# Efectividad clínica de las intervenciones con ozono

## Clinical effectiveness of ozone interventions. *Full text.*

**INFORMES, ESTUDIOS E INVESTIGACIÓN 2008**
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JUNTA DE ANDALUCIA
CONSEJERÍA DE SALUD

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# Executive abstract

**Title:** "Clinical effectiveness of ozone therapies"
**Authors**: Silvia Vidal Serrano and Teresa Hermosilla Gago

**Introduction**

The ozone used for therapeutic purposes (medicinal ozone) is a mixture of up to 95% oxygen (O2) and 5% ozone (O3). Ozone therapy entails a technology that is currently in use for the treatment of a broad range of diseases and is becoming more widely known in the medical community. This treatment is not exempt from risks which may, in certain cases, become quite severe. As a result of this, and in view of a previous report published by AETSA in 2003 on ozone therapy for herniated disc, an abridged report intended to examine the information currently available on the effectiveness of interventions with ozone for therapeutic purposes has now been drawn up.

**Methods**

Current literature was reviewed. Search strategies were run on MEDLINE, EMBASE and CINAHL. Other information sources reviewed included Tripdatabase, The Cochrane Library, Centre for Reviews and Dissemination (CRD), Evaluation Agencies belonging to the *International Network of Agencies for Health Technology Assessment* (INAHTA), web pages related to the topic and a manual search in references in relevant work and specialized journals.

The CRD check list was used to evaluate the validity and methodological quality in each study.

**Results**

The search strategy pinpointed 167 documents and 82 full texts were retrieved for review. Of these, 56 complying with the inclusion criteria set were included, namely 8 clinical trials, 10 quasi-experimental studies, 1 retrospective cohort study, 26 case studies, 3 systematic reviews, 1 evaluation report, 1 technical report, 1 narrative review and 5 clinical cases. In all, the documents included cover 13 diseases where ozone is being applied for therapeutic purposes, namely, asthma, dental caries, patellar chondromalacia, Menière´s disease, gonarthrosis, lower limb arterial ischaemia, temporomandibular joint diseases, spinal diseases, musculoskeletal soft tissue disease, athlete's foot, tendon disease, head and neck tumours and diabetic ulcer.

The quality of the methods used in the original papers is low. The main methodological limitations found include, amongst others: inappropriate randomisation of treatment groups; unclear definition of inclusion criteria and population characteristics; neither blinding of outcomes' assessors nor of participants; non-validated measurement scales; patients lost to follow up, or withdrawing from the study were unspecified; no description was provided on statistical analysis; and differences in treatment between compared groups unrelated to the study intervention.

Almost half of the documents examined focus on the effectiveness of ozone in the treatment of different spinal diseases, mainly lumbar disc herniation. The outcomes reported could not be combined for analysis as a result of the disparity in clinical conditions and the poor methodological quality of the studies.

Between 32.3% and 83.2% of patients with herniated discs reported disappearance and / or improvement in pain. Other outcomes indicate: that ozone is more effective than corticoids in the treatment of painful shoulders, than systemic antibiotic therapy in diabetic patients with ulcers and than prostacyclins in arterial ischaemia. Ozone is a good alternative to antifungal treatment for ringworm of the foot, and to the conventional treatment for tendonitis.

As for the safety of this technology, many studies provide no reports on adverse effects, while the most serious effects were published as case reports. Severe or life-threatening adverse effects included: one vertebro basilar stroke, one acute bilateral vitreo-retinal haemorrhage, one meningeal irritation, and the cause of deaths was arterial gas embolism in five cases.

**Conclusions**

Ozone has been attempted in the treatment of several different diseases, mainly for pain control in traumatological pathologies, mainly herniated disc.

No clinical trial or other type of study was found that provide good quality evidence.

The studies examined present a high bias probability.

Outcomes should be considered with caution given the poor methodological quality of the assessed studies in spite of the large number of the studies that reported good outcomes after applying ozone therapy. The effectiveness of ozone in the conditions studied can not be determined by the evidence currently available.

The use of ozone for therapy is not exempt of risks and adverse effects.

This report upholds the conclusions drawn in the first report drafted by the Andalusian Agency for Healthcare Technology Assessment in 2003 on the effectiveness and efficacy of ozone in the treatment of disc herniation, the low quality of the available scientific papers, and insufficient scientific evidence.

# Introduction

The term ozone comes from the Greek term *ozein,* "to have a smell", due to the fact that ozone is a pale blue, strong-smelling gas[a].

Ozone can be found in its natural state in the upper layers of the atmosphere forming what is commonly known as the "ozone layer". This layer is of vital biological importance as it mitigates the effects of ultraviolet radiation. However, on ground level, ozone is a highly toxic contaminant which is harmful to living beings as it damages cell membranes, mainly due to its powerful oxidising action. In humans, inhalation of this ozone, albeit at low concentrations, seems to be involved in the onset of respiratory symptoms in susceptible subjects, such as in asthmatic children[1].

Artificially obtained ozone is mainly used as a sterilising agent in many industrial applications, such as food preservation, whitening of fabrics and waxes, etc.

Ozone for therapeutic purposes (*medicinal ozone*) is actually a mixture of up to 95% oxygen and 5% ozone. Although ozone is known to have been used in medicine since the beginning of the 20th century, its use for therapeutic purposes in humans began to spread following the First World War when it was used to disinfect wounds.[2]

The ozone used in medicine is produced by devices known as ozone generators. An ozone molecule (O3) is formed when one oxygen molecule ($O_2$) bonds with a free oxygen atom. Free atoms and, as a result, ozone are the product of the breakdown of oxygen molecules when subjected to a strong, high-voltage, high-frequency electrical discharge. These devices give rise to ozone concentrations of between 1 and 100 mcg per ml of oxygen that vary according to the therapeutic purpose intended. These generators have not been authorized by the Food and Drug Administration (FDA), but are considered and regulated as healthcare products within the European Union.

Ozone may be administered in different ways with different techniques, depending on the disease it is being used to treat. The main techniques are as follows:

Autohaemotherapy (AHT). This entails extraction of between 50 and 250 ml of venous blood from the patient which is then mixed with blood

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a Ozone. (From Greek ὀζειν, to have a smell). n. Chem. Allotropic state of oxygen, produced by electricity. Its action gives rise to a highly oxidising gas, with a strong seafood smell, which turns blue when it becomes liquid. It is found in small proportions in the atmosphere after storms. Translation of entry in Diccionario de la Lengua española (Spanish Language Dictionary). Twentieth edition.

outside the body either in a bag or vial and is then transfused or injected through intramuscular injection into the patient.

- Ozonation and extracorporeal oxygenation of blood. This entails mixing blood with ozone in a closed circuit, using a technique that is similar to haemodialysis. It is different from AHT in that a higher volume of blood can be treated with ozone in the same session.
- Infiltrations. Ozone is injected either inside or around the joint, subcutaneously or inside the inter-vertebral disc, etc.
- Insufflation. Ozone gas is insufflated through a line into the rectum, vagina, bladder, pleura, peritoneum etc. Insufflation can also be administered under pressure in baths of mineral-medicinal water.
- Local. Ozone is insufflated inside an accessory or plastic bag that is placed around the area to be treated. Creams and oils containing ozone are also available, such as ozonated sunflower oil.

Many biological properties have been attributed to ozone, such as an anti-inflammatory or immune-modulating capacity, etc.

There are many medical areas and diseases where ozone therapy has been applied, from infectious diseases (tuberculosis, HIV infection, sinusitis, rhinitis, etc), orthopaedic disorders and injuries to degenerative or vascular disease, etc[3,4].

For several years now, ozone therapy has been used in different countries around the world, mainly Italy, Russia, Germany and Cuba. This technology is becoming more widespread. For instance, according to industry data regarding the number of devices sold up to June 2004, in the United Kingdom around one million people are estimated to have received ozone to treat dental caries. These data published in a systematic review[5] contrast sharply with the conclusions of the review on the lack of available evidence on effectiveness and cost-effectiveness of this technology.

In Spain, ozone is in clinical use mainly in the private medical sector, where no details of the number of patients treated to date are available Also, ozone therapy has been seen to arouse interest among citizens, which confirms the growing dissemination of this technology over the past few years. A fairly high percentage of requests (12/171, 7%) received from Citizens' Information Line by the Andalusian Agency for Healthcare Technology Assessment (AETSA) since May 2005, in fact referred to ozone therapy.

In 2003, the Andalusian Agency for Healthcare Technology Assessment (AETSA) published an assessment report [6] which concluded that the scientific evidence available to date is both insufficient and of too low a quality to enable the effectiveness of ozone therapy in the treatment of herniated disc to be considered as proven.

In this context, AETSA has identified a research topic of particular interest, namely **"Clinical Effectiveness of Interventions with Ozone"**, given its implications, expectations raised and the controversy raised over the past few years on its use in medicine. As a result, a proposal was made to the Spanish Ministry of Health and Consumer Affairs to conduct this research as a project within the framework of a collaboration agreement for the implementation of the Quality Plan for the National Health System.

## Aim

To summarise and analize the information available of the effectiveness of interventions using ozone for therapeutic purposes.

# Methods

Firstly, a search for general information was performed to give an outline for the study topic through Clinical Evidence, Best Evidence, Medscape and Critically Appraised Topics.

Afterwards, a systematic review was conducted starting with a search in published scientific literature as follows:

- Specialised search engines: TripDatabase, Scirus, SUMSearch and OMNI.
- Consultation on the main reference data bases (MEDLINE,EMBASE and CINAHL) as well as other data sources such as: The Cochrane Library (*The Cochrane Database of Systematic Reviews* and *The Controlled Trials Register)*, Current Contents, Centre for Reviews and Dissemination (CRD) and the clinical trials data base ClinicalTrials.gov.
- Searches on each of the Healthcare Technology Assessment Agencies belonging to the International Network of Agencies for Health Technology Assessment (INAHTA), as well as other bodies and institutions related to technology assessment that are not members of INAHTA.
- Identification of associations, specialised centres and scientific societies on Google.
- Secondary review of the bibliography appearing in the relevant literature retrieved together with a manual search on the contents of specialised journals and grey literature.

The steps involved in the bibliography search process together with the list of the main sources of information used are shown in **Appendix I**.

Two search strategies were used for the search on the MEDLINE, EMBASE and CINAHL databases. On the one hand, we applied the same strategy as was designed for the previously published report on herniated disc and ozone, but limiting the search to the period between January 2003 and June 2006. On the other hand, a new strategy was set for the period encompassing January 1999 to June 2006. Details of the search strategies used are provided in **Appendix II.**

The documents were selected according to the following inclusion and exclusion criteria:

# Inclusion criteria

**Types of studies**: meta-analysis, systematic reviews, clinical trials, cohort studies, cases series and before and after studies. Other documents, such as healthcare technology assessment reports and clinical practice guidelines were also taken into account.

**Types of participants**: People of both sexes regardless of their health problem.

**Types of intervention**: ozone alone or combined with another intervention) drug therapy, physiotherapy, etc).

**Types of outcome measures:**

Morphological changes.

Changes in the main symptoms and signs of the disease.

Changes in functional status.

Changes in quality of life.

Patient satisfaction.

Adverse effects: for this parameter, any study was included regardless of design and number of cases reported.

# Exclusion criteria

Experimental animal studies:

Studies conducted on environmental ozone.

Applications for ozone other than therapeutic purposes (for instance, beauty treatments).

Series of cases including fewer than 10 patients in follow up.

Opinion or narrative articles, letters to the editor, editorials and conference summaries.

Documents published in languages other than English, French, Italian and Spanish.

In the initial stages, the inclusion and exclusion criteria were used to select those documents that were to be retrieved in full text version according to the citation and/or abstract. Where there was no abstract or where there was any doubt on inclusion, the documents were also retrieved in full text version so that they could be assessed against the selection criteria.

The main outcomes and methodological quality of each paper were compiled in a summarised table. The validity and methodological quality was examined according to bias probability while the Centre for Reviews

and Dissemination (CRD) model devised at the University of York [7] was used as a checklist. The quality of the systematic reviews was assessed using the guideline by the UK National institute for Clinical Excellence [8].

# Results

In all, 135 citations and/abstracts were retrieved from the electronic databases MEDLINE, EMBASE and CINAHL, with 115 remaining after screening for duplicates. Thirty three articles were selected to be retrieved in full-text version; one of these could not be retrieved [9], which left a total of 21 final documents. A technical report, a healthcare technology assessment report and three systematic reviews were also found. Three documents on technology assessment were excluded.

Forty four articles were selected from the manual search conducted in specialised journals. Of these, 30 were included in this review after reading the full-text version.

The causes for exclusion of the citations and/or references are provided in Appendix III (table 1) together with the full-text documents retrieved from the data bases and from the manual search.

In all, 50 documents were included, namely, 8 clinical trials, 10 quasi-experimental studies, 1 retrospective cohort study, 26 cases series, 3 systematic reviews, 1 assessment report and 1 technical report. Besides these, a further 6 articles were included (1 narrative review and 5 clinical cases) which provide a description of adverse effects. It must be remembered that the same selection criteria in terms of study design were not applied in this section.

