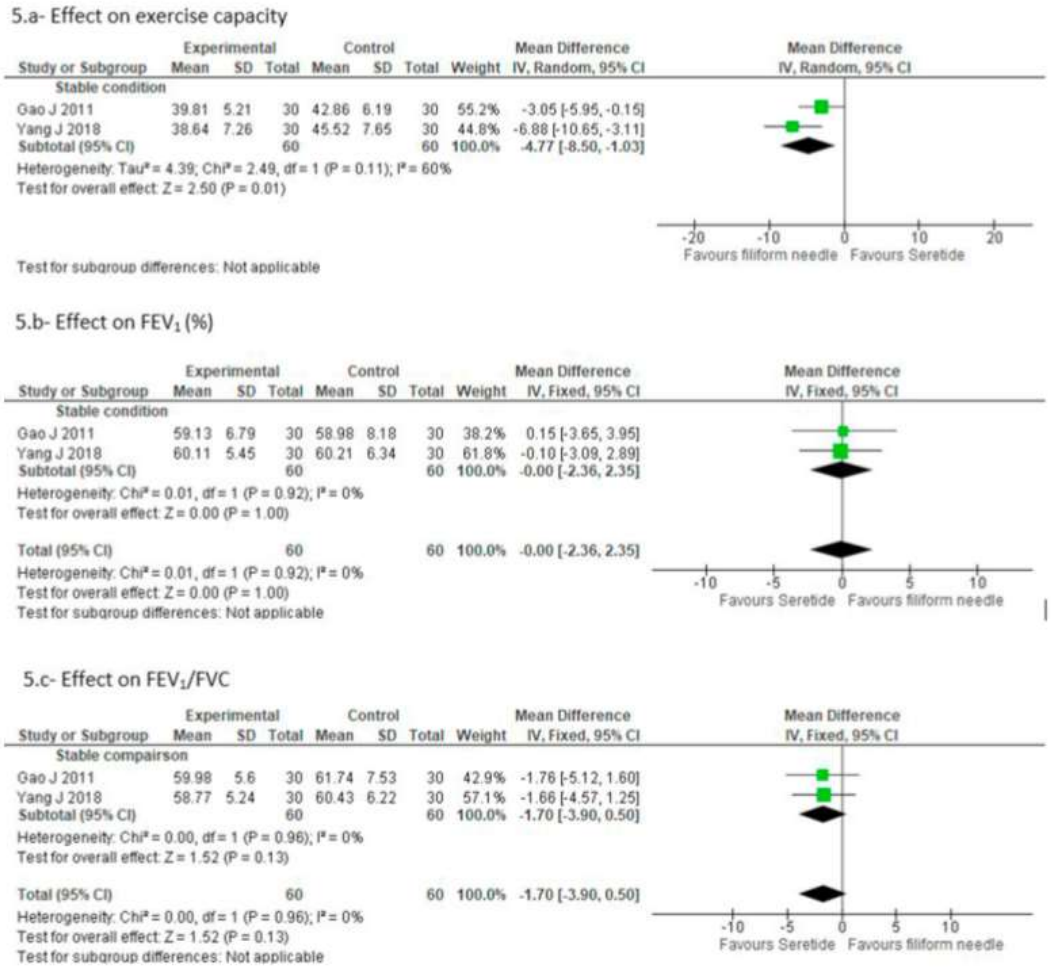

Fig. 5. Meta-analysis of filiform needle vs. drugs.

It is important to remark that even though we just included trials using filiform needle technique, in 15 trials this was used in combination with other techniques such as moxibustion or electrical stimulation (electroacupunture). We decided not to analyse those trials separately since these would have led to multiple very small groups making the analysis and interpretation of the results much more difficult.

5. Conclusions

This review found that in stable COPD patients, filiform needle acupuncture added to usual treatment improved dyspnoea, QoL and exercise capacity compared with a sham. Those benefits were also seen in QoL and exercise capacity when the comparator was no acupuncture. For lung function, mixed results were obtained, but those statistically significant were not clinically relevant.

We found great heterogeneity in treatment protocols, which included different types and numbers of acupuncture points, different treatment regimens and different treatment durations. Due the low methodological quality of some of the included trials and the low number of trials included in some comparisons such as dyspnoea, these results should be interpreted with caution. Further large well-designed randomised control trials are necessary to corroborate the effectiveness of filiform needle acupuncture in COPD.List of AbbreviationsAcuTENSAcupoint transcutaneous electrical nerve stimulationATS/ERSAmerican thoracic society/European respiratory societyCATCOPD Assessment TestCIConfidence intervalCOPDChronic obstructive pulmonary diseaseCRQChronic respiratory questionnaireFEV$_1$Forced expiratory volume in the first secondFVCForced vital capacityMDMean differencemMRCModified Medical Research CouncilQoLSQuality of Life ScaleSGRQSt. George's Respiratory QuestionnaireSOBShort of breathStd. MDStandardized mean differenceTSWTIncremental shuttle walking testVASVisual analogue scale6MWT6-minute walking test

List of Abbreviations

AcuTENS	Acupoint transcutaneous electrical nerve stimulation
ATS/ERS	American thoracic society/European respiratory society
CAT	COPD Assessment Test
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CRQ	Chronic respiratory questionnaire

FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
MD	Mean difference
mMRC	Modified Medical Research Council
QoLS	Quality of Life Scale
SGRQ	St. George's Respiratory Questionnaire
SOB	Short of breath
Std. MD	Standardized mean difference
TSWT	Incremental shuttle walking test
VAS	Visual analogue scale
6MWT	6-minute walking test

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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CF has been responsible for writing the protocol of the study, performing the electronic search in English, the extraction and analysis of the data and the writing and the submission of the manuscript.

JV and MS made substantial contributions to the conception and design of the review, extraction, analysis and interpretation of the data and writing and reviewing the manuscript.

YF, and CW and JL are responsible for the Chinese language electronic search, and data abstraction and contributed to the writing and reviewing of the manuscript.

NH, RX, XT, RH, MY, NG and MS, are responsible for trials inclusion, data extraction and critically reviewing the final manuscript.

All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests

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Carles Fernández is a PhD candidate from the Methodology of Biomedical Research and Public Health program at the Universitat Autonoma de Barcelona.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2019.08.016.

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Second publication

Background: This is the second part of a large spectrum systematic review which aims to identify and assess the evidence for the efficacy of non-pharmacological acupuncture techniques in the treatment of chronic obstructive pulmonary disease (COPD). The results of all techniques except for filiform needle are described in this publication.

Methods: Eleven different databases were screened for randomised controlled trials up to June 2019. Authors in pairs extracted the data and assessed the risk of bias independently. RevMan 5.3 software was used for the meta-analysis.

Results: Thirty-five trials met the inclusion criteria, which involved the follow techniques: acuTENS (7 trials), moxibustion (11 trials), acupressure (7 trials), ear acupuncture (6 trials), acupressure and ear acupuncture combined (1 trial) and cupping (1 trial). Due to the great heterogeneity, only 7 meta-analysis could be performed (acuTENS vs sham on quality of life and exercise capacity, acupressure vs no acupressure on quality of life and anxiety and ear acupuncture vs sham on FEV1 and FEV1/FVC) with only acupressure showing statistical differences for quality of life (SMD: -0.63 95%CI: -0.88, -0.39 I2= 0%) and anxiety (HAM-A scale MD:-4.83 95%CI: -5.71, -3.94 I2= 0%).

Conclusions: Overall, strong evidence in favour of any technique was not found. Acupressure could be beneficial for dyspnoea, quality of life and anxiety, but this is based on low quality trials. Further large well-designed randomised control trials are needed to elucidate the possible role of acupuncture techniques in the treatment of COPD.

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RESEARCH ARTICLE Open Access

Acupuncture techniques for COPD: a systematic review

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Abstract

Background: This is the second part of a large spectrum systematic review which aims to identify and assess the evidence for the efficacy of non-pharmacological acupuncture techniques in the treatment of chronic obstructive pulmonary disease (COPD). The results of all techniques except for filiform needle are described in this publication.

Methods: Eleven different databases were screened for randomised controlled trials up to June 2019. Authors in pairs extracted the data and assessed the risk of bias independently. RevMan 5.3 software was used for the meta-analysis.

Results: Thirty-three trials met the inclusion criteria, which involved the follow techniques: AcuTENS (7 trials), moxibustion (11 trials), acupressure (7 trials), ear acupuncture (6 trials), acupressure and ear acupuncture combined (1 trial) and cupping (1 trial). Due to the great heterogeneity, only 7 meta-analysis could be performed (AcuTENS vs sham on quality of life and exercise capacity, acupressure vs no acupressure on quality of life and anxiety and ear acupuncture vs sham on FEV_1 and FEV_1/FVC) with only acupressure showing statistical differences for quality of life (SMD: -0.63 95%CI: − 0.88, − 0.39 $I^2 = 0\%$) and anxiety (HAM-A scale MD:-4.83 95%CI: − 5.71, − 3.94 $I^2 = 0\%$).

Conclusions: Overall, strong evidence in favour of any technique was not found. Acupressure could be beneficial for dyspnoea, quality of life and anxiety, but this is based on low quality trials.
Further large well-designed randomised control trials are needed to elucidate the possible role of acupuncture techniques in the treatment of COPD.

Trial registration: PROSPERO (identifier: CRD42014015074).

Keywords: COPD, Acupuncture therapy, Dyspnoea, Quality of life, Systematic review, Meta-analysis

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most prevalent lung diseases, with 251 million cases globally in 2016, and is the 4th cause of death worldwide, with more than 3.2 million instances in 2015 [1]. These numbers are expected to increase [2].

COPD is characterised by a chronic and irreversible airflow obstruction caused by an inflammation in the airways and lung parenchyma which leads to structural abnormalities in the airways. These alterations specially affect force expiratory volume in the first second (FEV_1) compared to force vital capacity (FVC) [3]. The main symptoms of this disease are progressive dyspnoea, chronic cough, sputum production and recurrent respiratory infections. Those symptoms get worse as the disease evolves, with many effects on exercise capacity and quality of life [4].

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The usual treatment in COPD targets its main symptoms. Pharmacological treatment includes the use of corticosteroids and bronchodilators to reduce airway inflammation and obstruction, and non-pharmacological treatment such as pulmonary rehabilitation are used to improve perceived dyspnoea, exercise capacity and quality of life [3].

Acupuncture derives from Traditional Chinese Medicine, which uses different techniques to stimulate specific areas of the body surface, or acupuncture points, to restore health. Even though inserting needles is the best-known acupuncture technique (filiform needle acupuncture), there are several others, including heat stimulation (moxibustion), electricity (electroacupuncture or acupoint transcutaneous electrical nerve stimulation (AcuTENS)), and digital pressure (acupressure). These techniques have been traditionally used to treat all kinds of health problems including respiratory diseases like COPD, however there is little evidence about the effectiveness of those techniques and no previous review has studied different acupuncture techniques individually.

The aim of this review is to identify and separately evaluate the efficacy of non-pharmacological acupuncture techniques, excepting via filiform needle. These techniques include moxibustion (except when performed alongside use of an acupuncture needle), electroacupuncture (when not delivered using an acupuncture needle) AcuTENS, acupressure and ear acupuncture, and cupping therapy among others.

Methods

Protocol and registration

We followed the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [5] for this review and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6]. The protocol was previously registered at PROSPERO (CRD42014015074) and is available on: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015074).

Eligibility criteria

We included randomised controlled trials or quasi-randomised trials and crossover trials, meeting all the following criteria: [1] performed in COPD patients with different grades of obstruction (GOLD A to D) in exacerbation or stable periods [2]; assessing non-pharmacological modalities of acupuncture (filiform needle, electroacupuncture, acupressure, moxibustion, ear acupuncture, etc.) compared with a control group (sham acupuncture or no acupuncture), in addition to usual care (medication, physiotherapy, pulmonary rehabilitation, etc.); and [3] reporting at least one of the following outcomes: dyspnoea, quality of life, adverse effects, exercise capacity, lung function or anxiety and depression.

Exclusion criteria were: [1] if acupuncture was compared with a different acupuncture technique or a therapy not used in usual care; and [2] randomised cluster studies.

No language restriction was applied.

Due to the large number of acupuncture techniques found, we decided to exclude those that were mainly used only in China and to focus on those best known and practiced elsewhere in the world. Trials involving the techniques are listed in the results section, but were not analysed. This exclusion criteria was not applied in our original protocol.

Information sources

An electronic search was performed up to June 2019. The databases included were the Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, CINAHL, AMED (Ovid), PEDro, PsycINFO, CNKI, VIP, Wanfang and Sino-Med. the bibliographies of selected articles were also consulted in search of additional studies not detected in the initial searches. Manual reviews were also performed on international respiratory diseases conferences (European Respiratory Society and American Association for Respiratory Care) from 2010 to 2017.

Search

We conducted a comprehensive search using the following key words and their variations: "acupuncture", "moxibustion", "acupressure", "electroacupuncture", "AcuTENS", "ear acupuncture", "cupping", "COPD", "randomised control trial". The search strategy was adjusted for each database (see Supplementary material 1).

Study selection

The reviewers (CFJ, MSR, JV, WC, HN, XRY, TX, HRX MS, NGT) worked in pairs and independently identified the articles that met the inclusion criteria, first through title and abstract and afterwards through full text paper.

Data collection process

Reviewers (CFJ, MSR, JV, WC, HN, XRY, TX, HRX MS, NGT), both in pairs and independently, extracted data using a standardised data extraction form. A pilot test was performed prior to data extraction to check the suitability of the form, as well as its understanding by the reviewers. A third author was consulted in the case of discrepancies. Lack of data or inconsistent data were managed by contacting trial authors; if this was not possible the data was not included in the meta-analysis.

Risk of bias in individual studies

The Cochrane Risk of Bias Assessment Tool [7] was used to assess the risk of bias in the papers. Due to the nature of acupuncture techniques, the Cochrane risk of bias tool was modified to add "blinding of outcome assessment". "Blinding of personnel" was removed because a person providing acupuncture treatment cannot be blinded.

Summary measures

Continuous outcomes were expressed as mean difference (MD) with 95% confidence interval (CI) or standardised mean difference (Std. MD) when different scales were used. For trials with different arms using acupuncture, the results were combined before meta-analysis using the Cochrane Handbook [8].

Synthesis of results

The heterogeneity of the studies was evaluated using the I^2 statistic. Post-treatment data from each group or post treatment differences between groups were used for the meta-analysis. When this was not reported or large baseline differences were found between the groups, the difference from baseline data from each group were used. The results were combined in a meta-analysis using RevMan 5.3 software and applying a fixed effects model to summarise the results when heterogeneity was not relevant (I^2 < 30%). Otherwise, a random effects model was used. If I^2 value was over 70%, a narrative synthesis of the available data was performed.

Additional analyses

Since studies included patients with different conditions (stable and exacerbation) and this could lead to heterogeneity in our results, we decided to separate them into two subgroups in all meta-analyses. The results are therefore presented separately when heterogeneity was too big (I^2 > 70%) between subgroups or in one of the subgroups.

Results

Study selection

To identify potentially eligible studies, reviewers in pairs independently screened all 5030 unduplicated titles and abstracts retrieved, and the full text of 163 articles was obtained for decisions about final inclusion. Forty-eight articles were excluded for the reasons shown in Fig. 1. As mentioned in the methods section, several acupuncture techniques used only in China were not included in the analysis: catgut implant (17 studies), tree-edge needle (1study), thumb-tack needle (1 study), thick needle (2 studies), acupoint incision (1 study), wet cupping (3 studies) or floating needle (1 study) and intradermal needle (1 study). Sixty-two studies (36 publications) were included and analysed in the review.

In this publication we included the results from 35 trials (36 publications) which used all other techniques except filiform needle: AcuTENS (7 trials) [9–15], moxibustion (13 trials) [8, 16–27], acupressure (7 trials from 8 publications) [28–35], ear acupuncture (6 trials) [36–41], acupressure combined with ear acupuncture (1 trial) [42] and cupping technique (1 trial) [43] (one trial with multiple arms was included in the filiform needle group and the ear acupuncture group) (Fig. 1).

Study characteristics

The details of all trials included, classified for intervention, are summarised in Table 1.

Design

All trials were classified as randomised control trials since they all reported that groups were generated randomly, however, 14 trials did not provide sufficient information about the sequence generation process. Only one trial used a cross-over design [30].

Participants

The mean age of participants ranged from 52 to 78 years and was similar across all interventions. From the 34 included trials, severity was not reported in 29. Most trials included mild to severe participants. After reading each paper carefully, 29 trials were classified as treating stable patients [8–12, 14–27, 29–34, 37–40] and 6 trials were classified as treating exacerbated patients [12, 27, 35, 40–42].

Interventions and comparisons

AcuTENS Seven trials using AcuTENS were included. All trials used a similar protocol that consisted of using a stimulation pulse of between 2 and 4 Hz with a wave width of 200 microseconds and a stimulation time of 40–45 min. Five out of seven papers used a single point treatment, with four papers using Ding Chuan (EX-B1) [9, 11, 12, 15] and one using BL 13 [14]. Only two papers used a combination of several points [10, 13]. The main differences between protocols were seen in the treatment regime, with two papers using a single session intervention [9, 12] whereas in the other five papers stimulation was used from 10 to 20 sessions and a frequency between seven and four sessions a week.

All seven trials were sham-controlled using an AcuTENS device with no electric output.

Moxibustion The thirteen studies included used multiple moxibustion techniques, including moxa stick [16, 18, 20, 22, 23, 26], heat sensitivity moxibustion [23, 24, 27], cone moxibustion [8, 17], moxibustion boxes [25] and ginger moxibustion [19, 21]. There were a number of acupuncture points used, ranging

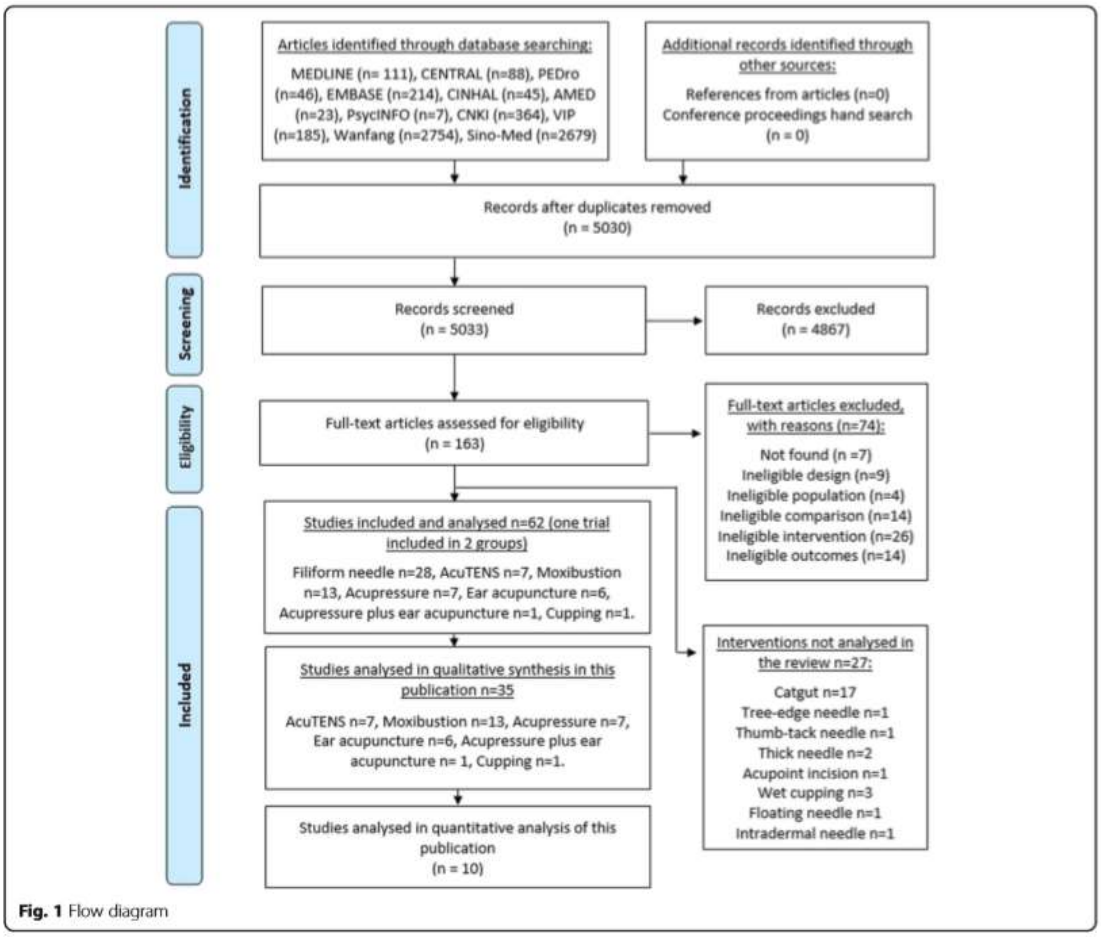

Fig. 1 Flow diagram

from 1 to 12, but most of the trials used from 3 to 7 points [8, 18–20, 23]. Most common acupuncture points used were.

Bl13 (7 trials, 53%), GV14, BL20 and ST36 (5 trials, 28%). Treatment regimens were also different, with two studies using from 3 to 6 treatment courses of 10–14 consecutive days during a year [16, 18], three studies using daily treatments for a period of 2 to 4 weeks [19, 20, 23], two using from 2 to 5 treatments a week over a month [8, 21], two trials using 5 treatments a week over 3 to 4 months [24, 25], one using nine treatments every 10 days over 3 months [17] and one trial using one treatment per month [22]. In all thirteen papers, moxibustion was added to the usual treatment and compared with the usual treatment alone.

Acupressure Out of the 7 included trials using acupressure, 5 trials included used 5–7 points 26–28, [32, 34] while 2 trials used 3 points [33, 35]. Most common used point were GV14 (4 trials, 57%) and BL13 (3 trials, 43%). Most trials used rubbing and pressing stimulation (1–3 min per point), in 5 to 15 min sessions but differed in the acupoints used, and in the session regime, which ranged from at least one treatment a day to five treatments a week over 4–24 weeks [29–31]. One study differed clearly from the others in using two points of stimulation plus the ear acupuncture point Shenmen in a daily treatment regime for 10 days [28].

Acupressure was compared with sham acupressure in two studies (three publications) using the stimulation of non-specific points [29–31]. Acupressure plus the usual treatment was compared with the usual treatment alone in five trials [28, 32–35].

