Table C-1. Study and population characteristics, randomized controlled trials

| **Author, year**  **Country**  **Setting**  **Risk of Bias** | **Eligibility** | **Intervention and Comparator** | **Population Characteristics** | **Outcomes** |
| --- | --- | --- | --- | --- |
| Frey, 201917  United States  Setting: ED  Risk of bias: Low | 8-17y old with acute extremity injury & VAS≥35/100  Exclusions: Significant head, chest, abdomen or spine injury, GCS<15 or inability to report a VAS score, nasal trauma or aberrant nasal anatomy, active epistaxis, drug allergy, history of psychosis, opioid administration prior to arrival, non-English speaking, in police custody, postmenarchal without a negative pregnancy test | A: Fentanyl 2 mcg/kg IN (max 100 mcg, median 1.9 mcg/kg IQR 1.7 to 1.9) (n=42)  B: Ketamine 1.5 mg/kg IN (max 100 mg, median 1.5 mg/kg IQR 1.5 to 1.5) (n=44)  Rescue: NR | Age A:12.2(2.3) B:11.8(2.6)  Males A:74% B:59%  Weight A:50.8kg(22.8) B:45.8kg(14.4)  Race/ethnicity A/B: White 69%/68%, Black 24%/25%, other 7%/7%  Pain etiology/location A/B: Fracture 81%/85%, dislocation 5%/9%, sprain/strain 12%/2%, other 2%/4%  Pain Classification: Traumatic | Any AE  Diastolic blood pressure  Dissociation  Heart rate  Hypotension  Oxygen saturation  Pain severity  Respiratory depression  Respiratory rate  Systolic blood pressure |
| Sotoodehnia, 201990  Iran  Setting: ED  Risk of bias: low | >18y old presenting to the ED with acute renal colic  Exclusions: Sensitivity to ketamine or ketorolac, ischemic heart disease, hypertension, intracerebral vascular abnormalities, fibromyalgia, chronic pains managed with morphine, use of analgesics within 4 h before presenting to the ED, pregnancy, lactation, renal or hepatic failure, psychosis, trauma to the head or eye, and unstable vital signs | A: Ketamine 0.6mg/kg IV (n=67)  B: Ketorolac 30mg IV (n=74)  Rescue: Morphine 0.1 mg/kg IV for intolerable pain | Age A: 34.2(9.9) B: 37.9(10.6)  Males A:71% B: 81.2%  Weight NR  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain classification: Non-traumatic | Any AE  Heart rate  Mental status changes  Nausea  Pain severity  Systolic blood pressure |
| Vahedi, 201991  Iran  Setting: ED  Risk of bias: low | ≥18y old and addicted to opioids, presenting to the ED with acute pain of 6 or more on a 0 to 10 scale, from traumatic limb injury  Exclusions: history of allergic reactions to fentanyl or morphine, GCS<14, NRS<5, SBP<90mmHg | A: Morphine 0.1 mg/kg IV (n=152)  B: Fentanyl 1 mcg/kg IV (n=155)  Rescue: If pain remained ≥3 or did not decrease by at least 50% after 60 min, ketorolac 60 mg IV was administered | Age A: 31.8(10.4) B: 31.0(10.7)  Males A:92.8% B: 89%  Weight NR  Race/ethnicity NR  Pain etiology/location: Limb injury 100%  Pain classification: Traumatic | Diastolic blood pressure  Heart rate  Nausea  Pain severity  Respiratory rate  Systolic blood pressure  Oxygen saturation |
| Verki, 201951  Iran  Setting: ED  Risk of bias: low | 18-55 years old with limb fracture, VAS score higher than 3  Exclusions: Consumed anti-psychotic, sedative, TCA, MAOI, SSRI drugs, opioid addicts, patients with underlying acute or chronic renal and hepatic disease, cardiac disease, upper and/or lower respiratory infection, asthma, COPD, or allergies, pregnant or breast-feeding women, fentanyl-prohibited patients, those with multiple myeloma, a history of convulsion, ketamine allergy, head injury, or avulsion fractures, and patients with unstable hemodynamic factors | A: Fentanyl 4mcg/kg nebulized (n=62)  B: Ketamine 0.4mg/kg IV over 10 min (n=65)  Rescue: VAS>3 after 60 min-treated with morphine 0.1 mg/kg IV | Age A: 34.5(11.97) B: 36.28(10.73)  Males A:72.6% B:66.2%  Weight NR  Race/ethnicity NR  Pain etiology/location: Limb fracture 100%  Pain classification: Traumatic | Pain severity |
| Abbasi, 201871  Iran  Setting: ED  Risk of bias: Low | 18-65y old previously diagnosed with nephrolithiasis or urinary stone by a urologist w/VAS ≥6/10  Exclusions: Unstable vitals (SBP<90 mmHg, HR<60 or >120, RR <8 or >22, O2 saturation <92%, narcotic analgesic before admission, history of liver disease, kidney disease, chronic respiratory, CVD, known blood coagulation, chronic mental illness, use of psychiatric drugs, addiction to drugs and psychotropic substances, drug allergy, inability to understand the concept of VAS | A: Morphine 0.1 mg/kg + ketamine 0.15 mg/kg IV (n=53)  B: Morphine 0.1 mg/kg + placebo IV (n=53)  Rescue: Morphine IV continued until a VAS ≤3/10, 120 min or 30mg of morphine max | Age A: 51.58 (NR) B: 49.42 (NR)  Males total study 67%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B: Renal colic 100%  Pain Classification: Nontraumatic | Hypotension  Nausea or vomiting  Pain severity  Respiratory depression |
| Al, 201880  Turkey  Setting: ED  Risk of bias: Low | 16-65y old w/suspected renal colic subsequently confirmed with imaging, pain onset within 12h, VAS≥4/10  Exclusions: Hx of direct blunt trauma to the CVAT within the last week, drug allergy, SBP<90, hx prostate, renal and adrenal, and bladder malignancy or surgery on these regions within the last 6m, hx chronic pain syndrome, use of pain-killer, antidepressant, anticonvulsant, muscle relaxant, or steroid within 12h, hx of substance or alcohol dependency, pregnant, nursing mothers, PID | A: Fentanyl 2 mcg/kg IV (n=100)  B: Paracetamol 10mg IV (n=100)  Rescue: Study drugs, diclofenac or tramadol to those who needed them, physician discretion | Age NR  Males A:67% B:67%  Weight NR  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain Classification: Nontraumatic | Hypotension  Mental status changes  Vomiting |
| Burnett, 201828  USA  Setting: ED  Risk of bias: Unclear | 3-17y old with medical/traumatic condition requiring IV opioid analgesics  Exclusions: Trauma team activation, drug allergy, inability to provide informed consent, patient unwilling to provide assent, high suspicion of injury related to child abuse, patient/family member is non-English speaking, patient is incarcerated | A: Morphine 0.05 mg/kg IV (n=32)  B: Ketamine 0.3 mg/kg IV (n=31)  Rescue: Morphine given at the discretion of the treatment team | Age A:12.7(3.7) B:13.3(3.6)  Males A:72% B:61%  Weight NR  Race/ethnicity NR  Pain etiology/location NR  Pain Classification: Mixed | Nausea or vomiting |
