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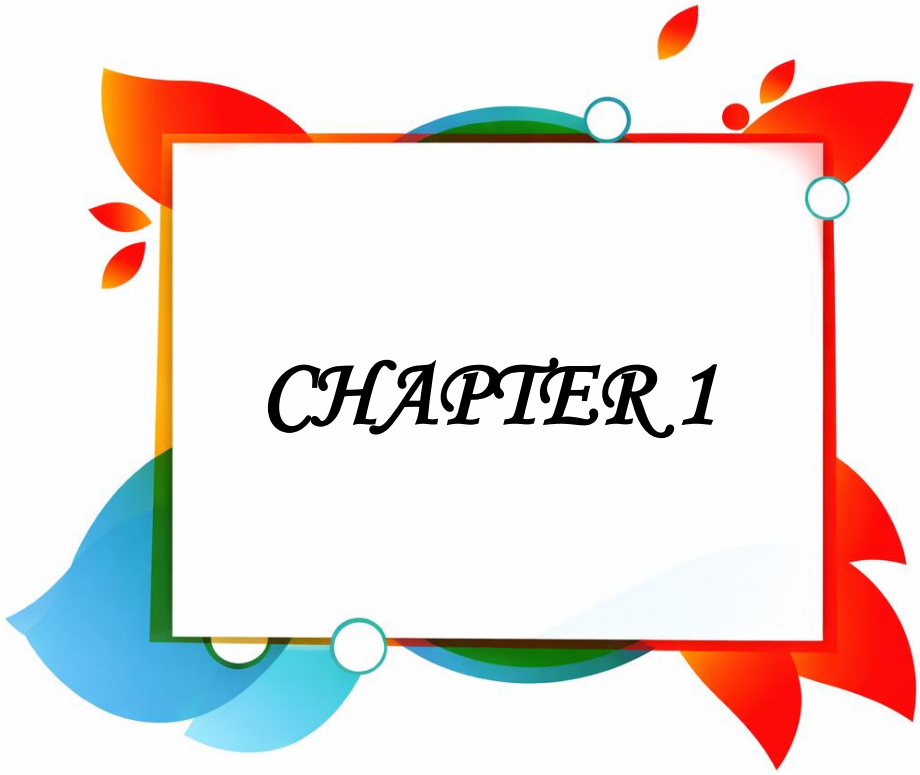
CHAPTER 1

Phthalates: Environmental Exposure, Toxicokinetics and Molecular Toxicity Mechanisms

Zozan Garip Teke [1]

1. Introduction

Phthalate acid esters are environmental pollutants that are released into the environment because they are not covalently bonded to the polymer matrix. Individuals are continuously exposed primarily through oral, dermal, and inhalation routes, and these compounds are detected in various biological samples, including urine, semen, blood, placenta, and fetal tissues. This situation also raises health concerns about the potential effects and safety of phthalates and their metabolites on human health. Adverse effects of phthalates and their metabolites on the nervous, endocrine, and reproductive systems are known. These effects manifest through multiple molecular targets and mechanisms of action, including oxidative stress, hormonal imbalance, activation of apoptotic pathways, and steroidogenesis disorders; however, the underlying mechanisms have not yet been fully elucidated. In this book chapter, environmental exposure to phthalates and their current molecular mechanisms are evaluated with a holistic approach, aiming to lay the foundation for future studies.

2. Sources and environmental exposure

In 2018, 5.5 million tons of phthalates were produced worldwide and are considered "global pollutants" (Dueñas-Moreno et al., 2024; Arcanjo et al., 2023). China produces over 1,000,000 tons of phthalate acid esters (PAEs) annually, representing one-fifth of global production (Fang et al., 2022). Di(2-ethylhexyl) phthalate (DEHP), di-iso- and di-n-butyl phthalate (DiBuP, DnBuP), dibutyl phthalate (DBP), butyl-benzyl phthalate (BBP), diisononyl phthalate (DiNP), di-n-octyl phthalate (DnOP), diisodecyl phthalate (DiDP) are commonly used types of phthalates (Kiralan et al., 2020; Erkekoğlu, 2022).

DEHP and DBP are two of the most used PAEs and are frequently associated with environmental pollution. DEHP is used in polyvinyl chloride, packaging

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films, baby and children's toys, automobiles, coating materials, plastic food containers, paint, pesticides, paper packaging and labels, electronic devices, and various household chemicals. DEHP is also found in medical equipment and devices, particularly in the healthcare sector, such as intravenous bags, umbilical artery catheters, enteral feeding bags, blood bags, dialysis bags, infusion tubes, and nasogastric tubes (Latini et al., 2008; Rowdhwal & Chen, 2018). It has been reported that 15% of DEHP originates from medical devices (Dostalova et al., 2020). DBP, the second most used phthalate ester; Phthalates are used in the production of polishes, varnishes, solvents, coatings, plasticizers for cellulose acetate, and in some pharmaceuticals (Akinlolu et al., 2023; Aydemir et al., 2023; Batool et al., 2022). Phthalates are also used in cosmetics and personal care products as color and fragrance stabilizer (Akinlolu et al., 2023; Aydemir et al., 2023; Balcı et al., 2022).

3. Absorption, distribution, and metabolism

Because PAE polymers are not covalently bonded, they are rapidly released from industrial products, making them ubiquitous environmental pollutants (Latini et al., 2008; Aydemir et al., 2023). Phthalates are released into the environment from products after repeated use, heating, and cleaning (Rattan et al., 2019). According to the Organization for Economic Cooperation and Development (OECD), people are exposed to phthalates every day (Arcanjo et al., 2023). This is a significant concern regarding its potential impact on human health (Rowdhwal & Chen, 2018). Phthalates are absorbed into the body daily through skin contact (dermal), ingestion (oral), or inhalation. Although oral and dermal routes are the most common, exposure in children occurs through ingestion of foods and plastics (Bornehag et al., 2014).

Phthalates are easily absorbed from the gastrointestinal tract. In humans, DEHP is absorbed at a rate of over 50%, while DBP is absorbed at a rate of almost 80%. Following absorption, phthalates enter the systemic circulation, are distributed to various tissues, primarily the liver, and are rapidly metabolized (Fréry et al., 2020).

After entering the organism, phthalates undergo rapid biotransformation. In the first stage of metabolism, diester phthalates are hydrolyzed by esterase enzymes in the intestine, liver, and other tissues, biologically converting them into monoester metabolites. While monoesters formed in low molecular weight phthalates (e.g., diethyl phthalate [DEP] and dibutyl phthalate [DBP]) constitute the main metabolites, the metabolic process is more complex in high molecular weight phthalates. Specifically, DEHP is first converted to mono-(2-ethylhexyl)phthalate (MEHP), and MEHP is then further converted to oxidized metabolites such as mono-(2-ethyl-5-hydroxyhexyl)phthalate, mono-(2-ethyl-5-

oxohexyl)phthalate, and mono-(2-ethyl-5-carboxypentyl)phthalate through oxidation reactions involving the cytochrome P450 enzyme system. Similarly, high molecular weight phthalates such as DiNP and DPHP also form numerous oxidized metabolites.

Oxidation reactions occur predominantly at ω and ω-1 carbon atoms, and the variety of metabolites increases with increasing alkyl chain length. The resulting monoesters and oxidized metabolites are then conjugated by glucuronidation and, to a lesser extent, sulfation reactions to become water-soluble and are mainly eliminated from the body via urine. In low molecular weight phthalates, monoester metabolites are predominantly found in urine, while in high molecular weight phthalates such as DEHP and DiNP, oxidized metabolites constitute the dominant biomarkers in urine. Therefore, it is recommended that in human biological monitoring studies, not only monoesters but also oxidized metabolites should be measured to assess high molecular weight phthalate exposure.

Although phthalate metabolism generally shows similarities across species, significant variations can be observed among individuals depending on age, sex, genetic makeup and metabolic enzyme activities. In particular, the incomplete development of oxidation and conjugation enzyme systems in newborns and fetuses can alter the pharmacokinetics and toxic effects of phthalates. Furthermore, the metabolic process plays a critical role in the toxicity mechanisms of phthalates because some monoester metabolites, especially MEHP, exhibit higher biological activity compared to the parent compound (National Research Council, 2008; ATSDR, 2019; Erkekoğlu, 2022).

Phthalates have been commonly detected in biological samples such as urine, fetus, blood, placenta, and semen (Akinlolu et al., 2023; Aydemir et al., 2023). Because phthalates are rapidly absorbed, undergo extensive metabolic transformations, and their metabolites are quickly excreted in urine, urinary metabolites are the most used biomarkers in assessing human exposure (National Research Council, 2008; Agency for Toxic Substances and Disease Registry (ATSDR), 2019; Erkekoğlu, 2022).

4. Biological monitoring and human exposure

Numerous reports in Europe and Asia have indicated that plastics industry workers have higher levels of phthalate metabolites in urine, blood, and semen samples compared to the general population (Fong et al., 2014; Huang et al., 2014; Wang et al., 2018; ATSDR, 2019). Some studies have indicated that women, particularly beauty salon workers, have higher exposure levels than men due to occupational exposure to cosmetic products. While DEHP exposure is estimated to range from an average of 3 to 30 μg/kg/day, occupational exposure

can reach 200 µg/kg/day (Boyle et al., 2021; Kolena et al., 2017). A study by Koppen et al. (2019) showed that children (6-11 years old) are primarily exposed to phthalates through food consumption and daily activities. The same study found that in Brussels, Belgium, urinary levels of DEHP metabolites in children were 1.7 times higher than those in their mothers. Exposure to phthalates through fast food, plastic-packaged foods, skincare, and cosmetics has also been reported in adolescents and young adults (16-20 years) (Koppen et al., 2019). Despite growing concerns about the harmful effects of phthalates, data on occupational exposure, such as that of plastics factory workers who are exposed to high concentrations of phthalates daily, are quite limited (Batool et al., 2022). The International Agency for Cancer Research has also classified DEHP as a probable human carcinogen, and more comprehensive tools and actions are needed to limit exposure (United Nations Environment Programme [UNEP], 2017).

5. Toxicity Mechanisms

Studies on DEHP in animal models and humans have determined its effects on the endocrine system, testes, ovaries, and nerves both in vitro and in vivo (Rowdhwal & Chen, 2018). Phthalate exposure causes liver fibrosis, hepatic cell apoptosis, insulin resistance, inflammatory cell infiltration, irregular cholesterol metabolism, and oxidative stress (Ding et al., 2021).

Synthetic endocrine disruptors (EDCs) can accumulate in living organisms by spreading into the environment through soil and groundwater or indirectly through the food chain. These substances disrupt endocrine balance, affecting many essential processes such as growth, sex development, stress, insulin production, reproductive ability, and metabolic rate. EDCs are synthetic or natural chemicals that disrupt the normal functioning of the body, mimicking or inhibiting the effects of hormones. The European Union has reported DEHP and DBP as two plasticizers that can act as EDCs and cause developmental toxicity. These substances cause reproductive and developmental problems due to their significant effects on the endocrine system (Balcı et al., 2022; Kiralan et al., 2020).

6. Mechanisms of Endocrine Disruption

There is growing concern about phthalate-related adverse health effects in humans and wildlife due to their endocrine-disrupting effects through interference with hormone metabolism (Akinlolu et al., 2023; Aydemir et al., 2023). Further research and information regarding the health effects of DEHP (Aydemir et al., 2023) have been indicated. Phthalates cross the placental and blood-brain barriers, causing fetal anomalies and structural dysfunction of the nervous system during pregnancy. Furthermore, EDCs that cross the placental

barrier have been shown to cause reproductive disorders such as low birth weight, premature birth, abortion, and decreased fertility. The placenta synthesizes steroid hormones such as estradiol (E2), estriol (E3), and progesterone to maintain pregnancy (Bornehag et al., 2014; Akinlolu et al., 2023; Aydemir et al., 2023).

a. Receptor Interactions

The molecular mechanisms of endocrine disruption involve multiple molecular targets and mechanisms of action, including receptor activation and disruption of steroidogenesis, by mimicking or inhibiting hormonal signaling and disrupting various biological processes. Although intergenerational effects of maternal phthalate exposure have been demonstrated in mouse models, the underlying mechanisms are not yet fully understood (Quinnies et al., 2015; Pocar et al., 2017).

b. PPAR Activation

Phthalate monoesters negatively affect fetal growth and development in both sexes by influencing metabolic sensor signaling through the activation of the proliferator-activated receptor (PPAR), thereby reducing estrogen and progesterone levels in the placenta (Latini et al., 2008; Fang et al., 2022). MEHP causes complete inhibition of aromatase gene expression by activating both PPARα and PPARγ in cultured rat granulosa cells (Latini et al., 2008).

c. Steroidogenesis Interference

Phthalates alter ovarian and testicular function by disrupting hormone biosynthesis and sex hormone signaling. Phthalates can reduce androgen production by the testes, and studies in rodents have shown that DEHP and dibutyl phthalate (DBP) disrupt androgen signaling when administered during a critical period for reproductive system development (Bornehag et al., 2014). It is also suggested that DEHP may cause hormonal imbalance through estrogen-like effects (Erkekoğlu, 2022).

7. Oxidative Stress and DNA Damage

Phthalates cause disturbances in lipid metabolism, which also plays a role in the pathogenesis of diabetes, obesity, cancer, cardiovascular diseases, and neurological disorders (Aydemir et al., 2023). Decreased antioxidant capacity, oxidative stress, and disturbances in energy metabolism have been reported in the liver of rats administered oral phthalates (Aydemir et al., 2023). It has been stated that phthalate-induced neurotoxicity in rats causes upregulation of pro-apoptotic proteins (Bax and caspase-3) and downregulation of anti-apoptotic proteins (Bcl-2). DEHP exposure similarly led to increased levels of pro-inflammatory

cytokines (tumor necrosis factor-α and interleukin-1β) and oxidants (malondialdehyde, nitric oxide, 8-hydroxy-2-deoxyguanosine), and decreased levels of antioxidants (glutathione peroxidase, superoxide dismutase, and catalase) in the cerebral cortex, striatum, and brainstem (Pogrmic-Majkic et al., 2022; Akinlolu et al., 2023).