Ear acupuncture The six studies included used from four to seven ear acupuncture points. Most common

Table 1 Details from all trials

First author, year	Study design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes
AcuTENS vs. sham AcuTENS								
Stable patients								
Lau, 2008 [9]	RCT	46 (31:15) Mild to moderate	75 (7.0)	AcuTENS at Ding Chuan (EX-B1). Frequency of 4 Hz and pulse width 200 μs. Intensity at the highest tolerable by the participant.	Placebo TENS with no electrical output at same point as treatment group	45 min	Single session	Dyspnoea (SOB VAS) Lung Function (FEV_1, FVC)
Liu, 2015 [10]	RCT	50 (25:25) Moderate to very severe	66.3 (9.0)	AcuTENS at Ding Chuan (EX-B1), BL13, BL23, ST36 Frequency of 2 Hz + Usual treatment	Placebo TENS with no electrical output at same points as treatment group + Usual treatment	40 min	Every 2 days for 4 weeks (14 sessions)	Dyspnoea (DVAS after 6mwd), QoL (CAT), Exercise capacity (6mwd), Lung function (FEV_1, FVC)
Ngai, 2010 [11]	RCT	18 Not mentioned	71.8 (1.2)	AcuTENS at Ding Chuan (EX-B1). Frequency of 2 Hz, pulse width of 200 μs.	Placebo TENS with no electrical output at same point as treatment group	45 min	20 sessions. 5 sessions per week for 4 weeks	QoL (SGRQ) Exercise capacity (6mwd) Lung function (FEV_1, FVC)
Jones, 2011 [12]	RCT	44 (25:19) Not mentioned	69.1 (1.6)	AcuTENS at Ding Chuan (EX-B1). Frequency of 2 Hz, pulse width of 200 μs	Placebo TENS with no electrical output at same point as treatment group	45 min	Single session	Dyspnoea (VAS) Lung function (FEV_1, FVC_1)
Shou, 2014 [14]	RCT	30 (10:20) Mild to moderate	I: 68.3 (10.2) C: 70.0 (9.2)	TENS at bilateral BL13 Frequency of 4 Hz, pulse width of 200 μs	Placebo TENS with no electrical output at same point as treatment group	40 min	20 sessions. Five times a week for 4 weeks	Lung Function (FVC, FEV_1)
Wen, 2011 [15]	RCT	40 (14:26) Not mentioned	I: 69.7 (8.09) C: 66.9 (6.71)	TENS at Ding Chuan (EX-B1) Frequency of 4 Hz, pulse width of 200 μs. + conventional treatment	Placebo TENS with no electrical output at same point as treatment group + conventional treatment	40 min	Once a day for 10 days	Lung function (FEV1, FVC)
Exacerbated patients								
Öncü, 2017 [13]	RCT	70 (54:16) Not mentioned	Not mentioned	AcuTENS at Ding Chuan (EX-B1) and LU7. Frequency 4 Hz, pulse width of 200 μs +Conventional treatment	Placebo TENS with no electrical output at same point as treatment group +Conventional treatment	45 min	20 sessions. Daily at hospital and 3 times a week at home	Dyspnoea (mMRC, Borg), QoL (SGRQ) Exercise capacity (6mwd)
Moxibustion vs. no moxibustion								
Stable patients								
Bai, 2018 [26]	RCT	80 (44: 36) Mild to severe	I: 64.6 (5.0) C: 63.7 (5.2)	Moxibustion with a moxa stick at GV14 and CV17 + Routine treatment	Routine treatment	5 min per point	Once a day for 30 days	QoL (SGRQ) Lung Function (FEV_1)
Cheng, 2011 [23]	RCT	60 (42:18) Not mentioned	I1: 65.07 I2: 68.15 C: 69. 21	I1: Heat-sensitive point's moxibustion (gentle moxibustion at heat-sensitive points) I2: Moxa stick. 3–5 points selected depending on symptom. BL12, BL13, BL20, BL23, LU7, LU9,	Western medicine standard therapy (Anti-inflammatory, relieve panting, eliminating phlegm to stop cough)	I1: Until diathermy disappeared and patients felt burning pain. I2: 30 min	Once daily. 30 days	Lung function (FEV_1, FEV_1/FVC)

Table 1 Details from all trials (*Continued*)

First author, year	Study design	Subjects analysed (M/F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes
				CV12, ST36, SP6, KI3, ST40 + Western medicine standard therapy				
Cui, 2015 [22]	RCT	60 (34:26) Not mentioned	56 ± 8.1	Moxa sticks at GV14 and GV2 + Routine treatment	Routine treatment (theophylline sustained-release capsules and ambroxol tablets)	Not mentioned	Once a month for 3 months	Lung function (FEV_1, FEV_1/FVC)
Guang, 2017 [25]	RCT	60 (31:29) Not mentioned	I: 56 (1) C: 55 (2)	Moxibustion with 3 moxibustion boxes from GV14 to GV2 + Tiotropium bromide inhalation powder spray	Tiotropium bromide inhalation powder spray	20 min	5 time per week for 12 weeks	Dyspnoea (mMRC) QoL (CAT)
He, 2013 [21]	RCT	93 (63:30) Not mentioned	I: 66.11 (9.34) C: 67.25 (8.75)	Ginger moxibustion at BL13 bilateral. Each time 3 / 5 wicks + Compound methoxamine capsule	Compound methoxamine capsule	Not mentioned	Once every 3 days, a total of 14 times Oral treatment: 3 times a day for 6 weeks	Lung function (FEV_1, FEV_1/FVC, FVC)
Liang, 2018 [27]	RCT	88 (51:37) Moderate to severe	I: 65. 69 (7.22) C: 65. 96 (7.19)	Heat sensitivity moxibustion between BL13 and BL17 points +Routine treatment	Routine treatment	5 min per point	5 times a week for 8 weeks	Lung function (FEV_1, FEV_1/FVC)
Liu, 2015 [20]	RCT	100 (61:39) Not mentioned	67.5 (9.2)	Moxibustion therapy with moxa stick at GV14, BL13, Ding Chuan (EX-B1), ST40, ST36 +Routine treatment	Routine treatment (low flow oxygen therapy and bronchodilator and antibiotic)	30 min	Once a day for 14 days	QoL (SGRQ), Exercise capacity (6mwd), Lung function (FEV_1, FVC, FEV_1/FVC)
Tang, 2012 [19]	RCT	40 (29:11) Not mentioned	I: 75.5 (13) C: 77.8 (2.3)	Moxibustion at BL12, BL20, KI1, ST36, ST40 + Western medicine treatment	Western medicine treatment (continuous low-flow oxygen inhalation, anti-inflammatory, relieving asthma, eliminating phlegm, stopping cough and immune support)	10–15 min	Once a day for 4 weeks	TCM syndrome (cough, phlegm, asthma, full attack time)
Wang, 2016 [18]	RCT	70 (56:14) Not mentioned	I: 65.2 (6.1) C: 66.3 (6.3)	Moxibustion with moxa stick and moxibustion box at RN8, RN6, RN4, BL12, CV12, ST36 +Routine treatment	Routine treatment (oxygen therapy, nutrition support, respiratory rehabilitation)	10–15 min per point	3 treatment courses. Each course consisted in 14 daily consecutive sessions.	Lung function (FEV_1, FVC)
Wen, 2013 [8]	RCT	108 (67:41) Not mentioned	Not mentioned	Cone Moxibustion at BL13, BL15, BL18, BL20, BL23 Patients feel burning sensation, intolerance, to remove residual wick, replace with a new wick. +Western medicine treatment	Western medicine treatment (spasmolytic, relieving asthma, eliminating phlegm, stopping cough drug treatment)	Not mentioned	5 times a week for 4 weeks	QoL (SGRQ)
Yang, 2016 [17]	RCT	60 (42:18)	54.1 (9.75)	Moxibustion with cones	Routine treatment (oxygen	2 h	9 sessions, once every	Lung function (FEV_1,

Table 1 Details from all trials *(Continued)*

First author, year	Study design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes
		Not mentioned		from GV3 to GV14 +Routine treatment	inhalation, thiamethoxam bromide, budesonide)		10 days for 3 months	FEV_1/FVC)
Zhang, 2016 [16]	RCT	510 (308:202) Not mentioned	62 (9)	Moxibustion with moxa stick at BL13, BL20, GV12, LU1, CV6, ST36, ST40, KI3 +Montelukast	Montelukast (10 mg/day, oral)	5–10 min per point	4 to 6 courses during a year. Each course consisted in 10 daily sessions	Lung function (FEV_1, FEV_1/FVC)
Zhe, 2017 [24]	RCT	80 (44:36) Mild to severe	I: 58.2 (11.7) C: 57.5 (12.3)	Moxibustion to 6 to 7 heat sensitive points found between the horizontal lines of BL13 and BL17 + Conventional treatment	Conventional treatment (bronchodilators, glucocorticoids, expectorant cough and respiratory exercises)	30 to 40 min	5 times a week for 3 months	QoL (SGRQ) Lung function (FEV_1, FEV_1/FVC)
				Acupressure vs. sham acupressure				
				Stable patients				
Wu, 2004[a] [31] 2007[b] [29]	RCT	44 (36:8) Not mentioned		Effleurage: hold, rub and press the neck and each shoulder Press and rub GV14 3 min. Press the CV22 for 1.5 min. Press and rub the BL13 for 3 min. Press and rub the BL23 for 1.5 min. Press and rub LU10 for 3 min	Effleurage: hold, rub and press the neck and each shoulder Rub and press Sp5 for 4 min. Rub and press Sp3 for 4 min. Point (using finger-tip pressure only) and press Liv1 for 4 min.	16 min	20 sessions. Five times a week for 4 weeks.	Dyspnoea (PFSDQ-M)[a], (VAS)[b] Exercise capacity (6mwd)[a] Anxiety (SSAI)[a], Depression (GDS)[b]
Maa, 1997 [30]	CRCT	31 (19;12) Not mentioned	67.32 (8.17)	Acupressure at LU1, LU2, LU10, PC8, ST36, LI4, GV14 +Pulmonary rehabilitation	Sham acupressure: pressure to no specified sham points +Pulmonary rehabilitation	1 or 2 min per acupoint	at least once a day for 6 weeks Pulmonary rehabilitation: 21–36 sessions	Dyspnoea (mBorg and VAS) Exercise capacity (6mwd) Anxiety (BESC)
				Acupressure vs no acupressure				
				Stable patients				
Guo, 2017 [32]	RCT	200 (not mentioned) Not mentioned	Not mentioned	Acupressure at GV14, Ding Chuan (EX-B1), BL23, BL13, BL17, CV12 and CV17 +Regular treatment	Regular treatment (drug treatment and respiratory exercises)	2–3 min per point	Once a day for 6 months	QoL (SGRQ), Anxiety (HAM-A), Depression (HAM-D) Pulmonary function (FEV_1, FEV_1/FVC)
Huang, 2018 [33]	RCT	68 (not mentioned) Not mentioned	I: 52.4 (3.9) C: 54.4 (1.2)	Acupressure at BL13, BL20 and GV14 + Routine drug treatment	Routine drug treatment	2 min per point	Twice a day for 3 months	Exercise capacity (6mwd), QoL (CAT), Pulmonary function (FEV_1, FVC, FEV_1/FVC)
Wu, 2017 [34]		64 (38:26) Not mentioned	73.6 (6.7)	Acupressure at GV20, GB20, Taiyang, ST36, PC6 and LI11 + Regular treatment	Regular treatment (drug treatment, psychological nursing, health guidance and diet adjustment)	5–10 min per point	Twice a day for 4 weeks	QoL (GQOL - 74)

Table 1 Details from all trials *(Continued)*

First author, year	Study design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes
Xu, 2018 [35]	RCT	98 (51:47) Not mentioned	63.1 (15.2)	Acupressure at CV12, CV4, CV6 + Regular treatment	Regular treatment	10 min per point	Not mentioned	Anxiety (HAM-A, SCL-90)
				Exacerbated patients				
Tsay, 2005 [28]	RCT	52 (25:27) Not mentioned	73.88 (7.19)	Acupressure at LI4, PC6 and Ear ShenMen + 3 min shoulders massage + Regular treatment	3 min shoulders massage + Regular treatment (inhaled bronchodilators and mechanical ventilation)	15 min	Once a day for 10 days	Dyspnoea (VAS) Anxiety (SSAI)
				Ear acupuncture vs. sham ear acupuncture				
				Exacerbated patients				
Cao L, 2012 [36]	RCT	30 Not mentioned	I: 76.9 (5.84) C: 77.6 (5.70)	Ear acupressure with seeds at: Shenmen, Lung, Trachea, Throat, Inter-tragus + Sham acupuncture + Usual treatment	Sham auricular therapy at irrelevant acupoint + Sham acupuncture + Usual treatment (bronchodilator, anti-inflammatory, anti-choline drug)	Pressing the seeds: 3–5 times a day	20 days	Dyspnoea (mMRC) QoL (CAT) Lung Function (FEV_1, FEV_1/FVC)
				Ear acupuncture vs no ear acupuncture				
				Stable patients				
Jin RF 2009 [37]	RCT	60 (39:21) Not mentioned	Not mentioned	Ear acupressure with seed at: Lung, Spleen, Kidney, Trachea, Under sebum, Sympathetic + Regular treatment	Regular treatment (eliminating phlegm, bronchodilator, regular nursing)	Not mentioned	Once a day for 12 days	Lung Function (FVC, FEV_1, FEV_1/FVC)
Li 2017 [40]	RCT	82 (not mentioned) Not mentioned	Not mentioned	Acupressure using magnets at: Anti-asthmatic point, Trachea, Lung, Shenmen, Occiput, Adrenal gland +Regular treatment	Regular treatment	Press 1020 times per point	I1: once every 6 h, (at least 3 times a day) for 6 months. I2: at least 3 times a day from 3 am to 5 am and 3 pm to 5 pm for 6 months.	Dyspnea (mMRC) Lung function (FEV_1, FVC, FEV_1/FVC)
Pang CL, 2014 [39]	RCT	52 (31:21) Not mentioned	I: 62.5 (6.4) C: 68.2(6.0)	Ear acupressure with seeds at: Spleen, Kidney, Lung and Sanjiao + Inhaled Seretide	Inhaled Seretide.	Not mentioned	Press seeds 3 times a day for 3 months	Lung Function (FEV_1, FEV_1/FVC)
Pang CL, 2016 [38]	RCT	38 (25:13) Severe and very severe	I: 65.5 (6.4) C: 67.2(6.3)	Ear acupressure at: Spleen, Kidney, Lung, Sanjiao and Relieving asthma + Salmeterol Inhalation powder	Salmeterol inhalation powder	2 min	Massage 3 times a day for 3 months	Lung Function (FEV_1, FEV_1/FVC)
				Ear acupuncture vs drugs				
				Exacerbated patients				
Hu ZH, 1997 [41]	RCT	32 (19:13) Not mentioned	I: 63.5 (12.06) C: 60.33 (12.45)	Ear acupuncture with manual needle stimulation at: Lung, Trachea and Inter-tragus	Inhaled salbutamol	30 min	1 session	Lung function (FEV_1, FVC,)

Table 1 Details from all trials *(Continued)*

First author, year	Study design	Subjects analysed (M:F) Severity	Age: Mean (SD)	Intervention (I)	Control (C)	Stimulation time	Treatment regimen	Outcomes
				Cupping vs no Cupping				
				Exacerbated patients				
Xiao W, 2009 [43]	RCT	60 (33:27) Not mentioned	I: 72 (51–81) C: 70 (48–85)	Flash Fire Cupping therapy at BL13, BL20 and BL23 + Western medicine treatment	Western medicine treatment (oxygen inhalation, spasmolytic, relieving asthma, eliminating phlegm, stopping cough treatment)	Not mentioned	28 sessions, once a day for 4 weeks	TCM syndrome integral (cough, expectoration, dyspnoea, wheezing)

RCT randomised control trial, *CRCT* Cross-over randomised control trial, *SOB* shortness of breath, *VAS* visual analogue scale, *FEV1* forced expiratory volume in one second, *FVC* forced vital capacity, *QoL* quality of life, *SGRQ* St George's respiratory questionnaire, *6MWD* 6-min walking distance, *PEFR* peak expiratory flow rate, *RR* respiratory rate, *QoL* quality of life, *CAT* COPD assessment test, *COPD* chronic obstructive pulmonary disease, *PaO2* arterial oxygen partial pressure, *PaCO2* arterial partial pressure of carbon dioxide, *PFSDQ-M* pulmonary functional status and dyspnoea questionnaire, *SSAI* Spielberger's state anxiety inventory, *VAS* visual analogue scale, *BESC* bronchitis-emphysema symptom checklist, *GDS* geriatric depression scale, *HAM-A* Hamilton anxiety rating scale, *HAM-D* Hamilton depression rating scale, *GQOL–74* generic quality of life inventory-74, *SCL-90* symptom checklist-90

points were Lung (6 trials, 100%) and Trachea (4 trials, 66%). Ear acupuncture was performed using seed stimulation [36–38], acupressure stimulation [39], stimulation with magnets [40] or filiform needle stimulation [41]. In four trials [36–39], the intervention duration ranged from 12 days to 6 months and only one trial used a single session treatment [41].

Sham control was used in only one trial using irrelevant ear points [36]. Four trials compared the usual treatment plus ear acupuncture with the usual treatment alone [37–40]. One compared ear acupuncture with inhaled salbutamol [41].

Acupressure plus ear acupuncture One trial combined acupressure plus ear acupuncture added to usual treatment compared with usual treatment alone [42].

Cupping One trial studied the effect of cupping plus usual treatment compared with usual treatment alone [43]. In this trial fire cupping with flash stimulation at BL13, BL20 and BL23 was used for 28 sessions for 4 weeks.

Risk of bias within studies

An assessment of the risk of bias for the included trials is summarised in Table 2.

For AcuTENS trials, seven studies (100%) had a low risk of bias in "random sequence generation" and six (86%) in the "blinding of participants" (the other trial was considered unclear), however the most critical items were "allocation concealment" and "blinding of outcome assessment" with five (71%) and three (43%) trials classified as unclear due the lack of reporting. "Selective outcome reporting" was mainly classified as unclear (6 trials) due the fact that we could not find trials protocols.

We found an important lack of reporting in all trials and items for moxibustion, meaning that there was an unclear risk of bias for this technique.

Reporting was also poor for acupressure, and therefore the risk of bias was considered unclear. Low risk of bias was considered in only four trials (57%) for "random sequence generation", none (0%) for "allocation concealment", two trials (28%) for "blinding of participants" and one (14%) for "blinding of outcome assessment".

Only one trial (16%) reported enough information for ear acupuncture to assess the risk of bias, which was classified low for "random sequence generation", "allocation concealment", "blinding of participants" and "blinding of outcome assessment".

Regarding the trial combining acupressure and ear acupuncture, only the risk of bias for "random sequence generation" was classified as low.

The only trial included for cupping therapy, had an unclear risk of bias in all items except "incomplete outcome data" which was classified as having a low risk of bias.

Synthesis of results

AcuTENS

AcuTENS vs. sham AcuTENS *Dyspnoea*

Four trials assessed dyspnoea, comparing AcuTENS vs sham AcuTENS, three included stable patients [9, 10, 12] and one included exacerbated patients [13]. The Dyspnoea Visual Analogue Scale (DVAS) was used in three trials [9, 10, 12], and the other one used the Borg Scale [13]. A meta-analysis could not be performed due to the high heterogeneity (I^2 = 96%). In the three trials with stable participants, two showed an improvement in dyspnoea in a single session treatment [9, 12], and the other showed no difference between groups in a 4 week treatment [10]. The trial with exacerbated participants [13] did not show any effect compared with the sham intervention (Fig. 2a).

Quality of life

Three trials assessed QoL, two including stable patients [10, 11] and one with exacerbated patients [13]. QoL was assessed with the St Gorge's Respiratory Questionnaire (SGRQ) in 2 trials [11, 13] and the COPD Assessment Test (CAT) in the other one [10]. Meta-analysis of all three trials (128 participants) did not show statistical differences between real and sham AcuTENS (Std. MD: -0.35 95%CI: − 0.70, 0.00 I^2 = 0%) (Fig. 2b).

Exercise capacity

Three trials assessed exercise capacity, two with stable patients [10, 11] and one including exacerbated patients [13]. All trials used the six minutes walking distance test (6MWD). Meta-analysis of the three trials (128 participants) did not show a statistical improvement between AcuTENS and Sham (6MWD MD: 6.59 95%CI: − 2.00, 15.19 I^2 = 0%) (Fig. 2c).

Lung function

Lung function (FEV_1 and FVC) was assessed in seven trials, six including stable patients [9–12, 14, 15] and one with exacerbated participants [13]. Meta-analysis was not possible for FEV_1 due heterogeneity (I^2 = 73%), even in the subgroup analysis (stable subgroup I^2 = 71%). Of the seven trials, two [9, 10] showed statistic benefit for AcuTENS and five other trials indicated no difference between groups [11–15] (Fig. 2d). Meta-analysis of the seven trials [9–15] (288 participants) for FVC showed no benefit for the AcuTENS group (Std. MD: 0.12 95%CI: − 0.16, 0.39 I^2 = 25%) (Fig. 2e).

ADVERSE EVENTS

Only two trials attempted to report adverse events, Shou [14] reported that the technique was safe and Ngai [12] reported no associated adverse effects.

