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Opioid Prescribing in the Elderly: A Systematic Review

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Abstract

Objective: To characterize the literature describing the therapeutic use of opioids in the elderly. **Data Sources:** Two electronic databases, EMBASE and MEDLINE, were searched from years 1990 to September 5, 2018. Relevant reference lists were reviewed. Searches were restricted to English language. **Study Selection and Data Extraction:** Two reviewers independently screened 827 citations to identify observational studies, population-based cohort studies, retrospective analyses, and control trials looking at the management of persistent pain in patients aged ≥65 years and/or frail patients. **Data Synthesis:** Thirty-nine articles were included in the systematic review. More specifically, 17 observational studies, 7 population-based cohort studies, 10 retrospective analyses, and 4 controlled trials. The most common etiology of persistent pain was musculoskeletal (50%), and the most often adverse effects reported were central nervous system related (41%) and falls/fractures (39%). **Relevance to Patient Care and Clinical Practice:** As there is a lack of strong evidence-based recommendations for opioid use in the elderly, this review aims to evaluate opioid use in the elderly and compare their efficacy and safety among this population. **Conclusions:** Overall, central nervous system adverse effects were most commonly seen in the elderly. However, higher quality evidence is required to further appreciate the dose-related effects on efficacy and safety of opioids in the elderly.

Keywords

opioid, elderly, older adult, persistent pain

Introduction

In 2017, the incidence of persistent pain in a European study conducted in Switzerland was 38.5%, and this number is projected to rise as the average age of the population increases.[1,2] In 2009, the American Geriatric Society published now inactive guidelines for management of persistent pain in the elderly that suggested nonopioid pharmacotherapy with acetaminophen as first-line, especially for musculoskeletal pain due to its demonstrated effectiveness and favorable safety profile (evidence level of 1-A).[3] The authors also suggest that nonselective nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective inhibitors be considered rarely and with extreme caution as the risks of therapy often outweigh the benefit in the elderly population (evidence level of 1-A), which limits nonopioid analgesic options.[3-5] In patients with moderate to severe pain with accompanying functional impairment or diminished quality of life and who have had little or no benefit with nonopioid therapy, guidelines suggest initiating treatment with low doses of opioids, with careful upward titration, while continually monitoring for adverse effects (evidence level of 3a; expert opinion).[3] This recommendation provides no specific guidance with regard to specific agent, initial dosing, or key monitoring parameters and reflects a low level of evidence.

When considering analgesia in the elderly, parameters such as expected benefits based on etiology, age-related physiological changes, comorbidities, and potential adverse effects should all be assessed.[2,3,6-10] Pharmacokinetic parameters of opioids can vary greatly in the aging population.[2,3,6-10] The rate at which certain drugs are absorbed is altered due to a decrease in gastrointestinal transit time and an increase in gastric pH. The distribution of lipophilic drugs is enhanced due to an increase in adipose tissue. Metabolism slows down due to reduced hepatic blood flow and impaired phase I reactions (ie, oxidation, hydroxylation, and dealkylation). Elimination can

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be altered due to age-related reductions in renal blood flow and glomerular filtration rate.[7] Common comorbidities in older adults such as frailty, visual impairment, hearing impairment, cardiovascular disease (ie, hypertension, coronary artery disease, and congestive heart failure), musculoskeletal conditions (ie, arthritis), dementia, stroke, and diabetes mellitus may either increase the risk of side effects (ie, confusion, dizziness, sedation, falls, constipation) from opioid use or attenuate the benefits.[3,6]

Although opioids are recommended for management of moderate to severe pain in guidelines (evidence level 3-A), there is still a lack of strong evidence-based recommendations for their use in older adults. The objective of this review is to determine which opioids have been studied in older adults and describe their efficacy and safety, if possible.

Methods

Protocol and Registration

A prespecified protocol for our systematic review was created and was registered with PROSPERO, an international database of prospectively registered systematic reviews in health and social care (Registration Number: CRD42018084201).

Eligibility Criteria

We included observational studies, crossover studies, population-based cohort studies, retrospective analyses, case-control studies, nested case-control studies, and randomized control trials in our systematic review. The search was limited to publications from 1970 to September 5, 2018, that were available in English. Studies that included patients ≥65 years old or frail patients who were receiving opioids for the management of persistent pain (defined as pain that continues for greater than 3 months) were eligible for inclusion. Opioids were defined as any of the following: codeine combination products, oxycodone, hydrocodone, hydromorphone, oxymorphone, morphine, methadone, buprenorphine, fentanyl, sufentanil, and tapentadol. Narrative reviews; editorials; studies analyzing acute pain, postoperative pain, and palliative pain; and animal studies were excluded.