| Cenker, 201887  Turkey  Setting: ED  Risk of bias: Low | 18-60y old presenting w/flank pain ultimately diagnosed as renal colic  Exclusions: Analgesic within 6h, fever or hemodynamically unstable, peritoneal irritation signs, cardiac failure, hx of renal or hepatic failure, drug allergy, pregnancy, vision problems. | A: Ibuprofen 800mg IV (n=100)  B: Paracetamol 1g IV (n=100)  Rescue: Inadequate pain relief at 30min received fentanyl 1 μg/kg IV | Age total study 36(9)  Males total study 64.5%  Weight NR  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain Classification: Nontraumatic | Any AE  Pain severity  Vomiting |
| Cozzi, 201888  Italy  Setting: ED  Risk of bias: Low | 4-18y old w/moderate to severe acute abdominal pain and pain score of ≥6/10 (Wong-Baker 4-7y, NRS ≥8y)  Exclusions: drug allergy, analgesic drugs in the 8h before the medical evaluation, hx nephropathy, liver disease, metabolic or neurologic disease and thrombocytopenia or bleeding disorders, abdominal pain was due to fecal stasis or severe dehydration | A: Ketorolac 0.5 mg/kg oral drops SL (max 30mg) (n=70)  B: Paracetamol melt in the mouth powder 20 mg/kg melt in the mouth powder (max 1g) (n=70)  Rescue: Pain score ≥6/10 at 2h, rescue analgesic of ED pediatrician’s choice was given | Age A:12(9-14) B:12(9-14.3)  Males A:30% B:45.7%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B: Appendicitis 7.1%/11.4%, gynecological 12.9%/14.3%, urological 4.3%/4.3%, viral infection 45.7%,41.4%, colic 22.9%/21.4%, functional 0%/2.9%, other 7.1%/4.3%  Pain Classification: Mixed | Any AE  Mental status changes  Nausea  Pain severity  Presence of pain  Vomiting |
| Hosseininejad, 201868  Iran  Setting: ED  Risk of bias: Low | 18-65y old w/kidney stones and VAS≥6/10  Exclusions: Unstable vital signs, drug allergy, pregnancy, breastfeeding, contraindications to morphine, history of opium addiction, any analgesic/narcotic within past 6h, peritoneal s/sx on abdominal exam, hx chronic CV, liver, kidney diseases, psychosis | A: Morphine 0.1 mg/kg + ketamine 0.2 mg/kg IV (n=100)  B: Morphine 0.1 mg/kg IV (n=100)  Rescue: Morphine 0.05 mg/kg IV | Age A:35.29(7.12) B:35.91(9.13)  Males A:67% B:70%  Weight A:70.3kg(7.02) B:69.86kg(8.56)  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain Classification: Nontraumatic | Diastolic blood pressure  Mental status changes  Nausea  Pain severity  Respiratory rate  Systolic blood pressure  Vomiting |
| Jahanian, 201860  Iran  Setting: ED  Risk of bias: Low | 18-65y old, upper or lower extremity long bone fractures caused by blunt trauma, pain score ≥7/10  Exclusions: Mental or neurological disorders, liver, kidney, stroke, asthma and other respiratory diseases, heart diseases, <45kg or >155kg, pregnant or lactating, SBP>180 or <90mmHg, HR <50 or >150, RR <10 or >30, decreased LOC, blow to the head or eyes, multiple trauma, drug allergy, drug addiction/IV use, other fractures, severe displacement, need of reduction, open fracture, compartment syndrome, analgesic before the study | A: Morphine 0.1 mg/kg IV (n=80)  B: Ketamine 0.5 mg/ kg IV (n=79)  Rescue: In the absence of pain relief at any time of the study, half of the previous doses of the same group was administered. If the pain score remains 9 or 10 out of 10, or more than 2 times to the administered drug, fentanyl 1 µg/kg IV was given. | Age A:36.38(9.3) B:35.87(7.3)  Males A:70.5% B:71.8%  Weight NR  Race/ethnicity NR  Pain etiology/location: Road traffic accidents 71.8%/69.3%, fall 23.1%/24.3%, assault 5.1%/6.4%  Pain Classification: Traumatic | Mental status changes  Nausea or vomiting  Pain severity |
| Mohammadshahi, 201872  Iran  Setting: ED  Risk of bias: Low | >18y old w/limb pain resulting from traumatic injuries within the last 24h, NRS≥7/10  Exclusions: open fracture, closed fracture in more than one site, fracture plus dislocation, acute traumatic pain in more than two limbs, BP< 90/60 or > 160/100, HR> 120 or <60, GCS<15, non-limb traumatic injuries, pregnancy, drug allergy, patients leaving the hospital for any reason within 3h of drug administration | A: Morphine 0.05 mg/kg IV + ketamine 1mg/kg IN using a dropper (n=40)  B: Morphine 0.05 mg/kg IV + 0.02 ml/kg distilled water IN using a dropper (n=40)  Rescue: After 10 min if patient requested more analgesics morphine 0.05 mg/kg IV was given | Age A:31.42(10.3) B: 31.75(8.2)  Males total study 54.9%  Weight NR  Race/ethnicity: NR  Pain etiology/location: Traumatic limb 100%  Pain classification: Traumatic | Any AE  Heart rate  Oxygen saturation  Pain severity  Systolic blood pressure  Vomiting |
| Motov, 201855  USA  Setting: ED  Risk of bias: Low | ≥65y old w/ acute pain (within 7d onset), NRS≥5/10 requiring opioid analgesia, abdominal, flank, back, or musculoskeletal pain  Exclusions: Altered mental status, drug allergy, weight <40 or >115kg, SBP <90 or >180, HR<50 or >150, RR<10 or >30, hx of acute head or eye injury, seizure, intracranial hypertension, severe COPD, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4h before) opioid use | A: Morphine 0.1 mg/kg IV (mean 6.8mg(1.5)) (n=30)  B: Ketamine 0.3 mg/kg IV over 15 min (mean 21.0mg(6.2)) (n=30)  Rescue: Fentanyl 0.5 mcg/kg if NRS ≥5/10 and requested by patient | Age A: 77.1(8.5) B: 77.3(8.4)  Males A:23.3% B:23.3%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B:  Abdominal 33.3%/46.7%, cancer 16.7%/6.7%, back 3.3%/16.7%, musculoskeletal 10%/3.3%, fracture 23.3%/16.7%, flank 13.3%/10%  Pain Classification: Mixed | Any AE  Mental status changes Nausea  Pain severity  Presence of pain  Respiratory depression |
