Chapter

Analgesic Poisoning

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Abstract

According to the 2018 Annual Report of the American Association of Poison Control Centers (AAPCC), published in 2019, the most common cause of poisoning was medicines in all human exposures. According to the data in this report, the most common group of drugs that cause poisoning in humans are analgesics. The first three drugs that cause poisoning among analgesics are fentanyl, acetaminophen, and oxycodone, respectively. Fentanyl and oxycodone are analgesic drugs with an opioid nature. Opioid analgesics are the drugs of choice for acute and chronic pain management, but after repeated exposure, they cause addiction as a result of stimulation in the brain reward center, are used in higher doses to achieve the same effect, and lead to withdrawal syndrome when medication is not taken. Acetaminophen, which takes the second place in analgesic-related poisoning, is a non-opioid analgesic and antipyretic drug. Acetaminophen is often found in hundreds of over-the-counter (OTC) medications. In addition to being an OTC drug, acetaminophen often causes poisoning as it is cheap and easily accessible. This chapter reviews pharmacological properties of fentanyl, acetaminophen, and oxycodone, in addition to poisoning signs and treatments.

Keywords: fentanyl, acetaminophen, paracetamol, oxycodone, intoxication

1. Introduction

Poisoning is a medical emergency representing a major health problem worldwide, and the rate of poisoning of both prescription and over-the-counter (OTC) drugs is increasing day by day [1]. According to the American Association of Poison Control Centers (AAPCC) 2018 Annual Report, the most common cause of drug poisonings was analgesics in all human exposures [2]. Analgesics are used to manage mild, moderate, and severe, as well as acute and chronic, pain [3]. Generally, opioid and non-opioid drugs are used for analgesia [3]. According to the AAPCC 2018 Annual Report, most frequent causes of analgesic poisoning are fentanyl, acetaminophen, and oxycodone, respectively [2]. Fentanyl and oxycodone are opioid analgesics, whereas acetaminophen is a non-opioid analgesic [3].

Opioids are potent analgesics, but their use is limited as they cause addiction, withdrawal, and tolerance [4]. Opioids exert their effects by stimulating classical opioid receptors [μ (mu), δ (delta), and κ (kappa)] that are widely distributed in the body [5, 6]. These receptors show seven transmembrane domain structures specific to G-protein-coupled receptors, are induced by morphine and antagonized by naloxone (NLX), and had similar analgesic effect [4]. According to the studies, μ receptor was also related with addiction [7]. Opioid addiction develops in both psychic and physical dependence [4]. After physical dependence development, opioid consumption is maintained to prevent withdrawal symptoms [4]. Treatment

of opioid addiction is long and difficult. For this purpose, opioid agonists, such as methadone and buprenorphine, an opioid antagonist naltrexone, or abstinence-based treatment may be preferred [8]. This disease, referred to as "opioid abuse and opioid dependence" in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSMIV-TR), has been changed to "opioid use disorder" in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [9].

Classical opioid receptors are distributed in the peripheral tissue as well as central nervous system (CNS) [4]. Stimulation of these receptors in the central nervous system results in analgesia, drowsiness, euphoria, a sense of detachment, respiratory depression, nausea and vomiting, depressed cough reflex, and hypothermia [4]. When these receptors are stimulated in peripheral tissues, miosis, orthostatic hypotension, constipation, urinary retention, etc. emerge [4]. After stimulation of these Gi/0-coupled opioid receptors, the adenylate cyclase enzyme is suppressed, and the level of cyclic AMP decreases [4]. In addition, the voltage-gated calcium channels in the axon ends or neuron soma are closed, and intracellular calcium levels are reduced, and potassium channels are opened, leading to an increase in potassium conductance [4]. As a result, inhibition and hyperpolarization of neurons occur when opioid receptors are stimulated [10, 11]. Analgesic or antinociceptive effects, which are indicated for use of opioids, develop at the level of the brain and spinal cord [12]. At the brain level, attenuation of impulse spread is weakened and the perception of pain is inhibited, and at the spinal cord level, the transmission of pain impulses is suppressed [12].

Non-opioid or non-steroidal anti-inflammatory drugs (NSAIDs) are used to manage mild and moderate pain, as well as to reduce fever [13]. Although NSAIDs exact mechanism of action has not been fully established, according to the previous studies, it inhibits the cyclooxygenase pathways, which are involved in prostaglandin synthesis [14]. Prostaglandins are responsible for eliciting pain sensations [14]. NSAIDs do not cause addiction and withdrawal like opioid analgesics, and tolerance to analgesic effect does not develop [13].

