

Clinically significant drug–drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review

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Background: Opioids are the most frequently used drugs to treat pain in cancer patients. In some patients, however, opioids can cause adverse effects and drug–drug interactions. No advice concerning the combination of opioids and other drugs is given in the current European guidelines.

Objective: To identify studies that report clinically significant drug–drug interactions involving opioids used for pain treatment in adult cancer patients.

Design and data sources: Systematic review with searches in Embase, MEDLINE, and Cochrane Central Register of Controlled Trials from the start of the databases (Embase from 1980) through January 2014. In addition, reference lists of relevant full-text papers were hand-searched.

Results: Of 901 retrieved papers, 112 were considered as potentially eligible. After full-text reading, 17 were included in the final analysis, together with 15 papers identified through hand-searching of reference lists. All of the 32 included publications were case reports or case series. Clinical manifestations of drug–drug interactions involving opioids were grouped as follows: 1) sedation and respiratory depression, 2) other central nervous system symptoms, 3) impairment of pain control and/or opioid withdrawal, and 4) other symptoms. The most common mechanisms eliciting drug–drug interactions were alteration of opioid metabolism by inhibiting the activity of cytochrome P450 3A4 and pharmacodynamic interactions due to the combined effect on opioid, dopaminergic, cholinergic, and serotonergic activity in the central nervous system.

Conclusion: Evidence for drug–drug interactions associated with opioids used for pain treatment in cancer patients is very limited. Still, the cases identified in this systematic review give some important suggestions for clinical practice. Physicians prescribing opioids should recognize the risk of drug–drug interactions and if possible avoid polypharmacy.

Keywords: opioids, pain, cancer patients, drug–drug interactions

Introduction

Opioid analgesics are the most frequently used drugs to treat pain in patients with cancer.¹ In some patients, however, opioids cause adverse effects.² The most frequent adverse effects in cancer patients treated for pain with opioids are sedation, nausea/vomiting, and constipation, but other infrequent adverse effects, such as myoclonus, hallucination, and respiratory depression, are also feared.^{1–3} Adverse drug reactions from opioids are most often caused by the opioid itself, but can also be a result of the combination of the opioid and another drug, a drug–drug interaction (DDI).⁴ The risk of DDIs is high in cancer patients because of the large number of concomitant drugs.⁵

DDIs can be categorized as pharmacokinetic, that is, one drug influences the pharmacokinetic properties – absorption, distribution, metabolism, or excretion – of another

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drug. DDIs can also be pharmacodynamic, when the effects of two drugs either potentiate or antagonize each other.⁶

DDIs are reported to lead to serious adverse drug reactions in patients treated with opioids for pain.^{7,8} Still, no advice concerning the combination of opioids and other drugs is given in the current guidelines.² Some studies have assessed the number of potentially harmful drug combinations in cancer pain patients, but do not report the number of clinically observed adverse drug reactions actually resulting from such combinations.^{5,9} Thus, the real risk of clinically important DDIs related to opioid therapy in cancer patients is not established.

The lack of advice on drug combinations in current guidelines may be a result of this limited clinical information. Therefore, a systematic review of the literature is indicated to identify studies that report clinically relevant DDIs associated with opioid analgesics used for the treatment of pain in patients with cancer.

Methods

Search strategy

Systematic searches were performed in Embase and MEDLINE through OvidSP and in the Cochrane Central Register of Controlled Trials, from set up of the databases (Embase from 1980) through January 2014. The last day searched was March 14, 2014. The full search string for Embase is presented in Table 1. Titles and abstracts of the retrieved citations were reviewed independently by two of the researchers (DFH, AKL), and potentially relevant papers were read in full text (DFH, AKL). In cases of doubt or disagreement, papers were reassessed by all three investigators (DFH, AKL, PK).

Additionally, reference lists of all the papers read in full text were hand-searched for relevant papers.

Inclusion criteria

- Publications reporting clinically significant DDIs involving WHO step II or step III opioids, as assessed by the authors.
- The DDI observed in one or more adult patients with a diagnosis of malignant disease and treated with an opioid for pain.

- Any type of publication: randomized controlled trial, other controlled study, observational study, case report, case series, or letter to the Editor, except for publications available only in abstract form.
- Publications in English language.

Exclusion criteria

- Experimental studies.
- Nonhuman studies.
- Only pharmacokinetic investigations (no clinical outcome).
- Studies in noncancer patients.
- Opioids used for indications other than pain or perioperatively.
- Duplicate publications.

Content analysis

The identified publications were grouped according to clinical presentation and probable underlying mechanism of the DDI. The DDIs and underlying mechanisms were presented as assessed and interpreted by the authors in each publication.

