Review

Adverse Effects of Opioid Analgesics in Osteoarthritis Treatment: A Global Meta-Analysis, 2000–2022

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ABSTRACT

Osteoarthritis (OA) treatment commonly depends on nonsteroidal anti-inflammatory drugs and opioid medications. Nevertheless, the clinical use of opioids is controversial due to their adverse effects and addiction potential. This study, drawing on 24 randomized controlled trials (RCTs) with a total of 9,586 patients, thoroughly explored the various side effects associated with opioid use in OA treatment. The results provide additional insight into the non-addictive risks of opioids and may assist clinicians in their judicious use, potentially fostering the advancement of safer treatment options. By reducing the risks of misuse and addiction, public health and safety can be enhanced.

With the global increase in the aging population, osteoarthritis (OA) has become a significant chronic disease that impairs quality of life (*1*). Nonsteroidal anti-inflammatory drugs are commonly used to manage OA, yet their long-term use is restricted due to gastrointestinal and cardiovascular side effects. Although opioids can be used for managing moderate to severe pain (*2*), concerns about their potential for addiction and misuse have led to clinical debates (*3–4*). Opioid addiction mechanisms include neural adaptation, tolerance, symptoms of anxiety and pain during withdrawal, and increased dependency on neurotransmitters. Emotional regulation and environmental factors also play crucial roles in the addiction process. The systemic effects of oral opioids increase the likelihood of adverse side effects, and the efficacy and safety of their local administration require further validation through strong evidence (*5*). Despite extensive clinical trials and observational studies, differences in study designs and outcome assessment criteria result in inconsistencies. Therefore, a thorough, scientific evaluation of opioid safety in OA management is essential. This study conducted an exhaustive literature review across Chinese and English databases, included only randomized controlled trials (RCTs) that met specific criteria and used Cochrane Collaboration tools for data synthesis. The findings offer more reliable evidence concerning the safety of long-term opioid use in OA management, support conservative opioid use, help reduce risks of misuse and addiction, and thus protect patient health and wellness.

MATERIALS AND METHODS

Literature Search Strategy

Comprehensive computerized searches were conducted across multiple databases including PubMed, Embase, the Cochrane Library, Medline, Web of Science, and National International Trial Registers, complemented by key Chinese platforms such as China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Chinese Journal Service Platform (VIP CJSP), and Chinese Biomedical Literature Database (CBM). The study period extended from the inception of each database up to May 2024. There were no restrictions on the language of the literature. The search terms used were OA, knee arthritis, hip arthritis, opioids, RCT, and placebo. Details of the search strategies for each database are provided in Supplementary Table S1(available at https://weekly.chinacdc.cn/).

Literature Inclusion and Exclusion Criteria

Inclusion criteria: 1) Studies were RCTs with no restrictions on language or publication status. 2) Participants were diagnosed with OA, with included subtypes such as hip and knee OA. 3) Interventions included opioids as a treatment for OA in the experimental group, with detailed reports on specific regimens (e.g., drug name, dose, treatment duration), and placebo administered to the control group. 4) Outcome measures focused on the type and frequency of opioid-related adverse drug reactions.

Exclusion criteria: 1) Non-clinical studies, case

reports, reviews, comments, conference abstracts, and studies not addressing OA treatment; 2) Duplicate publications; 3) Studies with incomplete data reporting, which precluded a reasonable assessment of findings; 4) Studies classified as high risk in RCTs according to the Cochrane Risk of Bias tool, failing to meet a predefined quality threshold.

Literature Screening and Data Extraction

Two independent reviewers conducted a thorough literature screening, adhering stringently to predetermined inclusion and exclusion criteria. This process was followed by the creation of a standardized data extraction form to gather relevant information. Discrepancies were addressed by an expert committee, which reached a consensus depicted in Supplementary Figure S1 (available at https://weekly.chinacdc.cn/). Data extraction from the selected studies included: 1) bibliographic information such as titles and authors; 2) study characteristics outlining research designs, sample populations, and intervention strategies; and 3) primary observational outcomes, focusing on the types and frequencies of opioid-related adverse events, as detailed in Supplementary Table S2 (available at https://weekly.chinacdc.cn/).

Literature Quality Assessment and Statistical Analysis

The integrity and quality of the studies were rigorously assessed using the Cochrane Risk of Bias Tool. Analytical procedures were conducted using RevMan (version 5.4; Cochrane Collaboration, London, UK). Detailed experimental approaches are thoroughly described in the Supplementary Materials (available at https://weekly.chinacdc.cn/).

RESULT

From an initial selection of 2,561 published studies in this field, 24 met the established inclusion criteria and involved a total of 9,586 OA patients. Of these participants, 4,782 were allocated to the opioid treatment group and 4,804 to the placebo control group. Analysis of gastrointestinal side effects revealed a higher incidence of nausea in the opioid group compared to placebo [relative risk (*RR*)=3.17, 95% confidence interval (*CI*): 2.83, 3.56, *P*<0.001] (Figure 1A). Similarly, constipation (*RR*=3.57, 95% *CI*: 3.15, 4.06, *P*<0.001) (Figure 1B) and vomiting (*RR*=3.65, 95% *CI*: 2.96, 4.49, *P*<0.001) (Supplementary Figure S2, available at https://weekly.chinacdc.cn/) were more prevalent in the opioid group. Dry mouth also occurred more frequently in this group (*RR*=4.14, 95% *CI*: 3.12, 5.50, *P*<0.001) (Supplementary Figure S3, available at https://weekly.chinacdc.cn/). However, the incidence of upper abdominal pain (*RR*=0.85, 95% *CI*: 0.50, 1.46, *P*=0.56) (Supplementary Figure S4, available at https://weekly.chinacdc.cn/) and diarrhea (*RR*=1.11, 95% *CI*: 0.90, 1.37, *P*=0.33) (Supplementary Figure S5, available at https://weekly.chinacdc.cn/) showed no significant differences between the two groups.

We conducted an analysis of adverse reactions related to the nervous system, and general disorders at the administration site, as well as those involving skin, musculoskeletal, and connective tissues. Our results indicated a significantly higher incidence of dizziness (*RR*=3.06, 95% *CI*: 2.66, 3.52, *P*<0.001) (Figure 2A) and somnolence (*RR*=3.61, 95% *CI*: 3.01, 4.33, *P*<0.001) (Supplementary Figure S6, available athttps://weekly.chinacdc.cn/) in the treatment group compared to the control group. Conversely, the difference in the incidence of headache was not statistically significant between the groups (*RR*=1.10, 95% *CI*: 0.97, 1.23, *P*=0.13) (Supplementary Figure S7, available at https://weekly.chinacdc.cn/). Fatigue occurrence was also higher in the treatment group (*RR*=2.52, 95% *CI*: 1.98, 3.22, *P*<0.001) (Figure 2B), along with incidences of hyperhidrosis (*RR*=4.85, 95% *CI*: 3.30, 7.13, *P*<0.001) (Figure 2C) and pruritus (*RR*=4.88, 95% *CI*: 3.70, 6.42, *P*<0.001) (Supplementary Figure S8, available at https://weekly.chinacdc.cn/). In contrast, the incidence of back pain was lower in the treatment group (*RR*=0.29, 95% *CI*: 0.15, 0.56, *P*=0.0002) (Figure 2D).

Our analysis revealed that the rate of treatment discontinuation due to intolerable drug-related adverse effects was significantly higher in the experimental group compared to the control group, with an *RR* of 6.00 (95% *CI*: 4.53, 7.95, *P*<0.001) (Figure 3A). Additionally, the incidence of total adverse events was also higher in the experimental group (*RR*=1.22, 95% *CI*: 1.14, 1.31, *P*<0.001) (Figure 3B). Specifically, the risk of experiencing severe adverse events was approximately 3.12 times higher in the experimental group than in the control group (95% *CI*: 1.65, 5.90, *P*<0.001) (Figure 3C). Severe adverse events identified in this study included respiratory depression, severe allergic reactions, intestinal obstruction from severe constipation, sedation-induced coma, cardiovascular incidents, and serious outcomes related to addiction.

The criteria for classifying these events are detailed in the Supplementary Material.

DISCUSSION

This study, based on 24 RCTs, provides a detailed evaluation of the adverse effects associated with opioid analgesics for OA pain management. The results demonstrate that opioids effectively alleviate pain but also cause a range of adverse reactions. These include 1) Activation of central and gastrointestinal μ-opioid receptors, leading to delayed gastric emptying and vagal nerve activation, which may cause nausea and vomiting; 2) Reduced intestinal motility and decreased secretory activities, resulting in constipation; 3) Diminished central nervous system activity, which can cause sedation and drowsiness, potentially affecting cognitive functions, especially at higher doses or with long-term use (*5*). Additionally, a subgroup analysis involving three studies found a significantly lower incidence of back pain in the experimental group compared to the control group (P=0.0002). Although these results suggest that opioid treatment could reduce back pain in OA patients, the limited number of studies introduces the possibility of random error, limiting the generalizability of these findings to a larger OA patient population. The safety profile of opioid therapy for OA identified in this study is consistent with other research on opioid treatment for OA-related pain (*6*–*8*). The review of the included literature identified common opioids used for OA pain management in clinical practice, including Tapentadol ER, Oxycodone CR, Tramadol ER, and Hydrocodone ER. Standard dosages are 100 to 250 mg twice daily, 10–40 mg every 12 hours, 100–400 mg daily, and 15–90 mg every 12 hours, respectively. Some studies show that the incidence and types of medication-related adverse reactions vary with dosage (*4*–*5*,*7*).

