

Chapter

Does Morphine Abuse Harm Male Reproductive System?

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Abstract

Opioids have been used for both medicinal and recreational purposes (abuse) since ancient times. One of the most important opioids is morphine, a natural alkaloid obtained from the poppy plant (*Papaver somniferum*). The word morphine comes from Greek Mythology, derived from the name of “Morpheus,” known as the god of sleep in mythology. It is the most common opioid used to treat moderate to severe pain. Morphine is a mu opioid receptor agonist, and is a very powerful analgesic that also has affinity for other opioid receptors. Opioids are natural or semisynthetic compounds that have morphine-like effects. They are generally used as powerful analgesics in pain management. However, long-term use of opioids can lead to serious side effects such as addiction, respiratory depression, sedation, and sexual dysfunction. Studies on male reproductive system show that opioids suppress testosterone production and negatively affect gonadotropin secretion and spermatogenesis. The effect of opioids can inhibit the sperm production process in the testicles by reducing follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels. Long-term use of opioids such as morphine can lead to decreased testicular weight, sperm count, and degeneration of testicular cells. Despite these effects, number of studies show that some physiological changes can be reversed after stopping opioid use. The effects of opioids on male reproductive system should be investigated in more detail and these side effects should be taken into account during the treatment process.

Keywords: morphine, opioid receptor, male, testis, abuse

1. Introduction

Opioid drugs are defined as any natural or semisynthetic derivative that has morphine-like effects. The term opioid has come into use due to the development of synthetic drugs and the discovery of substances that have morphine-like effects in the brain. The term “opioid” also includes opioid receptor agonists and antagonists, as well as endogenous opioid peptides such as enkephalins, dynorphins, and endorphins that bind to the same receptors [1]. Opioids are powerful and systemically effective analgesics used for both chronic and acute pain treatment. Despite their use in pain treatment, they have very serious side effects. Some of these are sedation, respiratory depression, addiction, sleep disorders, and sexual dysfunction [2].

Opioid substances stimulate receptors, which belong to G protein-coupled receptor (GPCR) family and are normally activated by endogenous opioid peptides. These opioid receptors are μ , κ , δ receptors. While all opioid receptors are promising drug targets for different aspects of pain and mood, μ receptors are unique receptors that can be activated by opioids such as morphine to induce potent analgesia. μ receptor agonists prescribed for pain management include fentanyl and morphine. μ receptor-targeted opioids are the most clinically effective analgesics usable, but they also have the potential to cause addiction [3].

2. Opioid receptors

Opioid receptors are found in both peripheral and central nervous systems [4]. In addition to its analgesic effect caused by the activation of opioid receptors, many side effects such as respiratory depression, inhibition of gastrointestinal transit, and effects on anxiety may occur. Agonists for μ or δ receptors produce analgesic and rewarding effects, while κ receptors agonists are dysphoric. Morphine and similar opioids are frequently used in treatment of chronic pain. In most patients, a decrease in analgesic effects is observed with the development of physiological tolerance during long-term drug use. Besides physiological tolerance, physiological dependence may also occur. This situation may cause the dose of the drug to be increased in some patients to avoid development of opioid withdrawal symptoms. To understand these complex physiological mechanisms, animal models of tolerance and dependence have been developed [5].

2.1 μ receptor (Mu, MOR)

μ receptor was the first opioid receptor to be discovered. It triggers euphoria and plays an important role in stimulating the reward center [6]. This receptor is found throughout the central nervous system in sensory and motor areas, including regions involved in the integration and perception of these sensations, such as cerebral cortex and amygdala. μ receptor subtype plays a critical role in opioid addiction [7]. μ receptors are most abundant in caudate putamen, located presynaptically on principal afferent neurons in the spinal cord, where they inhibit glutamate release and thus the transmission of nociceptive stimuli from A and C delta fibers.