8. Neurotoxicity and other systemic effects

Exposure to DEHP causes downregulations in norepinephrine, dopamine, and acetylcholine esterase activity (Pogrmic-Majkic et al., 2022; Akinlolu et al., 2023). In children, possible links between exposure to DEHP and increased risks for learning, behavior, and attention problems have been noted (Akinlolu et al., 2023). Exposure to phthalates in the womb has adverse health effects in adulthood, such as diabetes, cardiovascular diseases, obesity, metabolic disorders, and cancer. It has been stated that exposure to PAEs during the fetal period is associated with abnormal conditions in development and reproduction (Fang et al., 2022; Latini et al., 2008).

9. Epigenetic mechanisms

It is stated that phthalates can permanently alter gene expression through DNA methylation and histone modifications, and these effects can be transferred to future generations (transgenerational inheritance). It has been stated that maternal phthalate exposure disrupts the function of histone demethylases, leading to misregulation of essential reproductive and demethylation genes (Li et al., 2018). Another possible mechanism uncovered in *Caenorhabditis elegans* is changes in chromosome structure and germline-specific gene expression patterns that lead to increased double-strand breaks and activation of cell apoptosis (Cuenca et al., 2020).

10. Conclusion

Consequently, phthalates pose a significant global public health issue due to their widespread exposure and their multi-systemic toxic effects, particularly on reproductive health. Therefore, developing regulatory policies to reduce phthalate exposure or limit exposure to proven toxic substances like DEHP with safe alternatives is of great importance in developing comprehensive regulatory policies. To better inform current regulatory strategies, further experimental research is needed to elucidate the underlying epigenetic mechanisms and the effects of low-dose mixtures.

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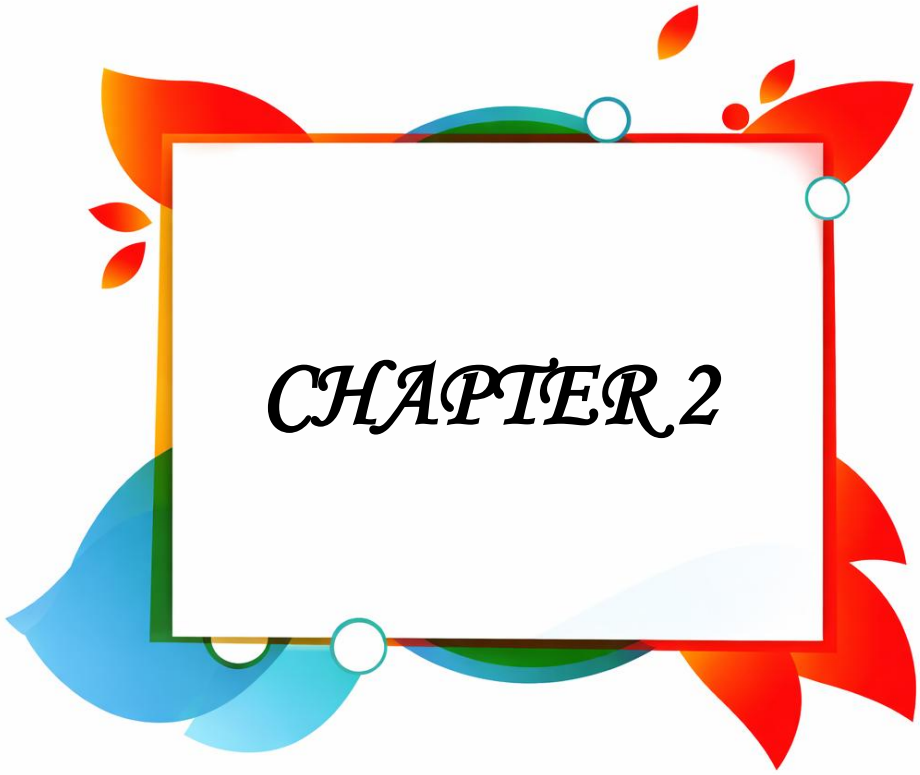
CHAPTER 2

Pharmacological Properties, Clinical Use, Addiction Mechanisms and Toxicological Evaluation of Morphine

Zeynep Özdemir[1] & İsmet Yılmaz[2]*

INTRODUCTION

1. *Papaver somniferum*

Papaver somniferum (Poppy) is a plant of great historical, medicinal, and cultural importance, with high industrial value, primarily for alkaloid production. The word "Somniferum" is of Latin origin and means "sleep-inducing". The Papaver somniferum plant consists of two parts: seeds and capsules. Opium is obtained by scoring the unripe capsules with a special knife in the early morning hours, and then allowing the milky sap that comes out of the capsule to solidify upon contact with air. The sap from the capsule is initially white, later turning dark brown, and in some varieties, black. When fresh, it is soft and has a sharp, unpleasant odor and a bitter taste. This solidified sap is called "opium gum" and is used to obtain the alkaloids contained within this material [1].

Crude opium contains approximately 30–35 different alkaloids; among these, the most abundant and the one with the strongest pharmacological effect is **morphine** (5–25%). Besides morphine, narcotine, codeine, narceine, thebaine, pseudomorphine, papaverine, cryptopine, roadine, lantopine, meconidine, codemine, lavdanine, lavdonacin, hydrocotarine, oxinarcotine, protepine, xanthangine, papaveramine, aporein, neopine, porphidroxine and narcotolin are also among the components of opium [2]. For Papaver somniferum, Turkey, India, Australia, France, Spain and Hungary are considered the main legal

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producing countries under the supervision of the United Nations. In our country, cultivation and production of unscratched capsules are carried out only in some provinces with a permit. These are: all of the provinces of Afyonkarahisar, Amasya, Burdur, Çorum, Denizli, Isparta, Kütahya, Tokat and Uşak, and some districts of other provinces [3].

2. Morphine

Morphine was the first pure alkaloid isolated from opium in 1804 by the German pharmacist Friedrich Wilhelm Adam Sertürner. Observing its powerful sedative effect, Sertürner named it "Morphine," inspired by Morpheus, the Greek god of sleep. This discovery is considered a turning point in the history of pharmaceutical sciences, marking the beginning of alkaloid chemistry. Sertürner first communicated his discovery to the pharmacist J.B. Trommsdorff, publisher of the "Journal der Pharmacie," in 1805, using the name "Säure im Opium" (Sedative in Opium). He subsequently submitted it to numerous other journals without success. Its publication in the "Annalen der Physik in Leipzig" in 1817 attracted the attention of the French physician Joseph Louis Gay-Lussác, who then employed his student to study it. While Sertürner received the "Institut de Franve Montyon" award in 1804 for introducing the alkaline nature of morphine, some scientists argue that the identity of the first discoverer of morphine is disputed, as the French pharmacist Charles Louis Derosne distributed the narcotic morphine mixture he isolated under the name "Sel de Derosne". Two chemists from the "Prussian Academy of Sciences," E. Vongerichten and H. Schrötte, elucidated the structure of morphine in 1881, naming the basic structure "Phenanthrene" and including this name in their thesis. They also distilled morphine with zinc powder, a process that led structural research in the wrong direction for 40 years. R. Robinson (1925) and other researchers only managed to define the correct structural formula in the early 1920s. The final clarification and synthesis of morphine continued until 1963. After a certain degree of structural certainty was achieved, research focused on altering the molecular structure to avoid addictive properties, and in medicine, hydrochloride, sulfate, acetate, and tartrate salts are used [4].

Morphine has a complex structure containing a phenanthrene core, and the complete elucidation of its chemical structure continued until the mid-20th century. Currently, hydrochloride and sulfate salts are most commonly used. Morphine, a potent opioid analgesic, is one of the main drugs in the treatment of severe acute and chronic pain, and its molecule has also formed the basis for the development of semi-synthetic opioids. For example, heroin is a semi-synthetic diacetylmorphine derivative of morphine, obtained by acetylation of morphine, and has a faster and stronger effect on the central nervous system. Heroin is 2-10

times stronger than morphine, and other derived opioids include oxycodone and some synthetic analogs [1].

2.1. Methods of Obtaining Morphine

Traditional production of morphine involves obtaining it from opium in solution, evaporation, and re-dissolving with calcium chloride solution. After separation of this solution, the liquid part is evaporated several times, and the remaining morphine and codeine crystals are collected. These are dissolved with the help of ammonia, and then recrystallization is performed. In this way, it has been observed that morphine is separated from the codeine remaining in the solution, and the resulting morphine crystals are colorless and odorless [5].

Nowadays, the process begins with the preparation of standard solutions and continues with the preparation of the poppy capsule for use. Poppy capsules are dried at 70°C for 24 hours and the capsules are ground to strengthen them. After that, a separation technique (mostly chromatographic methods are preferred) and then an extraction method are used [6].

Chromatographic methods are classified as follows:

A- According to separation mechanism;

1. Adsorption Chromatography

2. Partition Chromatography

3. Ion Exchange Chromatography (Ion Chromatography)

4. Gel Permeability or Gel Filtration (Molecular-Exclusion, Size-Exclusion) Chromatography

5. Zone Electrophoresis

6. Affinity (Bioaffinity) Chromatography

7. Chiral Chromatography

B- According to the mobile phase;

1. Liquid Chromatography (LC)

2. Gas Chromatography (GC)

C-According to the technique used:

1. Column Chromatography

2. Plane Chromatography (Thin Layer Chromatography, TLC; Paper Chromatography, PC)

D- According to intended use:

1. Analytical Chromatography (Qualitative Chromatography; Quantitative Chromatography)

2. Preparative Applications (Obtaining pure substances from mixtures)

The next stage is the extraction stage, and traditional extraction methods require more solvent, high temperature and long time, resulting in low yields. Today's extraction techniques increase the yield by using less solvent and allowing operation at lower temperatures [6].

Advanced extraction techniques:

1. Soxhlet Extraction

2. Ultrasonic Extraction

3. Microwave Extraction

4. Magnetic Stirrer Extraction

5. Accelerated Solvent Extraction

6. Supercritical Fluid Extraction

Using ultrasonic extraction, a technique that has gained popularity in recent years, the cell wall of the plant is broken down with ultrasonic sound waves and mass transfer is carried out. Compared to other extraction methods, this method is frequently preferred because it is a simpler and cheaper method to use [7].

2.2. Pharmacology of Morphine

Morphine is the oldest known, most potent, and inexpensive opioid analgesic, and is the first example of a drug used. The fact that morphine has a widespread depressive effect on the central nervous system while preventing pain has led to morphine and its derivatives being called "**Narcotic Analgesics**" for many years. However, opioids, including morphine and its derivatives, produce a strong analgesic effect without causing loss of consciousness. For this reason, the term "**Opioids**" or "**Opioid analgesics**" has begun to be used instead of the term narcotic. It has a rather complex mechanism of action. The difference between opioid analgesics and non-opioid analgesics is that opioid analgesics do not have antipyretic and anti-inflammatory effects and tolerance, psychic and physical dependence develop on the drug with long-term use [8].

From a medical standpoint, its most important analgesic effect is achieved by blocking the transmission of painful impulses in the spinal cord and brain. It affects synapses on pain pathways at both the spinal and supraspinal levels. At

the spinal level, the site of action is thought to be the synapse between the first and second pain neurons in the dorsal horn of the spinal cord. Morphine exerts presynaptic inhibition at this synapse by activating presynaptic opioid receptors. It also raises the pain threshold, doing so through its receptors. The existence of receptors affected by opioids in the central nervous system was demonstrated in the early 1970s. Morphine mimics the effects of endogenous peptide neurotransmitters (endorphins, enkephalins, and dynorphins) by binding to specific opioid receptors in the body. The receptors to which opioids bind are: Mu (μ) (OP3; μ1); Morphine consists of five types: μ2, Delta (δ; OP1), Kappa (ε; OP2), Sigma (σ), and Epsilon (ε). It is also thought that there are other cough suppressant receptors. Morphine has a strong agonistic effect on Mu (μ) receptors and a weak agonistic effect on Kappa (ε) receptors (Table 1) [9, 10].

Morphine-Affected Receptors:	Main Effect/Function Examples
Mü (μ) (OP_3), μ_1	Supraspinal and spinal analgesia Slowing of acetylcholine turnover in the brain Prolactin secretion Catalepsy Nutrition, learning and memory Regulation of immune functions
μ_2	Inhibition of the respiratory center Slowing of gastrointestinal transit Euphoria Central control of the cardiovascular system Constipation Nutrition
Kappa (κ) (OP_2)	Spinal and supraspinal analgesia Sedation Dysphoria Diuresis Regulation of secretion of some other pituitary hormones Nutrition

Table 1: Receptors affected by morphine and effects mediated through these receptors [10].

The transmembrane transduction mechanisms that mediate the inhibitory effects of morphine at the neuronal level are:

1. Inhibition of adenyl cyclase,

2. Prevention of pain transmission by reducing the entry of Ca into the cell through voltage-dependent Ca channels in the neuronal membrane at the presynaptic level,

3. Prevention of postsynaptic transmission by opening K channels in the neuronal membrane via Gi protein at the postsynaptic level [11,12].

2.3. Pharmacokinetic and Pharmacodynamic Properties of Morphine

The pharmacokinetic and pharmacodynamic properties of morphine vary depending on the route of administration, formulation type, age, and individual patient factors. The onset of analgesic effect differs depending on the route of administration. In oral preparations, the effect generally begins within approximately 30 minutes, while with intravenous administration, analgesia is achieved in a short time, such as 5-10 minutes. When administered via intramuscular or subcutaneous injection, the onset of effect is approximately 20 minutes on average. The duration of effect also depends on the route of administration and pharmaceutical form; for rapid-release tablets, oral solutions, and injection forms, the duration of analgesic effect is generally between 3-5 hours. In extended-release capsules and tablets, this period can be extended up to 8-24 hours depending on the formulation. While a single dose of epidural or intrathecal medication can provide analgesia lasting approximately 24 hours, the duration of action in suppository forms varies between 3–7 hours, and the average duration of action in intramuscular and subcutaneous applications is reported to be 4-6 hours. Therefore, the morphine dose needs to be individualized according to the clinical response [13].