Poisoning may lead to more dangerous consequences when taking more than one medication [2]. It is due to pharmacokinetic (PK) and pharmacodynamic (PD) drug-drug interactions (DDIs). According to Lexicomp, there are five DDI types (**Table 1**), which are clinically important (X, D, and C) and insignificant (B and A) [15].

DDI types	Approach	Explanation
X	Avoid combination	The risks associated with simultaneous use of this drug outweigh the benefits. Simultaneous use of this drug is contraindicated
D	Consider therapy modification	The rate of benefit and risk due to simultaneous use of this drug needs to be evaluated, and aggressive monitoring of the patient, empirical dosage changes, or selection of alternative agents should be considered
C	Monitor therapy	The benefits associated with simultaneous use of this drug outweigh the risks, and dosage adjustments of one or both drugs may be considered
B	No action needed	No intervention required
A	No known interaction	No intervention required

Table 1.
DDI types and treatment approach [15].

2. Analgesics that often lead to poisoning

2.1 Fentanyl

International Union of Pure and Applied Chemistry (IUPAC) name: N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide.

Fentanyl is a synthetic and lipophilic phenylpiperidine opioid agonist with molecular formula $C_{22}H_{28}N_{20}$ and a molecular weight of 336.5 g/mol [16]. Fentanyl, 100 times more potent than morphine, was developed in the 1950s and approved by the FDA in 1968 [17]. Fentanyl is used for pain management, induction and maintenance of general anesthesia, recovery from general or regional anesthesia, and analgesia and sedation in intensive care unit patients [18–20]. It is applied by injection (i.v., i.m., epidural, intrathecal), transdermal (device and patch), transmucosal (buccal film and tablet, sublingual spray and tablet, lozenge), and intranasal means [16]. Pharmacodynamics and pharmacokinetics are summarized in **Table 2**.

Adverse effects (**Table 3**) occur when serum fentanyl concentration rises above 2 ng/mL [16]. CNS depression occurs above 3 ng/mL, whereas profound respiratory depression usually occurs at concentrations of 10 to 20 ng/mL [16].

Since it is an opioid drug, fentanyl has the potential for abuse [4]. As mentioned above, with repeated use of fentanyl, tolerance develops, which allows higher doses to achieve the same effect [4]. Therefore, fentanyl can be administered at toxic doses when abused. In addition, toxicity may develop with fentanyl used for therapeutic purposes [2]. These usually occur after accidental ingestion, following use in opioid non-tolerant patients and improper dosing [2]. Known and expected adverse reactions occur more severely, whether administered for abuse or therapeutic purposes [16]. The most important of these is respiratory depression, which can have fatal consequences. Concomitant use of fentanyl with drugs inhibiting CYP3A4 (e.g., erythromycin, ketoconazole, voriconazole, ritonavir) may cause potentially fatal respiratory depression (**Table 4**). Fentanyl may be associated with the development of serotonin syndrome. This risk increases when used concomitantly with

PDs and PKs	**Routes of administration**				
	Intranasal	**i.m.**	**i.v.**	**Transdermal patch**	**Transmucosal**
Onset of action	5–10 min	7–8 min	Immediately	6 h	5–15 min
Duration	—	1–2 h	0.5–1 h	72–96 h	—
Absorption	—	—	—	12–24 h	Rapidly
Distribution	—	—	4 L/kg	—	25.4 L/kg
Protein binding	Alpha-1-acid glycoprotein (mainly), albumin, and erythrocytes				
Metabolism	In the liver (primarily via CYP3A4) and intestinal mucosa • n-Dealkylation to *norfentanyl* (active metabolite) • Amide hydrolyzation to *despropionylfentanyl* • Alkyl hydroxylation to *hydroxyfentanyl*				
Bioavailability	64%				50–76%
Half-life elimination	15–25 h		Adults: 2–4 h Children: 2.4–36 h	20–27 h	3–14 h
Excretion	• Urine (primarily) • Feces				

Table 2.
PDs and PKs of fentanyl at therapeutic doses [16, 21–23].