The periaqueductal gray area is an important area for central control of nociceptive pain transmission. The periaqueductal gray area has a high distribution of μ receptors. It is known that the analgesic effect of some opioids is mediated by inhibitory γ -amino butyric acid (GABA) in this region of the brain. GABA acts to reduce antinociceptive output from periaqueductal gray area [7]. The most important side effect of μ agonists is respiratory depression through decreased sensitivity of central and peripheral chemoreceptors to hypercapnia. μ receptor agonists also have gastrointestinal side effects. They have an inhibitory effect on gastrointestinal secretions and peristalsis. μ receptor activation can also affect cardiovascular system, immune function, hormone secretion, and thermoregulation. μ receptors located in the intestines are responsible for gastrointestinal evacuation and secretion. μ receptor agonists inhibit gastric emptying by reducing peristalsis. This is the most prominent side effect of morphine and other opioid drugs [5, 7].

2.2 δ receptor (delta, DOR)

It is less widely distributed than other opioid receptors. It is found in the highest density in cerebral cortex, olfactory bulb, caudate putamen, and nucleus accumbens. δ

receptors are located presynaptically on primary afferents to inhibit neurotransmitter release. These receptors participate in the analgesic effects of some opioids through both spinal and supraspinal regions. However, it has been determined that δ receptor agonists reduce gastrointestinal system motility and cause respiratory depression. In some experiments with mice lacking δ receptors, excessive locomotor activity was observed, and it was observed that this receptor could reduce locomotor activity under some conditions. In addition, anxiety and depression-like behaviors were observed in these mice and it was thought that it may be possible to regulate mood *via* δ receptor [7, 8].

2.3 κ receptor (kappa, KOR)

Another member of the opioid receptor family is the receptors called kappa or KOR. They are widely found in hypothalamus and periaqueductal gray area. Dynorphin binds to kappa receptor and creates a dysphoric and analgesic effect [6].

3. Morphine

Morphine is a natural alkaloid obtained from poppy plant (*Papaver somniferum*). The word morphine comes from Greek mythology. In this mythology, it is derived from the name Morpheus, known as the god of sleep. It is the most common opioid used to treat moderate to severe pain. Morphine is a weak base that is highly soluble under acidic conditions in water and poorly soluble at physiological pH in lipids (**Figure 1**) [9]. Although the medical use of morphine has decreased recently, it is known as the most powerful analgesic and pain-relieving agent [10]. Morphine is a μ receptor agonist, and all of the effects of morphine occur through this receptor. Morphine also has a weak affinity for κ and δ receptors and shows various effects through these receptors. After oral morphine administration, almost 100% is absorbed from the gastrointestinal system [9, 11].

4. Opioid dependence and withdrawal syndrome

Opioid addiction is a public health problem. Also known as substance addiction, this condition is a very serious chronic recurring disorder characterized by an increase in desire to seek and take the addicted substance when individual's access to drug or substance is denied, loss of control at the limit of intake, and the emergence



Figure 1.
Structural formula of morphine.

of negative mood states. According to Diagnostic and Statistical Manual of Mental Disorders (DSM-5), substance addiction disorders are defined as a cluster of symptoms including development of tolerance, withdrawal, uncontrolled increased intake, and craving for a substance [12].

Although opioid drugs have different mechanisms of action, all opioid drugs have been shown to activate the mesolimbic dopamine system. It has been shown that substances of abuse release more dopamine in these pathways than natural rewards and have a longer release time [13]. The basis of morphine addiction is how the brain's reward system changes as addiction develops. The mesocorticolimbic-dopamine system has been central to research on the neurobiology of the positive reinforcement effects of drugs. Opioids, and morphine, the most addictive form, inhibit GABAergic inhibition in the ventral tegmental area, which has a high density of μ -opioid receptors, causing dopamine release. Overstimulation of dopamine causes dysregulation of brain's natural reward pathways and learning processes, and development of sensitization and tolerance [14].