Results

Systematic review of the literature

After removal of duplicates, 901 papers were retrieved (Figure 1). A total of 112 of these papers were considered potentially eligible for inclusion. After reading the full-text papers, 17 publications were included in the final analysis. In addition, 15 relevant papers were identified through hand-searching the reference lists of the articles read in full text, adding up to a total number of 32 included publications (Table 2).^{10–41} Additionally, two papers that commented on two of the included publications were identified,^{42,43} but not included as cases in the review.

No randomized controlled trials or other controlled studies were found. All of the included publications were case reports or case series, reporting on 2–19 patients. Nine of the papers were published in the period 1983–2000, and 23 in the period 2001–January 2014 (Table 2). In some case series, DDIs in both cancer patients and patients with

Table 1 Search strategy

Search strategy in Embase for drug–drug interactions (DDIs) involving opioid analgesics used for pain treatment in cancer patients (#1 or #2 or #3)

#1 (exp opiate agonist/it or exp narcotic analgesic agent/it or exp narcotic agent/it or exp morphine derivative/it) and exp neoplasm/

#2 (exp opiate agonist/or exp narcotic analgesic agent/or exp narcotic agent/or exp morphine derivative/) and exp neoplasm/and (drug interaction/or drug antagonism/or drug competition/or drug inhibition/or drug potentiation/) and (exp pain/or analgesia/or analgesic activity/or pain relief/)

#3 (exp opiate agonist/or exp narcotic analgesic agent/or exp narcotic agent/or exp morphine derivative/) and exp neoplasm/and polypharmacy/

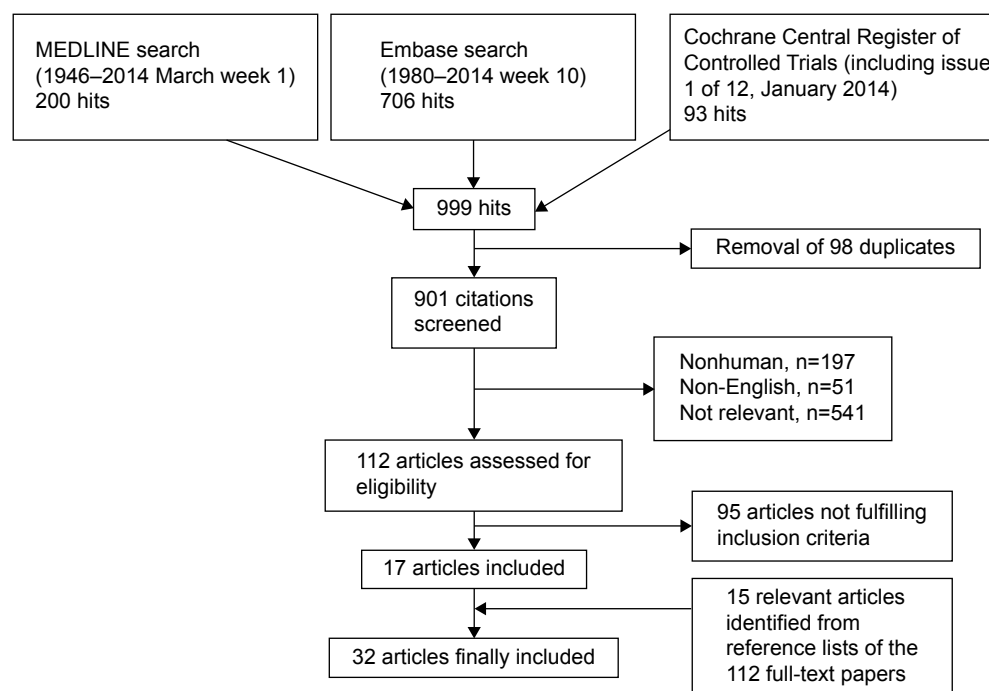


Figure 1 PRISMA flow chart showing the selection of papers.

nonmalignant diseases were reported.^{11,12,18,41} From these case series, only cases of DDIs due to opioids in patients with a diagnosis of malignant disease treated for pain were included in the review.

Opioids involved in DDIs

The majority of included publications report DDIs related to opioids that are in common clinical use (Table 2):

- morphine, administered by various routes; oral, subcutaneous, intravenous, epidural, and intrathecal (nine publications),^{14–22}
- fentanyl, transdermal, and intravenous (nine publications,^{27–35} of which seven described DDIs associated with transdermal preparations),
- oral methadone (six publications),^{16,37–41}
- oral oxycodone (three publications),^{24–26}
- tramadol combined with pethidine,¹⁰ tapentadol,¹³ hydromorphone,²³ and buprenorphine³⁶ was reported in one paper each.

