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| **Appendix Table E9. Trials of Opioid Dose Escalation Versus Dose Maintenance or Use of Maximum Dose Ceilings** |
| **Author Year** | **Study Design Duration** | **Setting Country** | **Eligibility Criteria** | **Interventions** | **Sample Characteristics** | **Screened Eligible Enrolled Analyzed****Loss to Followup** | **Outcomes Assessed** |
| Naliboff 2011 | RCT12 months | VA pain clinic U.S. | Patients referred to chronic pain clinic; nonmalignant chronic pain for at least 6 months; clinician determination that patient was eligible for long-term opioids.Excluded: anticipated surgery, post-op pain, pulmonary disease or CHF, current or history of substance abuse disorder, hospitalization for psych disorder in past 2 years | 1. Escalating opioid dose; mean morphine equivalent 52 mg (n=67)
2. Stable opioid dose; mean morphine equivalent 40 mg (n=73)
 | A vs BMean age 53 vs 52 years89% vs 99% male Race not reported Pain:-78% vs 77% musculoskeletal-19% vs 19% neuropathic-3% vs 4% complexInitial morphine equivalent 29.2 (SD 19.6) vs 32.3 (SD 23.1) mgMean usual VAS 7.0 (SD 1.9) vs 6.7 (SD 1.8)Mean worst VAS 8.4 (SD 1.2) vs 8.0 (SD 1.7)Mean ABC score 1.5 (SD 2.0) vs 1.6 (SD 2.1)Mean ODI 48.6 (SD 12.6) vs 47.8(SD 14.0) | Screened: not reported Eligible: 140Enrolled: 140Analyzed: 134Loss to followup: 10/140 (7%) | Pain Functional disabilityUse of nonopioid medications |
| Note: The references are located in Appendix C.CI=confidence interval, NSAID=nonsteroidal anti-inflammatory drug, ODI=Oswestry Disability Index, RCT=randomized controlled trial, SD=standard deviation, US=United States, VA=Veterans Affairs, VAS=Visual Analog Scale |

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| **Author Year** | **Results** | **Adverse Events and Withdrawals Due To Adverse Events** | **Sponsor** | **Quality** |
| Naliboff 2011 | A vs BMean VAS usual pain at 12 months: 5.6 (SD 1.5) vs 6.2 (SD 1.5); p=0.11\*Usual pain VAS decrease ≥1.5 points: 19/67 (28%) vs 15/73 (20%); RR 1.38; 95% CI 0.76to 2.49Mean VAS pain relief at 12 months: 6.0 (SD 1.7) vs 5.3 (SD 1.8); p=0.11\*Increase in pain relief ≥1.5 points: 19/67 (29%) vs 11/73 (15%); RR 1.88; 95% CI 0.97 to 3.66Worst pain VAS decrease ≥1.5 points: 9/67 (14%) vs 4/73 (6%); RR 2.45; 95% CI 0.79 to 7.59Mean ODI at 12 months: 45.8 (SD 14.8) vs 45.0 (SD 19.4); p=0.85\*ODI decrease ≥10 points: 19/67 (29%) vs 20/73 (23%); RR 1.04; 95% CI 0.61 to 1.76 Use of nonopioid treatments (A: n=64; B: n=70):-NSAID: 35/64 (55%) vs 42/70 (60%); RR 0.92; 95% CI 0.68 to 1.22-Muscle relaxant: 10/64 (15%) vs 14/70 (20%); RR 0.78; 95% CI 0.37 to 1.63-Anti-seizure: 40/64 (63%) vs 46/70 (66%); RR 0.95; 95% CI 0.74 to 1.23-Anti-anxiety: 19/64 (29%) vs 24/70 (34%); RR 0.87; 95% CI 0.53 to 1.42-Antidepressants: 45/64 (71%) vs 48/70 (69%); 1.03; 95% CI 0.82 to 1.28-Topical: 11/64 (17%) vs 11/70 (16%); RR 1.06; 95% CI 0.49 to 2.28-Injectable: 17/64 (26%) vs 25/70 (36%); RR 0.74; 95% CI 0.44 to 1.24-Physical therapy: 31/64 (48%) vs 44/70 (63%); RR 0.77; 95% CI 0.57 to 1.05*\*p-value calculated based on completers (A: n=34; B: n=32)* | A vs BAll-cause withdrawals: 33/67 (49%) vs 41/73 (56%); RR 0.88; 95% CI0.64 to 1.20Withdrawal due to opioid misuse: 16/67 (24%) vs 22/73 (30%); RR 0.79; 95%CI 0.46 to 1.38 | Department of Veterans Affairs | Fair |