Opioid antagonists, such as naloxone, reverse the effects of opioid overdose by inhibiting μ -opioid receptor. μ -opioid receptor inhibition causes acute withdrawal symptoms in opioid addicts. μ -opioid receptor antagonists are commonly used in rapid detoxification to facilitate transition from addiction to abstinence. Since μ -opioid receptor blockade results in decreased efficacy of administered opioids, it can also be used to prevent relapse of symptoms [15]. Naloxone is widely used to prevent the effects of opioid overdose. Half-life of naloxone is approximately 30 minutes, which is considerably shorter than that of opioids. Therefore, respiratory distress caused by opioids may return after the effects of naloxone wear off [16].

5. Opioid effects on male reproductive system

While opioid addiction has always been a serious problem, it has recently become a global problem. Morphine addiction and withdrawal syndrome have many negative effects on human health.

Morphine and reproductive system studies have a long history. In the mid-70s, electrical stimulation studies were conducted on the muscles of experimental animals. It was determined that morphine prevented electrically stimulated contractions of longitudinal muscle of mouse vas deferens. This effect was stereospecific, and it was also determined that it could be antagonized *via* naloxone or naltrexone [17].

Opioid use disorder causes many different effects, most of which have been investigated in the central nervous system. Its role in reproductive system and testicular functions has also been investigated in many studies. Plasma testosterone, loss of libido, decreased ejaculate volume, and decreased sperm motility have been found to be associated with heroin and methadone [18, 19]. In recent years, efforts have been made to interfere with the complex network of opioid signaling at the molecular level, aiming to preserve analgesic effects while reducing the serious side effects associated with opioid use [20].

Some studies have revealed that motor activity of testicular capsule plays a role in the transport of sperm from seminiferous tubules to caput epididymis, in maintaining testicular interstitial pressure and in controlling testicular blood flow [21]. Opioid receptors are found in many places in our body. They are also located in many different places in the reproductive system, and endogenous opioids are found in different testicular cells.

The existence of three types of opioid receptors in rat testes has been proven. There are many studies showing its presence in Sertoli cells, spermatozoa, and Leydig

cells [22, 23]. In addition the presence of μ , δ and κ receptors in the human sperm membrane have been reported. It has been also recorded that μ , δ , and κ opioid receptors are found in spermatogenic cells [24].

In a human study, the expression of μ receptors in sperm cells was investigated *via* immunoblot and immunocytochemistry analyses. The results showed that receptor was localized in the acrosomal region and the neck of sperm head. These results suggest a possible role for the μ receptors in mediating the effects of endogenous opioid peptides on sperm cells during complex and poorly characterized cellular events that enable spermatozoa to fertilize oocytes [25].

Infertility is a significant problem affecting a considerable number of couples of reproductive age. It is generally estimated that the main cause of infertility is the male partner. Genetic diseases, injuries, anatomical defects, low sperm count, and hormonal disorders can be considered as the main causes. The opioid system shows its effects through many hormones. FSH and LH act directly on the testicles and stimulate somatic cells that contribute to spermatogenesis. The synthesis and release of FSH and LH are controlled by gonadotropin-releasing hormone secreted from hypothalamus. The main function of FSH is to stimulate the proliferation of Sertoli cells during puberty, while LH regulates testosterone synthesis in adult testes. While the use or administration of morphine is associated with the suppression of LH release from these hormones, opioid antagonists such as naloxone and naltrexone cause an increase in serum LH levels in humans and many animal species [26].

It is known that Sertoli and Leydig cells of testis are affected by the local opioid system. LH and corticotropin-releasing factor also stimulate the production of endogenous opioid peptides from Leydig cells. Opioids may indirectly affect testosterone levels by inhibiting the production of androgen-binding protein. Endogenous opioids can exert an inhibitory effect on Sertoli cells, which provide metabolic support for germ cell differentiation [27, 28].