Through the documents consulted, a total of 50 disorders were identified (Appendix IV) where ozone therapy is applied even though the articles selected for review and applying with the inclusion and exclusion criteria set, cover 13 diseases in all, namely asthma, dental caries, patellar chondromalacia, Menière´s disease, gonarthrosis, lower limb arterial ischaemia, temporomandibular joint disease, spinal diseases, musculoskeletal soft tissue diseases, athlete's foot, tendon disease, head and neck tumours and diabetic ulcer.

The articles selected were all of poor quality. The main methodological flaws noted in the eight clinical trials are related to either uncertain or doubtful randomisation, absence of blinding for outcome evaluators and patients and uncertainty on the comparability of the groups at the start of the study.

Insufficient or missing information on the following topics were the main methodological flaws affecting the validity in most of the studies assessed: inclusion criteria, population characteristics, patients lost to follow-up or who withdrew from the study and statistical analysis of the outcomes. The outcomes reported were descriptive in most cases and either no contrasting hypothesis was made or no proof of statistical significance was provided.

The two systematic reviews on the effectiveness of ozone in preventing central dental caries were of good quality while the study on ozone in rheumatic disease was of medium quality.

The most important characteristics of the studies included (except the papers on adverse events), as well as the assessment of the methodological quality of each document individually are all shown in Appendix V.

Below a description is given of the outcomes reported in the papers reviewed according to diseases to facilitate appraisal of these outcomes.

# 1. Spinal disease

Almost half of the documents assessed deal with ozone treatment in various spinal diseases. Most of these (19/26) focused exclusively on ozone treatment for herniated disc. The remainder of the papers included patients with low back pain or neck pain, secondary to different spinal diseases, while one article included only patients with spondylolisthesis. As had already been mentioned, all the articles examined are of poor quality and present major methodological limitations.

## 1.1 Herniated disc

Disc herniation occurs when a disc is displaced beyond the inter-vertebral space. Hernias are more common in the lumbar region of the spine. Clinically, a herniated disc is characterised by mechanical-type pain (worsening on exertion, coughing, laughing, etc) that may radiate to the glutei, legs and feet (lumbar sciatica). Other symptoms that may appear due to nerve impingement range from tingling, numbness, loss of sensitivity to motor disorder, etc., while in more advanced cases weakness and muscle atrophy may also be present.

Most of the articles reviewed address the effectiveness of ozone therapy in the treatment of herniated disc in the lumbar and/or lumbosacral region. Of the remaining articles, three focus on cervical hernia [10-12] and one included patients with cervical or lumbar hernia [13].

In terms of study design, 3 studies were quasi-experimental, there was 1 retrospective cohort study, 14 case series and one systematic review.

## Population

In general terms, the inclusion criteria for the patients studied encompassed back pain refractory to conservative treatment (medical and/or physiotherapy) and signs of herniated disc confirmed by CT and/or nMRI. The minimum duration of pain refractory to conservative measures among the patients studied ranged from a question of days to years, according to the various studies.

Most papers included patients with hernias located at various levels. Three papers included patients with a single hernia [14-16]. The kind of hernia included varies with each study, ranging from non-contained hernias [17-19] to contained hernias[20,21] The remaining studies use another kind of classification, such as prolapse, protrusion, extrusion, migrated hernia, etc.[12-14,22,23] or provided no specific classification[10,11,15,16,24,25]

Different exclusion criteria were used in each of the studies, i.e. while some included calcified hernias[23] or spinal canal stenosis[26], other papers excluded this kind of lesion. Most papers excluded patients with signs of severe neurological motor deficit, except for two, namely, the Paradiso[14] paper had no clearly defined inclusion criteria, while in the Alexandre study[10], 78.99% of the patients studied had motor deficits with differing degrees of severity.

Lastly, while some papers include patients with recurrent herniated disc after undergoing spinal surgery[20,21,23], others exclude patients with previous hernia surgery.[17-19]

## Intervention

Ozone infiltrations are applied under either fluoroscopy and/or CT guidance in most of the studies involving inter-vertebral (or intra-discal) disc cases. In some studies, infiltrations are combined with injections at other sites close to the disc (paravertebral musculature, paraspinal space, periganglionic...). In one of the papers [13] the patients with cervical hernia are treated with intradiscal ozone while patients with lumbar hernias are treated with bilateral paravertebral infiltrations.

The dose and concentration of ozone given varied from one study to another, with dosage ranging between 1.5 and 20 ml and concentration from 10 to 40 mcg ozone /ml oxygen. There was no consistency in the number of sessions either, for instance, in some studies a single session was given, in others a given number of sessions was set for each of the patients[11,13,15]. In

some papers, only a certain percentage of the patients recruited received more than one session, but the criteria for repeat ozone injections were not specified [18,22,24,25].

As for the additional medication taken by patients to control pain symptoms, only two studies[10,13] specifically state that oral corticoids cannot be combined with ozone therapy. In other papers, either local and/or systemic corticoids are combined with ozone [11,12,16,21,25,27] and in one study, patients were allowed to take non-steroidal anti-inflammatory drugs (NSAIDs) but this parameter was not considered as an outcome.

## Outcome Measures and outcomes that the studies included

**Pain**

As the most important symptom of disc disease, pain was measured in all the studies reviewed.

The instruments used to assess pain include the standard[25] or modified Mac Nab method[11,12,15,20-24,27] and the Visual Analog Scale (VAS)[14,17-19] No study specified the validation of these scales in the original language. In five studies [10,13,16,26] no description was provided on the measurement scale used.

Bearing in mind the longest follow-up period for each study, the percentage of patients with total pain resolution ranged from 32.2% to 83.2% for lumbar hernia patients and between 57% and 94% for cervical hernias.

Patients with little or no improvement to their pain symptoms ranged between 2.5 and 50% in lumbar hernia cases, and between 0% and 24% in cervical hernias

Follow-up time and outcome appraisal differ between studies from between 2 months and 3 years. In those papers measuring outcomes at different time points, a drop is seen over time in the percentage of cases with total recovery from pain or diminished pain [14,24]. For instance, the Paradiso paper mentions 98% of cases at 4-6 months which drops to 85.3% at 3 years while the paper by Venza refers to 87.6% at week one and 83.2% at 6 months. Conversely, in another study[25], there was a higher percentage of cases with no pain at 12 months (39.17%) than after the first week of treatment (28.17%).

According to hernia type, to whether the fibrous ring is spared or not (contained and non-contained herniated disc respectively), the outcomes for complete recovery and improvement to pain seem to be better in non-contained hernia cases[14,17-19]

According to two papers[21,23], each with a fairly high number of patients, the percentage of cases where pain symptoms were resolved is similar in patients with a single hernia to that seen in patients with hernias at different levels. Also, the worst outcomes, according to one study[23], are seen in patients with recurrent herniated disc after surgery, with calcified herniated discs and with herniated disc and spinal canal stenosis (% of treatment failure in 35%, 45% and 50%, respectively).

Three quasi-experimental studies and one retrospective cohort study, all of low quality, compared ozone with other therapies. The outcomes for resolution or improvement to pain are detailed in the table below:

| Reference | Methodological Quality | Outcome (months) | Resolution or improvement in pain (%) | | p |
|---|---|---|---|---|---|
| | | | Ozone | Ozone + corticoids | |
| Andreula[20] | Low | 6 | 70.3 | 78.3 | <0.05 |
| | | | Ozone | Ozone+ other therapies | |
| Arena[15] | Low | np | 65.6 | 75.9 | Np |
| | | | Ozone | Surgery | |
| Buric[17] | Low | 18 | 90 | 93.3 | Nd |
| Paradiso[14] | Low | 36 | 79.3 | 85.3 | Np |
| Nd: no differences; Np: not provided | | | | | |

In the study by Andreula[20], there was a higher percentage of patients where treatment failed (minor improvement to pain or case referred for surgery) in the group treated with ozone alone compared with the group receiving ozone therapy and corticoids ( 29.7% vs. 21.7%). Also, Arena[15] found that the percentage of cases without improvement to their pain symptoms was similar in both treatment arms (5.1%% vs. 5 %). In the remaining papers[14,17] the number of cases where treatment did not bring about any change in pain symptoms was not provided.

**Disability or functional limitations**

The degree of disability or limitations experienced by patients for activities of daily living was studied in three papers using the Roland Morris [17,19] and the Oswestry questionnaires[16]. In the papers published by Buric[17,19], there was improvement in disability in 90% of the patients, with statistically significant differences compared with pre-treatment status ($p<0.001$). In the last study[16], improvement was noted in the degree of disability secondary to both sub-acute and chronic lumbar pain.

**Sensory and motor dysfunction**

These symptoms were reported in four of the papers examined[10,13,14,18] and were assessed in two[18,39] using the Japanese Orthopaedics Association (JOA) scale.

In the paper by Buric[18], an overall improvement was seen in the JOA scale compared to baseline in 54.7% of the patients. In the paper by Alexandre[1], complete regression of sensory dysfunction was seen in around 80 % of the cases, and of motor dysfunction in 62% of cases. Lastly, Paradiso[149] reported complete regression of sensory dysfunction at 3 years in 80.4% of ozone-treated cases, with similar outcomes in the group treated by surgery (82.5%). Complete remission of motor dysfunction was also similar in both groups (85.7% vs. 86.65%). In the article by Alvarado[13], the percentage of cases recovering sensitivity after treatment was higher is patients with cervical hernia than in patients with lumbar hernias (94% and 68%, respectively).

**Satisfaction with treatment**

Patients' satisfaction with treatment was assessed by Buric in all three of his studies[17-19]. The mean for satisfaction at 12 and 18 months is 79.3% ±28,7 in two of the studies[17,19]. In the paper[11] comparing ozone with surgery, no significant differences were noted between both treatment groups. The third paper[18] shows a mean improvement of 71.77% from baseline at 18 months.

**Morphological changes**

Some papers examined the reduction in herniated mass by CT and/or MRI [10,14,17-19,22,23] . While some authors assess this parameter as a percentage of reduction in herniated mass compared with baseline, others provide no definition of percentages of reduction and show very disparate outcomes, as seen in the table below:

| | Alexandre[10] | Buric[19] | Buric[17] | Buric[18] | He X[22] | Muto[23] | Paradiso[14] |
|---|---|---|---|---|---|---|---|
| Time (months) | 7 | 3-5 | 3-5 | 5 | 3 | 6 | 12 |
| % reduction in herniated mass | Ns | >50 | >50 | >80 | Ns | ns | 100 |
| % success ful cases | 39.6 | 47% | 53.3 | 37% | 3.7 | 63 | 57.3 |
| ns: not specified | | | | | | | |

Lastly, a systematic review was also included in this section[28] on the role of ozone therapy in the treatment of musculoskeletal diseases. This review includes 6 studies, 5 on herniated discs and 1 on Raynaud's syndrome. This last study has not been taken into account as it failed to meet the inclusion criteria for the number of patients considered for this review (n≥10). Two of the studies on disc herniation were reviewed in the previous report and the remaining two [20,23] have been appraised in this report. This review emphasises the poor quality and high probability of bias in the clinical trials examined.

## 1.2. Spondylolisthesis with spondylolysis

The underlying lesion in spondylolysis is a defect or rupture of the vertebral arch lamina. Spondylolisthesis, or forward displacement of one vertebra on the adjacent one, is the most common sequella from spondylolysis. The main symptom of this condition is lumbar pain which may radiate to the gluteal region and down to the lower limbs.

A case series was retrieved[29] including 18 patients with grade I spondylolisthesis and spondylolysis. Of the 18 patients, 72.2% showed no pain 6 months after the ozone infiltration.

## 1.3. Other painful conditions of the spine (low back pain and/or neck pain)

In this group, we provide a description of papers assessed that focus on ozone therapy in the treatment of lower back pain or neck pain secondary to a series of different spinal diseases. Herniated disc is among the disorders included in these studies in all cases except for the clinical trial, while none of the remaining studies provide outcomes in disease-related subgroups.

## Low back pain

Low back pain or pain in the lumbar region is a common condition and is as a major cause for healthcare consultation, leading to limitations in working and personal activities. Around two thirds of the adult population suffer from back pain at some time in their lives[30]. Lumbar pain can radiate to the leg (sciatica) or not (simple lumbar pain). According to the persistence, pain can be classed as acute, sub-acute or chronic (>12 weeks). No underlying cause is found in a high percentage of cases. The effectiveness of ozone in the treatment of back pain was examined in two of the case series [31,32], one clinical trial[33] and two healthcare technology assessment reports [34,35]. These studies include patients with pain secondary to a pre-established cause (herniated disc, spondylolysis, disc degeneration, etc). None of the papers retrieved focussed on lower back pain that was either non-specific or of unknown cause.

In the Moretti et al case series[31], the subjects were divided into two groups according to whether they required one cycle (high responders) or two cycles of ozone infiltrations (low responders) to achieve a significant decrease in their pain symptoms. In both groups, a significant decrease in pain was seen ($p<0.05$) after completion of the treatment compared with previous status and was maintained up to 12 months after treatment.

Another case series included elderly patients with chronic lower back pain secondary to degenerative spinal diseases[32]. Thanks to ozone infiltration, 34% of the patients were both pain free and able to return to activities of daily living at one-year follow-up.