Systems	Symptoms
CNS	Confusion, dizziness, drowsiness, fatigue, headache, sedation, abnormal dreams, abnormal gait, abnormality in thinking, agitation, altered sense of smell, amnesia, anxiety, ataxia, chills, depression, disorientation, euphoria, hallucination, hypertonia, hypoesthesia, hypothermia, insomnia, irritability, lack of concentration, lethargy, malaise, mental status changes, neuropathy, paranoia, paresthesia, restlessness, speech disturbance, stupor, vertigo, withdrawal syndrome
Respiratory	Dyspnea, atelectasis, cough, epistaxis, hemoptysis, flu-like symptoms, wheezing, hyperventilation/hypoventilation, pharyngolaryngeal pain, rhinitis, sinusitis, nasopharyngitis, pharyngitis, laryngitis, bronchitis, asthma, pneumonia, nasal discomfort, postnasal drip, rhinorrhea
Cardiovascular	Arrhythmia, pulmonary embolism (intranasal), chest pain, palpitations, deep vein thrombosis, hypertension/hypotension, myocardial infarction, edema
Gastrointestinal (GI)	Constipation, nausea, vomiting, abdominal distention, abdominal pain, anorexia, decreased appetite, diarrhea, dysgeusia, dyspepsia, flatulence, gingivitis, glossitis, stomatitis, tongue disease, xerostomia, gastroesophageal reflux, gastritis, gastroenteritis, hemorrhage, ulcer, hematemesis, intestinal obstruction, rectal pain
Hepatic	Ascites, increased serum alkaline phosphatase, increased serum AST, jaundice
Genitourinary (GU)	Renal failure, urinary retention, dysuria, erectile dysfunction, mastalgia, urinary incontinence, urinary tract infection, urinary urgency, vaginal hemorrhage, vaginitis
Ophthalmic	Blepharoptosis, blurred vision, diplopia, strabismus, swelling and drying of eye, visual disturbance
Hematologic and oncologic	Anemia, leukopenia, neutropenia, thrombocytopenia, lymphadenopathy
Dermatologic	Alopecia, cellulitis, decubitus ulcer, diaphoresis, erythema, hyperhidrosis, night sweats, pallor, pruritus, skin rash
Endocrine and metabolic	Dehydration, hot flash, hypercalcemia/hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypoalbuminemia, hyperglycemia, weight loss
Neuromuscular and skeletal	Asthenia, arthralgia, back pain, lower limb cramp, limb pain, myalgia, tremor
Miscellaneous	Hypersensitivity reaction, fever, abscess

Table 3.
Common adverse reactions of fentanyl [16, 21–26].

drugs at risk of serotonin syndrome (**Table 4**). Population that are particularly at risk and need attention are children; geriatric, cachectic, or debilitated patients; and patients with renal and hepatic impairment, underlying pulmonary conditions, known or suspected paralytic ileus and gastrointestinal obstruction, mucositis (sublingual spray), and cardiac bradyarrhythmias [16]. Clinically important DDIs are summarized in **Table 4**.

2.2 Acetaminophen

IUPAC name: N-(4-hydroxyphenyl)acetamide

Acetaminophen is an NSAID with molecular formula $C_8H_9NO_2$ and a molecular weight of 151.16 g/mol and approved by the FDA in 1951 [27]. Acetaminophen is used by oral, injection (i.v.), and rectal means for mild to moderate pain

Possible effects	Clinically important DDI types		
	X	**D**	**C**
Increase in the CNS depressant effects	Azelastine, bromperidol, orphenadrine, oxomemazine, paraldehyde, thalidomide, mifepristone	Blonanserin, chlormethiazole, CNS depressants, droperidol, flunitrazepam, lemborexant, meperidine, methotrimeprazine, opioid agonists, oxycodone, perampanel, phenobarbital, primidone, sodium oxybate, suvorexant, zolpidem, tramadol, tricyclic antidepressants (TCA), CYP3A4 inhibitors (strong, moderate)	Ethanol, alizapride, dimethindene, brimonidine, bromopride, tetrahydrocannabinol, cannabidiol, *Cannabis*, chlorphenesin carbamate, dronabinol, lisuride, lofexidine, magnesium sulfate, metoclopramide, minocycline (systemic), nabilone, piribedil, pramipexole, ropinirole, rotigotine, rufinamide
Enhancement in the serotonergic effects and serotonin syndrome	Dapoxetine, monoamine oxidase inhibitors (MAOI)	Linezolid, meperidine, methylene blue, nefazodone, ozanimod, tramadol, TCA	Almotriptan, alosetron, amphetamines, antiemetics (5HT3 antagonists), dexmethylphenidate-methylphenidate, dextromethorphan, eletriptan, ergot derivatives, buspirone, lorcaserin, ondansetron, oxitriptan, ramosetron, selective serotonin reuptake inhibitors (SSRI), serotonin 5-HT1D receptor agonists (triptans), serotonin/norepinephrine reuptake inhibitors (SNRI), St John's wort, Syrian rue
Constipation	Eluxadoline	—	Anticholinergic agents, ramosetron
Urinary retention	—	—	Anticholinergic agents
Enhancement in the bradycardia effects	Fexinidazole	Ceritinib, siponimod	Bradycardia-causing agents, ivabradine, lacosamide, midodrine, ruxolitinib, succinylcholine, terlipressin, tofacitinib
Enhancement in the psychomotor impairment	—	—	SSRI

Table 4.
Fentanyl and clinically important DDIs [15].

management and reduction of fever [27]. Acetaminophen is often found in hundreds of OTC and prescription medicines [28]. PDs and PKs are summarized in **Table 5**.

