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PHARMACOLOGICAL APPROACHES IN PAIN MANAGEMENT FROM OPIOIDS TO NON-OPIOID ALTERNATIVES

Sidra Arif[*1], Qurratulaen Raza[2], Zumar Rizvi[3], Sadia Azad[4], Isma Idrees[5], Reeka Zulfiqar[6], Abbas Shahid[7], Shumaila Yousaf [8]

[*1] *Department of Pharmacology, University of Islamia University Bahawalpur, Pakistan*
[2, 3, 4] *College of Pharmacy, Margalla Institute of Health Sciences, Rawalpindi, Pakistan*
[5, 7, 8] *Faculty of Science & Technology, University of Central Punjab, Lahore, Pakistan*
[6] *Institute of Pharmaceutical Sciences, University of Veterinary and Animal Sciences, Lahore*

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Corresponding Author: *
Sidra Arif

Abstract

Pain management is an important part of healthcare, with opioids typically acting as the foundation for treating moderate to severe pain. Nevertheless, the increasing anxieties regarding opioid addiction, abuse, and toxicity have led to a transition to the investigation of non-opioid alternatives for pain relief. This study offers a comprehensive overview of pharmacological methods to pain management, emphasizing both opioid and non-opioid treatments. The initial section investigates the mechanisms of action of opioids, their effectiveness in pain relief, and the obstacles that arise from their extended use, such as the potential for dependency and adverse effects and side effects. Consequently, the review explores the emerging non-opioid alternatives, with an emphasis on both novel therapeutic approaches and pharmacological agents, in response to these challenges. Antidepressants, anticonvulsants, topical analgesics, and NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are among the medications that are used. Additionally, newer agents such as monoclonal antibodies and cannabidiol-based therapies are used. Furthermore, the function of adjuvant interventions, including cognitive-behavioral therapy and physical therapy, is investigated. The significance of personalized pain management strategies is also examined in the article, which underscores the necessity of an approach focused on patients that integrates safety and efficacy. The objective of this paper is to enhance comprehension of the evolving nature of pain management and to emphasize the potential for safer, more effective alternatives in clinical practice by examining the current pharmacological landscape and emergent alternatives.

INTRODUCTION

More Americans suffer from pain than from diabetes, heart disease, or cancer combination (NIH, 2013). There are millions of individuals who experience acute or chronic pain annually, and the annual national economic cost of pain is as high as $560–635 billion (NIH, 2013). In the past two decades, pain medicine has emerged as a dynamic clinical speciality that integrates a variety of treatments, such as pharmacological, surgical, physical, and homoeopathic methods, to alleviate pain, particularly chronic pain. Many different medications have been used to manage pain in the past, including opioids, non-steroidal anti-inflammatory drugs, antidepressants, antiepileptics, local anaesthetics, and even natural products. Unfortunately, the analgesics currently available are insufficient to address clinical needs, leaving a vast population with uncontrolled pain. Actually, the pain reduction that can be

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achieved by all currently available treatments is only approximately 30% in approximately half of the chronic pain patients who have been treated (Turk et al., 2011).

The large number of people who are in severe pain makes this a very difficult health problem. So, it is quite important for doctors to come up with new and useful drugs. Opioids are the most effective analgesics for treating a variety of painful conditions and are commonly used to alleviate acute pain, surgical pain, and pain associated with fatal illnesses. However, using opioids, especially for a long time to treat chronic pain, can cause a number of side effects. These can range from less severe and manageable effects like nausea and vomiting, sedation, and urinary retention to more serious ones like physical dependence, constipation, and addiction (Busse et al., 2018; Niemi-Murola et al., 2011; Wickham,2017).

