

Appendix A: Literature Review

| Author / Title / Journal / Year | Type of Study | Outcomes Studied | Patient Characteristics | Results | HCFA Comments |
|---|---------------|--|--|--|---|
| Choffie M, Duarte L / Low intensity pulsed ultrasound and effects on ununited fracture / Presented at Orthopaedic Health Conference, Sao Paulo, Brazil / 1994 | Case Series | Clinically healed (weight-bearing without pain) and Radiologically healed (bridging of three cortices) | <p>86 non- or delayed unions (64 male/22 female) Mean age 37 years (12-80)</p> <p>26 were > 9 months post-fracture (nonunion)</p> <p>Once ultrasound was started, no surgical procedures were performed.</p> <p>Device was applied to fracture site 20 minutes daily.</p> | <p>100% of nonunions healed with an average heal time of 3.4 months. Overall success rate (healed) was 91%.</p> <p>Results were stratified based on fracture site (scaphoid, femur, tibia, humerus, radius, ulna), type of internal fixation, presence of infection, and prior bone graft, for all 86 cases. No significant differences in terms of heal rates were cited.</p> | <p>Authors only indicate that no surgical procedures were performed at the same time as the ultrasound treatment, but they do not exclude patients with recent surgery before the ultrasound therapy. Therefore, one cannot make certain that a surgery near the start date of treatment did not affect the outcome.</p> <p>Patients were treated between 1979-1985 but this data was reported in 1994. This seems to be an unusually long delay from completion of study to reporting of results.</p> <p>Limited statistical analysis. Significant age range of patient population; did not do any subgroup analyses for older patient populations.</p> <p>No specific inclusion criteria, with the exception of the 9 month fracture age, were determined for nonunion.</p> |

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| <p>Duarte LR, Xavier CA, Choffie M / Review of nonunions treated by pulsed low-intensity ultrasound / Presented at International Society of Orthopedic Surgery and Traumatology 20th World Congress / 1996</p> | <p>Case Series</p> | <p>Clinically healed (no pain upon stress or palpation) and Radiographically healed (3 of 4 bridged cortices)</p> | <p>380 pseudoarthroses Mean age =40 yrs (3-83) Male/Female =251/129</p> <p>Only fracture > 6 months were included.</p> <p>Fractures with gap > 1 cm were excluded.</p> | <p>324/380 (85.2%) healed both clinically and radiographically. Avg heal time was 77 days.</p> <p>Results were stratified based on bone type (tibia, femur, radius, ulna, scaphoid, and clavicle) with varying rates of success: clavicle 60%, scaphoid 92.8%),</p> | <p>This study focused exclusively on pseudoarthroses, and not necessarily nonunions. Success rates for nonunions (defined by >9 mos) were not separately reported. However, some authors do consider 6 months to be the age for nonunion.</p> <p>Little statistical analysis on the stratified data. Different bone types had different heal rates, and it would be noteworthy to determine if these differences are significant, and if so, what might account for such differences.</p> |

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| Frankel VH, Koval KJ, Kummer FJ / Ultrasound treatment of tibial nonunions / submitted to Journal of Bone and Joint Surgery (British volume) / | Case Series | Clinically united (no pain upon gentle stress) and radiographically united (3 of 4 bridged cortices) | 174 cases Average age 43.4 years (18-69) 111 male/63 female Mean fracture age 692 days Patients treated 10/94-9/97 Inclusion criteria: -Tibia and tib/fib nonunions -9 months after surgery -No surgical intervention within 4 months of treatment -Radiographic assessment of clean fracture line Treatment applied for 20 minutes daily. | Overall, 146/174 (84%) healed Tibia- 111/131 (85%) healed Tib/fib- 35/43 (81%) healed Average heal time: 166 days (17-522) Results stratified based on fracture age (<2 or >2 yrs) without statistical significance. Patient age, sex, original fracture type, and treatment were not significant predictors of successful treatment. Duration of nonunion prior to treatment and smoking status had a negative effect on treatment success: 63% of nonunions > 3 years duration, and 68% of smokers united. | No p-values were presented in the data charts. Unclear why fracture age of 2 years was chosen as a factor to stratify data. Authors do note that age was not a predictor of success. Follow-up done in early '98 showed 105/146 united cases were still healed. However, the 41 other cases were lost to follow-up. |