Opioids generally reduce not only LH but also testosterone and estradiol, which have effects on testicular function [29]. In fact, opioid abuse primarily leads to hypogonadism, including decreased libido and erectile dysfunction and infertility in men [30]. Administration of opioid antagonists such as naltrexone may improve symptoms of hypogonadism and erectile function, but antagonists do not increase testosterone or LH levels, suggesting a central rather than peripheral regulation [31]. The male reproductive system efficiency depends on regular functioning of a complex system consisting of many organs, the proper secretion of gonadotropes, and the cooperation of androgens and local hormones. It is essential for all these systems mentioned to function properly for spermatogenesis [32].

Opioids and their agonists reduce LH secretion in healthy men through a variety of effects on pulsatile gonadotropin-releasing hormone secretion. LH secretion decreases during continuous infusion of 5- α dihydrotestosterone, but LH secretion can return to baseline levels through an opioid receptor antagonist. FSH levels are known not to change significantly with opioid infusions. The effect of opioids has been shown to depend on puberty. This emphasizes the relationship between steroid sex hormones and opioid system. It has been reported that LH secretion in males increases in late adolescence under the influence of naloxone. Conversely, in the early stages of puberty, LH secretion has been noticed to decrease after administration of opioid antagonists [33–35]. Endogenous opioid peptides reduce testosterone production by inhibiting testosterone release and gonadotropin-releasing hormone. The effect of any opioid in terms of FSH levels was not determined [30].

Opioid and derivative drugs adversely affect male reproductive functions, including spermatogenesis, androgen capacity, sperm quality, and sexual drive. These drugs directly cause testicular toxicity by promoting ROS-induced testicular and sperm oxidative damage, inflammation, and apoptosis and also affect the hypothalamic-pituitary-testicular axis. This results in the suppression of circulating androgen, ruined spermatogenesis, and decreased sperm quality. Abuse of opioid drugs not only damages male sexual functions, namely, testosterone concentration, spermatogenesis, and sperm quality, but also alters testicular histoarchitecture through a series of events in multiple pathways [36].

6. Opioid effects on experimental models of male reproductive system

Results from numerous studies on effects of opioid use on the male reproductive system are associated with a significant decrease in the efficiency of sex hormones and spermatogenesis [29, 37, 38]. In addition to these effects, a significant decrease in LH levels in general, but no decrease in FSH and testosterone levels, has been shown [29]. As a result of these studies, it has been revealed that chronic opioid exposure causes some significant changes in sexual functions and sex hormones, but more detailed and meticulous studies are required.

Various studies have been conducted to evaluate addictive effects of morphine and morphine derivatives on rat spermatogenesis, and changes in spermatogenesis function were observed in opioid addicted rats. The population of spermatogonia, spermatocyte, spermatid, and spermatozoa stages in addicted rats was significantly reduced compared to the group not receiving opioids. Histological studies also supported this situation; it was revealed that changes in different opioid administration groups could affect sperm formation. It was determined that morphine in particular caused a decrease in sperm count and could affect all stages of spermatogenesis [37].

In an addiction study, male rats were given intraperitoneal morphine injections. After bilateral orchiectomy, hormonal and histological evaluations were made. According to morphine-addicted group, sex hormone characteristics and spermatogenesis levels were significantly reduced compared to the control group. While there was no decrease in FSH and testosterone levels, there was a significant decrease in LH levels. When histological sections were examined, mature sperms were significantly reduced. Chronic use of opioids can lead to changes in sexual hormones and functions. Therefore, opioids have the potential to cause infertility. These changes may result from the direct effects of the drugs on the seminiferous tubules, their effects on the pituitary or hypothalamus, or both [39].

In a prospective experimental study, the administration of tramadol, an agonist to the μ opioid receptor, was examined for sex hormones, FSH, LH, and histopathological changes. Unlike other studies, FSH levels in the blood showed a significant decrease. In addition, degeneration occurred in the seminiferous tubules [40]. In another study examining the effect of long-term tramadol administration on testicular functions, a significant decrease occurred in plasma FSH, LH and testosterone levels, and sperm count. It also increased testicular nitric oxide (NO) and lipid peroxidation and decreased the activity of antioxidant enzymes [41]. Morphine administration decreased LH and testosterone concentrations and caused a significant decrease in testicular weight in a different experimental animal research. In addition, there was a significant decrease in spermatogenic cell population that governs spermatogenesis in morphine-treated testes. All observed effects were reversed within 13 weeks after discontinuation of the drug [42].