Four publications report DDIs associated with opioids of minor current clinical relevance: propoxyphene, dextro-propoxyphene, and nalbuphine.^{11,12,15,16}

Clinical presentation of DDIs

Eleven papers reported DDIs resulting in sedation and respiratory depression.^{18,19,22,24,30,32,36–40} Fifteen papers reported DDIs causing various other central nervous system (CNS)

symptoms, including delirium,^{10,20,23–25,29,31,34–36} serotonin syndrome,^{25,26,35} myoclonus,^{14,29,35} hyperalgesia,¹⁴ extrapyramidal symptoms,²¹ catatonia,¹⁰ neuroleptic malignant syndrome,³⁴ or carbamazepine toxicity.^{11,12} Seven papers reported DDIs causing impairment of pain control and/or opioid withdrawal.^{15–17,24,27,28,33} Finally, in three publications, other symptoms believed to be associated with opioid-related DDIs were reported: hypertension,¹³ hypotension,²⁴ vomiting,²⁴ sweating,²⁴ ventricular tachycardia/torsades de pointes.⁴¹

Mechanisms underlying DDIs of opioids used for pain treatment in cancer patients

The mechanisms underlying DDIs involving opioid analgesics used for pain treatment in patients with cancer in the publications included in this review are presented in Table 3.

Quality of evidence

The included studies have several limitations. Only case reports and case series were identified (Table 2). Most of the reports included in this review provide poor level of evidence. Some may also not represent true DDIs, but other opioid-related complications. However, we decided to include the reports as they were clinically evaluated and presented by the authors and published by the respective journals.

Table 2 Overview of included publications reporting drug–drug interactions (DDIs) involving opioids used for pain treatment in cancer patients

Author (year)	Study design (number of patients)	Patients	Primary treatment (dose, route of administration)	Coadministered drug (dose, route of administration)	Clinical presentation	Underlying mechanism as proposed by the authors	Additional information provided by the authors of the included papers and the present review
Tramadol Huang et al ¹⁰ (2007)	Case report	39-year-old woman with lymphoma	IV tramadol (150 mg/day)	Pethidine (25 mg injection)	Confusion with agitation and visual hallucinations 2 hours after pethidine injection, followed by catatonia with mutism and immobile standing, for 2 days	Anticholinergic and serotonergic effects; imbalance between cholinergic and dopaminergic systems in the CNS	Other drugs (pantoprazole, cyclophosphamide, prednisolone) could have contributed to the symptoms
Dextropropoxyphene/propoxyphene							
Yu et al ¹¹ (1986)	Case series (one patient)	69-year-old woman with myelofibrosis	Carbamazepine (600 mg/day)	Dextro-propoxyphene (32 mg q4h)	Drowsiness progressing to coma on the fifth day of the co-treatment	Inhibition of carbamazepine metabolism	Two other cases of patients with nonmalignant diseases are also reported
Oles et al ¹² (1989)	Case series (two patients)	Two patients; 60-year-old man and 23-year-old woman with brain tumors	Carbamazepine (~9–23 mg/kg/day)	Propoxyphene	Lightheadedness, blurred vision, double/triple vision, ataxia, nausea and vomiting after 2–3 days of co-treatment	Inhibition of carbamazepine metabolism (CYP450)	Six other cases of patients with nonmalignant diseases are also reported
Tapentadol Sanders ¹³ (2013)	Case report	58-year-old woman with endometrial carcinoma	PO clonidine (400 mg/day)	PO tapentadol (50 mg per dose)	Blood pressure increase within 24 hours after tapentadol initiation. Similar episode 2 hours after tapentadol was resumed	Inhibition of norepinephrine reuptake	
Morphine Potter et al ¹⁴ (1989)	Case series (seven patients)	Nineteen patients; ten men and nine women aged 34–75; with malignant disease, and high dose of morphine or morphine-related side effects	PO morphine (120–1,200 mg/day), SC morphine (210–800 mg/day)	Antidepressants (TCA), antipsychotics (phenothiazines and haloperidol), antiemetics, NSAIDs	Side effects in 13 of the 19 patients (myoclonus in 12, and hyperalgesia in 1). Antidepressants and antipsychotics were used only in patients with side effects (7/13). A greater proportion of patients with side effects used thiethylperazine and NSAIDs	Antagonistic effect on dopamine receptors (phenothiazines); inhibition of catecholamines release (NSAIDs); promotion of proconvulsant properties of opioids	Abnormal concentrations of electrolytes in some patients could have contributed to the symptoms
Smith and Guly ¹⁵ (2004)	Case report	60-year-old woman with metastatic renal cell carcinoma	SR morphine (90 mg q12h)	IV nalbuphine (30 mg)	Symptoms of opioid withdrawal, resistance to additional doses of intravenous morphine	Antagonistic effect on mu opioid receptors	