The clinical trial retrieved [33] compared peri-radicular corticoid injection with intraforaminal injection of ozone in 3406 patients (166 with disc disease and 140 with non-disc related spinal disease). Although, in general terms, the percentage of patients in complete remission of their pain was higher in the ozone-treated group, the differences only achieved significance in the group of patients with disc disease at 6-month follow-up (74.4% vs. 57.5%, $p<0.021$).

The short technical report[34], conducted by the Instituto de Efectividad Clínica Sanitaria (IECS) in the city of Buenos Aires, assessed the effectiveness of ozone therapy for spinal disc disease. In all, 15 relevant studies were originally included in this report even though only seven were thoroughly examined later. The authors concluded that the outcomes achieved from the reviewed papers were part of poor quality studies, meaning that no conclusions regarding the effectiveness and safety of ozone therapy in the mid- and long-term could be extrapolated.

AVALIA-t[35] issued a report intended to evaluate the efficacy/effectiveness and safety of ozone therapy in herniated disc and other painful diseases involving the lumbar region. In this report, in all 13 documents have been found and examined (1 clinical practice guideline (CPG), 1 short technical report, 1 RCT and 10 case series). All the documents except for the RCT have been included and examined in the present report. The CPG[68] included is the Spanish version of the GPC on non-specific lower back pain drawn up in the framework of the European programme COSTB13. In this version, ozone therapy is not recommended in the absence of any study on the efficacy and effectiveness of this treatment.

### Neck pain

Neck pain secondary to spinal disease may be accompanied by other symptoms when the nerves are compromised, i.e. numbness, tingling or weakness in the hand or arm, etc.

One paper[37] focusing on patients with neck pain secondary to herniated disc, disc degeneration, etc., compared two groups of patients, namely one treated with paravertebral ozone and the other with injections of a mix of anti-inflammatory drugs, muscle relaxants and local anaesthetic. The percentage of patients who became pain-free was higher in the ozone treated group (30 % vs 14%). This percentage remained higher in the ozone-treated group at 12-month follow-up.

## 2. Bronchial Asthma

Asthma is a chronic respiratory disease characterised by obstruction of the airway that can be reversed either spontaneously or with treatment. This disease has a high prevalence and can develop with long-lasting cough, dyspnoea, wheezing, and chest tightness feeling.

The only study selected for review[38] in a quasi-experimental study that recruited 113 subjects diagnosed with extrinsic asthma, divided into three treatment arms, namely group 1 and group 2 who received ozone with major autohaemotherapy above a dosage of 4 mg and 8 mg, respectively; and group 3 treated with rectal insufflations of ozone. Among the outcomes reported, a improvement was seen in pulmonary function (forced expiratory volume and forced vital capacity) after treatments compared with baseline. This improvement was statistically significant in the group treated by

autohaemotherapy at the 8 mg dosage and in patients treated with rectal insufflations. An improvement of symptomatology (dyspnoea and wheezing) and a reduction in the rescue medications were also reported.

# 3. Dental caries

Caries are perforations that damage the structure of teeth and are a very common disorder and the most frequent cause of tooth loss in young people.

Two systematic reviews [5,39] and 2 clinical trials [40,41] were retrieved.

The reviews included randomised clinical trials (RCT) with a follow-up of at least 6 months addressing the effectiveness of ozone therapy in the treatment of dental caries. The method for application of the ozone used for dental caries is known as "HealOzone". This procedure entails direct application of the gas on the dental surface followed by a re-mineralising solution and dental hygiene materials (toothpaste, mouthwash and fluoride spray.

The Cochrane review[39] examined three RCTs that were also evaluated in the later systematic review undertaken by Brazelli et al.[5] We shall provide here comments on the main results of this latest review both because it is a more recent publication and because it also includes a systematic review on economic assessment.

Five full-text RCTs were retrieved and examined together with five further trials published as abstracts in conference proceedings. The effect on ozone of primary carious lesions of the root was studied in two full-text RCTs and in one abstract. Three full-text RCTs and four abstracts addressed ozone treatment for the management of pit and fissure caries.

The studies on primary, non-cavitated carious lesions (only one of which was published) achieved high success rates as regards the decrease in the degree of severity of the lesions treated with ozone at 12 and 18 months. The low percentages seen in lesions not receiving ozone should be stressed. The effect of ozone on the pit and fissure caries was addressed in three full-text RCTs (none of them published) that formed part of two PhD dissertations. Two of the full-text studies examined failed to show any major benefit for ozone in the treatment of non-cavitated and cavitated lesions compared with non-treatment. All this contrasts sharply with the outcomes reported in the conference abstracts that refer to high success rates (from 86.6% to 100% in the reversal of caries). Lastly, one full-text trial also found a major drop in the severity of non-cavitated lesions in primary dentition in children aged 7 to years.

The economic assessment was based on the analysis of an unpublished document issued by the manufacturer of the equipment used for ozone application in the dental field (HealOzone). This analysis was limited given that no evidence on the effectiveness nor any information on long-term adverse effects was provided.

No quantitative summary of the studies' outcomes was drawn from either of the two reviews retrieved due to the differences between the two studies in terms of the intervention, dosage and outcome measures used. In both reviews, the RCTs examined were classed as low quality.

The two clinical trials found in our search were not included in the reviews examined. One of them was excluded [40] due to the follow-.up time under 6 months and the other [41] due to publication after the bibliography search date. This last report failed to meet the inclusion criteria set in the reviews retrieved since outcomes were measured before 6 months had elapsed after therapy.

The paper by Baysan and Lynch[40] is a clinical trial where 70 primary root caries were randomised to treatment with ozone for 10 or 20 seconds. Half of the lesion was used as the control group. In both treatment arms, a significant decrease was noted in the number of micro-organisms compared with controls. A greater reduction was seen in smaller, non-cavitated and less severe lesions. The grade of severity compared to pre-treatment status also decreased in 92% of the lesions treated with ozone.

The other trial [41] compared with effect of ozone in non-cavitated fissure caries in permanent dentition in 41 patients with two contra-lateral lesions who were randomised to be treated with ozone or to receive no treatment. At three months, the authors found significant differences in the number of reversed lesions or lesions with signs of halted progression in the subgroup of patients at high risk for caries.

# 4. Patellar chondromalacia

Patellar chondromalacia is the softening and degeneration of the cartilage found under the patella. Symptoms affecting the knee area include sensitivity, pain and a sensation of rubbing or friction on extension.

The only study found [42] compared ozone treatment with no treatment in patients who had persistent pain and functional limitations following surgery for this condition. Both the time (days) for disappearance or improvement of pain and recovery of mobility were lesser in the group receiving ozone.

## 5. Menière´s disease

This inner ear condition affects balance and hearing and is mainly characterised by the onset of vertigo, dizziness, loss of hearing and ringing in the ears (tinnitus).

A small series of patients with Menière´s disease[43] were treated with inhaled ozone combined with pressure massage of the tympanic membrane. The outcomes for audiometric parameters showed no significant improvement although patients reported a subjective improvement of their symptoms after therapy.

## 6. Gonarthrosis

Gonarthrosis, arthrosis or osteoarthritis of the knee involves progressive degeneration of the cartilage in the knee that causes pain and progressive functional disability.

One quasi-experimental study[44] compared the effectiveness of ozone therapy against hyaluronic acid infiltration in patients with bilateral gonarthrosis. In the same patient, one knee was treated with ozone and the other with hyaluronic acid. The outcomes referred to improvement to pain, to functionality and stiffness in both knees vis à vis pre-treatment status, with no differences seen between the two therapies.

## 7. Chronic lower limb arterial ischaemia

Atherosclerosis is the main cause of chronic lower limb arterial ischaemia or peripheral artery disease. The main symptom of this condition is pain that appears progressively on walking that fades at rest (*intermittent claudication*). The condition is classified in four stages of lesser to greater severity according to the severity of the obstruction.

The four studies selected included 2 case series, 1 quasi-experimental study and 1 clinical trial recruited patients with intermittent claudication and/or lower limb ulcers.

- The clinical trial[45] compared ozone with i.v. prostacyclin for the treatment of ulcerous lesions in patients with stage IV Fontaine lower limb arterial ischaemia. After completion of therapy (7

weeks), the area and degree of severity of ulcers had decreased in the ozone-treated group. A significantly greater improvement was also seen in the ozone group as regards certain related symptoms (intermittent claudication, itching, heavy legs, quality of life and joint pain)

- The quasi-experimental study[46] included a small sample of dialysis patients with Fontaine grade II intermittent claudication, who were given 9 treatment sessions with oxygen (placebo) and then 9 sessions with ozone. The distance walked without pain and the maximum distance that could be covered were both greater in the ozone treatment group versus placebo, with significant differences ($p<0.03$ and $p<0.03$, respectively). There was a higher percentage of patients reporting subjective improvement after ozone treatment than after placebo (90% vs. 40%, $p<0.025$).
- Tylicki[47] studied dialysis patients with Fontaine grades II, III and IV intermittent claudication. The results reported show that 91.6% (11/12) of the patients reported improvement to their pain, with a clear or very clear improvement in 7 patients (58.3%). The mean distance patients were able to cover without experiencing pain was greater after treatment compared with baseline ($p=0,01$).
- Luongo[48] recruited patients with intermittent claudication, Fontaine grades III and IV, with ulcerous lesions; 35 out of the 63 patients also had Type 2 diabetes mellitus. The results show an improvement in all outcomes (pain, walking, peripheral artery pressure) compared with pre-treatment scores. The percentage of full ulcer healing was higher among the diabetic patients.

# 8. Temporomandibular joint (TMJ) disease

Under this heading are all disorders involving the TMJ and that can cause symptoms such as jaw clicking, inability to open the jaw fully and pain either in the jaw, teeth or face, etc.

One case series [49] of patients with different diseases involving the TMJ received intra-articular infiltration. The outcomes reported 1 month after treatment were as follows: pain symptoms disappeared entirely in 11 out of the 19 patients (57.9%) with menisco-condylar alterations; a clinical benefit was seen in 12 patients with osteoarthrosis and/or osteoarthritis while there was only limited benefit for the only patient with avascular osteonecrosis.

# 9. Athlete's foot, or ringworm of the foot

Ringworm of the foot or athlete's foot is a fungal infection. The most common symptom is cracked or flaking skin that sheds between the toes.

In a randomised clinical trial [50] conducted by Menéndez et al in patients diagnosed with athlete's foot or *tinea pedis*, the effectiveness of ozonated sunflower oil was compared with a conventional topical antifungal (Ketoconazol). At 6 weeks of treatment, no significant difference was noted between the two treatments in terms of cure (disappearance of lesions with negative culture), (75% vs. 81%, p=0.570). At 6 months, on completion of the therapy, the patients treated with ozone cream had no recurrence while 4% of the patients in the antifungal-treated group experienced recurrence of their lesions.

# 10. Tendon disease

This section contains articles addressing the effect of ozone on different conditions involving the tendons. A tendon may be injured by a sharp blow that leads to rupture or laceration or by repetitive overload.

Five articles were examined in all, two of these (1 clinical trial and 1 quasi-experimental study) addressed patients with different conditions. As for the remaining papers, one clinical trial and 1 quasi-experimental study focused on painful shoulders and a further paper (case series) on jumper's knee.

## 10.1. Lateral humeral epicondylitis or tennis elbow

Eighteen patients with humeral epicondylitis secondary to repeated injuries were treated with ozone infiltrated around the tendon[51]. The authors reported that the ozone injections in the lesion led to improvement or disappearance of the pain in 61 % of patients.

## 10.2. Painful shoulder

Ikonomidis ST et al[52] conducted a clinical trial in patients with a painful should secondary to rotator cuff tendonitis where one group received corticoid infiltrations and the other ozone infiltrations. The outcomes reported reflect a shorter overall rehabilitation time for the ozone-treated group (56.1 vs. 131.2 days) and a higher non-responder rate in the group treated with corticoids (18% vs. 7.24%).

One quasi-experimental study [53] with a small sample size included patients with painful shoulders secondary to a lesion in the supraspinous tendon; here therapy with ozone infiltrations was compared with injections of a mixture of vasodilators and local anaesthetic (mesotherapy). At 60 days, treatment was successful in 67% of the ozone-treated patients and in 54 % of patients in the other treatment arm. There was also a greater improvement to joint function in the ozone-treated group.

## 10.3. Acute or chronic tendonitis

One study conducted on patients with tendonitis[54] (acute or chronic) at different sites compared ozone therapy on the affected tendon with classic treatment (non-steroidal anti-inflammatory drugs and rehabilitation). At the end of treatment and at 6-weeks follow-up, there was a higher absolute number of patients who remained symptom free in the ozone-treated group.

This paper also considered 12 patients with patellar tendonitis and 44 with supraspinous tendonitis (or tendonitis of the rotator cuff). However, given that the outcomes for these groups are not provided separately, they have not been described in the section addressing these two conditions specifically.

## 10.4. Patellar tendonitis or jumper's knee

One series [55] was considered that included 38 athletes diagnosed with painful patellar tendinitis limiting sports practice who were treated with ozone infiltrations around the tendon. Good outcomes were achieved in 71% of the patients; at 10 weeks alter starting therapy, 75% of these patients were symptom free.