95% of acetaminophen undergoes biotransformation, while 5% is excreted unchanged into the urine [29]. Approximately 45–55% of acetaminophen transforms into glucuronide conjugates via UDP-glucuronosyltransferase, 30–35% into sulfate conjugates via sulfotransferase, and only 5% into toxic metabolite NAPQI

PDs and PKs	Routes of administration	
	Oral	**i.v.**
Onset of action	Above 1 h	5–10 min
Duration	4–6 h	4–6 h
Absorption	Small intestine (primarily) and stomach	
Distribution	Adults: 4–6 L/kg Children: 5–30 L/kg	
Protein binding	10–25%	
Metabolism	In the liver • Metabolism to glucuronide and sulfate conjugates (primarily) By CYP2E1 to toxic intermediate, N-acetyl-p-benzoquinone imine (NAPQI, **Figure 1**)	
Bioavailability	88%	
Half-life elimination	Adults: 2–3 h Children: 4–10 h	
Excretion	Urine (mainly)	

Table 5.
PDs and PKs of acetaminophen at therapeutic doses [29–31].

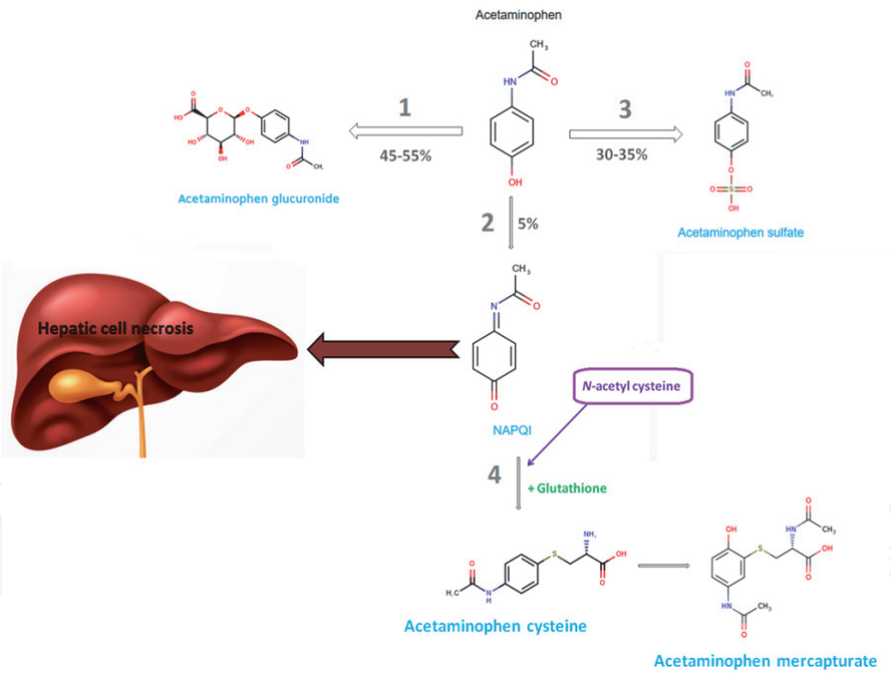

Figure 1.
Metabolism of acetaminophen. NAPQI, N-acetyl-p-benzoquinone imine; (1) UDP-glucuronosyltransferase (1-9, 1-6, 1-1, and 2B15 isoforms); (2) CYP2E1; (3) sulfotransferase (1A1 and 1A3/1A4 isoforms) and bile salt sulfotransferase; (4) glutathione S-transferase (P and theta-1 isoforms) [33–35].

through the CYP2E1 (**Figure 1**) [32–34]. NAPQI, produced in small amounts in therapeutic dose intakes, and hepatic glutathione are immediately transformed into nontoxic cysteine and mercapturate metabolites via glutathione S-transferase and excreted into the urine [34]. With intakes above the maximum daily dose (4 g in adults and 75 mg/kg in children), the increased formation of NAPQI depletes hepatic glutathione, covalently binds to critical cellular proteins and other vital molecules, and thereby causes acute liver toxicity (hepatic damage, liver failure) or

even death [29, 35, 36]. Additional mechanisms such as mitochondrial injury, oxygen, and nitrogen stress deepen hepatic cell damage [37].

