Appendix 4B: Characteristics of randomized, placebo-controlled trials involving patients with nociceptive pain that were included in the meta-analysis

Study report	Study population, *n* (withdrawals)	Intervention and dosage	End points and outcomes
Roth 1998, USA Parallel groups Quality: 2	Osteoarthritis, site unspecified 42 (8)	Tramadol 200-400 mg/d for 2 wk	Primary: time to exit from the study due to therapeutic failure Secondary: severity of pain* (0-3 numeric scale), ability to perform activities Results: see Appendix 5
Silverfield 2002, USA Parallel groups Quality: 5	Osteoarthritis, site unspecified 308 (68)	Tramadol 37.5-70 mg/d + acetaminophen 325-650 mg/d for 1.5 wk	Primary: pain intensity* (0-3 numeric scale), Pain relief Secondary: SPID, WOMAC* (physical function subscale) Results: see Appendixes 5 and 8
Emkey 2004, USA Parallel groups Quality: 3	Osteoarthritis, site unspecified 307 (80)	Tramadol 37.5-300 mg/d + acetaminophen 325-2600 mg/d for 11.5 wk	Primary: pain intensity* (100-mm VAS) Secondary: pain relief, WOMAC* (physical function subscale), SF-36 survey Results: see Appendixes 5 and 8
Fleischmann 2001, USA Parallel groups Quality: 5	Osteoarthritis of knee 129 (93)	Tramadol 50-400 mg/d for 12 wk	Primary: pain intensity* (0-4 Likert scale) Secondary: pain relief, WOMAC* (overall), global assessment, time to failure Results: see Appendixes 5 and 8
Babul 2004, USA Parallel groups Quality: 5	Osteoarthritis of knee 246 (122)	Tramadol 100-400 mg/d for 11 wk	Primary: pain intensity* (100-mm VAS) Secondary: WOMAC* (physical function subscale), CSPI Results: see Appendixes 5 and 8
Ruoff 1999, USA Parallel groups Quality: 5	Chronic joint pain 465 (6)	Tramadol daily for 2 wk, starting at 200 mg/d; 50 mg => 200 mg on day 4; 50 mg => 200 mg on day 10	Primary: discontinuation due to adverse effect or ineffectiveness Results: 40 patients (30.8% of group taking 200 mg/d from day 1) reached the primary end point; 31 (24.0%, from day 4); 20 (15.2%, from day 10); and 3 (4.4% of placebo group)
Schnitzer 1999, USA Parallel groups Quality: 3	Osteoarthritis of knee 240 (4)	Tramadol 200 mg/d + naproxen 750 mg/d reduced by 250 mg/d every 2 wk (8-wk study)	Primary: minimum effective naproxen dose Results: addition of tramadol allowed a significant reduction in the dosage of naproxen without compromising pain relief
Schnitzer 2000, USA Parallel groups Quality: 5	Low-back pain 254 (22)	Tramadol 200-400 (mean 242) mg/d for 4 wk	Primary: time to exit the double-blind trial Secondary: pain intensity* (10-cm VAS), Pain relief, SF-MPQ, RDQ* Results: see Appendixes 5 and 8
Ruoff 2003, USA Parallel groups Quality: 4	Low-back pain 322 (157)	Tramadol 37.5-300 (mean 157.5) mg/d + acetaminophen 325-2600 mg/d for 11.5 wk	Primary: pain intensity* (100-mm VAS) Secondary: PRRS, SF-MPQ, RDQ,* SF-36 Results: see Appendixes 5 and 8
Peloso 2004, Canada Parallel groups Quality: 4	Low-back pain 338 (191)	Tramadol 37.5-300 (mean 158) mg/d + acetaminophen 325-2600 mg/d for 13 wk	Primary: pain intensity* (100-mm VAS) Secondary: PRRS, SF-MPQ, SF-36, RDQ,* overall medication assessment Results: see Appendixes 5 and 8
Boureau 1991, France Parallel groups Quality: 3	Rheumatoid arthritis 40 (2)	Codeine 90 mg/d + acetaminophen 1500 mg/d for 1 wk	Primary: pain intensity (100-mm VAS* and 5-point Likert scale) Secondary: pain relief, activity, sleep, overall efficacy Results: see Appendix 5
Arkinstall 1995, Canada Crossover design Quality: 4	Mixed nociceptive pain 46 (16)	CR codeine 200-400 mg/d for 1 wk	Primary: pain intensity (100-mm VAS* and 5-point categorical scale) Secondary: rescue acetaminophen + codeine consumption, PDI* Results: see Appendixes 5 and 8
Peloso 2000, Canada Parallel groups Quality: 4	Osteoarthritis of hip or knee 103 (37)	CR codeine 100-400 mg/d for 4 wk	Primary: WOMAC pain intensity* (0-500 VAS) Secondary: WOMAC* stiffness and physical function, sleep, global assessment Results: see Appendixes 5 and 8
Roth 2000, USA Parallel groups Quality: 3	Osteoarthritis 133 (70)	CR oxycodone for 2 wk: A) 20 mg/d* B) 40 mg/d	Primary: pain intensity* (4-point numeric scale) Secondary: quality of sleep, BPI, Interference of pain during key functional activities Results: see Appendix 5
Caldwell 1999, USA Parallel groups Quality: 4	Osteoarthritis 107 (36)	Oxycodone for 4 wk: A) IR 20 mg/d + acetaminophen 1300 mg/d* B) CR 20 mg/d	Primary: pain intensity* (4-point numerical scale) Secondary: global measure of sleep Results: see Appendix 5
Caldwell 2002, USA Parallel groups Quality: 3	Osteoarthritis of hip and/or knee 295 (111)	Morphine 30 mg/d for 4 wk: A) ER (morning)* B) ER (evening) C) CR 15 mg b.i.d.	Primary: WOMAC pain (0-500) and overall arthritis pain intensity* (0-100) Secondary: WOMAC stiffness and physical function* (0-1700) Results: see Appendixes 5 and 8
Moran 1991, UK Crossover design Quality: 2	Rheumatoid arthritis 20 (16)	CR morphine 20-120 mg/d for 2 wk	Primary: pain intensity* (100-mm VAS) Secondary: FIHAQ,* RS, GSS Results: see Appendixes 5 and 8
Moulin 1996, Canada Crossover design Quality: 2	Musculoskeletal pain 61 (18)	SR morphine 30-120 (mean 83.5) mg/d for 6 wk	Primary: pain intensity* (10-cm VAS) Secondary: pain relief, MPQ, drug liking, use of rescue medication, SCL-90, POMS, SIP, PDI,* HSCS, patients' preferences Results: see Appendixes 5 and 8