Opioids typically activate μ-opioid receptors (MOR) to cause analgesia and undesired side effects. The overuse and abuse of opioids has become a nationwide problem, and the number of opioid overdose deaths is rising rapidly (Volkow et al., 2019). More than 49000 persons died from opioid overdoses in 2017, accounting for roughly 70% of all drug overdose deaths (Volkow and Wargo, 2018). The misuse of prescription opioid analgesics was a significant factor in the early phases of the current opioid crisis, despite the fact that a significant number of overdose deaths are attributable to the abuse of illegal opioids, including heroin, fentanyl, and its analogues (Madras, 2018). In recent years, significant attempts have been undertaken to create novel analgesics with better therapeutic characteristics. Combination therapy is a highly desirable technique. For instance, the FDA recently gave Heron Pharmaceuticals' HTX-011 the breakthrough therapy designation for treating pain after surgery (www.herontx.com/). The nonsteroidal anti-inflammatory medication (NSAID) meloxicam is combined with the local anaesthetic bupivacaine in a fixed-dose formulation known as HTX-011.

Figure 1: Plant Opioid

The addition of low-dose meloxicam to HTX-011 decreases local inflammation and neutralizes the acidic environment that results from surgery. This enables bupivacaine to penetrate the nerves more effectively, amplifying its action. Both of these substances are already utilized in medicine and have well-defined therapeutic characteristics. The combination therapy strategy may prove to be an effective method for the development of new pain control drugs in the event of a pressing clinical need for safe and effective analgesics and the difficulty of creating new drugs with innovative mechanisms of action.

1.1. Combination therapy

In clinical practice, combination therapy is frequently employed to treat neurological disorders, cardiovascular diseases, infectious diseases, and cancer. In general, combination therapy tries to raise the therapeutic index, which is a number that shows how safe a drug is by comparing the amount of drug needed to cause an unwanted effect to the amount needed to cause a therapeutic effect. Larger therapeutic index values typically suggest a better separation of potential therapeutic and unpleasant effects, as well as increased safety. There are more than 10,000 clinical trials going on right now in the US alone that are looking at combination therapy for

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different diseases. There are also a lot more preclinical investigations on drug combinations (Editorial, 2017). The technique of mixing two or more medications to treat certain conditions in the expectation of improving (i.e., safer and/or more effective) therapeutic outcomes is known as combination therapy (Orru et al., 2014; Smith, 2008). The World Health Organization issued the pain analgesic usage guideline for adult cancer pain patients in 1985. This is an example of combination therapy (Ventafridda et al., 1985). A **table 1** showing various opioid and non-opioid combinations that enhance analgesic effects while reducing side effects.

Table 1: ***Combination Therapy of Opioids with Non-Opioid Analgesics***

Opioid	Non-Opioid	Combination Effect	Common Uses
Oxycodone	Acetaminophen	Synergistic analgesic effects	Postoperative pain, chronic pain
Morphine	Gabapentin	Additive analgesia, reduced opioid dose	Neuropathic pain, cancer pain
Tramadol	NSAIDs	Reduced opioid dose and side effects	Moderate pain relief
Fentanyl	Naloxone	Abuse-deterrent, reduced euphoria	Pain management with abuse deterrence

The main goal of combination therapy for pain management is to make painkillers like MOR agonists work better or to lower adverse effects by using lesser doses of each drug (Gilron et al., 2013; Smith, 2008). The goal of combination therapy is to keep or boost the strong pain-relieving effects of MOR agonists while also lowering the negative effects that come with opioids. A **table 2** comparing the effectiveness, side effects, and therapeutic profiles of opioids (e.g., morphine, oxycodone) versus non-opioid analgesics (e.g., antidepressants, anticonvulsants, NSAIDs, monoclonal antibodies, cannabinoids).