Mild to moderate elevations in serum aminotransferase (aspartate aminotransferase, alanine aminotransferase) levels are the first sign of liver damage; sometimes it can even occur in chronic treatment at the maximum daily dose [35, 36]. These elevations are generally asymptomatic and resolve rapidly with stopping therapy or reducing the dosage [35] and most commonly arise after taking more than 7.5 g as a single overdose [38]. If hepatotoxicity is not too severe, serum aminotransferase levels fall promptly, and recovery is rapid [39]. Instances of unintentional overdose in children are often due to errors in calculating the correct dosage or use of adult-sized tablets instead of child or infant formulations [39]. Concomitant use of acetaminophen (single) and acetaminophen-containing (combined) products may also cause toxicity [39]. Acetaminophen overdose may be manifested by renal tubular necrosis, hypoglycemic coma, and thrombocytopenia [39]. Acetaminophen has been associated with a risk of rare but serious skin reactions. These are Stevens-Johnson syndrome, toxic epidermal necrolysis, and acute generalized exanthematous pustulosis, and they can be fatal [39, 40]. Population that are particularly at risk and need attention are children, since they have less glucuronidation capacity of the drug than adults, and patients with alcoholism, hepatic impairment or active hepatic disease, chronic malnutrition, severe hypovolemia, and severe renal impairment [29, 38]. Adverse reactions and clinically important DDIs of acetaminophen are summarized in **Tables 6** and 7, respectively.

2.3 Oxycodone

IUPAC name: (4R,4aS,7aR,12bS)-4a-hydroxy-9-methoxy-3-methyl-2,4,5,6,7a,13-hexahydro-1H-4,12-methanobenzofuro[3,2-e]isoquinolin-7-one

Systems	Symptoms
CNS	Trismus, fatigue, headache, agitation, anxiety, insomnia
Respiratory	Atelectasis, hypoxia, pleural effusion, pulmonary edema, stridor, wheezing
Cardiovascular	Tachycardia, hypertension/hypotension, edema
GI	Constipation, nausea, vomiting, abdominal pain, diarrhea
Hepatic	Increased serum transaminases, hyperbilirubinemia
GU	Nephrotoxicity, hyperammonemia, oliguria
Ophthalmic	Periorbital edema
Hematologic and oncologic	Anemia
Dermatologic	Pruritus, skin rash
Endocrine and metabolic	Hypocalcemia, hyponatremia, hypokalemia, hypomagnesemia, hypophosphatemia, hyperchloremia, low bicarbonate levels, hypoalbuminemia, hyperuricemia, hyperglycemia, hypervolemia
Neuromuscular and skeletal	Muscle spasm, limb pain
Miscellaneous	Hypersensitivity reaction, fever

Table 6.
Common adverse reactions of acetaminophen [29, 38, 39].

Possible effects	Clinically important DDI types		
	X	D	C
Hepatotoxicity	—	Dasatinib, sorafenib, probenecid	Ethanol, barbiturates, carbamazepine, imatinib, mipomersen, fosphenytoin-phenytoin, isoniazid, metyrapone
Methemoglobinemia	—	—	Dapsone, local anesthetics, nitric oxide, prilocaine, sodium nitrite
High anion gap metabolic acidosis	—	—	Flucloxacillin
Enhancement in the anticoagulant effects	—	—	Vitamin K antagonists

Table 7.
Acetaminophen and clinically important DDIs [15].

Oxycodone is a semisynthetic opioid agonist, produced from thebaine and codeine found in the raw *Papaver somniferum L.* plant and approved by the FDA in 1968, with molecular formula $C_{18}H_{21}NO_4$ and a molecular weight of 315.4 g/mol [41–43]. It is used alone or in combination with acetaminophen in the management of moderate to severe pain [3]. It binds to classical opioid receptors such as fentanyl and mediates similar mechanisms of action [6]. Oxycodone also inhibits the release of vasopressin, somatostatin, insulin, and glucagon and nociceptive neurotransmitters, such as substance P, GABA, dopamine, acetylcholine, and noradrenaline [44]. The analgesic effects of oxycodone are mediated by both itself and its active metabolites, noroxycodone, oxymorphone, and noroxymorphone [21]. It can be applied both orally and rectally. PDs and PKs are summarized in **Table 8**.