Information Sources and Search

A search strategy was developed with assistance from the designated Pharmaceutical Sciences research librarian located at the University of British Columbia. The databases MEDLINE and EMBASE were searched using the following terms: (narcotic analgesic agent/ OR opiate* or opioid or fentanyl or buprenorphine or sufentanil or hydromorphone or morphine or oxycodone or methadone or codeine or hydrocodone or oxymorphone or tapentadol) AND (elder* or senior* or geriatric* or older adult* or frail*) AND (chronic pain/ OR persistent pain or chronic pain) for EMBASE; and (exp Analgesics, Opioid/ OR opiate* or opioid or fentanyl or buprenorphine or hydromorphone or morphine or oxycodone or methadone or codeine) AND (elder* or senior* or geriatric or older adult* or frail*) AND (Chronic Pain/ OR persistent pain or chronic pain) for MEDLINE. Limits applied to both databases included English language and year = "1970–Current (September 5, 2018)." Gray literature was searched using Google Scholar.

Study Selection and Search

Two reviewers (both MJ and HH) independently screened articles. If disagreements occurred, a third reviewer (either KD or GE) resolved any disagreements.

Data Collection Process

The data were extracted by one reviewer (MJ) from all included articles using a prespecified data collection form contained within Excel for Mac 2011, version 14.7.7.

Data Items

Extracted data included information regarding study design, etiology of persistent pain, type of opioid used, dose of opioid, pharmacokinetic parameters assessed, comorbidities, assessment of frailty, adverse effects, drug interactions, hospitalization secondary to opioid toxicity, and overall recommendation for use of opioids. For comorbidities, we were primarily interested in dementia, Parkinson's disease, history of prior stroke, cardiovascular disease, chronic renal impairment, cirrhosis, and malignancy. For adverse effects, we were interested primarily in respiratory depression, falls, dizziness, confusion, and constipation. The comorbidities and adverse effects were chosen as they were felt to be most relevant to an elderly population and most likely to lead to potential adverse effects.

Risk of Bias in Individual Studies

To assess for bias in individual studies, the Cochrane Risk of Bias tool[5] was applied to randomized studies and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I,[11] Table 2) was applied to nonrandomized studies.

Synthesis of Results

Descriptive analysis of the identified studies was completed using information collected from the prespecified outcomes.

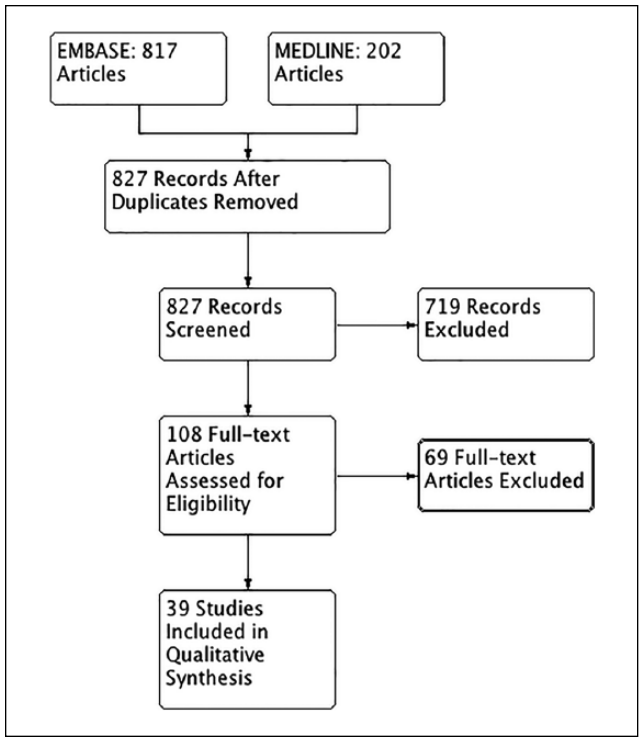

Figure 1. PRISMA flow diagram for the studies included in the analysis of opiate prescribing in the elderly.

Results

Study Selection

Of the 827 non-duplicate articles screened, there were 39 articles that met inclusion criteria (Figure 1).[12-50] There were 719 articles excluded after the initial screening of titles and abstracts with an additional 57 articles excluded after full-text review. In total, 39 articles met the eligibility criteria and were included in the systematic review (Figure 1). No articles were found in the gray literature. Overall, 17 observational studies,[12-29] 7 population-based cohort studies,[30-36] 10 retrospective analyses,[37-46] and 4 controlled trials were included.[47-50] The study population sizes ranged from 10 to 800 patients.[12-50] Studies were published from 1970 to 2017, with 29 studies published recently from 2010 to 2017. The published journal impact factor ranged from 1.69 to 8.955.[12-50]

Study Characteristics

The range of mean ages across individual studies was 60.5 to 83 years, and 66.6% of participants in the included studies were female.[12-50]