## 10.5. Tendon conditions and impingement syndromes

One paper addressed patients[56] with pain secondary to tendon conditions and impingement syndromes at different sites. Two treatment groups were set up, one treated with ozone infiltrations and another with injected anti-inflammatory drugs. In terms of pain, the outcomes reported in both groups were compared according to lesion site. In patients with painful shoulders, the improvement to pain compared with pre-treatment levels was significantly greater in the ozone-treated group compared with the NSAID-treated group. For other sites, no significant differences were found between the two therapies. Pain at the injection site, allergic reactions and recurrence of pain were reported in the NSAID-treated group. No adverse effects were reported for the ozone-treated group.

# 11. Painful disorders of skeletal soft tissues

This section refers to a heterogeneous group of painful conditions of the peri-articular soft tissue, muscle, tendons, etc. secondary to different causes.

One recent article[57] reported clinical response in pain following ozone infiltration in a total of 141 patients with different skeletal soft-tissue conditions (osteoarthritis, sprains, painful heel). The outcomes at two months of therapy are provided according to conditions, with the percentage of patients reporting either the disappearance or significant improvement to their pain ranging between 71.4% and 93.3%.

Overall at two months, the percentage of patients reporting relief or improvement to their pain was higher than at 6 months (85% and 70%, respectively).

# 12. Head and neck tumours

This term encompasses different kinds of cancer, where the course depends largely on the original site. The most common head and neck cancer is squamous cell carcinoma and the main treatments involve radiotherapy, surgery and chemotherapy.

One quasi-experimental study[58] that considered patients with advanced stage (Stage IV) head and neck tumours was reviewed. All patients were given

hypofractionated radiotherapy and/or hyperfractionated radiotherapy and daily chemotherapy (5-fluorouracil). Two patient groups were set, one to receive intravenous chemotherapy and the other to receive ozone therapy via autologous blood transfusion and/or oral insufflations. There was a greater clinical response in the irradiated area in the chemotherapy group and longer overall survival in the ozone-treated group, although none of these differences were significant.

## 13. Diabetic ulcer

Diabetic foot ulcers are wounds that usually occur on the sole of the foot in diabetic patients.

Treatment with ozone applied by rectal insufflation and topically was compared in one clinical trial[59] with antibiotic therapy in patients with Type 2 diabetes mellitus with ulcers on their feet and lower limbs. The decrease in the affected area and the perimeter of the ulcer was significantly greater in the ozone-treated group (p 0.017 and 0.004, respectively). Significant decrease in hospital stay was also noted in the ozone treated group. There were no significant differences in the percentage of patients cured in each group. Biochemical parameters were also measured, such as the level of glycaemia and other by-products of oxidative stress, using 50 healthy controls. Both groups experienced improvement in blood sugar levels compared with baseline.

# Adverse effects associated with ozone therapy

This section provides a compilation of the different adverse effects related to ozone treatment and described in the articles appraised. The side effects reported may be related to administration technique, administration route, concentration of ozone administered, etc.

Also, given that there is a broad clinical use of ozone, any study reporting adverse effects has been included for appraisal, regardless of design and number of cases reported.

The side effects described below were reported in four of the studies reviewed on the effectiveness of ozone in herniated disc.

Andreula[20] described the onset of reduction of sensitivity in the legs of two patients in the group treated with ozone and corticoids that remitted

in two hours. He XF[22] remarked that some patients reported a feeling of local heat and slight pain during the ozone injection that remitted in a short space of time. In the study by Ying WZ[25], five patients reported lumbar or leg pain after the ozone injection that resolved spontaneously; and eight patients showed mild corneal irritation and reversible dyspnoea after the administration of oxygen. Lastly, D'Aprile[26] reported a haematoma at the ozone infiltration site in one patient.

The following side effects were reported in two articles studying ozone applied in auto-haemotherapy for the treatment of lower limb artery ischaemia, namely 4 patients reported the sensation of itching on lips and tongue at the end of the session[46], 3 patients described nausea and a bad taste in the mouth during re-infusion of ozonated blood[46,47] while one patient suffered dyspnoea during the administration of therapy[46]. Lastly, the onset of euphoria was another side effect described after the application of ozone using the oxygenation and extracorporeal ozonation of blood in 15 patients treated for skin lesions secondary to arterial ischaemia. When ozone was administered by rectal insufflation, cases of bloating and constipation were reported[58].

Severe side effects reported and also related to intradiscal application of ozone to treat hernia included the following: one vertebrobasilar stroke[60], one acute bilateral vitreo-retinal haemorrhage[61] and one case of meningeal irritation[62.] In a recent article[63] one case of gas embolism was reported in the peri-ganglionic venous plexus involving the vertebrobasilar artery which manifested clinically as local pain for several minutes that cleared in a few days.

In one case series[64] three cases of viral hepatitis with the same virus C genotype were reported in patients undergoing auto-haemotherapy or intramuscular injection of ozone in the same time period.

Finally life-threatening effects were reported in 5 patients, four of which were mentioned in the three narrative reviews3,4,65 and one in a case report66. The five patients died as a result of a gas embolism after administration of ozone by direct intravenous injection and one further death following ozone application by auto-haemotherapy to treat psoriasis.

# Discussion

One of the main results stemming from this report is that ozone is being used to treat a broad range of different conditions, although never, in general terms, as first-line therapy.

Pain is the most frequently studied symptom, both pain related to injury and the characteristic pain of chronic lower limb arterial ischaemia. Ozone has also been applied as an attempt to halt and/or reverse dental caries and to control other symptoms related to such different conditions as bronchial asthma or Menière's disease.

Most papers reviewed in this report have been conducted in Italy (around 55%) which may be accounted for by the widespread implementation of this technology in the country. Other countries (Cuba, Russia, Germany, etc), have undertaken studies that have not been included in this report, either because the papers were published in non-indexed journals or were excluded on the basis of language criteria. As for Spanish papers, two of the articles included had a Spanish group taking part [10] while another [58] was conducted entirely in Spain.

## Spinal disease

Almost half of the documents reviewed focus on the application of ozone in diseases involving the spine. Intervertebral disc herniation particularly in the lumbar region features in a number of articles. It should however, be pointed out that most of the papers examined are observational studies with no control group.

The different methodological flaws (absence of blinding for participants, outcome evaluators, etc.) together with the issue of heterogeneity (population, technique used, etc. ) in the different studies make it impossible to draw conclusions on the effectiveness of this treatment in disc herniation, despite the favourable outcomes of ozone therapy reported in many of such studies.

The only clinical trial [32] identified on the effectiveness of ozone therapy for lower back pain secondary to different spinal conditions (herniated disc, osteoarthritis, spondylolisthesis, etc) has poor internal quality. In this trial, the method used to ensure blinded randomisation is not clearly specified, casting some doubt on the randomisation process. Also, the patients were not blinded and the degree of comparability between both groups at the

beginning of the study is unknown.

This report has conducted a qualitative analysis of the outcomes given the poor methodological quality of the publications and the high degree of heterogeneity between papers. All the above made it impossible to devise a summary together with a statistical appraisal of the outcome data set.

The previous report issued by AETSA on ozone[6] in the treatment of herniated disc revealed that the evidence supporting the use of ozone in this condition was of poor quality. As for the quality of the studies examined here, the results in this report are consistent with other systematic reviews conducted on this same topic [28,34,35].

## Other conditions

The remaining publications are devoted to a wide range of diseases from asthma to dental caries. As for study design, there are two systematic reviews on dental caries, seven clinical trials (dental caries [40,41], painful shoulder[52], chronic lower limb arterial ischaemia[45], athlete's foot[50], acute or chronic tendonitis [54] and diabetic ulcer [59]), seven quasi-experimental studies and seven case series.

The systematic reviews identified on dental caries are of sound methodological quality. Given the poor quality of the studies, however, none of these were able to draw definite conclusions on the effectiveness of ozone to halt the progression or reverse dental caries. The two clinical trials[40,41] examined in this report still present a high probability of bias linked to the absence of any information on the generation of the randomisation sequence, on the blinding of the assignments and of blinding patients and outcome assessors.

In view of the methodological flaws in the remaining clinical trials, we must cast some doubt both on the results obtained and on any conclusions to be drawn from them. In line with the conclusions of the authors themselves, with the currently available clinical evidence, ozone cannot be considered as a sound alternative to antifungal treatment in athlete's foot. Nor can it be considered as more effective than corticoids in treating a painful shoulder or than conventional treatment for tendonitis or to provide greater efficacy than systematic antibiotic therapy in diabetic patients with ulcers or to prostacyclins in peripheral artery ischaemia.

Apart from an inappropriate design to prove the effectiveness of an intervention, the remaining papers examined show major flaws in conception and methodological implementation.

# Safety

Adverse effects related to this technology have not been systematically investigated in the papers examined in this report. Only twenty report adverse effects. Most papers provide no data on the absence or presence of side effects derived from the administration of ozone.

The side effects that were reported in some of the papers examined are, mild, in general. Although most authors state that ozone therapy is a procedure with few adverse effects, we cannot overlook the severe and life-threatening effects that have been reported. The severe complications related to intradiscal or systemic application of ozone are published in the literature as case reports. Objective appraisal of adverse effects over an appropriate period is vital to assess the risk-benefit ratio for any treatment.

As for the limitations of this report, it is assumed that the mass reference databases MEDLINE and EMBASE have a language bias for the publications indexed. A further limitation lies in the inclusion criteria for articles according to language of publication that has led to the exclusion of publications identified. This may have had an impact on the kind and number of conditions ultimately included in the review.

To conclude, we are dealing here with a technology that has been rolled out and implemented without having first proven its effectiveness and safety. After several decades of ozone use for different clinical indications, the effectiveness and safety of ozone in medicine, in both the short and long term, remain unclear.

# Conclusions

- Ozone has been used the treatment of several different diseases, mainly for pain control in traumatological pathologies, specially to herniated disc.
- No clinical trial or other type of study was found that provide good quality evidence.
- The studies examined present a high bias probability.
- Outcomes should be considered with caution given the poor methodological quality of the assessed studies in spite of the large number of the studies that reported good outcomes after applying ozone therapy. The evidence currently available does not enable the effectiveness of ozone in the conditions studied to be determined.
- The use of ozone for therapy is not exempt of risks and adverse effects.
- This report upholds the conclusions drawn in the first report drafted by the Andalusian Agency for Healthcare Technology Assessment in 2003 on the effectiveness and efficacy of ozone in the treatment of disc herniation, the low quality of the available scientific papers, and insufficient scientific evidence.

# Recommendations

- Methodological studies are still needed to enable the clinical application and indications for ozone therapy to be either supported or rejected.
- The widespread use of ozone therapy, insufficient quality of the studies currently available, together with the severity of certain adverse effects indicate the need to devise strategies aimed at delivering sound quality information to both healthcare professionals and patients.
- The severity of certain adverse effects already published call for a review of current legislation regulating the use of ozone for therapeutic purposes.

# Appendices

## Appendix I: Literature search

**Search in Basic literature** (June 2006).

Clinical Evidence, Best Evidence, Medscape and Critically Appraised Topic

**Specialised search engines** (June 2006): TripDatabase, Scirus, SUMSearch and OMNI

**Data bases**

- Reference databases: Medline, Embase and Cinahl.
- The Cochrane Library (Issue 3, 2006): The Cochrane Database of Systematic Reviews and The Controlled Trials Register.
- Current Contents (June 2006)
- Effectiveness database (June 2006): NHS Centre for Reviews and Dissemination (CRD)
- Clinical trials data base (June 2006): ClinicalTrials.gov

**Healthcare Technology Assessment Agencies** (June 2006), included in the INHATA database in French, English or Spanish. And other technology assessment agencies and institutions not affiliated to INHATA.

**Websites** (accessed on 28/06/06 ) **for:**

**Scientific societies:**

- Cervical Spine Research Society: http://www.csrs.org/
- National Center for Complementary and Alternative Medicine (NCCAM): http://nccam.nih.gov/
- North American Spine Society: http://www.spine.org/index.cfm
- Sociedad Española de Cirugía ortopédica y traumatología: http://www.pulso.com/secot/index.html
- Sociedad Española del Dolor: http://www.sedolor.es/
- Sociedad Española del Raquis (o Grupo de estudio de enfermedades del raquis GEER): http://www.geeraquis.org/
- Sociedad Española de Reumatología: http://www.ser.es/
- Scoliosis Research Society: http://www.srs.org/

**Associations and centred related to this topic**

- Centro de investigaciones del ozono, Cuba: http://www.ozono.cubaweb.cu/
- European Cooperation of Medical Ozone Societies: http://www.

ozone-association.com/

- Hand search in contents of specialised journals (June 2006)
- Acta Neurochirurgica
- Acta Orthopaedica Scandinavica
- American Journal of Neuroradiology
- BMC Complementary and Alternative Medicine
- British Journal of neurosurgery
- Clinical Orthopaedics and Related Research
- European Spine Journal
- Interventional Neuroradiology
- Joint, Bone, Spine
- Journal of Neurosurgery
- Revue di Chirugie Orthopédique
- Rivista di Neuroradiologia
- Spine
- Rivista Italiana di Ossigeno-Ozonoterapia

# Appendix II: Search strategy

The search strategies run on the reference databases MEDLINE, EMBASE and CINAHL were as per edition by Ovid-Silver Platter and were consulted via the Winspirs interface (version 5).