To evaluate the effects of morphine addiction on reproductive hormone levels and fertility-related markers, 30 male Wistar rats were administered two single daily doses of morphine intraperitoneally for 20 days. Male reproductive parameters (blood serum testosterone, LH, and FSH) and mRNA and protein expression of some genes, which play a role in fertility-related pathways, were evaluated using real-time polymerase chain reaction and western blot, and histological analysis was performed on testicular samples. LH and testosterone levels decreased, and expressions of all five target genes and target proteins were downregulated. By this study, it was concluded that morphine could reduce reproductive parameters in male rats [38].

Decreased libido is one of the major problems experienced by addicts. Erectile dysfunction has been reported in men using opioids for the treatment of heroin addiction. A study was conducted to investigate the effects of morphine addiction and detoxification with methadone on the male reproductive system as causes of sexual dysfunction in addiction. Serum testosterone levels, FSH, LH, testicular weights, partial weights of prostates, seminal vesicles, and seminal vesicle contents decreased in addicted group compared to the control group. In morphine-dependent animals detoxified with methadone, testosterone concentrations and seminal vesicle contents remained lower than the levels in control group. The results suggest that morphine addiction may impair reproductive function in male rats [43]. Low testosterone levels are characterized by fatigue, mood swings, erectile dysfunction, and decreased libido in men. This condition poses a significant obstacle to the treatment of opioid addicts [44].

Morphine is a psychoactive chemical substance that can negatively affect spermatogenesis by causing increased free radical production. So, what might be the effects of morphine use in men on sperm parameters, DNA integrity, and apoptosis? In a case-control study, sperm parameters (number, motility, and morphology) and sperm chromatin quality were compared with histological stains in samples taken from 30 men using morphine and 30 healthy men. According to data obtained from this study, sperm progression and motility in men with morphine addiction showed a significant decrease compared to the control group. In morphine abuse, it was observed that morphine reduced sperm chromatin condensation and increased sperm apoptosis rate. When these results are evaluated, it can be interpreted that morphine addiction may reduce male fertility by affecting sperm parameters [45].

Opium derivatives include morphine, heroin, and codeine; synthetic opium analogs include methadone, pethidine, meperidine, and so forth. Opioid addiction is usually treated with long-acting agonist opioids such as methadone and buprenorphine, which can affect the male reproductive system. It was investigated whether morphine detoxification with buprenorphine and methadone was related to male reproductive disorders in mice. Oral morphine addiction was induced in NMRI male mice (an outbred strain commonly used as controls in selection experiments and as experimental animals in biology, pharmacology, and toxicology), and then, detoxification programs were implemented using buprenorphine or methadone. According to the research results, number of Leydig cells and germinal epithelial thickness decreased after morphine use and significantly increased after detoxification with buprenorphine or methadone. Morphine altered oxidative stress, mitochondrial activity, and chromatin integrity in sperm, while detoxification with methadone improved mitochondrial activity but worsened chromatin integrity, whereas detoxification with buprenorphine did not improve either chromatin integrity or mitochondrial activity. The study reveals that long-term morphine use followed by detox with buprenorphine or methadone impairs testicular structure and sperm parameters [46].

The use of different types of opioids is known to cause sexual dysfunction. Testosterone levels were found to be higher in addicted individuals treated with buprenorphine compared to methadone. Therefore, opioid-mediated effects on steroid sex hormones and sexual function-behavior were seen in both chronic opioid users who need pain management and opioid addicts [47, 48].