MOXIBUSTION

Moxibustion vs. no moxibustion

Dyspnoea Only one trial assessed dyspnoea [25]. In this trial authors reported a greater reduction on the mMRC

Table 2 Detailed risk of bias of each trial

	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
			AcuTENS				
Lau, 2008 [9]	Low	Low	Low	Low	Low	Unclear	Low
Liu X, 2015 [10]	Low	Low	Low	Low	Low	Unclear	Low
Ngai, 2010 [11]	Low	Unclear	Low	Low	Low	Unclear	Low
Jones, 2011 [12]	Low	Unclear	Low	Low	Unclear	High	Unclear
Öncü, 2017 [13]	Low	Unclear	Low	Unclear	Unclear	Unclear	Unclear
Shou, 2014 [14]	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Wen Q 2011 [15]	Low	Unclear	Low	Unclear	Low	Unclear	Unclear
			Moxibustion				
Bai 2018 [26]	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
Cheng AP, 2011 [23]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Cui XX, 2015 [22]	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Guang, 2017 [25]	Low	Unclear	High	Unclear	Unclear	Unclear	Unclear
He F, 2013 [21]	Unclear	Unclear	High	High	Unclear	Low	Low
Liang, 2018 [27]	Low	Unclear	High	Unclear	Unclear	Unclear	Unclear
Liu SR, 2015 [20]	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Tang J 2012 [19]	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Wang WH, 2016 [18]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Wen X, 2013 [8]	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Yang XQ, 2016 [17]	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Zhang QY, 2016 [16]	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Zhe, 2017 [24]	Low	Unclear	High	Unclear	Unclear	Unclear	Unclear
			Acupressure				
Guo 2017 [32]	Low	Unclear	High	Unclear	Unclear	Unclear	Unclear
Huang 2018 [33]	Low	Unclear	High	Unclear	Unclear	Unclear	Unclear
Maa, 1997 [30]	Low	Unclear	Low	Unclear	Low	Unclear	Low
Tsay, 2005 [28]	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Wu, 2004 [31], 2007 [29]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wu, 2017 [34]	Low	Unclear	High	Unclear	Unclear	Unclear	Unclear
Xu 2018 [35]	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
			Ear acupuncture				
Cao L, 2012 [36]	Low	Low	Low	Low	Low	Unclear	Unclear
Hu ZH, 1997 [41]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Jin RF, 2009 [37]	Unclear	Unclear	Unclear	Unclear	Low	Low	Unclear
Li, 2017 [40]	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear
Pang CL, 2014 [39]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Pang CL, 2016 [38]	Unclear	Unclear	High	Unclear	Low	Low	Unclear
			Acupressure plus ear acupuncture				
Rao, 2017 [42]	Low	Unclear	High	Unclear	Unclear	Unclear	Unclear
			Cupping				
Xiao W, 2009 [43]	Unclear	Unclear	High	Unclear	Low	Unclear	Unclear

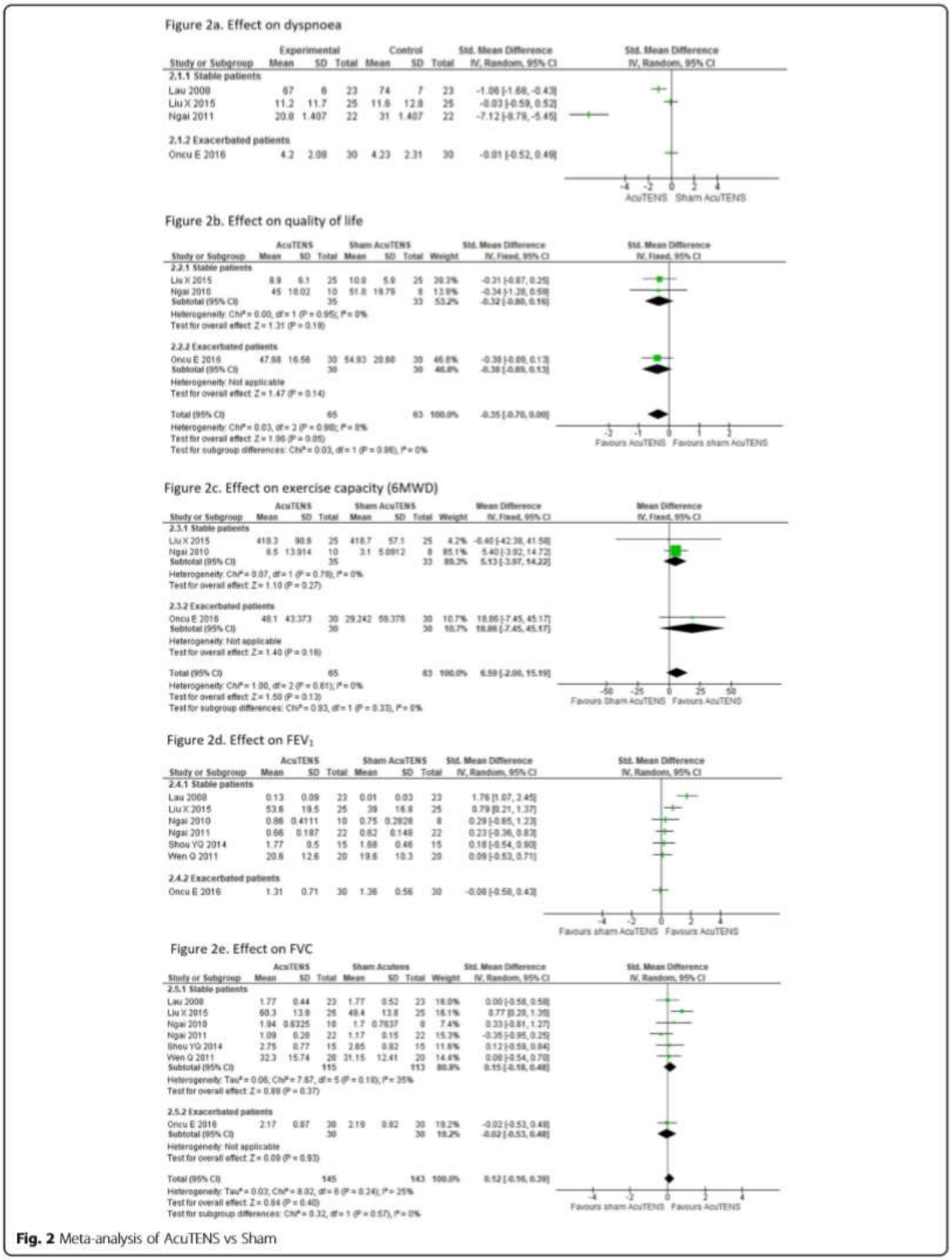

Fig. 2 Meta-analysis of AcuTENS vs Sham

scale in the moxibustion group compared with the control after a 12 week intervention (MD: − 1.70, Sd: 0.47 vs MD: − 1.03, Sd: 0.18, $p < 0.05$).

Quality of life Five trials assessed QoL, four using the SGRQ [8, 20, 24, 26] and one using the CAT [25]. One trial did not report total scores of the SGRQ but only scores from each component separately [20], we calculated total scores using that data. Meta-analysis was not possible due the great heterogeneity ($I^2 = 92\%$). Out of five trials, four showed an improvement in QoL in the moxibustion group [8, 20, 24, 25] while one trial did not observe statistical differences [26]. (Fig. 3a).

Exercise capacity Only one trial studied the effect of moxibustion on exercise capacity [20]. In this trial with 100 participants the authors reported an improvement in this outcome using the 6MWD ($t = 3.568$, $p < 0.001$), but no difference between groups was reported.

Lung function Ten trials analysed lung function, all using FEV_1 [16–18, 20–24, 26, 27], eight using FEV_1/FVC [16, 17, 20–24, 27] and three trials using FVC [18, 20, 21]. Meta-analysis was not possible due to the high heterogeneity for FEV_1 and FEV_1/FVC ($I^2 = 93$ and 80% respectively). Seven trials for FEV_1 showed a statistical benefit for moxibustion [16, 17, 20, 22–24, 27] and

Figure 3.a Quality of Life: SGRQ

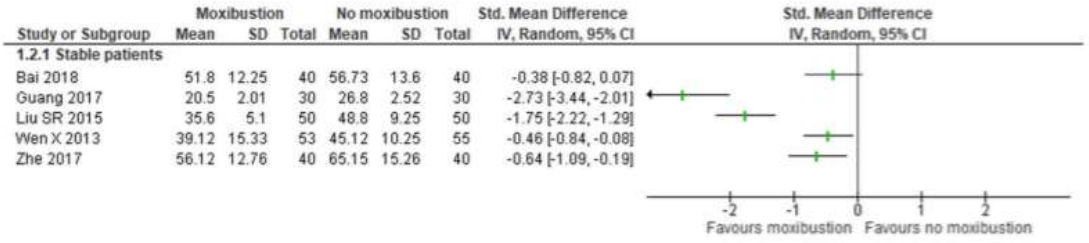

Figure 3.b FEV_1

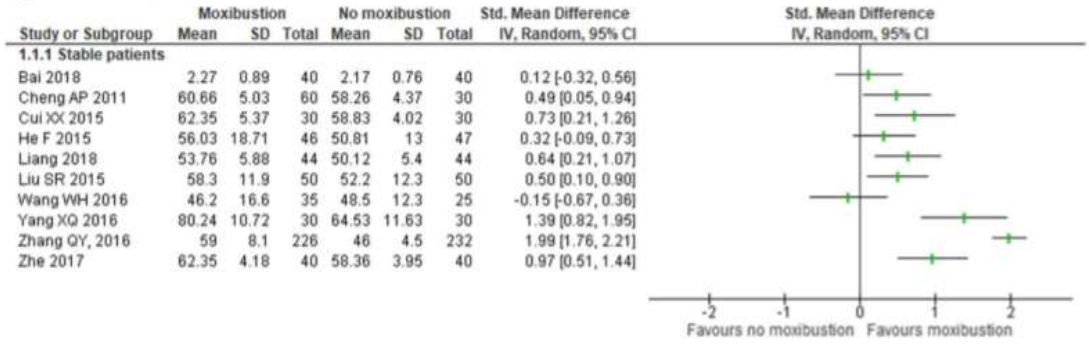

Figure 3.c FEV_1/FVC

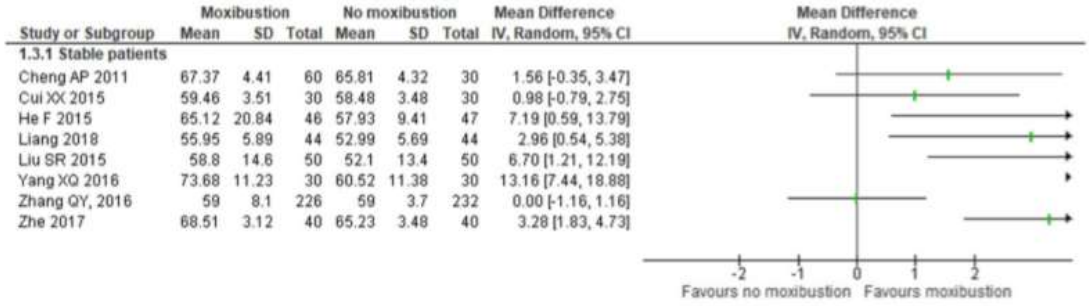

Fig. 3 Meta-analysis of Moxibustion vs no Moxibustion

three showed no effect [18, 21, 26] (Fig. 3b). Five trials for FEV_1/FVC showed benefits for moxibustion [17, 20, 21, 24, 27] and the other three did not show statistical differences [16, 22, 23] (Fig. 3c).

Adverse events No trials reported adverse events.

Acupressure technique

Acupressure vs. sham acupressure

Dyspnoea Dyspnoea was assessed in 2 trials (3 publications) using VAS (2 trials) [29, 30], the modified Borg scale (1 trial) [25] and the Pulmonary Function Status and Dyspnoea Questionnaire-Modified (PFSDQ-M) (1 trial) [31]. Meta-analysis was not possible since the study by Maa [30] used a cross-over design. Wu et al. reported a statistical improvement in the real acupressure group using VAS (43.43 mm vs 48.97 mm $p < 0.01$) [29] and the dyspnoea subscale of the PFSDQ-M (MD: − 0.98, $p < 0.01$) [31]. Maa [30] reported a statistical improvement in the real acupressure group using the VAS ($p = 0.009$) but not with the Borg scale ($p = 0.38$).

Exercise capacity Two trials, both including stable patients, studied the effect of acupressure on exercise capacity using the 6MWD [30, 31]. Again, due to the cross over design used by Maa [30], a meta-analysis was not performed. While Maa did not report statistical differences between groups ($p = 0.67$), Wu et al. [26] did report a statistical improvement in the acupressure group ($p < 0.001$), none of the trials reported mean differences between groups.

Anxiety Two trials reported anxiety in stable patients [30, 31]. The scales used for measuring were the Spielberger's State Anxiety Inventory (SSAI) [31] and the anxiety subscale of the Bronchitis-Emphysema Symptom Checklist (BESC) [30]. Meta-analysis was not possible due to the cross-over design of Maa et al. Wu et al. reported statistical improvement in the acupressure group compared with sham intervention in the SSAI (− 8.50 vs − 0.14, $p < 0.01$) [31]. Ma et al. reported a significant improvement in the acupressure group using the BESC ($p < 0.05$) but the mean difference between groups was not reported [30].

Depression One trial [29], which included stable participants, reported a greater reduction on the Geriatric Depression Scale (GDS) in the acupressure group than the sham group (− 2.09 vs 0.14 $p < 0.001$).

Acupressure vs no acupressure

Dyspnoea Only one trial, comparing the addition of acupressure to usual care with usual care alone in patients under mechanical ventilation, assessed dyspnoea [28]. The authors reported a statistical reduction in dyspnoea of 6.77 points on VAS scale (SE: 2.59, $p = 0.009$).

Quality of life Three trials studied QoL in stable participants, with one trial using the SGRQ [32], one trial using the CAT scale [33] and one trial using the Generic Quality of Life Inventory-74 (GQOL-74) [34]. The trial from Wu et al. [34] could not be included in the meta-analysis since authors did not report the GQOL-74 global score. Meta-analysis of the other two trials showed a statistically significant improvement on QoL (SMD: -0.63 95%CI: − 0.88, − 0.39 $I^2 = 0\%$) (Supplementary material 2.a).

Exercise capacity One trial assessed exercise capacity using the 6MWD in stable participants [33]. Authors reported a greater distance walked in the acupressure group compared with the control (MD: 384.38 m, SD: 21.08 vs MD: 370.00 m, SD:23.74, $p = 0.010$).

Anxiety Tree trials assessed anxiety, with two including stable participants [32, 35] and one with exacerbated participants [28]. The scales used were the VAS [28] and the Hamilton Anxiety Rating Scale (HAM-A) [32, 35]. Meta-analysis if the two trials with stable participants (332 participants) showed a statistical reduction of 4.83 points in the HAM-A scale (95%CI: − 5.71, − 3.94 $I^2 = 0\%$) (Supplementary material 2.b). The trial including exacerbated participants did not report enough data to be included in the analysis but also reported a statistical improvement compared with the control group (VAS MD: -6.74, SE: 2.68, $p = 0.011$).

Depression Only one trial including sable participants reported depression using the Hamilton Depression Rating Scale (HAM-D) [32]. In this trial authors reported lower depression levels in the experimental group after the intervention (MD: 12.4, SD:4.36 vs MD: 19.1, SD: 6.1, $p < 0.05$).

Lung function Lung function was assessed in two trials with stable participants [32, 33], both trials reported no statistical differences between acupressure and control group in FEV_1, FVC and FV_1/FVC.

Adverse events Only one trial considered the possibility of adverse events and reported no skin reactions at the areas where acupressure was applied [30].

Ear acupunture

Ear acupuncture vs sham ear acupuncture

Only one trial, including 30 exacerbated participants, compared ear acupuncture vs sham [36]. In this trial the investigators found a significant improvement in quality

of life and lung function (FEV_1, FEV_1/FVC) ($p < 0.05$) after a 20-day intervention. Data on the effect size was not reported.

Ear acupuncture vs no ear acupuncture

Dyspnoea Only one trial including stable participants assessed dyspnoea, reporting a statistical reduction in the mMRC scale in the two ear acupuncture groups compared with the control [40].

Lung function Four trials assessed lung function [37–40], all of them assessing FEV_1 and FEV_1/FVC. Meta-analysis (224 participants) showed no statistical difference for this comparison on FEV_1 (MD: 0.05 L 95%CI: − 0.05, 0.14 I^2 = 0%) (Supplementary material 3.a) and FEV_1/FVC (MD: 1.03 95%CI: − 1.16, 3.22 I^2 = 0%) (Supplementary material 3.b).

Ear acupuncture vs drugs

One trial compared a single intervention treatment with salbutamol inhalation in 32 exacerbated patients [41]. The authors found a significant improvement in FEV_1 ($t = 2.62$, $p < 0.05$), and no difference in FVC ($t = 0.34$, $p > 0.05$).

Adverse events No trials reported adverse events.

Acupressure plus ear acupuncture

One trial analysed the effect of acupressure combined with ear acupuncture plus standard therapy compared with standard therapy alone in lung function [42]. This trial, which included 120 stable participants, reported a significant improvement in the intervention group in FEV_1, FVC, FEV_1/FVC compared with the control group ($p < 0.05$).

Cupping

Only one trial with 60 participants studied the effect of cupping [43]. The authors reported an improvement in cough, expectoration, dyspnoea and wheezing ($p < 0.05$) using the TCM syndrome integral. Data on the effect size was not reported. No adverse events were reported.

Discussion

This is the first systematic review that evaluates independently the effectiveness of the different non-filiform needle acupuncture techniques for COPD. For practical reasons we only analysed the techniques that are most commonly used outside China; AcuTENS, moxibustion, acupressure, ear acupuncture and cupping (33 trials).

Our results do not show strong evidence for any non-filiform acupuncture techniques, only acupressure seams to improve dyspnoea and anxiety, based in low quality trials. The low number of trials assessing important outcomes, the great heterogeneity and the small size of most of the studies implies that these results must be interpreted with caution.

Overall, only six meta-analysis could be performed, with only two of them showing positive results. Heterogeneity was a big issue, even using subgroups for stable and exacerbated participants. This issue was even greater for the moxibustion technique, with no possible meta-analysis from three comparisons. We also found that very few trials reported important clinical outcomes commonly assessed in COPD such as dyspnoea (7/33), QoL (11/33), exercise capacity (7/33), anxiety (5/33) and depression (2/33). No important adverse events were reported for any technique.

Dyspnoea was improved in all 3 acupressure trials (2 trials vs sham and 1 trial vs no acupressure). For the other non-filiform acupuncture techniques only 1 trial using ear acupuncture and 2 trials using AcuTENS had positive results on dyspnoea, remarkably, both studies used a single session treatment. Acupuncture techniques mainly target the stimulation of cutaneous and muscular afferent fibres which lead to the stimulation of many brain nuclei networks, leading to the release of opioid peptides [44]. This mechanism has been usually accepted to explain acupuncture analgesic effects, but could also be used to explain acupuncture effects on dyspnoea, since endogenous opioids modulate dyspnoea in patients with COPD [45]. This mechanism has been better studied for the AcuTENS technique, which has been shown to increase B-endorphin levels which correlate with respiratory rate reduction [12]. However, improvements on dyspnoea were only seen for AcuTENS in single session trials but not in longer trials.

Quality of life is one of the main patient-related outcomes in clinical trials, however it was only studied in 11 trials. While meta-analysis of the 3 AcuTENS trials showed a tendency for improvement, results were not statistically significant. Quality of life was improved in 5 moxibustion trials with stable participants (2 vs sham and 3 vs no acupressure) and one ear acupuncture trial with exacerbated participants, all low-quality trials. It is to note that bowth trials comparing acupressure with sham acupressure lasted from 14 to 20 days and while seeing those changes in exacerbated patients in such a short time seems reasonable, it is quite surprising to find them in stable participants.

Exercise capacity is an important marker that results from a range of effects of COPD. Statistical differences in the 6MWD were not seen in the meta-analysis of the 3 AcuTENS trials however, while in the two trials with stable participates differences between groups were inexistent, in the trial with exacerbated participants an improvement was observed although CI was too wide to show statistical significance. One moxibustion trial and two acupressure trials reported benefits while another

acupressure trial did not, but only one did report data of differences between groups.

Anxiety is strongly related to dyspnoea perception in COPD since the lack of breath is one of the most limiting symptoms experimented by patients. This correlation is seen in acupressure trials were all trials showing improvement on anxiety (5 trials) and dyspnoea (3 trials). Surprisingly this outcome was not studied in any other technique.

Finally, the effects on pulmonary function should be taken with caution. The heterogeneity of the results and the unexpected changes because the chronicity of the disease, prevent to any deeply interpretation. This outcome has been the most studied in the included trials (25/33), however, since pulmonary function is not expected to improve in COPD, no matter what treatment is used, we think future trials should not consider it as one of the main outcomes.

Coyle et al. [46] and Wang et al. [37] previously examined the effect of different acupuncture techniques for COPD. Coyle reviewed 16 trials (published between 1995 and 2007) of all kinds of acupuncture interventions, including non-pharmacological (filiform needle, moxibustion and acupressure, etc.) and pharmacological (herb plasters on acupuncture points). They concluded that acupuncture was beneficial for COPD patients in outcomes like dyspnoea, exercise capacity and quality of life, however evidence was low due to the methodological flaws of the included studies. Moreover, they plotted together all acupuncture techniques which might have caused some bias in the results. Wang's review included 19 trials and concluded that acupuncture might be effective in improving functional effects and quality of life in COPD patients. However, this review only included acupuncture techniques such as manual acupuncture, warm acupuncture, electroacupuncture and ear acupuncture, but all other non-invasive technique such as single moxibustion, acupressure or acuTENS were excluded.

This review has several limitations. First, due to the great heterogeneity between trials, only seven meta-analyses could be performed. Secondly, important clinical outcomes for COPD, such as dyspnoea, QoL, exercise capacity, anxiety and depression were only studied in a small number of trials, reducing the number of trials that could be combined in each meta-analysis. Combined with the first point, this led to a low inspection efficiency of the results. Third, the trials included had inadequate reporting, especially for random sequence generation and allocation concealment, meaning that they had an uncertain risk of bias. Fourth, although no important adverse events were reported, this outcome has not been systematically explored. Fifth, it is difficult to extrapolate these results for different populations since, except one, all trials were performed in China. Finally, we identified other non-pharmacological acupuncture interventions in this review, such as catgut implant, thick needle, acupoint incision, wet cupping, floating needle and intradermal needle, however, due to the rare use of those techniques outside China, and the complexity of the review, we did not include them in this review analysis.

Conclusions

No strong evidence was found for any of the included outcomes for patients with COPD treated with non-filiform needle acupuncture techniques. Acupressure could improve dyspnoea, quality of life and anxiety, but this is only based on low quality trials.

Evidence is very low in this review due to the unclear risk of bias in the trials included, and the great heterogeneity between them. Further studies should include main outcomes for COPD assessment such as dyspnoea, quality of life, exercise capacity and anxiety since we found many studies mainly targeting pulmonary function. Well-designed trials are needed to elucidate its possible role in the treatment of COPD.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12906-020-02899-3.

Additional file 1. Supplementary material 1: Search strategies.

Additional file 2. Supplementary material 2: Meta-analysis of Acupressure vs no Acupressure.

Additional file 3. Supplementary material 3: Meta-analysis of Ear acupuncture vs no Ear acupuncture.