The strategy to pinpoint documents related to ozone and spinal disease was identical to that used for the previously published AETSA report, as follows:

**MEDLINE** (2003-June week 1-3, 2006)
#1 "Sciatica-" / surgery ,therapy in MIME,MJME
#2 "Low-Back-Pain" / surgery ,therapy in MIME,MJME
#3 "Intervertebral - Disk - Displacement"/surgery, therapy in MIME, MJME
#4 spine or lumbar or sciatica or ntervertebral or vertebral or dis? or hernia* or "back pain"
#5 "Ozone-"/administration-and-dosage, dverse-effects, contraindications, poisoning, toxicity, therapeutic-use in MIME, MJME
#6 #5 and (#1 or #2 or #3 or #4)

**EMBASE** (2003- March 2006)
#1 spine or lumbar or sciatica or intervertebral or vertebral or dis? or

hernia* or “back pain”
#2 “low-back-pain” / disease-management, drug-therapy, surgery, therapy ,intraspinal-drug-administration
#3 “intervertebral-disk-hernia” / disease-management, drug-therapy, surgery ,therapy, intraspinal-drug-administration
#4 “ischialgia-” / disease-management, drug-therapy, surgery, therapy, intraspinal-drug-administration
#5 “ozone-” / all SUBHEADINGS
#6 #5 and (#1 or #2 or #3 or #4)

**CINAHL** (2003- May 2006)
#1 “Sciatica-“ / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE) #2 “Intervertebral-Disk-Displacement” / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#3 low back pain
#4 “Ozone-Therapy” / all TOPICAL SUBHEADINGS / all AGE SUBHEADINGS in DE
#5 (#1 or #2 or #3) and #4

The search strategy to pinpoint documents on the use of ozone in medicine began with a general search on Medline for ozone used using the term “ozone” as the key word (or Mesh).

#1 explode “Ozone-“ / therapeutic-use in MJME, MIME
#2 (tg=animals) not (tg=human)
#3 #1 not #2
#4(“Air-Pollutants-Environmental”/all SUBHEADINGS in MIME,MJME)or (“Environmental-Pollutants” / all SUBHEADINGS in MIME,MJME) or (“Environmental-Medicine” / all SUBHEADINGS in MIME,MJME
#5 #3 not #4

A catalogue of diseases where ozone is applied for therapeutic purposes was drawn up from the references retrieved, without any limitations on language. Later, a common search strategy for ozone was devised for the Medline database that was linked to a specific search for each clinical setting (or Mesh) using the Boolean “AND” link. The general exploratory search for ozone on the EMBASE database was not very productive and added few new sources of information to those already identified on MEDLINE.

**MEDLINE** (1999- June week 1-3, 2006)
#1 "Ozone-" / therapeutic-use in MIME,MJME
#2 ozone* in ti
#3 ozonetherapy or (ozone and therapy)
#4 ozone near5 ((treatment or therapy) in ti)
#5 oxygen-ozone
#6 #1 or #2 or #3 or #4 or #5
#7 (tg= animals) not (tg=humans)
#8 #6 not #7
#9 "Gastrointestinal-Hemorrhage" / surgery ,therapy in MIME,MJME
#10 #8 and #9
#11 "Peritonitis-" / surgery ,therapy in MIME,MJME
#12 #8 and #11
#13 "Myocardial-Ischemia" / surgery ,therapy in MIME,MJME
#14 #8 and #13
#15 "Anemia-Sickle-Cell" / therapy in MIME,MJME
#16 #8 and #15
#17 "Renal-Dialysis" / all SUBHEADINGS in MIME,MJME
#18 #8 and #17
#19 "Choroid-Diseases" / therapy in MIME,MJME
#20 #8 and #19
#21 "Thyroid-Nodule" / all SUBHEADINGS in MIME,MJME
#22 #8 and ("Thyroid-Nodule" / all SUBHEADINGS in MIME,MJME)
#23 "Sepsis-" / therapy in MIME,MJME
#24 #8 and #23
#25 "Tonsillitis-" / surgery ,therapy in MIME,MJME
#26 #8 and #25
#27 "Frontal-Sinusitis" / surgery ,therapy in MIME,MJME
#28 #8 and #27
#29 "Fasciitis-Necrotizing" / surgery ,therapy in MIME,MJME
#30 #3 and #29
#31 "Soft-Tissue-Infections" / all SUBHEADINGS in MIME,MJME
#32 #8 and #31
#33 "Osteomyelitis-" / therapy in MIME,MJME
#34 #8 and #33
#35 ("Otitis-Media-Suppurative" / therapy in MIME,MJME) or ("Otitis-Media-with-Effusion" / therapy in MIME,MJME)
#36 #8 and #35
#37 "Meniere's-Disease" / therapy in MIME,MJME
#38 #8 and #36
#39 ("Tuberculosis-Pleural" / therapy in MIME,MJME) or

("Tuberculosis-Pulmonary" / therapy in MIME,MJME)
#40 #8 and #39
#41 "Respiratory-Insufficiency" / therapy in MIME,MJME
#42 #8 and #41
#43 "Rhinitis-" / all SUBHEADINGS in MIME,MJME
#44 #8 and #43
#45 "Eczema-" / therapy in MIME,MJME
#46 #3 and #45
#47 "Migraine-" / therapy in MIME,MJME
#48 #8 and #47
#49 explode "Neoplasms-" / all SUBHEADINGS in MIME,MJME
#50 #8 and #49
#51 "Intermittent-Claudication" / all SUBHEADINGS in MIME,MJME
#52 #8 and #51
#53 explode "Burns-" / all SUBHEADINGS in MIME,MJME
#54 #8 and #53
#55 explode "Pre-Eclampsia" / all SUBHEADINGS in MIME,MJME
#56 #8 and #55
#57 (explode "Dental-Fissures" / all SUBHEADINGS in MIME,MJME) or (explode "Root-Caries" / all SUBHEADINGS in MIME,MJME) or (explode "Dental-Caries" / all SUBHEADINGS in MIME,MJME)
#58 #8 and #57
#59 (explode "Diabetic-Foot" / all SUBHEADINGS in MIME,MJME) or (explode "Foot-Ulcer" / all SUBHEADINGS in MIME,MJME) or (explode "Diabetic-Angiopathies" / all SUBHEADINGS in MIME,MJME)
#60 #8 and #59
#61 explode "Liver-Diseases" / all SUBHEADINGS in MIME,MJME
#62 #8 and #61
#63 "Mandibular-Fractures" / all SUBHEADINGS in MIME,MJME
#64 #8 and #63
#65 explode "Fetal-Diseases" / all SUBHEADINGS in MIME,MJME
#66 #8 and #65
#67 explode "Cholelithiasis-" / all SUBHEADINGS in MIME,MJME
#68 #8 and #67
#69 explode "Asthma-" / all SUBHEADINGS in MIME,MJME
#70 #8 and #69
#71 (explode "Bronchitis-Chronic" / all SUBHEADINGS in MIME,MJME) or (explode "Bronchitis-"/ all SUBHEADINGS in MIME,MJME)

#72 #8 and #71
#73 explode “Asthma-” / therapy in MIME,MJME
#74 #8 and #73
#75 explode “Eye-Infections” /surgery, therapy in MIME,MJME
#76 #8 and #75

# Appendix III: Grounds for exclusion of the documents retrieved

| | ABSTRACT/CITATION | FULL TEXT | |
|---|---|---|---|
| | | Medline/Embase | Hand search |
| Under 10 cases | 3 | | 6 |
| Editorial /Letter/ Opinion article | 3 | 3 | |
| Narrative review | 1 | 3 | 3 |
| Environmental ozone | 32 | | |
| No measure for clinical effectiveness | 6 | 5 | 4 |
| Language | 37 | | |
| Drug withdrawn from market | | | 1 |
| Total | 82 | 11 | 14 |

# Appendix IV: Diseases identified in the abstracts and/or articles after applying the search strategya

1. Anaemia
2. Asthma*
3. Athlete's foot*
4. Bronchitis
5. Burns
6. Cancer*
7. Cholelithiasis and peptic ulcer
8. Choroid diseases
9. Chronic fatigue syndrome
10. Chronic inflammatory bowel disease
11. Chronic kidney failure
12. Dental caries*
13. Diabetic foot*
14. Diabetic retinopathy
15. Disorders of the temporomandibular joint*
16. Dry eye syndrome
17. Eczema
18. Endophthalmitis
19. Fibromyalgia
20. Edematous fibrosclerotic panniculopathy
21. Frontal sinusitis
22. Gastrointestinal haemorrhage
23. Glioblastoma
24. Gonarthrosis
25. Ischaemic heart disease
26. Liver diseases
27. Lower limb arterial ischaemia*
28. Maxillary infection
29. Menière's disease*
30. Metatarsalgia
31. Migraine
32. Necrosing fasciitis
33. Painful disorders of musculo-skeletal soft tissue*
34. Patellar chondromalacia*

* Diseases studied in the articles that were finally included in this report.

35. Peritonitis
36. Placental failure
37. Pleural empyema
38. Preeclampsia
39. Quervain's tenosynovitis
40. Raynaud's syndrome
41. Respiratory failure
42. Rheumatoid Arthritis
43. Rhinosinusitis
44. Sepsis
45. Spinal diseases (disc herniation, spondylolysis, etc)*
46. Suppurative otitis media
47. Tendinopathies (tennis elbow, jumper's knee, painful shoulder*
48. Thyroid-nodule
49. Tonsillitis
50. Tuberculosis