Chronic morphine use has harmful effects on testicular function through the activation of inflammatory, oxidative, and apoptosis biomarkers mediated by suppression of somatic cells such as germ cells and Sertoli cells. Whether the deleterious effects of morphine dependence are reversed by spontaneous morphine withdrawal or incubation with methadone and/or naloxone in Sertoli cells was investigated using an *in vitro* cell model of morphine dependence. CAMP levels were measured to assess morphine dependence in Sertoli cells. Cell viability and inflammatory, oxidative, apoptosis, and glial-derived neurotrophic factor biomarkers were measured at the end of treatment following incubation of cells with methadone and naloxone and spontaneous withdrawal from morphine. Morphine dependence was shown to decrease cell viability and glial-derived neurotrophic factor levels and increase pro-inflammatory, prooxidant, and apoptotic biomarker levels in Sertoli cells. Spontaneous withdrawal from morphine and naloxone was found to reduce pro-inflammatory and apoptotic biomarker levels in Sertoli cells. It appears that morphine addiction increases apoptosis in Sertoli cells, probably through oxidative stress and inflammation pathways [49].

When the effects of morphine and methadone on the endocrine control of sexual function in male rats were studied many years ago, it was shown that these narcotics caused a marked decrease in serum testosterone levels, which markedly reduced the structural and functional integrity of the secondary sex organs. Serum LH levels were undetectable in narcotic-treated animals, but serum FSH levels were unchanged. Based on these observations, it seems reasonable to conclude that narcotics inhibit LH secretion by an action on the hypothalamus or directly on the pituitary gland, resulting in a decrease in serum testosterone levels and a subsequent decrease in wet tissue weight and secretory activity of the secondary sex organs [19].

Opioid analgesics such as morphine and methadone are widely used to manage severe pain, but their potential for abuse and adverse effects on the brain and reproductive system are of concern. Their effects on spermatogenesis and cognitive function were investigated in male rats. Methadone and morphine were administered intraperitoneally. Long-term exposure to morphine and methadone resulted in memory impairment (short-term and long-term memory), chronic stress (anxiety and stress), hormonal disturbances (FSH, LH, testosterone, and estradiol levels), changes in gene expression (Tp53, CatSper1), and fertility complications. High doses of methadone reduced the number of offspring significantly. These effects were more pronounced at higher doses, emphasizing importance of careful dosing in opioid therapy [50].

It is already known that methadone is one of the most widely used methods in the treatment of opioid addiction. Although methadone is effective in the treatment of opioid addiction, sexual dysfunction and infertility have been reported as significant problems in patients receiving methadone treatment. The effects of melatonin and N-acetylcysteine on morphine and methadone-induced oxidative stress, apoptosis, suppression of blood sex hormones, deterioration in sperm parameters, and sexual dysfunction were evaluated in adult male Wistar albino rats. Exposure to morphine, methadone, and the shift of morphine to methadone caused testicular degeneration attributable to stress oxidative-induced apoptotic testicular cell death and impaired spermatogenesis. N-acetylcysteine and melatonin alone and especially in combination

with each other improved testicular degeneration, testicular antioxidant capacity, sex hormone suppression, and testicular mechanism mediated by inhibition of apoptosis pathway. The study suggests that oral administration of antioxidants may be an effective treatment to alleviate some opioid-associated testicular degeneration and dysfunction [51].

Previous studies have shown that morphine negatively affects male fertility, while *Phoenix dactylifera* (dates) extract has been suggested to treat male infertility by exhibiting antagonistic effects. Thus, possible curative effects of dates on histological features of male rat reproductive organs caused by morphine addiction were investigated. In male Sprague Dawley rats treated with morphine, a honeycomb-like appearance with flattened columnar cells was not observed in seminal vesicle, while the absence of eosinophilic secretion from glandular lumens in the prostate gland was noted. *Phoenix dactylifera* administration improved the histoarchitecture of seminal vesicle and prostate gland with complex mucosal folds and glands with secretion-filled lumens. They claimed that *Phoenix dactylifera* extract has a protective effect against the negative effects of morphine on male rat reproductive systems [52].