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Authors' contributions

CF has been responsible for writing the protocol of the study, performing the electronic search in English, the extraction and analysis of the data and the writing and the submission of the manuscript. JV and MSR made substantial contributions to the conception and design of the review, extraction, analysis and interpretation of the data and writing and reviewing the manuscript. YF, and CW and JL are responsible for the Chinese language electronic search, and data abstraction and contributed to the writing and reviewing of the manuscript. NH, RX, XT, RH, NG and MSM, are responsible for trials inclusion, data extraction and critically reviewing the final manuscript. MY and LW are responsible for the latest update of Chinese databases including, trail inclusion and data extraction process. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.
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Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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Third publication

Background: The completeness of reporting completeness of reporting of acupuncture interventions is critical to ensure the applicability and reproducibility of acupuncture clinical trials. In the past, different publications have evaluated the quality completeness of reporting of acupuncture interventions for different clinical situations, such as knee osteoarthritis, neurological diseases or cancer. However, this has not been done for acupuncture trials for chronic obstructive pulmonary disease (COPD).

Objective: To assess the quality completeness of reporting of acupuncture interventions in trials for COPD.

Methods: A total of 11 English and Chinese databases were screened up until May 2019 for randomised or quasi-randomised control trials of acupuncture for COPD. The STRICTA checklist was used to determine the quality of the reporting of acupuncture interventions.

Results: A total of 28 trials were included in our review. Out of the 16 STRICTA checklist subitems analysed, only 43 were considered appropriately reported in more than 70% of the trials, while 7 were correctly reported in less than 4030%.

Conclusion: The adherence to STRICTA guidelines of acupuncture trials for COPD is suboptimal, and future efforts need to be addressed to improve the quality completeness of reporting.

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RESEARCH ARTICLE

REVISED Quality of reporting acupuncture interventions for chronic obstructive pulmonary disease: Review of adherence to the STRICTA statement [version 2; peer review: 2 approved with reservations]

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Abstract

Background: The quality of reporting of acupuncture interventions is critical to ensure the applicability and reproducibility of acupuncture clinical trials. In the past, different publications have evaluated the quality of reporting of acupuncture interventions for different clinical situations, such as knee osteoarthritis, neurological diseases or cancer. However, this has not been done for acupuncture trials for chronic obstructive pulmonary disease (COPD).
Objective: To assess the quality of reporting of acupuncture interventions in trials for COPD.
Methods: A total of 11 English and Chinese databases were screened up until May 2019 for randomised or quasi-randomised control trials of acupuncture for COPD. The STRICTA checklist was used to determine the quality of the reporting of acupuncture interventions.
Results: A total of 28 trials were included in our review. Out of the 16 STRICTA checklist subitems analysed, only 3 were considered appropriately reported in more than 70% of the trials, while 7 were correctly reported in less than 40%.
Conclusion: The adherence to STRICTA guidelines of acupuncture trials for COPD is suboptimal, and future efforts need to be addressed to improve the quality of reporting.

Keywords

Quality of Reporting, Acupuncture, COPD

Open Peer Review

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	Invited Reviewers	
	1	**2**
version 2 (revision) 23 Oct 2020		? report
version 1 02 Apr 2020	? report	

1. **Erik Cobo**, Polytechnic University of Catalonia, Barcelona, Spain

2. **David Blanco**, Universitat Internacional de Catalunya, Barcelona, Spain

Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 1**

No major differences exist with the previous published version.

Minor changes were made to clarify some aspects of the previous version.

Any further responses from the reviewers can be found at the end of the article

Introduction

Recent systematic reviews have assessed acupuncture's efficacy for chronic obstructive pulmonary disease (COPD)[1–3]. These reviews have concluded that, even though acupuncture could have some benefits, the risk of bias of the included trials is too high to draw any strong conclusion. Risk of bias is certainly a critical aspect in randomised control trials; however, the quality of reporting is also a key point.

Complete and clear information regarding clinical trial methodology is not only essential to adequately assess health research but also for its applicability and reproducibility. This is especially important in complex interventions, such as acupuncture, that can be practiced in many different styles and variations. Aspects such as point selection, depth of the insertion, stimulation method and response sought, which may be very different between practitioners, could have an impact on the therapeutic effect[4]. Therefore, to be able to replicate an acupuncture intervention in clinical practice or reproduce it in another trial, it is necessary to fully describe how it is applied.

The STandards for Reporting Interventions in Controlled Trials of Acupuncture (STRICTA) guidelines were created to improve the quality of reporting in acupuncture trials and facilitate transparency in published reports[5]. These guidelines were updated in 2010 as an extension of the CONsolidated Standards Of Reporting Trials (CONSORT) guidelines[6] and consist of 6 key items and 17 subitems addressing aspects such as acupuncture rationale, needling details, treatment regime, other components of the treatment, practitioner background and details about the control or comparator.

Although there is evidence that STRICTA guidelines have helped to improve acupuncture's reporting, there is still a lot of room for improvement[7]. This has also been seen in recent publications for some specific conditions such as neurological diseases[8–10] or cancer[11], concluding that reporting is still suboptimal in these conditions. However, to our knowledge, there is currently no publications regarding the quality of reporting of acupuncture interventions in COPD trials.

Evaluating the adherence of acupuncture clinical trials for COPD to SRICTA guidelines is crucial to detect underreported subitems and therefore highlight current deficiencies. This will help to improve the reporting of future trials and facilitate their applicability in clinical practice and the reproducibility of future research.

The aim of this study is to comprehensibly evaluate the adherence to STRICTA guidelines of trials using acupuncture for COPD.

Methods

Study selection

In this study, we used the results of our previous systematic review, which included randomised or quasi-randomised trials using filiform needle acupuncture for COPD[2]. Published studies were comprehensively searched in the following databases from their inception to May 2019: Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Embase, CINAHL, AMED (Ovid), PEDro, PsycINFO, CNKI, VIP, Wanfang, and Sino-Med. Detailed descriptions of the inclusion criteria, information sources, search strategies and study selections are published elsewhere[2] and the protocol is available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014015074.

Data collection process

Data from each trail was extracted independently by two reviewers (CFJ, MSM, MY and CHL) using a standardised data extraction form, and disagreements were solved by consensus.

For data collection and STRICTA assessment, a specific extraction table with instructions of how to assess each of the 16 STRICTA subitems was created by the authors (*Extended data*[12]). This extraction table was tested with pilot data of 3 papers to solve disagreements on its understanding and ensure its usability.

Our aim was to assess the acupuncture interventions, and therefore, the 17th STRICTA subitem "precise description of the control or comparator" was not considered. However, we did include the 16th STRICTA subitem "rationale of the chosen comparator", since it is critical to justify which component of the acupuncture treatment is being assessed.

Since some STRICTA subitems refer to multiple aspects (e.g., "names of points used" subitem refers not only to the name or location of points but also to if they are used unilaterally or bilaterally), besides considering items just as reported or not reported, we also considered partially reported items and recorded the reasons for there being. This was done to provide more detailed information regarding the aspects that should be improved in the reporting of future trials. Partial reporting was also considered when the authors reported information in other sections, such as the introduction or the discussion. Although some subitems were considered that could potentially be "not applicable" (NA) for some pragmatic designs, none of the trials required this.

Data analysis

A descriptive analysis was used to summarise the results using percentages and absolute numbers.

Results

Number of publications and characteristics

In our systematic review, we screened all 5030 unduplicated titles and abstracts retrieved, and obtained 166 full text articles. Finally, we included 28 trials using filiform needles for COPD (Figure 1). Of those, only 6 were published in English-language journals, 1 in a German-language journal and 21 in Chinese-language journals. Details regarding the study characteristics and inclusion process have been published elsewhere[3].

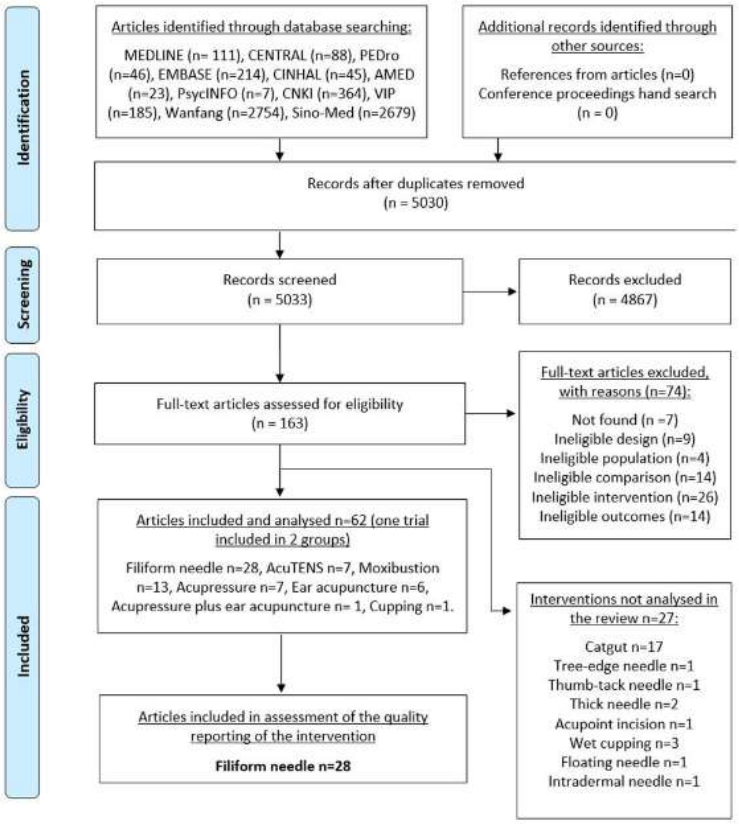

Figure 1. Flow diagram.

Quality of reporting

Ratings for STRICTA domains are summarized in Figure 2. Details for each trial are shown in Table 1, including reasons for considering partial reporting.

Acupuncture rationale. Acupuncture rationale was considered adequately reported in 20 trials (71%) regarding acupuncture style, 18 trials (64%) regarding reasoning of the treatment and 24 trials (85%) regarding treatment variation. Trials classified with partial reporting mentioned acupuncture style (3 trials) and reasoning (4 trials) in the introduction section but not in the methods section.

Details of needling. Adequate reporting of needling details was very heterogenous along all 4 subdomains. Best reported subdomains were "needle retention time" (21 trials, 75%) and "needle stimulation" (19 trials, 67%). Worse reported items were "name of the points" (10 trials, 35%), "depth of insertion" (8 trials, 28%) and "needle type" (6 trials, 21%). Partial reporting was observed in great proportion in "name of acupuncture points" (16 trials, 57%) being the main reason not describing if points were used unilaterally or bilaterally. Regarding the 46% of the trials classified with a partial reporting in the "needle type" item, there was missing information about the needle manufacturer (32.1%, 9 trials), material (25%, 7 trials) and length and diameter (10.7%, 3 trials).

Treatment regime. While "frequency and duration of the treatment sessions" was considered adequately reported for all trials (100%), the "number of treatment sessions" was considered completely reported in none of them (0%). Although this might seem a contradiction, since the number of treatment sessions can be calculated from the treatment regime, in STRICTA, the number of treatment sessions does not only include the planned number of sessions but also the actual number of treatments received. This information was missing or considered not clear in all trials.

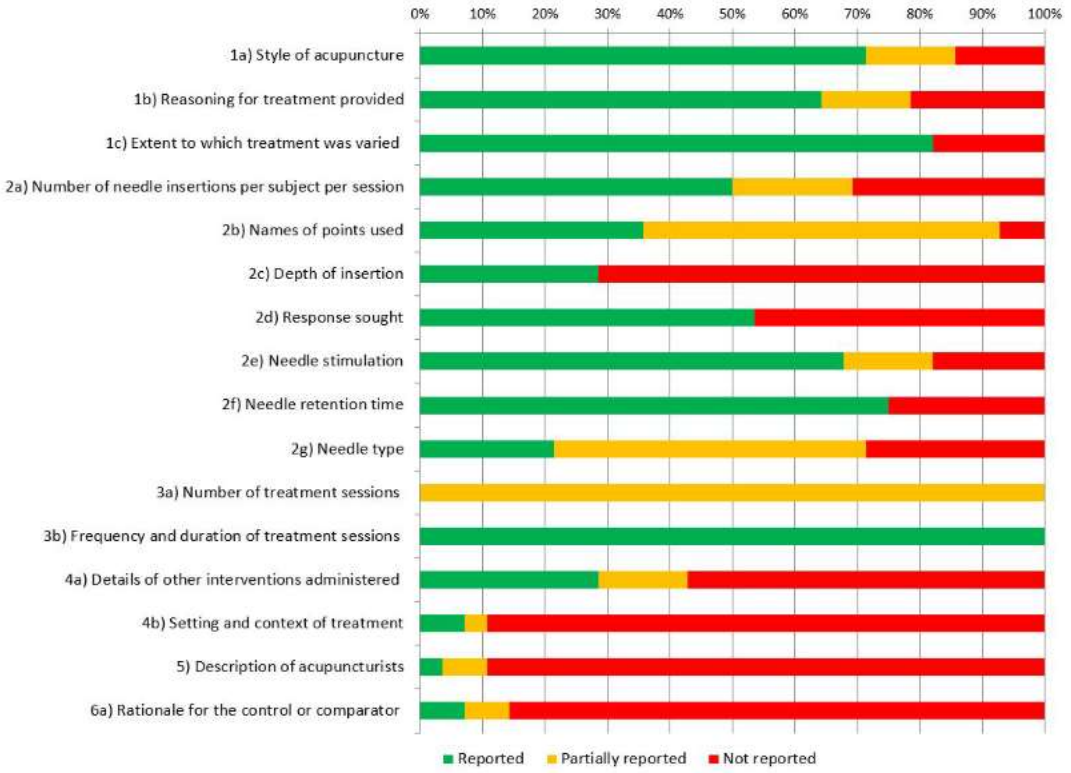

Figure 2. Summary of quality of reporting according to STRICTA guidelines.

Other components of treatment. Other components of treatment were one of the poorer described items. "Details of other interventions administrated" was only reported in 8 trials (28%) and "settings and context of treatments", which refers to "instructions to practitioners that might modify their normal practice, for example, prescribing or proscribing explanations to patients about their diagnosis", were only reported in 2 trials (7.1%).

Practitioner background. This item was only addressed completely in 1 trial (3.5%), and only 2 more trials (7.1%) partially reported it without stating practitioner's years of experience.

Control or comparator. The "rational of the chosen comparator" was only correctly described in 2 trials (7.1%), while in 2 more trials (7.1%), this was mentioned in the introduction but not in the methods section.

Discussion

We found important limitations in the quality of reporting of acupuncture interventions in trials for COPD, especially regarding "depth of insertion", "needle type", "number of treatment sessions", "details of other interventions administered", "setting and context of treatments", "description of acupuncturist" and "rationale for the control or comparator".

Recently, several similar studies have been published. Lu *et al.*[11] and Hughes *et al.*[13] used STRICTA to evaluate trials with cancer patients, and Wei *et al.* used STRICTA to evaluate trials with stroke patients[8]. Although they all concluded that reporting should be improved, there were also some differences. While Hughes *et al.* found better reporting regarding details of needling and treatment regimen, other reviews found lower reporting on these subitems, especially regarding number of needles per session and depth of insertion. Poor reporting on "details of other interventions administered", "description of acupuncturist" and "rationale for the control or comparator" subitems was found in all studies. The differences between studies could be due to several reasons.

First, Lu's and Weis's reviews, as well as our own, included Chinese-language trials, while Hugs' study included only English-language trials. Trials published in English-language journals seem to have greater quality of reporting than those

Table 1. Quality of reporting according to STRICTA guidelines.

STRICTA Items		Reported, % (n)	Not reported, % (n)	Partially reported, % (n) Reason, % (n)
1) Acupuncture rationale	1a) Style of acupuncture	71.4 (20)	14.2 (4)	14.2 (4) Not reported in the correct section, 14.2 (4)
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate	64.2 (18)	21.4 (6)	14.2 (4) Not reported in the correct section, 14.2 (4)
	1c) Extent to which treatment was varied	82.1 (23)	17.8 (5)	0 (0)
2) Details of needling	2a) Number of needle insertions per subject per session	46.4 (13)	28.5 (8)	17.8 (5) Do not mention the number of needles, 17.8 (5)
	2b) Names	35.7 (10)	7.14 (2)	57.14 (16) Do not mention uni or bilateral insertion, 53 (15) Not all point locations are described, 3.5 (1)
	2c) Depth of insertion, based on a specified unit of measurement or on a particular tissue level	28.5 (8)	71.4 (20)	0 (0)
	2d) Responses sought	53.5 (15)	46.4 (13)	0 (0)
	2e) Needle stimulation	67.8 (19)	17.8 (5)	14.2 (4) Manual stimulation is mentioned but the specify the method is not, 10.7 (3) Electrical stimulation is mentioned but not parameters used, 3.5 (1)
	2f) Needle retention time	75 (21)	25 (7)	0 (0)
	2g) Needle type	21.4 (6)	28.5 (8)	50 (14) Material is not reported, 25 (7) Manufacturer is not reported, 32.1 (9) Diameter and length are not reported, 10.7 (3)
3) Treatment regime	3a) Number of treatment sessions	0 (0)	0 (0)	100 (28) The actual number of treatments received is not reported or not clear, 100 (28)
	3b) Frequency and duration of treatment sessions	100 (28)	0 (0)	0 (0)
4) Other components of treatment	4a) Details of other interventions administered to the acupuncture group	28.5 (8)	57.1 (16)	14.2 (4)
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients	7.1 (2)	89.2 (25)	3.5 (1)
5) Practitioner background	5) Description of participating acupuncturists	3.5 (1)	89.2 (25)	7.1 (2) Years of experience not mentioned, 7.1 (2)
6) Control or comparator interventions	6a) Rationale for the control or comparator	7.1 (2)	85.7 (24)	7.1 (2) Not reported in the correct section: 7.1 (2)

STRICTA, STandards for Reporting Interventions in Clinical Trials of Acupuncture.

in Chinese-language journals, according to Lu's review. However, Wei *et al.* found better reporting of the subitems "treatment reasoning" and "response sought" in Chinese journals and better reporting on "practitioner's background" in English journals.

Second, since STRICTA does not clearly specify how items should be judged, authors might have used different criteria. For example, regarding the subitem "number of treatment sessions", the STRICTA statement says that "the actual number of treatments received by participants should be reported in the Results section" not only the planned ones. Whereas in our review, we did not consider that this subitem was fully reported unless this information was explicitly stated; others might have been more permissive. Also, the criteria to consider proper reporting on "other components of treatment" might vary widely between reviewers.

Third, sometimes information might have been reported in sections different from the ones they should appear in. While some authors might not have given much importance to this, we decided to take it into consideration.

Strengths and limitations

To our knowledge, this is the first study to assess the quality of reporting of acupuncture interventions for COPD. We included all acupuncture trials for COPD published until May 2019 with no language restriction, which is important since we only found 6 acupuncture trials published in English. Also, we did not only assess if STRICTA subitems were adequately reported or not but also analysed partial reporting and its reasons, which might be more helpful for authors to realise what specific information is currently missing.

Limitations of this study include that the STRICTA guidelines are not a rating scale; therefore, there are no clear indications of how to judge each subitem and when to consider it fully reported. This issuer must be addressed in the future by developing a proper quality of reporting assessment tool for acupuncture interventions. To minimise this problem, each item was assessed by two reviewers independently, and a standardised extraction form was developed to unify reviewers' criteria. Also, it would have been interesting to compare the quality of reporting depending on the language of publication, so we could explore differences in journal standards. However, due to the low number of non-Chinese-language publications found (1 in German and 6 in English), we decided not to do so. Finally, STRICTA guidelines are specific for the filiform needle acupuncture technique and are not suitable to assess other interventions. Therefore, we did not include trials using only moxibustion, acupressure or transcutaneous electrical nerve stimulation.

Conclusion

The quality of reporting of acupuncture interventions in COPD trials according to STRICTA guidelines is suboptimal. Strategies for improving the understanding of the guides for authors, reviewers and journal editors are needed, as well as to improve its implementation.

Data availability

Underlying data

Figshare: Raw data file, https://doi.org/10.6084/m9.figshare.11999970.v1[14].

Extended data

Figshare: Extended data 1 Extraction form, https://doi.org/10.6084/m9.figshare.11999994.v1[12].

Acknowledgements

We would like to thank the students from the Beijing University of Chinese Medicine Liu Kexin, Zhang Zixuan, Ming Yang, Gao Jiaqi, Li Yilin, Zhang Zhijia, Luo Lingxiao, Shi Yixin, Zhao Luming, Zhang Bingrui, Zhao Leying, Liu Jinjun, Ding Maoyu, Fan Shixuan and Ren Yiming for participating in the project and helping to define the suitability of the data extraction form. The corresponding author is a PhD candidate at the Universitat Autònoma de Barcelona, Spain.

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F1000Research F1000Research 2020, 9:226 Last updated: 13 NOV 2020

Open Peer Review

Current Peer Review Status: ? ?

Version 2

Reviewer Report 13 November 2020

https://doi.org/10.5256/f1000research.30190.r73827

?

David Blanco
Physiotherapy Department, Universitat Internacional de Catalunya, Barcelona, Spain

Thank you for allowing me to review this manuscript. The subject is the evaluation of the degree of adherence to STRICTA guideline items in the context of acupuncture trials. Overall, I find the manuscript attractive and well-written.
I hope the authors find the following suggestions helpful:

General comments

- Despite being a term commonly used in the literature, I would suggest authors to avoid using "quality of reporting", as "quality" is an ambiguous and problematic word, and to use "completeness of reporting", which is clearer and more connected to reporting guidelines[1,2].

Abstract

- If you include the sentence: "Out of the 16 STRICTA checklist subitems analysed, only 3 were considered appropriately reported in more than 70% of the trials, while 7 were correctly reported in less than 40%." you would also need to include this information in the Results section (perhaps as a first paragraph of the "Quality of reporting" subsection). As a reader, I would appreciate to have in the main body of the article some sort of "overall summary" of the completeness of the included papers and not just the results for each separate item.

Introduction

- In the last sentence of the first paragraph, you seem to imply that the risk of bias of a certain study and its quality of reporting have no connection. In fact, complete and transparent reporting is what makes it possible for a reviewer to assess the risk of bias of a study. I believe this point deserves to be reflected in the paper.
- Importantly, the fact that you state, "The aim of this study is to comprehensibly evaluate the adherence to STRICTA guidelines of trials using acupuncture for COPD", could make the reader think that you are going to use the percentage of completeness per trial as the unit of interest. However, you are analysing the percentage of completeness per STRICTA item. I would therefore suggest to reformulate the study aim to avoid confusion: "The aim of this study is to comprehensibly evaluate the degree of completeness of reporting for each STRICTA item in randomised trials using acupuncture" or something similar.

Methods

- It would be helpful that you explain in a few words what was the structure of the standardized data extraction form and what you were interested in looking at.
- Were the three papers you used for the pilot also included in the final analysis? This should be mentioned.