Summary of Included Studies

Musculoskeletal pain (50%; arthritis, back/hip/knee pain) was the primary etiology of persistent pain in 29 studies.[12,16,18,20-23,25-31,33-36,38,39,42,46-50] Other causes of persistent pain identified included peripheral/diabetic neuropathy (24%),[12,16,22,31,32,35,36,41,48,49] cancer pain (16%),[25,35,48] osteoporosis (11%),[21,25,30,33] headache (8%),[30,41,46] fibromyalgia (8%),[32,36,41] radiculopathy (5%),[31,32] postherpetic neuralgia (5%),[17,31] gout (3%),[41] rheumatoid arthritis (3%),[38] ischemic heart disease (3%),[38] multiple sclerosis (3%),[26] and abdominal pain (3%).[46]

The most common comorbidities identified across all studies included cardiovascular disease (26%)[19,23,25,28,30,33,37,39,43,48] and dementia/cognitive impairment (21%).[13,14,18,33,34,37,39,46] Other comorbidities identified included previous stroke (13%),[19,25,32,33,37] depression (13%),[23,25,26,27,33] renal impairment (8%),[28,37,43] Parkinson's disease (8%),[32,33,39] malignancy (8%),[19,32,37] frailty (5%),[42,45] concomitant substance use (5%),[20,33] cirrhosis (3%),[37] and asthma/chronic obstructive pulmonary disease (3%).[33] Congestive heart failure was considered the primary cause of cardiovascular disease in approximately half of the studies that reported on this outcome.[28,33,37,39] In one of the studies, frailty was defined according to the frailty criteria used in the Cardiovascular Health Study: shrinking/sarcopenia, weakness, poor endurance and energy, slowness, and low physical activity level.[45] Participants were considered frail if they met 3 or more of the 5 frailty criteria.[45] In the other study, participants were categorized as robust, intermediate, or frail using the Study of Osteoporotic Fractures Frailty Index.[42]

Overall, 28 of the included studies reported on type of opioid assessed.[13-19,21-23,25,28-38,44,46-50] The 12 remaining studies were primarily population-based cohort studies and were designed to describe the characteristics of elderly patients receiving opioids for management of persistent pain.[12,20,24,26,27,39-43,45] Of the studies that did describe type of opioid used, 13 assessed morphine,[13,17,19,25,28,32-34,36-38,44,46] 12 assessed oxycodone,[13,15,18,25,28,31,32,34,37,38,44,46] 11 assessed codeine,[13,25,28,33,34,35,38,44,46,49,50] 9 assessed fentanyl,[13,14,16,25,28,33,34,37,44] 9 assessed buprenorphine,[22,23,29,30,33,35,44,47,48] 6 assessed hydromorphone,[13,21,25,34,38,44] 5 assessed methadone,[13,25,37,38,44] and 1 assessed sufentanil.[44] Of the 28 studies that reported on type of opioid used, 16 of these reported on dosing. Dosing regimens of morphine varied across the studies, and included a range of 9 to 120 mg immediate release by mouth over a 24-hour period or 15 mg slow release by mouth once daily.[17,19,32,36,37] The study looking at slow release morphine also looked at other long-acting oral formulations of opioids, such as oxycodone 10 mg controlled release by mouth twice daily and compared this with transdermal fentanyl at a dose of 25 µg/h.[37] An open-label study evaluating the efficacy and safety of buprenorphine sublingual at a dose of 0.1 mg 3 to 4 times per day over a 14-day period was included in our review.[29] In this study, sublingual buprenorphine at this dose was effective in 6 of the 26 patients who completed the study and associated with a higher incidence of nausea, vomiting, and confusion.[29] Of the 4

control trials included, 2 looked at buprenorphine transdermal system (BTDS) at doses of 5 to 20 μg/h, and 35, 40, and 50 μg/h, and 2 looked at codeine 30 to 60 mg/acetaminophen 300 mg to 600 mg.[47-50] The 2 control trials evaluating BTDS found this agent to be ineffective in reducing arthritic pain and was associated with an increased risk of both dizziness and pruritis.[47,48]

The most common adverse effects reported in the studies were central nervous system (CNS) related (dizziness, confusion, mental status changes, lethargy, depression, headache, somnolence) and falls/fractures, with the proportion of studies that reported this adverse effect being 41% and 39%, respectively.[12,15,18,19,21-23,28-30,34,36,39,40,47-50] In a population-based cohort study assessing the association between opioid dose and fractures, the authors concluded that higher doses of opioids (equivalent to 50 mg equivalent of codeine daily) was associated with a 2-fold increase in risk of fractures.[45] Gastrointestinal-related (constipation, N/V) adverse effects contributed to ~15% of adverse effects identified in these studies.[12,18,21-23,28-32,34,36,39,47-50]

