Opioids in chronic osteoarthritis pain. A systematic review and meta-analysis of efficacy, tolerability and safety in randomized placebo-controlled studies of at least 4 weeks duration.

The efficacy, tolerability and safety of opioid therapy in chronic osteoarthritis (OA) pain is under debate. We updated a Cochrane systematic review on the efficacy and safety of opioids in chronic OA pain published in 2009. We screened MEDLINE, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) up until October 2013, as well as reference sections of original studies and systematic reviews of randomized controlled trials (RCTs) of opioids in chronic osteoarthritis (OA) pain. We included double-blind randomized placebo-controlled studies lasting $\geq$ 4 weeks. Using a random effects model, absolute risk differences (RD) were calculated for categorical data and standardized mean differences (SMD) for continuous variables. We included 20 RCTs with 33 treatment arms and 8545 participants. Median study duration was 12 (4-24) weeks. Oxycodone and tramadol were each tested in six studies; buprenorphine, hydromorphone, morphine and tapentadol each in two studies and codeine, fentanyl and oxymorphone in one study each. Results are reported with 95 % confidence intervals (CIs). Opioids were superior to placebo in reducing pain intensity (SMD - 0.22 [-0.28, -0.17], $p < 0.00001$; 16 studies with 6743 participants). Opioids were not superior to placebo in 50 % pain reduction (RD - 0.00 [-0.07, 0.07], $p =$
Opioids were superior to placebo in terms of reports of much or very much global improvement (RD 0.13 [0.05, 0.21], p = 0.002; three studies with 2251 participants). Opioids were superior to placebo in improving physical functioning (SMD - 0.22 [-0.28, -0.17], p< 0.00001; 14 studies with 5887 participants). Patients dropped out more frequently with opioids than with placebo (RD 0.17 [0.14, 0.21], p< 0.00001; 15 studies with 6834 participants; number needed to harm 5 [4-6]. There was no significant difference between opioids and placebo in the frequency of serious adverse events (SAE) or deaths over the respective observation periods. Opioids were superior to placebo in terms of efficacy and inferior in terms of tolerability. The effect sizes of average reduction in pain intensity and physical disability were small. Opioids and placebo did not differ in terms of safety. The conclusion on the safety of opioids compared to placebo is limited by the low number of SAE and deaths. Short-term opioid therapy may be considered in selected chronic OA pain patients. No current evidence-based guideline recommends opioids as first-line treatment option for chronic OA pain. To provide superior evidence for future treatment guidelines, RCTs must directly compare existing pharmacological and nonpharmacological therapies and administer these in various combinations and sequences. The English full-text version of this article is freely available at SpringerLink (under "Supplemental").