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| Fujioka H, Tsunoda M, Noda M, Matsui N / Treatment of ununited fracture of the hook of hamate by low-intensity pulsed ultrasound: a case report / The Journal of Hand Surgery / 2000 | Case Report | Union as determined by CT and x-ray | <p>18 yo female who had fractured the hook of the hamate in a motorcycle accident</p> <p>Pt did not seek treatment for 4 months and grip strength was 18 kgf in affected hand (30 kgf in unaffected).</p> <p>Pt was treated with low-intensity ultrasound (20 min/day) for 4.5 months.</p> | <p>Union of fracture as determined by CT and x-ray.</p> <p>Grip strength improved (29 kgf), and area of hamate was not tender.</p> | <p>There were no previous x-rays to show that healing had ceased. It is unclear whether ultrasound was solely responsible for the healing from that point.</p> <p>Authors admit that this fracture may be considered a delayed union stating "it is difficult to state whether this case represented a nonunion."</p> |

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| Gebauer D, Mayr E, Orthner E, Heppenstall RB, McCabe JM, Ryaby J / Pulsed, low-intensity ultrasound--effects on nonunions / Unpublished study submitted to Journal of Bone and Joint Surgery (US) / | Case Series | Clinically healed (no pain or motion upon gentle stress or weightbearing) and Radiographically healed (3 of 4 bridged cortices for long bones and bridging callus for others) | <p>German and Austrian patients (7/95-4/97)</p> <p>Inclusion: -8 month fracture age -4 months without surgery -Radiographic assessments prior to, and at start of treatment to indicate that healing had stopped for 3 months prior to treatment</p> <p>67 patients (26 females/41 males) met 8 month and 4 month requirements, but only 48 of those patients had the radiographic validation. Those 48 patients were subset A while the other 19 were subset B.</p> <p>Mean age=46 years</p> <p>Patients used device for 20 minutes a day for an average of 168 days.</p> <p>Pregnant patients, and cases that were mal-aligned, actively infected, grossly unstable, or with extensive bone loss were excluded.</p> | <p>41/48 (85%) of subset A healed 16/19 (84%) of subset B healed</p> <p>57/67 (85%) healed overall.</p> <p>Self-paired controls were used, and comparison to an assumed heal rate of less than or equal to 5% was significant (p<0.00001) for all groups.</p> <p>An intention-to-treat analysis (which included all excluded cases) reported a heal rate of 82% (70/85)</p> <p>Comparisons across gender, age, total failed surgeries, displaced fractures, long bone type, initial frx type, fixation type, prior shockwave therapy, and smoking status were not statistically significant.</p> <p>Comparisons across nonunion type, long bone vs others, bone type, and prior days without surgery were statistically significant.</p> <p>Scaphoid and ankle fractures had less than a 50% success rate. Long bones had success rate of 90% vs 69 % for other bones (p=0.05)</p> | <p>Heal rate may be overestimated because patients that may be difficult to treat were excluded (infections, mal-aligned, unstable fractures).</p> <p>Though radiographic assessment was used to verify nonunion, a blind reading by an independent radiologist would have improved the study.</p> <p>Intention-to-treat analysis was not well-described.</p> <p>No differences based on age- of 8 patients > 65 years of age, all healed. Differences in healing rates noted for long vs other bones.</p> <p>Follow up conducted between 2/98-3/98 showed that all patients were still healed.</p> |