Toxic effects occur when the serum oxycodone concentration is approximately 0.69 mg/L in single oxycodone administration and 0.72 mg/L in the oxycodone-combined drug administration [50]. When the serum oxycodone concentration is

PDs and PKs	Oral administration	
	Immediate release	Extended release
Onset of action	10–15 min	—
Duration	3–6 h	≤12 h
Distribution	Adults: 2.6 L/kg Children: 2.1 L/kg	
Protein binding	38–45% • Albumin (primarily) and alpha-1-acid glycoprotein	
Metabolism	In the liver • By CYP3A4 and CYP3A5 to noroxycodone and then by CYP2D6 to noroxymorphone. Noroxycodone (active) can also be reduced to alpha or beta noroxycodol • By CYP2D6 to oxymorphone and then by CYP3A4 to noroxymorphone (active). Oxymorphone (active) can also be reduced to alpha or beta oxymorphol 6-keto-reduced to alpha and beta oxycodol	
Bioavailability	60–87%	
Half-life elimination	3.2–4 h	4.5–5.6 h
Excretion	Urine (mainly)	

Table 8.
PDs and PKs of oxycodone at therapeutic doses [21, 45–49].

about 0.93 mg/L in a single-drug administration and 1.55 mg/L in the combined drug administration, it is fatal [51]. Common adverse reactions are summarized in **Table 9**.

Since oxycodone is an opioid drug, like fentanyl, it has the potential for abuse and develops tolerance. Repeated use of oxycodone causes the development of tolerance, which can lead to overdose and death [45–47]. Serious, life-threatening, or fatal respiratory depression may occur with use of oxycodone orally [45]. Accidental ingestion of even one dose of oxycodone preparations by children can result in death [47]. Long-term use during pregnancy can result in neonatal opioid withdrawal syndrome [45]. Concomitant use of oxycodone with CYP3A4 inducers (e.g., carbamazepine, phenytoin, and rifampin) may result in increasing clearance and decreasing plasma concentrations of oxycodone, with possible lack in therapeutic effectiveness [45]. Concomitant use of oxycodone with CYP3A4 inhibitors may result in reduced clearance and increased plasma concentrations of oxycodone, possibly resulting in increased or prolonged opiate effects, including an increased risk of fatal respiratory depression [52]. These effects could be more pronounced with concomitant use of oxycodone and inhibitors of both CYP2D6 and CYP3A4 [52]. Population that are particularly at risk and need attention are children; geriatric, cachectic, or debilitated patients; and patients with renal and hepatic impairment, underlying pulmonary conditions, and significant genetic variability in CYP2D6 activity [45, 53]. There is no evidence to prove hepatotoxicity when used alone, whereas oxycodone-acetaminophen and other opioid-acetaminophen combinations can lead to acute liver damage caused by unintentional overdose with acetaminophen [54]. Clinically important DDIs are summarized in **Table 10**.

Systems	Symptoms
CNS	Dizziness, drowsiness, headache, fatigue, abnormal dreams, twitching, abnormality in thinking, agitation, anxiety, chills, depression, hypertonia, hypoesthesia, insomnia, irritability, confusion, lethargy, nervousness, paresthesia, neuralgia, personality disorder, withdrawal syndrome
Respiratory	Dyspnea, cough, epistaxis, flu-like symptoms, oropharyngeal pain, rhinitis, sinusitis, pharyngitis, laryngismus, pulmonary disease
Cardiovascular	Flushing, tachycardia, palpitations, cardiac failure, deep vein thrombosis, hypertension/hypotension, edema
GI	Constipation, nausea, vomiting, hiccups, upper abdominal pain, abdominal pain, anorexia, diarrhea, dyspepsia, dysphagia, gingivitis, glossitis, xerostomia, gastroesophageal reflux, gastritis, gastroenteritis
Hepatic	Increased serum alanine aminotransferase
GU	Urinary retention, dysuria, urinary tract infection
Ophthalmic	Blurred vision, amblyopia
Hematologic and oncologic	Anemia, leukopenia, neutropenia, thrombocytopenia, hemorrhage
Dermatologic	Pruritus, diaphoresis, hyperhidrosis, skin rash, skin photosensitivity, excoriation, urticaria
Endocrine and metabolic	Hypochloremia, hyponatremia, hyperglycemia, weight loss, gout
Neuromuscular and skeletal	Asthenia, arthralgia, ostealgia, back pain, neck pain, limb pain, myalgia, tremor, arthritis, laryngospasm, pathological fracture
Miscellaneous	Hypersensitivity reaction, fever, infection, sepsis, seroma, accidental injury

Table 9.
Common adverse reactions of oxycodone [45–47].