Discussion

- In the first paragraph of the discussion, it would be good to mention in brackets the criteria that you chose to highlight these underreported items (% of adequate reporting less than X%?)
- The sentence "The differences between studies could be due to several reasons" should be placed at the beginning of the next paragraph as it is heavily connected with it. For example, "The differences between the studies we mentioned above could be due to several reasons."
- Concerning the (very appropriate) point you make in the fourth paragraph, you could also mention that RGs are originally just guidance for writing and they are not intended to be evaluation forms despite everyone uses them as such[3].
- I would also better argue why you took into consideration (and considered as "partially reported" instead of fully reported) those items that were reported in a different section. I guess that when you say section you refer to the main 4 sections (IMRaD) – perhaps you could make it clearer in the methods.
- For me, it is not enough to say "Strategies for improving the understanding of the guides for authors, reviewers, and journal editors are needed, as well as to improve its implementation". You should definitely include a paragraph in the Discussion section reflecting on what kind of strategies targeting authors, peer reviewers, or journal editors could work in the particular context of acupuncture journals (or more generally, if you prefer so). In the introduction, you mentioned, "This will help to improve the reporting of future trials and facilitate their applicability in clinical practice and the reproducibility of future research." However, I believe that it is not enough to point out that there are reporting issues without reflecting on what kind of strategies should journals follow to turn things around. As you probably know, some recent experiments are testing out different editorial strategies[4 5 6 7 8] as well as different scoping and systematic reviews/surveys exploring this issue.

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Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Journal policies, peer review, reporting guidelines

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Version 1

Reviewer Report 06 October 2020

https://doi.org/10.5256/f1000research.25221.r71710

Erik Cobo
Statistics and Operations Research Department, Polytechnic University of Catalonia, Barcelona, Spain

I read this paper and I think it could be accepted provided authors correct my three major suggestions and address my minor suggestions.

Major suggestions:

- Please revise the numbers in your flow diagram and add explanations (maybe in a legend) about your more important labels, such us ineligible population/comparison/... Regarding the numbers, please note that the box "records screened" has more records than the previous one. Or than 62 >< 28+7+13+7+6+1+1=63. Please also note that studies are not the same unit as articles. Please, unify.

- Please consider to re-write your conclusions clarifying which recommendations could potentially improve quality in the future. I mean, recommendations to STRICTA authors; recommendations to journals; recommendations to reviewers, recommendations to authors; and so on.

- Please, allow access to your data to other scientists. Please, consider a public repository.

Minor suggestions:

- As you stated, "the STRICTA guidelines are not a rating scale". However, you are repeating through the text that you are attempting to "assess the quality of reporting". I wonder if you should also highlight the need to further develop reporting guidelines to provide such a tool to assess the quality of reporting. Should you speak about the completeness of reporting? I definitively like much more your statement "evaluate the adherence to Stricta guidelines".

- In the introduction, I wonder if you should clarify that "risk of bias" applies to the study; and "quality of reporting" to the paper.

- Also in the introduction, you use the terms "replication" and "reproducibility". I would like you to clarify your meanings, perhaps with some references. For example, are you following the definition from Goodman, Fannelly & Ioanidis in "What does research reproducibility mean?"[1]

- Please, further specify how reviewers "worked in pairs"? Did they split the sample? Did both pairs of reviewers analyze some papers?

- Please, consider to explain the pilot process and how did you "ensure" its usability.

References

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Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
No

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: RCTs, reporting guidelines, causal modeling, meta-researcch

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 11 Oct 2020

Carles Fernández, School of Health Science Blanquerna, Ramon Llull University, Barcelona, Spain

We thank you for your time and comments on the manuscript. Please find below a point by point response to them:

Major suggestions:
Please revise the numbers in your flow diagram and add explanations (maybe in a legend) about your more important labels, such us ineligible population/comparison/... Regarding the numbers, please note that the box "records screened" has more records than the previous one. Or than 62 >< 28+7+13+7+6+1+1=63. Please also note that studies are not the same unit as articles. Please, unify.

As it is already explained in the figure, one trial included two interventions, that is why the total number of studies included is 62 but the summation of all the interventions is 63. Studies has been changed for articles in the diagram

Please consider to re-write your conclusions clarifying which recommendations could potentially improve quality in the future. I mean, recommendations to STRICTA

authors; recommendations to journals; recommendations to reviewers, recommendations to authors; and so on.

Conclusions have been re-written to include the mentioned recommendations
"The quality of reporting of acupuncture interventions in COPD trials according to STRICTA guidelines is suboptimal. Strategies for improving the understanding of the guides for authors, reviewers and journal editors are needed, as well as to improve its implementation."

Please, allow access to your data to other scientists. Please, consider a public repository.
The data is already public and available in the "data availability" section.

Minor suggestions:
As you stated, "the STRICTA guidelines are not a rating scale". However, you are repeating through the text that you are attempting to "assess the quality of reporting". I wonder if you should also highlight the need to further develop reporting guidelines to provide such a tool to assess the quality of reporting. Should you speak about the completeness of reporting? I definitively like much more your statement "evaluate the adherence to Stricta guidelines".

We agree on highlighting the need of developing a reliable tool for assessing the quality of reporting and this has been added in the discussion section.

We would prefer not to change the nomenclature as the real the objective of the study is to assess the quality of reporting, and using the adherence to current reporting guidelines is the method to do so. We believe that introducing the term "completeness of the reporting" may confuse reader.

In the introduction, I wonder if you should clarify that "risk of bias" applies to the study; and "quality of reporting" to the paper.

This has been clarified in the introduction section
"Risk of bias of bias of the studies is certainly a critical aspect in randomised control trials; however, the quality of reporting of the published papers is also a key point."

Also in the introduction, you use the terms "replication" and "reproducibility". I would like you to clarify your meanings, perhaps with some references. For example, are you following the definition from Goodman, Fannelly & Ioanidis in "What does research reproducibility mean?"[1]

Here replication and reproducibility are used in a common language sense and the meaning is clarified at the end of the introduction section:

"Therefore, to be able to replicate an acupuncture intervention in clinical practice or reproduce it in another trial, it is necessary to fully describe how it is applied."

We believe that using the terms "methods reproducibility", "Results reproducibility" or "inferential reproducibility" might not clarify but confuse the reader.

Please, further specify how reviewers "worked in pairs"? Did they split the sample? Did both pairs of reviewers analyze some papers?

Every paper was analysed by two reviewers, this has been now clarified in the methods section:

"Data from each trail was extracted independently by two reviewers (CFJ, MSM, MY and CHL) using a standardised data extraction form, and disagreements were solved by consensus."

Please, consider to explain the pilot process and how did you "ensure" its usability.

This has been now clarified in the "data collection process" section.

"This extraction table was tested with pilot data of 3 papers to solve disagreements on its understanding and ensure its usability."

Competing Interests: No competing interests were disclosed.

DISCUSSION

The discussion of this thesis is presented below in four sections.

In the first section, the discussion derived from the publications is presented. These publications include our two SR analysing the efficacy/effectiveness of filiform needle and other non-pharmacological acupuncture techniques in the treatment of COPD and a completeness of reporting evaluation of filiform needle interventions in COPD trials.

In the second section, future methodological challenges of acupuncture research are discussed, including aspects related with the intervention and control types and guidelines for proper reporting.

In the third section, current research derived from the results of this thesis is presented. This includes the description of a RCT using acuTENS in the treatment of acute COPD exacerbated patients is presented that is currently being carried out in two main Catalonian Hospitals and its preliminary results.

Finally in the fourth section, concerns regarding the lack of regulation and recognition of acupuncture practice in Spain are described including how this affects the development of future research on the field.

Discussion derived from the publications

Filiform needle and acupuncture techniques for COPD

For the first objective of this thesis, we performed large spectrum SR with 62 randomised or quasi-randomised controlled trials, 28 included in our first publication and 35 in our second one.

This review identified several acupuncture techniques commonly used to treat COPD such as filiform needle acupuncture (including electroacupuncture) (28 trials), moxibustion (13 trials), acuTENS (7 trials), acupressure (7 trials) and ear acupuncture (6 trials) and the combination of acupressure and ear acupuncture (1 trial). We also identified other less common techniques such as catgut implant (17 trials), tree-edge needle (1 trial), thumb-tack needle (1 trial), thick needle (2 trials), acupoint incision (1 trial), wet cupping (3 trials), floating needle (1 trial) and intradermal needle (1 trial); however these techniques were not included in the results since they are used mainly in China and therefore we focused on the most well-known and practiced techniques in the world.

Regarding participants, most studies included COPD participants in stable condition (49 trials, 79%) and only 13 included exacerbated participants (21%). Patient disease severity was poorly reported since this information was only stated in 11 of the included trials (17%) and ranged from moderate to severe condition, according to the GOLD classification. Participants severity is an important aspect that needs to be taken in to consideration when analysing the results of an intervention for COPD, since it has been associated with an increase in hospitalizations and all-cause mortality (244). Moreover, it has been found that in patients with severe/very sever condition show early differential dropout that can impact study outcomes, reducing estimation of treatment effects on the studied outcomes (245).

With respect to the studied outcomes, we found that dyspnoea, which is the most disabling COPD symptom, was only studied in 18 trials (29%). Similarly, exercise capacity and quality of life were included in only 16 (26%) and 26 (42%) trials, respectively. We found this quite remarkable since dyspnoea, exercise capacity and quality of life are the main patient-centred measures. In contrast, lung function (FEV_1 and FVC) was the most studied outcome with 43 trials (69%), despite the fact that there is no strong correlation between increased lung function and clinically relevant COPD improvements (246). An explanation for this could be that researchers preferred to use objective outcomes due to the difficulties in the blinding of participants in acupuncture clinical trials. Moreover, anxiety and depression were included in only one small pilot trial using filiform needle and five acupressure trials. This is a very low number of trials

taking into consideration that there are several systematic reviews that have suggested that acupuncture could be effective in patients with depression (225,247) or depression related to another clinical situation such as postpartum (248) and stroke (249). Finally, we only found only five trials, two using filiform needle, two using acuTENS and one using acupressure, assessing adverse events.

Regarding the risk of bias of the studies, there was a high percentage of trials graded with an unclear risk of bias in most of the Cochrane risk of bias tool items due to lack of reporting. For random sequence generation, the results varied depending on the technique; acuTENS was the only intervention where all seven trials were classified with a low risk of bias. In all other interventions the percentage of trials classified with a high or unclear risk of bias ranging from 38% in filiform needle and moxibustion trials to an 83% in ear acupuncture trials. Allocation concealment and blinding of outcome assessment were also poorly reported, with an overall 82% and 79% of trials classified with an uncertain risk of bias on these items, respectively; the reporting of these items was similar in all acupuncture interventions. Lack of information to properly rate the risk of bias was found in other similar trials. For example, in trials of acupuncture analgesia using filiform needle, Li et al. found a high percentage of trials with an unclear risk of bias allocation concealment (71.4%), blinding of participants and personnel (50.5%), and for blinding of outcome assessors (53.9%) (250). Another similar report in the field was the evaluation of the risk of bias of acupuncture trials in the last five decades by Long et al., concluding that although some improvements have been observed in more recent trials, important issues remain specially for allocation concealment and blinding (251).

Our SRs also offered some preliminary data about the clinical effect of several acupuncture interventions in COPD.

For filiform needle interventions, we found some evidence that they could improve quality of life compared with sham acupuncture (Std.MD:-0.81; 95%CI:-1.12,-0.49; I^2=24%) or no acupuncture (Std.MD:-0.62; 95%CI:-0.90,-0.34; I^2=50%) in stable and exacerbated participants. Also, benefits were observed for exercise capacity in stable participants in both comparisons with an improvement of 76.68 meters in the 6MWT compared with sham acupuncture (158 participants; 95%CI:39.93,113.43; I^2= 0%) and 33.05 meters compared with no acupuncture (95%CI: 19.11,46.99; I^2= 67%). For dyspnoea, results varied between comparisons since statistical benefits were observed in the sham comparison in stable participants, while no differences were observed when compared with no acupuncture. For lung function, results were heterogeneous with some small but statistically significant benefits in FEV_1 and FVC in the sham

comparison which included only stable participants, while those differences were only seen in exacerbated participants but not stable ones in the no acupuncture comparison. Finally, no conclusions could be drawn for anxiety and depression since we only found one small pilot trial.

These results can be compared with a recent review published in 2018 by Wang et al. (252) which examined the effect of needle acupuncture techniques including manual acupuncture, electroacupuncture, warm acupuncture and ear acupuncture in stable participants. In the review, authors found statistical benefits for exercise capacity but not for quality of life. However, the results regarding quality of life are not that different from the ones in our review, since Wang's meta-analysis showed a reduction in SGRQ total score to 6.58, but the confidence interval was too wide for statistical significance (95%CI: −13.19, 0.03). A reason for this could be due to the fact that our review was published later, and therefore included recently published trials, but also because we included trials using not only the SGRQ but also the CAT, the QoL score and the CRQ using a standardised mean difference.

Regarding the usefulness of acuTENS in stable participants, our meta-analysis failed to detect statistically significant benefits for any outcome. For dyspnoea, two trials showed positive results while another one did not; a meta-analysis could not be performed due to due to the high heterogeneity (I^2= 96%). For quality of life and exercise capacity, a benefit was found but confidence intervals were not narrow enough for a statistical difference (QoL, Std.MD: -0.35 95%CI: -0.70, 0.00 I^2= 0% and 6MWD MD: 6.59 95%CI: -2.00, 15.19 I^2= 0%). Finally, lung function results were diverse between trials. For exacerbated participants, we only found one trial that did not find significant differences with a placebo group in the dyspnoea score after a 20-session intervention.

The possible use of moxibustion in COPD is not clear, especially as there is little or no data on important outcomes such as dyspnoea or exercise capacity. For quality of life, FEV_1 and FVC, most trials seem to show a benefit, but the heterogeneity in the results was too great to perform any metanalysis. Recent trials have only been performed in stable participants.

For acupressure, we found some evidence in the improvement of dyspnoea, quality of life and anxiety based on two trials comparing acupressure with sham intervention and one of them comparing acupressure with no acupressure; however, a meta-analysis was not possible due to the low number of trials and the cross-over design of one of them.

The role of ear acupuncture and cupping in COPD it is currently not known. We found only one small trial for each intervention including 30 and 60 participants, respectively, that reported

significant differences in quality of life and lung function for ear acupuncture and dyspnoea, wheezing and cough for cupping. However, it only reported p-value with no data on effect size.

This is the most updated large spectrum review to perform a large spectrum review for different non-pharmacological interventions in all kinds of COPD conditions. We included seven international and four Chinese databases with no language restriction. However, despite including a large number of trials, we could not draw firm conclusions due to several limitations. The first was due to the low quality of the included studies and their uncertain risk of bias. Second, several of the outcomes were only included in a small number of trials; for example, in filiform needle trials, only three out of 17 trials in the no acupuncture comparison and six out nine of trials in the sham acupuncture comparison assessed dyspnoea. Third, a meta-analysis was not possible in many comparisons due to the high heterogeneity between trials. Fourth, most of the trials were performed in China, making the results difficult to extrapolate to other populations. Finally, due to the large number of acupuncture interventions identified, we did not analyse less common acupuncture interventions such as catgut implant, thick needle, acupoint incision, wet cupping, floating needle and intradermal needle.

Completeness of reporting of acupuncture interventions for COPD

In our third publication, we analysed the completeness of reporting of filiform needle acupuncture interventions. As a complex and non-pharmacological intervention, acupuncture practice is composed of needling, specific non-needling and generic non-specific non-needling components; each of them may play a role in the therapeutic effect (253). Moreover, the interaction of those components may produce a greater effect than only the sum of each separate component (254). For this reason, a complete description of those components is crucial for the assessment, reproducibility and implementation of acupuncture clinical trials.

According to the results of our third publication, currently there are several under-reported STRICTA items in acupuncture COPD trials. Items with the greatest percentages of trials classified as ‘not reported’ were: ‘description of the participating acupuncturist’, ‘rationale of the comparator or control’ and ‘settings and context of the treatment’, all over 85%. Acupuncturist background is an extremely important item in trials were the treatment completely rely on the practitioner’s criteria; however, this can also be relevant in trials using fixed acupuncture protocols specially regarding acupoint localisation, stimulation technique and interaction with participants. The rationale for the control is also a relevant since authors must justify its selection according to the trial’s aims and take into consideration its limitations. Regarding the ‘settings and context of the treatment’ item, it refers not only to where the trial took place but

also the instructions given to practitioners about how to deliver the interventions and information given to patients that could modify their outcomes, for example regarding the trial control intervention.

We also found several items with a high percentage of trials classified as 'partially reported'. We believe this might be because some authors are not be fully aware of all aspects that each item includes. This could be because they might only use the STRICTA checklist, where items are mentioned but not fully described, or incomplete STRICTA guidelines. The clearest example might be the reporting of the treatment regime. For this item, not only the total number of planed sessions must be stated, which was reported in all trials, but also the actual number of treatments received by patients. This last piece of information was not given in any trial and is crucial to assess not only the adherence to acupuncture treatment but also the real acupuncture dose received by participants. Other similar examples of this are were seen in the description of acupuncture points, with 53% of the trials not reporting if the points were unilateral or bilateral and information about needle type, which lacked information about needle material (25%), needle manufacturer (32%) and needle diameter and length (10%).

Our results have similarities with similar studies by Lu et al. (255) and Hughes et al. (256) in cancer trials and Wei et al. in stroke trials (242), since they all concluded that reporting should be improved. However, Hughes et al. found better reporting regarding acupuncture needling details, especially regarding number of needles per session and depth of insertion, as well as the treatment regimen. This could be because Hughes et al. only included trials published in the English language; according to a subanalysis in Lu's review, trials published in English-language journals seem to have better completeness of reporting than those in Chinese-language journals. However, Wei et al. found better reporting of the subitems 'treatment reasoning' and 'response sought' in Chinese journals and better reporting on 'practitioner's background' in English journals. Another explanation for some of the differences could be because the STRICTA guidelines are not designed as a tool to assess the completeness of reporting and therefore they do not clearly specify how items should be judged.

Future methodological challenges in acupuncture research

Although one of the aims of performing an SR is to draw a conclusion about the efficacy of an intervention, they can be limited by the lack or deficiencies of previous primary research. In our case, with the current evidence, none of the studied acupuncture techniques have enough solid evidence to be recommended as part of the usual treatment of COPD. However, we found some evidence that acupuncture and acupressure may provide some benefits regarding dyspnoea, exercise capacity and quality of life. To derive firmer conclusions, more research is needed; however, acupuncture research presents several challenges that need to be taken into consideration.

When designing an acupuncture trial, authors may face several critical methodological decisions that will play a great role in the validity of the final results. Some of those decisions, such as the randomization method, allocation concealment or the statistical analysis, are not different from other pharmacological or non-pharmacological trials however, there are others which are specific to acupuncture research. Those specific challenges are present below in tree main groups; challenges related to the selection of acupuncture interventions, challenges related control group selection and challenges related with the risk of bias assessment and the quality reporting.

Acupuncture interventions

As it has already been explained, acupuncture is a very heterogeneous practice with different styles and techniques. This it is certainly a challenge for the acupuncture research community.

As we also saw in our systematic reviews, acupuncture treatments used in RCT also show great differences, not only in the acupuncture points used, but also in the duration and frequency of the interventions. Those differences might explain the observed differences between trials results. For example, recent publications have suggested that a greater number of acupuncture needles and sessions are associated with better outcomes in chronic pain trials (257). Also, a relationship between the number of acupuncture sessions and its effects has been found in a recent publication using the meta-regression approach in trials of prostatitis and chronic pelvic pain syndrome (258) and other authors have also considered other treatment parameters such as the sensation obtained after acupuncture stimulation (De Qi sensation) and the treatment frequency (259). Moreover, it has been claimed that the therapeutic effect of acupuncture may not only rely on needling components, such as the number of needles or its location and

stimulation, but also on other non-needling components (253). Non-needling acupuncture components include both components specifically related to the acupuncture treatment, such as its style, the diagnostic method used or other treatment components such as lifestyle advice, as well as generic components shared by any other intervention such as beliefs, expectations or the therapeutic setting (see Table 6).

Table 6: Components of an acupuncture treatment. Modified from Langevin HM et al. (253).

Needling components	Needle size, retaining time, depth, stimulation, location and frequency.
Specific non-needling components	Diagnosis method and rationale (e.g. TCM syndrome differentiation, Japanese style acupuncture, Western medical acupuncture), acupoint and meridian palpation, use of other treatment components (e.g. moxibustion, cupping, herbs, exercises, lifestyle advice).
Generic nonspecific non-needling components	Beliefs and expectations, therapeutic setting, time and attention.

Therefore, when designing an acupuncture trial all those components need to be taken in to consideration. To do so, authors can consider using three main strategies, using a standardised acupuncture protocol, an open acupuncture protocols or a semi-standardised acupuncture protocol.

Standardised acupuncture protocols, on one hand, allow the performance of a homogeneous and controlled intervention defining all acupuncture components, which strengthens the internal validity of the trial (260). On the other hand, standardised protocols have a weak external validity, since in usual clinical practice it is believed that a tailored acupuncture intervention according to an individualised diagnosis is more effective than a standardised protocol. Because of this, standardised protocols is more suitable for explanatory trials, which aim to assess efficacy or to study the impact of the different acupuncture components, such as the number of needles, their location and stimulation, the treatment regime, etc. but not to assess the effectiveness of current acupuncture practice (261).

Open acupuncture protocols are exactly the opposite of standardised protocols. In this type of intervention, the person delivering the acupuncture intervention is allowed to freely deliver the intervention according to his/her clinical expertise, just as it would happen in real clinical practice, weakening internal validity but increasing external validity. This type of intervention is more suitable for pragmatic trials that investigate the effectiveness of real-life interventions (262). However, to do so, acupuncture style used should be representative of real practice or involve multiple practitioners to take in to consideration common differences in clinical practice.

Semi-standardised acupuncture interventions are a compromise between standardised and open protocols. This type of treatment uses a core of fixed acupuncture points but then, several prespecified extra points can be selected depending on the practitioner's diagnosis or patient-specific symptoms. This type of intervention can be more or less standardised or open depending on the protocol and therefore can be adapted to either explanatory or pragmatic designs.

Table 7 summarises the aims and limitations of the mentioned strategies.

Table 7: Intervention types in acupuncture trials.