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| Hadjiargyrou M, McLeod K, Ryaby JP, Rubin C / Enhancement of fracture healing by low intensity ultrasound / Clinical Orthopaedics and Related Research / 1998 | Review | NA | NA | NA | <p data-bbox="1719 272 1976 548">The authors do a concise review of the effects of various intensity ultrasound treatments on different aspects of fracture healing. The clinical focus of the review is on delayed union and nonunion, but they also discuss the biologic effects of ultrasound on tissues.</p> <p data-bbox="1719 581 1976 995">They note the effect of even small thermal disturbances on some enzymes, the increased calcium incorporation in cartilage and bone cell cultures, and the increased expression of the aggrecan gene. They conclude that ultrasound may offer an advantage because "it does not depend overtly on a singular mechanism or a single phase of the healing process."</p> |

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| Heppenstall RB, Frey JJ, Ryaby JP, McCabe J / Non-invasive nonunion treatment by pulsed low-intensity ultrasound / Unpublished study presented at the AAOS Annual Meeting / 1999 | Case Series | Clinically healed (no pain upon gentle stress or weightbearing) and Radiographically healed (3 of 4 bridged cortices for long bones or callus bridging fracture site for other bones) | 593 nonunions 313 core group 280 non-core group Mean age=44 years (7-89) 47% female Patients from Exogen registry (10/17/94-10/17/96) Inclusion criteria: -9 month fracture age Cases then separated into a core and non-core group. Core group: -min. 3 month interval since last surgical intervention Non-core group: -all incomplete cases (deceased, still healing, lost to follow up, non-compliant, or withdrawal) -cases with surgery within 3 months Pregnant patients and spine, skull, and tumor-related nonunions were excluded | 80% (249/313) of core group healed. Compared to a self-paired control (assumed less or equal to 5% heal rate), results were significant (p=0.00001) Non-core group heal rate was 88%. Statistical comparisons based on gender and age were not significant for either core or non-core group. A modified intention-to-treat analysis was computed. Because 164 cases were incomplete (deceased, lost to follow up, non-compliant, withdrew), those incomplete cases which had only 30 days or less from start of therapy to outcome were excluded. This left 551 cases in the intention-to-treat group. 351/551 (64%) in this modified ITT group healed. Compared to the 5% null hypothesis, this value was significant (p=0.00001) Within the core group, non-significant comparisons were reported based on weight, fracture age, total surgical procedures, prior days without surgery, bone type, long bone vs others, long bone type, prior electrical stimulation, and smoking | This study offers a more detailed examination of the registry data. The three month requirement for interval since surgery limits the possible effects of surgery performed near the start of ultrasound therapy. At long-term follow-up (average of 630 days), 204/249 (82%) of core group cases were still healed. The other 45 cases were unable to be contacted. Authors provide little justification for their modified intention-to-treat analysis. Their approach would overestimate healing rate. |

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| | | | | status. A significant difference (p=.005) was found for patients with long bone IM rods. Patients with rods had a 66% heal rate vs 84% for those without. Other types of fixation were compared and non-significant. | |

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| Mayr E, Frankel V, Ruter A / Ultrasound-- an alternative healing method for nonunions / Archives of Orthoedic Trauma Surgery / 2000 | Case Series | Healed fracture. For US patients, healing was determined by individual physicians. For German patients, healing required 3 of 4 bridged cortices in 2 x-ray planes or 80% trabecular bridging of cancellous fractures. | 951 delayed unions (91-269 days post-fracture) and 366 nonunions (>270 days post-fracture) from US patient registry 42 German patients with no change of therapy 2 months before treatment and no further change after the initiation of ultrasound treatment | <p>US patients: Nonunions: 86% (314/366) healed</p> <p>Patients > 71years had a healing rate of 71%</p> <p>Results were stratified based on fracture site, prior orthopedic procedure, prescribed medications, comorbidities, and smoking status.</p> <p>Patients on calcium channel blockers showed a healing rate of 67% for nonunions. For all patients, renal disease and vascular insufficiency affected healing rates (76% and 70%)</p> <p>US results were compared to German results. The German patients had a nonunion healing rate (94%) that was similar to the US rate. Fracture age and healing times were compared and differences were not statistically significant.</p> | <p>The 42 German patients are involved in a more structured study than the patients in the registry. No radiographic documentation is available for the US patients, so the comparison is used to validate the US data. However, this does not necessarily "validate" the data.</p> <p>Only 16 of the German patients studied had nonunion. Furthermore, statistical comparison was not performed between US and German nonunion heal rates. Article is on nonunion, yet delayed union constitute major portion of German study.</p> <p>Authors provide little statistical data.</p> <p>No specific criteria other than fracture age were outlined for the US patients.</p> |