Hartree ¹⁶ (2005)	Case series (one patient)	49-year-old man with metastatic prostate cancer	SR morphine (360 mg q12h)	IM nalbuphine (10 mg)	Increased pain and symptoms of opioid withdrawal	Antagonistic effect on mu opioid receptors	Another patient (treated with methadone and nalbuphine) is reported below
Ripamonti et al ¹⁷ (1998)	Case series (three patients)	Three patients; one man and two women aged 20–58; with sarcomas and cervical carcinoma	PO, SC, spinal morphine (in increasing doses; 20–2,000 mg MEDD)	SC or IV somatostatin (3 mg)	Increased pain, difficulty in controlling pain	Opioid antagonistic properties of somatostatin	One patient initially on oral methadone with poor analgesic effect, switched to morphine
Piquet et al ¹⁸ (1998)	Case series (one patient)	72-year-old man with metastatic bladder carcinoma	IT morphine (10 mg)	IT bupivacaine (7.5 mg) with epinephrine	Coma and respiratory depression 10 minutes after IT injection of morphine and bupivacaine (morphine was resumed in the same dose after 4 days)	Inhibition of the stimulating effect of pain on respiration	A case of a patient with nonmalignant disease is also reported
Upadhyay et al ¹⁹ (2008)	Case report	80-year-old man with metastatic lung cancer	PO morphine (dose increased from 15 mg to 30 mg q4h)	PO amitriptyline (dose increased from 25 mg/day to 50 mg/day), ranitidine (300 mg/day)	Deep and prolonged sedation, not responding to painful stimuli with respiratory rate eight per minute during titration rate of the analgesic dose	Sedating effect of amitriptyline; inhibition of morphine metabolism (amitriptyline and ranitidine)	Patient with hypoalbuminemia
Martinez-Abad et al ²⁰ (1988)	Case report	42-year-old man with cancer of the larynx	IV ranitidine (150 mg q8h)	IV morphine (50 mg/day)	Three episodes of confusion with agitation after three subsequent doses of ranitidine during morphine infusion	Mechanism not clear (according to the authors)	Inhibition of morphine metabolism by ranitidine has been demonstrated ^{45,46}
Guo et al ²¹ (2006)	Case report	18-year-old woman with nasopharyngeal carcinoma	IM haloperidol (4 mg/day), IV morphine (up to ~10 mg/h) and ED injection of morphine (2 mg)	IV naloxone (3 injections of 0.1–0.2 mg at 30-minute intervals)	Three episodes of extrapyramidal symptoms (restlessness, torticollis, oculogyric response) 5 minutes after each naloxone injection	Reversal of opioid-related protection from haloperidol-induced extrapyramidal side effects	
Bortolussi et al ²² (1994)	Case series (four patients)	Four patients; three men and one woman aged 53–56; with metastatic renal cell carcinoma	SR morphine	IV recombinant interleukin-2 (rIL-2)	Coma and/or respiratory depression	Toxic synergy on CNS; accumulation of morphine metabolites due to acute renal failure (induced by rIL-2)	
Hydromorphone Fainsinger et al ²³ (1993)	Case report	85-year-old woman with breast cancer	PO hydromorphone (24 mg q4h, 12 mg prn)	Captopril (50 mg/day)	Confusion with agitation and hallucinations, after a few days of co-treatment	Accumulation of hydromorphone metabolites due to renal failure (induced by captopril)	

(Continued)

Table 2 (Continued)

