

**Li S, Yu B, Zhou D, and et al. Electromagnetic fields for treating osteoarthritis (Review).
Cochrane Database of Systematic Reviews 2013, Issue 12. Art. No.: CD003523.**

Design: Meta-analysis of randomized clinical trials

Date: 12-18-14 LM

Study Question: To assess the benefits and harms of electromagnetic fields for the treatment of osteoarthritis as compared to placebo or sham.

PICOs:

- Patients: Participants over 18 years of age with clinical or radiological confirmation of knee osteoarthritis as defined using the American College of Rheumatology (ACR) criteria for classification of osteoarthritis
- Interventions: All types of pulsed electromagnetic fields and pulsed electrical stimulation
- Comparison interventions: Usual care with or without placebo pulsed electromagnetic fields (EF) or placebo pulsed electrical stimulation (ES)
- Outcomes: Pain, as measured by visual analogue scales (VAS), the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scale for pain, and the Lequesne Functional Severity Index. Function, measured using the WOMAC physical function scale (on a 100 mm VAS) or the WOMAC disability score on a 20 cm VAS of the EuroQol.
- Study types: Randomized controlled trials or quasi-randomized trials which examined the effects of electromagnetic fields for treating osteoarthritis compared to usual care with or without placebo EF or ES, with 4 or more weeks treatment duration.

Study selection:

- Databases included MEDLINE, PreMEDLINE, CINAHL, and PEDro through October 2013 and the Cochrane Central Register of Controlled Trials through 2013, Issue 9.
 - o Bibliography references
 - o Specialized journal abstracts
 - o Conference proceedings
 - o Clinical trial registries
- Two authors independently assessed articles on trial quality for inclusion and resolved any disagreements through consensus or consulting a third review author. Both independently extracted data from studies and assessed articles for risk of bias, with 3 levels of quality of evidence; low risk, high risk or unclear risk.
- Risk of bias was assessed using the Cochrane Collaboration 'risk of bias' tool which uses the following criteria; random sequence generation, allocation concealment, blinding of participants, providers, and outcome assessors, incomplete outcome data and follow-up data addressed, selective outcome reporting, and other potential sources of bias.

- Mean differences (MDs) in outcomes from each trial were pooled to obtain a summary estimate of the effectiveness of EF/ES. The effect of EF/ES was estimated by taking the difference in the mean outcome of the groups that did and did not receive EF/ES. When different scales were used to measure the same concept or outcome, standardized mean difference (SMD) was used. For dichotomous data, risk ratio (RR) was used.
- Heterogeneity in meta-analysis was assessed with the I^2 statistic: If considerable between-group statistical heterogeneity was detected ($I^2 > 75\%$), the causes of heterogeneity were explored. Data was pooled using the fixed effect model for meta-analysis for homogeneous studies if I^2 was less than 25%. If I^2 was $> 25\%$, studies were pooled using the random-effects models.
- An a priori sensitivity analyses was planned for studies of low methodological quality regarding:
 1. concealment of allocation;
 2. blinding of outcome assessors;
 3. extent of drop-outs (20% was considered as a cut-point).
- Subgroup analyses were planned to look for small sample bias by comparing results between the random-effects estimate and the fixed-effect estimate. Funnel plot data was compared to assess reporting bias. If data were available, subgroup analysis to examine the efficacy of electromagnetic fields with different application methods and modalities, including frequency, length of treatment, and different techniques was also planned.

Results:

- Overall 9 studies were included, 636 participants were randomized, 327 participants in active electromagnetic field treatment groups and 309 participants in placebo groups.
- Six trials used pulsed electromagnetic fields while three studies used pulsed electrical stimulation.
- Six studies were included in the meta-analysis for the pain outcome with 434 participants
- Three studies were included in the meta-analysis for the function outcome with 197 participants
- Nine RCTs with a shorter duration than four weeks were excluded, since this time frame may be too short to assess harms and benefits based on biological plausibility.
- Six new studies since the last update in 2002 were included in this update
- For the 6 studies included in the meta-analysis, EF/ES was administered at frequencies from 1 to 3,000 MHz, from 15 minutes to 9 hours a day, 2 to 5 times a day or continuously, and for between 4-6 weeks.
- Some of the 9 trials were vulnerable to bias because the criteria used to assess methodological quality were not always satisfied.
 - o Seven trials were at low risk of bias for blinding
 - o All 9 concealed allocation
 - o 7 trials were at low risk of bias for random sequence generation
 - o No info on selective outcome reporting was present in all 9 trials