While the primary focus of this study is on the adverse effects of opioids in managing OA, the significant risk of addiction associated with these drugs warrants attention. Prior research has revealed that the

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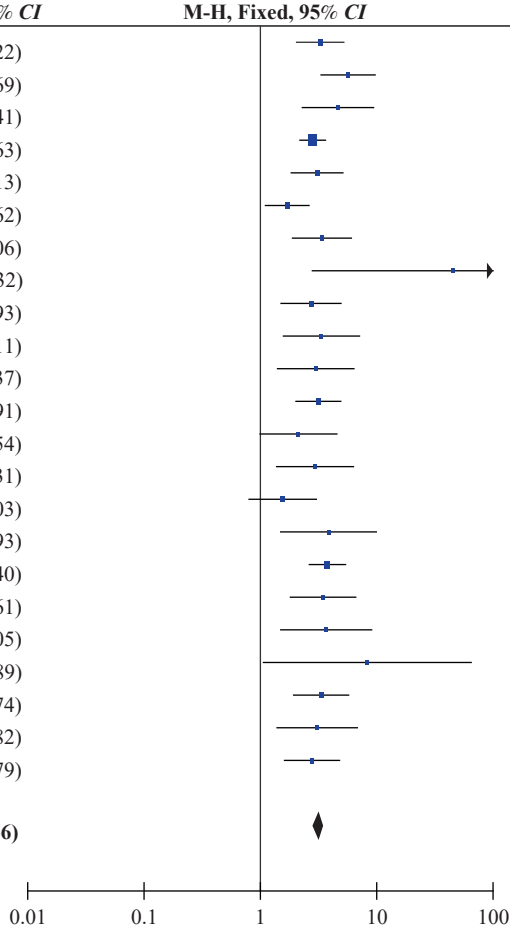
Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk ratio M-H, Fixed, 95% *CI*
Alain Serrie 2017	65	319	21	337	6.0%	3.27 (2.05, 5.22)
Alan K. Matsumoto 2005	72	121	13	124	3.8%	5.68 (3.32, 9.69)
Alan Kivitz 2006	38	93	8	91	2.4%	4.65 (2.30, 9.41)
Bernd Lange 2010	203	980	73	993	21.4%	2.82 (2.19, 3.63)
Byron P. DeLemos 2011	52	199	17	200	5.0%	3.07 (1.84, 5.13)
Carter Thorne 2008	40	94	22	88	6.7%	1.70 (1.11, 2.62)
Catherine Munera 2010	41	152	13	163	3.7%	3.38 (1.89, 6.06)
Egilius L.H. Spierings 2013	25	158	0	141	0.2%	45.55 (2.80, 741.32)
Francis Burch 2007	66	432	12	214	4.7%	2.72 (1.51, 4.93)
Hugues Malonne 2004	25	111	8	119	2.3%	3.35 (1.58, 7.11)
Joseph A. Markenson 2005	23	56	7	51	2.2%	2.99 (1.40, 6.37)
Marc Afilalo 2010	74	344	23	337	6.9%	3.15 (2.02, 4.91)
Martin E Hale 2015	19	146	9	147	2.7%	2.13 (0.99, 4.54)
Najib Babul 2004	24	124	8	122	2.4%	2.95 (1.38, 6.31)
Nathaniel Katz 2010	20	171	13	173	3.8%	1.56 (0.80, 3.03)
Richard L. Rauck 2015	21	146	5	134	1.5%	3.85 (1.50, 9.93)
Richard Rauck 2013	120	330	32	332	9.4%	3.77 (2.63, 5.40)
Ritchard L. Fishman 2007	22	111	13	227	2.5%	3.46 (1.81, 6.61)
Sanford H. Roth 2000	18	44	5	45	1.5%	3.68 (1.50, 9.05)
Shinichi Kawai 2022	8	78	1	81	0.3%	8.31 (1.06, 64.89)
Theophilus J. Gana 2006	49	201	15	205	4.4%	3.33 (1.93, 5.74)
Vishala L. Chindalore 2005	37	102	6	51	2.4%	3.08 (1.39, 6.82)
Walter F. Kean 2009	26	131	20	280	3.8%	2.78 (1.61, 4.79)
Total (95% *CI*)		**4,643**		**4,655**	**100.0%**	**3.17 (2.83, 3.56)**
Total events	1,088		344			

Heterogeneity: Chi²=26.23, df=22 (P=0.24); I^2=16%

Test for overall effect: Z=19.82 (P<0.001)



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Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% *CI*
Alain Serrie 2017	116	319	31	337	11.2%	3.95 (2.74, 5.70)
Alan K. Matsumoto 2005	39	121	14	124	5.2%	2.85 (1.64, 4.98)
Alan Kivitz 2006	25	93	4	91	1.5%	6.12 (2.22, 16.88)
Bernd Lange 2010	166	980	69	993	25.5%	2.44 (1.87, 3.18)
Byron P. DeLemos 2011	40	199	5	200	1.9%	8.04 (3.24, 19.95)
Carter Thorne 2008	22	94	5	88	1.9%	4.12 (1.63, 10.40)
Catherine Munera 2010	15	152	3	163	1.1%	5.36 (1.58, 18.16)
Egilius L.H. Spierings 2013	24	158	2	141	0.8%	10.71 (2.58, 44.50)
Francis Burch 2007	61	432	9	214	4.5%	3.36 (1.70, 6.63)
Hugues Malonne 2004	11	111	2	119	0.7%	5.90 (1.34, 26.01)
Joseph A. Markenson 2005	27	56	5	51	2.0%	4.92 (2.05, 11.80)
Jozef Vojtaš̌s̆ak 2011	27	139	3	149	1.1%	9.65 (2.99, 31.09)
Marc Afilalo 2010	65	344	22	337	8.3%	2.89 (1.83, 4.58)
Martin E Hale 2015	19	146	7	147	2.6%	2.73 (1.18, 6.30)
Najib Babul 2004	26	124	6	122	2.3%	4.26 (1.82, 9.99)
Nathaniel Katz 2010	12	171	7	173	2.6%	1.73 (0.70, 4.30)
Richard L. Rauck 2015	5	146	3	134	1.2%	1.53 (0.37, 6.28)
Richard Rauck 2013	155	330	39	332	14.5%	4.00 (2.91, 5.49)
Ritchard L. Fishman 2007	16	111	3	227	0.7%	10.91 (3.25, 36.65)
Sanford H. Roth 2000	14	44	3	45	1.1%	4.77 (1.47, 15.47)
Shinichi Kawai 2022	2	78	0	81	0.2%	5.19 (0.25, 106.41)
Theophilus J. Gana 2006	45	201	12	205	4.4%	3.82 (2.09, 7.01)
Vishala L. Chindalore 2005	19	102	4	51	2.0%	2.38 (0.85, 6.62)
Walter F. Kean 2009	19	131	12	280	2.9%	3.38 (1.69, 6.76)
Total (95% *CI*)		**4,782**		**4,804**	**100.0%**	**3.57 (3.15, 4.06)**
Total events	970		270			

Heterogeneity: Chi²=29.42, df=23 (*P*=0.17); *P*=22%

Test for overall effect: *Z*=19.58 (*P*<0.001)

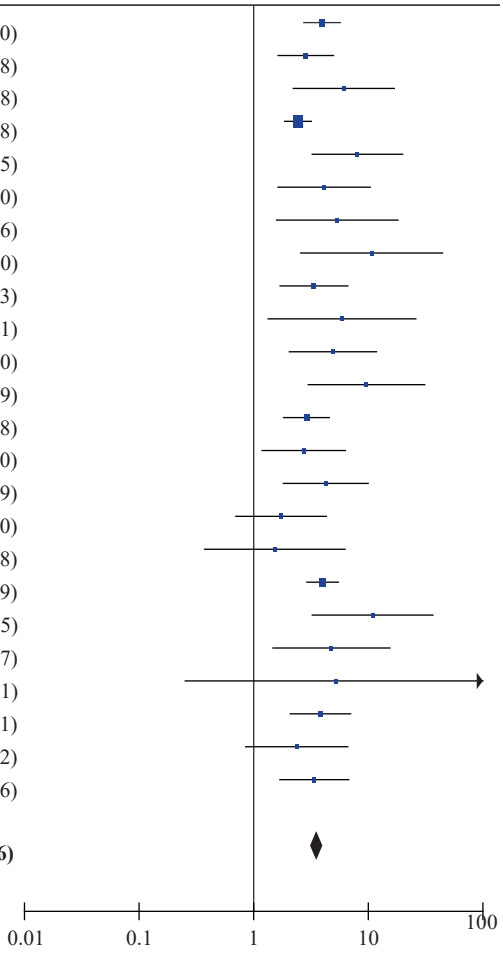

FIGURE 1. Occurrence of gastrointestinal-related adverse effects. (A) Meta-analysis of the incidence of nausea in the experimental (opioid treatment) and control (placebo) groups. (B) Analysis of constipation in both groups.
Abbreviation: *CI*=confidence interval.

addiction rates for patients under long-term opioid therapy are considerably higher compared to other analgesics (*9*). Addiction is often driven by intricate neurobiochemical alterations, such as dysregulation in the dopaminergic system and disturbances in reward mechanisms (*10*). Specifically, the dosage and duration of opioid administration are directly linked to its addictive potential, with higher dosages and extended use markedly amplifying the risk of dependency and abuse (*10*). Additionally, certain individuals are more vulnerable to addiction due to genetic factors or a history of substance misuse. Based on the findings of our study, we strongly recommend that clinicians prescribe opioids according to the principle of using "the lowest effective dose for the shortest effective duration." Moreover, we support the formulation and execution of a comprehensive multimodal treatment plan that includes physical therapy, psychological support, lifestyle changes, and suitable pharmacological treatments. This approach aims to comprehensively address pain and functional impairments, reduce medication-related side effects, and enhance overall disease management and quality of life.