Table 2: *Comparison of Opioid and Non-Opioid Analgesics*

Drug Class	**Effectiveness**	**Common Side Effects**	**Potential for Abuse**	**Examples**
Opioids	High	Nausea, vomiting, sedation, addiction	High	Morphine, Oxycodone, Fentanyl
Antidepressants	Moderate	Drowsiness, weight gain, sexual dysfunction	Low	Amitriptyline, Duloxetine
Anticonvulsants	Moderate	Dizziness, fatigue, cognitive impairment	Low	Gabapentin, Pregabalin
NSAIDs	Moderate	GI irritation, renal issues	Low	Ibuprofen, Meloxicam
Monoclonal Antibodies	Moderate	Infusion reactions, immune suppression	Very Low	Infliximab, Adalimumab
Cannabinoids	Low to Moderate	Dry mouth, dizziness, fatigue	Low	CBD, Dronabinol

This approach has already been applied with opioid analgesics. For example, the opioid oxycodone along with paracetamol is commonly used in therapeutic settings under the brand names Percocet®, Endocet® (Endo Health Solutions), Roxicet® (West-Ward Pharmaceuticals), and Primlev® (Akrimax Pharmaceuticals). What is not expected is that the specific medicines and dose ratios in the oxycodone/acetaminophen tablets or oral solutions vary greatly within and between brands. Therefore, Percocet® tablets have oxycodone doses between 2.5 and 10 mg and acetaminophen doses between 325

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and 500 mg, whereas Primlev® pills contain a fixed dose of acetaminophen (300 mg) with different oxycodone doses (5, 7.5, or 10 mg). Whether the combinations are superior to the individual medications and how the dose a combination were determined are unknown. The literature analysis revealed that the research evidence supporting the oxycodone/acetaminophen dose combinations is remarkably limited, despite the fact that these medicines have been clinically used for many years (Raffa et al., 2010).

Changing the ratios and actual doses of the constituent drugs may significantly alter the drug effects, which is problematic due to the difficulty of predicting the pharmacological effects of drug combinations. This is demonstrated by a study that found that, depending on the ratio of the two medications employed in the combination trial, the effects of meloxicam and gabapentin on antinociceptive function varied from additive to synergistic (Espinosa-Juarez et al., 2016). From a therapeutic perspective, the main purpose of opioid/non-opioid combination is to raise the therapeutic index, resulting in more effective and safer analgesics. Increasing or maintaining the analgesic effects of opioids while lowering the side effects are two strategies that can be used to optimise opioid/non-opioid combinations for pain treatments, given the known side effects of opioids (such as tolerance, dependence, abuse liability, respiratory suppression, constipation, and pruritus).

1.2. Medications to Improve Opioid-Induced Pain Relief

In order to decrease the amount of opioid dosages needed for clinical analgesia, the majority of research on the combination of MOR agonists and non-MOR agonists focusses on increasing the analgesic potency of opioids. This method is advantageous because it can result in improved patient compliance and fewer adverse effects when opioid doses are reduced. Numerous medications have demonstrated encouraging outcomes when used in conjunction with opioids, including adrenergic α2 receptor agonists (Blaudszun et al., 2012), COX-2 inhibitors (Martinez et al., 2017), antidepressants (Kane et al., 2018), and antiepileptic medications (Tomic et al., 2018). Some are still in the preclinical stages, while others have already been applied in clinical settings. For instance, antiepileptic medications have been demonstrated to work better with opioids in models of chronic pain (Tomic et al., 2018), but further research is needed to validate these results. Antidepressants have no therapeutic effect when used alongside opioids to treat cancer pain (Kane et al., 2018).

The goal of combination therapy is to increase the therapeutic index of pain management. Research on opioid-drug interactions must adhere to specific guidelines, which include testing various drug ratios, evaluating both therapeutic and side effects, and examining drug interactions using dose-ratio or isobolographical analysis. It is also necessary to investigate acute and chronic pharmacological therapies. 2-BFI and CR4056 are examples of imidazoline I2 receptor agonists that have strong pain-relieving effects in several forms of chronic pain (Comi et al., 2017; Ferrari et al., 2011). A Phase II experiment using CR4056 revealed efficacy in patients with knee osteoarthritis (Rovati, 2017). According to research, 2-BFI intensifies the effects of opioids such as morphine and tramadol. This suggests that combining MOR agonists with I2 receptor agonists may lower the dosage of opioids used to treat pain (Thorn et al., 2011). Morphine and oxycodone shown additive effects with 2-BFI in models of inflammatory pain (Li et al., 2014; Thorn et al., 2015). The way opioid medicines work affects the way they interact with their other. For example, lower-efficacy MOR agonists work better with 2-BFI, while higher-efficacy agonists like fentanyl work better with each other (Siemian et al., 2016).