# Appendix V: characteristics of the studies included and quality of the evidence

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Alexandre A, 2005[10] Italy, Espain, Argentina Acta Neurochir** | 252 patients with cervical disc herniation. 39.8 % of patients had hernias at various different levels | Intradiscal ozone injection (2-3ml) at a concentration of 20 mcg / ml preceded and followed by 5 paravertebral injections (20 ml at a concentration of 10 mcg/ml). | Pain<br>Impaired sensitivity<br>Motor dysfunction<br>Size of herniation: CT/nMRI | Pain disappeared entirely in 79.3% of the cases; there was improvement in 9.9 and a poor outcome in 10.7%.<br>Impaired sensitivity was eradicated in 78.1%. Motor dysfunction present at varying grades in 78.9% of patients resolved in 61.9% of cases.<br>At 7 months,<br>In 39.6% of the cases, hernia volume was reduced.<br>No significant correlation with symptoms was observed. | Case series<br>Bias probability: high<br>Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Alvarado R, 2006[13] Bolivia Rev Ital Ossigeno-Ozonoter** | 120 patients, 17 with herniated cervical disc and 103 lumbar disc herniation ( 68 men) | Cervical hernia: intradiscal injection of 7 to 10 ml of ozone (30-40 mcg/ml). A mean of 8 sessions (6-12)<br>Lumbar hernia: paravertebral infiltration of 20 ml (30-40 mcg/ml). A total of 20 sessions | Pain<br>Loss of sensitivity | At 4 –5 months:<br>The outcome was excellent (disappearance of pain and loss of sensitivity) in 86 patients (82.4%): 94 % in patients with cervical hernia and 68% with lumbar hernia.<br>17 patients showed no clinical improvement, and 8 of these accepted to undergo surgery. | Case series<br>Bias probability: high<br>Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Andreula CF, 2003[20] Italy AJNR Am J Neuroradiol** | 600 patients with contained herniated lumbar or lumbosacral disc (L1-S1). | Group A (300): intradiscal (4ml) and periganglionic (8ml) ozone at a concentration of 27 mcg/ml Group B (300): the same plus periganglionic injection of corticoids and anaesthetics | Pain: modified Mac Nab method | At 6 months, Therapy was successful (excellent or good outcome) in more patients in group B than in group A (78. 3% vs. 70.3%, $p<0.05$). Treatment failed (poor outcome or indication for surgery) in 21.7% of patients in group B and in 29.7% in group A. Two patients from group B developed diminished sensitivity in their low er limbs. | Quasi-experimental study. Methodological quality: low Bias probability: High |
| **Andreula C, 2003[21] Italy Rev Ital Ossigeno-Ozonoter** | 500 patients with contained lumbar and/ or lumbosacral hernia Age between 15 and 89 years | Intradiscal and periganglionic-peri-radicular injection of ozone (3 -10ml at a concentration of 27 mcg/ml) plus anaesthetic and corticoids. | Pain: modified Mac Nab method | At 3 months, Pain remitted in 59.4% of patients with multiple herniated discs, in 53.8% of patients with a single herniated disc, in 46.3% of patients with associated degenerative disease and in 32.3% of patients with post-surgical hernia and/ or fibrosis. No adverse effects were reported | Case series Methodological quality: low Bias probability: High |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Arena M, 2003[15] Italy Rev Ital Ossigeno-Ozonoter** | 40 patients with lumbar or lumbosacral hernia (L3 - S1). Age between 35-65 years, 25 men | Group A: paravertebral injection of ozone (10-15 ml) at a concentration of25-30 mcg/ml. Between 15 and 20 sessions. Group B: the same combined with another therapy (posture re-education, osteopathy, laser) | Pain: modified Mac Nab method | Complete remission of pain was achieved in 65.6% of patients in Group A and in 75.9% in group B A similar percentage of patients in both groups experienced no change in their symptoms. | Quasi-experimental study. Methodological quality: low Bias probability: High |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Buric J, 2005[19]**<br>**Italy**<br>**Acta Neurochir** | 30 patients with non-contained lumbar and/ or lumbosacral disc herniation L3-S1<br>16 men and 14 women, mean age 45 ±14.2 | Intradiscal injection of 10-15 ml of ozone at a concentration of 40mcg/ml. | Pain: visual analog scale (VAS)<br>Degree of disability or limitations for daily living activities: Roland-Morris Questionnaire (RMQD)<br>Satisfaction with treatment: percentage of overall patient satisfaction (OPSR)<br>Size of herniation: nMRI | At 12 months,<br>There was an improvement to pain and disability in 90% of the cases, this being a significant improvement from pre-treatment status ($p<0.001$, 95% CI: 2.9-5 y 5.3-8.4, respectively).<br>Mean satisfaction at 12 months was 79.3% (28.7). 80% reported satisfaction levels of >80%. Two patients suffered worsening of symptoms.<br>Between 3-5 months<br>The N-MR images in the 17 patients who showed clinical improvement, revealed evidence of a decrease in volume >50% in 8 of the cases | Case series<br>Bias probability: High<br>Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Buric J, 2005[17] Italy Rev Ital Ossigeno-Ozonoter** | 45 patients with non-contained lumbar and/or lumbosacral disc herniation (L3-S1) Mean age 45 (14.2), 23 men | 30 patients received intradiscal injection of ozone (10-15 ml) at a concentration of 30 mcg/ml 15 patients were treated by surgery (microdiscectomy) | Pain: VAS Disability or limitation to activities of daily living: Roland-Morris Questionnaire Satisfaction with therapy: OPSR Size of herniation : nMRI | At 18 months, In the ozone-treated group, both pain and disability improved in 90% of the cases, there was no change in 3.3% while 6.6 % worsened (2 patients, referred for surgery). In the intervention arm, pain improved in 93.3% of patients and worsened in one patient. Disability improved in 86.6% of patients, with no change in the remainder. Improvement in pain and function compared with pre-treatment status was statistically significant in both treatment arms ($p<0.001$), but no significant differences existed when compared. The mean satisfaction rate was 79.3 (28.7) in the ozone-treated group and 82.1 (31.2) in the surgery group. There were no statistically significant differences when both groups were compared. Between 3-5 months, the reduction in herniated mass was > 50% in 8 out of 15 patients in the ozone group. | Quasi-experimental study Bias probability: High Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Buric J, 2003[18] Italy Rev Ital Ossigeno-Ozonoter** | 104 patients with non-contained lumbar and/or lumbosacral hernia (L2-S1) Ages between 20-60 years | Intradiscal injection of 1.5 -2 ml of ozone at a concentration of 40 mcg/ml. 4 patients received a second session | Pain: VAS Degree of pain Sensory and motor disorder: Japanese Orthopaedics Association scale (JOA) Satisfaction with treatment: OPSR Size of herniation: nMRI | At 18 months, Mean improvement to pain compared with baseline was 3.77. Overall improvement (JOA) was 54.7% compared with baseline The mean improvement in satisfaction compared with baseline was 71.77% At 5 months, Reduction in hernia volume was >80% in 37% of the cases, between 40-80% in 41 % and no change was seen in 22% of cases. 5 patients underwent surgery due to treatment failure. | Case series Bias probability: High Methodological quality: low |
| **Carmona L, 200628 Spain Reumatol Clin** | 6 documents: 5 articles on herniated disc 1 article on Raynaud's syndrome | Ozone therapy in bone and joint diseases | Systematic review | The use of ozone therapy in rheumatic diseases is based on biased clinical trials. There are currently no arguments to suggest an appropriate risk/benefit ratio for ozone therapy in rheumatic diseases. | Methodological quality: average |

<table>
<tr><th colspan="6">LUMBAR SPINE DISEASES</th></tr>
<tr><th>Author, year, country and journal</th><th>Population</th><th>Intervention</th><th>Outcome measures</th><th>Outcomes</th><th>Design, bias probability and methodological quality</th></tr>
<tr><td>D'Aprile P, 2004[51]<br>Italy<br>Rev Ital Ossigeno-Ozonoter</td><td>80 patients with lumbar and/ or lumbosacral disc herniation)<br>45 men</td><td>Intraforaminal injection of between 8-10 ml ozone at a concentration of 30 mcg/ml.<br>32 patients with partial improvement to pain received NSAID treatment (rocecoxib) for 2 weeks prior to undergoing a second ozone treatment.</td><td>Pain: disappearance, improvement and little or no improvement.</td><td>Outcomes in terms on pain after the first or second treatment:<br><table><tr><td>Pain</td><td>1st treat. (n)</td><td>2nd treat. (n)</td></tr><tr><td>Disappear</td><td>22</td><td>11</td></tr><tr><td>Improvement</td><td>17</td><td>10</td></tr><tr><td>No improvement</td><td>11</td><td>9</td></tr></table>One patient developed a haematoma at the injection site.</td><td>Case series<br>Bias probability: High<br>Methodological quality: low</td></tr>
<tr><td>Fabris G, 200311<br>Italy<br>Rev Ital Ossigeno-Ozonoter</td><td>16 patients with herniated cervical disc, aged 34 to 78 years</td><td>Bilateral paraverterbal injection of 4-5 ml of ozone at concentrations of 10-15 mcg/ml<br>Each patient received a mean of 10 sessions</td><td>Pain: modified Mac Nab method</td><td>Between 3-9 months,<br>Cure or improvement of pain occurred in 14 (87.5%) patients and pain remained unchanged in the other two patients.</td><td>Case series<br>Bias probability: High<br>Methodological quality: low</td></tr>
</table>

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **He XF, 2003[22] China Rev Ital Ossigeno-Ozonoter** | 258 patients with lumbar-lumbosacral hernia (L4-L5 y L5 S1). Mean age 44.6 years and 152 men. | Intradiscal ozone (4-6ml a concentration of 30-40mcg/ml) and ozone (15 ml) combined with corticoids (55mg prednisolone) in the paraspinal space Afterwards, iv antibiotics and corticoids are given for 3 days. 60% of patients received 2 sessions | Pain: modified Mac Nab method Size of herniation: CT/nMRI | From 3 to 28 months, there was complete remission of pain in 62% of the cases, with no improvement in 22.9%. According to the kind of herniation, treatment was successful in 87.2% (prolapse), in 71.8% (protrusion) and 25% (extrusion) At 3 months, a reduction in disc volume was seen in 5 out of 135 cases. Some patients experienced a local sensation of heat and mild pain during the ozone injection. | Case series Bias probability: High Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **He XF, 2005[12] China Rivista de Neuroradiologia** | 58 patients with herniated cervical disc, with a total of 126 disc lesions. Mean age 52 years and 35 men | Intradiscal ozone (2-3ml, at a concentration of 30-40 mcg/ml) and 3ml at paraspinal level. Afterwards, iv antibiotics and corticoids are given for 3 days. | Pain: modified Mac Nab method | From 3 to 30 months, There was complete remission of pain in 56,9% of the cases, improvement in 19% and no change in a further 24.1%. No complications were reported | Case series Bias probability: High Methodological quality: low |
| **Leonardi M, 2006[16] Italy Rev Ital Ossigeno-Ozonoter** | 89 patients with a single lumbar hernia. Group A:37 patients with at least a 6-month history of symptoms Group B: 52 patients with a history of symptoms ranging between 6 months and 20 years. | Intra-disc ozone (4ml) and periganglionic (10ml) at a concentration of 27 mcg/ml followed by periganglionic injection of corticoids and anaesthetics Single session | Pain Degree of physical disability due to pain: modified version of the Oswestry disability questionnaire | At 18 months, Treatment had a positive effect (complete or almost complete remission of symptoms) in 56 patients (62.9%), in 20 (54%) in group A and in 35 (67.3%) in group B. Outcomes were negative or negligible for the remaining patients In group A: the mean in the Oswestry questionnaire rose from 19.5 (pre-treatment) to 9.75 (post-treatment) and in group B from 18 to 7.17. No complications were reported. | Case series Bias probability: High Methodological quality: low |

<table>
<tr><th colspan="6">LUMBAR SPINE DISEASES</th></tr>
<tr><th>Author, year, country and journal</th><th>Population</th><th>Intervention</th><th>Outcome measures</th><th>Outcomes</th><th>Design, bias probability and methodological quality</th></tr>
<tr><td>Muto M, 2004[23] Italy J Neuroradiol</td><td>2200 patients with lumbar- and/or lumbosacral hernia (L4-S1)<br>Aged between 13 and 89 years</td><td>Intradiscal (3-4 ml) and periganglionic (10 ml) injection at a concentration of 30 mcg/ml.</td><td>Pain: modified Mac Nab method<br>Size of herniation: CR and/or nMRI.</td><td>At 18 months,<br>Complete remission or improvement of symptoms occurred in 75% of cases.<br>At 6 months,<br>The volume of herniated material dropped in 63% (420 subjects).<br>No adverse effects occurred.</td><td>Case series<br>Bias probability: High<br>Methodological quality: low</td></tr>
<tr><td>Paradiso R, 2005[14] Italy Acta Neurochir</td><td>Patients with lumbar or lumbosacral hernia (L1-S1).<br>150 treated by microdiscectomy (78 men)<br>150 treated with ozone (76 men)</td><td>Intradiscal injection of ozone</td><td>Pain: VAS<br>Sensory and motor dysfunction: JOA scale.<br>Size of herniation: CT and /or nMRI</td><td>At 3 years,<br><table><tr><th>Decrease in symptoms</th><th>Surgery (% of cases)</th><th>Ozone (% of cases)</th></tr><tr><td>Pain</td><td>85,3</td><td>79,3</td></tr><tr><td>Sensory dysfunction</td><td>82,5</td><td>80,4</td></tr><tr><td>Motor dysfunction</td><td>86,6</td><td>85,7</td></tr></table>At one year, the reduction in herniated mass was complete in 85.3% of the cases in the intervention group and 57.3% in the ozone group</td><td>Retrospective cohort<br>Bias probability: High<br>Methodological quality: low</td></tr>
</table>

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Qing H, 2005[27] China Rev Ital Ossigeno-Ozonoter** | 602 patients with lumbar disc protrusion (346 men, between 18 and 83 years) 238 with disc disease at one level and the remainder at several different levels, in all 1078 treated discs | Intradiscal injection of between 4-9 ml of ozone and outside the disc of 10 ml of ozone at a concentration of 45-55mg/ L. Together with an infusion of local anaesthetic (xilocaine) and dexamethasone. | Pain: modified Mac Nab method | Between 3-24 months; 55.6% of patients were symptom free, while 32.2% improved; outcomes were tolerable for 7% and poor for a further 3.4%. | Case series Bias probability: High Methodological quality: low |
| **Venza G, 2005[24] Italy Rev Ital Ossigeno-Ozonoter** | 275 patients with herniated lumbar disc, average age 45.6 years, 115 men | Intraforaminal and periganglionic injection of 3 ml of ozone at a concentration of 25mcg/ml 30% of patients received 2 to 4 sessions | Pain: modified Mac Nab method | At 6 months, Excellent in 83.2%, good in 14.1% and poor in 2.5% of the patients. 5 patients required surgery. | Case series Bias probability: High Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Ying WZ, 2005[25] China Rev Ital Ossigeno-Ozonoter** | 322 patients lumbar and/ or lumbosacral disc herniation (L2 - S1) 67.5% had hernias at different levels. In all 433 treated discs. | Intradiscal injection of between 6-15 ml of ozone and between 5-10 ml of ozone outside the disc; in both cases, at a concentration of 35-45mcg/ ml Later, endovenous corticoids were given for 3 days. Some patients needed a second treatment 48 hours later | Pain: standard Mac Nab method | At one year, Outcomes were excellent in 39.31%, good in 38.39% and poor in 12.69% of the cases. Outcomes were better in the presence of a ruptured fibrous ring and when the degree of herniation was < or equal to 30%. Adverse effects: 5 patients presented with lumbar pain or mild leg pain and 8 patients developed mild corneal irritation and reversible dyspnoea after the administration of oxygen. | Case series Bias probability: High Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Moretti B, 2003[31] Italy Rev Ital Ossigeno-Ozonoter** | 224 subjects, with a history of at least 6 months of lower back sciatic pain secondary to a herniated disc, protrusion, arthrosis and disc disease, refractory to conservative treatment. OJO INCOMPLETO EN ORIGINAL ESPAÑOL 118 men, mean age 55.9 years ( 27-79) with low back pain | Ozone injection (30 ml and concentration between 12-25 mcg/ml) in paravertebral musculature - Low responders: 112 required a second cycle - High responders: 112 did not require a further cycle 1 cycle= 6 sessions | Pain: VAS | In both groups, at the end of treatment a statistically significant decrease in pain was observed ($p<0.05$) that was maintained to 12 months follow-up. In the group of low responders: previous VAS was 8.55 and decreased after treatment to 3.48. Later, this dropped to 3 at 3 months, rising to pre-treatment levels at 12 months. In the group of high responders: previous VAS was 9.34 which dropped to 3.42 after treatment and there was no major change in the successive controls (at 3, 6 and 12 months). | Case series Bias probability: High Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Bonetti MJ, 2005[33] Italy AJNR Am J Neuroradiol** | 306 patients, 178 men, mean age 48 years with acute or chronic lower back pain and sciatica. Symptoms had lasted between 1 and 20 months. 6 patients had already received epidural infiltration with corticoids with no improvement to symptoms. | Periradicular corticoid injection (80 mg of methylprednisolone) vs intraforaminal injection of 3 ml ozone ( at a concentration of 25 mcg/ml and 5ml in the joint surface region). 166 with disc disease: 80 corticoids and 86 ozone 140 with non-disc vertebral disease (spondylolysis, osteophytosis, etc): 70 corticoids and 70 ozone. | Pain: modified Mac Nab method | There was a higher percentage of patients with excellent outcome (complete remission of pain) among patients treated with ozone than among patients treated with corticoids in the groups both with and without disc disease; statistical significance was reached only in the group with disc disease (74.4% vs. 57.5%, p<0.002) at 6 months. In patients without disc disease, the percentage of patients with poor outcomes (resolution of pain <30%) was significantly higher in the patients treated with steroids (p<0.033). | Clinical trial Bias probability: High Methodological quality: low |