The findings of this study have significant implications for policy-making and public health: 1) Drug regulatory agencies are urged to bolster the monitoring of opioids to curb abuse and illicit distribution. Additionally, the establishment of an exhaustive drug utilization registry system is essential for tracking and assessing opioid use and related adverse events. 2) Public health education efforts need to be escalated to enhance understanding of the

benefits and risks associated with opioids, especially in community settings and primary healthcare facilities, to promote their judicious use. 3) It is advisable that local or regional pain management guidelines be

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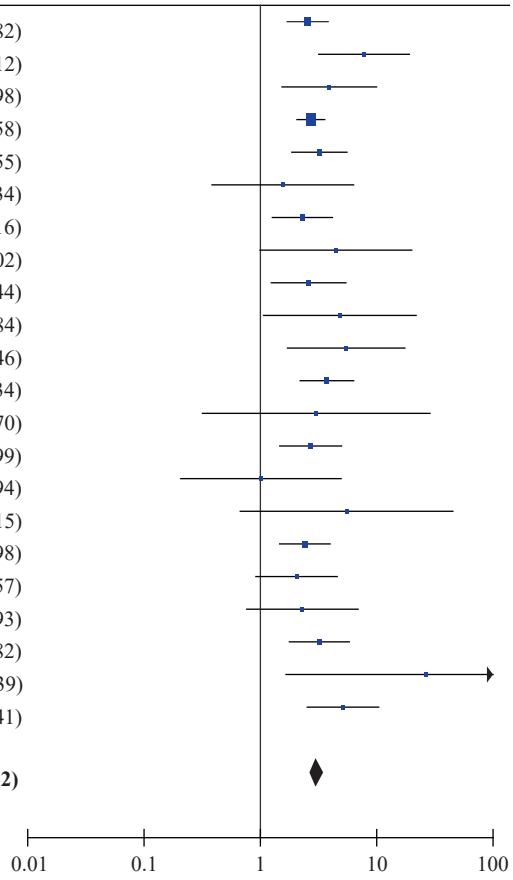
Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% *CI*
Alain Serrie 2017	70	319	29	337	12.0%	2.55 (1.70, 3.82)
Alan K. Matsumoto 2005	38	121	5	124	2.1%	7.79 (3.17, 19.12)
Alan Kivitz 2006	20	93	5	91	2.2%	3.91 (1.53, 9.98)
Bernd Lange 2010	169	980	63	993	26.7%	2.72 (2.06, 3.58)
Byron P. DeLemos 2011	48	199	15	200	6.4%	3.22 (1.86, 5.55)
Carter Thorne 2008	5	94	3	88	1.3%	1.56 (0.38, 6.34)
Catherine Munera 2010	30	152	14	163	5.8%	2.30 (1.27, 4.16)
Egilius L.H. Spierings 2013	10	158	2	141	0.9%	4.46 (0.99, 20.02)
Francis Burch 2007	42	432	8	214	4.6%	2.60 (1.24, 5.44)
Hugues Malonne 2004	9	111	2	119	0.8%	4.82 (1.07, 21.84)
Joseph A. Markenson 2005	18	56	3	51	1.3%	5.46 (1.71, 17.46)
Marc Afilalo 2010	61	344	16	337	6.9%	3.73 (2.20, 6.34)
Martin E Hale 2015	3	146	1	147	0.4%	3.02 (0.32, 28.70)
Najib Babul 2004	33	124	12	122	5.2%	2.71 (1.47, 4.99)
Nathaniel Katz 2010	3	171	3	173	1.3%	1.01 (0.21, 4.94)
Richard L. Rauck 2015	6	146	1	134	0.4%	5.51 (0.67, 45.15)
Richard Rauck 2013	48	330	20	332	8.5%	2.41 (1.47, 3.98)
Ritchard L. Fishman 2007	11	111	11	227	3.1%	2.05 (0.91, 4.57)
Sanford H. Roth 2000	9	44	4	45	1.7%	2.30 (0.76, 6.93)
Theophilus J. Gana 2006	41	201	13	205	5.5%	3.22 (1.78, 5.82)
Vishala L. Chindalore 2005	26	102	0	51	0.3%	26.76 (1.66, 430.39)
Walter F. Kean 2009	24	131	10	280	2.7%	5.13 (2.53, 10.41)
Total (95% *CI*)		**4,565**		**4,574**	**100.0%**	**3.06 (2.66, 3.52)**
Total events	724		240			

Heterogeneity: Chi²=18.81, df=21 (*P*=0.60); *I*²=0%

Test for overall effect: *Z*=15.59 (*P*<0.001)

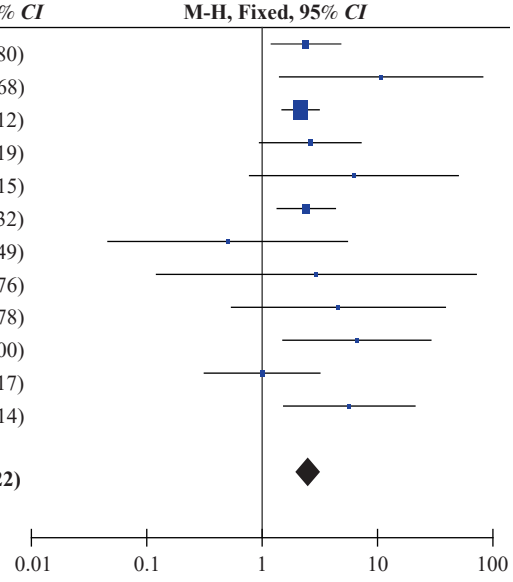


B

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk ratio M-H, Fixed, 95% *CI*
Alain Serrie 2017	25	319	11	337	12.7%	2.40 (1.20, 4.80)
Alan Kivitz 2006	11	93	1	91	1.2%	10.76 (1.42, 81.68)
Bernd Lange 2010	83	980	39	993	45.9%	2.16 (1.49, 3.12)
Byron P. DeLemos 2011	13	199	5	200	5.9%	2.61 (0.95, 7.19)
Egilius L.H. Spierings 2013	7	158	1	141	1.3%	6.25 (0.78, 50.15)
Marc Afilalo 2010	37	344	15	337	18.0%	2.42 (1.35, 4.32)
Martin E Hale 2015	1	146	2	147	2.4%	0.50 (0.05, 5.49)
Najib Babul 2004	1	124	0	122	0.6%	2.95 (0.12, 71.76)
Richard L. Rauck 2015	5	146	1	134	1.2%	4.59 (0.54, 38.78)
Theophilus J. Gana 2006	13	201	2	205	2.3%	6.63 (1.52, 29.00)
Vishala L. Chindalore 2005	8	102	4	51	6.3%	1.00 (0.32, 3.17)
Walter F. Kean 2009	8	131	3	280	2.3%	5.70 (1.54, 21.14)
Total (95% *CI*)		**2,943**		**3,038**	**100.0%**	**2.52 (1.98, 3.22)**
Total events	212		84			

Heterogeneity: Chi²=11.10, df=11 (*P*=0.43); *I*²=1%

Test for overall effect: *Z*=7.41 (*P*<0.001)



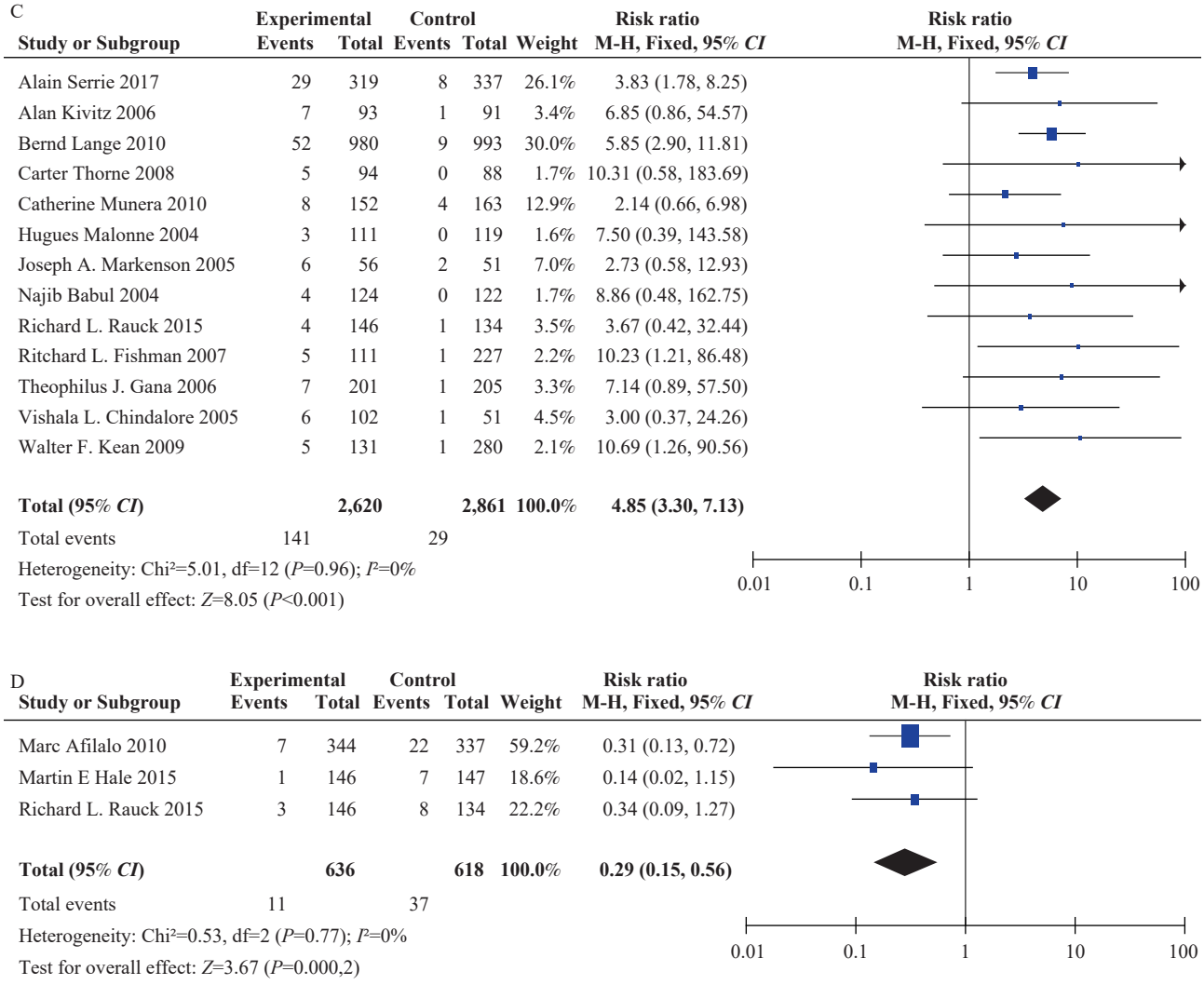


FIGURE 2. Occurrence of nervous system disorders, general disorders/administration site conditions, and adverse reactions related to skin, musculoskeletal, and connective tissue in the two study groups: (A) dizziness, (B) fatigue, (C) hyperhidrosis, (D) back pain.
Abbreviation: *CI*=confidence interval.

revised and updated by the latest research findings to guarantee the safety and effectiveness of pain management practices.