	ACUPUNCTURE TREATMENT	SPECIFIC AIMS	LIMITATIONS
EXPLANATORY TRIAL: TEST EFFICACY	Standardised acupuncture protocol	To separately investigate acupuncture components: -Needling components: Needle size, retaining time, depth, stimulation, location, and frequency - Specific non-needling components: Diagnosis method and rationale, acupoint and meridian palpation, use of other treatment components - Generic nonspecific non-needling components: Beliefs and expectations, therapeutic setting, time and attention	It does not represent real life acupuncture practice It is considered to be less effective than a tailored acupuncture intervention according to each patient's characteristics The intervention should be detailly reported to be reproductible
	Semi-standardised acupuncture protocol	Similar to standardised acupuncture or open acupuncture protocol depending on its flexibility	Similar to standardised acupuncture or open acupuncture protocol depending on its flexibility
PRAGMATIC TRIAL: TEST EFFECTIVENESS	Open acupuncture protocol	To study the effect of acupuncture components as a whole To study the efficacy of real-life clinical practice	The number of practitioners involved should be large or the practitioner's style should be representative to real practice It cannot be used to study the effect of specific acupuncture components

Control selection

The selection of the control is also crucial in acupuncture clinical trials. Sham comparisons are usually considered the best comparator to assess the effectiveness of an intervention since they can control the placebo effect, which is caused by the expectations and beliefs of participants and personnel administering the interventions. To do so, a physiologically inert intervention indistinguishable from the real treatment is used to blind participants and personnel. This procedure is easily used in pharmacological interventions, but it can be really difficult or even impossible to perform in non-pharmacological interventions such as surgery, technical interventions, rehabilitation, behavioural interventions, psychotherapy and acupuncture (101).

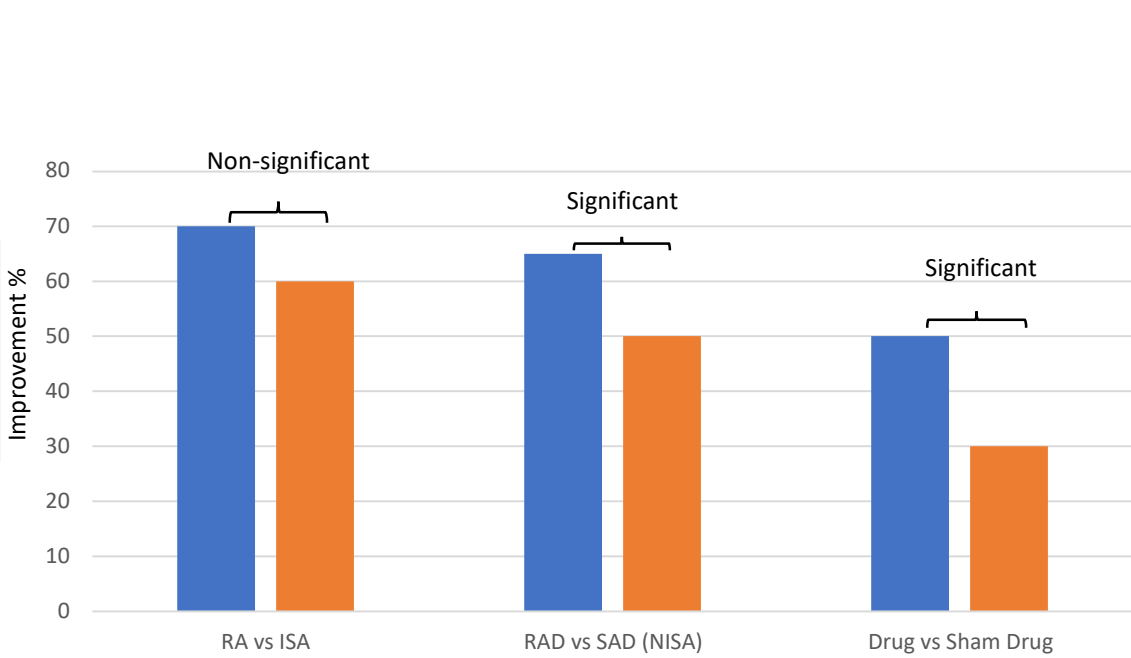
Acupuncture does not have an ideal sham intervention however, needle-insertional and non-insertional sham controls are used in RCT. It is important to know that different sham procedures may have different effects as suggested by a SR published in 2016 (263). This review concluded that, in acupuncture RCT treating pain conditions, greater results were observed in trials using non insertional sham controls compared with insertional ones. This influence of the control group was also seen in a large Individual patient data meta-analysis by MacPherson et al., also in pain conditions (264). This meta-analysis concluded that although acupuncture was significantly superior to all control subtypes, its effect size was smaller when compared with insertional sham controls, suggesting an important physiological effect of this kind of procedure. A possible explanation for this phenomenon is that puncturing any place on the surface of the body, even superficially, stimulates peripheral sensory nerve fibres, producing a similar but smaller response compared to regular acupuncture. For this reason, many researchers do not recommend the use of penetrating sham acupuncture controls in trials assessing pain conditions.

Although this could lead to the conclusion that non-penetrating sham devices are the best option for acupuncture research, it is not that simple. When using non-penetrating sham devices, a real acupuncture device must be used to ensure patient blinding, but this acupuncture procedure might not be as effective as real-world acupuncture, as suggested by a recent network meta-analysis (265). In this research, which included studies of acupuncture for hot flashes in menopausal women, authors compared the effect of real acupuncture in needle-insertion sham controlled trials (real world acupuncture) and real acupuncture in non-insertional sham control trials (real acupuncture device), concluding that real world acupuncture had a greater effect size. This might be explained by the smaller stimulation dose that real acupuncture devices can produce, since needle depth and stimulation are limited.

This differences in the effects of different acupuncture and sham acupuncture procedures may lead to what is known as the efficacy paradox, were a treatment that is efficacious is less effective than a treatment that is not efficacious (266). This happens because not all sham interventions have the same effectiveness; for example, it has been found that sham acupuncture and sham surgery interventions are associated with higher responder ratios than oral pharmacological placebos (267).

Figure 7 represents a possible explanation for this complex situation using the hypothetical effectiveness of real acupuncture, insertional sham acupuncture, real acupuncture device, sham acupuncture device, drug treatment and sham drug treatment. Notice that the most effective intervention (real acupuncture) does not show statistical differences compared with penetrating sham acupuncture (lack of efficacy). However, drug treatment shows the greatest difference with its sham intervention but is the least effective of all treatments.

Figure 7: Hypothetical example of the efficacy paradox in acupuncture trials. Own source.



RA: Real acupuncture; ISA: Insertional sham acupuncture; RAD: Real acupuncture device; SAD: Sham acupuncture device; NISA: None-insertional sham acupuncture.

For those reasons, control groups in acupuncture RCT must be chosen considering the strengths and limitations of the three main comparison options, which are the waiting list group, penetrating and non-penetrating sham interventions and active treatment.

Waiting list controls are usually not used in acupuncture trials as not performing any kind of treatment induces performance bias. In this case, possible differences between groups could not only be attributed to preferences and expectations regarding the treatment, but also to the extra attention received by the intervention group. Also, not allowing participants to receive any medical treatment during the study may bring up ethical concerns (268). However, this kind of control may be used in some initial research stages to collect preliminary data, as this type of comparison group can be used to control factors such as the natural disease process.

Sham interventions, which are used in explanatory trials to test efficacy, can be used to control performance bias and study specific acupuncture needling components (269). Non-insertional sham interventions can also be used to avoid non-specific needling effects, which may be very important for pain studies; however, it is an expensive and difficult to implement procedure, especially for long-term trials. Also, real acupuncture devices my limit the acupuncture stimulation in the intervention group, reducing the therapeutic effect. Needle-insertional sham interventions allows for research on the specific effects of acupuncture points, but it is likely to produce important non-specific physiological effects due to needling (270).

Active controls are usually used in pragmatic trials to test effectiveness. This type of control is used to study acupuncture as a whole, including all acupuncture components. Also, it compares acupuncture with a conventional treatment or as an adjuvant treatment to it, which may be more suitable for clinical and health policy decision making. Also, it allows for a safety and cost-effectiveness analysis (271). On the other hand, active controls cannot blind participants or be used to examine the importance of each acupuncture component separately.

Tables 8 summarises the different control types according to the specific aims of the study.

Table 8: Controls types in acupuncture trials. Modified from Chen et al. (272)

	CONTROL	SPECIFIC AIMS	LIMITATIONS
EXPLANATORY TRIAL: TEST EFFICACY	Waiting list	To control for remissions to mean in the natural disease process. To collect preliminary data for a large RCT	Induces performance bias May have ethical problems
	Non-Insertional Sham	To eliminate the non-specific effects of needling, particularly for studying pain related symptoms/disorders	Difficult and expensive to implement in long term studies, real sham devices may have lower therapeutic effect, does not test for acupoint specificity
	Needle-insertional sham	To test specific effects of acupoints, particularly for studying symptoms/disorders not relevant to pain	Likely to produce nonspecific physiological effects of needling
PRAGMATIC TRIAL: TEST EFFECTIVENESS	Active control	To identify the effectiveness of acupuncture, alone or as an adjunct treatment, compared to a conventional treatment or standard care. To examine safety and cost-effectiveness To allow clinical and health policy decision making	Cannot blind patients or practitioners, requires large sample size, cannot specify questions related to basic acupuncture theories such as acupoint specificity, needle manipulation, etc.

Risk of bias assessment and completeness of reporting

As previously mentioned, bias is a systematic error that can lead clinical trials to over or under-estimation of the effects of an intervention. To assess the risk of bias of clinical trials tools such as the Cochrane risk of bias tool (55) or the PEDro scale (57) are used to systematically evaluate most relevant sources of bias including the comparability of the study participants, problems with the measurement of the outcomes due to the lack of blinding of assessors and missing information regarding the study outcomes or participants dropout. But, to be able to adequately assess those sources of bias, complete information needs to be reported.

To improve trials completeness of reporting, international initiatives such as the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network have been launched to promote transparent and accurate reporting and a wider use of robust RG by making them accessible and developing online resources, tools and materials and support in its implementation (273). Moreover, RG like SPIRIT and CONSORT for RCT or PRISMA for SR have been developed and expanded with several specific extensions for particular study designs or interventions.

In the case of acupuncture research, STRICTA is the specific extension for reporting acupuncture RCT and just recently a new extension called PRISMA-Acupuncture (PRISMA-A) has been added as an official extension of PRISMA for SR of acupuncture trials (274). For trials using other acupuncture techniques, several non-official new guidelines have been proposed to target specific characteristic of those practices, such as STRICTOM for moxibustion (105) and STRICTOC for cupping (106). For other interventions such as acupressure or acuTENS, general guidelines can be considered such as the Template for Intervention Description and Replication (TIDieR) guidelines (275). A summary of the available RG for acupuncture research is shown in table 9.

Table 9: Summary of reporting guidelines in acupuncture research

ARTICLE TYPE	GUIDELINE	EXTENSIONS
Clinical trial Protocols	SPIRIT	Filiform needle: STRICTA Moxibustion: STRICTOM Cupping: STRICTOC Others: TIDieR
Clinical trials	CONSORT	
Systematic Review Protocols	PRISMA-P	Acupuncture: PRISMA-A
Systematic Reviews	PRISMA	

However, although research has found that the introduction of RG has improved the reporting quality of trials (276), including the reporting in acupuncture research (277,278), even the adherence to some of the most extended RG such as CONSORT is still suboptimal (279).

Regarding STRICTA adherence, recent publications (92,242,280), including our own on acupuncture interventions in COPD trials (281), have also observed several deficiencies. The implementation of extensions for specific techniques may be more difficult than general RG for common epidemiologic designs, therefore lack of knowledge regarding acupuncture research and STRICTA is expected from editors of non-specific acupuncture journals. In fact, according to the STRICTA web page, only 13 international journals, all acupuncture-related, have endorsed STRICTA (282), compared with the 585 endorsing CONSORT (283). Moreover, even some of the journals that do endorse STRICTA do not even explicitly request its use for potential manuscripts (284). Also, STRICTA, such as other RG, is composed by statement paper with a detailed explanation of how each item should be reported, and a checklists to be used as a guide or writing starting point. The lack of knowledge of these guidelines may make authors only take in to consideration the checklist, which is insufficient to guaranty complete reporting. Journals must also be aware of this since the request of the checklist in the submitting process is not enough to ensure proper reporting. Also, it has been suggested that many trials might have inconsistencies between what is claimed in the submitted checklist and what was reported in the published paper (285).

To try to improve the adherence to RG several strategies have been proposed including training on the use of RG, improving understanding, encouraging adherence, checking adherence and providing feedback, and the involvement of experts. Unfortunately, the effectiveness of many of those interventions is still unknown (286).

Current research derived from the results of this thesis

With the aim to integrate all the knowledge derived from our results and its implementation, we started a research line to test those acupuncture techniques in our clinical settings.

In our SR, we found some trials concluding that acuTENS could reduce dyspnoea in COPD patients by increasing beta-endorphin levels (239) however, those trials have mainly been conducted on patients with stable condition. Although dyspnoea may be present during COPD stable conditions, it is during acute exacerbation of chronic obstructive pulmonary disease (AECOPD) that it worsens, being the main symptom during hospital admissions (287). In this context it seems plausible that acuTENS could play a role in the acute treatment of this clinical situation.

For this reason, we designed a multicentric patient and assessor-blinded RCT with the aim to determine if the administration of acuTENS could reduce dyspnoea in patients hospitalized for AECOPD. To do so, a sample of 60 patients will be randomized to receive 45 minutes of either real acuTENS or sham acuTENS treatment once a day during 5 consecutive days. For the main outcome, dyspnoea, the Borg scale at baseline and day 1 to 5, will be used . Secondary outcomes will be the duration of the hospitalization, quantity of drugs administrated, expiratory peck flow adverse effects and mortality and readmissions at 3 months.

To ensure the transparency of our trial, we registered our protocol with Clinicaltrials.gov and can be consulted with the identifier NCT02998957. Moreover, we also published the protocol in open access using the SPIRIT RG to provide complete access and reporting of our objectives and methods (288) (annex 3).

Although in our SR we identified several techniques, we finally decided to design a trial using acuTENS for several reasons. First, the identification of several small trials suggested that acuTENS may produce a fast anti-dyspnoeic effect and increase FEV_1 (40,239), which could be helpful to treat AECOPD; however, specific research on this particular application is lacking. The only RCT that we identified using acuTENS in exacerbated participants did not find statistically significant differences with placebo in a 20-session intervention; however, this could be because both groups might had nearly completely recovered when the outcomes were assessed. Second, acuTENS is a non-invasive acupuncture intervention that uses conventional TENS to stimulate acupuncture points, which makes it easier to learn and implement than other acupuncture techniques such as filiform needle, especially in a hospital environment. Third, due to its non-

invasive nature, acuTENS is a safer intervention since it avoids possible adverse events such as infections or internal organ injuries, which are rare but possible when using filiform needle techniques (289). Fourth, the acuTENS technique is applied in a much more standardised method compared with other traditional acupuncture techniques, where stimulation methods and the selection of acupuncture points are very heterogeneous between trials. AcuTENS uses a standard stimulation pulse of 2-4 Hz with a wave width of 200 microseconds and a stimulation time of 40-45 minutes, and most trials have used a single stimulation of the Dingchuan acupuncture point. This allows for the use of a standardised intervention that can be applied by personnel not trained in traditional Chinese medicine. Finally, the use of acuTENS allows for easy patient blinding using a sham TENS device, which is the same device used for acuTENS but with no electrical output. This is easier and cheaper than sham methods used to blind filiform needle interventions.

Sample calculation was performed by considering the minimal clinically important difference in our main outcome, dyspnoea, which is two points on the Borg scale. We also assumed a common standard deviation of 2.6 according to previous trials and assumed a dropout rate of only 10% since we were going to use a short intervention in hospitalised participants. With all this, we calculated a sample of 60 participants to perform the trial.

To minimise possible selection, performance and assessment bias, personnel involved in recruitment, usual treatment and assessment do not have access to the randomisation table used for patient's allocation. This list was created by an external researcher and protected by password so it can only be accessed by the person delivering the acuTENS and sham-acuTENS interventions.

Regarding the outcomes and measurement methods, we tried to use valid and reliable methods but also avoid complicated processes that might cause any extra trouble to participants and hospital personnel. With this in mind, we chose the modified Borg scale to measure our main outcome, dyspnoea, as it is a fast assessment scale and is easy to complete. Also, to assess lung function, we decided to use peak expiratory flow instead of using FEV_1, as the latter would have required much more time and equipment. Finally, the other secondary outcomes, i.e. blood gas measures, hospitalisation days, readmissions and mortality at three months after discharge, could be extracted from the patient's hospital records.

The trial started in 2017; however, due to several problems, the study has not yet been completed. The project started at the Sant Joan de Deu Hospital in Sant Boi as a pilot test of the interventions; however, the RCT could not be started there due to major difficulties with

recruitment. After several months without any inclusion of participants at Sant Boi, the Hospital de Manresa was contacted and recruitment began in 2018 after obtaining research ethics committee approval (annex 4); however, recruitment was very slow and only six participants were included during the first year. To try to improve this situation, other hospitals were contacted and finally the Hospital del Mar also joined the project (see research ethics committee approval in annex 5) and is currently the centre with the largest number of participants. Unfortunately, the study was paused in 2020 at all centres due to the health emergency caused by the COVID-19 pandemic.

Currently, 19 of the 60 required participants have completed the study. Preliminary results are shown in Annex 6. At the time, no harm or adverse events have been detected and there have not been any withdrawals. Due to the small sample size, currently no statistical differences can be seen between groups in any outcome, but the results show a tendency toward lower dyspnoea levels during the first three days but not during days 4 and 5 in patients receiving acuTENS. With these results, we can hypothesise that acuTENS could have a role during the first hospitalisation days, but its effect may decrease with time due to adaptation to the stimulation or the improvement of the patients. This could explain why some trials using single treatment sessions have found benefits of the technique while others using longer treatment sessions have not. Also, the results currently show a tendency toward a reduction in hospitalisation duration in the treatment group (a difference of 5 days).

It is still too early to draw definitive conclusions with current results however, if future results confirm our preliminary findings, acuTENS could be considered as a new non-pharmacological, non-invasive, and inexpensive intervention for patients with an AECOPD. This intervention could also help to reduce treatment costs since in Spain as it is estimated that the hospitalisation cost for acute COPD exacerbations is on average 344.96 € per person per day (290).

Lack of regulation and recognition of acupuncture practice

Acupuncture research does not only face methodological challenges, such as the previously mentioned, but also others related to the lack of regulation of its practice and education, which is directly related to its lack of recognition.

Acupuncture is considered in most countries a complementary and alternative medicine (CAM). The World Health Organization (WHO) defines CAM as "a broad set of health care practices that are not part of that country's own tradition or conventional medicine and are not fully integrated into the dominant health-care system" (291). This term includes very diverse practices such as acupuncture, homeopathy, traditional medicines, naturopathy, osteopathy, yoga, reflexology or chiromassage.

Practice and regulation of different CAM, including acupuncture, is very diverse. In Europe, only 3 countries (Malta, Switzerland and Portugal) have a regulated acupuncture profession, while 23 countries have no acupuncture profession regulation but treatment regulations. Those treatment regulations are very different and while some countries only allow doctors to provide acupuncture, in others there is a mixture of regulations for health professionals, such as physiotherapists, nurses, midwives, and practitioners without medical education (292).

In Spain, although the Law 44/2003, of November 21, on the organization of the health professions regulates that only accredited health professionals can provide therapeutic intervention (293), there are also non-health professionals practicing acupuncture. This is allowed by the different autonomous communities as long as they work in centres not registered as a healthcare facility and carry out corporal practices for personal well-being . In any case, there are no educational minimum standards for practicing acupuncture, which means that acupuncture is learned in different institutions with very different academic levels, from private school courses (294) to official University master degrees (295). This situation does not only lead to great differences between practitioners' knowledge, competencies and skills, but also reduces the number of acupuncture practitioners who are capacitated to research or develop a research career.

Another important factor that limits acupuncture research is the lack of recognition of CAM on the part of the medical and research community. Regarding acupuncture, the fact that traditional theories are still used in clinical practice and the lack of knowledge of its scientific rationale and current research, has made many people claim that acupuncture is an unscientific

practice based only on esoteric ideas. This is aggravated by the great heterogeneity in acupuncture practitioners education levels mentioned before, which can include from charlatans to fully qualified health professionals. This situation has caused a certain distrust in various sectors of society towards the practice of acupuncture, leading to several controversies and initiatives to discredit or even ban acupuncture practice. One of the latest examples of this is the inclusion of acupuncture in the "Plan for the protection of health against pseudotherapies" which was presented in November 2018 by the Ministries of Health, Consumption and Social Welfare and Science Innovation and Universities (296). In the document it is stated that acupuncture is not supported by the available scientific evidence, although the same ministry of health recognised, in a 2011 report, that acupuncture was effective for postoperative nausea and vomiting and those induced by chemotherapy and postoperative dental pain, and might also be a useful for frequent episodic or chronic tension-type headache, migraine attacks and non-specific chronic low back pain (297). The presentation of the plan, along with a media campaign that was launched with it, has created a very difficult background for the development of acupuncture research projects, making it even harder to get access to grants or the acceptance of performing trials in public services such as hospitals and primary care centres. This creates difficulties to break vicious circle where the lack of acupuncture evidence results in even more difficulties for its research.

In summary, acupuncture research, especially in Spain, is limited by the lack of qualified professionals, the lack of academic structures, the lack of integration with the dominant health care system and prejudices against its practice and even research. Acupuncture's therapeutic value must be assessed by rigorous high quality research, like any other therapeutic intervention, but to do so, it also needs the same space and opportunities for its development. For this reason, efforts must be made to develop a proper research ecosystem, composed by acupuncture practitioners, researchers, academic and research institutions and the health care system facilities. However, to do so, proper regulation of the acupuncture profession and education must be established.

CONCLUSIONS

Clinical practice implications

- Filiform needle acupuncture is likely to be beneficial for dyspnoea, quality of life and exercise capacity compared with a sham acupuncture and quality of life and exercise capacity compared with no acupuncture control. These results are mainly applied to stable COPD participants.

- Acupressure may possibly improve dyspnoea, quality of life and anxiety but results are based in a small number of low-quality trials.

- There is not enough evidence to draw conclusions on the efficacy of moxibustion, acuTENS, ear acupuncture and cupping for COPD.

- Acupuncture techniques appear to be safe for COPD as no important side effects have been reported in current trials. However, more research has to be done on possible side effects.

Research implications

- Further large well-designed randomised controlled trials are necessary to confirm the effectiveness of acupuncture techniques for COPD.