Author (year)	Study design (number of patients)	Patients	Primary treatment (dose, route of administration)	Coadministered drug (dose, route of administration)	Clinical presentation	Underlying mechanism as proposed by the authors	Additional information provided by the authors of the included papers and the present review
Oxycodone							
Watanabe et al ²⁴ (2011)	Case series (seven patients)	Nine patients; two men and seven women aged 39–82; with maxillary tumor or hematologic malignancies	PO oxycodone (~0.2–2.0 mg/kg/day)	PO or IV voriconazole (~2.2–8.0 mg/kg/day) coadministered or discontinued	Adverse events (vomiting, drowsiness, hypopnea, delirium, sweating, hypotension, uncontrolled pain) in seven of nine patients; after 1–10 days of co-treatment	Inhibition of CYP3A4	Commented in Hagelberg et al ²
Walter et al ²⁵ (2012)	Case report	77-year-old woman with lung cancer	SR oxycodone (50 mg q12h), IR oxycodone (5 mg prn)	Citalopram (20 mg/day)	Tremor, weakness, inability to coordinate motor movements, confusion (serotonin syndrome). The symptoms resolved within 48 hours after oxycodone was changed to morphine	Hyperstimulation of central 5-HT1A and 2A receptors (citalopram); disinhibition of serotonergic neuronal activity by suppressing GABA-mediated inhibition (oxycodone)	The patient also used esomeprazole, which could have inhibited citalopram clearance
Rosebraugh et al ²⁶ (2001)	Case report	34-year-old man with lymphoma	PO sertraline (50 mg/day)	PO oxycodone (200 mg over 48 hours)	Severe tremor and visual hallucinations (probable serotonin syndrome). The symptoms resolved within 12 hours after sertraline was stopped and cyproheptadine administered	Hyperstimulation of central 5-HT1A and 2A receptors (sertraline); disinhibition of neuronal activity by suppressing GABA-mediated inhibition (oxycodone)	
Fentanyl							
Takane et al ²⁷ (2005)	Case report	61-year-old man with parotid gland adenocarcinoma	TD fentanyl (dose increased from 2.5 mg to 7.5 mg; every 3 days)	PO rifampin (300 mg/day)	Severe pain after rifampin initiation. Patient continued to have pain despite three-fold increase in fentanyl dose	Induction of CYP3A4	The ratio of serum fentanyl concentration/dose decreased to 20%–50% of baseline value
Morii et al ²⁸ (2007)	Case report	64-year-old man with colon cancer	Rifampicin (450 mg/day)	TD fentanyl (dose increased from 0.6 mg/day to 2.5 mg/day)	Poor analgesia	Induction of CYP3A4	
Mercadante et al ²⁹ (2002)	Case report	67-year-old man with head and neck cancer	TD fentanyl (50 µg/h)	PO irinotecan (400 mg/day)	Agitated delirium with myoclonus 24 hours after starting irinotecan	Inhibition of CYP3A4	Patient also used omeprazole and ibuprofen, which could have contributed to the event (by inhibition of fentanyl metabolism and renal excretion)

Hallberg et al ³⁰ (2006)	Case report	46-year-old man with tonsillar cancer	TD fentanyl (150 µg/h)	PO fluconazole (50 mg/day)	Death after 3 days of co-treatment	Inhibition of CYP3A4	Postmortem blood analysis showed toxic concentration of fentanyl. Patient used also other drugs that could have contributed to the event (morphine, oxazepam, zolpidem) Patient with chronic renal insufficiency
Levin et al ³¹ (2010)	Case report	85-year-old man with lung cancer	IV fentanyl (25 µg/h)	Diltiazem	Hypoaactive delirium, somnia, miosis after 3 days of coadministration	Inhibition of CYP3A4	
Cronnelly and Pegrum ³² (2012)	Case report	72-year-old woman with metastatic breast cancer	TD fentanyl (87 µg/h)	PO clarithromycin (1 g/day)	Coma and respiratory depression 2 days after clarithromycin initiation	Inhibition of CYP3A4	Patient with kidney disease on hemodialysis
Tsutsumi et al ³³ (2006)	Case report	47-year-old woman with leukemia	TD fentanyl (25 µg/h), discontinued	Cyclosporine	Opioid withdrawal syndrome 1 day following fentanyl cessation. Symptoms disappeared after fentanyl was resumed	Inhibition of CYP3A4	
Morita et al ³⁴ (2004)	Case report	67-year-old man with esophageal cancer	IV fentanyl (500 µg/ day)	IV haloperidol (2.5–7.5 mg/day)	Worsening of pre-existing delirium (days 3–6). On day 7 muscle rigidity, fever, severe diaphoresis, tachycardia, hypertension, tachypnea, and coma (neuroleptic malignant syndrome)	Antagonistic effect on dopamine receptors (haloperidol); modification of dopamine metabolism in the CNS (fentanyl)	Hypocalcemia, hypophosphatemia and hypomagnesemia in this patient could have contributed to the symptoms
Alawadhi et al ³⁵ (2007)	Case report	65-year-old woman with myeloproliferative disease	Citalopram	TD fentanyl (25 µg/h)	Confusion, agitation, tremors, hyperreflexia, myoclonus, unsteady gait, tachycardia (serotonin syndrome) within 24 hours of fentanyl initiation. The symptoms resolved within 24–36 hours after fentanyl was replaced by oxycodone	Overstimulation of serotonin receptors (citalopram); inhibition of serotonin reuptake and increase of serotonin release in the CNS (fentanyl)	
Buprenorphine Moro et al ³⁶ (2006)	Case report	34-year-old man with metastatic osteosarcoma	Ifosfamide (2 g/m ² /day for 3 days)	TD buprenorphine (35–52.5 µg/h)	Confusion, miosis, respiratory depression and bradycardia within 36 hours of the co-treatment	Inhibition of CYP3A4 (due to saturation of the enzyme by ifosfamide)	Commented by Davis (best interpretation for the event was rapid increase in buprenorphine dose) ⁴³
Methadone Hartree ³⁶ (2005)	Case series (one patient)	54-year-old man with rectal carcinoma	PO methadone (20 mg/day)	IM nalbuphine (10 mg)	Increased pain and symptoms of opioid withdrawal	Antagonistic effect on mu opioid receptors	Another patient (treated with morphine and nalbuphine) is reported above