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Bonetti M, 2005[29] Italy Acta Neurochir** | 18 patients, lower back pain and sciatica secondary to spondylolisthesis (grade I) with spondylolysis. Mean age 32.6 years (18-42), 12 men. | Periganglionic infiltration of ozone and at lysis sites (3-4ml, at a concentration of 25mcg/ml) | Pain: modified Mac Nab method | Outcome was excellent (resolution of pain and return to activities of daily living), at one month in 15/18 (83.3%) of the cases and between 3-6 months in 13/18 (72.2%)<br>Pain was reduced by >50% in 2/18 (11.1%) of cases at 3 and 6 months<br>Pain was reduced by < 70% in 3 patients (16.7%). | Case series<br>Bias probability: High<br>Methodological quality: low |
| **López A, 2005[34] Argentina Instituto de Efectividad Cínica y Sanitaria.** | 15 relevant documents were retrieved. | Ozone therapy for the treatment of lower back pain. | Not specified | Most of the studies were observational and only one clinical trial was retrieved; as a result, it was difficult to draw conclusions on the effectiveness and safety of ozone. | Methodological quality: average |
| **Paz-Valiñas L, 2006[35] Spain Avaliación de Tecnoloxías Sanitarias de Galicia** | 13 documents were retrieved | Ozone therapy in the treatment of herniated disc and other painful disorders of the lumbar spine. | Systematic review | In the light of the methodological quality and the level of scientific evidence from the existing studies, it can be stated that there are no arguments sound enough to recommend the implementation of ozone therapy in the treatment of herniated discs and other painful diseases of the lumbar region. | Methodological quality: high |

<table>
<tr><th colspan="6">LUMBAR SPINE DISEASES</th></tr>
<tr><th>Author, year, country and journal</th><th>Population</th><th>Intervention</th><th>Outcome measures</th><th>Outcomes</th><th>Design, bias probability and methodological quality</th></tr>
<tr><td>Moretti B, 2004[37]<br>Italy<br>Rev Ital Ossigeno-Ozonoter</td><td>152 patients with neck pain (herniated disc or protrusion, or cervicoarthrosis/), refractory to conventional treatment for at least 6 months.<br>35 men, mean age 58 years (35-62)</td><td>76 patients received ozone infiltrations (10-15 mcg/ml). A mean of 8 sessions (6-12)<br>76 mesotherapy (injections with a mixture of anti-inflammatory drug, muscle relaxant and local anaesthetic).<br>A mean of 10 sessions</td><td>Pain: EVA</td><td>At the end of treatment,<br><table><tr><th>Pain resolution (VAS)</th><th>Ozone (% of patients)</th><th>Mesotherap. (% of patients)</th></tr><tr><td>Excellent</td><td>30</td><td>14</td></tr><tr><td>Good</td><td>48</td><td>41</td></tr><tr><td>Poor</td><td>22</td><td>45</td></tr></table>At 12 months post-treatment,<br>The mean VAS score achieved after ozone treatment was significantly higher than the scores obtained with mesotherapy.</td><td>Case series.<br>Bias probability: High<br>Methodological quality:</td></tr>
</table>

| LUMBAR SPINE DISEASES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Bonetti M, 2006[32] Italy Rev Ital Ossigeno-Ozonoter** | 129 patients with chronic lower back pain with signs of degeneration and arthrosis of the lumbar spine Mean age 76 years (between 65 and 93) and 57 men) | Periganglionic infiltration of between 3 and/or 5 ml de ozone at a concentration of 25mcg/ml and paravertebral infiltrations with 10 ml of ozone at the same concentration. | Pain: modified Mac Nab method | At 3 months, 57.3% (74/129) of the showed a clear improvement in terms of pain, with a partial reduction in 24.8% and little or no improvement in 17.9% of the cases. At one year, 33.9% (43/127) of the patients reported good quality of life with almost complete disappearance of pain and, even though pain returned, it was less severe in 26.7%. There was no improvement in 39.4% of patients after treatment. | Case series Bias probability: High Methodological quality: low |

| ASTHMA | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Hernández Rosales F, 2005[38] Cuba Arch Med Res** | 113 patients with extrinsic asthma between 15 and 50 years of age. | Group 1 (n=35): 3 cycles of autohaemotherapy (1 cycle= 15 sessions). The dose of ozone was 4 mg (20 mcg/ml). Group 2 (n=41): same as group 1 but the ozone dose was 8 mg (40mcg/ml) Group 3 (n=37): 3 cycles of rectal insufflation (1 cycle= 20 sessions). The ozone dose was 10 mg (50 mcg/ml). The cycles were administered every 5-6 months. | Respiratory function tests: forced expiratory volume at 1 second (FEV1, litres and %) and forced vital capacity (FVC, %) Dyspnoea, wheezing and medication use | Before the first cycle and alter the last cycle, Respiratory function Group 1: no differences were seen in this parameter before and after treatment. In Group 2: a statistically significant improvement in was seen in FVC, VEF1 y VEF1 (%) after treatment ($p<0.02$, $p< 0.01$ and $p< 0.01$ respectively). After treatment, a significant improvement was noted in FEV1 (l y %) in group 3, $p<0.05$. Symptoms Improvement to symptoms and medication use were greater in group 2. | Quasi-experimental study Bias probability: High Methodological quality: low |

| DENTAL CARIES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Brazzelli M, 2004[5] United Kingdom Health Technol Assess** | Inclusion criteria: randomised clinical trials (RCT) on the effectiveness of ozone in the treatment of dental caries published in English.<br>Exclusion criteria: in- vivo studies, follow-up under 6 months.<br>Number of RCTs included: 5<br>Only one was published in a peer-reviewed journal.<br>Total number of subjects and lesions: 287 and 768, respectively | Kind of intervention assessed: Curative ozone including: ozone, re-mineralising agents, material and information of oral hygiene. | Progression/ regression of caries, use of dental services, adverse effects, satisfaction and quality of life<br>Time required for restorative interventions, need for restorative interventions and time between interventions, symptoms of pulp involvement. | Overall, the quality of the studies was only moderate with major methodological flaws.<br>Ozone therapy seems to achieve better outcomes in root caries that in pit and fissure caries.<br>Two of the studies on the effectiveness of ozone for the treatment of non-cavitated root caries found a high success rate in lesions treated with ozone compared with control lesions.<br>Two studies conducted on pit and fissure caries do not show benefits for ozone, although in one of these there was only improvement in hardness and the visual score.<br>No study provided details of adverse effects<br>Authors' conclusions<br>Currently, there is no reliable evidence available on the effectiveness of ozone applications to halt or prevent caries. | Systematic review<br>Methodological quality: High |

| DENTAL CARIES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Rickard GD, 2004[39] The Cochrane Database of Systematic Reviews** | Inclusion criteria: randomised clinical trials (RCT) with follow-up period over 6 months that recruited patients with dental caries. Exclusion criteria: None reported Number of RCTs included: 3, ( included in the NICE review) Total number of subjects and lesions: 137 and 432, respectively. | Intervention group: ozone alone or combined with oral hygiene or other health-promotion measures together with conventional therapy Control group: no ozone/ placebo in combination with oral hygiene or other health-promotion measures together with conventional therapy. | Main outcome measures: Progression/ regression of caries Secondary measures of outcomes: need for additional conventional dental treatment, intervention time, pain (rated by the patient), cost, adverse effects and patient satisfaction | There seems to be a high risk of bias in all the papers reviewed. Only one study stated the absence of adverse effects. Individual studies show inconsistent effects of ozone on caries. Authors' conclusions There is no convincing proof that ozone is effective in halting and reversing dental caries. Ozone therapy must not be used in general practice unless valid evidence of its clinical effectiveness is had. | Systematic review Methodological quality: high |

| DENTAL CARIES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Baysan A, 2004[40] United Kingdom Am J Dent** | 26 patients (58% male, mean age 65.9 years). 2 subjects were lost to FU. In all, 70 primary root caries | Group 1(n=35):ozone for 10 seconds Group 2 (n=35): ozone for 20 seconds Half of the lesion was used as control | Microbiological test: Colony-forming units (CFU) Clinical assessment (size, hardness, colour, cavitation, severity, etc) | Between 3 and 5.5 months: Significant reduction in CFU in both groups compared with controls ($p<0.001$). There was a significant correlation between the reduction in micro-organisms and the hardness, size, distance to gingival margin and cavitation of the ozone-treated lesions at 10 seconds. This correlation was not significant in lesions treated with ozone for 20 seconds. In 60/65 lesions the severity score diminished from baseline (33 to hard lesions, 27 from a score of 2 to 1) and no change in the remainder. No adverse effects were reported | Clinical trial Bias probability: High Methodological quality: low |

| DENTAL CARIES | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Huth KC, 2005[41] Germany Am J Dent** | 41 patients (20 males, age range between 5 and13 years) with a total of 57 pairs of molars with primary non-cavitated fissure caries. The lesions were randomly assigned in the same patient to receive treatment with or without ozone. | Treated group: Ozone for 40 seconds Control group: no treatment The number of lesions included in each group is unclear. | Progression and regression of caries: laser fluorescence (DIAGNOdent) | 3 months: In the subgroup of patients at high risk for caries, significant differences were found in the changes in DIAGNOdent scores between lesions treated with ozone or not (p=0.035). No adverse effects were reported. | Clinical trial Bias probability: High Methodological quality: low |

| PATELLAR CHONDROMALACIA | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Manzi R, 2002[42] Italy Rev Ital Ossigeno-Ozonoter** | 120 patients having undergone surgery for painful femoro-patellar chondromalacia and limited mobility | Group1 (n=60): infiltration with ozone (15-20ml at a concentration of 10 mcg/ml). 10 sessions<br>Group2 (n=60): no treatment | Pain and mobility: recovery time (days). | Improvement or disappearance of pain occurred in fewer days in the ozone group than in the untreated group (11±2 vs. 30±5, respectively).<br>The ozone-treated group recovered joint mobility earlier. | Quasi-experimental study<br>Bias probability: High<br>Methodological quality: low |

| MENIERE´S DISEASE | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Pawlak-Osinska K, 2004[43] Poland Int Tinnitus J** | 15 patients, 8 men, mean age 43.7 years (38-56), diagnosed with Menière's disease (mean duration of symptoms of 2.1 years). | Inhaled ozone (8 mg/l) for 10 minutes a day, for 10 days, combined with tympanic membrane massage | Hearing tests: otoacoustic emissions (spontaneous and evoked) and sensitivity score for small increments<br>Clinical status: severity and frequency of attacks | There were no significant differences in auditory tests after treatment compared with baseline.<br>There was improvement in terms of severity, frequency and kind of attack after treatment | Case series<br>Bias probability: High<br>Methodological quality: low |

| GONARTHROSIS | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Moretti B, 2004[44] Italy Rev Ital Ossigeno-Ozonoter** | 40 patients with bilateral osteoarthritis of the knee Mean age 65 years, 18 men | Ozone infiltration in one knee (10ml at a concentration of 10 mcg/ml) and infiltration of local anaesthetic and chondroprotectant (hyaluronic acid) in the contralateral knee. Five sessions | Pain, functionality and stiffness: Osteoarthritis Score from West Ontario MacMaster University (WOMAC) and Lequesne functional score | Decreased pain, improved functionality and stiffness in both groups, though there were no differences between both treatments. An improvement to the Lequesne score was also reported (55% decrease compared with pre-treatment scores) in both knees. No intolerance to treatment was seen | Quasi-experimental study Bias probability: High Methodological quality: low |