- A great diversity in treatment protocols, which included different types and number of acupuncture points, different treatment regimens and different treatment durations, was seen in current trials. Since there is some evidence that acupuncture dose might affect its efficacy, more research should be done on this particular issue to guide future trials.

- Several clinically important outcomes such as dyspnoea, quality of life, exercise capacity and anxiety, were found to be studied in only a small number of trials. Further studies should include those outcomes as they are essential for a proper COPD assessment.

- Important information related with the trial's methods, such as the randomization sequence generation, allocation concealment and outcome assessors blinding, are underreported. Future study reports should follow the CONSORT statement and its extensions to allow a proper assessment of the results and risk of bias by end-users so they can make well informed decisions.

- Filiform needle interventions are not properly described in study reports, which limit its potential replicability and applicability. Future trials should follow STRICTA guidelines. Besides not being official CONSORT extensions, STRICTOM and STRICTOC guidelines can be used to report moxibustion and cupping interventions while TIDieR can be used for the rest of acupuncture-based interventions. This would also help to explore trial's results heterogeneity and the role of potential effect modifiers such as acupuncture dose in the context of systematic reviews.

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ANNEXES

Annex 1: PROSPERO registration

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Acupuncture for COPD: a systematic review

Carles Fernandez, Jordi Vilaró, Mercè Sitjà, Yutong Fei, Jianping Liu, Wang Congcong

Citation

Carles Fernandez, Jordi Vilaró, Mercè Sitjà, Yutong Fei, Jianping Liu, Wang Congcong. Acupuncture for COPD: a systematic review. PROSPERO 2014 CRD42014015074 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42014015074

Review question

To determine the efficacy and safety of acupuncture in the treatment of dyspnoea for improving the quality of life of patients with COPD.
To determine the effects of acupuncture on pulmonary function variables (FEV1, FVC), exercise tolerance, anxiety and depression.
To determine the effects of different acupuncture techniques.

Searches

Search methods:
Electronic search:
Articles search will be held in the following databases:
1- The Cochrane Central Register of Controlled Trials (CENTRAL) (up to date)
2- MEDLINE (1950 to present)
3- EMBASE (1974 to present)
4- CINAHL (1981 to present)
5- AMED (Ovid) (1985 to present)
6- PEDro (1950 to present)
7- PsycINFO (1806 to present)
We will also include three Chinese databases
8- CNKI (1994 to present)
9- VIP (1989 to present)
10- Wanfang (1998 to present)
11- CBM
Following the recommendations of the Cochrane Hand book for Systematic Reviews of Interventions, we have created a high sensitivity search although it may have low accuracy.
The search strategy for CENTRAL and MEDLINE databases will be:
1- "Acupuncture Therapy" (Mesh)
2- Acupuncture (Mesh)
3- "Acupuncture, Ear" (Mesh)
4- "Acupuncture, points"(Mesh)
5- Electroacupuncture (Mesh) or electro-acupuncture (tw)
6- Acu-TENS (tw) or "AcuTENS" (tw)
7- Moxibustion (Mesh)
8- Acupressure (Mesh)
9- Acup*(tw)
10- Or/1-9
11- COPD (Mesh)
12-"Pulmonary Disease, Chronic obstructive" (Mesh)
13- Bronchitis (Mesh)
14- "Obstructi*lung disease" (tw)
15- "Obstructi*airway disease" (tw)
16- Emphysema (Mesh) or "Pulmonary Emphysema" (Mesh)
17- "Chronic Air flow Limitation" (tw)
18- "Chronic Air flow obstruction" (tw)
19- "Chronic respiratory disease" (tw)

20- Or/11-19
21- 10 And 20
22- Randomized controlled trials (pt)
23- Controlled Clinical Trials (pt)
24- Randomized (tiab) or Randomly (tiab)
25- Placebo (tiab)
26- Trial (tiab)
27- Or/22-26
28- 21 And 27
For other databases, the search will be adapted to each of them.
Additional searches:
We will consult the bibliography of selected articles seeking additional studies not detected in the initial search. Manual review of national and international respiratory diseases and acupuncture conferences will also be performed.

Types of study to be included
Randomized controlled trials or quasi-randomized including crossover studies

Condition or domain being studied
Chronic Obstructive Pulmonary Disease (COPD) affects 9.1% of the population between 40 and 70 years in Spain and is the 4th leading cause of death worldwide. COPD presents with a progressive and not reversible airflow decrease causing major symptoms like breathlessness, chronic cough, abnormal sputum and significant reduction in quality of life

Participants/population
COPD patients with different grades of obstruction (GOLDI to IV) in exacerbation or stable periods.

Intervention(s), exposure(s)
Criteria for considering studies included in review
Intervention:
Non-pharmacological modalities of acupuncture (filiform needle, electroacupuncture, acupressure, moxibustion, ear acupuncture...) or acupuncture plus another standard intervention (medication, physiotherapy, pulmonary rehabilitation...)

Criteria for excluding studies from the review
1- Studies comparing two different techniques of acupuncture or comparing acupuncture to a non-Standard therapy
2- Randomized Cluster studies
3- Not comparative
4- Studies in animals
5- Studies published in not indexed journals
6- Not indexed conference proceedings publications

Comparator(s)/control
Control group (sham acupuncture or no treatment) or with a standard intervention (physical therapy or drug treatment, among others).

Main outcome(s)
1- Dyspnea (Borg Scale, Visual Analog Dyspnea Scale, mMRC, etc.)
2- Quality of life (COPD Assessment Test, St. George's Respiratory Questionnaire, Chronic Respiratory Questionnaire, CAT, etc.)
3- Adverse effects

* Measures of effect

Timing: Post treatment

Efect measures: Mean diference or Standarized mean difference

Additional outcome(s)

1- Exercise capacity (6-minute walking test, Shuttle walking test, etc.)
2- Lung Function (FEV1, FVC, FEV1/FVC, TLC, RV, etc.)
3- Anxiety and Depression level (HAD, BDI, etc.)

* Measures of effect

Timing: Post treatment
Efect measures: Mean diference or Standarized mean difference

Data extraction (selection and coding)

Study selection:
Two reviewers will independently read the titles and abstracts of the studies found in the initial search to identify those that met the inclusion criteria. Once identified, full articles will be obtained to review the results and determine their suitability. In case of discrepancies between the two reviewers, these will be resolved by consensus; if this is not possible, a third reviewer will decide the final inclusion of studies. If necessary, studies will be translated.
Extraction of results and data management:
Two reviewers will independently extract the data from studies using a standard data extraction form, discrepancies will be resolved by consensus.
There will be a pilot test prior to the start of data extraction to check the suitability of the formulary, as well as their understanding by reviewers. Corrections will be made if necessary.
Following the methodology described in the Cochrane Handbook for Systematic Reviews of Interventions and revised STRICTA (Standard for Reporting Interventions in Clinical Trials of Acupuncture) guide, the following data will be collected:
1- Risk of bias (Random sequence generation, allocation concealment, blinding of participants and personnel, incomplete outcome data, selective reporting, other bias)
2- Characteristics of the study (study design, number of groups, controlled before-and-after, number of participants, description of the number and the causes of follow-up loss).
3- Study participants (Number of participants and gender, age)
4- COPD characteristics (severity, exacerbation/stable condition)
5- Description of intervention groups (Name of the group, intervention used, number of participants, intervention description, reproducibility, length of follow up).
6- Outcomes and results (Method of measurement or scale, baseline results, post intervention results and period of measure, adverse effects)
7- Additional information (Main conclusions of the authors, references to other relevant studies, missing information)

Risk of bias (quality) assessment

Risk of bias will be assesed using the Cochrane risk of bias assessment tool

Strategy for data synthesis

If possible, the results will be combined in a meta-analysis using RevMan 5.1 software. We will use a fixed effects model to summarize the results if the heterogeneity is not relevant (I-squared <30%). Otherwise, a random effects model will be used. If I-squared value is over 70%, we will consider too high heterogeneity to make the meta-analysis and we will provide a narrative synthesis of the available data.

Analysis of subgroups or subsets

Subgroup analysis and investigation of heterogeneity:
There will be a subgroup analysis according to each acupuncture technique (acupuncture needles, electroacupuncture, moxibustion, ear acupuncture...) compared to no intervention, sham intervention or standard intervention.
If sufficient information and substantial heterogeneity (I2>50%), we will also analyse the following subgroups:
1 Severity (GOLD)
2 Exacerbation and stable period
3 Doses of the intervention (number of sessions, frequency, duration of the study...)
4 Studies risk of bias (high risk of bias vs. low risk of bias)

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Type and method of review
Systematic review

Anticipated or actual start date
03 November 2014

Anticipated completion date
11 April 2018

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Col·legi de Fisioterapeutes de Catalunya

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None known

Language
English

Country
Spain

Stage of review
Review Completed published

Details of final report/publication(s) or preprints if available
Fernández-Jané C, Vilaró J, Fei Y, Wang C, Liu J, Huang N, et al. Filiform needle acupuncture for copd: A systematic review and meta-analysis. Complement Ther Med. 2019 Dec;47:102182.

https://www.ScienceDirect.com/science/article/abs/pii/S0965229919302110?via%3Dihub

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Acupuncture Therapy; Humans; Pulmonary Disease, Chronic Obstructive

Date of registration in PROSPERO
20 November 2014

Date of first submission
05 October 2018

NIHR | National Institute for Health Research

PROSPERO
International prospective register of systematic reviews

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

The status of the review has been changed to "published"

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

20 November 2014
31 October 2018
16 October 2020

Annex 2: Systematic review data extraction form

Trial: _____ (author, year)

Journal: _____

Reviewer: _____

Date: _____

VERIFICATION OF STUDY ELEGIBILITY (cross the option that apply)

Randomized clinical trial or quasi-randomized control trial but not a cluster study?	Yes	No	Unclear
Are the participants human and diagnosed with COPD?	Yes	No	Unclear
Is the intervention used a non-pharmacological acupuncture intervention? (filiform needle, acupressure, ear acupuncture…)	Yes	No	Unclear
Is the control a sham intervention, no treatment or a standard intervention (medication, pulmonary rehabilitation…)?	Yes	No	Unclear
Main or secondary measures? (Dyspnoea, QoL, adverse events, exercise capacity, lung function, anxiety or depression)	Yes	No	Unclear

Briefly describe the diagnostic criteria/assessments listed in the trial

Exclude if any of the previous answers is “no”.

Other exclusion reasons

_____

☐ Included ☐ Excluded ☐ Awaiting assessment

ASSESSMENT OF RISK OF BIAS

Is the study free of bias in relation to…

Random sequence generation High Low Unclear

Quote: _____

Allocation concealment High Low Unclear

Quote: _____

Blinding of participants High Low Unclear

Quote: _____

Blinding of personnel High Low Unclear

Quote: _____

Blinding of outcome assessment High Low Unclear

Quote: _____

Incomplete outcome data High Low Unclear

Quote: _____

Selective outcome reporting High Low Unclear

Quote: _____

Other sources of bias High Low Unclear

Quote: _____

CHARACTERISTICS OF THE STUDY

Study design

Two intervention groups Yes No Unclear

More than two intervention groups Yes No Unclear

Controlled Before-and-after Yes No Unclear

		Group 1	Group 2	Group 3	Total
N included					
N randomised					
N analysed					
Drop outs	N.				
	Reason				

Study participants

Gender: M_____ F_____

Not mentioned

Age: mean (SD) Total _____ Group 1_____Group 2_____Group 3___

Not mentioned □

COPD characteristics

Severity

Score used _____

Mild (GOLD I) Yes _____(n, %) No Unclear

Moderate (GOLD II) Yes _____(n, %) No Unclear

Severe (GOLD III) Yes _____(n, %) No Unclear

Very severe (GOLD IV) Yes _____(n, %) No Unclear

Not mentioned ☐

Exacerbation or stable condition?

Stable Yes _____n weeks no symptoms No Unclear

Exacerbated Yes _____n weeks exacerbation No Unclear

Not mentioned ☐

Study treatments

Number of groups:

GROUP 1:

Name of the group:

Interventions used:

Number of participants:

Acupuncture intervention

Add text: As it was literally described in the original study (translate to English)

If not mentioned in the original study add “not mentioned”

Item	**Detail**	**Page number**
1. Acupuncture rationale (Explanations and examples)	1a) Style of acupuncture (e.g. Traditional Chinese Medicine, Japanese, Korean, Western medical, Five Element, ear acupuncture, etc) Add text:	
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or	

	consensus methods, with references where appropriate Add text:	
	1c) Extent to which treatment was varied Add text:	
2. Details of stimulation (Explanations and examples)	2a) Number of points stimulated per subject per session (mean and range where relevant) Add text:	
	2b) Names (or location if no standard name) of points used (uni/bilateral) Add text:	
	2c) Description of the stimulation method Add text: If acupuncture needles are used describe: Depth of insertion, based on a specified unit of measurement Add text: Needle stimulation (e.g. manual, electrical) Add text: Needle type (diameter, length, and manufacturer or material) Add text:	
	2d) Response sought (e.g. *de qi*, muscle twitch response, slight pressure, comfortable heat sensation…) Add text:	
	2e) Stimulation time Add text:	
3. Treatment regimen (Explanations and examples)	3a) Number of treatment sessions Add text:	
	3b) Frequency and duration of treatment sessions Add text:	

4. Other components of treatment (Explanations and examples)	4a) Details of other interventions administered to the acupuncture group (e.g., drugs, exercises, lifestyle advice) Add text:	
	4b) Setting and context of treatment, including instructions to practitioners, and information and explanations to patients Add text:	
5. Practitioner background (Explanations and examples)	5) Description of participating acupuncturists (qualification or professional affiliation, years in acupuncture practice, other relevant experience) Add text:	

Length of follow up? _____

GROUP 2:

Name of the group:

Interventions used:

Number of participants:

Intervention description:

Control group

Item	**Detail**	**Page number**
6. Control or comparator interventions (Explanations and examples)	6a) Rationale for the control or comparator in the context of the research question, with sources that justify this choice Add text:	
	6b) Precise description of the control or comparator (6b1-6b2). If sham acupuncture or any other type of acupuncture-like control is used, provide details using Items 1 to 3 above.	
	6b1) Description of the intervention Add text:	
	6b1) Duration per session Add text:	

	6b2) Frequency and number of sessions Add text:	
Sham or acupuncture-like intervention (only if necessary)		
1. Rationale (Explanations and examples)	1a) Style of acupuncture (e.g. Traditional Chinese Medicine, Japanese, Korean, Western medical, Five Element, ear acupuncture, etc) Add text:	
	1b) Reasoning for treatment provided, based on historical context, literature sources, and/or consensus methods, with references where appropriate Add text:	
	1c) Extent to which treatment was varied Add text:	
2. Details of stimulation (Explanations and examples)	2a) Number of points stimulated per subject per session (mean and range where relevant) Add text:	
	2b) Names (or location if no standard name) of points used (uni/bilateral) Add text:	
	2c) Description of the stimulation method Add text: If acupuncture needles are used: Depth of insertion, based on a specified unit of measurement (if needles are used) Add text: Needle stimulation (e.g. manual, electrical) (if needles are used) Add text: Needle type (diameter, length, and manufacturer or material) (if needles are used) Add text:	
	2d) Response sought (e.g. *de qi*, muscle twitch response, slight pressure, comfortable heat sensation…)	

	Add text:	
	2e) Stimulation time Add text:	
3. Treatment regimen (Explanations and examples)	3a) Number of treatment sessions Add text:	
	3b) Frequency and duration of treatment sessions Add text:	

Length of follow up? _____

(Add an additional group if needed copping table from group 2 and renaming it)

Outcomes and results

	Group 1		Group 2		Group 3		
CONTINUOUS VARIABLES	Mean (SD)	Nº patients assessed	Mean (SD)	Nº patients assessed	Mean (SD)	Nº patients assessed	Method of Measurement or Scale
PRIMARY							
DYSPNEA							
Baseline							
Post intervention (Period of mesure)							
QUALITY OF LIFE							
Baseline							
Post intervention (Period of mesure)							
SECONDARY							
EXERCISE CAPACITY: (Define outcome)							
Baseline							
Post intervention (Period of mesure)							
LUNG FUNCTION: (Define outcome)							
Baseline							

Post intervention (Period of mesure)							
ANXIETY AND DEPRESION							
Baseline							
Post intervention (Period of mesure)							
OTHER							

	Group A		Group B		Group C		
DICHOTOMOUS VARIABLES	Nº patients with outcome	Nº patients assessed	Nº patients with outcome	Nº patients assessed	Nº patients with outcome	Nº patients assessed	Method of Measurement
ADVERSE EVENTS							

Additional information	
Autors main conclusions	
Relevant references from other studies	
Missing information	
Notes:	

Annex 3: Acupoint transcutaneous electrical nerve stimulation in hospitalized COPD patients with severe dyspnoea: study protocol for a randomized controlled trial

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https://doi.org/10.1186/s13063-019-3757-x

Trials

STUDY PROTOCOL Open Access

Acupoint transcutaneous electrical nerve stimulation in hospitalized COPD patients with severe dyspnoea: study protocol for a randomized controlled trial

Carles Fernández-Jané[1,2*] and Jordi Vilaró[1,2]

Abstract

Background: Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major cause of hospital admissions and dyspnoea is its main symptom. Some studies have concluded that a new modality of acupuncture, called acupoint transcutaneous electrical nerve stimulation (acuTENS), could reduce dyspnoea in patients with COPD by increasing β-endorphin levels. However, those trials have been conducted mainly on patients in stable condition. This study aims to determine whether the administration of acuTENS can reduce dyspnoea in patients hospitalized for AECOPD.

Methods: A multicentre randomized control trial with blinding of participants and assessors will be conducted. A sample of 60 patients will be randomly assigned to receive 45 min of either real acuTENS or sham acuTENS treatment once a day for five consecutive days. The trial will be conducted at the "Hospital del Mar" in Barcelona (Spain) and the "Hospital Sant Joan de Déu de Manresa" in Manresa (Spain). The Borg scale at baseline and days 1 to 5 will be the primary outcome. Secondary outcomes will be the duration of the hospitalization, quantity of drugs administrated, expiratory peak flow adverse effects and mortality and readmissions at 3 months.

Discussion: AcuTENS is a non-pharmacological, non-invasive and inexpensive intervention. This trial will help to elucidate the potential role of acuTENS in the treatment of AECOPD.

Trial registration: ClinicalTrials.gov identifier: NCT02998957. Recruitment status: Recruiting. First posted: 21 December 2016. Last update posted: 2 October 2018. Trial registration dataset is available in Additional file 1. Protocol version 03. Issue date: 20 March 2018. Author: Carles Fernández.

Keywords: AcuTENS, Acupuncture, COPD, AECOPD, Dyspnoea, Randomized control trial, Protocol

Background

Chronical obstructive pulmonary disease (COPD) is characterized by persistent and progressive airflow limitation associated with a chronic inflammatory response in the airways and lung parenchyma to noxious particles or gases [1]. COPD is a major cause of morbidity and mortality worldwide and its prevalence is expected to increase over the next decade because of continuous exposure to risk factors and the aging of the population [2]. It is estimated that in 2030 COPD will be the fourth leading cause of death globally [3]. Currently, the prevalence of the disease in Spain is 10.2% of the population between 40 and 80 years of age [4].

Dyspnoea, along with chronic cough and sputum production, is one of the main symptoms of COPD. Its severity and magnitude increase as the disease progresses and this disease is the main cause of disability and reduced quality of life in patients with COPD [5].

Patients may experience periods of acute exacerbation of COPD (AECOPD), defined as "a sustained worsening of the patient's condition, from the stable state and

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beyond normal day-to-day variations, which is acute in onset and necessitates a change in regular medication in a patient with underlying COPD" [6]. These can be particularly severe exacerbations requiring hospitalization. In Spain, it is estimated that hospitalizations for AECOPD have an average cost of 344.96 euros per person per day [7], most of which is due to stays in hospital. These exacerbations are associated with 12% of mortality and 35% of readmissions up to 3 months after discharge [8].

Treatment of AECOPD includes bronchodilators, corticosteroids, antibiotics, oxygen therapy and non-invasive mechanical ventilation [9]. In the case of severe dyspnoea, oral or parenteral administration of opioids is recommended, although these have side effects and can cause respiratory depression [5]. However, dyspnoea remains a major symptom in patients hospitalized for an AECOPD [7].

The acupoint transcutaneous electrical nerve stimulation (AcuTENS) is a modern technique based on traditional acupuncture. It involves the stimulation of acupuncture points by using transcutaneous electrical nerve stimulation (TENS) instead of needles, which makes it a very-easy-to-learn, non-invasive method without the traditional acupuncture adverse effects such as infections or puncture of internal organs [10].

Several clinical studies using AcuTENS in patients with COPD have recently been published. All studies have used the stimulation of the acupuncture point named Dingchuan (EX-B1), traditionally used to treat dyspnoea. In those studies, a decrease in dyspnoea and an increase in forced expiratory volume in 1 second (FEV 1), β-endorphin level and quality of life have been observed [11–13]. However, these studies have been conducted on patients in stable condition, and little is known about the possible effect of this technique in patients with an AECOPD. Only one case study suggesting possible benefits for shortness of breath besides an increase in the level of oxygen saturation and β-endorphins has been published to date [14], and properly designed randomized placebo-controlled trials are needed to confirm these results.

The objectives of this study are to determine whether the use of AcuTENS at the Dingchuan point (EX-B1) could be beneficial for patients hospitalized for AECOPD by reducing dyspnoea, days of hospitalization, and consumption of regular medication. Moreover, we will assess possible adverse effects of this technique and its effect on mortality and readmissions at 3 months after discharge.

Trial design

This is a multicentre, randomized controlled trial with blinded patients and assessors with a 1:1 allocation and two parallel groups. Trial registration dataset and SPIRIT 2013 checklist are available in Additional files 1 and 2.

Methods

Study setting

The study will be performed at the "Hospital del Mar" in Barcelona (Spain) and the "Hospital de Sant Joan de Déu de Manresa" in Manresa (Spain).

Participants

The study subjects will be patients admitted at the study centres for an AECOPD. Participants will be recruited at the time of their admission by the pulmonology service and hospital emergency staff by using the following inclusion criteria: (1) patients between 45 and 75 years of age with a diagnosis of COPD in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, (2) patients with one episode of hospitalization for COPD exacerbation in the past year but not more than three episodes, (3) smoking habit history of more than 10 packs a year, (4) patients able to correctly understand and answer the modified Borg scale, (5) patients with an initial degree of dyspnoea with a score of at least 5 in the modified Borg scale at recruitment, (6) patients recruited for the study during the first 48 h of hospitalization, and (7) patients who agree to participate in the study and sign the informed consent form.