Possible effects	Clinically important DDI types		
	X	D	C
Increase in the CNS depressant effects	Azelastine, bromperidol, orphenadrine, oxomemazine, paraldehyde, thalidomide	Blonanserin, chlormethiazole, CNS depressants, droperidol, flunitrazepam, lemborexant, methotrimeprazine, perampanel, phenobarbital, primidone, sodium oxybate, suvorexant, voriconazole, zolpidem, CYP3A4 inhibitors (strong)	Alizapride, brimonidine, bromopride, tetrahydrocannabinol, cannabidiol, *Cannabis*, dimethindene, dronabinol, lisuride, lofexidine, magnesium sulfate, metoclopramide, metyrosine, minocycline (systemic), nabilone, piribedil, pramipexole, ropinirole, rotigotine, rufinamide, CYP3A4 inhibitors (moderate)
Enhancement in the serotonergic effects and serotonin syndrome	MAOI	—	Serotonergic agents
Constipation	Eluxadoline	—	Anticholinergic agents, ramosetron
Urinary retention	—	—	Anticholinergic agents
Enhancement in the bradycardia effects	—	—	Succinylcholine
Enhancement in the psychomotor impairment	—	—	SSRI

Table 10.
Oxycodone and clinically important DDIs [15].

2.4 Fentanyl, acetaminophen, and oxycodone toxicity, clinical manifestations, and management

The toxicity, teratogenicity (FDA pregnancy category), and carcinogenicity (by the International Agency for Research on Cancer), clinical manifestations, and management of fentanyl, acetaminophen, and oxycodone poisoning are summarized in **Tables 11–13**, respectively.

Drugs	Fentanyl	Acetaminophen	Oxycodone
LD50 (mouse, i.p.) (mg/kg)	76	367	320
TDLo (human, oral) (mg/kg)	0.1	490	0.14
FDA pregnancy category	C	C	B
Classification by the IARC	NA	3	NA

LD50, median lethal dose; TDLo, lowest toxic dose; NA, not assigned [55–63]

Table 11.
Toxicity, teratogenicity, and carcinogenicity of fentanyl, acetaminophen, and oxycodone.

Drugs	Clinical manifestations
Fentanyl	Respiratory depression, somnolence, sleepiness, stupor, coma, amnesia, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death
Acetaminophen	Stage I (0.5 to 24 h): nausea, vomiting, diaphoresis, pallor, lethargy, malaise or asymptomatic
	Stage II (24 to 72 h): • Recovery in stage I symptoms • Increase in hepatic enzymes (aspartate aminotransferase, alanine aminotransferase) and total bilirubin, PT elongation, oliguria (occasionally)
	Stage III (72 to 96 h): • Jaundice, hepatic encephalopathy, a marked elevations of hepatic enzymes (exceed 10,000 IU/L) and total bilirubin (above 4.0 mg/dL), hyperammonemia, prolongation of the PT/INR, hypoglycemia, lactic acidosis, death (multiorgan system failure)
	Stage IV (4 days to 2 weeks): • Regression in symptoms and recovery phase
Oxycodone	Respiratory depression, sleepiness, stupor, coma, skeletal muscle flaccidity, cold sweat, constricted pupils, bradycardia, hypotension, QT interval prolongation, partial or complete airway obstruction, atypical snoring, and death

Table 12.
Clinical manifestations of fentanyl, acetaminophen, and oxycodone poisoning [16, 61, 64–71].

Management steps	Fentanyl	Oxycodone	Acetaminophen
ABC	Secure airway, breathing, and circulation as necessary		
Decontamination • GI • Patch	Activated charcoal: within 4 h of ingestion, unless contraindicated • Adult: 50 g orally Children: 1 g/kg orally or by nasogastric tube, max. 50 g • Must be removed		
Basic measures and treatment	1. Ensure adequate ventilation 2. Apply antidotal therapy with NLX. With a total of 5 to 10 mg, repeat administration until ventilation is adequate 3. Require supplemental oxygen, endotracheal intubation, and positive end-expiratory pressure, if response is inadequate to NLX or if pulmonary edema is present		1. Poisoning severity following an acute ingestion is quantified by plotting a timed serum acetaminophen concentration on the modified Rumack-Matthew nomogram 2. Antidotal therapy with N-acetyl cysteine (NAC)
Antidotal therapy dosing	Adults: • O_2 saturation is <90%: 0.05 mg i.v. or i.m. • For apneic patients: 0.2 to 1 mg i.v. or i.m. • Patients in cardiorespiratory arrest: min. 2 mg i.v. Children: • <20 kg: 0.1 mg/kg i.v. or intraosseous (i.o.), max. 2 mg per dose • ≥20 kg: 2 mg i.v. or i.o. Adolescents suspected of opioid addiction: • 0.04 to 0.4 mg per dose repeated every 3–5 min and titrated to patient response		**Oral dosing:** 140 mg/kg loading dose, followed by 17 doses of 70 mg/kg every 4 h **21 h i.v. protocol**: 150 mg/kg loading dose over 60 min, followed by 50 mg/kg infused over 4 h, with the final 100 mg/kg infused over the remaining 16 h • INR <2: 21 h i.v. protocol • INR >2: 21 h i.v. protocol, followed by a continuous i.v. NAC infusion at 6.25 mg/kg/h until INR is <2