Absorption: Varies depending on the route of administration. When taken orally, it is largely absorbed from the gastrointestinal tract, however, rapid absorption also occurs when applied as a solution to the nasal mucosa. The intranasal ingestion of heroin, a diacetyl derivative of morphine, in abuse is based on this characteristic. When morphine is mixed into cigarettes and inhaled, it can also be absorbed from the respiratory tract mucosa, and absorption from the rectal mucosa is also possible [14].

Distribution: Its extends to many tissues, including skeletal muscle, liver, kidneys, lungs, gastrointestinal system, spleen, and brain. It binds to opioid receptors in the central nervous system and peripheral tissues. The volume of distribution (Vd) varies with age and its approximately 7.1 L/kg in children under 11 years of age, which is higher than in children over 11 years of age (approximately 4.7 L/kg). In adults, it is reported to be in the range of 1–6 L/kg. The plasma protein binding rate is less than 20% in premature infants, while it is between 20–30% in adults [14].

Metabolism: Its occurs largely in the liver, the main metabolic pathway is the formation of morphine-3-glucuronate by glucuronidation of the phenolic hydroxyl group; this metabolite is considered pharmacologically inactive in

humans. To a lesser extent, morphine-6-glucuronate is formed by glucuronidation of the alcoholic hydroxyl group; this metabolite is an active metabolite with higher intrinsic analgesic activity than morphine and can cross the central nervous system. Approximately two-thirds of morphine in human plasma is in the form of morphine-3-glucuronate, and a smaller portion is in the form of morphine-6-glucuronate. Small amounts of sulfate conjugates are also formed; morphine-3-sulfate has been shown to have analgesic activity. Minor metabolites include morphine-3,6-diglucuronide, normorphine, and morphine-3-ether sulfate. Morphine also reacts with small amounts of codeine via O-methylation. It can be converted to normorphin via N-demethylation and these metabolites are also pharmacologically active [15].

Oral bioavailability is variable. Although morphine is well absorbed from the gastrointestinal tract, its systemic bioavailability is relatively low due to significant first-pass metabolism, averaging around 30%, but varying between 15-64% among individuals. Because of the high first-pass elimination, the oral dose of morphine is usually 3-10 times higher to achieve an effect equivalent to analgesia obtained parenterally. However, with continued oral administration, first-pass metabolism is partially reduced and bioavailability increases; in this case, the equivalence ratio decreases to approximately 2-3 times. For example, an oral dose of 20-30 mg of morphine can provide analgesia approximately equivalent to that of 10 mg of parenteral morphine [16].

The elimination half-life of morphine varies significantly with age. The half-life has been reported to be between 10-20 hours in premature infants, an average of 7.6 hours (4.5-13.3 hours) in newborns, 6.2 hours (5-10 hours) in 1-3 month old infants, 4.5 hours (3.8-7.3 hours) in the 3-6 month period, and 2.9 hours (1.4-7.8 hours) in the 6 month-2.5 year age group. It has been determined to be 1-2 hours in preschool children, approximately 1.3 hours in children aged 6-19 years with sickle cell disease, and the half-life for the rapid-release form in adults is generally 2-4 hours [17]. The time to reach maximum plasma concentration (tmax) varies depending on the route of administration. It is reported to be approximately 1 hour for tablets, oral solutions, and epidural administration; 3-4 hours for extended-release tablets; 20-60 minutes for suppositories; 50-90 minutes for subcutaneous administration; 30-60 minutes for intramuscular administration; and 10-20 minutes for intravenous administration. In cerebrospinal fluid, morphine concentrations peak in approximately 8 hours after a controlled-release oral dose [16,17].

Excretion: Its occurs primarily through the kidneys, with morphine and its metabolites excreted in the urine mostly in the form of morphine-3-glucuronide (3-15% unchanged morphine excretion in neonates; 2-12% in adults has been

reported). Accumulation of morphine-6-glucuronide can increase the risk of toxicity, especially in renal failure, and all metabolites have been associated with potential neurotoxicity. Morphine-6-glucuronide formation is greater with oral administration than with parenteral administration, and accumulation of this metabolite with long-term oral use may contribute to analgesia. Morphine is eliminated in small amounts in bile as glucuronate conjugates, and approximately 7-10% of the dose is eliminated in the feces. Some of the morphine that passes into the intestine via bile may enter the enterohepatic circulation; in fact, a decrease in the amount of morphine excreted in the feces has been reported in addicts. After parenteral administration, morphine can pass into gastric juice due to the ion trapping mechanism [18].

2.4. Central Effects of Morphine

Analgesia: The most important therapeutic effect of morphine on the central nervous system is analgesia. It reduces the sensation of pain by raising the pain threshold at the spinal cord level and modulating the way pain is perceived in the brain. Although it does not always completely eliminate the perception of pain, it weakens the response to pain, increasing the individual's tolerance to pain; even if the patient receiving morphine can feel pain, they feel more comfortable and at peace. In terms of the selectivity of its analgesic effect, morphine is superior to general anesthetics. In general anesthetics, analgesia occurs only with certain agents and is accompanied by significant central nervous system depression; when analgesia is achieved, consciousness is often lost or significantly suppressed. In contrast, it at doses that produce analgesia, does not significantly alter the five senses and different sensory modalities from the periphery; however, it may indirectly lead to a decrease in visual acuity due to miosis [19].

Euphoria: Morphine can produce a distinct feeling of pleasure and happiness. It leads to euphoria by reducing or eliminating anxiety and mental tension in the patient. It is accepted that euphoria develops as a result of the disinhibition of dopaminergic neurons in the ventral tegmental area. The degree to which morphine produces euphoria in healthy individuals without pain may vary from person to person. In some healthy individuals, instead of euphoria, a dysphoria picture may occur along with anxiety, worry and fear. In some cases, euphoria develops initially and is followed by dysphoria, therefore, the effect of morphine in the absence of pain may not create a pleasant experience in every individual [20].

Sedation: Sedation may occur following morphine administration. Mental confusion, decreased attention and concentration, slowed movements, and disinterest in the environment may develop. In most individuals given morphine, drowsiness occurs as a mild form of sedation, and it may be difficult to maintain

the flow of ideas during thinking. A decrease in psychomotor and cognitive performance may occur, although generally more limited compared to alcohol and hypnosedatives. Therefore, some individuals who abuse morphine may be able to carry out their daily activities in a relatively normal manner. Sedation may manifest as decreased movement, reluctance to move, and decreased interest in the environment; in some individuals, it may be pronounced enough to lead to sleep. The sedative effect is observed more pronounced in the elderly than in the younger. On the other hand, morphine is considered an effective option for insomnia due to severe pain, and dream content can cause significant sleep [14].

Respiratory depression: Morphine suppresses respiration by reducing the sensitivity of neurons in the respiratory center of the medulla to carbon dioxide, leading to respiratory depression. This effect is considered one of the most clinically significant side effects of morphine. As a result of respiratory depression, carbon dioxide accumulation may develop; consequently, acidosis may occur, vasodilation may occur in the brain vessels, and an increase in cerebrospinal fluid pressure may result. It is generally reported that doses of 10 mg do not have a significant effect on respiration, whereas respiratory depression becomes noticeable at higher doses such as 15-20 mg. Morphine reduces both the rate and depth of respiration; the decrease in rate is more pronounced and usually occurs after the decrease in depth [10].

Even with the usual therapeutically accepted doses of morphine, respiratory depression can develop in individuals who have not used opioids; as the dose increases, this depression can become more pronounced, progressing to respiratory arrest. Respiratory depression is the most critical cause of death in acute morphine overdose; the respiratory rate can drop to 3-4 breaths per minute, and irregular or periodic breathing patterns may appear. This picture may be more pronounced, especially in elderly patients. In cases of severe respiratory depression, the functioning of the respiratory center can be largely maintained by impulses from chemoreceptors stimulated by hypoxia. Therefore, in such cases, administering only oxygen inhalation can reduce hypoxia and eliminate respiratory stimulation, increasing the risk of complete respiratory arrest if adequate support is not provided [10]. Morphine can exhibit a strychnine-like convulsive effect when administered in high doses to species unaffected by respiratory depression, such as frogs. It causes behavioral depression in dogs, monkeys and rats as well as in humans, but it can cause excitation in some species such as mice, pigs and horses, and the behavioral excitation observed in cats can sometimes be severe enough to be described as "morphine frenzy" [21].

Antitussive: Morphine produces a significant antitussive effect by suppressing the cough center in the medulla oblongata. It is thought that the

receptor mechanisms mediated by the antitussive effect are not exactly the same as those that produce analgesia. However, although morphine can exhibit a strong antitussive effect, its use is generally not preferred in clinical situations where cough can be controlled with lower-risk agents due to its potential for addiction and serious adverse effects such as respiratory depression. On the other hand, although morphine is known for its antitussive effect, it has been reported that cough can develop, especially after intravenous administration. It is suggested that this side effect occurs through reflex mechanisms and may be affected by factors such as the dose and injection rate/duration. Opioid-induced cough often does not cause significant harm or discomfort to the patient; however, in some cases, severe cough may complicate imaging, diagnostic, or therapeutic procedures. It may also pose a problem in clinical situations where increased intracranial, intraocular, or intraabdominal pressure is undesirable [22].

Emesis: Morphine causes nausea and vomiting by stimulating the chemoreceptor trigger zone (CTZ) in the area postrema. This effect is prevented by phenothiazine drugs or trimetobenzamide. Morphine depresses the vomiting center when given in high doses, therefore vomiting may not occur in a person who has taken an overdose of morphine despite chemoreceptor stimulation [23].

Miosis: Morphine causes miosis in the human eye, but in acute poisoning, mydriasis may occur due to excessive sympathetic activity resulting from asphyxia in the terminal phase. Miosis is dependent on the central effect of morphine, therefore, instilling morphine solution into the conjunctival sac does not cause miosis. Miosis occurs as a result of the inhibition by morphine of supranuclear inhibition on the parasympathetic center located in the mesencephalon and related to the eye, i.e., miosis occurs as a result of disinhibition, the risk of developing tolerance to the miotic effect of morphine is low [24].

Hypotension: When 10 mg of morphine is administered to healthy volunteers, it generally does not affect heart rate and blood pressure; however, higher doses (30-32 mg) cause hypotension. Bradycardia develops with hypotension; hypotension may not be pronounced in bedridden patients, but may appear as orthostatic hypotension in ambulatory patients and can lead to fainting. Its hypotensive effect is partly due to histamine release and partly due to vasodilation in the periphery as a result of inhibiting the vasomotor center in the brainstem. Morphine can also cause dizziness, which may be partly due to orthostatic hypotension. Cerebral blood flow is increased due to vasodilation caused by accumulated carbon dioxide; the hypotensive effect of morphine may be more dangerous if hypovolemia is present, as in hemorrhagic conditions. In the presence of hypovolemic shock, administering morphine can lead to metabolic

acidosis. The use of neuroleptic drugs (especially phenothiazine derivatives) in combination with morphine exacerbates respiratory depression and hypotension. It causes hypothermia by affecting the heat regulation center in the hypothalamus [24, 25].

Other Effects:

-It stimulates the secretion of antidiuretic hormone, prolactin, and somatotropic hormone from the pituitary gland by affecting the hypothalamus; however, it inhibits the secretion of adrenocorticotropic hormone (ACTH). It also inhibits the secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus.

-Through its central effect, it increases the release of catecholamines from the adrenal medulla, raises plasma catecholamine levels, and can cause hyperglycemia [10].

-It does not cause a significant impairment in muscle coordination. It depresses libido and sexual performance. It has no anticonvulsant effect; on the contrary, it has a convulsive effect in overdose; it increases sensitivity to convulsive drugs [10].

2.5. Peripheral Effects of Morphine

Gastrointestinal system: Morphine inhibits salivary gland secretion and can cause dry mouth, reduces gastric HCl secretion and motility, delays emptying and increases gastric tone. It increases the tone of intestinal circular smooth muscles, increases water absorption from intestinal contents and causes constipation. It also increases the tone of the anal sphincter. In the individual, indifference to stimuli from the rectum related to the defecation reflex occurs. It causes spasm in the bile duct, increases bile pressure and can cause biliary colic, reduces bile and pancreatic secretions [26].

Bladder: It constricts both the sphincter and detrusor muscles; it can cause difficulty urinating and urinary retention. It causes a decrease in the volume of urine excreted as a result of increased antidiuretic hormone. In those given morphine, sometimes, conversely, an urgent need to urinate may be observed. It can increase ureteral tone and worsen ureteral colic if not given with an antispasmodic drug [27].

Uterus: It is generally ineffective against the contractions of the uterus in labor. If uterine contractions have been increased by injecting oxytocin, morphine normalizes the number and intensity of these contractions and usually prolongs labor. Morphine given to a woman in labor crosses the placenta into the fetal circulation and can lead to respiratory depression and asphyxiated birth [28].

Histamine release: Morphine causes urticaria, sweating, and vasodilation by releasing histamine from mast cells. It can cause bronchoconstriction and sometimes asthma attacks in patients with bronchial asthma. It is contraindicated in patients with bronchial asthma because it causes asthma attacks and reduces ventilation volume through respiratory depression. It reduces the secretion of glands in the respiratory tract mucosa and inhibits mucociliary transport. In patients given morphine, flushing of the face and neck, along with skin itching and urticaria, may occur due to histamine release. It can inhibit salivary gland secretion and cause dry mouth. Morphine causes arteriolar and venous dilation both by directly affecting vascular smooth muscle and by causing histamine release. Because morphine causes significant vasodilation in the periphery, it reduces the preload and posterior load of the heart, thus reducing the workload and oxygen demand of the myocardium [27].

Immune System: Long-term use of morphine can depress cellular and humoral immune mechanisms, and it is thought that this effect occurs by affecting the central nervous system [26, 27].