Epigenetic marks can be affected by a variety of factors, including age, early life experiences, lifestyle, and exposure to drugs or chemicals such as “opioids.” Previous studies have focused on how morphine epigenetically regulates different brain regions that play a role in dependence, tolerance, and other psychiatric disorders that are more related to pathophysiological effects of opioids. There is a wealth of information on the effects of chronic use on other organs and systems. A study was conducted on effects of chronic morphine exposure on DNA methylation and histone modification levels in individual organs of male and female mice. The results revealed that chronic morphine treatment caused systemic changes in DNA methylation/hydroxymethylation and histone modification *in vivo*, suggesting a potential physiological effect on regulation of gene expression. It is noteworthy that morphine-induced epigenetic modification is gender-dependent, suggesting different mechanisms underlying epigenetic modification in female and male mice [53].

7. Opioid effects on male urogenital system cancers

Recent studies have suggested agonism or antagonism of opioid receptors has important effects on cancer-related outcomes. Retrospective reviews suggest that increased perioperative opioid administration is associated with poorer survival in patients undergoing prostate or bladder cancer surgery for urogenital tract cancers, but the data are controversial. κ receptors have been implicated in both proliferation and inhibition of prostate cancer cell growth in *in vitro* studies. Similarly, the opioid growth factor receptor is highly expressed in prostate cancer cells and is suppressed by androgens. Prostate cancer tissue stains more intensely for mu opioid receptor. *In vitro*, opioid agonism induces urothelial cell carcinoma proliferation and invasion. Agonism of μ , δ , and κ receptors induces renal cell carcinoma tumorigenesis; opioid growth factor receptor agonism has the opposite effect on renal cell carcinoma. Evidence regarding the role of opioids and their receptors in urological malignancy is controversial. The effects of opioids on urogenital cancers require further investigation [54]. Preclinical studies suggest that opioids stimulate angiogenesis and tumor progression *via* the mu opioid receptor. Higher mu opioid receptor expression and greater opioid requirements are associated with shorter progression-free survival and overall survival in patients with metastatic prostate cancer [55].

Interestingly, opioid dependence can be observed frequently after urological cancers. In a study evaluating the risk of rational opioid use after radical orchiectomy for testicular cancer. A total of 2911 men underwent radical orchiectomy for testicular cancer, and 89.8% of them were prescribed opioids at the time of orchiectomy. Patients prescribed postoperative opioids for orchiectomy had a statistically higher risk of developing new persistent opioid use. Postoperative opioid prescription after radical orchiectomy was found to be significantly associated with developing new persistent opioid use [56]. Castration resistance is a failure of prostate cancer therapy and is associated with ligand-independent activation of the androgen receptor. Loss of function of opioid kappa 1 receptor, which is upregulated in androgen deprivation, delayed the acquisition of castration resistance and prevented castration-resistant growth of prostate cancer both *in vitro* and *in vivo*. These data suggest that opioid kappa 1 receptor is involved in cellular adaptation to post-castration survival and castration-resistant progression of prostate cancer, accelerating the clinical application of opioid kappa 1 receptor-targeted therapy in the management of this deadly disease [57]. Opioids are preferred as a treatment option, especially for pain control. Metastatic prostate cancer may cause skeletal pathological fractures, bone surgery and/or radiation, and spinal cord compression. Opioids are frequently used in the treatment of skeletal pathologies. Long-term opioid use and dependence increase significantly after skeletal pathologies develop in metastatic prostate cancer [58].

8. Conclusion

Morphine is like a double-edged sword. While trying to benefit from its analgesic effect, it can cause undesirable effects on many systems of the body, such as the three-dimensional damage it causes to the male reproductive system.

Opioids, particularly those acting on the μ -opioid receptor, play a central role in both pain management and the development of addiction. However, their impact on the male reproductive system is concerning, with many studies showing that chronic opioid use can significantly impair reproductive health, reduce testosterone levels, and affect spermatogenesis by altering oxidative stress, mitochondrial activity, and chromatin integrity in sperm. These effects may be reversed to some extent after opioid discontinuation, but more research is needed to fully understand long-term consequences of opioid use on male reproductive health.

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