Three of the included studies reported on hospitalizations. In a retrospective analysis conducted by Reid et al in 2010 to describe the characteristics of older adults receiving opioids for chronic noncancer pain, 7 (5%) patients were hospitalized, 5 were hospitalized for altered mental status, 1 for obstipation, and 1 for unintentional overdose.[34] In a population-based cohort study looking at the association between fractures and opioid use (codeine in this study), 117 (36.6%) patients were hospitalized for a fracture and 6 (1.9%) died within 2 months of hospitalization for fracture.[46] The last study that reported on hospitalizations was a retrospective analysis evaluating the safety of BTDS. In this study, 103 (6%) patients were reported being hospitalized for cardiac failure, chest pain, fall, and transient ischemic attack.[30]

Summary of Control Trials (Table 1)

Four controlled trials were included in our review. The 2 most recent studies (2008 and 2010) evaluated BTDS and the other 2 (1990 and 1994) evaluated codeine/acetaminophen.[47-50] All of these studies evaluated the respective agents in the management of musculoskeletal pain, with the primary etiology of pain consisting of arthritis.[47-50] For efficacy outcomes, each study used standardized scales to measure pain intensity, similar to what is used in regular practice at most sites.[47-50] As presented in Table 1, BTDS was not more effective in reduction of pain compared with placebo.[47,48] Similarly, codeine-acetaminophen was not more effective than acetaminophen alone but was slightly more effective when compared with tramadol.[49,50] As expected, there was an increased incidence of adverse effects with both BTDS and codeine/acetaminophen.[47-50]

Risk of Bias Across Studies

Of the 4 controlled trials included, only one was considered to be a low risk of bias as per the Cochrane Risk of Bias Assessment Tool[10,47] (Table 2). Two of the studies had an unknown risk of bias,[49,50] and one was an open-label trial and subsequently had a high risk of bias.[48] None of the studies provided much information regarding loss to follow-up and how this was accounted for contributing to the high/unclear risk of bias with regard to outcome data seen in these studies. Last, all of the studies reported on prespecified primary and secondary outcomes, resulting in a low risk of selective reporting of outcome data.

For the nonrandomized studies included, the ROBINS-I tool was applied for assessment of bias.[11-46] The majority of these studies had a serious risk of bias (Tables 3 and 4).

Discussion

To our knowledge, this is the first systematic review of studies on opioids use in an elderly population. The majority of evidence we have for opioid use in managing persistent pain in the elderly is for musculoskeletal pain, which is reflected within the current guidelines. A high risk of bias was present in the majority of nonrandomized trials and in all but one of the controlled trials, which precludes drawing any concrete results on efficacy and safety from the observational studies.

Of the included studies, 29 were published in 2010 and onward, with 20 of these published within the past 5 years (2013-2018). Thus, it is clear that this is a topic of interest for many experts, and there will be likely more studies evaluating opioid use in the elderly within the next decade. Given the findings of our systematic review, well-designed clinical trials in the elderly are required in order to inform safe prescribing practices.

Overall, the most common opioids studied are morphine, oxycodone (combination products), and codeine (combination products). The combination of oxycodone/naloxone was found to be both effective and safe for the management of moderate to severe persistent pain in opioid-naïve patients in 2 observational studies and a retrospective analysis included in our review.[13,15,18]

The most commonly seen adverse effects across the studies were CNS related, specifically dizziness (6.7% to 53.3%), mental status changes (16%), lethargy (9%), depression (9.8% to 25.4%), headache (6.7% to 12.5%), somnolence (2.7% to 20.3%), falls (7.6% to 13.7%), constipation (9.6% to 70%), nausea (0.3% to 40%), and vomiting (1.3% to 16.7%).[12,15,18,19,21-23,28-30,34,36,39,40,47-50] Overall, the incidence of respiratory depression was quite low; only one individual was identified as having respiratory depression across the studies.[36] In a study that evaluated falls in older

Table 1. Summary of Nonrandomized Studies Included in the Analysis of Opiate Prescribing in the Elderly.