2.6. Indications of Morphine

2.6.1. Management of Moderate and Severe Pain: Morphine is considered a component of a comprehensive, multimodal, and patient-specific treatment plan for pain management. Doses are generally determined based on approved dose ranges, but some patients may require lower or higher doses depending on their clinical response. Therefore, doses and dosing intervals should be personalized considering the individual characteristics of the patient and readjusted as needed in line with the determined treatment goals. The basic principle in treatment is to administer the medication for the shortest possible duration and at the lowest effective dose [29,30]. In acute pain of a severity requiring morphine that is not related to cancer, a multimodal analgesia approach is recommended, and its use in combination with a non-opioid analgesic can be considered to increase its effectiveness. It is stated that in most cases, prescribing morphine for 3 days or less is sufficient for acute pain, and the need for treatment for up to 7 days rarely arises. The use of long-acting morphine preparations in the treatment of acute pain is not recommended in patients who have not previously used morphine or similar opioids [29].

The primary indication for morphine is pain control; in clinical practice, it is used in the management of various conditions including acute, chronic, and obstetric pain. In acute pain situations, morphine can be used to relieve severe pain associated with postoperative pain, fractures, trauma, and various injuries. In this process, it can not only reduce the sensation of pain but also suppress the emotional and autonomic responses accompanying the pain. However, if the pain

is mild to moderate, nonsteroidal anti-inflammatory analgesics, which can be administered orally or intramuscularly, may be preferred; it has been reported that anti-inflammatory analgesics can be more effective than morphine in some types of postoperative pain. In colic and similar internal organ-related pains, it is recommended to determine the possible etiology before starting analgesics, as clinical monitoring and definitive diagnosis may become more difficult after analgesia [30]. Long-term use of morphine in chronic pain can lead to the development of tolerance and physical dependence. Therefore, in clinical approach, terminal cancer pain and non-cancerous chronic pain should be evaluated separately. In chronic pain other than terminal cancer, combined/non-opioid analgesic approaches should be reviewed first. In contrast, in terminal cancer patients, if pain cannot be adequately controlled with non-opioid analgesics, weak opioids or combinations thereof, the basic approach is the administration of morphine in appropriate doses and at regular intervals; if necessary, morphine-only therapy can be initiated. Cancer pain is one of the most established areas of morphine use [31]. Morphine has historically been an important option in obstetric analgesia. Labor pain is considered one of the most severe pain experiences in clinical practice, and current guidelines emphasize the need for effective treatment of labor pain. Morphine has been used in obstetric analgesia in situations where regional methods are not feasible, but its use has significantly decreased today due to maternal effects such as nausea and vomiting, delayed gastric emptying, sedation, and hypoventilation, as well as the risk of neonatal sedation/respiratory depression that may develop due to its crossing the placenta. Although titration can be facilitated by reducing variability in peak plasma levels with small dose intravenous boluses, the risk of neonatal depression is not completely eliminated [28]. The route of morphine administration is chosen according to the clinical situation. Oral use is often initiated at 10 mg every 4 hours and can be increased according to response; in hospitalized patients at low risk of respiratory depression, it is stated that the dose can be increased up to 30 mg every 4 hours for severe acute pain. In terminally ill cancer patients, oral morphine is widely used in accordance with the World Health Organization approach, with an initial dose of usually 5-10 mg, and the daily dose is gradually increased if insufficiency occurs. After determining the daily requirement with short-acting preparations, a switch can be made to slow-release preparations administered every 8-12 hours; oral solution forms can be used in addition to tablets.

For intravenous administration, the starting dose is usually 1-4 mg and can be repeated at 1-4 hour intervals and increased as needed; titration with wider dose intervals can be performed in severe acute pain. In situations such as trauma, titration at more frequent intervals (e.g., every 5-15 minutes) may be considered

initially; the intervals should be extended after pain control is achieved. It is recommended to administer the drug slowly over several minutes; if analgesia is insufficient, dose adjustment and "rescue" boluses may be considered [32]. Intramuscular administration is usually planned as 5-10 mg every 3-4 hours, but it is less preferred due to injection pain, absorption variability, and delayed peak. In subcutaneous administration, adult doses may vary according to individual sensitivity; in children, dosing is done according to weight, and it should be remembered that frequent repeated injections may lead to local irritation. In rectal administration, doses and intervals can also be adjusted according to clinical need [33]. In neuroaxial applications, long-lasting analgesia in the lower extremity/pelvic region can be achieved by activating opioid receptors in the posterior horn of the spinal cord with very low doses via the intrathecal route; however, epidural application, which is considered more controlled due to the risk of respiratory/circulatory depression due to rostral spread, has gained prominence. Epidural application can provide rapidly onset and long-lasting regional analgesia in pelvic-abdominal-lower extremity pain; itching, nausea-vomiting, and urinary retention may occur. The most serious complications are respiratory and circulatory depression, and systemic absorption and/or subarachnoid spread may contribute. Furthermore, it is not recommended in chronic pain due to rapid tolerance and cross-tolerance. Morphine can also be administered intravenously/epidurally with patient-controlled analgesia systems [32,33].

2.6.2. Acute Coronary Syndrome: Acute coronary syndrome encompasses all clinical manifestations of myocardial ischemia resulting from decreased coronary artery blood flow; acute myocardial infarction, unstable angina pectoris, and sudden cardiac death, which can occur as a result of sudden disruption in coronary blood flow, are located at different points on this spectrum. Morphine may be preferred in patients with persistent ischemic chest pain despite maximum tolerated anti-ischemic treatment. However, routine use of morphine in acute coronary syndrome has been reported to be associated with more unfavorable clinical outcomes. Morphine is used to control fear, anxiety, and panic that accompany severe pain. Treatment is usually started with 4–8 mg of morphine administered intravenously; this is followed by additional doses of 2–8 mg at 5–15 minute intervals until pain subsides or signs of toxicity (hypotension, respiratory depression, or severe vomiting) appear. Intramuscular injections should be avoided as much as possible. Although doses of morphine reaching 2–3 mg/kg have been reported to be necessary and tolerated in some cases, the general approach is to avoid such high doses. In elderly and frail patients, halving the dose is appropriate, and it is known that morphine-induced hypotension and bradycardia respond favorably to atropine, while respiratory depression responds

favorably to naloxone [34, 35]. In a study on patients with segment elevation acute myocardial infarction, patients treated with morphine in addition to other treatments were compared with those who were not treated; patients who had morphine added to their treatment benefited in many cases, especially in survival, dyspnea and contrast-induced nephropathy [36].

2.6.3. Acute Pulmonary Edema: Acute pulmonary edema is a clinical condition requiring urgent treatment, characterized by impaired gas exchange due to increased fluid accumulation in the lungs. The underlying pathology is an abnormal accumulation of fluid in the interstitial space and alveolar cavities. In a normal adult, pulmonary capillary pressure averages 6-8 mmHg, and plasma oncotic pressure is approximately 28 mmHg. For fluid accumulation to occur in the alveoli, the pulmonary capillary wedge pressure needs to increase by an average of four times. The main mechanisms leading to this increase are the rise in pulmonary capillary pressure and/or the increased permeability of the alveolar-capillary barrier. Morphine can be used to reduce the patient's stress, suppress respiratory workload and sympathetic discharge, and consequently reduce the preload and posterior load on the heart. For this purpose, 5-10 mg is usually administered intramuscularly; in severe cases, 3-5 mg can be given intravenously. It can be repeated at 15-minute intervals if necessary, but it is recommended that the total dose does not exceed 15 mg. If respiratory depression develops, naloxone at a dose of 0.4 mg can be administered intravenously every 2-5 minutes; the use of morphine is considered contraindicated in patients with severe chronic lung disease [35].

2.6.4. Dyspnea: Dyspnea (shortness of breath) is a common and significantly distressing symptom in patients with advanced cancer and those with non-cancerous life-limiting illnesses. The American Thoracic Society defines dyspnea as "a subjective experience of respiratory discomfort consisting of varying degrees of severity and qualitative differences," and states that morphine therapy may be initiated in cases where dyspnea persists despite maximum treatment for the underlying disease. In patients who have not previously used opioids, 2.5 mg can be administered orally every 2 hours for moderate dyspnea; if necessary, the dose can be adjusted to 5 mg every 2-4 hours. In severe dyspnea, it is recommended to initially administer 2.5 mg intravenously, and if well tolerated, repeat the dose via the same route at 15-30 minute intervals. In patients who have developed opioid tolerance, it is considered appropriate to increase the dose according to the clinical response [37]. In a randomized, double-blind, controlled study, the effects of placebo and morphine administration on the severity of dyspnea were compared using the Visual Analog Scale (VAS) in patients with metastatic lung involvement causing dyspnea and underlying diseases of lung

cancer, breast cancer, or bladder cancer in a 120-bed geriatric hospital for 9 months, and it was shown that the severity of dyspnea decreased in the group given morphine [38].

2.6.5. Acute Left Heart Failure: Morphine is reported to have a protective effect in heart failure by increasing atrial natriuretic peptide levels. Clinical evidence suggests that its use is more supported in patients with acute heart failure compared to those with end-stage/advanced heart failure. Morphine is usually administered by injection in doses of 5-10 mg to relieve dyspnea caused by pulmonary edema in acute left heart failure. Hemodynamically, morphine reduces the backload of the heart by causing vasodilation and peripheral pooling in the venules, and reduces the preload by reducing peripheral vascular resistance. In addition, it can provide symptomatic relief by reducing anxiety in the patient. In some cases, oxygen inhalation may accompany morphine treatment to correct hypoxia [39]. A study conducted in patients diagnosed with chronic heart failure evaluated the effects of morphine on pulse, respiratory rate and blood pressure. Patients were monitored for 4 days receiving either oral morphine solution or placebo; it was observed that low-dose oral morphine administration generally resulted in few side effects and chronic dosing was well tolerated in patients with advanced chronic heart failure [40].

2.6.6. Chronic Cough: Cough lasting 3-8 weeks is defined as subacute cough, and cough lasting longer than 8 weeks is defined as chronic cough. Chronic cough is a symptom frequently encountered in chest disease outpatient clinics, mostly associated with chronic lung diseases, but in some cases it can also be seen due to non-pulmonary causes. Morphine, which can have an antitussive effect, is considered an effective option in certain patient groups, especially in chronic (refractory) cough. In this context, morphine can be used in cases of severe cough that do not respond to codeine or non-opioid antitussives [41]. In a study conducted in a cough clinic, slow-release morphine sulfate or equivalent placebo was administered for 4 weeks and it was shown that morphine provided clinically significant benefit in severe and persistent chronic cough [42].

2.6.7. Preanesthetic Medication/ Balanced Anesthesia/ Neuroleptic Anesthesia-Neuroleptic Analgesia: Administering one or more drugs to the patient before general anesthesia is called "preanesthetic medication". This practice facilitates the patient's more comfortable administering anesthesia, makes it easier to maintain anesthesia, and contributes to the anesthesiologist working in safer conditions. The main goal is to prepare the patient for the surgical procedure both psychologically and pharmacologically. In this context, morphine, thanks to its analgesic effect, can help shorten the awakening time by reducing the need for anesthesia. To reduce possible side effects of morphine

(such as nausea, dizziness, flushing, and respiratory depression), its use in combination with other drugs may be considered. Since morphine frequently causes vomiting, it is considered contraindicated in intraocular surgeries. In cases where morphine is administered, pulmonary secretions may accumulate in the postoperative period due to the significant suppression of the cough reflex, and this may pose a risk for the development of atelectasis, especially in patients with lung disease [30]. Morphine, a substance used in premedication for many years, produces sedation, reduces fear, and may cause euphoria in a small number of patients. However, it can increase the likelihood of preoperative and postoperative nausea and vomiting. While it can cause hypotension and bradycardia, these effects are generally not significant as long as the patient remains in a supine position. It can relieve existing pain and its analgesic effect usually lasts 4-6 hours. Carbon dioxide retention due to respiratory depression may develop; this can lead to cerebral vasodilation and increased intracranial pressure. It can also increase the risk of constipation and urinary retention in the postoperative period [43].

In one study, the effects of morphine administration at different times were evaluated in female patients scheduled for abdominal hysterectomy, and morphine sulfate was administered in three different administration schemes: intramuscular morphine 1 hour before surgery (i.m.-pre), preoperative intravenous morphine during anesthesia induction (i.v.-pre), and postoperative intravenous morphine after surgery (iv-post). At the end of the study, it was determined that the total morphine dose administered in the i.m.-pre and i.v.-pre groups was lower compared to the i.v.-post group. In parallel, it was shown that low-dose preoperative morphine administration reduced the need for morphine in the postoperative period [44].

In addition to nitrous oxide inhalation, general anesthesia is maintained by administering an opioid and one or more short-acting barbiturates intravenously at appropriate intervals throughout the anesthesia, and a neuromuscular blocking agent as needed. This approach is called "**Balanced anesthesia**". In this method, premedication is performed by giving an opioid analgesic before anesthesia. Morphine is often preferred as an opioid analgesic in balanced anesthesia, especially in cardiac surgery and in high-risk patients. This is because morphine, even at high doses, does not cause a significant undesirable deterioration in myocardial function and hemodynamic dynamics, and allows for the adequate maintenance of cardiac output. In balanced anesthesia, morphine is usually administered intravenously at a dose of 1-3 mg/kg as a slow infusion spread over 15-20 minutes. Naloxone may be given after surgery if necessary to eliminate the residual effects of morphine on respiration and consciousness [45].

“**Neurolept analgesia**” is an analgesia method achieved by administering an opioid drug in combination with a neuroleptic such as droperidol intravenously. The combined use of morphine and droperidol produces a significant sedation and indifference to environmental stimuli, however, consciousness is not completely lost and the patient does not completely lose the ability to follow commands. If nitrous oxide inhalation is also applied in addition to neurolept analgesia and anesthesia is achieved with this combination, this application is called “neurolept anesthesia” [10,29].