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| Mayr E, Wagner S, Ecker M, Ruter A / Ultrasound therapy for nonunion (pseudarthrosis) / Unfallchirurg / 1999 | Case Report | Complete bony union on x-ray and tomography | <p>1) 45 yo male with right femoral fracture. After multiple failed therapies, ultrasound was started at 41 months. Complete union was noted 8 months later.</p> <p>2) 63 yo with Monteggia frx of right arm. Ultrasound was tried after frx was considered nonunion. The first tx phase resulted in a callus that did not bridge site; but the position of the device was changed and a bony union was seen less than 2 months later.</p> <p>3) 47 yo with closed tibial frx. 10 months after a second re-fracture, pt was tx with low-intensity ultrasound for 4 months and showed a complete bony union.</p> | All three patients healed. | <p>No specific criteria were given to define "complete union"</p> <p>No set criteria were offered for the determination of nonunion.</p> <p>These three cases are very specific, complicated cases that may not be generalizable to the overall nonunion population.</p> |

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| Mayr E, Wagner S, Ruter A / Treatment of nonunions by means of low-intensity ultrasound / Der Unfallchirurg / 1997 | Case Series | Healed fracture as determined by the individual physician | <p data-bbox="1129 272 1394 354">US patients: 241 nonunions (>270 days post-fracture)</p> <p data-bbox="1129 386 1394 435">636 delayed unions are also included in the study.</p> <p data-bbox="1129 467 1394 743">52 German patients with healing disorders (includes both delayed and nonunion). 13 patients were excluded because they had undergone additional therapy while 4 dropped out. Only 29 of the remaining 39 completed tx. Those 29 were used as the basis for comparison.</p> <p data-bbox="1129 776 1394 938">For German cases, inclusion required comparison to a radiograph 2 months prior to initiation of ultrasound therapy to ensure that healing had stopped.</p> | <p data-bbox="1425 272 1690 354">US patients: Nonunion: 83% (201/241) healed</p> <p data-bbox="1425 386 1690 467">67% of humerus nonunions healed while all other bones were > 80%</p> <p data-bbox="1425 500 1690 548">For the German patients, 93% of nonunions healed.</p> <p data-bbox="1425 581 1690 711">Comparison of data from German and US patient groups showed no statistically significant differences.</p> | <p data-bbox="1719 272 1986 329">The number of German nonunions is not identified.</p> <p data-bbox="1719 362 1986 467">Authors compare 29 German patients to US patients but do not report p-values.</p> <p data-bbox="1719 500 1986 605">Other than fracture age, specific inclusion criteria were not included for the US patients.</p> <p data-bbox="1719 638 1986 800">Data was stratified according to fracture type, comorbidities, and age. However, complete data was not provided from these analyses.</p> <p data-bbox="1719 833 1986 911">No explanation for dropouts. Did not perform an intention-to-treat analysis.</p> |