- 7 trials were at low risk of bias for incomplete outcome data
- 6 trials reported loss to follow-up ranging from 5% to 20%
- There was moderate-quality evidence from 6 studies (434 participants) that showed that EF/ES does have a statistically significant beneficial effect for patient pain relief. The mean change in the control group was 10.7 points, and 25.8 points in the EF/ES group on a 100 point VAS scale. The mean difference was 15.10 points lower with decreased pain in the EF/ES group (95% CI = 9.08 to 21.13). This equates to a 21.03% relative improvement.
- There was low-quality evidence from 3 studies (197 participants) showing that EF/ES does not have statistically significant effects or clinically important effects on function. The mean change in physical function in the control group was 1.7 points and 6.25 points in the EF/ES group. EF/ES increased function by 4.55 points (95% CI = -2.3 to 11.3) on a 100-point WOMAC function scale. This equates to a 10.1% relative improvement.
- The total number of adverse events from 4 studies (288 participants) was not statistically significantly increased in electromagnetic field-treated patients (19.9%) compared to 16.7% of placebo-treated patients, after six weeks (RR 1.17, 95% CI 0.72 to 1.92).

Authors' conclusions:

- The current, limited evidence shows a moderate clinically important benefit of electromagnetic field treatment for the relief of pain in the treatment of knee osteoarthritis.
- There is inconclusive evidence that electromagnetic field treatment improves physical function. The quality of evidence is low for the effects of EF/ES on function. The finding on this outcome was only based on 3 small trials.
- More trials are needed in this field. New trials should compare different treatments and provide an accurate description of the length of treatment, dosage and the frequency of the applications. Larger trials are needed to confirm whether the statistically significant results shown in the trials included in this review confer clinically important benefits.
- There are currently insufficient data to draw conclusions about the efficacy of electromagnetic field interventions in the management of osteoarthritis.
- This meta-analysis did not reveal clinically important results overall and the analysis was limited by the paucity of literature on electromagnetic fields for osteoarthritis. However, the statistically significant benefits seen here do support the undertaking of further large-scale studies to allow definite conclusions to be drawn.

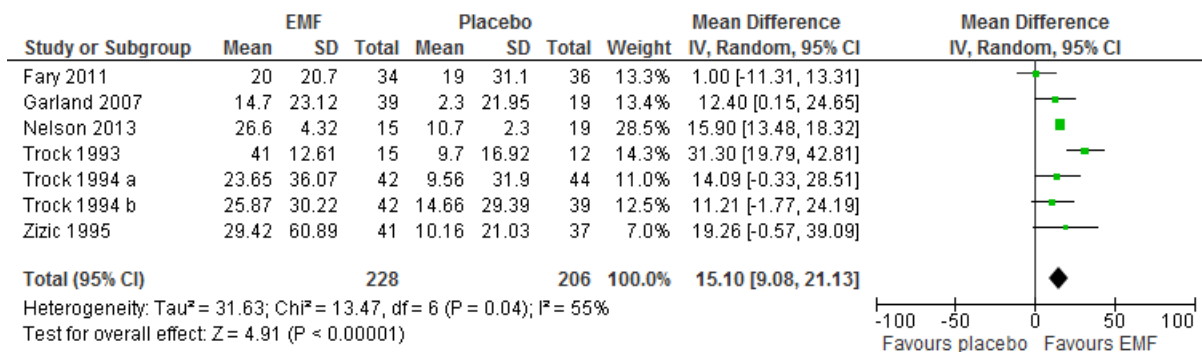
Comments:

- The small number of contributing studies that could be included prevented the planned subgroup analysis of variations in EF/ES treatment, such as electromagnetic field modes and application duration. The protocols for pulsed electrical stimulation or pulsed electromagnetic field device setting and application varied widely between studies, as did the outcome measures. Some pulsed electrical stimulation devices delivered a low-frequency (100 Hz), low amplitude signal. Other devices used in the

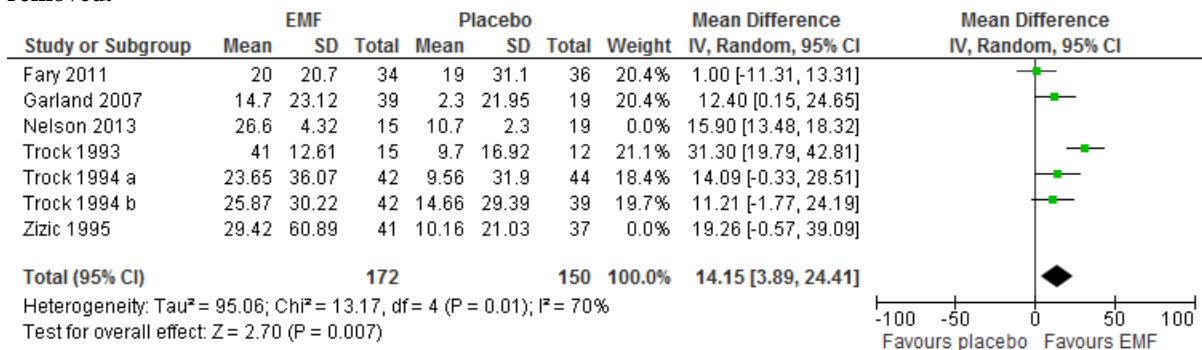
included trials generated a pulsating electromagnetic field with a mean intensity of 40 μT (the frequency of the pulsed magnetic field ranged: 1 Hz to 3000 Hz). Some generated pulses of magnetic energy via a soft iron core with base frequencies (3 Hz, 7.8 Hz and 20 Hz) G50V in 50 Hz pulses changing voltage in 3 ms intervals and extremely low-frequency pulsed waves at 5 Hz, 10 to 15 gauss for 10 minutes, 10 Hz 15 to 25 gauss for 10 minutes and 12 Hz 15 to 25 gauss for 10 minutes. These extreme differences in treatment dosage and duration make it impossible to develop recommendations for effective treatment.

- For the main results, there was moderate-quality evidence from 6 studies (434 participants) that showed that EF/ES does have a statistically significant beneficial effect for patient pain relief. However, two of the studies, Nelson (2013) and Zizic (1995), should not have been classified as moderate quality evidence, but rather low quality evidence. Nelson had high or unclear risk of bias in 3 of 7 domains, and Zizic had unclear risk of bias in 4 of 7 domains. In order to review these results with these two low quality studies omitted, another pooled comparison was performed. The authors' original and the revised pooled comparison are shown below.

Pooled effect of EMF vs placebo for VAS pain score for all 6 studies as reported by the authors'.



Pooled effect of EMF vs placebo for VAS pain score for only 4 moderate quality studies with Nelson and Zizic removed.