(Continued)

Table 2 (Continued)

Author (year)	Study design (number of patients)	Patients	Primary treatment (dose, route of administration)	Coadministered drug (dose, route of administration)	Clinical presentation	Underlying mechanism as proposed by the authors	Additional information provided by the authors of the included papers and the present review
Benitez-Rosario et al ³⁷ (2006)	Case report	61-year-old woman with metastatic lung cancer	PO methadone (210 mg/day)	Carbamazepine (1,200 mg/day), discontinued	Loss of consciousness and respiratory depression eleven days after carbamazepine discontinuation	Disappearance of carbamazepine inducing effect on metabolizing enzymes	The dose of methadone was increased within a week before the incident
Tarumi et al ³⁸ (2002)	Case report	60-year-old man with gastric cancer	PO methadone (45–75 mg/day)	IV fluconazole (100 mg/day)	Unresponsiveness and respiratory depression 4 days after fluconazole initiation	Inhibition of CYP3A4 and 2C9	Patient also used omeprazole, which could have contributed to the accumulation of methadone (by inhibition of CYP2C19 and CYP3A4)
Sorkin and Ogawa ³⁹ (1983)	Case report	76-year-old man with metastatic lung cancer	PO methadone (5 mg q8h), SC morphine (8 mg prn)	IV cimetidine (1.2 g/day)	Respiratory depression 6 days after cimetidine initiation, 3 h after the rescue dose of morphine	Inhibition of liver enzymes	Cimetidine is a weak CYP3A4 inhibitor ⁴⁴
Elsayem and Bruera ⁴⁰ (2005)	Case report	70-year-old man with gastric cancer	Methadone (10 mg q8h, 2 mg prn)	Sertraline (100 mg/day)	Coma and respiratory depression 3 days after sertraline dose was increased from 50 mg/day to 100 mg/day	Inhibition of CYP3A4	Severely malnourished patient with a history of alcoholism
Walker et al ⁴¹ (2003)	Case series (one patient)	61-year-old woman with rectal cancer	PO methadone (600–700 mg/day)	Sertraline (50 mg/day), midazolam, IV fentanyl (prn)	Two episodes of ventricular tachycardia (torsades de pointes)	Interference with methadone metabolism (sertraline, midazolam, and fentanyl, substrates of CYP3A4); increase in methadone blood levels	High dose of methadone and preexisting cardiac disease in the patient Two other cases of patients with nonmalignant disease are also reported

Abbreviations: PO, oral; IR, immediate release; SR, slow release; SC, subcutaneous; IV, intravenous; TD, transdermal; ED, epidural; IT, intrathecal; q4h, every four hours; q12h, every 12 hours; prn, as required; MEDD, morphine equivalent daily dose; NSAIDs, nonsteroidal anti-inflammatory drugs; TCA, tricyclic antidepressants; CNS, central nervous system; BP, blood pressure.

Table 3 Mechanisms underlying DDIs involving opioid analgesics used for pain treatment in patients with cancer**Mechanisms underlying DDIs of opioid analgesics****Pharmacokinetic DDIs**

- 1) Inhibition or induction of opioid metabolism through CYP450 or other metabolizing enzymes^{19,20,24,27–33,36–41}
- 2) Decreased renal elimination of an opioid^{22,23}
- 3) Inhibition of the metabolism of other drugs exerted by an opioid^{11,12}

Pharmacodynamic DDIs

- 1) Potentiation of analgesic efficacy and toxicity through opioid and nonopioid mechanisms^{18,19}
- 2) Inhibition or reversal of the effect of an opioid by antagonism at opioid receptors, or by other mechanisms^{15–17}
- 3) Modification of cholinergic, adrenergic, dopaminergic, and serotonergic activity in the CNS^{10,13,14,25,26,34,35}

Others (including DDIs with unknown mechanism)²¹**Abbreviations:** CNS, central nervous system; DDI, drug–drug interactions.

Discussion

Evidence for DDIs involving opioids used for pain treatment in cancer patients is very limited. This systematic review of publications on clinically significant DDIs involving opioid analgesics used for pain treatment in patients with cancer identified only case reports and case series (Table 2).^{10–41} As no systematic studies were identified, it was not possible to do any statistical analysis.

The three major categories of DDIs identified in the review were increased opioid effects causing sedation and respiratory depression, other CNS toxicities, and decreased opioid effects causing more pain and/or acute withdrawal symptoms. The lack of controlled studies precludes specific conclusions on the risk of DDIs associated with opioids. Still, based upon the reported cases, it can be concluded that physicians treating patients for cancer pain should be aware of and closely monitor patients for DDIs.