Author	Study Design	N	Mean Age	Opiate Studied	Population Characteristics (Incidence %)	Adverse Effects (Incidence %)
Kennedy et al[12]	Observational	28	Not reported	Not reported	• Etiology of pain: back/neck pain (47.1), neuropathy (23.5), rheumatic disease (23.5) • Comorbidities not reported	GI upset, sedation; incidence not reported
Fain et al[13]	Observational	15 432	Not reported	• Codeine/acetaminophen • Oxycodone • Hydromorphone • Morphine • Methadone • Fentanyl	• Etiology of pain not reported • Comorbidities: cognitive impairment—borderline intact (20.4), mild (22.2), moderate (25.8), moderately severe (3.7)	Not reported
Fain et al[14]	Observational	17 052	Not reported	Fentanyl	• Etiology of pain not reported • Comorbidities: cognitive impairment—mild (19.7), moderate (37.1), moderately severe (10.9)	Not reported
Guerriero, 2016[15]	Observational	60	81	Oxycodone/naloxone: • Initial dose: 5/2.5 mg po BID • Mean daily dose of oxycodone at 4 weeks = 14.4 mg ± 4.9 mg • Mean daily dose of oxycodone at 52 weeks = 17.4 mg ± 7.7 mg	Etiology of pain and comorbidities not reported	• Dizziness (46)
Lee et al[16]	Observational	451	60.52	Fentanyl: • Mean dose: 15.5 ± 7.72	• Etiology of pain: low back pain (27.7), spinal stenosis (21.7), arthritis (12.64) • Comorbidities not reported	Not reported
Turner et al[17]	Observational	1311	64.5	Specific opiate not reported. Provided morphine daily equivalents and categorized into frequency of use: • Minimal/no use: <5 mg • Intermittent/lower dose use: 5-15 mg • Regular/high-dose use: >15 mg	Etiology of pain and comorbidities not reported	Not reported
Petro et al[18]	Observational	53	83	Oxycodone/naloxone: • Initial dose: 5/2.5 mg po BID • Max: 20/10 mg po BID • Mean daily dose of oxycodone: 10.8 ± 4.9 mg	Etiology of pain: arthritis (47.2), previous fracture (35.8), arthroplasty (11.3), dementia (mean MMSE score = 18.6 ± 3.0)	Severe constipation (9.4), drowsiness (9.4), nausea (5.7), xerostomia (3.8)
Dublin et al[19]	Observational	3434	Not reported	Provided cumulative morphine in past 10 years: • 0-300 mg = 54% • 330-900 mg = 24.2% • 930-8100 mg = 13.8% • >2730 mg = 79.5%	• Etiology of pain not reported • Comorbidities: cardiovascular disease (66), malignancy (11), depression (10), previous stroke (6)	Dementia (23)

(continued)

Table 1. (continued)

Author	Study Design	N	Mean Age	Opiate Studied	Population Characteristics (Incidence %)	Adverse Effects (Incidence %)
Enthoven et al[20]	Observational	484	66	Not reported	• Etiology of pain: back pain (100) • Comorbidities: alcohol use disorder (50), nicotine use disorder (18)	Not reported
Ringe et al[21]	Observational	630	68	Hydromorphone: • 4 mg/day = 22.3% • 8 mg/day = 40.2% • 16 mg/day = 7.9%	• Etiology of pain: osteoarthritis, osteoporosis; incidence not reported • Comorbidities not reported	Nausea (19.2), constipation (15.7), dizziness (10.8), fatigue (9.2)
Uberall et al[22]	Observational	891	72.8	BTDS: • 5 µg/h = 67.1% • 10 µg/h = 27.3% • 20 µg/h = 5.5%	• Etiology of pain: back pain (40.5), neuropathy (37.3), arthritis (12.1) • Comorbidities not reported	Sleep disturbance (18.2), constipation (8.9), dizziness (1.9)
Gianni et al[23]	Observational	93	79.7	BTDS: • 11.7 µg/h = 3.5% • 17.5 µg/h = 11.6% • 35 µg/h = 74.4% • 52.5 µg/h = 9.3% • 70 µg/h = 1.2%	• Etiology of pain: back pain; incidence not reported • Comorbidities: depression (26.9), cardiovascular disease (incidence not reported)	Constipation/nausea (15.7), sleepiness (14.2), pruritus (11.2)
Gianni et al[24]	Observational	367	78	Not reported	Etiology of pain and comorbidities not reported	Not reported
Park and Lavin[25]	Observational	163	72.8	• Acetaminophen/codeine • Oxycodone • Hydromorphone • Morphine • Methadone • Fentanyl	• Etiology of pain: arthritis (85.3), back/neck pain (75.5), cancer pain (23.3), osteoporosis (19.6) • Comorbidities: type II diabetes (36.2), cardiovascular disease (33.7), depression (22.6), previous stroke (8)	Not reported
Unützer et al[26]	Observational	13	72.2	Not reported	• Etiology of pain: arthritis (100) • Comorbidities: depression (100)	Not reported
Unützer et al[27]	Observational	1801	71.6	Not reported	• Etiology of pain: arthritis (55.6) • Comorbidities: depression (100)	Not reported
Won et al[28]	Observational	4426	Not reported	• Codeine/acetaminophen • Oxycodone • Morphine • Fentanyl	• Etiology of pain: arthritis (66.3) • Comorbidities: cardiovascular disease (17.8), chronic renal impairment (2.2)	Depression (25.4), constipation (10.1), falls (7.6)