The study is subject to some limitations: 1) The incompleteness of the dataset presents a significant challenge, as some findings are either unpublished or inaccessible, potentially leading to systematic biases. Future research should broaden the scope of database searches to ensure a more comprehensive and equitable data integration. 2) There is variability in adverse event reporting across studies, which often lack consistent detail in descriptions and classifications, impairing the accurate interpretation and comparison of safety data. Subsequent studies should conform to the guidelines established by international drug monitoring organizations or the World Health Organization to standardize the reporting of adverse events. 3) The duration of observation in some studies is relatively short (2–4 weeks), which restricts the evaluation of long-term adverse reactions, including addiction or other sustained effects. Future research should prioritize long-term follow-ups to assess drug safety fully.

Opioid analgesics provide transient relief from pain and enhance functionality in patients with OA. However, their severe adverse effects, such as pruritus, hyperhidrosis, dry mouth, vomiting, somnolence, constipation, nausea, dizziness, and fatigue, must not

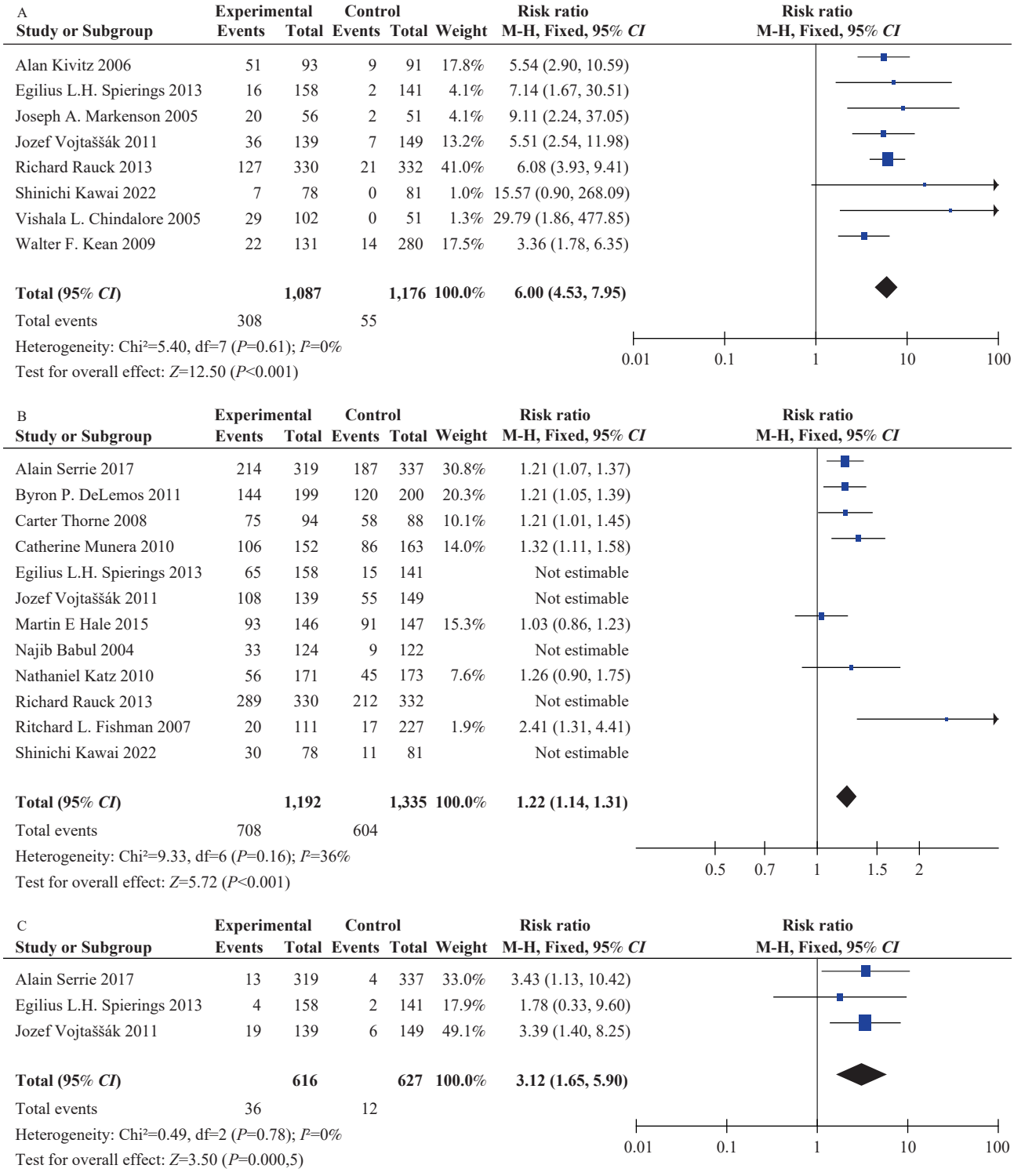


FIGURE 3. Comparative analysis of adverse reaction incidences in the experimental and control groups. (A) Therapy discontinued. (B) Total adverse events. (C) Serious adverse events.
Abbreviation: *CI*=confidence interval.

be underestimated. Moreover, prolonged usage carries risks of drug dependence and potential addiction. Therefore, it is imperative that future research focuses on assessing the long-term efficacy and safety of opioid

analgesics while also developing strategies to minimize these negative outcomes. Employing more stringent research methodologies will improve our global understanding of the safety profile of these medications.

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SUPPLEMENTARY MATERIAL

Literature Search Strategy

Comprehensive electronic searches were conducted across various databases such as PubMed, Embase, Cochrane Library, Medline, Web of Science, and National International Trial Registers, along with major Chinese databases including China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Chinese Journal Service Platform (VIP CJSP), and Chinese Biomedical Literature Database (CBM). The search covered the period from each database's inception to May 2024. There were no language restrictions. Search terms included "osteoarthritis," "knee arthritis," "hip arthritis," "opioids," "opioid," "randomized controlled trial," "randomized," and "placebo."

Literature Inclusion and Exclusion Criteria

Inclusion criteria: 1) Only randomized controlled trials (RCTs) were included, without restrictions on language or publication status. 2) Participants were patients diagnosed with osteoarthritis (OA), including specific conditions like hip and knee OA. 3) Interventions involved the use of opioids in the treatment of OA in the experimental group, with detailed reporting on factors such as drug name, dosage, and treatment duration. The control group received placebo treatments. 4) Primary outcomes were the types and frequency of opioid-related adverse drug reactions. Exclusion Criteria: 1) Excluded studies included non-clinical research, case reports, reviews, editorials, conference abstracts, and any studies not addressing OA treatment. 2) Studies that were duplicate publications. 3) Studies with incomplete data reporting, making it impossible to adequately assess the findings. 4) Studies classified as "high risk" according to the Cochrane Risk of Bias tool, falling below a predetermined quality threshold.

Literature Screening and Data Extraction

In conducting this systematic review, two researchers independently screened the literature following explicitly defined inclusion and exclusion criteria. A standardized data extraction form was utilized to carefully extract relevant information from the included studies. Discrepancies in interpretation were resolved through discussion by an expert committee (Supplementary Figure S1). When publications contained ambiguities or incomplete data, efforts were made to contact the original authors to obtain additional details, thus enhancing the quality of the dataset. Each piece of data was precisely annotated with its source page or bibliographic reference, facilitating later validation and re-evaluation. The extracted data included: 1) General bibliographic information such as the publication title, author list, and publication date; 2) Key study characteristics including research design, sample size, interventions in experimental and control groups, drug types and dosages, and the duration of treatment; 3) Primary outcome measures, specifically the type and frequency of adverse reactions associated with opioid use (Supplementary Table S2).

Literature Quality Assessment

In this study, we rigorously evaluated the methodological quality of the included literature using the Cochrane Risk of Bias Assessment Tool. The evaluation covered various dimensions, including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective outcome reporting, and other potential sources of bias. Each dimension was critically assessed, classifying risks as low, unclear, or high. This comprehensive process involved a detailed examination of the execution of randomized control trials, the effectiveness and implementation of blinding techniques, participant attrition and withdrawal rates, adequacy of sample sizes, and the complexities introduced by opioids, such as the variety in types, administration methods, and duration of use. The goal of this assessment was to meticulously quantify the quality and credibility of each study, establishing a solid foundation for further analysis. Following the evaluation, the literature demonstrated a low risk of bias and high credibility, providing substantial support for our conclusions.