| Quinn, 201852  USA Setting: ED  Risk of bias: Low | 3-17y old, moderate to severe pain (NRS≥6/10 or equivalent Wong-Baker FACES Pain Scale)  Exclusions: Weight>64kg, insufficient intensity to warrant opioid, facial trauma or any abnormality of the nasal anatomy, circulatory insufficiency, developmental delay, head trauma/increased intracranial pressure/altered consciousness, drug allergy, inability to provide pain scale assessment, opioid pain medication immediately before arrival to the ED | A: Fentanyl 1.5 μg/kg IN (n=11)  B: Ketamine 1 mg/kg IN (n=11)  Recue: Morphine 1mg/kg IV if a patient or parents requested additional pain relief | Age A:9.58(2.92) B:9.77 (2.51)  Males A:73% B:91%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B: Musculoskeletal 73%/73%, abdominal 27%/27%  Pain Classification: Mixed | Any AE  Mental status changes  Pain severity  Presence of pain |
| Farina, 201754  Iran  Setting: ED  Risk of bias: Low | ≥15y old, renal colic pain and didn't require surgical intervention  Exclusions: opioid addiction, prior use of analgesics, pregnancy, drug allergy, nasal occlusion, SBP >180 or <90, respiratory distress, altered level of consciousness | A: Morphine 0.1 mg/kg IV + placebo IN (n=20)  B: Ketamine 1mg/kg IN + placebo IV (n=20)  Rescue: If no decrease in VAS at 30min fentanyl 1–2 mcg/kg every 5min was titrated to effect | Age A:34.75(11.71) B:39.25(10.75) Males A:85% B:40%  Weight A:76.14(10.32) B:74.10(9.98)  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain Classification: Nontraumatic | Any AE  Emergence delirium  Hypotension  Mental status changes  Nausea  Pain severity |
| Le May, 201786  Canada  Setting: ED  Risk of bias: Low | 6-17y old w/musculoskeletal injury to upper or lower limb, VAS>29/100  Exclusions: drug or color allergy, suspected child abuse, inability to self-report pain, chronic pain requiring daily analgesics, NSAIDs or opioid use within 3h before triage, injury to >1 limb, known hepatic or renal disease and/or dysfunction, known bleeding disorder, neurocognitive disability precluding assent and participation in the study, hx of sleep apnea or loud snoring in the past 5d | A: Morphine 0.2 mg/kg PO, max 15 mg (n=201)  B: Ibuprofen 10 mg/kg PO, max 600mg (n=99)  Rescue: Eligible to receive rescue analgesia at any time | Age A:11.7(2.7) B:12.2(2.6)  Males A:56.4% B:58.2%  Weight NR  Race/ethnicity NR  Pain etiology/location: Fracture 35.6%/47.3%, soft tissue 62.2%/52.74%, missing 2.1%/0%  Pain Classification: Mixed | Any AE  Mental status changes  Nausea  Pain severity  Presence of pain |
| Mahshidfar, 201756  Iran  Setting: ED  Risk of bias: Low | 18-70y old, musculoskeletal trauma, NRS≥5/10  Exclusions: instability in vital signs, head trauma, GCS score <15, opiate users, psychiatric or cardiac problem, drug allergy, pregnancy, breast-feeding, renal or hepatic insufficiency, contraindications to interventions | A: Morphine 0.1 mg/kg IV (mean 6.8mg(1.2)) (n=155)  B: Ketamine 0.2 mg/kg IV (mean 14.9mg(3.3)) (n=153)  Rescue: <3/10 point decrease in pain score, morphine 3mg IV every 5 minutes | Age A:34.1(7.3) B:34.4(7.6)  Males A:82% B:84%  Weight A:68.4kg(12.9) B:75.1kg(14.6)  Race/ethnicity NR  Pain etiology/location A/B: Fracture 24%/28%, soft tissue injury 76%/72%  Pain Classification: Traumatic | Hypotension  Mental status changes  Nausea  Pain severity  Respiratory depression |
| Masoumi, 201784  Iran  Setting: ED  Risk of bias: Low | ≥18y old w/long bone fractures  Exclusions: Asthma, COPD, rheumatoid fever, peptic ulcer disease, GI bleeding, drug allergy, without complete consciousness, hemodynamic instability and symptoms of respiratory distress and GIB during the pain relief injection | A: Morphine 5mg IV bolus then 2.5mg q5min X 20min if VAS≥4/10 (n=44)  B: Ketorolac 10mg IV bolus then 5mg q5min X 20min if VAS≥4/10 (n=44)  Rescue: NR | Age A:33.2(11.4) B:29.1(12.5)  Males A:70.5% B:63.6%  Weight NR  Race/ethnicity NR  Pain etiology/location: Long bone fracture 100%  Pain Classification: Traumatic | Any AE  Hypotension  Mental status changes Nausea  Pain severity  Vomiting |
| Reynolds, 201729  USA  Setting: ED  Risk of bias: Low | 4-17y old w/suspected fracture of any single extremity requiring analgesia, Wong-Baker FACES (4-10y) or VAS (11-17y) ≥3/10  Exclusions: GCS<15, drug allergy, pregnancy, intoxication, age-adjusted hypotension at presentation (SBP<70 +2x age if <10y, or <90 for those >10y), weight > 70kg, opioid analgesia administered prior to arrival, multiple injuries, nonverbal from developmental delay, or aberrant nasal anatomy that precluded IN medications | A: Fentanyl 1.5 mcg/kg IN (n=44)  B: Ketamine 1 mg/kg IN (n=43)  Rescue: 2nd dose ≥20 mins after 1st dose of ketamine 0.5 mg/kg IN or fentanyl 0.75 mcg/kg IN | Age A: 4-10y 73%, 11-17y 27% B: 4-10y 72%, 11-17y 28%  Males A:64% B:61%  Weight NR  Race/ethnicity NR  Pain etiology/location: Single extremity fracture 100%  Pain Classification: Traumatic | Any AE  Dissociation  Hypotension  Mental status changes  Nausea  Pain severity  Presence of pain |
| Sin, 201769  USA  Setting: ED  Risk of bias: Low | ≥18y old w/chief complaint of acute pain (w/in 15d), moderate to severe (NRS≥3)  Exclusions: RR not within 12–20, HR not within 60–110, BP<90/50 or >180/100, O2 sat <94%, altered mental status, weight >166kg, pregnancy or breastfeeding, drug allergy, opioid use within 4h, hx of schizophrenia, depression, or substance abuse, traumatic head injury with or without LOC, myocardial ischemia, headache, migraine, or increase in intracranial or intraocular pressure | A: Morphine 0.1 mg/kg IV push, max 10mg (mean 6.6mg(1.4)) + ketamine 0.3 mg/kg infused over 15 min (n=30)  B: Morphine 0.1 mg/kg IV push, max 10mg (mean 5.9 mg (1.7)) + placebo infusion (n=30)  Rescue: Morphine 0.1 mg/kg IV push (max 10mg) was offered at 5, 15, 30, 45, 75, 90, 105, and 120 after initial dose if the patients reported NRS≥4/10 | Age A:41(16) B:48(17)  Males A:40% B:40%  Weight A: 81kg(22) B:85kg(24)  Race/ethnicity A/B: White 10%/16.7%, African American 60%/60%, Hispanic 30%/16.7%, Asian/Pacific Islander 0%/6.7%  Pain etiology/location: Abdominal 63.3%/73.3%, musculoskeletal 20%/16.6%, back 6.6%/0%, elbow fracture 0%/3.3%, abscess 0%/3.3%, hip 0%/3.3%, testicular 3.3%/0%, renal colic 6.6%/0%  Pain Classification: Mixed | Dissociation  Emergence delirium  Nausea  Pain severity  Respiratory depression |