(continued)

Table 1. (continued)

Author	Study Design	N	Mean Age	Opiate Studied	Population Characteristics (Incidence %)	Adverse Effects (Incidence %)
Nassar et al[29]	Observational study	51	Not reported	• Sublingual buprenorphine	• Etiology of pain: osteoarthritis (62.7), other (37.4) • Comorbidities: not reported	Nausea (15.7), vomiting (9.8), confusion (9.8), dizziness (5.9), drowsiness (3.9), depression (2.0), headache (2.0), hallucinations (2.0), diarrhea (2.0), constipation (2.0), sweating (2.0)
Pergolizzi et al[30]	Retrospective analysis	1715	72.3	BTDS	• Etiology of pain: arthritis (61), osteoporosis (16.4), back pain (14.1) • Comorbidities: cardiovascular disease; hypertension (62.9), dyslipidemia (21)	Nausea (24), dizziness (16.2), constipation (14.5), somnolence (14.1), headache (12.5), falls (3)
Lazzari et al[31]	Retrospective Analysis	186	80.7	Oxycodone/naloxone	• Etiology of pain: radiculopathy (37.1), arthritis (18.3), neuropathy (10.8), postherpetic neuralgia (10.2)	Constipation (35.9)
Lee et al[32]	Retrospective Analysis	10	75.5	Morphine: • Initial dose: 1-3 mg TID • Maintenance dose: 5-30 mg/day	• Etiology of pain: back pain (60), neuropathy (60), radiculopathy (60), arthritis (20) • Comorbidities: Parkinson's disease (10), previous stroke (10), malignancy (10)	Constipation (70)
Veal et al[33]	Retrospective analysis	19 581	77	• Codeine/acetaminophen • Oxycodone • Morphine • BTDS • Fentanyl	• Etiology of pain: musculoskeletal pain (11.7) • Comorbidities: depression (8.3), cognitive impairment (4.1), cardiovascular disease (2.6), Parkinson's disease (1.0), previous stroke (1.0)	Not reported
Reid et al[34]	Retrospective analysis	133	82	• Codeine/acetaminophen • Oxycodone • Hydromorphone • Morphine • Fentanyl	• Etiology of pain: back pain (36), arthritis (35) • Comorbidities: dementia; incidence not reported	Constipation (22), mental status changes (16), nausea (10)

(continued)

Table 1. (continued)

Author	Study Design	N	Mean Age	Opiate Studied	Population Characteristics (Incidence %)	Adverse Effects (Incidence %)
Gallagher et l[35]	Retrospective analysis	47 282	Not reported	• Codeine/acetaminophen • Buprenorphine	• Etiology of pain: arthritis (48.7), back pain (35.3), cancer pain (16.6) • Comorbidities not reported	Not reported
Raffaeli et al[36]	Retrospective Analysis	32	72.3	Morphine (given intrathecally): • Mean initial dose: 0.41 ± 0.28 mg/day • Mean dose at 48 months: 1.03 ± 0.61 mg/day	• Etiology of pain: neuropathy (65.6), arthritis (34.3) • Comorbidities not reported	Drowsiness (21.9), nausea (21.9), urinary retention (18.8), dizziness (12.5), vomiting (12.5), pruritus (12.5)
Rigler et al[37]	Retrospective analysis	766	Not reported	• Oxycodone CR: 10 mg po BID • Morphine SR: 15 mg po BID • Methadone—no dose provided • Fentanyl 25 μg/h	• Etiology of pain not reported • Comorbidities: cardiovascular disease (28.5), previous stroke (16.4), dementia (11.6), malignancy (10.4), renal impairment (5.0), cirrhosis (1.4)	Not reported
Solomon et al[38]	Retrospective analysis	1861	Not reported	• Codeine/acetaminophen • Oxycodone • Hydromorphone • Morphine • Methadone	• Etiology of pain: rheumatoid arthritis (38.6), osteoarthritis (33.7), back pain (27.6) • Comorbidities not reported	Not reported
Won et al[39]	Retrospective analysis	813	82.5	Not reported	• Etiology of pain: musculoskeletal (87.6) • Comorbidities: dementia (18.5), Parkinson's disease (7.6)	Falls/fractures (12.3), sleep disturbance (7.7), constipation (7.6), depression (3.9)
Kung et al[40]	Retrospective analysis	193	74	Not reported	Etiology of pain and comorbidities not reported	Depression (9.8)
Dobscha et al[41]	Population-based cohort	12 924	Not reported	Not reported	• Etiology of pain: arthritis, back pain, neuropathy, gout, headache/migraine, fibromyalgia; incidence not reported • Comorbidities not reported	Not reported
Krebs et al[42]	Population-based cohort	129	74.7	Not reported	• Etiology of pain: knee pain (65.1), arthritis (61.2), hip pain (59.7) • Comorbidities: frailty (34.9)	Not reported