2.6.8. Diarrhea: Diarrhea is defined as "passage of ≥3 loose or watery bowel movements per day according to a typical diet or passage of ≥200 g of stool per day". Since one of the main pathophysiological components of diarrhea is increased intestinal motility, drugs that reduce bowel movements and transit speed may be beneficial in symptom control. Morphine suppresses intestinal motility via μ-opioid receptors in the gastrointestinal system and prolongs transit time; this effect may contribute to the reduction of diarrhea by increasing net fluid/electrolyte absorption. The European Society of Medical Oncology's clinical practice guidelines for diarrhea in adult cancer patients include deodorized opium tincture (equivalent to 10 mg/mL morphine) as an alternative to loperamide; the recommended dosage is 10-15 drops every 3-4 hours. However, it is emphasized that studies supporting this approach with a strong level of evidence are limited and the current recommendations are based on a lower level of evidence [37].

2.6.9. Mucositis: Mucositis refers to inflammatory-erosive-ulcerative lesions that can develop in cancer patients undergoing chemotherapy and/or radiotherapy, appearing on various mucosal surfaces, primarily in the oral cavity and gastrointestinal system. Therefore, the condition may manifest with symptoms such as burning and pain in the mouth, diarrhea if there is gastrointestinal involvement, and vaginitis/vaginal pain if there is vaginal involvement. Oral mucositis, in particular, is a significant source of pain and loss of quality of life in patients receiving radiotherapy and/or chemotherapy to the head and neck region. Topical morphine applications are among the approaches aimed at reducing this symptom burden. In studies in the literature, it has been shown that topical morphine can reduce mucositis pain and associated symptoms in studies where morphine gargle alone ("morphine rinse") or in mixtures prepared with antacids, viscous lidocaine, etc., is used comparatively [46]. A study conducted in adult patients with oral mucositis pain due to chemotherapy and/or radiotherapy reported that mouthwash containing morphine reduced oral pain. Vaginal mucositis (vaginitis) is an acute inflammatory condition characterized by erythema and erosion of the vaginal mucosa, which can lead to

severe vaginal pain, discharge, and related complications. In vaginal mucositis, it has been reported that approaches such as the "magic vaginal douche" containing "morphine + viscous lidocaine" and other antiseptic/antimicrobial components can provide symptomatic relief; however, this use is mostly based on case reports and the level of clinical evidence is limited [46, 47].

2.7. Contraindications

Morphine is contraindicated in patients with significant respiratory depression, acute bronchial asthma attack, and severe chronic respiratory failure. In cases with head trauma or increased intracranial pressure, it may worsen the clinical picture by causing cerebral vasodilation due to carbon dioxide retention. In cases of hypovolemia and shock, caution should be exercised due to the risk of developing severe hypotension due to vasodilation. Caution should be exercised in patients at risk of paralytic ileus, significant biliary tract spasm, and urinary retention (Table 2) [33].

Contraindications	Relative Contraindications/ Points to Consider
Hypersensitivity, Significant respiratory depression in an unmonitored/unequipped environment, Acute/severe bronchial asthma (especially unmonitored), Gastrointestinal obstruction / paralytic ileus.	COPD/low respiratory reserve, sleep apnea, obesity Hypovolemia, hypotension, shock, Head trauma, altered consciousness, Biliary tract disease/acute pancreatitis, Seizure disorder, Renal/hepatic failure, Elderly, opioid-sensitive patients, Pregnancy, childbirth, breastfeeding (indication/alternative and monitoring required).

Table 2: Contraindications of morphine.

2.8. Side Effects of Morphine

The most serious adverse effect of morphine is dose-dependent respiratory depression, which may be more pronounced in patients with increased sensitivity to opioids. Sedation, confusion, miosis, and dizziness are among the frequently encountered central effects. Constipation, nausea, and vomiting are commonly seen in terms of the gastrointestinal system. Itching, redness, and orthostatic hypotension may develop due to histamine release. Urinary retention is also among the side effects that may occur. The development of tolerance and physical dependence with long-term use is a clinically significant problem (Table 3) [48].

Percentage	Type of Side Effects
>% 10	Itching (≤80%) Urinary retention (Epidural/Intrathecal) (15-70%) Vomiting (7-70%) Constipation (>10%) Headache (>10%) Drowsiness (>10%)
% 1-10	Abdominal pain (5-10%) Asthenia (5-10%) Back pain (5-10%) Depression (5-10%) Diarrhea (5-10%) Dyspnea (5-10%) Fever (5-10%) Insomnia (5-10%) Loss of appetite (5-10%) Nausea (5-10%) Paresthesia (5-10%) Peripheral edema (5-10%) Rash (5-10%) Sweating (5-10%) Xerostomia (Dry mouth) (5-10%) Respiratory depression (Intrathecal) (4-7%) Anxiety (6%) Dizziness (6%) Abnormal liver function test results (<5%) Amblyopia (<5%) Hiccups (<5%) 5) Orthostatic hypotension (<5%) Syncope (<5%) Urinary retention (Oral) (<5%)
<% 1	Respiratory depression (Epidural) (% 0.25-0.4)
Frequency Undefined	Anaphylaxis (Rare) Cardiac arrest

	Circulatory depression
	Presence of intracranial pressure
	Ileus
	Dizziness
	Weakness
	Miosis
	Myoclonus
	Shock
	Thinking disorders
	Vertigo

Table 3: Side effects and percentages associated with morphine use.

2.9. Special Cases

2.9.1. Pregnancy: During pregnancy, long-term use of morphine for medical or non-medical purposes can lead to physical dependence in the newborn shortly after birth and neonatal opioid withdrawal syndrome. Because morphine can cross the placenta, it carries the risk of causing respiratory depression and various psychophysiological effects in the newborn; therefore, an opioid antagonist such as naloxone should be readily available to reverse opioid-induced respiratory depression in the newborn. Morphine use during and before labor is generally not recommended when shorter-acting analgesics or alternative analgesia techniques are available. One reason for this is that morphine can prolong labor by temporarily reducing the strength, duration, and frequency of uterine contractions. Morphine is classified as pregnancy category C [49].

2.9.2. Breastfeeding: Morphine can pass into breast milk, and it has been reported that variable morphine concentrations are detected in breast milk after the use of rapidly released morphine in the early postpartum period in breastfeeding women. However, the current data are not sufficient to clearly reveal the effects of morphine on breastfed infants and its possible effects on milk production [49].

2.9.3. Renal Failure: Morphine clearance is generally similar in patients with normal renal function and those with impaired renal function. However, morphine glucuronide metabolites tend to accumulate significantly as renal function decreases. As this accumulation progresses, toxicity symptoms such as central nervous system depression, increased sedation and more severe/prolonged respiratory depression may occur in patients [50].

2.9.4. Hepatic Impairment: Although it has been reported that no significant change in the pharmacokinetics of morphine has been identified in patients with mild hepatic impairment, it is stated that extrahepatic metabolism of morphine may occur to a considerable extent. In contrast, the observation of an increase in the half-life of morphine in patients with cirrhosis may indicate the need for dose reduction and/or extension of the dose interval in this group [50].

2.10. Synthetic Morphine Agonists

Meperidine: A synthetic opioid derivative of phenylpiperidine, it is one of the first examples to enter clinical use among those exhibiting morphine-like effects. Its effect profile is generally similar to morphine; due to its strong local analgesic effect, it may be preferred for administration via epidural, especially during childbirth. Unlike morphine, it is not used in the treatment of cough and diarrhea**.**

Fentanyl, Remifentanil, Sufentanil, and Alfentanil: These are among the opioid analgesics with the highest gravimetric analgesic efficacy. Fentanyl and sufentanil are used in anesthesia, particularly for analgesia via epidural administration in the postoperative period or during childbirth, due to their rapid onset and short duration of action. The use of other analgesics besides fentanyl is not widespread as a routine analgesic [10].

Methadone: A synthetic opioid derivative of diphenylpropylamine used in the treatment of chronic pain. The most important difference from morphine is that the effect starts later and lasts longer. With repeated doses, the duration of effect can be extended up to 48 hours. It is also used in the treatment of opioid addiction [10].

2.11. Morphine Antagonists

The developments that can be considered a turning point in antagonist therapy began with the development of the partial antagonist known as N-allylnormorphine (nalorphine). In 1954, it was shown that the nalorphine molecule possessed both agonist and antagonist properties, and in the subsequent period, naloxone and naltrexone entered clinical use. These exert their antagonistic effects primarily through μ-opioid receptors; much higher doses are generally needed to produce a significant effect through κ and δ receptors. Naloxone and naltrexone, being competitive antagonists, do not produce a clinically significant effect in the absence of an opioid agonist. Naloxone, the first narcotic antagonist to enter medical use, is more potent than nalorphine and exhibits a fully antagonistic effect. It does not produce psychomimetic effects, does not cause respiratory depression, and has no potential for developing addiction. In acute opioid analgesic poisoning, it is usually administered intravenously at 2 mg in adults and children; the dose can be increased if high

dose opioid ingestion occurs. Since the duration of action is short, the dose is repeated at 20-60 minute intervals if necessary. Naltrexone is another full antagonist with a significantly longer duration of action (24-48 hours) compared to naloxone [51].

2.12. Acute Morphine Poisoning

Acute morphine poisoning most often occurs as a result of suicide attempts and overdose in opioid addicts. The clinical picture classically features three main findings:

1. Coma / marked depression of consciousness
2. Severe respiratory depression and often irregular breathing
3. Symmetrical, marked miosis in the pupils (pinpoint pupils).

The respiratory rate is significantly reduced; an irregular breathing pattern may develop, and if left untreated, death is usually due to respiratory arrest. Hypothermia, muscle weakness, and loss of consciousness may accompany the picture. Pupil dilation may be seen due to asphyxia developing in the terminal stage. The basic approach in treatment is airway and respiratory support along with the administration of the opioid antagonist naloxone, naloxone is given intravenously, and the patient is monitored with supportive methods [52]. The cornerstone of treatment is securing the airway, supporting respiration, and administering an opioid antagonist. Repeated doses of naloxone may be administered if necessary. If oral ingestion occurs, early gastrointestinal decontamination may be considered. Patients should be closely monitored for hemodynamic and respiratory parameters [53].

3.Substance Addiction

3.1.The Concept of Narcotic Substances

Narcotics, a term derived from the Greek word "Narke" (sleep), refers to substances that have a narcotic effect and can cause addiction.

According to the World Health Organization, narcotic substances are defined as substances that create an irresistible craving or desire, a tendency to increase the amount of substance used, and a state of psychological and physical dependence; they also alter bodily functions in living organisms, cause physical and mental immobility, and create stagnation in the central nervous system.

For a substance to be considered a narcotic, it must:

1. Be designated and declared in lists governed by international agreements,
2. Have a toxic effect,

3. Show a tendency to use it in increasing amounts,

4. Cause physical, psychological, or both dependence upon use, and produce withdrawal symptoms upon discontinuation.

Two types of addiction can develop in a person to narcotic substances. The first is "**physical dependence**". It is defined as the physiological state in which the body establishes a new balance with the substance and withdrawal symptoms are seen when it is not taken. Often, psychological symptoms accompany this condition and tolerance develops along with physical dependence. The other is "**psychological dependence**", which manifests itself with the urge to continue taking the substance, and in this context, morphine is a substance that causes strong psychological dependence [54].

3.2. The Concept of Substance Addiction

Substance addiction is a condition resulting from the non-therapeutic use of substances that affect the central nervous system and alter behavior, leading to physical, mental, and social problems. In other words, it is a situation where, despite the negative effects of a substance causing physical, psychological, and social problems, the desire to use it continues to increase, and the craving cannot be suppressed despite the desire to quit [55].

Substance abuse and addictive substances were not considered a serious public health problem until the 1960s. During these years, while the addictive nature of substances like cannabis, barbiturates, and alcohol, and the fact that substance abuse is a behavioral disorder, entered the medical literature, studies on their causes, treatment, and prevention began to become widespread from the 1980s onwards. Substance abuse is a growing social problem faced by all countries worldwide. It causes serious harm, primarily to the individual, but also to their family and society. Addictive substances can lead to many situations that negatively impact social life, such as troubled childhood and adolescence, unsuccessful academic life, irregular work life, and problematic marriages and family life. Many personal, environmental, and familial factors can contribute to the development of substance addiction, sometimes individually and sometimes in combination. A person's introduction to substances may occur within the family environment, or later in life within a family they form, or a family with addictive members may be formed if the individual marries while using substances. Parental parenting attitudes have been shown to have a significant impact on individuals developing addictive behaviors. Minimizing interaction within the family, a constant atmosphere of conflict, and inconsistent and inconsistent messages from parents to their children all contribute to individuals turning to addictive substances. The vast majority of addicts come from broken

families, and alcohol and substance abuse is common in their families. There are many studies on the causes of drug addiction. According to these studies, eight important factors are closely related to drug use [55]:

1. Personality problems,
2. Poor environment,
3. Adjustment problems,
4. Peer influence,
5. Usage areas,
6. Lack of self-esteem,
7. Weak ego,
8. Stress.

According to the Diagnostic and Statistical Manual of Mental Disorders, a person who exhibits all or some of the following symptoms repeatedly for at least one year may be considered "**substance dependent**":

1. Significantly increasing the dose or repeatedly taking the same dose to experience the pleasurable effect of the substance, resulting in the inability to perceive the initial pleasurable effect (i.e., development of tolerance to the effects of the substance),

2. Exaggerated increase in the frequency and amount of substance use,

3. The occurrence of withdrawal symptoms when the substance is not taken, and these symptoms lessen or disappear completely with substance use,

4. Unsuccessful attempts to control or completely stop substance use,

5. The individual spending a significant amount of time on activities related to obtaining and stockpiling the substance.

6. The gradual decrease in social and work activities due to substance use,

7. The emergence of physical and psychological symptoms due to the substance used and the continuation of substance use even knowing that these symptoms are caused by the substance used. Among the above symptoms, especially the development of tolerance, withdrawal crisis and the disappearance of the crisis when the substance of addiction is taken are the most valid and sufficient symptoms for making a definitive diagnosis of addiction. An important point to note is that in many substance addicts, some symptoms of withdrawal

crisis such as tremor, agitation, muscle cramps and epileptic seizures can be confused with the symptoms of other diseases. Substance-related crises can only disappear completely when the substance in question is taken [56].