The DDIs with increased opioid efficacy, resulting in sedation and respiratory depression, were caused by decreased opioid metabolism,^{19,24,30,32,36–40} impaired renal excretion,²² or an additional therapy that also relieves pain and possesses sedative and respiratory depressant effect (eg, amitriptyline or intrathecal bupivacaine added to morphine)^{18,19} (Tables 2 and 3). Most examples identified in the review refer to opioids metabolized by cytochrome P450 (CYP450), and cytochrome P450 isoenzyme CYP3A4 (CYP3A4) in particular, such as fentanyl, methadone, oxycodone, or buprenorphine, either by concomitant use of CYP3A4 substrates and inhibitors (voriconazole, fluconazole, clarithromycin, cimetidine, and sertraline) or by discontinuation of a CYP3A4 inducer (carbamazepine) (Tables 2 and 4).^{24,30,32,36–40,44} Morphine pharmacokinetics were reported to be affected by a DDI

leading to sedation and respiratory depression only in two case reports.^{19,22} In one of these publications, morphine was coadministered with amitriptyline and ranitidine,¹⁹ two drugs which can affect morphine glucuronidation^{45,46} (Table 2). Morphine may also indirectly be affected by renal failure caused by another drug.²² Additionally, other drugs with sedative effects can cause pharmacodynamic DDIs with an opioid. A typical observation in clinical practice is the combination of an opioid and a benzodiazepine, both contributing to sedation.

CNS symptoms (other than sedation and respiratory depression) associated with opioids included hyperactive or hypoactive delirium with or without hallucinations, serotonin toxicity, myoclonus, hyperalgesia, extrapyramidal symptoms, catatonia, and neuroleptic malignant syndrome (Table 2). CNS symptoms were related both to decreased clearance of an opioid due to decreased metabolism^{20,24,29,31,36} or impaired renal elimination²³ and to a variety of interactions influencing several biological systems in the CNS^{10,14,21,25,26,34,35} (Table 3). Additionally, two reports presented cases of carbamazepine neurotoxicity related to inhibition of its metabolism by propoxyphene and dextropropoxyphene, opioids with an inhibitory effect on cytochrome P450 enzymes (Table 2).^{11,12,47}

DDIs involving opioids can cause acute exacerbations of pain, or withdrawal symptoms (Table 2). In the identified cases, these symptoms resulted from the addition of an opioid with a mixed agonist–antagonist effect (nalbuphine),^{15,16} and increased or decreased metabolism of an opioid due to the coadministration of a CYP3A4 inducer (rifampin)^{27,28} or inhibitor (cyclosporine)³³ or cessation of CYP3A4 inhibition (voriconazole)²⁴ (Table 3). Nalbuphine, which is an agonist at kappa opioid receptors and an antagonist at mu opioid receptors,⁴⁸ reverses the analgesic effect of mu opioid agonists when used concomitantly.^{15,16} Rifampin is a potent inducer of metabolizing enzymes, including CYP3A4, and may enhance clearance and attenuate the clinical effects of opioids.^{27,28,49–53} The withdrawal syndrome reported after discontinuation of a low dose of transdermal fentanyl (25 µg/h) was attributed to increased blood concentration of fentanyl (and increased effect) due to coadministration of cyclosporine, a CYP3A4 inhibitor.³³ Additionally, one case series described impaired pain control in three patients who were given somatostatin as part of their antineoplastic treatment.¹⁷ The exact mechanism for this DDI is not certain. The authors suggest opioid antagonistic effect of somatostatin, demonstrated in animal studies.^{17,54}

Table 4 CYP3A4 enzyme inhibitors and inducers reported to have caused clinically significant drug–drug interactions with opioids metabolized by CYP3A4 (oxycodone, methadone, fentanyl) in papers included in the present review^{24,27–33,37–39,44}

Drugs	Effect on CYP3A4 activity	Resulting effects when coadministered with opioid	Resulting effects after withdrawal of interacting drug
CYP3A4 inhibitors			
Voriconazole	Strong	Decreased rate of opioid metabolism, increased opioid effect, increased risk of opioid toxicity	Increased opioid metabolism, decreased clinical effect of opioid
Itraconazole	Strong		
Fluconazole	Moderate		
Clarithromycin	Strong		
Diltiazem	Moderate		
Cyclosporine	Weak		
Cimetidine	Weak		
CYP3A4 inducers			
Rifampin	Strong	Increased metabolism of opioid, requirement for higher opioid doses, deterioration of pain control	Decreased rate of opioid metabolism, increased risk of opioid overdose
Carbamazepine	Strong		

Finally, some other important DDIs were identified (Table 2). Prolonged QT time and ventricular arrhythmias (torsades de pointes) were seen in a patient receiving a high dose of methadone, and at the same time, three drugs that were CYP3A4 substrates. The authors suggest that these coadministered drugs may have interfered with methadone metabolism and caused elevation of its level in the blood.⁴¹

Multiple complex mechanisms, often not fully understood, underlie DDIs involving opioid analgesics (Table 3). In this review, we refer to the mechanisms of DDIs as they were understood and presented by the authors. In some cases, alternative causes for the observed complications may be found.