Note: Studies are ordered according to the opioids investigated, from weaker to stronger. SPID = Sum of Pain Intensity Differences, WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index, SF-36 = Short Form 36 Health Survey, VAS = visual analog scale, CSPI = Chronic Sleep Pain Inventory, SF-MPQ = short form of the McGill Pain Questionnaire, RDQ = Roland Disability Questionnaire, PRSS = Pain-Related Self-statement Scale, CR = controlled-release, PDI = Pain Disability Index, IR = immediate-release, ER = extended release, FIHAQ = Fries Index Health Assessment Questionnaire, RS = Ritchie Score, GSS = grip strength score, MPQ = McGill Pain Questionnaire, SCL = symptom checklist, POMS = Profile of Mood State, SIP = Sickness Impact Profile, HSCS = high sensitivity cognitive screening.

*Data used in the meta-analysis.

References

Arkinstall W, Sandler A, Goughnour B, et al. Efficacy of controlled-release codeine in chronic non-malignant pain: a randomized, placebo-controlled clinical trial. *Pain* 1995;62:169-78.

Babul N, Noveck R, Chipman H, Roth SH, Gana T, Albert K. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. *J Pain Symptom Manage* 2004;28:59-71.

Boureau F, Boccard E. Placebo-controlled study of analgesic efficacy of 500 mg paracetamol 30 mg codeine association combined with a low dose of diclofenac versus high dose of diclofenac in rheumatoid arthritis. *Acta Ther* 1991;17:123-36.

Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal antiinflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. *J Rheumatol* 1999;26:862-9.

Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. *J Pain Symptom Manage* 2002;23:278-91.

Emkey R, Rosenthal N, Wu S-C, et al. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. *J Rheumatol* 2004;31:150-6.

Fleischmann RM, Caldwell JR, Roth SH, et al. Tramadol for the treatment of joint pain associated with osteoarthritis: a randomized, double-blinded, placebo-controlled trial. *Curr Ther Res* 2001;62:113-28.

Moran C. MST continus tablets and pain control in severe rheumatoid arthritis. *Br J Clin Res* 1991;2:1-12.

Moulin DE, Iezzi A, Amireh R, et al. Randomised trial of oral morphine for chronic non-cancer pain. *Lancet* 1996;347:143-7.

Peloso PM, Bellamy N, Bensen W, et al. Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol* 2000;27:764-71.

Peloso PM, Fortin L, Beaulieu A, et al. Analgesic efficacy and safety of tramadol/acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: a multicenter, outpatient, randomized, double blind, placebo controlled trial. *J Rheumatol* 2004;31:2454-63.

Roth SH, Fleischmann RM, Burch FX, Dietz F, Bockow B, Rapoport RJ, Rutstein J,Lacouture PG. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. *Arch Intern Med* 2000;160:853-60.

Roth SH. Efficacy and safety of tramadol HCl in breakthrough musculoskeletal pain attributed to osteoarthritis. *J Rheumatol* 1998;25:1358-63.

Ruoff GE, Rosenthal N, Jordan D, et al. Tramadol/acetaminophen combination tablets for the treatment of chronic lower back pain: a multicenter, randomized, double-blind, placebo-controlled outpatient study. *Clin Ther* 2003;25:1123-41.

Ruoff GE. Slowing the initial titration rate of tramadol improves tolerability. *Pharmacotherapy* 1999;19:88-93.

Schnitzer TJ, Gray WL, Paster RZ, et al. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol* 2000;27:772-8.

Schnitzer TJ, Kamin M, Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain: a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 1999;42:1370-7.

Silverfield JC, Kamin M, Wu SC, et al. Study Group. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: a multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. *Clin Ther* 2002;24:282-97.