Statistical Analysis

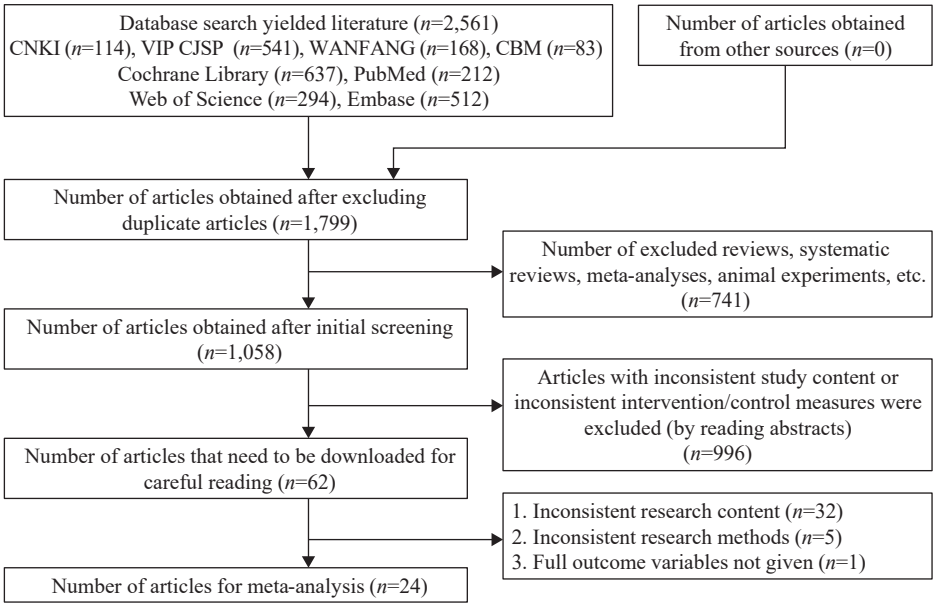
Statistical analyses were conducted using RevMan (version 5.4; Cochrane Collaboration, London, UK). Dichotomous outcomes were evaluated using relative risk (*RR*) or odds ratio (*OR*), and continuous outcomes were

assessed using either weighted mean difference (WMD) or standard mean difference (SMD), all presented with their corresponding 95% confidence intervals to measure the synthesized effect sizes. Inter-study heterogeneity was assessed using the I^2 test. Low heterogeneity was indicated by $P>0.1$ and $I^2<50\%$, prompting the use of a fixed-effect model. In cases of significant heterogeneity ($P<0.1$, $I^2\geq50\%$), a random-effects model was applied. Subgroup analyses were performed to investigate potential sources of heterogeneity, focusing on varied study characteristics such as study design, participant conditions, and intervention type. Sensitivity analyses were conducted to ascertain the robustness of the findings upon the exclusion of certain studies. A funnel plot was utilized to assess publication bias among the included studies. In meta-analyses, a P-value of <0.05 was deemed statistically significant.

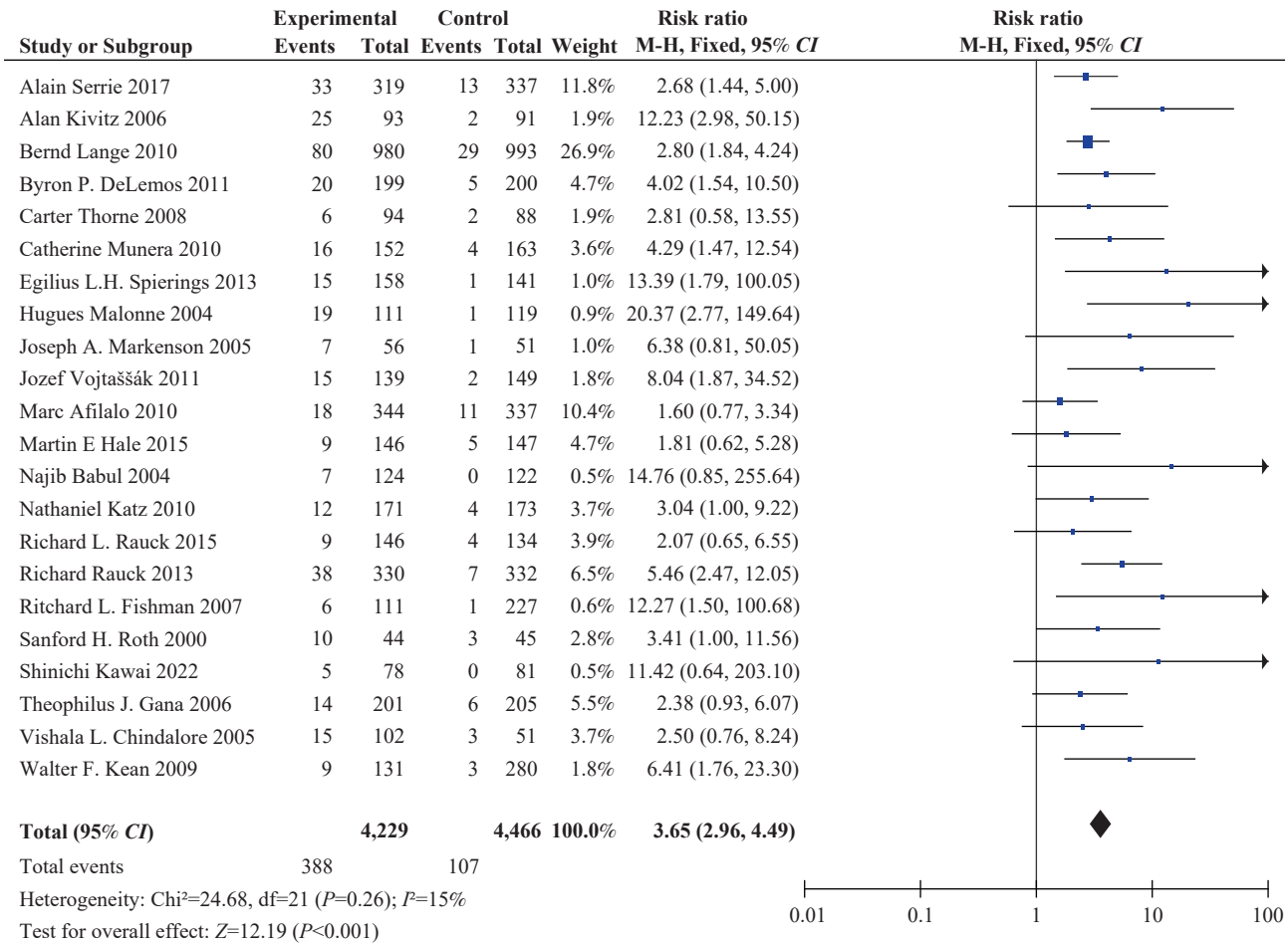
Standards for Severe Adverse Events

According to definitions provided by the International Council for Harmonisation (ICH) and the U.S. Food and Drug Administration (FDA), a severe adverse event is characterized as an undesirable experience linked to the use of a medicinal product that satisfies one or more of the following criteria: 1) Results in Death: any adverse event that directly or indirectly leads to a patient's death. 2) Life-Threatening: any adverse event that could result in death if not promptly treated, thus considered life-threatening. 3) Hospitalization or Prolongation of Existing Hospitalization: any adverse event necessitating inpatient hospitalization or prolonging an existing hospital stay. 4) Results in Significant or Persistent Disability/Incapacity: any adverse event causing a substantial and enduring impairment in physical or mental functions, thereby leading to disability or incapacity. 5) Congenital Anomalies/Birth Defects: any adverse outcome that results in congenital anomalies or birth defects in newborns. 6) Other Important Medical Events: adverse events that may not meet the previous criteria but, according to medical judgment, might endanger the patient or necessitate intervention to prevent one of the listed outcomes, such as the urgent treatment of a myocardial infarction or anaphylactic reaction.

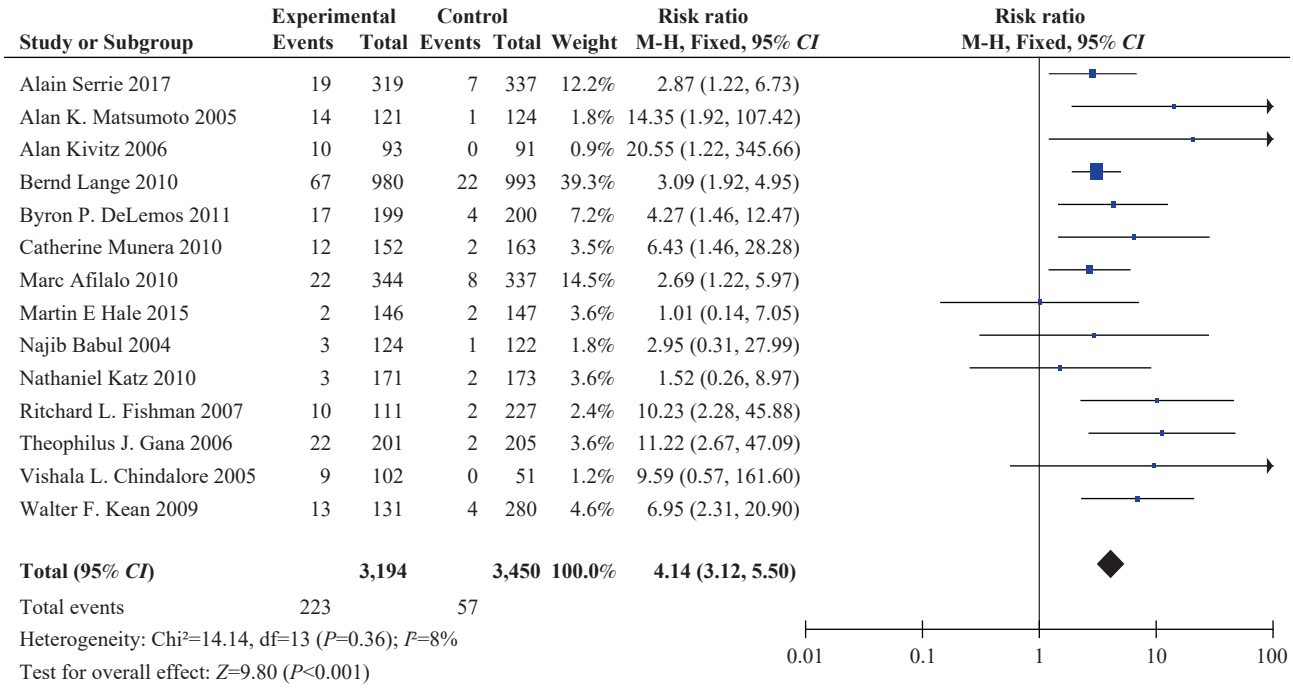
In this study, severe adverse events associated with opioid use in OA patients include, but are not limited to the following: 1) Respiratory Depression: this well-documented severe side effect, especially prevalent at high doses, can lead to potentially fatal respiratory compromise. 2) Severe Allergic Reactions: these reactions can include acute anaphylactic shock, which requires immediate medical intervention to prevent life-threatening or disabling outcomes. 3) Severe Constipation Leading to Intestinal Obstruction: chronic opioid usage may cause severe constipation that can progress to intestinal obstruction, potentially requiring surgical intervention. 4) Sedation-induced Coma: excessive sedation from opioid use can cause coma states necessitating emergency management. 5) Cardiovascular Events: these severe incidents, such as arrhythmias or myocardial infarction, require urgent medical attention, particularly in vulnerable patients. 6) Severe Outcomes Due to Addiction: these include outcomes like acute overdose or significant societal issues stemming from opioid addiction and abuse.