3.3. Disorders Caused by Substance Use

Substance Intoxication: A reversible substance-specific syndrome develops as a result of recent ingestion (or exposure to) a substance. Clinically significant inappropriate behavioral or psychological changes occur during or immediately after substance use, and are due to the substance's effect on the central nervous system; these symptoms are not attributable to a general medical condition and cannot be explained by another mental disorder [57].

Substance Withdrawal: A substance-specific syndrome develops as a result of the cessation of excessive and prolonged substance use. This substance-specific syndrome causes clinically significant distress or impairment in social, occupational or other important areas of function. These symptoms are not due to a general medical condition and cannot be explained by another mental disorder [57].

3.4. Assessment of Addicts

Assessment objectives:

- To establish the diagnosis or diagnoses,

- To determine suitability for treatment,

- To make initial treatment recommendations and plans,

- To plan for psychosocial treatment,

- To ensure there are no contraindications for the recommended treatments,

- To identify other medical comorbidities and conditions and consult other departments during early treatment if necessary,

- To identify other psychiatric and psychosocial conditions and consult other departments during early treatment if necessary [57].

Analysis of samples taken regularly from a person allows for the creation of a detailed profile of that person's substance use. Addictive substances can be detected in samples such as urine, blood, saliva, hair, sweat, and exhaled air. Biological fluids are considered the most suitable samples for detecting drug use. Drug testing consists of immunoassay screening followed by confirmation with GC and MS. It is essential that they are confirmed with methods and devices such as GC/MS, LC/MS, and LC/MS/MS that provide definitive identification [58].

3.5. Opioid Use Disorder

Classification of opioid use disorders [57]:
-Opioid dependence,
-Opioid abuse,
-Opioid-induced disorders,
-Opioid intoxication,
-Opioid withdrawal,
-Opioid intoxication delirium,
-Opioid-induced psychotic disorder; with delusions,
-Opioid-induced psychotic disorder; with hallucinations,
-Opioid-induced mood disorder,
-Opioid-induced sexual dysfunction,
-Opioid-induced sleep disorder.

4. Morphine Addiction

4.1. History

While it's not certain whether Sertürner, the first discoverer of morphine, was addicted to it, it's thought he was very close to the first recognition of this phenomenon. After the introduction of subcutaneous injections of morphine by Charles Gabriel Pravaz in 1853 and Alexander Wood in 1855, morphine addiction rapidly increased in Central Europe. In 1850, the Scotsman Robert Christison described "withdrawal" as the abrupt or gradual cessation of morphine administration. This is evidence that morphine addiction emerged in the 19th century and that there were those who hoped to control it through therapeutic methods [4].

The role of military incidents involving morphine in Europe and the United States, and the related injuries, make the first waves of morphine addiction understandable. During these wars, the practice of wounded soldiers pricking their hands to alleviate pain became uncontrolled, leading to the rapid spread of morphine addiction. The difficulties faced by addicts returning to their post-war communities, their struggles to reintegrate into society, the illegal activities they resorted to in their search for the substance, and the resulting rise of new addicts, all significantly contributed to understanding the seriousness of substance abuse as a public health problem [4].

In 1911, the Hague Convention in the Netherlands addressed the issue of narcotics; Germany joined the Convention in 1920 with the German Opium Act. From 1946 onwards, the United Nations assumed centralized administration, with appropriate national and international legislation following in short intervals. In the second half of the 19th century, curative methods of combating addiction

were limited to only partial and often temporary successes, driving people to seek alternative methods [4]. In the 1950s, when attempts were made to synthesize centrally acting analgesics free from side effects that could replace morphine, a group of compounds were synthesized, the best known being **meperidine** and **methadone**. Expectations regarding the central analgesic effect of these drugs were met, but the hope that the habit-forming component would be eliminated was not fulfilled. Therefore, in 1953, a new approach was taken to restrict habituation by law. The consequences of the American Civil War and the prescribing habits of American doctors led to the enactment of the "Harrison Act" by the American Congress. This law became the basis of a worldwide control system for the use and addiction to opioids [4].

The Hippie movement, which was widespread in Western Europe in the late 1960s, fueled by its initial tolerant approach, quickly created an environment for the abuse of addictive substances among young people. Although these groups were primarily known for their anti-war activism and music, they significantly contributed to the spread of substance abuse and addiction. Even today, substance abuse is often concentrated among members and fans of certain hard rock and metal bands [59].

Because Turkey is a transit country, this abuse has increased in our country as well, and the production of "cocaine and narcotics" was banned by a decree in 1925. From 1933 onwards, poppy cultivation and opium production in Turkey were brought under government control, the provinces where cultivation would be allowed were determined by the Council of Ministers every year, and from the autumn of 1972 onwards, poppy cultivation and opium production were completely banned. Morphine addiction and nowadays more commonly heroin, which is a diacetyl derivative of morphine, have become an increasingly serious social problem [59].

4.2. Etiology

Morphine addiction is considered a biopsychosocial disorder in which multiple factors interact in terms of initiation of use, continued use, and relapse after abstinence. These include pharmacological, social, environmental, personality, psychopathology, genetic, and familial factors [57].

Psychosocial factors: Although the incidence of opioid dependence is higher in lower socioeconomic classes compared to higher socioeconomic classes, it is not limited to lower socioeconomic classes alone [59].

Biological and genetic factors: There is evidence that factors increasing the likelihood of developing substance dependence are genetically transmitted. Monozygotic twins have a higher risk of opioid dependence compared to

dizygotic twins. Individuals with morphine-related disorders may have a genetically determined hypoactivity in the opioid system, and it is being investigated whether this hypoactivity is due to too few or undersensitive opioid receptors, too little endogenous opioid release, or a high concentration of the presumed endogenous opioid antagonist. It is thought that biological predisposition to morphine-related disorders may be due to impaired functionality in dopaminergic or noradrenergic neurotransmitter systems [57].

4.3. General Characteristics

Morphine addicts most often take morphine subcutaneously; it is also used intravenously, intramuscularly, and as a nasal solution. When taken subcutaneously, 60% is absorbed in the first 30 minutes; absorption is faster when taken through the nasal mucosa or parenterally. With intramuscular administration, it reaches maximum levels in the blood in 60-90 minutes; with oral administration, distribution to the kidneys, liver, lungs, and spleen reduces the effect of morphine. In chronic use, although tolerance varies, 200 mg is considered a lethal dose in adults. However, while 30-40 mg of subcutaneous morphine can cause severe poisoning in an intolerant person, it has been reported that a very high dose of 2000 mg in some toxicomaniacs only leads to decreased respiration [60].

Morphine metabolites, morphine-6-glucuronide and normorphine, have twice the analgesic effect of morphine but have less of a respiratory depressant effect. 90% of ingested morphine is excreted in the urine within the first 24 hours after ingestion as morphine-3-glucuronide, morphine-6-glucuronide, morphine-3,6-diglucuronide, and morphine sulfate. Morphine can also be detected in the use of codeine, heroin, and opium poppy. Morphine passes into bile, feces, and the fetus; after determining its presence in the blood, measuring the amount and ratio of free and total morphine is important in revealing deaths due to morphine overdose.

Heroin, a diacetyl derivative of morphine, is the most common and dangerous of all narcotic substances. Its greater availability and lower cost compared to morphine make it widely used throughout the world. It can cause sudden death by inducing respiratory arrest and asystole [61].

Heroin is the acetylated compound of morphine and is 2-3 times more potent than morphine. To separate the active substance, it is heated and melted, then administered usually intravenously, sometimes by snorting, and rarely by instilling it into a skin incision. When purchased from street vendors, it is used diluted with sugar, talc, soda, fluoride, and other drugs. The lethal dose is 200 mg, but addicts can use up to 10 times that amount. Absorption is rapid; 6-

monoacetyl-morphine (6-MAM) is detected in urine only after heroin use, and it is 4 times more potent than heroin. 6-MAM slowly converts to morphine in the blood. Heroin use is confirmed by the presence of 6-MAM in urine within the first 2-8 hours, and excretion can take up to 3-6 days [60, 61].

4.4. Current Situation

Substance addiction has become one of the most significant problems threatening public health on a global scale today. According to the United Nations Office on Drugs and Crime (UNODC) World Drug Report, approximately 292 million people, or about 5.6% of the world's population, have used drugs at least once. This rate has increased compared to previous years and reveals that substance use continues to spread globally. The report states that cannabis is the most frequently used substance, followed by opioids used through non-pharmaceutical routes, amphetamine derivatives, cocaine, and ecstasy. Within this picture, opioids have a special importance due to their addiction potential and high risk of death. In particular, the misuse of opioids such as morphine and heroin is characterized by the development of tolerance, physical and psychological dependence, withdrawal syndrome, and the risk of death due to overdose. Opioid-related deaths are a major cause of mortality worldwide, and the uncontrolled use of these substances leads not only to individual health problems but also to increased economic burdens on health systems and social security issues. Therefore, opioid addiction is not only a clinical problem but also a multifaceted public health problem with social, economic and legal dimensions [62].

According to the 2025 Turkey Drug Report, the drug problem in Turkey has become more complex in recent years, not only due to an increase in quantity but also due to the diversification of substance profiles and the spread of higher-risk substances. The report emphasizes that drug markets are dynamic in terms of production-smuggling-use patterns, and that the risk is increased, especially due to the accessibility and rapid effects of synthetic substances. The report states that new generation substances pose a significant threat, particularly to the young population, due to their low cost and easy accessibility, and therefore the fight against drugs should not only focus on security but also be carried out with multidisciplinary and holistic strategies that include health and social dimensions. Current reports in the field of drugs emphasize the importance of holistic approaches based on monitoring risky substance groups by considering indicators such as use, smuggling, treatment, and substance-related deaths together [62, 63].

The Turkish Drug Report states that the devastating effects of synthetic opioids on a global scale have increased the need for sustainable strategies in the fight against them. In this context, morphine addiction is a multidisciplinary issue

requiring assessment, representing a delicate balance between the necessity of clinical use and the risk of abuse/addiction. In Turkey, the fight against substance abuse is carried out through a multi-component structure that includes early intervention, referral to treatment, clinical treatment, psychosocial support, and follow-up. Within this framework, **the ALO 191 Drug Addiction Counseling and Support Line** is a crucial first point of contact that provides counseling on substance use/addiction, directs individuals to appropriate health units, and facilitates the follow-up of the application process when necessary. Through ALO 191, individuals and families can obtain information about access to treatment, legal processes, and application procedures [63].

At the primary care level, **Healthy Life Centers (HLCs)** and their psychosocial support units provide counseling and assessment to individuals at risk of addiction and their families, refer cases requiring treatment to appropriate specialist services, and offer follow-up support throughout the process. At the clinical treatment stage, **AMATEM** and **ÇEMATEM** units provide detoxification, addiction treatment, and, when necessary, inpatient/outpatient follow-up services [63].

Another important structure supporting the continuity of the treatment and recovery process is the **Yeşilay Counseling Centers (YEDAM)**. YEDAM plays a complementary role to clinical treatment by providing psychosocial counseling, motivational support and structured interviews aimed at preventing relapse for addicted individuals and their families. Thus, the fight against addiction in Turkey is addressed in a more holistic way, not only through punitive sanctions but also through the operation of accessible counseling, treatment and rehabilitation services together within the health system [63].

4.5. Treatment of Morphine Addiction

There are two main pharmacological approaches to the treatment of morphine addiction: detoxification therapy and opioid maintenance therapy. The current approach is based on the combination of pharmacotherapy with psychosocial support; drug therapy alone is usually insufficient [10].

4.5.1. Detoxification Therapy

Detoxification aims to enable the patient to safely discontinue opioids and control acute withdrawal symptoms. It consists of two main phases: induction (stabilization) and dose reduction. Abrupt discontinuation is generally not recommended as it can lead to severe withdrawal symptoms [10].

This approach aims to discontinue the drug using appropriate methods, thereby clearing the addict from the drug. In many countries, it is performed as

rapid detoxification, where the goal is to shorten the duration of the acute phase of opioid withdrawal by using an opioid antagonist to remove morphine that binds to opioid receptors. Such an application results in a more intense, accelerated withdrawal syndrome compared to situations where the substance is stopped abruptly. It has been reported that if the procedure is initiated under anesthesia lasting 3-4 hours, acute withdrawal symptoms can be reduced to less than 2 days. Limited follow-up data is available on patients who have undergone this detoxification procedure, and there are few results showing it to be more effective than detoxification lasting 4-10 days, and the cost is concerning due to the medical complexity of the procedure. Many clinicians state that death is almost never seen in opioid detoxification treatments using traditional methods, and therefore rapid detoxification puts patients at unnecessary risk. Detoxification treatment generally consists of two phases: induction phase and dose reduction phase [64].

Induction Phase: Before starting treatment, the patient must have stopped using opioids and be experiencing early withdrawal symptoms. The aim of induction is to stabilize the patient as quickly as possible, reduce withdrawal symptoms as much as possible, and eliminate the possibility of future illicit opioid use. The dose reduction phase is only started in patients who have completely stopped using opioids; if the patient is not in a controlled environment, the cessation of opioid use must be documented by toxicology tests [64].

Dose Reduction Phase:

-**Long-Term Reduction**; Although there is little research on this subject, the literature argues that long-term gradual Buprenorphine detoxification is more effective than short- and medium-term rapid detoxification. Patients who do not have access to agonist therapy, rehabilitation services, or do not wish to apply for them may not be suitable for short-term detoxification; such patients may only benefit from long-term detoxification [57].

-**Medium-Term Weaning**; For patients who do not require short-term detoxification and whose aim is to get rid of morphine, detoxification can be done with a gradual treatment of 10-14 days, starting with stabilization and reducing the dose every 2-3 days. It is very important for patients who adhere to the rehabilitation program during the detoxification treatment to continue to adhere to the treatment program after the detoxification process is completed [64].

-**Short-Term Reduction**; For patients who need to get rid of morphine quickly, a treatment protocol can be applied in which the dose is reduced and discontinued within 3 days [57].