The mechanical allodynia test tested fentanyl's therapeutic index. The dosage ratio for fentanyl alone was 2.86, meaning that its ability to produce antinociception was 2.86 times more effective than its ability to decrease the response rate. The dosage ratio was 1.39 for 2-BFI alone. A dose ratio of 4.63 was obtained with the fentanyl/2-BFI combination at a 1:3 ratio, indicating a notable rise in the therapeutic index. This combination may improve the therapeutic profile by lowering the necessary fentanyl dosage and reducing adverse effects like sedation. BU224 and 2-BFI are two examples of I2 receptor agonists that exhibit promise in treating opioid-induced physical dependency. In morphine-dependent mice, BU224 decreased withdrawal

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symptoms (Hudson et al., 1999), and 2-BFI inhibited naltrexone-induced body weight loss and helped prevent the development of morphine tolerance (Thorn et al., 2016b). In order to manage chronic pain, these findings support the possibility of combining MOR agonists with I2 receptor agonists by indicating that I2 receptor agonists can lessen the negative effects of MOR agonists.

Furthermore, although they are rarely thoroughly examined, the pharmacokinetics of medication combinations are essential. If one drug changes how another drug works in the body, it could change how well it works as a treatment. For instance, by raising ketoprofen blood levels, coffee improved the antinociceptive impact of the medication in arthritic rats (Medina-Lopez et al., 2018). However, without pharmacokinetic interactions, tramadol and metamizol demonstrated synergistic benefits (Moreno-Rocha et al., 2016). Drug-drug interactions and their therapeutic relevance are frequently evaluated using functional measures such medication action duration and pain-related behaviours, however few research examine pharmacokinetic interactions in analgesic combinations (Thorn et al., 2015). The evaluation of pain-related behaviours as a marker for analgesic interactions is ultimately informative in the context of drug combinations.

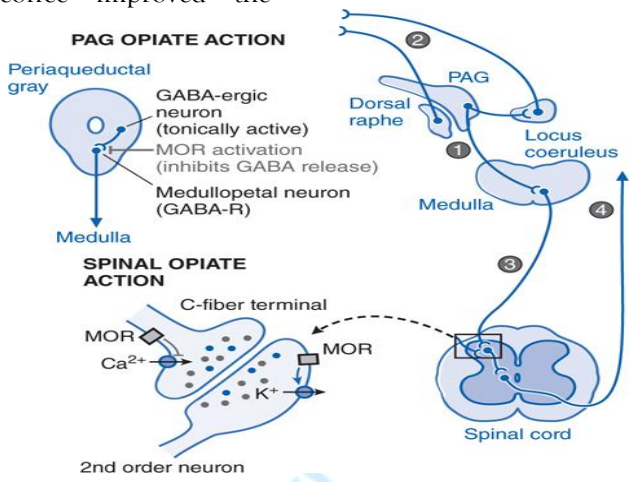

Figure 2: ***Mechanisms of opiate action in producing analgesia***

This **figure 2** explains the mechanism of opioid action at both the periaqueductal gray (PAG) in the brain and the spinal cord. In the PAG, opioids activate mu-opioid receptors (MOR), which inhibit the release of GABA from GABA-ergic neurons. The activation of pain-relieving pathways is made possible by this inhibition, which lessens the suppression of pain signals. The medulla receives the signal after which it further modulates pain signals. Opioids bind to MORs on C-fiber terminals in the spinal cord, preventing calcium influx and encouraging potassium efflux. This stops the release of neurotransmitters that send pain signals, which stops the pain signals from getting through. Consequently, opioids alleviate pain by affecting both the brain and spinal cord.