(continued)

Table 1. (continued)

Author	Study Design	N	Mean Age	Opiate Studied	Population Characteristics (Incidence %)	Adverse Effects (Incidence %)
Kuo et al[43]	Population-based cohort	800 664	Not reported	Not reported	• Etiology of pain not reported • Comorbidities: cardiovascular disease—HTN (37.9), renal impairment (4.3)	Not reported
Prunuske et al[44]	Population-based cohort	9 325 603	Not reported	• Codeine/acetaminophen • Oxycodone • Hydromorphone • Morphine • Methadone • Buprenorphine • Fentanyl • Sufentanil	Not reported	Not reported
Koponen et al[45]	Population-based cohort	605	81.9	Not reported	• Etiology of pain: musculoskeletal pain (52.9) • Comorbidities: frailty (11.4)	Not reported
Saunders, 2010[46]	Population-based cohort	2341	72.9	• Codeine/acetaminophen • Oxycodone • Morphine	• Etiology of pain: back pain (41.6), pain in extremities (33.6), arthritis (24.9) • Comorbidities: cognitive impairment—borderline intact (20.4), mild (22.2), moderate (25.8), moderately severe (3.6)	Fracture (13.7)

Abbreviations: GI, gastrointestinal; po, by mouth; BID, twice a day; MMSE, Mini-Mental State Exam; BTDS, buprenorphine transdermal patch; TID, thrice a day; CR, controlled release; SR, slow release; HTN, hypertension.

Table 2. Summary of Controlled Trials Included in the Analysis of Opiate Prescribing in the Elderly.

Author	Design	N	Mean Age	Intervention	Control	Population Characteristics (Incidence %)	Efficacy Outcomes		Adverse Effects (Incidence %)
Breivik et al[47]	PC, DB, RCT	100	62.9	BTDS 5-20 μg/h	Placebo	Etiology of pain: osteoarthritis (100)	WOMAC; Osteoarthritis	NSS	Dizziness (25) Constipation (24), nausea (37), vomiting (16) Pruritus (61)
Likar et al[48]	OL	30	74.3	BTDS at doses 35, 40, and 50 μg/h	No control	• Etiology of pain: MSK causes (63), neuropathy (13), cancer (6.5) • Comorbidities: cardiovascular disease (80)	VAS NRS	NSS NSS	Dizziness (53.3), malaise (30) Nausea (40), constipation (30), vomiting (16.7) Pruritus (20)
Rauck et al[49]	DB, RCT	156	72	Codeine 30-60 mg/ acetaminophen 300-600 mg q 4-6 h prn	Tramadol 50-100 mg po q 4-6 h prn (max: 4000 mg/24 h	Etiology of pain: arthritis (72), back/ neck pain (14), neuropathy (7)	Pain intensity score	NSS	Dizziness (4.5) Constipation (9.6), nausea (4.5)
Kjaersgaard-Andersen et al[50]	DB, RCT	158	66	Codeine 60 mg/ paracetamol 1000 mg	Paracetamol 1000 mg po TID	Etiology of pain: arthritis (100)	Pain intensity score	$P < .01$ for codeine/ paracetamol group	Dizziness (3), somnolence (20.3) Constipation (36.1), nausea (32.3), vomiting (14.6)

Abbreviations: PC, placebo controlled; DB, double blind; RCT, randomized control trial; BTDS, buprenorphine transdermal system; WOMAC, Western Ontario and McMaster Universities Arthritis Index; NSS, normal saline solution; OL, open label; MSK, musculoskeletal; VAS, Visual Analog Scale; NRS, Numerical Rating Scale; q 4-6 h, every 4 to 6 hours; prn, as needed; po, by mouth; max, maximum; TID, thrice a day.

Table 3. Assessment of Risk of Bias of Controlled Trials Using the Cochrane Risk of Bias Tool.[5]

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Incomplete Outcome Data	Selective Outcome Data
Breivik et al[47]	Low	Low	Low	Low	Low
Likar et al[48]	High	High	High	Unknown	Low
Rauck et al[49]	Unknown	Unknown	Low	Unknown	Low
Kjaersgaard-Andersen et al[50]	Unknown	Unknown	Low	Low	Low

patients with persistent pain, the authors were unable to find an association between opioids and falls and concluded that bigger studies need to be done to evaluate this effect.[42] Given the elderly are already at a higher risk of both falls and fractures, it would be prudent to only use opioids once non-opioid options have been exhausted and then use the lowest effective dose with close monitoring for CNS side effects and risk of falls.