| Jalili, 201674  Iran  Setting: ED  Risk of bias: Low | ≥18y old w/acute limb trauma and pain score >3/10  Exclusions: drug allergy or contraindication, SBP<90, pregnancy, any analgesic drug use within 6h, known pulmonary, cardiac, renal, or hepatic failure | A: Morphine 0.1 mg/kg IV (n=30)  B: Paracetamol 1g IV (n=30)  Rescue: Morphine IV titrated to effect at 30min if NRS>4/10 | Age NR  Males NR  Weight NR  Race/ethnicity NR  Pain etiology/location: Acute limb trauma 100%  Pain Classification: Traumatic | Mental status changes  Pain severity |
| Mollaei, 201681  Iran  Setting: ED  Risk of bias: Low | 15-60y old with forearm or leg fractures, moderate to severe pain (VAS>4/10)  Exclusions: GCS<15, weight<60 or >100kg, hemodynamic instability, lung problems, previous use of pain killer drugs and narcotics, addiction, previous liver or kidney disease, concussion, pregnancy, previous use of monoamine oxidase, sleeping and sedative drugs, phenobarbital and isoniazid, multiple vomiting incidents and nausea | A: Morphine 0.1 mg/kg IV over 10-15min (n=28)  B: Acetaminophen 1g IV over 10-15min (n=27)  Rescue: VAS>5/10 after 30min morphine will be prescribed for patient | Age A:35(11.3) B:36.0(11.1)  Males A:60.7% B:63%  Weight A:65.0kg(3.0) B:65.5kg(2.9)  Race/ethnicity NR  Pain etiology/location: Traffic accident 82.1%/81.5%, falling from height 14.3%/18.5%, direct injuries 3.6%/0%  Pain Classification: Traumatic | Mental status changes  Nausea  Pain severity |
| Pathan, 201675  Qatar  Setting: ED  Risk of bias: Low | 18-65y old w/renal colic and NRS≥4/10  Exclusions: drug allergy, hx of asthma, known renal or liver failure or impairment, pregnancy, pain caused by a traumatic mechanism (in the setting of injury, for example motor vehicle crash, fall, or assault), or previous use of analgesia within 6h | A: Morphine 0.1 mg/kg IV (n=548)  B: Paracetamol 1g IV (n=549)  Rescue: Morphine 3mg IV q5min until NRS<2/10 or participant refused further analgesia (starting 30min after initial dose) | Age A:34.4(28.6-41.5) B:34.7 (28.8-41.7)  Males A:81% B:83%  Weight A:72kg(65-84.6) B:74.6kg(65-84)  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain Classification: Nontraumatic | Any AE  Pain severity  Presence of pain  Time to analgesic effect |
| Serinken, 201676  Turkey  Setting: ED  Risk of bias: Low | 21-65y old presenting w/pain radiating along sciatic nerve, VAS≥40  Exclusions: pain>1w, low back or leg trauma within 1w, sensory or motor deficit, drug allergy, unstable vital signs, fever>37.9°C, hx of malignancy, cauda equina syndrome, chronic pain syndromes, rheumatologic diseases, drug or alcohol addiction, pregnancy or lactation, analgesic, antidepressant, anticonvulsant, muscle relaxant medication, or steroid in past 6h | A: Morphine 0.1 mg/kg IV over 4-5min (n=100)  B: Acetaminophen 1g IV over 4-5min (n=100)  Rescue: Fentanyl 1 mcg/kg at 30min if needed | Age A:44.6(10.2) B:43.7(9.8)  Males A:48% B:43%  Weight NR  Race/ethnicity NR  Pain etiology/location: Sciatic nerve 100%  Pain Classification: Nontraumatic | Hypotension  Nausea  Pain severity |
| Shimonovich, 201653  Israel  Setting: ED  Risk of bias: High | 18-70y old w/mild-moderate blunt trauma causing moderate to severe pain (VAS≥80/100)  Exclusions: GCS<15, weight <50 or >110kg, HR>100, SBP <90 or >160, American Society of Anesthesiologists score other than 1 or 2, regular use of opiates, analgesia received within the prior 3h, drug allergy, a large meal ingested within the previous hour, pregnancy, deviated nasal septum or trauma to the nose, hx of psychiatric condition, head trauma, head injury complaining of LOC, dizziness, vomiting, or nausea | A: Morphine 0.1 mg/kg IV (n=24)  B: Morphine 0.15 mg/kg IM (n=27)  C: Ketamine 1 mg/kg IN (n=24)  Rescue: NR | Age A:42.9(38.0-47.8) B:37.7(32.8-42.6) C:37.9(32.3-43.5)  Males A:75% B:59.3% C:70.8%  Weight NR  Race/ethnicity: NR  Pain etiology/location: NR  Pain Classification: Traumatic | Emergence delirium  Mental status changes  Pain severity  Presence of pain  Time to analgesic effect |
| Weldon, 201692  Canada  Setting: EMS, ambulance transport in urban system  Risk of bias: Low | ≥18y w/ischemic type chest pain not relieved by oxygen, ASA, and nitroglycerin  Exclusions: SBP<100, O2 sat <95%, pregnancy, cognitive impairment, drug allergy, traumatic injury, evidence of right ventricular infarct identified by the presence of ST segment elevation | A: Morphine IV every 5min, max 4 doses (n=99)  <75y and >50 kg: 5mg  >75y and/or ≤50kg: 2.5mg  B: Fentanyl IV every 5min, max 4 doses (n=88)  <75y and >50kg: 50mcg  >75y and/or <50kg: 25mcg  Rescue: NR | Age A:66.1(15.8) B:64.5(16)  Males A:53% B:53%  Weight A:79.4kg(19.6) B:78.43kg(17.6)  Race/ethnicity NR  Pain etiology/location: Ischemic chest pain 100%  Pain Classification: Nontraumatic | Heart rate  Hypotension  Nausea  Respiratory depression  Respiratory rate  Vomiting |
| Deaton, 201519  USA Setting: ED Risk of bias: Medium | 18-65y old w/acute non-injury abdominal pain ≥5  Exclusions: Drug allergy, impairment in renal or hepatic function, hypothyroidism, Addison disease, prostatic hypertrophy, or urethral stricture, taking monoamine oxides inhibitors, tricyclic antidepressants, sedative hypnotics, or known cytochrome P450 3A4 inhibitors within 14d, oral or IV or IM pain medications before enrollment | A: Morphine 0.1 mg/kg IV (n=16)  B: Fentanyl 2 mcg/kg NEB (n=16)  Rescue: Available at any point during the study according to treating physician preference | Age A:32.38(10.76) B:30.19(10.7)  Males A:50% B:38%  Weight NR  Race/ethnicity A/B: White 75%/56%, African American 12.5%/12.5%, Hispanic 6.25%/25%, Asian American 6.25%/6.25%  Pain etiology/location: Abdomen 100%  Pain Classification: Nontraumatic | Hypotension  Nausea  Pain severity |