1.3. Drugs to control opioid use-related side effects (symptomatic control)

Pharmacologic effects of MOR agonists use are far-reaching and complex. Opioids can produce sedation, nausea, emesis, and pruritis in clinical practice to relieve pain. In severe or acute cases, such occurrences may lead to medical intervention that seeks to alleviate the symptoms. As an example, methylphenidate, donepezil and modafinil have been employed to treat opioid induced sedation (Reissig and Rybarczyk, 2005). At the same time, the antiemetic, ondansetron, has shown effectiveness not only as preventative of intrathecal morphine-induced pruritis but also as a preventive strategy in post-operative nausea and vomiting (Koju et al., 2015). Taking into account the fact that such interventions are not necessarily confined to MOR agonists and, thus, these issues do not need additional detailed consideration, the

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following sections will focus mainly on side effects that are of special concern on long-term opioid use.

*1.*3.1. Reduction of analgesic tolerance

Tolerance can be defined as the steady augment in dosage necessary to produce a standard pharmacologic effect subsequent to regular use. The effect is reproducible in a wide range of therapeutics. Laboratory experiments studying μ-opioid receptor (MOR) agonist-induced tolerance exhibit a dose- and time-dependent tolerance progression curve, and this response is dampened by a particular pharmacodynamic effect (Schug et al., 1992; Volkow and McLellan, 2016; Wang and Ho, 1994). However, the clinical trial results are not as conclusive (Rosenblum et al., 2008). Nevertheless, despite frequent escalations in chronic pain patients on steady-state opioid regimens over time (Collett, 1998; Tobias, 2000), many patients on an effective dose of opioids stabilize beyond the initial phases (Cowan et al., 2001) Tolerance is not accurately quantifiable in these environments, and there is still debate over the extent of the tolerance issue (Farrar et al., 2010). Adverse events and poor pain control may trigger the need to stop treatment, but the disease itself can also increase doses (Portenoy, 1994). There is also evidence that tolerance is limited during voluntary laboratory administration of opioids. In comparison, marked tolerance and dose escalations are frequently seen in the circumstance of abusing opioids (Cowan et al., 2001), and informal testimonies have reported magnitudes of tolerance above 500x typical morphine dosage in addicted human subjects (Wikler, 2010).

Tolerance to clinical opioid analgesia is seen as a troubling issue, but its role in this direction is rather controversial. There are limited efforts to specifically design therapeutics to overcome tolerance, although in pre-clinical reports, thousands of substances have been described which can reduce opioid-induced tolerance, and many are posited as adjuvant agents in the treatment of pain. However, the potentiation of opioid-induced antinociception is the main goal of most such studies, and tolerance reduction represents a secondary consequence. As examples, agonists of the cannabinoid CB1 receptor and N-methyl-D-aspartate (NMDA) receptor antagonists have been shown to alleviate morphine antinociceptive tolerance in mice (Fischer et al., 2010; Trujillo and Akil, 1991). On the other hand, a large-scale clinical trial of morphine plus a nonselective NMDA receptor antagonist did not show any benefit of treatment of chronic pain; the combined administration of dextromethorphan did not augment the analgesic effects of morphine or lower the incidence of morphine tolerance (Galer et al., 2005). Based on these results, an urgent need to develop combination therapies to target the development of tolerance to opioid analgesia does not seem apparent. However, future agents that can block the tolerance and at the same time provide analgesia would certainly be useful.