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| Moyen B, Mainard D, Azoulay J et al. / The efficacy of treating nonunions with pulsed low-intensity ultrasound / Unpublished study / | Case Series | Clinical healing (no pain upon gentle stress or weightbearing) and Radiographic healing (3 of 4 bridged cortices for long bones and callus bridging the fracture site for other bones) | <p>Inclusion criteria: -6 month frx age -radiographic assessment that healing had not progressed or had stopped</p> <p>Pregnant patients and spine, skull, or tumor-related fractures were excluded.</p> <p>Patients in French clinics between 7/95-11/98</p> <p>52 cases (16 female/36 male) met inclusion/exclusion criteria. 8 patients were incomplete due to withdrawal, loss to follow-up, or non compliance.</p> <p>20 cases had surgery within 3 months.</p> | <p>39/44 (89%) patients healed</p> <p>Compared to a assumed heal rate of less than or equal to 5%, the heal rate was significant (p=0.00001)</p> <p>Patients with more than three month interval before treatment had an 88% (21/24) heal rate.</p> <p>Intention to treat showed 39/52 (75%) healed. This result was also significant when compared to the 5% null hypothesis (p=0.00001)</p> <p>Stratification of the results based on gender, age were done for completed cases and separately for patients with a minimum of 3 months without surgery before treatment.</p> <p>None of the results were significant.</p> <p>For the 44 completed cases, heal rates were compared across frx age, number of surgical procedures, days since last surgery, bone type, long bones vs. others, frx type, type of fixation, smoking status, and nonunion type. None of comparisons were significant.</p> | <p>13/44 completed patients had surgery within one month of treatment. Surgery this close to treatment could affect the healing rate.</p> <p>34/39 (87%) healed cases were contacted for long term follow up (average of 768 days). All of these cases were still healed.</p> <p>P value provided only on limited data.</p> |

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| Nolte PA, van der Krans A, Patka P, et al. / Low-intensity pulsed ultrasound in the treatment of non-union in the Netherlands / unpublished study; submitted to Clinical Orthopaedics / | Case Series | Radiologic healing (3 of 4 bridged cortices for long bones or fracture line bridged by callus) and Clinical healing (weightbearing without pain or normal function of limb) | <p>Patients treated from 11/95-5/97</p> <p>Inclusion criteria: -6 month fracture. age minimum -Radiographic healing had not progressed or had stopped -3 months since last surgical intervention before treatment.</p> <p>PIs reviewed x-rays for inclusion</p> <p>29 (12 females/17 males) cases met all three criteria</p> <p>Mean age=47 years (18-90)</p> | <p>25/29 (86%) cases healed</p> <p>Heal rate was significant (p<0.00001) when compared to self-paired control. Assumed heal rate of control group was 5%.</p> <p>Intention to treat heal rate was 33/41 (80%)</p> <p>Heal rates were compared across gender, age, fracture age, interval without surgery, smoking status, and nonunion type. Only the comparison across smoking status yielded a significant result (p=.05).</p> | <p>Intention to treat is misleading because 8 patients were excluded because they had surgery within three months. This recent surgery could have a positive effect on healing.</p> <p>Review of radiographic evidence by PIs ensures that all cases are meeting similar radiological definitions of nonunion. However, they are not blinded and could be biased towards reading healing on patients using the device.</p> |
| Rubin C, Bolander M, Ryaby JP, Hadjiargyrou M / The use of low-intensity ultrasound to accelerate the healing of fractures / Submitted to Journal of Bone and Joint Surgery / 2000 | Review | Healed or Failed to heal-- no criteria specified | <p>-fracture age >270 days -US patients in the Exogen registry that completed ultrasound treatment as of 12/20/99</p> | <p>Results from the registry were as follows:</p> <p>Nonunions 1054/1246 (85% healed)</p> <p>Femur (82%), Humerus (72%), Metatarsal (90%), Radius-Ulna (88%), Scaphoid (89%), Tibia/Fibula (85%)</p> | <p>This article is a comprehensive review of both the biological and clinical effects of ultrasound therapy for fractures.</p> <p>The updated registry data is not statistically compared to a self-paired control. Also, the reasons for incomplete results are not given in the article.</p> |