| Graudins, 201530  New Zealand  Setting: ED  Risk of bias:  Low | 3-13y old w/acute limb injury with moderate to severe pain of 6 or more at triage  Exclusions: serotonergic antidepressants; previous administration of parenteral or IN analgesics or opioid analgesia; opioid antagonist use; allergy to ketamine, fentanyl, or ibuprofen; aberrant nasal anatomy or acute or chronic nasal problems or nasal trauma that may have precluded adequate intranasal delivery; multiple trauma or head injury with loss of consciousness or cognitive impairment. | A: Fentanyl 1.5mcg/kg IN (n=37)  B: Ketamine 1mg/kg IN (n=36)  Rescue: Additional IN fentanyl or IV morphine, based on provider preference | Age A:9(6 to 11) B:7(6 to 9.5)  Males A:65% B:61%  Weight NR  Race/ethnicity  Pain etiology/location: Upper limb fracture (73%/88.9%), upper limb soft tissue injury (13.5%/8.3%), lower limb fracture (13.5%/0%), lower limb soft tissue injury (0%/2.8%)  Pain classification: Traumatic | Any adverse event  Emergence delirium  Mental status changes  Nausea  Pain presence  Pain severity |
| Miller, 201558  USA Setting: ED  Risk of bias: Low | 18-59y old w/abdominal, flank, low back or extremity pain warranting IV opioid treatment  Exclusions: O2 sat<95%, SBP<90 or >180, HR<50 or >120, RR<10 or >30, altered mental status, intoxication, fibromyalgia or other chronic pain condition requiring the use of opioids or tramadol as an outpatient, ischemic heart disease, heart failure or unstable dysrhythmias, use of an opioid or tramadol within 4h, drug allergy, required pain medication immediately, pregnant or breast-feeding, history of chronic oxygen-dependent pulmonary disease, hepatic cirrhosis, or dialysis dependent, presence of intracranial mass, a history of psychosis, weight<45kg or >115kg, presence of acute ocular or head trauma | A: Morphine 0.1 mg/kg IV over 5min (max 8mg), second dose could be given as early as 20min (n=21)  B: Ketamine 0.3 mg/kg IV infusion over 5min (max 25mg), second dose could be given as early as 20min (n=24)  Rescue: If the patient requested a third dose of pain medication the data collection stopped and patient was eligible for open label pain medication of the providers choosing. | Age A:29(10) B:31(12)  Males A:43% B:58%  Weight NR  Race/ethnicity NR  Pain etiology/location: Abdomen 71%/65%, back 19%/35%, extremity 10%/0%  Pain Classification: Mixed | Any AE  Diastolic blood pressure  Dissociation  Emergence delirium  Heart rate  Mental status changes  Nausea  Oxygen saturation  Pain severity  Respiratory depression  Respiratory rate  Systolic blood pressure  Vomiting |
| Motov, 201557  USA  Setting: ED  Risk of bias: Low | 18-55y old w/acute (within 7d) abdominal, flank, back or musculoskeletal pain NRS≥5/10 and required opioid analgesia  Exclusions: pregnancy, breast-feeding, altered mental status, drug allergy, weight <46kg or >115kg, SBP<90 or >180, HR<50 or >150, RR<10 or >30, hx of acute head or eye injury, seizure, intracranial hypertension, chronic pain, renal or hepatic insufficiency, alcohol or drug abuse, psychiatric illness, or recent (4h) opioid use | A: Morphine 0.1 mg/kg IV push over 3 to 5min (mean 7.7mg (1.6)) (n=45)  B: Ketamine 0.3 mg/kg IV push over 3 to 5min (mean 21.8mg (4.9)) (n=45)  Rescue: NRS ≥5/10 and requested additional pain relief, fentanyl 1 mcg/kg was administered | Age A:36(10.5) B:35(9.5)  Males A:37.8% B:33%  Weight A:78kg(16.6) B:74kg(15.9)  Race/ethnicity: NR  Pain etiology/location A/B:  Abdominal 69%/73%, flank 20%/16%, back and musculoskeletal 11%/11%,  Pain Classification: Mixed | Any AE  Diastolic blood pressure  Heart rate  Mental status changes  Nausea  Oxygen saturation  Pain severity  Presence of pain  Respiratory rate  Systolic blood pressure |
| Beaudoin, 201470  USA Setting: ED  Risk of bias: Low | 18-65y old w/moderate to severe acute pain (NRS≥5/10) determined to require opioids by emergency physician, still study eligible if they received previous analgesics prior if NRS was still ≥5/10  Exclusions: Neurologic, respiratory, or hemodynamic compromise; drug allergy, acute psychiatric illnesses, history of stroke, renal impairment (creatinine >2mg/dL), liver failure, or history of cardiac disease (prior myocardial infarction, angina, cardiac stents, or bypass surgery); pregnant or breastfeeding | A: Morphine 0.1mg/kg IV (10mg max), after 10min ketamine 0.15mg/kg (n=20)  B: Morphine 0.1mg/kg IV (10mg max), after 10min ketamine 0.3mg/kg (n=20)  C: Morphine 0.1 mg/kg IV (10mg max) followed by placebo (n=20)  Rescue: Morphine 0.5 to 1mg/kg every 1h PRN targeting reduction of NRS by at least 50%, encouraged to wait at least 30min before determining if rescue analgesia was needed | Age A:37.5(25.5-46.0) B: 32.5 (25.5-41.0) C:37.5(31.5-44.0)  Males A:65% B:45% C:75%  Weight A: 80.6kg(67.4-99.8)  B:86.3kg(68.6-102.1) C:80.6kg (68.2-95.7)  Race/ethnicity A/B/C:  White 70%/50%/70%; Black 15%/20%/20%, Hispanic 15%/15%/0%, Asian 0%, Other 0%/15%/10%  Pain etiology/location:  Abdominal 25%/5%/0%; back pain/sciatica 20%/5%/5%; GI 10%/30%/10%; fracture 5%/20%/25%; genitourinary infection 10%/5%/10%; musculoskeletal 5%/10%/15%; orofacial pain/headache 5%/0%/15%; renal colic 10%/15%/5%; sickle cell disease 5%/0%/5%; skin and soft tissue infection 10%/10%/10%  Pain Classification: Mixed | Respiratory depression  Hypotension  Mental status changes  Nausea  Pain severity  Presence of pain  Vomiting |
| Majidinejad, 201459  Iran  Setting: ED  Risk of bias: Unclear | 18-55y old w/long bone fracture  Exclusions: drug abuse, trauma to the head, symptoms and signs of increased intracranial pressure, decrease LOC, respiratory problems, hx of asthma, contraindications for ketamine (hx of cardiac problems, especially congestive heart failure, ischemic cardiac conditions, HTN, CVA) and morphine (asthma, respiratory problems, hemodynamic instability), drug allergy | A: Morphine 0.1 mg/kg IV (n=63)  B: Ketamine 0.5 mg/kg IV (n=63)  Rescue: Half initial dose if NRS≥3/10 after 10min | Age A: 53.6(14.3) B:35.1(13.5)  Males A:81% B:71.4%  Weight NR  Race/ethnicity NR  Pain etiology/location: Long bone fracture 100%  Pain Classification: Traumatic | Emergence delirium  Pain severity  Presence of pain |