Detoxification treatment can be examined under 3 headings:

1. Detoxification with opioid derivatives

2. Detoxification with non-opioid drugs

3. Unconventional approaches to detoxification

4.5.1.1. Detoxification with Opioid Derivatives

Methadone: There is extensive clinical experience with the use of methadone in the treatment of opioid withdrawal. Methadone is effective in suppressing withdrawal signs and symptoms and can be safely administered under clinical supervision. In hospitalized patients, the primary goal is to ensure an adequate dose of methadone to control withdrawal. The initial dose is usually 10–30 mg orally, reassessed within 2–4 hours according to clinical need; if an additional dose is required on the first day, it is generally recommended not to exceed 10 mg, and the total dose should be kept within the range of 30–40 mg/day in most protocols. Dose titration is based on clinical history and current symptoms rather than waiting for spontaneous withdrawal symptoms. After stabilization is achieved, dose reduction is planned, and detoxification can be completed in approximately 7-14 days in most protocols. Since the relative potency of methadone compared to morphine is not constant and can vary depending on the previous opioid dose, equivalence calculations should be done carefully and titration with close monitoring should be preferred [65].

It has been reported that in outpatient methadone withdrawal treatment, slow dose reduction (e.g., approximately 3% per week) can be more successful than rapid reduction (e.g., 10% per week); furthermore, informing patients about the process and expected withdrawal symptoms can affect the results. Therefore, methadone dose reduction in outpatient patients can take weeks–months in most cases [64]. Methadone withdrawal treatment outcomes are generally quite poor, relapse is frequent, and clinical experience shows that patients are less likely to start using illicit opioids when the methadone dose is reduced below 20–25 mg/day. Patients with stable clinical conditions and slowly reduced methadone doses usually experience problems at doses of 30 mg/day and lower. Withdrawal symptoms begin to appear between methadone dosings when doses fall below 30 mg/day. When long-term results are considered in methadone detoxification, it has been observed that patients with a short history of substance use and who remain in treatment for a relatively long time but are used at lower doses are more successfully detoxified [57].

Levometadyl acetate (LAAM): LAAM, a long-acting opioid agonist approved by the FDA in 1993 for use in the treatment of opioid dependence, is a

complete opioid agonist like methadone. The long half-life of LAAM and its metabolites provides the advantage of long daily dose intervals. A decrease in morphine cravings has been observed with high-dose LAAM use, but since agonist effects are greater and consequently treatment discontinuation rates are higher, it is recommended that LAAM dose increases be made very slowly during treatment [57].

Buprenorphine: Buprenorphine is a reliable and effective drug for opioid withdrawal treatment. Buprenorphine has a relatively long duration of action. Patients tolerate withdrawal well, with minimal symptoms for 3-5 days and without significant stress complaints. In patients treated with buprenorphine on an outpatient basis, the use of hypnosedative drugs (especially benzodiazepines) is contraindicated. The sublingual form of buprenorphine is permitted for the treatment of opioid dependence and withdrawal, and is marketed in two forms:

1. Monotherapy product

2. Combination therapy product containing naloxone.

In patients receiving opioid agonist treatment with methadone or LAAM, a switch to medically monitored buprenorphine treatment can be made to relieve withdrawal, aiming for a comfortable recovery period from physical dependence under medical supervision. Switching from opioid agonist treatment to buprenorphine should be considered for patients with good medical and psychosocial stability [57].

4.5.1.2. Detoxification with Non-Opioid Drugs

α2-adrenergic agonists (Clonidine, Lofexidine) reduce autonomic withdrawal symptoms by suppressing locus coeruleus hyperactivity. Clonidine can cause sedation and hypotension; Lofexidine is preferred in some countries due to its lower risk of hypotension. These drugs do not prevent relapse, they only provide symptom control [57].

Clonidine: Clonidine, an antihypertensive drug, can be used to abruptly discontinue opioid use and alleviate withdrawal symptoms in patients relatively stabilized with low-dose opioids. Clonidine is started orally at a dose of 0.1-0.3 mg 3-4 times a day. Although higher doses (1.5-2.5 mg) may be used in hospitalized patients, it is not recommended that the total dose exceed 1 mg per day in outpatients. The main side effects seen with clonidine treatment are hypotension and sedation, which can be very serious; the dose should be carefully adjusted on an individual basis. Some studies have shown that outpatient treatment with clonidine is almost as successful as detoxification with methadone. Post-withdrawal muscle pain, lethargy, insomnia, restlessness, and

cravings are rarely observed with clonidine use. There is no evidence that it is effective in protecting against relapse after detoxification is complete. When the combination of clonidine and naltrexone is used regularly, the hospital stay required for detoxification has been shown to be less than 5 days [57].

Lofexidine: Although clonidine has been shown to be effective in the inpatient population, the same effect has not been replicated in the outpatient population. This is because patients receiving outpatient treatment have easier access to opioids, leading to sedation and orthostatic hypotension. Lofexidine is authorized and marketed in the UK for opioid withdrawal treatment. Since its authorization, there has been a steady increase in the sales of lofexidine in the UK, and it is more widely used than clonidine because it is believed to cause less hypotension. This medication has been shown to be effective in reducing methadone withdrawal symptoms, causes less hypotension than clonidine, and is clinically comparable to methadone in terms of overall efficacy, but it has not improved dependence, therefore it has not been licensed by many countries. The recommended doses are between 1.6-4.0 mg/day, and significant orthostatic hypotension has been observed in patients at maximum doses, which disappeared when the dose was reduced to 0.8 mg orally three times a day. Currently, the maximum dose in the UK is 2.6 mg/day [57].

4.5.1.3. Non-Traditional Approaches

Symptomatic treatments (analgesics, antiemetics, sleep regulators) can be used supportively. Although it has been suggested that methods such as acupuncture may increase endogenous opioid release, the level of evidence is limited. Opioid withdrawal is rarely life-threatening in healthy adults, and symptomatic treatment can be used to help the individual during spontaneous withdrawal. Medications to help with muscle and joint pain, nausea, vomiting, and sleep can be used. Acupuncture is used to alleviate opioid withdrawal. The release of endogenous opioids stimulated by acupuncture provides a rational basis for this approach [57].

4.5.2. Maintenance Therapy

Maintenance therapy is currently the primary treatment model for opioid addiction. The goal is to suppress withdrawal symptoms and substance-seeking behavior, reduce illicit opioid use, and improve the patient's social functioning. Medications used in maintenance therapy are divided into three groups: Full agonists (Methadone), Partial agonists (Buprenorphine), and Antagonists (Naltrexone) [57].

1. Agonists: They activate opioid receptors.

2. Antagonists: They do not bind to opioid receptors and produce activity. The high affinity of antagonists can displace the agonist from the receptor and cause sudden withdrawal syndrome in the addict.

3. Partial agonists: They bind to opioid receptors and produce limited effects. Partial agonists produce limited agonist effect when administered alone, and antagonist effect by somewhat inhibiting agonists when administered together [66].

Methadone, due to its long half-life, can be administered in a single daily dose and reduces the effect of illicit opioids by creating cross-tolerance. It is more effective at suppressing cravings at high doses.

Buprenorphine has a safer profile due to being a partial agonist and has a lower risk of respiratory depression. Treatment consists of induction, stabilization, and maintenance phases. Naltrexone is an opioid antagonist and blocks the euphoric effect [57, 66].

Methadone: Approved by the FDA in 1947 for analgesic and antitussive use, methadone was shown to be effective in treating opioid dependence in the mid-1960s and was approved in late 1972. Methadone is a typical μ-receptor agonist that produces euphoria, analgesia, and other typical morphine-like effects when administered acutely. The reliable absorption and bioavailability of methadone after oral administration, with peak plasma levels reaching 2-6 hours after ingestion, and its seemingly non-specific binding to tissues, creating a large methadone reservoir in the body, constitute a significant advantage for maintenance therapy. This methadone reservoir also tends to minimize sharp decreases that could trigger withdrawal. Thus, methadone can be administered once daily, and minor, short-term changes in the timing of administration do not lead to significant changes in biological effect. In patients undergoing methadone maintenance therapy, the half-life of the drug can range from 22 to 56 hours. Methadone alleviates cravings and withdrawal symptoms without causing patients to develop tolerance, thus allowing for consistent use without requiring dose increases to achieve sustained results. A daily dose of 80-100 mg of methadone is considered sufficient to suppress opioid cravings and block the effects of illicit opioids through cross-tolerance. When lower doses of methadone (<50 mg) are used, it has often been partially sufficient to keep patients on treatment and suppress drug-seeking behavior, but has not created sufficient cross-tolerance to high doses of morphine and heroin. Empirically, patients receiving lower doses of methadone maintenance therapy are prone to discontinuing treatment, and those who do so are unlikely to be able to maintain opioid abstinence. Patients who do not respond to methadone treatment are generally those who continue to use illicit opioids and other illicit substances,

those who consume excessive alcohol, those who do not attend programs regularly, and those who exhibit problematic behavior in the clinic [65].

The most common side effects of long-term use include constipation, which can sometimes lead to fecal impaction and intestinal obstruction, excessive sweating, decreased libido, and sexual dysfunction such as difficulty maintaining an erection. Opioids reduce plasma testosterone levels and plasma follicle-stimulating hormone (FSH) levels, but there is no strong correlation between abnormally low plasma levels of hormones and sexual dysfunction. Sleep disturbances and altered sleep habits are frequently observed in the first months of methadone treatment, and one of the side effects is mild to moderate withdrawal symptoms experienced before the next dose. Most patients do not develop tolerance to the euphoric effects of methadone [66].

Buprenorphine: Buprenorphine was first used in the treatment of opioid dependence in the 1960s. Buprenorphine is only a partial agonist and is widely used in primary care settings in Europe as an alternative to methadone in the treatment of opioid dependence. Buprenorphine and the Buprenorphine-Naloxone combination were approved by the FDA in 2002. Like methadone, buprenorphine and buprenorphine/naloxone have been shown to reduce hospital admission, morbidity, and mortality in maintenance therapy. Combining buprenorphine with the opioid antagonist naloxone exhibits the same benefits as buprenorphine alone while also reducing potential abuse [67]. Patients who are not physically dependent on opioids but have a known history of opioid dependence, have not been successful with other treatment methods, and need to discontinue opioid use may be suitable candidates for Buprenorphine. Patients without physical dependence should use the lowest possible Buprenorphine/Naloxone (2/0.5mg) dose, as withdrawal symptoms may occur with low and high dose Buprenorphine administration. In Turkey, maintenance therapy with Buprenorphine consists of 3 phases: induction, stabilization and maintenance phase [68].

Induction Phase: This is the first stage of the induction treatment protocol with buprenorphine and covers the transition process to buprenorphine in patients with opioid abuse. The aim of these stages is to find the lowest opioid dose at which the patient experiences no/minimal side effects, no withdrawal symptoms, no uncontrollable seeking behavior, and no need to use other opioids. Patients should avoid driving or operating other machinery until the buprenorphine dose stabilizes and they become accustomed to the effects of buprenorphine, which usually takes an average of 1 week [68].

Stabilization Phase: When the patient shows no withdrawal symptoms, distressing seeking behavior, or cravings, the induction phase is complete and the stabilization phase has begun. It usually lasts an average of 1-2 months.

-As with all pharmacotherapy, the aim in buprenorphine treatment is to achieve the expected benefit, the elimination of symptoms and signs, and the targeted laboratory findings at the minimum dose.

-The main goal sought in treatment is negative toxicology, which is the definitive proof of opioid cessation [67].

-The aim is to reduce the patient's self-reported illicit opioid use and craving. One goal is for the patient to start reporting little or no euphoria after self-administering opioids. Reducing positive opioid toxicology examples indicates successful treatment [68].

Maintenance Phase: This is the longest period the patient spends with buprenorphine. The length of this phase may be uncertain, physicians tend to be more relaxed during this period, but treatment still needs to be continued seriously. Psychosocial and family issues identified during the treatment process should be addressed, and other important issues include preventing cravings and opioid relapse [57].

Naltrexone: Theoretically, treatment with antagonists blocks the euphoric effects of opioids, leading to the exhaustion of acquired reinforced drug-seeking behavior and simultaneously preventing the re-establishment of physical dependence, thus relieving withdrawal symptoms. Its toxicity is low; however, the use of Naltrexone requires the clinician to ensure that the patient does not have continued physical dependence on morphine, as a single dose of naltrexone can rapidly cause a withdrawal syndrome lasting several hours. Naltrexone has been used in several clinical trials, and high rates of discontinuation have been observed; the most common side effect is nausea. Another major obstacle to the widespread use of naltrexone is premature discontinuation. Generally, patients come with a strong desire to stop, but they do not show up for an appointment during the final stages of detoxification and take a dose of morphine or heroin. Discontinuation of naltrexone does not cause withdrawal. There is a new treatment approach for naltrexone: "Depot Naltrexone". For this purpose, a 30-60 day long-acting injectable form of naltrexone is under development, in which naltrexone is combined with an insoluble polymer and released over a long period. With this treatment, it is envisioned that it will provide complete protection from opioid effects for up to 4 weeks [57].

LAAM (Levomethadyl acetate) : LAAM, like methadone, is an orally active μ-receptor agonist. It suppresses opioid withdrawal and blocks the effects of illicit

opioids. LAAM has a long biological half-life. Patients receiving high doses were more prone to discontinuation of treatment (compared to moderate and low doses). This indicates that careful dose adjustment is necessary when initiating LAAM in patients. It has been determined that some patients treated with LAAM develop prolonged QT intervals and potentially fatal arrhythmias. ECG monitoring before and during treatment should be part of the treatment plan for patients using LAAM; despite this safety issue, LAAM may be a beneficial agent for some patients [57].