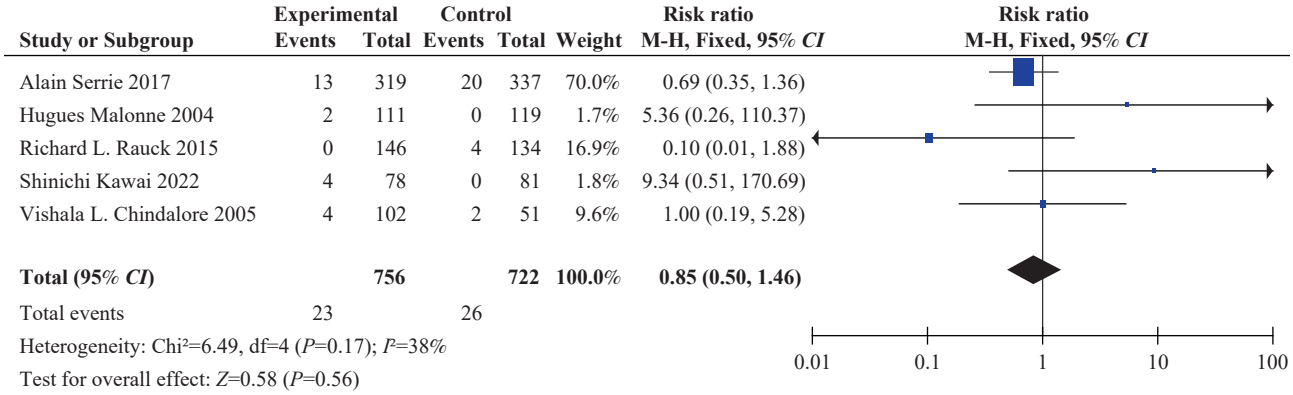
SUPPLEMENTARY FIGURE S1. Screening flow chart for literature search.
Abbreviation: CNKI=China National Knowledge Infrastructure; VIP CJSP=VIP Chinese Journal Service Platform; CBM=Chinese Biomedical Literature Database.



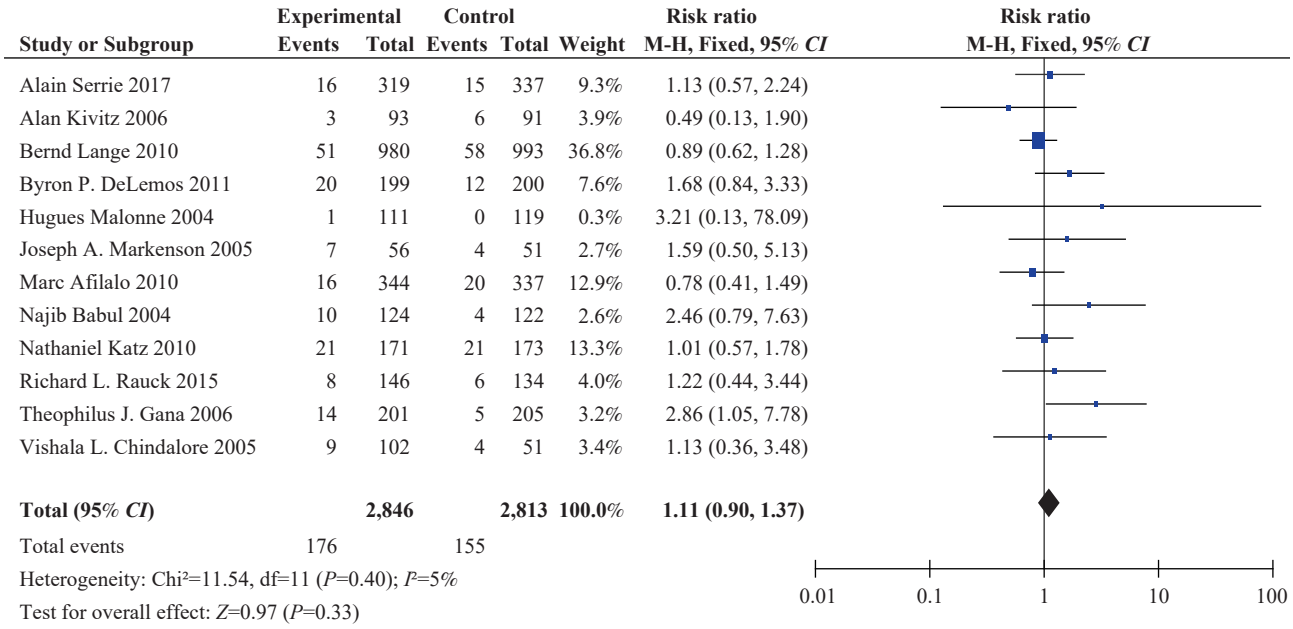
SUPPLEMENTARY FIGURE S2. Meta-analysis of the incidence of vomiting in the experimental (opioid treatment) and control (placebo) groups.
Abbreviation: *CI*=confidence interval.



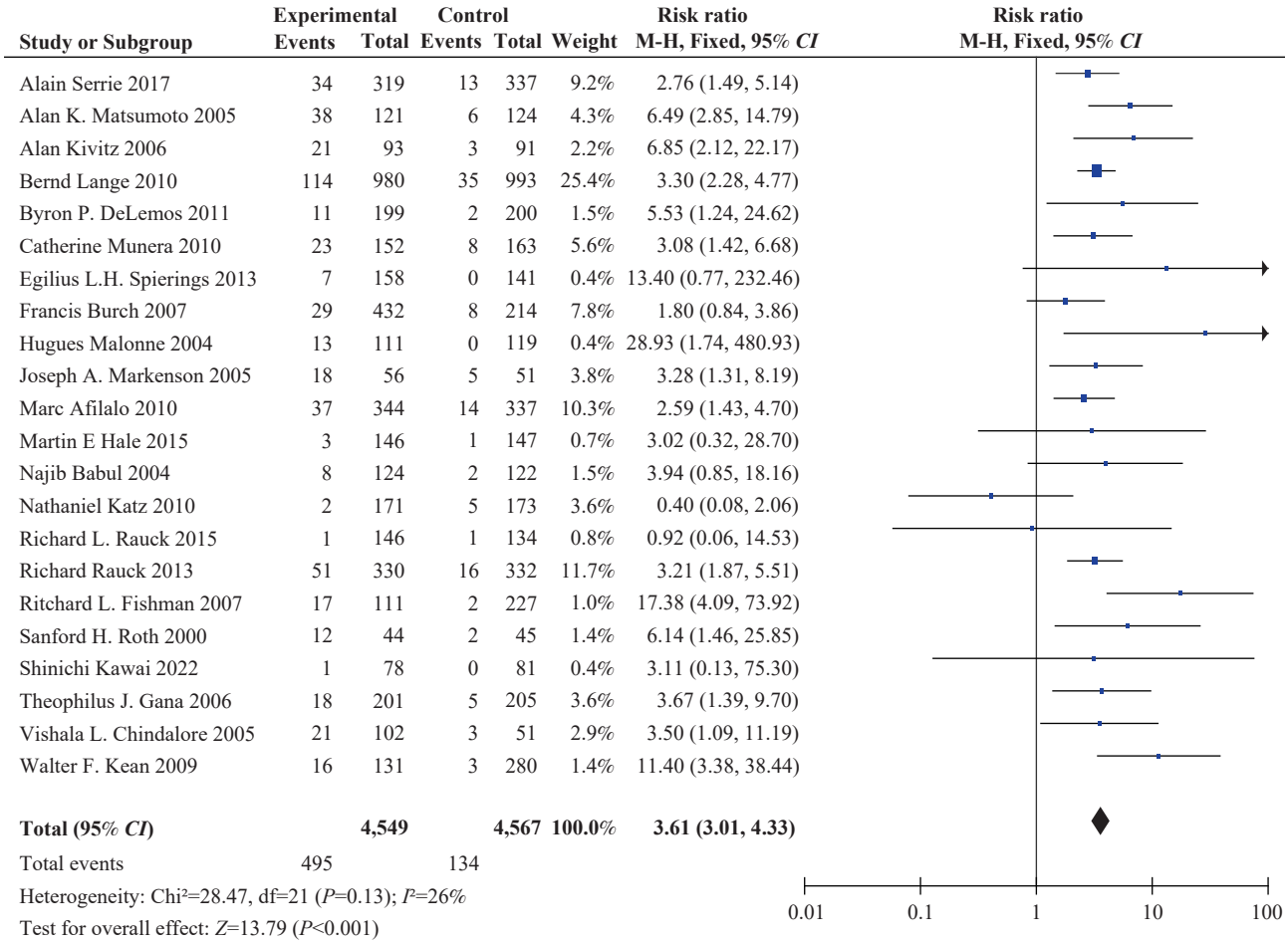
SUPPLEMENTARY FIGURE S3. Meta-analysis of the incidence of dry mouth in the experimental (opioid treatment) and control (placebo) groups.
Abbreviation: *CI*=confidence interval.