| Masoumi, 201482  Iran  Setting: ED  Risk of bias: Low | 18-55y old w/renal colic  Exclusions: drug allergy, fever >38C, hemodynamic instability, evidence of peritoneal inflammation, pregnancy, proven or suspected aortic aneurysm or dissection, use of any analgesic drug up to 6h prior, heart failure, renal failure, respiratory failure, liver failure, kidney transplant and opioid addiction | A: Morphine 0.1 mg/kg IV over 5-10 min (n=55)  B: Acetaminophen 1g IV over 5-10 min (n=55)  Rescue: After 30 minutes, if VAS≥5/10 fentanyl 1 mcg/kg IV was administered | Age A: 34.96(8.94) B:36.07(9.7)  Males A:72.2% B:79.6%  Weight NR  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain Classification: Nontraumatic | Any AE  Nausea  Pain severity  Vomiting |
| Shervin, 201420  Iran  Setting: ED  Risk of bias: Low | 15-50y old w/limb trauma in acute pain with NRS>5/10  Exclusions: opioid use or addiction, recent or hx of TCA, SSRI, MAOI, antipsychotics, and any nonspecified sedative/hypnotic, acute or chronic medical health problems w/ASA classification >2 including upper or lower respiratory tract infection, acute or chronic liver or kidney disease, reactive airway disease, unknown allergies, pregnancy, lactation | A: Morphine 0.1 mg/kg IV (n=43)  B: Fentanyl 4 mcg/kg NEB (n=47)  Rescue: If NRS≥5/10 after 15 min, morphine 1mg IV every 5 min until NRS<5/10 | Age A:26.86(7.73) B:26.8(7.45)  Males A:83.7% B:83%  Weight A:72.67kg(11.88) B:75.53(13.04)  Race/ethnicity NR  Pain etiology/location A/B:  Wound/soft tissue 34.9%/17%, fracture 41.9%/48.9%, sprain/strain 23.3%/34%  Pain Classification: Traumatic | Mental status changes  Nausea or vomiting  Pain severity |
| Tran, 201427  Vietnam  Setting: EMS transport for protracted evacuations in low resource, rural setting  Risk of bias: Medium | Trauma patients in need of analgesia, at least 30 months old  Exclusions: objections to pain treatment, coma, in-field anesthesia for invasive life support, deep unconsciousness upon first infield contact, prehospital evacuation time of <10min | A: Morphine 5mg (child) or 10mg (adult) IM (n=139)  B: Ketamine 0.2 to 0.3 mg/kg slow intermittent IV injection (mean dose 15mg) (n=169)  Rescue: NR | Age A:36.9(NR) B:35.5(NR)  Males A:80% B:75%  Weight NR  Race/ethnicity NR  Pain etiology/location: Road traffic accident casualties 61%, falls 24%, mine accidents 9%  Pain Classification: Traumatic | Nausea or vomiting  Pain severity  Presence of pain |
| Vahdati, 201473  Iran  Setting: ED  Risk of bias: Unclear | 18-55y old complaining of headaches due to trauma, VAS≥40  Exclusions: GCS<15, drug allergy or contraindication, fever (>38°C), hemodynamic instability, neurological findings, pregnancy, analgesic within 6h, liver, renal, pulmonary or cardiac disease, transplanted kidney or liver | A: Morphine 0.1 mg/kg IV over 10min (n=30)  B: Paracetamol 1g IV over 10min (n=30)  Rescue: NR | Age A:32.9(11.1) B:37.6(12.5) Males A:80% B:60%  Weight NR  Race/ethnicity NR  Pain etiology/location: Post-traumatic headache 100%  Pain Classification: Traumatic | Any AE  Hypotension  Mental status changes Nausea  Pain severity  Vomiting |
| Eken, 201377  Turkey  Setting: ED  Risk of bias: Low | 18-55y old w/moderate to severe acute mechanical low back pain according to 4 point VRS  Exclusions: analgesic medications in the last 6h, pregnancy, peritoneal irritation signs, hemodynamic instability, renal transplantation, renal, liver, cardiac or pulmonary failure, malignancy, pain indicating sciatica, positive Straight Leg Raise Test, neurological deficit, known allergy to study drugs, probable renal or biliary colic, illiterate | A: Morphine 0.1 mg/kg IV once (n=45)  B: Paracetamol 1g IV once (n=46)  Rescue: Fentanyl 1mcg/kg if inadequate relief after 30min | Age total study 31.5(9.5)  Males total study 60.6%  Weight NR  Race/ethnicity NR  Pain etiology/location: Acute, mechanical low back pain 100%  Pain Classification: Mixed | Any AE  Hypotension  Mental status changes  Nausea or vomiting  Pain severity |
| Craig, 201279  UK Setting: ED Risk of bias: Low | 16-65y old w/ isolated limb trauma and pain score ≥7/10  Exclusions: Weight <50kg, chest pain, GCS<15, drug allergy, liver disease, or patient clinically jaundiced, major trauma, pregnancy, breast feeding, requiring an immediate limb-saving procedure, extreme distress | A: Morphine 10mg IV infusion over 15min (n=28)  B: Paracetamol 1g IV infusion over 15min (n=27)  Rescue: Morphine IV titrated to effect in after the initial infusion the patient’s pain relief was judged to be inadequate | Age A:35(16-62) B:38(16-64)  Males A:53.6% B:55.6%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B:  Fracture 50%/59.2%, soft tissue 50%/40.7%  Pain Classification: Traumatic | Any AE  Pain severity |
| Jennings, 201264  Australia  Setting: EMS- single out-of-hospital ambulance provider  Risk of bias: Low/medium | ≥18y reporting traumatic pain with VNRS ≥5 after total dose of morphine 5mg IV, speaking and able to rate their pain  Exclusions: Drug allergy, pregnant or lactating, current ischemic chest pain or acute pulmonary edema, SBP>180 and evidence of a head injury, history of LOC or GCS score <15, inability to obtain venous access, presumed intoxication with alcohol/illicit substances | A: Ketamine 10 or 20mg bolus, repeat 10mg every 3min until pain free or serious adverse event or arrival at the ED, mean 40.6mg (25) (n=70)  B: Morphine 5mg bolus, repeat 1 to 5mg every 5min until pain free or a serious adverse event or arrival at the ED, mean 14.4mg (9.4) (n=65)  Rescue: No therapies other than those randomized were allowed | Age A: 41(26-56) B:45(31-66)  Males A:64% B:58%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B: Extremity fracture 37%/45%, soft tissue injury 24%/23%, fracture- other 20%/20%, dislocation 16%/11%, burn 3%/1%  Pain Classification: Traumatic | Any AE  Emergence delirium  Heart rate  Hypotension  Mental status changes  Nausea  Pain severity  Respiratory rate  Systolic blood pressure  Time to analgesic effect  Vomiting |