| ACUTE LOWER LIMB ARTERIAL ISCHAEMIA | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Biedunkiewicz B, 2004[46]**<br>**Poland**<br>**Int J Artif Organs** | 10 dialysed patients with occlusive peripheral artery disease diagnosed with Eco-Doppler or angiography findings and with symptoms of stable intermittent claudication (Fontaine grade II).<br>9 males, mean age 62.7 ±9.5 years. | Autohaemotherapy:<br>9 sessions with oxygen (placebo) and 9 sessions with ozone (50mcg/ml). | Walking test: Maximum distance walked (MDW) and Symptom-free distance (SFD) , both measured in metres<br>Patient's appraisal of overall efficacy of treatment<br>Adverse effects. | MDW and SFD were higher after ozone treatment than prior to therapy and after placebo, with significant differences (MDW $p<0.01$ and $p<0.03$, respectively and SFD $p<0.02$ and $p<0.03$, respectively).<br>The percentage of patients rating the treatment as successful was higher in the ozone-treated group, with significant differences (90% vs. 40% , $p<0.025$).<br>4 patients reported a sensation of itching on lips and tongue after receiving ozone, 3 reported nausea and a bad taste during re-infusion with ozone. These effects were not long lasting. 1 patients developed dyspnoea after ozone treatment. | Quasi-experimental study<br>Bias probability: High<br>Methodological quality: low |

| ACUTE LOWER LIMB ARTERIAL ISCHAEMIA | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Di Paolo N, 2005[45]<br>Italy<br>Int J Artif Organs** | Patients with peripheral artery disease with ulcerous lesion | 15 patients: Extracorporeal oxygenation and ozonation (14 sessions in 7 weeks)<br>13 patients (2 dropped out of the study due to adverse effects): Intravenous prostacyclin (28 days) | Lesion: lesion area and Leriche Scale (0-4) this scale is applied for intermittent claudication<br>Symptoms : numerical scale 0-4 | At 7 weeks<br>The reduction in the lesion area was greater in ozone-treated patients.<br>The stage of the lesion improved with ozone and there was no change in the other group.<br>Subjective improvement in the following symptoms: intermittent claudication, itching, heavy feeling, quality of life, joint pain was significantly greater in the ozone group<br>Euphoria after ozone treatment. | Clinical trial<br>Bias probability: High<br>Methodological quality: low |
| **Luongo C, 2002[48]<br>Italy<br>Rev Ital Ossigeno-Ozonoter** | 63 patients, diagnosed with chronic obliterating artery disease (Fontaine grade III- IV) with ulcerous lesion.<br>35 men, 65 and 81 years and 35 type I DM | Ozone administered via autohaemotherapy (20mcg/ml)<br>18 sessions | Peripheral artery pressure<br>Walking test<br>Pain : score from 0 to 10<br>Course of the ulcer: degree of healing<br>mg/day aspirin | Between 2-7 weeks, improvement in all measured parameters compared with pre-treatment scores.<br>The percentage of cases with complete healing of ulcers was higher in the diabetic patients<br>There was no change in the mean amount of aspirin taken after treatment. | Case series<br>Bias probability: High<br>Methodological quality: low |

| ACUTE LOWER LIMB ARTERIAL ISCHAEMIA | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Tylicki L, 2001[47]**<br>**Poland**<br>**Int J Artif Organs** | 12 dialysed patients with symptoms of lower limb ischaemia (Fontaine grade II-IV) and compatible Eco-Doppler.<br>8 men, mean age 58.22 (44 -76) years. | Ozone administered via autohaemotherapy<br>20-40 mcg/ml<br>14 sessions | Pain<br>Walking test: mean distance covered without pain<br>Adverse effects | 91.6% (11/12) of the patients reported improvement to pain, with a clear or very clear improvement in 7 patients (58.3%).<br>Walking test: a significant difference was seen before and after therapy (220.7± 186.9 m and 369.8±256.8, respectively), with significant differences ( p= 0.01).<br>10 patients reported taste sensations during ozone therapy | Case series<br>Bias probability: High<br>Methodological quality: low |

| TEMPOROMANDIBULAR JOINT DISEASE | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Bonetti M, 2004[49] Italy Rev Ital Ossigeno-Ozonoter** | 32 patients with temporomandibular joint disease. Mean age 37.4 years, 20 men | Intra-articular ozone infiltration (2-3 ml, at a concentration of 25 mcg/ml). | Not specified | At one month of treatment, In 11 of the 19 patients with menisco-condylar impairment, complete remission from the painful symptoms was achieved (57.9%), while clinical benefit was seen in 12 patients with osteoarthrosis and/or osteoarthritis and very little benefit in 1 case of avascular osteonecrosis. | Case series Bias probability: High Methodological quality: low |

| ATHLETE'S FOOT | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Menendez S, 2001[50]**<br>**Cuba**<br>**Mycoses** | 200 patients with characteristic athlete's foot lesions and positive culture for fungi.<br>Mean age 28 years, 87% men and 62% white. | Group 1 (100): sunflower oil and ozone, 2 times/day for 6 weeks<br>Group 2 (100): ketaconazol in cream, 2 times/day for 6 weeks | Cure: clinical disappearance of skin lesion and negative cultures at 6 weeks | At 6 weeks, there were no significant differences (p= 0.57) between both groups as regards the number of cured patients.<br>At 6 months, cultures were negative in all patients in group A while 4% of patients in Group B had recurrence.<br>No side effects or bacterial over-infections were found. | Clinical trial<br>Bias probability: High<br>Methodological quality: low |

| TENDON DISEASE | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Gaffuri M, 2003[51] Italy Rev Ital Ossigeno-Ozonoter** | 18 patients with humeral epicondylitis secondary to overuse and repetitive injury. Mean age 52 years(28-74) and 8 men | Peri-tendinous ozone infiltration at a concentration of 20 mcg/ml The number of sessions ranged from 6 to 10. | Pain | At the end of treatment, 11/18 (61%) remarkable reduction or total disappearance of pain 2/18 (11%) the outcome was only partial and there was no improvement in 5/18 (28%). | Case series Bias probability: High Methodological quality: low |
| **Gjonovich A, 2002[55] Italy Rev Ital Ossigeno-Ozonoter** | 38 athletes with patellar tendonitis or jumper's knee (stage III: pain before, during and after activity) Ages between 17 and 31 years with 26 males. | Peri-tendinous ozone infiltrations (maximum of 8 in 5 weeks) | Pain: visual analog scale | 27 (71%) of the patients experienced a 50% reduction in pain or a functional recovery that allowed them to practise their sport. At 10 weeks after the start of therapy, 75% were symptom-free. No adverse effects were reported | Case series Bias probability: High Methodological quality: low |

| TENDON DISEASE | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Gjonovich A, 2002[53] Italy Rev Ital Ossigeno-Ozonoter** | 30 patients with a history of painful shoulder for less than 3 months. Ages between 25 and 45 years, 22 males | Group A. Ozone infiltration Group B: mesotherapy ( injections with vasodilator and local anaesthesia) | Pain: visual analog scale Joint mobility | At 60 days, Treatment was successful in 67% of the ozone-treated patients and in 54 % of patients treated with mesotherapy Improvement to joint mobility was greater in the ozone group | Quasi-experimental study Bias probability: High Methodological quality: low |
| **Ikonomidis ST, 2003[54] Greece Rev Ital Ossigeno-Ozonoter** | 203 patients with acute or chronic tendonitis at different sites. Mean age: 38 years, 70 males. | Group A (n= 109): ozone infiltration (10-15 mcg/ml) in the affected tendon. Between 3 and 8 sessions. Group B (n=94) oral, non steroidal anti-inflammatory drugs and physiotherapy. | Pain and activity: scale with 5 levels from 0 (symptom-free) to 4 (constant pain and major limitation to daily living activities). | At 4 weeks of therapy, the percentage of symptom-free patients was higher in the ozone-treated group (73.4% and 20.2%). At 6 months, although the number of symptom-free patients drops in both groups, there was still a higher number in the ozone-treated group (64.2% and 1%) No adverse effects were reported, except for pain at the infiltration site. | Clinical trial Bias probability: High Methodological quality: low |

| TENDON DISEASE | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Ikonomidis ST, 2002[52] Greece Rev Ital Ossigeno-Ozonoter** | 163 patients (183 shoulders) with acute or chronic pain, leading to restricted mobility of the shoulder secondary to shock syndrome due to rotator cuff injury. | Group 1 (n= 94 patients, 108 shoulders): steroid infiltrations Group 2 (n= 69, 75 shoulders): ozone infiltrations. Both groups followed a 3-stage rehabilitation programme. | Pain: intensity and duration Mobility: Pain-free range of movement and time to reach maximum stretch in any group of muscles | The results for the outcomes measured were better in the ozone-treated group. The patients receiving ozone went on to the second stage of treatment (exercise programme) faster and with overall shorter rehabilitation time (56.1 vs. 131.2 days). There were more non-responders in group 1 (18% vs. 7.24%). | Clinical trial Bias probability: High Methodological quality: low |

| TENDON DISEASE | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Moretti B, 2005[56] Italy Rev Ital Ossigeno-Ozonoter** | 123 patients with painful shoulder and 209 with different disorders (tendonitis and various impingement syndromes at different sites) | Painful shoulder: 83 patients received ozone infiltrations Mesotherapy : NSAID injections (n=40) Other diseases: Ozone infiltrations (n=138) Mesotherapy (n=71) The concentration, dosage and sessions of ozone varied according to the site for each lesion | Pain: visual analog scale. | Painful shoulder, improvement to pain from baseline was significantly greater in the ozone-treated group than in the NSAID-treated group. Pain disappeared in >90% in 5% of the cases, but in none of the patients treated with mesotherapy. Outcomes were poor (decrease< 40% of pain) in 30% of the mesotherapy-treated group compared with 8% in patients treated with ozone. In the group with different disorders, no significant differences were seen when both treatments were compared. In the group treated with anti-inflammatory drugs, pain at the injection site, allergic reactions and pain recurrence were all reported. No adverse effects were seen in the ozone-treated group | Quasi-experimental study Bias probability: High Methodological quality: low |

| PAINFUL DISORDERS OF SKELETAL SOFT TISSUE | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Qing H, 2005[57] China Rev Ital Ossigeno-Ozonoter** | 141 patients with different painful syndromes of skeletal soft tissue | Infiltration with 3-5 m l of ozone at a concentration of 30-40mg/l | Pain | After two months,<br>85% of patients reported cure or major improvement to their pain ( 40.4% and 45.4%, respectively). At six months, this dropped to 70%.<br>10% improved but continued to suffer limitations, while there was no improvement in 4.1%. | Case series<br>Bias probability: High<br>Methodological quality: low |

| HEAD NECK TUMOURS | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Clavo B, 2004[58]**<br>**Spain**<br>**Evid Based Complement Alternat Med** | 19 patients, all male and diagnosed with advanced head neck cancer under radiotherapy and oral chemotherapy. | 12: intravenous chemotherapy<br>7: autohaemotherapy with ozone (twice / week) and/or rectal insufflations with ozone. Oral chemotherapy was withdrawn in two patients due to intolerance. | Response to treatment in the irradiated area<br>Mean survival | Patients treated with ozone were older and had more advanced disease than patients treated with chemotherapy (p=0.006 and p=0.080, respectively).<br>Clinical response in the irradiated area was greater in the ozone-treated group than in the second arm (29 and 50%, respectively).<br>Mean survival was 8 months in the ozone group and 6 months in the group receiving chemotherapy, but the differences were not significant.<br>Haematomas were reported in the injection area in the patients treated with autohaemotherapy while some of the patients treated with rectal insufflations had symptoms of bloating and constipation. | Quasi-experimental study<br>Bias probability: High<br>Methodological quality: low |

| DIABETIC ULCER | | | | | |
|---|---|---|---|---|---|
| **Author, year, country and journal** | **Population** | **Intervention** | **Outcome measures** | **Outcomes** | **Design, bias probability and methodological quality** |
| **Martínez-Sánchez G, 2005[59] Cuba and Italy Eur J Pharmacol** | Diabetic patients in hospital with foot and lower limb ulcers. 62% followed treatment with oral anti-diabetic drugs (ADO) while the remainder were under dietary control | 49: Systemic antibiotic therapy (according to antibiogram and renal function) and topical treatment for 20 days<br>51: ozone (rectal insufflation (10 mg at a concentration of 50mg/l, 20 sessions) and local application of ozone with plastic bag and ozonated sunflower oil. | Assessment of the lesions: Area and perimeter<br>Qualitative assessment<br>Length of hospital stay | In the ozone treated group, 80% of patients controlled their diabetes with oral anti-diabetic drugs, while 45% did so in the antibiotic treated group ($p<0.05$).<br>The reduction in the area and perimeter of the ulcer was significantly greater in the ozone-treated group (p 0.017 and 0.004, respectively).<br>There were no significant differences in the percentage of patients cured in each group.<br>Hospitalisation time dropped in the ozone-treated group compared with controls ($p= 0.010$).<br>No adverse effects were reported | Clinical trial<br>Bias probability: High<br>Methodological quality: low |

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