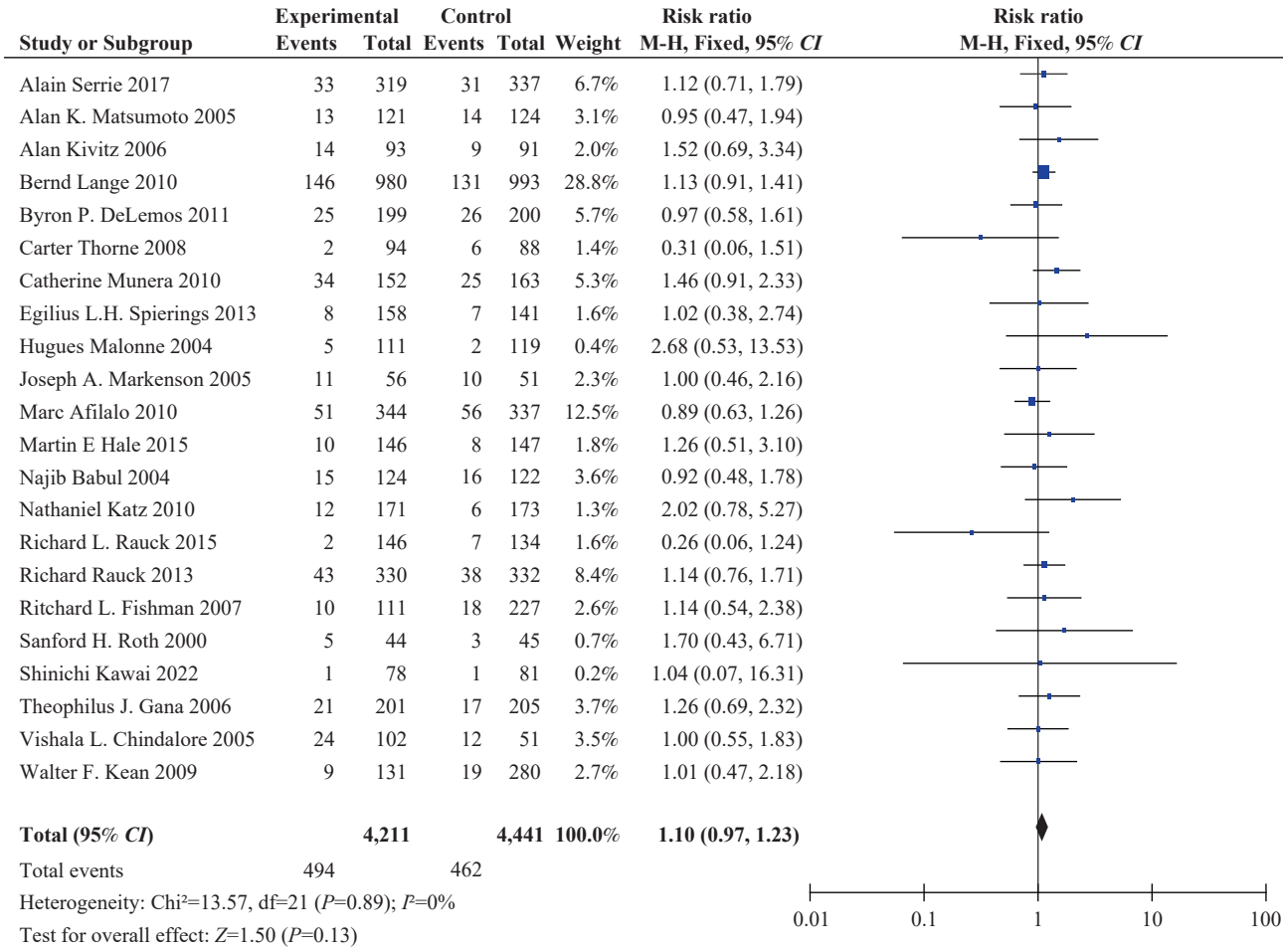
SUPPLEMENTARY FIGURE S4. Meta-analysis of the incidence of upper abdominal pain in the experimental (opioid treatment) and control (placebo) groups.
Abbreviation: *CI*=confidence interval.



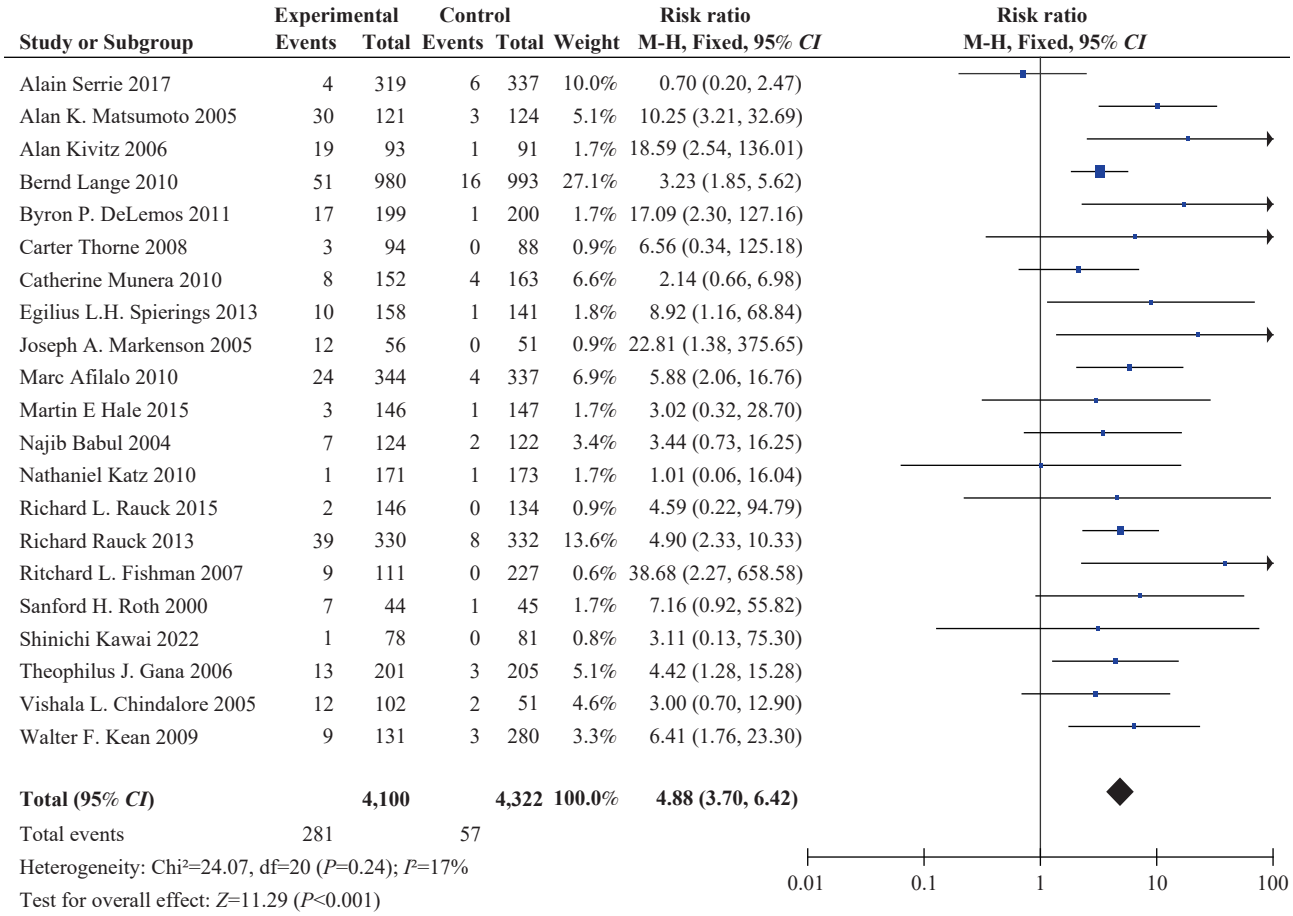
SUPPLEMENTARY FIGURE S5. Meta-analysis of the incidence of diarrhea in the experimental (opioid treatment) and control (placebo) groups.
Abbreviation: *CI*=confidence interval.



SUPPLEMENTARY FIGURE S6. Meta-analysis of the incidence of somnolence in the experimental (opioid treatment) and control (placebo) groups.
Abbreviation: *CI*=confidence interval.



SUPPLEMENTARY FIGURE S7. Meta-analysis of the incidence of headache in the experimental (opioid treatment) and control (placebo) groups.
Abbreviation: *CI*=confidence interval.



SUPPLEMENTARY FIGURE S8. Meta-analysis of the incidence of pruritus in the experimental (opioid treatment) and control (placebo) groups.
Abbreviation: *CI*=confidence interval.

SUPPLEMENTARY TABLE S1. Search strategies used for each database.