| Serinken, 201278  Turkey  Setting: ED  Risk of bias: Low | 18-55y old w/acute renal colic, moderate to severe pan on the 4-point verbal scale  Exclusions: analgesics within 6h, presented with fever or were hemodynamically unstable, signs of peritoneal irritation or cardiac failure, hx of renal failure, hepatic failure or drug allergy, pregnant, vision problems, ultimately diagnosed with other renal pathology | A: Morphine 0.1 mg/kg IV (n=35)  B: Paracetamol 1g IV (n=38)  Rescue: Fentanyl 1mcg/kg IV if inadequate pain relief | Age A:31.3(9.0) B:29.1(8.2)  Males A:65.7% B:73.7%  Weight NR  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain Classification: Nontraumatic | Any AE  Hypotension  Mental status changes  Nausea or vomiting  Pain severity  Respiratory depression |
| Smith, 201294  USA Setting: EMS- helicopter transport  Risk of bias: Medium | 18-65y old transported by helicopter for evaluation of traumatic injuries, could report pain and communicate to the medical crew their pain severity on NPS  Exclusions: Drug allergy, hypotensive before receiving the first dose of the study drug (SBP<100), in custody, pregnant | A: Morphine 4mg IV every 5min as needed (max 5 doses, mean 3) (n=104)  B: Fentanyl 50mcg IV every 5min as needed (max 5 doses, mean 3.3) (n=100)  Rescue: NR | Age A:38(NR) B:39(NR)  Males A:75% B:76%  Weight NR  Race/ethnicity A/B: Caucasian 80.8%/81%, African American 16.4%/14%, Other 2.9%/5%  Pain etiology/location A/B: Blunt 90%/85%, penetration 10%/15%  Pain Classification: Traumatic | Hypotension  Pain severity  Presence of pain  Vomiting |
| Kariman, 201183  Iran  Setting: ED  Risk of bias: Low/medium | 15-85y old w/isolated extremity trauma, moderate to severe pain per VAS≥4/10  Exclusions: Trauma >6h ago, associated injuries including head and trunk trauma, nonorthopedic limb injuries, GCS<15, abdominal distension, lung disease, hx of a recent dive, pneumothorax, hemothorax, received any form of prehospital analgesia | A: Fentanyl 2 mcg/kg IV, slow injection (n=50)  B: Nitrous oxide:oxygen (50:50) self-administered until VAS<4/10 or 15min (n=50)  Rescue: NR | Age A:35.8(19.9) B:37.0(20.2)  Males A:84% B:72%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B: Fracture 30%/52%, dislocation 70%/48%  Pain Classification: Traumatic | Any AE  Diastolic blood pressure  Heart rate  Mental status changes Oxygen saturation  Pain severity  Respiratory rate  Systolic blood pressure |
| Furyk, 200921  Australia  Setting: ED  Risk of bias: Medium | 4-13y old w/pain (sufficient to warrant narcotic analgesia) from a clinically suspected limb fracture  Exclusions: ASA grade >1, chronic medical condition (e.g. structural heart disease, hepatic or renal disease), active asthma (requiring preventers or current wheeze), concurrent upper respiratory tract infection or drug allergy | A: Morphine 0.1 mg/kg IV (n=37)  B: Fentanyl 4 mcg/kg NEB (max 200 mcg) (n=35)  Rescue: NR | Age A:9.4(2.5) B:8.6(2.8)  Males NR  Weight A:35.1kg(12.6) B:33.6kg(12.7)  Race/ethnicity NR  Pain etiology/location: Limb fracture 100%  Pain Classification: Traumatic | Any AE  Nausea  Pain severity |
| Johansson, 200965  Sweden  Setting: EMS  Risk of bias: Low/medium | Adults w/bone fractures in acute pain (NRS>4/10) after morphine 0.1 mg/kg IV  Exclusions: Inability to use the rating scale, long-term use of opioids, hx of chronic pain, hx of/or acute MI, unconsciousness | A: Morphine 0.1 mg/kg IV (n=11)  B: Ketamine 0.2 mg/kg IV (n=16)  Rescue: NR | Age A:70(16) B:74(14)  Males A:54.5% B:43.8%  Weight A:72.9kg (13.6) B:70.1kg (10.4)  Race/ethnicity NR  Pain etiology/location: Bone fracture 100%  Pain Classification: Traumatic | Heart rate  Mental status changes  Nausea  Oxygen saturation  Pain severity  Respiratory rate  Systolic blood pressure  Vomiting |
| Borland, 200797  Australia  Setting: ED  Risk of bias: Low | 7-15y old w/clinically deformed closed long-bone fractures  Exclusions: Received narcotic analgesic within 4h of ED arrival, head injury resulting in impaired judgment, drug allergy, blocked or traumatized nose, preventing nasal administration; or were unable to perform pain scoring | A: Morphine 0.1 mg/kg IV once then 1.0mg every 5min until relief, max dose or patient refused (mean total 0.11 mg/kg) (n=34)  B: Fentanyl 1.4 mcg/kg IN once then 15 mcg every 5min until relief, max dose or patient refused (mean total 1.7 mcg/kg) (n=33)  Rescue: For inadequate pain relief after 30min, morphine IV was offered and titrated | Age A:10.7(6-15) B:11.7(7-15)  Males NR  Weight A:41.9kg(19-80) B:45.7(26-88)  Race/ethnicity NR  Pain etiology/location: Long bone fracture 100%  Pain Classification: Traumatic | Pain severity  Vomiting |
| Clark, 200789  Canada  Setting: ED  Risk of bias: Low | 6-17y old presenting to ED w/pain from a musculoskeletal injury (extremities, neck, back) in preceding 48h  Exclusions: contraindication to a study drug, required resuscitation, open fracture, had an IV line in place, received 1 of the study drugs in the preceding 4h (APAP) or 6h (IBU), or had a significant cognitive impairment | A: Ibuprofen 10 mg/kg (max 600mg) by mouth once (n=112)  B: Acetaminophen 15mg/kg (max 650mg) by mouth once (n=112)  Rescue: 60min after study drug additional pain medication was allowed, asked every 30min | Age A:11.8(2.8) B:12.0(2.9)  Males A:56.9% B:66.4%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B: Soft tissue 41.3%/47.7%, fracture 58.7%/52.3%  Pain Classification: Traumatic | Pain severity  Presence of pain |