Exclusion criteria will be (1) patients with any contraindication for transcutaneous electrical stimulation (patients with pacemakers, skin injury in the application area, etc.) and (2) patients with any cardiovascular, neurological or psychiatric disease that may affect the perception of dyspnoea.

Interventions

In both groups, the Dingchuan point (EX-B1) will be localized bilaterally at 0.5 "cun" from the midline between the posterior spinous processes of C7 and T1 (Fig. 1). Afterwards, a conductive plastic sheet between the skin and the electrodes will be placed. These sheets have a hole of about 0.5 cm in diameter, which will coincide with the point above. Finally, the electrodes will be fixed with tape.

In the AcuTENS group (experimental), the stimulation is performed by using a portable TENS electrostimulation device (Sale & Service TN23) that uses a biphasic rectangular wave with a frequency of 2 Hz and a pulse width of 200 mS. The stimulation will be achieved by using the highest intensity tolerated by the patient without pain.

The TENS simulated group (control) will have electrostimulators that are the same make and model as the experimental group but that have been modified to have no electrical outlet, even though the screen will light up and display the same data as in the unmodified device. Patients in this group will be informed that, owing to the frequency of stimulation, it is unlikely they will feel the electric stimulation.

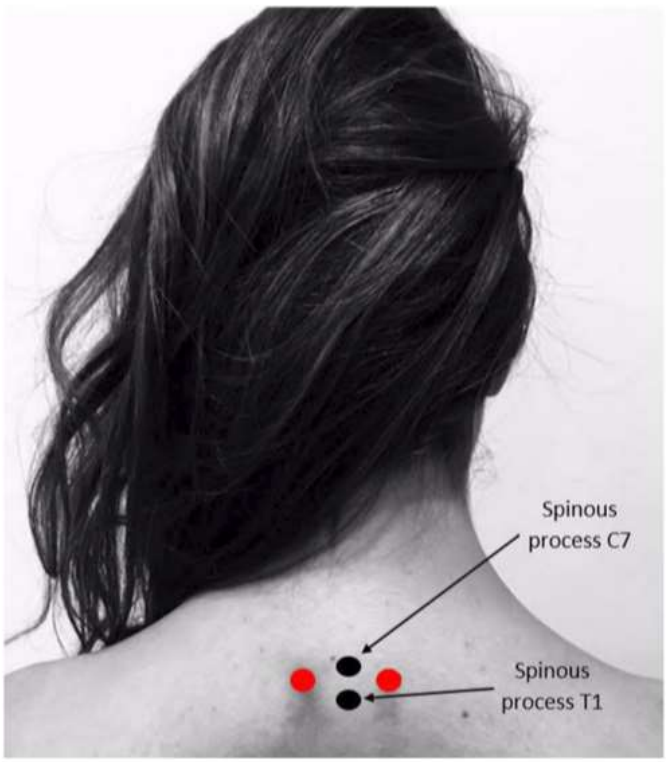

Fig. 1 Location of Dingchuan acupuncture point

In both groups, the session will last 45 min and will take place during a maximum of five consecutive days or until the patient is discharged.

If the acuTENS stimulation produces any kind of discomfort, the intensity of the current being applied to the patient will be reduced. If for any reason a treatment cannot be administered or is administered differently from the original protocol (e.g., only 30 min of treatment because the electrostimulation device had no battery), this will be reported. Any discomfort or skin reaction will be reported as an adverse event.

The interventions will be performed by physiotherapists or physicians who have a minimum of one year of clinical experience and who have been trained in the handling of the two treatment protocols. There will be a pre-pilot test to detect potential problems and ensure the adequacy of the implementation of the protocols.

Adherence to the treatment will be reported. No special stages for improving adherence will be taken since all patients will be hospitalized in the participating centres.

Both groups will receive the standard treatment for patients with AECOPD (bronchodilators, steroids, etc.) in accordance with medical criteria as well as the treatment with acuTENS or simulated acuTENS. No treatment is prohibited.

Outcomes

Primary outcome measure

The primary outcome of this trial will be dyspnoea using the modified Borg scale. Evaluators will show a printed Borg scale to patients and explain the meaning of each punctuation and then patients will be asked to rate their dyspnoea. Data will be assessed at baseline and after each treatment session (days 1 to 5). Differences will be assessed by comparing groups' mean scores at each day (days 1 to 5). The modified Borg scale is a valid and reliable assessment tool for dyspnoea in patients with an AECOPD [15].

Secondary outcome measures

Hospitalization length will be measured by using the number of days from the time of admission until the patient's discharge. Scores will be compared by using mean differences between groups.

Peak expiratory flow will be assessed by using a peak flow meter and using litre per minute units at baseline and after each treatment session. For each assessment, peak flow will be measured three times and only the highest score will be considered. Differences will be assessed between groups by using mean scores at each day (days 1 to 5).

Adverse events will be recorded after each treatment session; the evaluator will ask the patient for any adverse event related to the intervention. Description of each event and its frequency will be described for each group.

Blood gas analysis—partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide ($PaCO_2$), arterial blood pH, bicarbonate and oxygen saturation (SaO_2)—at days 1 to 5 will be recorded if available in the patient's clinical history since no specific analysis will be made for the trial. Differences will be assessed by comparing means at each day (days 1 to 5).

Relapse and readmissions at 3 months after discharge will be assessed by using the participant's clinical history. Mean number of relapses and readmissions during the 3-month period after discharge will be compared between groups.

Mortality will be assessed by using the ratio of patients who died during the 3-month period after discharge in each group.

Quantity of drugs administered during patient's hospitalization will be extracted from the patient's clinical history. Mean dosages will be compared between groups. Data will be collected by using a standard form designed by the study investigators, and database entry will be double-checked.

Participant timeline

Participant timeline is described in Fig. 2.

Randomization and allocation

Participants will be randomly assigned to the acuTENS or sham acuTENS group with a 1:1 allocation by using a computer-generated randomization list. A blocked randomization list will be generated for each centre by the main author, who will not be involved in recruitment or assessment. Randomization lists will be kept by using an electronic key and will be available only to the persons responsible for administering the treatments.

Once participants give consent for participation, a consecutive number will be assigned by the head of recruitment, and the staff responsible for administrating the treatment will match the patient's number with the randomization list to define the patient's allocation.

Blinding

Trial participants, outcome assessors and usual care providers will be blinded during the trial, and only the physiotherapists who will perform the acuTENS or sham acuTENS procedure will know the patient's allocation. To ensure that they remain blinded to allocation, the medical

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	day_1	day_2	day_3	day_4	day_5	*3 months*
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
INTERVENTIONS:								
AcuTENS			X	X	X	X	X	
Sham AcuTENS			X	X	X	X	X	
ASSESSMENTS:								
Dyspnea	X		X	X	X	X	X	
Duration of hospitalization								X
Quantity of drugs administrated	X		X	X	X	X	X	
Adverse effects or disadvantages	X		X	X	X	X	X	
Peak expiratory flow	X		X	X	X	X	X	
Blood gas analysis	X		X	X	X	X	X	
Mortality								X
Readmissions								X

Fig. 2 Schedule of enrolment, interventions and assessments

staff will not be present during the application of technology. There will be no circumstances under which unblinding is permissible. Data analysis will be performed by a blinded external statistician.

Sample size

Considering a minimal clinically important difference regarding dyspnoea, measured by the Borg scale, of 2 [16] and assuming a common standard deviation of 2.6, an α error of 0.05, a β error of 0.2 and a 10% rate of losses, we calculate that we will need to recruit 60 patients for this study. To reach this target sample size, pulmonology service and hospital emergency staff will be informed so they can detect possible candidates.

Statistical methods

There will be a descriptive analysis of the demographic data by using means and standard deviations (mean ± standard deviation) for continuous variables and absolute values and percentages for qualitative outcomes.

For the comparative analysis between the two groups, continuous outcomes (such as Borg scale score and number of hospitalization days) will be analysed by using mean differences with a 95% confidence interval with a Student *t* test or Mann–Whitney *U* test depending on the distribution of these. For dichotomous outcomes (such as mortality at 3 months), risk ratio will also be used with a confidence interval of 95% and chi-squared test.

The main analysis will be carried out by intention to treat, but there will be another per-protocol analysis for patients who have received at least three interventions. A *P* value of less than 0.05 will be considered significantly different.

In case of missing data, last value carried forward methods will be used. In case of significant baseline differences between the two groups, there will be an adjusted analysis for these outcomes.

Discussion

This protocol describes the design of a clinical trial investigating the effectiveness of adding acuTENS stimulation to usual treatment of dyspnoea in patients hospitalized with an AECOPD. If the results of this trial are positive, a new non-pharmacological and inexpensive intervention could be used in cases of intense dyspnoea. Moreover, dyspnoea improvement could lead to a reduction in medication and hospitalization days, reducing hospitalization costs. It is also important to highlight that this is quite a simple intervention to learn and TENS devices are usually available in any health centre; this is important as it would facilitate the technique's implementation and generalization.

Trial status

Protocol Admen Number: 03. Issue date: 20 March 2018. Recruitment start day: 1 April 2018. Estimated recruitment completion date: June 2020.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-3757-x.

Additional file 1. Trial registration dataset.

Additional file 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*.

Abbreviations

AcuTENS: Acupoint transcutaneous electrical nerve stimulation; AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; COPD: Chronical obstructive pulmonary disease; TENS: Transcutaneous electrical nerve stimulation

Acknowledgements

Not applicable.

Authors' contributions

CF-J has been responsible for writing the protocol of the study and the submission of the manuscript. JV helped with the study design and the sample size calculation. Both authors contributed to the refinement of the study protocol and approved the final manuscript.

Funding

This work was supported by a grant from the Professional College of Physiotherapists of Catalonia and the Scientific Society of Acupuncture of Catalonia and the Balearic Islands. Funders had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Availability of data and materials

The datasets used or analysed (or both) during this study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This protocol was approved by the research ethics committee of each centre (identification codes 2018/8153/I and CEI 17/97), has been registered in ClinicalTrials.gov (NCT02998957) and will be published in open access. All protocol modifications will be informed to all lead investigators and reported in the final manuscript. All patients will be informed about the nature of the study, its objective, and the possible adverse effects of the treatments as well as their voluntary participation. All patients must sign an informed consent form. The patients will be able to leave the study whenever they want without any detriment to their health care. The data collected during the study will be treated in accordance with the LOPD, Regulation (EU) n°2016 / 679 of the European Parliament and European Council on data protection (RGPD) that came into force on 25 May 2018. Data monitoring is not needed as the treatment used is expected to have a low safety risk. For the same reason, no interim analysis or stopping guidelines or post-trial care and compensations are considered. No additional insurance was needed for this trial since the TENS device is regularly used in the rehabilitation department. Results of the trial will be disseminated via publication. Authorship eligibility will be considered in accordance with the International Committee of Medical Journal Editors criteria. A professional writer will be used to review the final manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Published online: 11 December 2019

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Publisher's Note

Annex 4: Hospital de Manresa research ethics committee approval

INFORME DEL COMITÉ ÉTIC D'INVESTIGACIÓ

Dr. Miquel Nolla, com a President del Comitè d'Ètica d'Investigació de la FUNDACIÓ UNIO CATALANA HOSPITALS

C E R T I F I C A:

Que aquest Comitè en la seva reunió del dimarts, 27 de febrer, ha avaluat la proposta per que es realitzi l'estudi que porta per títol *"Eficàcia d'electorestimulació transcutania del punt Dingchuan (EX-B1) en pacients amb MPOC hospitalitzats amb disnea severa: Estudi amb control aleatoritzat i cegament de pacients i avaluadors."*, amb codi CEI 17/97 i considera que:

Es compleixen els requisits necessaris d'idoneïtat del protocol en relació amb els objectius de l'estudi i que estan justificats els riscos i les molèsties previsibles per al subjecte. La capacitat de l'investigador i els mitjans disponibles són apropiats per portar a terme l'estudi. Són adequats tant el procediment per obtenir el consentiment informat com la compensació prevista per als subjectes per danys que es puguin derivar de la seva participació a l'estudi.

Que aquest comitè accepta que aquest estudi es digui a terme a **Althaia, Xarxa Assistencial Universitària de Manresa**, amb **Amalia Martinez** com a investigadora principal. I que la investigadora principal no ha estat present en les deliberacions i aprovació d'aquest estudi.

En aquesta reunió s'han complert els requisits establerts en la legislació vigent – Orden SAS/347/2009, RD 1090/2015. El CEI tant en la seva composició, com en els PNT compleix amb les normes de BPC (CPMP/ICH/135/95).

MEMBRES DEL CEI DE LA FUNDACIÓ UNIÓ CATALANA D'HOSPITALS

Dr. Miquel Nolla	President	Metge
Dra. Anna Altés	Secretari	Metge
Dra. Encarna Martinez	Vocal	Metge
Dr. Ernesto Mònaco	Vocal	Metge
Dr. Jesús Montesinos	Vocal	Metge
Dr. Josep M Tormos	Vocal	Metge
Dra. Rosa Morros	Vocal	Farmacòloga Clínica
Dra. Concha Antolin	Vocal	Farmacèutica primària
Dra. Virginia Martinez	Vocal	Farmacèutica
Dr. Jaume Trapé	Vocal	Farmacèutic
Sra. Conxita Malo	Vocal	Infermera
Sra. Ana Barajas	Vocal	Psicòloga
Sra. Itziar Aliri	Vocal	Advocat
Sra. Anna Guijarro	Vocal	Filosofia
Sra. Vanessa Massó	Vocal	C. Empresarials

Barcelona, 19 de març de 2018

Comitè Ètic

Dr. Miquel Nolla
President del CEI

Annex 5: Hospital del Mar research ethics committee approval

CONFIRMATION

I hereby certify that "Parc de Salut MAR - Ethic Committee of Research" has reviewed and approved

- ✓ The clinical study entitled: *"Efficacy of transcutaneous electrical stimulation at Dingchuan (EX-B1) in hospitalized COPD patients with severe dyspnoea: Randomized placebo control trial, patient and assessor blinded "*.

In which Dr. Diego Agustín Rodríguez Chiaradía is the principal investigator.

- ✓ And the corresponding patient information sheet and informed consent form.

Under the reference number: 2018/8153/I

At the meeting of: September 12, 2018

COMITÉ ÉTIC D'INVESTIGACIÓ
CEIC - PARC DE SALUT MAR

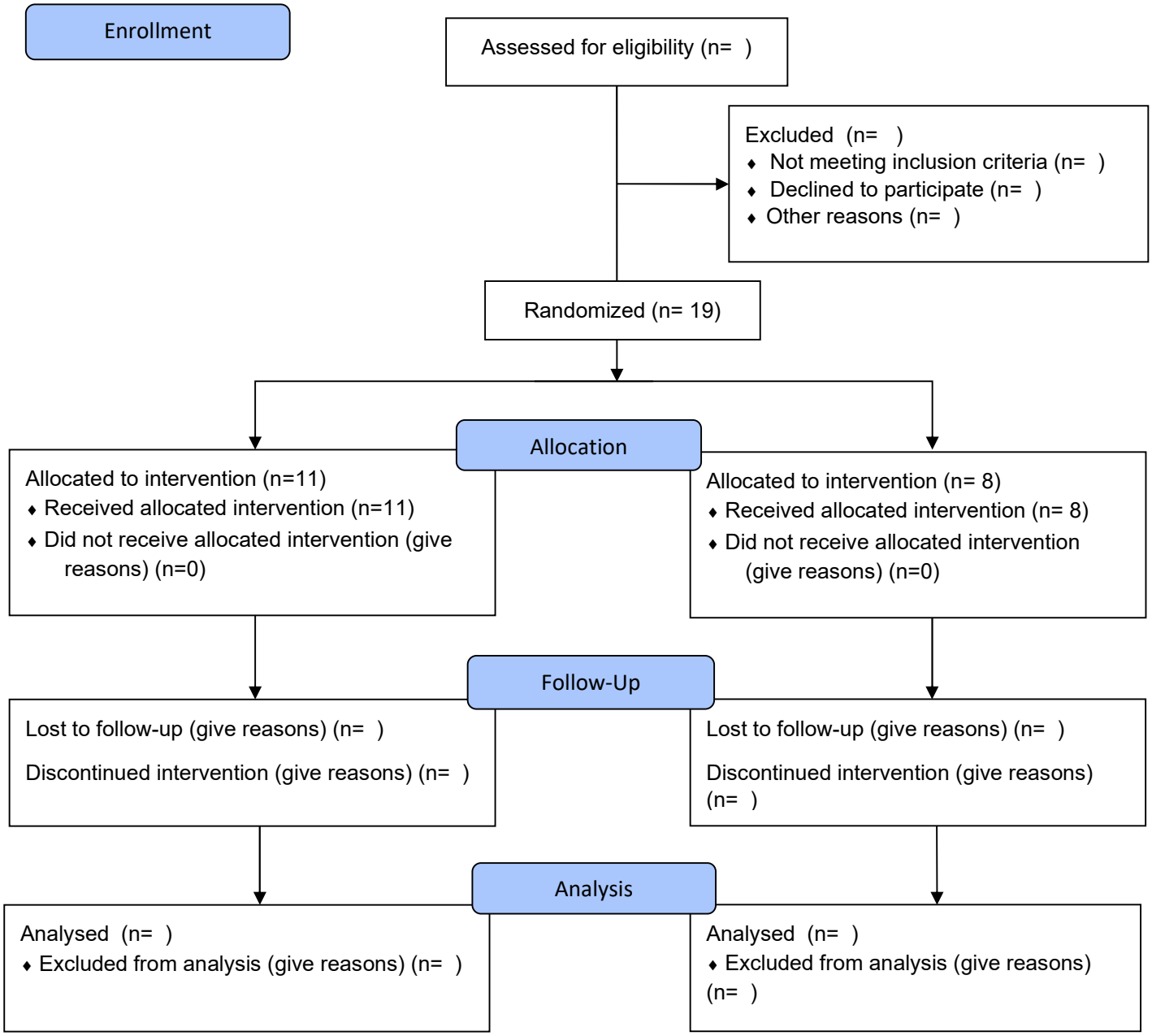
Cristina Llop Julià
Secretary
Ethic Committee of Research
Parc de Salut MAR

Barcelona, November 28th, 2018

Annex 6: Preliminary results of AcuTENS for acute COPD exacerbations RCT

Recruitment started on February 2017 and has not finished. To date 19 participants, of the 60 needed for the trial, had been analysed (Figure 1). Preliminary results based on the 19 participants how had completed the trial are shown below.

Figure 1: CONSORT 2010 Flow Diagram



Characteristics of the participants, 11 in the AcuTENS and 8 in the Sham AcuTENS groups, who had completed the trial are summarised in Table 1.

Table 1: Participants baseline characteristics

Characteristics	AcuTENS n=11	Sham AcuTENS n=8
Age(yr), mean (SD)	62.4 (7.7)	71.3 (3.4)
Missing, n	0	0
Males, n (%)	5 (45.5)	6 (75.0)
Missing, n	0	0
BMI (kg/m^2), mean (SD)	29.78 (13.86)	29.62 (6.95)
Missing, n	2	0
Severity, n (%)		
GOLD 1	1 (9)	0 (0)
GOLD 2	1 (9)	0 (0)
GOLD 3	4 (36)	5 (62.5)
GOLD 4	3 (27)	1 (12.5)
Missing, n	2 (18)	2 (25)
Last FEV_1 (mL), mean (SD)	775.45 (242.37)	775.00 (343.0)
Missing, n	0	0
Smoking status, n (%)		
Smoker	9 (81.8)	7 (87.5)
Ex-smoker	2 (18.2)	1 (12.5)
Non-smoker	0 (0)	0 (0)
Missing, n	0	0
Pack-years, mean (SD)	45.75 (21.37)	76.92 (24.17)
Missing, n	1	1
Borg	6.91 (1.57)	7.62 (1.40)
Missing, n	0	0
PEF	126 (51.6)	120 (46.59)
Missing, n	1	0
Blood gas, mean (SD)		
PaO_2	57.40 (14.27)	85.42 (35.38)
Missing, n	3	1
$PaCO_2$	58.58 (19.74)	56.34 (15.51)
Missing, n	3	1
SaO_2	88.48 (10.63)	89.60 (13.94)
Missing, n	4	1
Bic	35.16 (11.80)	30.36 (4.19)
Missing, n	3	2
pH	7.37 (0.06)	7.35 (0.09)
Missing, n	3	1

Primary outcomes

Results of dyspnoea changes at days 1 to 5 in both groups is shown in Table 2. No statistical differences are observed between groups however, this could be due the small number of participants included.

Table 2: Dyspnoea changes

	AcuTENS		Sham AcuTENS			
	n	Mean (SD)	n	Mean (SD)	Difference (95% CI)	P Value
Borg						
Day 1	11	6.45 (1.50)	8	7.00 (1.40)	-0.54 (-2.21, 1.12)	0.493
Day 2	11	5.45 (1.21)	7	6.00 (1.15)	-0.54 (-1.77, 0.68)	0.3551
Day 3	11	4.91 (1.70)	7	5.57 (1.27)	-0.66 (-2.15, 0.83)	0.3606
Day 4	10	4.10 (2.07)	7	4.14 (2.11)	-0.04 (-2.28, 2.19)	0.9676
Day 5	9	4.44 (1.81)	6	4.33 (1.86)	0.11 (-2.03, 2.25)	0.911

Secondary outcomes

Secondary outcomes are summarized in Table 3. Although some differences between groups are observed, with only 19 included participants, statistical power is too low to show significant results.

No adverse events were reported during the intervention by any of the 19 participants.

Table 3: Results of secondary outcomes

	AcuTENS		Sham AcuTENS			
	n	Mean (SD)	n	Mean (SD)	Difference (95% CI)	P Value
Hospitalization length, (days)	11	14.81 (19.86)	8	19.87 (19.84)	-5.06 (-24.69, 14.57)	0.5915
Re-admission	10	0.5 (0.70)	8	1 (1.19)	-0.5 (-1.55, 0.55)	0.3185
PEF						
Day 1	10	126 (51.68)	8	120 (46.59)	6,00 (-43.26, 55.26)	0.7993
Day 2	10	115.00 (59.11)	7	132.85 (41.51)	-17.85 (-69.88, 34.16)	0.4757
Day 3	11	126.36 (55.36)	7	140.00 (41.63)	-13.64 (-62.42, 35.15)	0.5609
Day 4	10	133.00 (52.08)	7	155.71 (46.85)	-22.71 (-74.61, 29.18)	0.3636
Day 5	9	141.11 (53.72)	6	150.00 (32.24)	-8.89 (-56.93, 39.15)	0.6957