4.5.3. Long-Term Treatment Approach and Treatment Termination

Treatment duration varies depending on the patient; it may last for months, and some patients may require lifelong maintenance. Long-term maintenance treatment has been shown to reduce illicit substance use and complications. Treatment success is assessed by negative toxicology, reduced cravings, and improved social functioning. Pharmacotherapy alone is insufficient without psychosocial support. Individual counseling, group therapies, and social rehabilitation are essential components of treatment; socioeconomic barriers affecting access to treatment should be considered, and the patient should be evaluated with a holistic approach. If the patient is stable, has a low risk of relapse, and can maintain a substance-free life, the dose can be gradually reduced. The termination process should be carried out in conjunction with psychosocial support; abrupt discontinuation may increase the risk of relapse [66].

4.6. Postmortem Examination

Postmortem examination in deaths related to morphine and other opioids requires the evaluation of crime scene findings, autopsy data, and toxicological analyses together. It is often not possible to determine the lethal dose precisely due to the development of tolerance. Therefore, the cause of death is determined by a holistic interpretation of the clinical history, pathological findings, and toxicological results. Immunoassay methods, which are rapid, practical, and suitable for screening a large number of samples, and mass spectrometry, liquid and gas chromatography, which provide advantages in terms of low cost and preliminary screening and are used in quantitative analysis with confirmation, are the most frequently used methods in the postmortem analysis of opioids. In forensic toxicology laboratories, a second specific method is usually applied to confirm the screening tests [60].

When evaluating morphine-related deaths, it should be determined whether the person has previously used opioids, whether there is pharmacological tolerance, and whether alcohol or other drugs were taken together with opioids. Knowing about other drug use will change the outcome. Morphine can usually

be detected in urine within 48 hours, and in some cases up to 72 hours. The presence of 6-MAM in heroin use is important for differential diagnosis. In opioid-related deaths, the presence of concomitant alcohol or other central depressants must also be investigated, as combined use significantly increases the risk of death [60].

In autopsies of cases suspected to be caused by drug use, urine samples, bladder lavage fluid (if the bladder is empty), skin, subcutaneous and muscle tissue from the area of the needle mark, and swabs from different body parts depending on the route of drug administration should be taken. If gastric lavage has been performed on the person due to intoxication, gastric lavage fluids should also be included in the toxicological examination. In autopsies of decomposed corpses, skin up to 10x10 cm, 100 gr of compact and spongy bone, and 250 gr of skeletal muscle can be taken for toxicological examination. Bile samples are important in morphine use; nasal mucosal samples are important in heroin use. Skin and intraocular fluid from the injection site and surrounding area are taken from intravenous morphine users for toxicological examination. Urine, blood, and internal organ samples should be taken for toxicological examinations; the most ideal samples are urine, brain, and kidney tissue [60].

In cases of intoxication, vital signs and consciousness should be assessed first, and basic and advanced life support should be provided if necessary. All poisonings are forensic cases; they should be reported to the forensic units and necessary examination samples should be taken before treatment [69].

In toxicological analyses, the selection, collection and storage of appropriate biological material, the preliminary analysis procedures to be applied to the sample, and the analysis stages are important considerations for obtaining accurate results. In the selection of biological material, the distribution of the substance to be analyzed in the organism is important. The analytical methods should be appropriate, accurate, reliable, sensitive, repeatable, fast, selective, responsive and economical. The findings obtained as a result of the analyses should be interpreted in terms of the route of administration, the dose taken, and whether the determined dose caused death or the determined toxic effect [60].

Biological samples used in the analysis of addictive substances have their own advantages and disadvantages. Therefore, substance analysis should be performed by selecting the biological sample most suitable for the purpose and result. The main samples recommended for postmortem examination are: blood, urine, bile, brain and kidney tissue, intraocular fluid, skin and muscle tissue from the injection site, bone and skeletal muscle from decomposed corpses. In addition, nasal mucosal samples are important in heroin use, and serological

examination is recommended for Hepatitis B, HIV and other infections in addicts [60, 69].

4.6.1. Clinical Table and Postmortem Findings

The primary mechanism of death from morphine is respiratory depression. In the terminal phase: Severe respiratory slowing, cyanosis, hypotension and bradycardia, hypothermia and miosis are observed. Macroscopically, the lungs are severe, hyperemic and edematous, and foamy fluid comes from the cut surface. Foam (mushroom foam) may be seen in the mouth and nose. Petechiae in the pleura and pericardium, and distended bladder are common findings. Edema and hyperemia may be found in the brain, and myocarditis and vasculitis may be observed in cardiac findings. In addition, infective endocarditis may occur with intravenous use, cholestasis, hepatitis or cirrhosis in the liver, and glomerulosclerosis, tubular degeneration and amyloidosis in the kidney may be seen [70]. External examination findings are characterized by recent and old needle marks, lesions, abscesses and scar tissue, poor hygiene, and poor general condition. Syringes, spoons, tourniquets, heating materials, and powdered substances may be found at the scene [64].

Morphine depresses the respiratory center, leading to severe pulmonary edema. Its effects on the cardiovascular system are hypotension and bradycardia. It causes hypothermia and miosis in the eyes; these findings worsen in the pre-death period of acute morphine intoxication. Respiratory rate, body temperature, and blood pressure decrease, cyanosis develops, and oliguria develops as blood pressure drops. Skeletal muscles are in a state of contraction, the tongue falls back, and the airways may become obstructed. Pulmonary edema developing in the terminal phase contributes to the worsening of the condition, and death usually occurs due to respiratory failure [53].

It is accepted that morphine leads to rapid and strong addiction after several doses. In withdrawal syndromes that develop with morphine and heroin use, although the symptoms alone are not thought to lead to death, they can cause the exacerbation of other existing disease symptoms and the development of unexpected complications, resulting in death [64].

Deaths due to morphine intoxication occur accidentally in addicts, and sometimes as a result of suicide. Although very rare, deaths resulting from the administration of morphine and other opioid analgesics for therapeutic purposes are also encountered. Individuals involved in drug trafficking carry packaged substances in their bodies. During oral ingestion, rectal or anal transport, large amounts of substance can be released onto the mucosal surface through ruptures in these packages, leading to death. Medical examinations and evaluations are

important not only for determining the cause of death but also for determining its origin and clarifying many possible legal issues. Therefore, autopsy and toxicological examinations carried out together with the crime scene investigation are of great importance [60].

In cases of death due to drug intoxication, the deceased are generally young. These individuals often have poor general personal hygiene, and the scene is usually a secluded, enclosed space such as a bathroom or toilet. The scene may contain syringes, needles, tourniquets, various bottles, spoons, powders, medications, heating materials, lemon juice, cotton, and other auxiliary materials. In cases where death is sudden and anaphylactic, the syringe is often found on or near the victim's arm. If vomit material is found on the victim or at the scene, a sample should be taken for examination. Repeated intravenous injections of morphine can lead to chronic scarring and thrombosis in the blood vessels, resulting in an irregular and wrinkled appearance in the area covering the vessels. Subcutaneous injections can cause small rings and oval scars on the skin (skin popping), and miosis of the eyes can develop due to morphine overuse. The lungs are usually hyperemic, swollen, and heavy, with abundant foamy edema fluid visible in cross-sections [60].

Pulmonary edema has been reported to be of cardiac origin, a condition typical of intravenous morphine and heroin use, and this appearance of the lungs is called "narcotic lung." The edema appears stained with blood, very similar to that seen in drowning cases. Petechial hemorrhages may be found in the pleura and pericardium; petechiae are small purple, red, or brown spots on the skin. Although petechiae appear as a rash, they are actually caused by bleeding under the skin. Aspiration pneumonia and lobular pneumonia in surviving cases may also occur. In deaths due to heroin inhalation, alveolar macrophages with brown pigmentation and spongioform demyelination can be determined in microscopic examination of the lungs [71].

Complications such as inflammation in the myocardium and endocardium, myocarditis, and vasculitis may be found in the heart. Intravenous injection is the cause of infective endocarditis in morphine and heroin addicts; endocarditis seen in drug addicts may develop due to reasons such as low immune resistance of the host and shared use of syringes [60].

The liver shows signs of acute or chronic disease due to the hepatotoxic effects of the substances and improper nutrition. Microscopic examination may reveal cholestasis, viral hepatitis, hepatopathy, degeneration of liver cells, reactions in mesenchymal cells, and foreign bodies due to additives. Gastrointestinal findings are non-specific; hyperemia and anoxic bleeding may be observed in the intestinal mesentery. In the kidneys, findings may be observed depending on the

type, amount, and duration of the substance (microscopically, lymphocyte and plasma cell infiltration at the border of the cortex and medulla, degeneration of tubule cells). In the central nervous system, macroscopic edema, hyperemia, and petechial hemorrhages may be observed [60,71].

4.6.2. Selection of Biological Material in Toxicological Analyses

The selection of suitable biological material in toxicological evaluation should be made according to the pharmacokinetic properties of the substance, and analytical methods should be sensitive, selective and reproducible [72].

Blood; Blood samples are generally used when determining the amount of substances and metabolites. In this way, approximate information about the dose and half-life of the substance can be obtained. Since there is a linear relationship between dose and effect, the intensity of the effect can be determined when the dose is determined. Since the substances used are eliminated from the blood quickly (morphine=3 hours, heroin=2 minutes), blood samples are not preferred for the analysis of recently used substances [72, 73].

Urine; Urine is one of the biological samples used to determine whether the substance was used a few days before the sample is taken, as it is one of the main routes of excretion from the body. Its most important advantages compared to blood samples are the high concentration of the substance used and its metabolites, and the easier sample collection stage. In addition, the absence of free serum proteins, lipids and other large molecular weight compounds in its structure facilitates toxicological preliminary analyses and sample preparation. Morphine is metabolized from the body into 3 and 6 glucuronides and excreted in urine or bile. 90% of morphine is excreted in the urine as glucuronides within 24 hours, and only 2-10% is excreted unchanged in the urine [73].

Heroin is converted into the intermediate product 6-acetyl-morphine to form morphine within minutes of ingestion. Both 6-acetyl-morphine and heroin are pharmacologically active despite their short presence in blood and tissues. Morphine is often the dominant of these active species. In heroin users, small amounts of codeine are found in the urine due to the presence of acetyl-codeine in heroin. 6-MAM, an indicator of heroin use, can be detected in urine only 24-36 hours after heroin use. The presence of 6-acetyl-morphine in urine helps to differentiate between morphine and heroin use [74].

Hair; In recent years, advancements in sensitive analytical techniques have made it possible to perform drug analysis on biological samples such as hair. These types of samples have advantages over other samples such as urine and blood, such as ease of sample collection, suitability of storage conditions,

prevention of disease transmission during sample collection, and ease of analysis [73].

The most important advantage of working with hair samples in the analysis of addictive substances is that it allows us to obtain information about chronic substance use from a more distant past (months or years ago) that cannot be detected with blood and urine samples. In fact, hair samples can be analyzed even centuries later due to their rigid and durable structure. In addition, the fact that a sterile environment and expert personnel are not required for the collection of hair samples facilitates the sample collection stage [73]. While it is not fully understood how substances enter the hair structure, it is thought that they enter from blood, sweat, or fat during hair formation. The physicochemical properties of each substance are believed to be important in determining its binding rate to the hair. Opioids, such as morphine, are basic substances and have the highest binding rate to body hair [75].

In addition to hair samples, substance analysis can also be performed on hair samples collected from different parts of the body such as the groin, armpit, arm, chest and buttocks [75]. Many studies have reported that the amount of substances in hair samples differs from the amount of substances detected in other body hairs. The amount of substances detected in samples collected from different regions also differs. It is thought that the reasons for this difference may be that hair samples that remain in the telogen phase for a longer time receive more substances from sweat and oil, differences in pigmentation, and different amounts of exposure to light and cosmetic products [58]. Substances accumulating in hair move 2.8-3.2 mm per week along the hair shaft, depending on the individual's hair growth. Therefore, the amount of substance is highest at the root (proximal) and lowest at the tip (distal). To cut samples from the upper back of the head, as close to the root as possible, the hair is held firmly and gently pulled to cut it near the root. The root and tip of the cut hair are noted, and a pencil-thickness (300 mg) hair sample is taken for analysis [58,73].

In one study, amphetamine, methamphetamine, 3,4-methylenedioxymetamfetamine, codeine, 6-acetylmorphine, diazepam, oxazepam, morphine, benzoylecgonine, cocaine, and THC were analyzed in breath, urine, and plasma samples. LC-MS method was used for the analysis of breath and plasma samples, while urine samples were analyzed using immunochemical reagents. In this study, morphine was found to be positive in breath, and compatibility was found between the examined urine, plasma and breath samples, demonstrating that breath samples can be used in the analysis of addictive substances [76].

Conclusion:

Morphine is one of the most effective and indispensable analgesics in modern medicine, but it is a potent opioid that requires careful and controlled use due to its high potential for addiction and life-threatening side effects. The main goal in clinical practice is to maximize analgesic efficacy while minimizing serious complications such as tolerance, addiction, and respiratory depression. This balance can be achieved through individualized dose titration, regular clinical monitoring, and appropriate patient selection [77].

Opioid addiction is not only a clinical problem today; it is a multifaceted public health problem with epidemiological, economic, social and legal dimensions. While long-term maintenance treatments have been shown to reduce mortality and illicit substance use, it is known that pharmacotherapy alone is not sufficient and that psychosocial support, rehabilitation and social integration programs are an integral part of the treatment. Early discontinuation increases the risk of relapse, which leads to a chronic and recurrent course [78].

From a forensic medicine and toxicology perspective, morphine and its derivatives are among the most frequently encountered substances in postmortem evaluations. While respiratory depression constitutes the primary mechanism of death, pulmonary edema, miosis, and other systemic findings provide important clues in clarifying the cause of death. The selection of biological material and the accuracy of analytical methods play a critical role in the correct interpretation of the cause of death [70].

In conclusion: Morphine is an active substance with high therapeutic benefit, but its misuse or uncontrolled use can lead to serious consequences. Therefore, the use of morphine and other opioids requires a collaborative approach involving clinical medicine, psychiatry, public health, and forensic medicine. Given the global scale of the opioid crisis, rational drug use, addiction prevention strategies, and effective treatment programs are critically important at both individual and societal levels.

We were declerate that no conflict of interest.

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