| Galinski, 200766  France  Setting: EMS – considered “mobile intensive care units” in route to ED  Risk of bias: Low | 18-70y old, trauma with severe, acute pain (VAS≥60/100)  Exclusions: Respiratory distress, SBP<90, GCS<15, psychiatric history; chronic respiratory, renal, or hepatic failure; drug allergy, treatment of chronic pain or treatment with opioids; incapacity to understand the VAS; pregnancy; indication for local or regional analgesia, already received an opioid analgesic | A: Morphine 0.1 mg/kg IV + ketamine 0.2mg/kg IV over 10min; then morphine 3mg every 5min until VAS≤30/100 (n=38)  B: Morphine 0.1mg/kg IV + placebo over 10min, then morphine 3mg every 5min until VAS≤30/100 (n=35)  Rescue: NR | Age A:35(13) B:40(14)  Males A:75.8% B:71.9%  Weight NR  Race/ethnicity NR  Pain etiology/location A/B: Suspicion of bone fracture 58%/75%; burns 6%/6%, other 36%/19%  Pain Classification: Traumatic | Heart rate  Mental status changes  Nausea or vomiting  Oxygen saturation  Pain severity  Presence of pain  Respiratory depression  Respiratory rate  Systolic blood pressure |
| Mahar, 200796  USA Setting: ED  Risk of bias: Low/medium | 8-18y old w/extremity deformity and/or suspected fracture with VAS>50/100  Exclusions: ASA status >2, hx of LOC, altered level of consciousness, multiple traumatic injuries, received prior medication for pain control | A: Morphine 0.1 mg/kg IV (n=40)  B: Fentanyl 10-15 mcg/kg, oral transmucosal lozenge (n=47)  Rescue: NR | Age A: 11.67(NR) B:11.34(NR)  Males A:65% B:64%  Weight A:47.6kg(NR) B:43.6kg  Race/ethnicity NR  Pain etiology/location A/B: Fracture 87.5%/100%, dislocation 5%/0%, soft tissue 7.5%/0%  Pain Classification: Traumatic | Any AE  Nausea  Pain severity  Respiratory depression  Vomiting |
| Rickard, 200795  Australia  Setting: EMS- 2 ambulance services  Risk of bias: Medium | 18-65y old, severe pain (VRS≥5/10 for cardiac type pain or discomfort persisting 5 minutes or more after glyceryl trinitrate or VRS≥2/10 for noncardiac pain  Exclusions: Hypoxia (SpO2 </=85%); hypotension (SBP<110); HR<50 or >150, GCS<15, vomiting, drug allergy, opiate use in the past 24h, unable to provide a VRS | A: Morphine 2.5-5mg IV, then 2 more doses of 2.5-5 mg at intervals ≥5min if the VRS≥3/10 (n=122)  B: Fentanyl 180mcg IN, then 2 more doses of 60mcg at intervals ≥5min if VRS≥3/10 (n=136)  Rescue: At 15min, morphine 2.5-5mg IV was available if VRS≥3/10, at ≥5min intervals to a max of 20mg | Age A:41.4(13.6) B:43(13.9)  Males A:70% B:56%  Weight A:80.7kg(16.5) B:81.8kg (14.9)  Race/ethnicity NR  Pain etiology/location A/B: Fracture/dislocation 37%/33%, chest 15%/14%, back 15%/17%, abdomen 13%/18%, other 20%/17%  Pain Classification: Mixed | Any AE  Pain severity |
| Safdar, 200685  USA Setting: ED  Risk of Bias: Low | 18-55y old w/clinical diagnosis of renal colic, VAS≥5/10 or at least "moderate" pain on a 4-category verbal pain scale  Exclusions: pregnancy, breastfeeding, contraindication to NSAIDs or opiates, renal dysfunction, analgesics within 6h, hx of bleeding diathesis, confirmed hx of peptic ulcer disease, current use of warfarin, hx of drug dependence or current use of methadone, peritonitis or presence of any peritoneal sign | A: Morphine 5mg IV, then 5 mg IV at 20min if incomplete relief (n=43)  B: Ketorolac 15mg IV, then 15mg IV at 20min if incomplete relief (n=43)  Rescue: Morphine 5mg IV for persistent pain at 40min, titrated at the discretion of the ED attending | Age A:37.3(10.0) B:39.3(9.9)  Males A:67% B:67%  Weight NR  Race/ethnicity NR  Pain etiology/location: Renal colic 100%  Pain Classification: Nontraumatic | Mental status changes  Nausea  Pain severity  Presence of pain  Vomiting |
| Galinski, 200593  France  Setting: EMS – 5 prehospital “mobile intensive care units”  Risk of bias: Low | 18-70y with severe, acute pain defined as VAS≥60/100  Exclusions: Presence of chronic respiratory, renal, or hepatic insufficiency, known opioid allergies, treatment of chronic pain or treatment with opioids, incapacity to understand the VAS, acute hemodynamic, respiratory, or neurological compromise, pregnancy, indication for local or regional analgesia, or patients who had already received an opioid analgesic | A: Morphine 0.1 mg/kg IV followed by additional 3mg doses until VAS≤30/100 (n=26)  B: Fentanyl 1 mcg/kg IV followed by additional 30mcg doses until VAS≤30/100 (n=28)  Rescue: NR | Age A:40(13) B:45(13)  Males A:88% B:79%  Weight NR  Race/ethnicity NR  Pain etiology/location: Trauma 73%/50%, nontrauma 27%/50%  Pain Classification: Mixed | Heart rate  Mental status changes  Nausea  Oxygen saturation  Pain severity  Presence of pain  Respiratory rate  Systolic blood pressure  Vomiting |
| Younge, 199916  Australia  Setting: ED  Risk of bias: Low/medium | 3-10y old w/limb fracture  Exclusions: patients with head injury, blocked nose or rhinorrhea, requiring immediate IV access, intellectual or visual impairment, hepatic or renal disease, with known allergy to either drug or those who had received opioid analgesia within the previous 24h | A: Morphine 0.2 mg/kg IM (n=23)  B: Fentanyl 1 mcg/kg IN (n=24)  Rescue: Could be given from 20min onwards | Age A:7.1(NR) B:6.6(NR)  Males A:65% B:62.5%  Weight NR  Race/ethnicity NR  Pain etiology/location: Limb fracture 100%  Pain Classification: Traumatic | Heart rate  Vomiting |

Abbreviations: APAP=acetaminophen; ASA=American Society of Anesthesiologists; COPD=chronic obstructive pulmonary disease; CVA=cerebrovascular accident; CVAT=costovertebral angle tenderness; ED=emergency department; EMS=emergency medical services; GCS=Glasgow coma scale; h=hours; HTN=hypertension; hx=history; IBU=ibuprofen; IN=intranasal; IV=intravenous; LOC=loss of consciousness; MAOI=monoamine oxidase inhibitor; mg=milligrams; mmHg=millimeters of mercury; NR=not reported; NSAIDS= nonsteroidal anti-inflammatory drugs; PID= pelvic inflammatory disease; SBP=systolic blood pressure; SSRI= selective serotonin reuptake inhibitors; TCA= tricyclic antidepressants; VAS=visual analog scale; VNRS=verbal numeric rating scale; VRS=verbal rating scale