Database	Search strategies
PubMed	((("Osteoarthritis"[Mesh]) OR ((((((((((Osteoarthritides[Title/Abstract]) OR (Osteoarthrosis[Title/Abstract])) OR (Osteoarthroses[Title/Abstract])) OR (Arthritis, Degenerative[Title/Abstract])) OR (Arthritides, Degenerative[Title/Abstract])) OR (Degenerative Arthritides[Title/Abstract])) OR (Degenerative Arthritis[Title/Abstract])) OR (Arthrosis[Title/Abstract])) OR (Arthroses[Title/Abstract])) OR (Osteoarthrosis Deformans[Title/Abstract]))) AND (("Analgesics, Opioid"[Mesh]) OR ((((((((((((((((((((Opioid Analgesics[Title/Abstract]) OR (Opioid Analgesic[Title/Abstract])) OR (Analgesic, Opioid[Title/Abstract])) OR (Opioids[Title/Abstract])) OR (Opioid[Title/Abstract])) OR (Partial Opioid Agonists[Title/Abstract])) OR (Agonists, Partial Opioid[Title/Abstract])) OR (Opioid Agonists, Partial[Title/Abstract])) OR (Opioid Partial Agonists[Title/Abstract])) OR (Agonists, Opioid Partial[Title/Abstract])) OR (Partial Agonists, Opioid[Title/Abstract])) OR (Full Opioid Agonists[Title/Abstract])) OR (Agonists, Full Opioid[Title/Abstract])) OR (Opioid Agonists, Full[Title/Abstract])) OR (Opioid Full Agonists[Title/Abstract])) OR (Agonists, Opioid Full[Title/Abstract])) OR (Full Agonists, Opioid[Title/Abstract])) OR (Opioid Mixed Agonist-Antagonists[Title/Abstract])) OR (Agonist-Antagonists, Opioid Mixed[Title/Abstract])) OR (Mixed Agonist-Antagonists, Opioid[Title/Abstract])) OR (Opioid Mixed Agonist Antagonists[Title/Abstract]))))) AND (randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract])
Embase	('osteoarthritis'/exp OR osteoarthritis OR 'osteoarthritides':ab,ti OR 'osteoarthrosis':ab,ti OR 'osteoarthroses':ab,ti OR 'arthritis, degenerative':ab,ti OR 'arthritides, degenerative':ab,ti OR 'degenerative arthritides':ab,ti OR 'degenerative arthritis':ab,ti OR 'arthrosis':ab,ti OR 'arthroses':ab,ti OR 'osteoarthrosis deformans':ab,ti) AND (opioids OR 'opioid analgesics':ab,ti OR 'opioid analgesic':ab,ti OR 'analgesic, opioid':ab,ti OR 'opioids':ab,ti OR 'opioid':ab,ti OR 'partial opioid agonists':ab,ti OR 'agonists, partial opioid':ab,ti OR 'opioid agonists, partial':ab,ti OR 'opioid partial agonists':ab,ti OR 'agonists, opioid partial':ab,ti OR 'partial agonists, opioid':ab,ti OR 'full opioid agonists':ab,ti OR 'agonists, full opioid':ab,ti OR 'opioid agonists, full':ab,ti OR 'opioid full agonists':ab,ti OR 'agonists, opioid full':ab,ti OR 'full agonists, opioid':ab,ti OR 'opioid mixed agonist-antagonists':ab,ti OR 'agonist-antagonists, opioid mixed':ab,ti OR 'mixed agonist-antagonists, opioid':ab,ti OR 'opioid mixed agonist antagonists':ab,ti) AND ('randomized controlled trial':ab,ti OR 'randomized':ab,ti OR 'placebo':ab,ti)
Cochrane Library	#1 Osteoarthritis #2 (Osteoarthritides):ab,ti,kw OR (Osteoarthrosis):ab,ti,kw OR (Osteoarthroses):ab,ti,kw OR (Arthritis, Degenerative):ab,ti,kw OR (Arthritides, Degenerative):ab,ti,kw OR (Degenerative Arthritides):ab,ti,kw OR (Degenerative Arthritis):ab,ti,kw OR (Arthrosis):ab,ti,kw OR (Arthroses):ab,ti,kw OR (Osteoarthrosis Deformans):ab,ti,kw #3 #1 OR #2 #4 Analgesics, Opioid #5 (Opioid Analgesics):ab,ti,kw OR (Opioid Analgesic):ab,ti,kw OR (Analgesic, Opioid):ab,ti,kw OR (Opioids):ab,ti,kw OR (Opioid):ab,ti,kw OR (Partial Opioid Agonists):ab,ti,kw OR (Agonists, Partial Opioid):ab,ti,kw OR (Opioid Agonists, Partial):ab,ti,kw OR (Opioid Partial Agonists):ab,ti,kw OR (Agonists, Opioid Partial):ab,ti,kw OR (Partial Agonists, Opioid):ab,ti,kw OR (Full Opioid Agonists):ab,ti,kw OR (Agonists, Full Opioid):ab,ti,kw OR (Opioid Agonists, Full):ab,ti,kw OR (Opioid Full Agonists):ab,ti,kw OR (Agonists, Opioid Full):ab,ti,kw OR (Full Agonists, Opioid):ab,ti,kw OR (Opioid Mixed Agonist-Antagonists):ab,ti,kw OR (Agonist-Antagonists, Opioid Mixed):ab,ti,kw OR (Mixed Agonist-Antagonists, Opioid):ab,ti,kw OR (Opioid Mixed Agonist Antagonists):ab,ti,kw #6 #4 OR #5 #7 (randomized controlled trial):ab,ti,kw OR (randomized):ab,ti,kw OR (placebo):ab,ti,kw #8 #3 AND #6 AND #7
Web of Science	1: TS=(Osteoarthritis OR Osteoarthritides OR Osteoarthrosis OR Osteoarthroses OR Arthritis, Degenerative OR Arthritides, Degenerative OR Degenerative Arthritides OR Degenerative Arthritis OR Arthrosis OR Arthroses OR Osteoarthrosis Deformans) Results: 82706 2: TS=(Analgesics, Opioid OR Analgesics, Opioid OR Analgesics, Opioid OR Analgesic, Opioid OR Opioids OR Opioid OR Partial Opioid Agonists OR Agonists, Partial Opioid OR Opioid Agonists, Partial OR Opioid Partial Agonists OR Agonists, Opioid Partial OR Partial Agonists, Opioid OR Full Opioid Agonists OR Agonists, Full Opioid OR Opioid Agonists, Full OR Opioid Full Agonists OR Agonists, Opioid Full OR Full Agonists, Opioid OR Opioid Mixed Agonist-Antagonists OR Agonist-Antagonists, Opioid Mixed OR Mixed Agonist-Antagonists, Opioid OR Opioid Mixed Agonist Antagonists) Results: 78031 3: TS=(randomized controlled trial OR randomized OR placebo) Results: 705452 4: #1 AND #2 AND #3 Results: 294

SUPPLEMENTARY TABLE S2. Basic characteristics of the included tallied studies.

The first author	Year of publication	Interventions		Sample size		Intervention time (weeks)	Opioid-related side effects
		Experimental group	Control group	Experimental group	Control group		
Alain Serrie (*1*)	2017	Tapentadol PR, 250 mg/12h	Placebo	319	337	15	1) 2) 3) 4) 5) 6) 7) 8) 9) 10) 11) 12)
Alan K. Matsumoto (*2*)	2005	Oxymorphone ER, 40 mg/12h	Placebo	121	124	4	1) 2) 4) 7) 8) 9) 12)
Alan Kivitz (*3*)	2006	Oxymorphone ER, 40 mg/12h	Placebo	93	91	2	1) 2) 3) 4) 5) 7) 8) 9) 10) 11) 12)
Bernd Lange (*4*)	2010	Tapentadol PR, 100-250 mg/12h	Placebo	980	993	12	1) 2) 3) 4) 5) 7) 8) 9) 10) 11) 12)
Byron P. DeLemos (*5*)	2011	Tramadol ER, 300 mg/d	Placebo	199	200	12	1) 2) 3) 4) 5) 7) 8) 9) 10) 12)
Carter Thorne (*6*)	2008	Tramadol CR, 150-300 mg/d	Placebo	94	88	8	1) 2) 3) 7) 9) 11) 12)
Catherine Munera (*7*)	2010	Buprenorphine, 0.12-0.48 mg/d	Placebo	152	163	4	1) 2) 3) 4) 7) 8) 9) 11) 12)
Egilius L.H. Spierings (*8*)	2013	Oxycodone CR, 10-40 mg/12h	Placebo	158	141	16	1) 2) 3) 7) 8) 9) 10) 12)
Francis Burch (*9*)	2007	Tramadol Contramid OAD, 200-300 mg/d	Placebo	432	214	12	1) 2) 7) 8)
Hugues Malonne (*10*)	2004	Tramadol LR, 200 mg/d	Placebo	111	119	2	1) 2) 3) 5) 6) 7) 8) 9) 11)
Joseph A. Markenson (*11*)	2005	Oxycodone CR, 10 mg/12 h	Placebo	56	51	12	1) 2) 3) 5) 7) 8) 9) 11) 12)
Jozef Vojtaššák (*12*)	2011	OROS Hydromorphone, ≥ 4 mg/d	Placebo	139	149	16	2) 3)
Marc Afilalo (*13*)	2010	Tapentadol ER, 100-250 mg/12h	Placebo	344	337	15	1) 2) 3) 4) 5) 7) 8) 9) 10) 12) 13)
Martin E Hale (*14*)	2015	Hydrocodone ER, 15-90 mg/12h	Placebo	146	147	12	1) 2) 3) 4) 7) 8) 9) 10) 12) 13)
Najib Babul (*15*)	2004	Tramadol ER, 200-400 mg/d	Placebo	124	122	12	1) 2) 3) 4) 5) 7) 8) 9) 10) 11) 12)
Nathaniel Katz (*16*)	2010	Morphine Sulfate and Naltrexone Hydrochloride ER Capsules, 20–160 mg/d	Placebo	171	173	12	1) 2) 3) 4) 5) 7) 8) 9) 12)
Richard L. Rauck (*17*)	2015	Oxycodone hydrochloride, 20-160 mg/d	Placebo	146	134	12	1) 2) 3) 5) 6) 7) 8) 9) 10) 11) 12) 13)
Richard Rauck (*18*)	2013	OROS Hydromorphone ER, 16 mg/d	Placebo	330	332	12	1) 2) 3) 7) 8) 9) 12)
Ritchard L. Fishman (*19*)	2007	Tramadol Contramid OAD, 200 mg/d	Placebo	111	227	12	1) 2) 3) 4) 7) 8) 9) 11) 12)
Sanford H. Roth (*20*)	2000	Oxycodone CR, 20 mg/12 h	Placebo	44	45	2	1) 2) 3) 7) 8) 9) 12)
Shinichi Kawai (*21*)	2022	Tramadol, 100-300 mg/d	Placebo	78	81	4	1) 2) 3) 6) 8) 9) 12)
Theophilus J. Gana (*22*)	2006	Tramadol ER, 300 mg/d	Placebo	201	205	12	1) 2) 3) 4) 5) 7) 8) 9) 10) 11) 12)
Vishala L. Chindalore (*23*)	2005	Oxycodone, 10–40 mg/d	Placebo	102	51	3	1) 2) 3) 4) 5) 6) 7) 8) 9) 10) 11) 12)
Walter F. Kean (*24*)	2009	Tramadol Contramid OAD, 200 mg/d	Placebo	131	280	12	1) 2) 3) 4) 7) 8) 9) 10) 11) 12)

Note: Opioid-related side effects include: 1) nausea; 2) constipation; 3) vomiting; 4) dry mouth; 5) diarrhea; 6) upper abdominal pain; 7) dizziness; 8) somnolence; 9) headache; 10) fatigue; 11) hyperhidrosis; 12) pruritus; 13) back pain.

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