Management steps	Fentanyl	Oxycodone	Acetaminophen
Supportive care	For possible coma, seizures, hypotension, and non-cardiogenic pulmonary edema		For vomiting

Table 13.
Management of acute fentanyl, acetaminophen, and oxycodone toxicity [72–82].

Antidotal therapy with NAC in acetaminophen poisoning should be applied orally (nonpregnant patients with a functional GI tract and no evidence of hepatotoxicity) or i.v. (patients with vomiting, contraindications to oral administration, and hepatic failure) if:

- Serum acetaminophen concentration is above the "treatment" line of the treatment nomogram
- Serum acetaminophen concentration is unavailable or will not return within 8 h of time of ingestion and acetaminophen ingestion is suspected
- Time of ingestion is unknown and serum acetaminophen level is >10 mcg/mL (66 μmol/L)
- There is evidence of any hepatotoxicity with a history of acetaminophen ingestion
- Patient has risk factors for hepatotoxicity, and the serum acetaminophen concentration is >10 mcg/mL (66 μmol/L) [80–82]

3. Conclusions

Drugs used in the treatment or prevention of diseases can lead to unintentional or intentional toxicity. Toxicity may be due to high-dose single-drug or multiple-drug intake. According to the AAPCC 2018 Annual Report, opioid and non-opioid analgesics often cause single-drug poisoning. The top three of analgesic poisoning are fentanyl, acetaminophen, and oxycodone, respectively.

Opioid analgesics, such as fentanyl and oxycodone, which are preferred in severe pain management, show central and peripheral effects by binding to classical opioid receptors that are widely distributed in the body. Repeated exposure causes an addiction; higher-dose usage to produce the same effect, i.e. tolerance; and withdrawal when stopping intake. Therefore, the dose and severity of toxicity differ between those who take opioid analgesics for the first time and those who are addicted. In poisoning with opioid analgesics, death due to respiratory depression is frequently observed. For this reason, in case of poisoning with opioid analgesics, first of all, adequate ventilation should be provided, subsequent antidote treatment with naloxone should be applied, the patient should be closely monitored for vital functions, and appropriate treatment should be performed when necessary. Since the effect of naloxone is short, application should be repeated when necessary. Supplementary oxygen, endotracheal intubation, and positive end-expiratory pressure should be considered if adequate response cannot be obtained despite a total of 5 to 10 mg of naloxone. Although high doses are not preferred, toxicity is more severe in patients using X and D interactive drugs together.

Acetaminophen, a non-opioid analgesic, found in hundreds of prescription and OTC medicines, with analgesia and antipyretic effects, often causes hepatotoxicity (hepatic damage, liver failure) or even death. Toxicity develops due to the overproduction of toxic NAPQI, which occurs during acetaminophen metabolism in the liver, which quickly consumes the glutathione necessary to convert it to the nontoxic metabolite and covalently binds to cell proteins and other vital molecules. Toxicity is more severe in patients with less glucuronidation capacity and/or concomitant use of X- and D-type interacting drugs. The use of activated charcoal within the first 4 h of acetaminophen poisoning and antidote treatment with NAC successfully heals liver damage.

After stabilizing the patient, it is necessary to investigate whether poisoning is performed unintentionally or intentionally. If there is substance abuse or suicidal tendency, the patient should be consulted to a psychiatrist, and psychosocial and/or medication for addiction treatment should be started. In unintentional poisonings, adults should be educated/warned by their health protectors about the drugs (effects, duration of action, daily maximum dose, conditions to be considered, side effects, and storage conditions) they use for themselves and/or their children, and additional arrangements should be made to increase the health literacy of the society. If poisoning has developed due to the X- and D-type interactions of the drugs used in therapeutic doses, it should be considered to be subject to periodical/continuous training of health protectors.

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