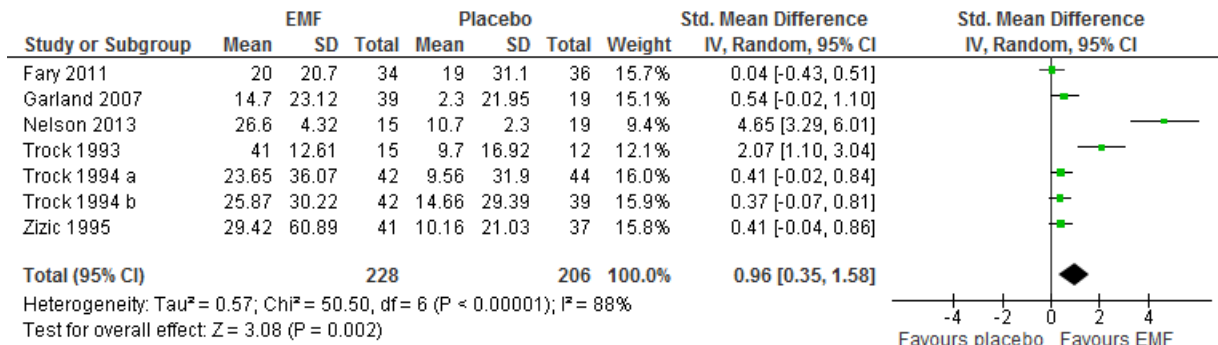


The pooled mean difference was 15.10 points as reported by the authors, and was changed very little to 14.15 points in the revised analyses. The unweighted mean differences do not materially affect the effect size. The heterogeneity increased somewhat from 55% to 70%. The Cochrane authors should have noticed and

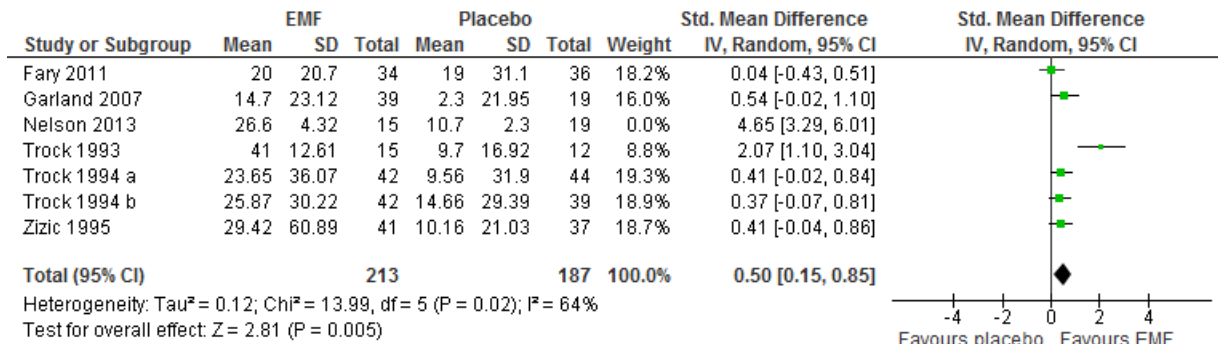
questioned why the standard deviation of the Nelson study was implausibly low and 10 times smaller than all the other studies. As a result, the quality of this Cochrane will be downgraded.

- The above analyses were repeated using standard mean differences to see how the effect sizes were affected by removing the outlying Nelson study. The authors' original data and the revised pooled comparison omitting the Nelson study are shown below.

Standard Mean Differences of EMF vs placebo for VAS pain score including all 6 studies



Standard Mean Differences of EMF vs placebo for VAS pain score with Nelson removed



The revised analysis eliminates some heterogeneity which was affected by Nelson's low standard deviation, but greatly reduces the large effect size of 0.96 to 0.50 in the revised analyses. The enormous effect size shown for Nelson was affected by the extremely small standard deviation. By removing the aberrant study, the moderate effect size of 0.50 for EF/ES is more accurate and seems more plausible.

- The MCID on the VAS scale for pain is around 17 points. Even though EF/ES reduced pain by only 14 points (95% CI = 9.08 to 21.13) on a 100-point VAS scale, the confidence interval encompasses the clinically important difference of 17 on the VAS scale, indicating a very small, but clinically important effect.
- The improvement in physical function in patients with knee osteoarthritis treated with pulsed electromagnetic fields was not statistically significant. There was high heterogeneity in the results. This might be due to the different measurement tools

used in the 3 included studies. Two studies used WOMAC physical function (on a 100 mm VAS) and one study used the WOMAC disability score on a 20 cm VAS of the EuroQol. The intervention duration also differed among these studies.

- There were no life-threatening adverse events reported among participants exposed to electromagnetic fields.

Assessment:

- Adequate quality Cochrane meta-analysis which supports good evidence that electromagnetic field treatment shows a small clinically important benefit for the relief of pain in people with osteoarthritis of the knee. The effect on function is very uncertain.