There are several limitations to our review. First, as the American Geriatric Society still defines aged persons as ≥65 years, we chose this as our parameter. However, as the population continues to age, the results of these studies may no longer reflect our elderly patient population. We were limited to the data that were reported in the studies, and there were no studies that assessed pharmacokinetic parameters or drug interactions, both of which were prespecified outcomes of interest. Only 2 studies included patients with frailty,[42,45] so we were unable to evaluate the impact of opioid therapy in this subset of an elderly population. Furthermore, the majority of studies did not evaluate dosing of opioids, making it difficult to provide specific dosing recommendations for the elderly population. There was also a large amount of heterogeneity among the studies included limiting the external generalizability of these results. Last, not all of the included studies reported on efficacy outcomes or safety.

Relevance to Patient Care and Clinical Practice

Central nervous system–related adverse effects and falls remain the most concerning adverse effects and should be monitored closely in susceptible patients. Moving forward, it is imperative for clinicians to continue to consider patient-specific parameters and goals of care when prescribing and dosing opioids in this population and strive to use the lowest effective dose possible.

Table 4. Assessment of Risk of Bias in Nonrandomized Studies Using the ROBINS-I Tool.[11]

Study	Bias Due to Confounding	Bias in Selection of Participants Into the Study	Bias in Classification of Interventions	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result
Kennedy et al[12]	Critical	Low	Moderate	Low	Low	Serious	Moderate
Pergolizzi et al[30]	Moderate	Low	Low	Low	Low	Low	Low
Dobscha et al[41]	Low	Low	Low	Low	Low	Serious	Low
Fain et al[13]	No information	Low	Moderate	Low	No information	Low	Low
Fain et al[14]	Moderate	Low	Low	Low	Low	Serious	Low
Guerriero et al[15]	Moderate	Low	Low	Low	Low	Serious	Low
Krebs et al[42]	Serious	Serious	Low	Low	Low	Moderate	Low
Kuo et al[43]	No information	Low	Low	Moderate	Low	Moderate	Moderate
Lazzari et al[31]	Serious	Low	Serious	Low	Low	Serious	Serious
Lee et al[16]	No information	Low	Serious	Low	Serious	Serious	Low
Turner et al[17]	Serious	Low	Low	Low	Low	Moderate	Low
Petro et al[18]	Serious	Low	Moderate	Low	Low	Serious	Low
Dublin et al[19]	Serious	Low	Low	Low	Low	Low	Moderate
Lee et al[32]	Critical	Low	Low	Low	Low	Low	No information
Veal et al[33]	Critical	Low	Serious	No information	Low	Low	No information
Enthoven et al[20]	Serious	Low	Low	Low	Low	Serious	Moderate
Prunuske et al[44]	No information	Moderate	Low	Low	Low	Low	Low
Koponen et al[45]	Critical	Low	Serious	No information	Moderate	Serious	Moderate
Ringe et al[21]	No information	Low	Moderate	No information	Low	Low	Moderate
Uberall et al[22]	No information	Low	Moderate	Low	Low	Serious	Moderate
Gianni et al[23]	Serious	Low	Serious	Low	No information	Serious	Moderate
Gianni et al[24]	No information	Low	Low	No information	Serious	Serious	Serious
Park and Lavin[25]	Low	Moderate	Low	Moderate	No information	Low	Moderate
Reid et al[34]	Low	Low	Low	Low	No information	Serious	Low
Saunders et al[46]	Serious	Low	Low	Low	Low	Serious	Low
Gallagher et al[7]	Moderate	Moderate	Low	Low	Low	Serious	Low
Raffaeli et al[36]	Serious	Low	Serious	Moderate	Low	Serious	Serious
Unützer et al[26]	Serious	Serious	Low	Low	Low	Serious	Low
Rigler et al[37]	Critical	Serious	Serious	Moderate	Low	Serious	Moderate
Soloman et al[38]	Low	Low	Low	Moderate	Moderate	Low	Low
Won et al[39]	Serious	Low	Serious	Low	Low	Serious	Moderate
Unützer et al[27]	Critical	Low	Low	Low	Low	Serious	Low
Won et al[28]	Serious	Low	Low	Moderate	Moderate	Low	Moderate
Kung et al[40]	Low	Low	Low	Low	Low	Serious	Moderate
Nassar et aal[29]	Moderate	Moderate	Low	Moderate	Low	Serious	Serious

Abbreviation: ROBINS-I, Risk of Bias in Nonrandomized Studies of Interventions.

Conclusions

Ultimately, the low quality of evidence and clinical heterogeneity limits the ability to draw broad conclusions on optimal opioid use in the elderly. As discussed, there is a high prevalence of persistent pain in the elderly population, and as the average age of the population continues to rise, the prevalence of pain will continue to increase. Thus, there is a strong need to continue to further explore and understand opioid use in the elderly population.

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