The most frequently reported mechanism of DDIs was associated with cytochrome P450 enzyme activity. In our review, the implicated opioids were fentanyl, methadone, oxycodone, and buprenorphine.^{24,27–33,36–41} Of these, orally administered oxycodone and methadone have been shown to be more susceptible to DDIs related to CYP3A4 or other CYP enzymes in studies in volunteers,^{49,50,55–58} while fentanyl pharmacokinetics were less affected in volunteer studies.^{51,59–62} Still, DDIs of fentanyl associated with CYP3A4 activity were reported in seven publications identified by this review.^{27–33}

Buprenorphine metabolism can be increased by strong CYP3A4 inducers as demonstrated in a study with rifampin,⁵² while the effect of CYP3A4 inhibitors is limited due to complex metabolism (conversion to norbuprenorphine by CYP3A4 and CYP2C8, and glucuronidation) as well as renal and extrarenal elimination of the parent drug and metabolites.^{50,63} As noted by Davis, the case report involving buprenorphine³⁶ should probably be best interpreted as a result of rapid dose increase before time to maximum concentration or steady state was reached, and not a DDI.⁴³

In our review, most drugs that precipitated serious CYP3A4-mediated DDIs (voriconazole, itraconazole, fluconazole, clarithromycin, diltiazem) are also drugs relevant for patients with advanced cancer, supporting the clinical importance of this finding. The vast majority of DDIs occur after a precipitating drug is introduced. The opposite effect of a decreased or increased opioid action may be caused if the use of a CYP3A4 inhibitor or inducer is stopped,^{24,37} thereby decreasing or increasing the serum concentration of the drug (Table 4). Defining a consequence of stopping a drug as an interaction, is perhaps counterintuitive, but it still represents symptoms related to a pharmacokinetic DDI. Interactions are less frequent if an opioid is introduced in a patient already using another drug. This may be related to titration of the opioid dose to obtain the desired clinical effect. Thus, a DDI may change the dose, but not the clinical outcome.

In cancer patients, the coexistence of other clinical factors can increase the risk of DDIs (Table 2). Impaired renal function is a common predisposing factor of DDIs^{31,32} and has added importance in cancer pain management because the incidence of renal impairment in patients with advanced cancer is high.^{64,65} Also, the concomitant use of other drugs and the frequent need to change coadministered drugs and their doses add to the complexity of DDIs of opioids in these patients.^{5,9}

The presence of DDIs seems to be underreported. This lack of formal evidence may have several explanations. First, the DDI may not be detected, or the symptoms are believed to be caused by the cancer disease and, therefore, not recognized as drug related. Second, DDIs are mostly observed by clinicians, who often do not have the time, the experience, or the interest to publish clinical observations. Third, several DDIs, even if not reported in the literature, may be considered as frequent and part of common knowledge, and therefore, not

reported. Finally, many journals only occasionally publish case reports and, perhaps, case reports are more often published in national journals and therefore not identified by a search strategy excluding non-English papers.

Conclusion

For obvious ethical reasons, there are no randomized controlled trials or other well-designed controlled studies exploring DDIs. Recommendations must therefore be based upon cases reporting serious adverse drug reactions and basic knowledge about drug mechanisms. The cases identified in this systematic review can give some suggestions for clinical practice:

- The combined use of an opioid and another drug with CNS depressant effect (eg, amitriptyline) increases the risk of acute opioid toxicity and respiratory depression. Such drugs should be carefully titrated according to effect.
- Opioids with antagonistic effects at the mu opioid receptor (eg, nalbuphine) should not be coadministered with another opioid analgesic.
- The concomitant use of an opioid and a drug, which affects the activity of cholinergic, dopaminergic, and/or serotonergic systems in the CNS (eg, selective serotonin inhibitors), can cause CNS-related complications (eg, delirium and serotonin syndrome) and should, therefore, be monitored carefully.
- Introduction of a CYP3A4 inhibitor in a patient treated with fentanyl, oxycodone, or methadone may result in opioid overdose and increased opioid toxicity (Table 4). Caution has to be undertaken when such drugs are implemented. The use of a major CYP450 inducer may impair pain treatment (Table 4). Opposite effects should be expected when these drugs are stopped (Table 4).
- Finally, the physician should recognize the risk for DDIs of opioids, monitor the patients carefully for interactions, and if possible avoid polypharmacy.

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