1.3.2. Reduction of abuse liability and drug diversion

The search to find new opioid therapeutics with reduced abuse liability continues to be one of the key goals in analgesic drug development involving MOR agonists, a search that has dominated the field over the past 100 years or so (Jacobson and Rice, 1992). No significant improvements have so far been developed (Kissin, 2010). Modern advances have focused more on interventions to the MOR system, via molecular engineering or modulatory approaches. Meanwhile, the pharmaceutical sector has shown great interest in developing abuse-deterrent formulation (ADF) opioids, with diverse technological strategies (Litman et al., 2018). The earliest commercialized example of this technology, OxyContin, an extended release variant of oxycodone, appeared in 1996 and gained rapid popularity as a first-line agent in treating moderate-severe chronic pain and focal point in drug diversion and abuse (Cicero and Ellis, 2015). The Food and Drug Administration (FDA) approved an improved OxyContin formula in 2010 with ADF dimensions.

This new formulation used proprietary thermal processing and curing of high-molecular-weight polyethylene oxide to form a coating around each tablet that impedes an abuser's ability to crush the pill and access the inner active drug (Maincent and Zhang, 2016). Since then, at least 6 other opioid ADF formulations with similar concept have been approved by FDA using different opioids (i.e., oxycodone, hydrocodone, morphine) and different technologies. These technologies create physical or chemical barriers to provide resistance to mechanical or chemical manipulations by drug abusers to deter

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drug diversion and abuse (Cicero and Ellis, 2015). Another strategy used in MOR agonist formulations to deter opioid abuse is combination therapy. In this regard, three opioid formulations have been approved by FDA, all of which combine an MOR agonist (oxycodone or morphine) with a MOR antagonist such as naloxone or naltrexone (Cicero and Ellis, 2015).

It involves the development of drug tablets that will provide opioid pain relief upon consumption in the form of a tablet. Its efficacy is based on the metabolic pathways of naloxone and naltrexone, which are mostly eliminated through hepatic first-pass effect, thus resulting into the development of very high local concentration at the portal zone. Conversely, after deliberate tablet crush-administeration using nasal snorting or intravenous route, the therapeutic-to-punitive extinction of the agonist-antagonist combination remains constant, thus reducing or negating the euphoric response to the opioid. A similar treatment philosophy lies behind Suboxone 3, a combination of buprenorphine with naloxone that is used to treat opioid dependence and help with moderate pain. No pharmacotherapeutic agent other than MOR antagonists has, to date, been approved by the Food and Drug Administration to be coadministered with MOR agonists as deterrent, new-formulation analgesics. However, the literature has shown that these alternative agents are effective as a deterrent. Histamine itself, as an example, was proven as an effective punisher with both natural reinforcers (food), as well as drug reinforcers (cocaine); infusion of this agent suppressed self-administration behaviors in animals (Freeman et al., 2014a; Podlesnik et al., 2010). Since histamine is mainly broken down through the hepatic first-pass mechanism, its combination with an opioid deserves further consideration. Other compounds can also enhance deterrence characteristics κ opioid receptors antagonists, such as salvinorin A and nalfurafine, have been able to suppress opioid self-administration in nonhuman primates (Freeman et al., 2014b; Townsend et al., 2017), thereby offering potential alternatives to opioid-containing formulations to counteract abuse and diversion concerns.

1.3.3. Peripherally-selective MOR antagonists

Constipation is the most common and hence the most obstructive adverse effect of using morphine-related (MOR) agonists over a long period of time (Lawlor and Bruera, 1998). These agents inhibit peristalsis, reduce intestinal secretion, and increase the tone of sphincters by activation of peripheral MOR. Acceptance of these gastrointestinal changes is rarely seen with prolonged opioid use (Benyamin et al., 2008). Since the constipation effect is due to MOR stimulation in the bowel, peripherally-selective MOR antagonists with specific activity in the gastrointestinal tract would likely reduce opioid-induced constipation in an opioid dose-responsive fashion without interfering with the analgesic effects of opioids mediated through the central nervous system. Therefore, a number of peripherally-selective MOR antagonists are now clinically approved by the Food and Drug Administration (FDA) to treat opioid-induced constipation during long-term opioid analgesia used in palliative care and noncancerous conditions. (Fischer et al., 2005).

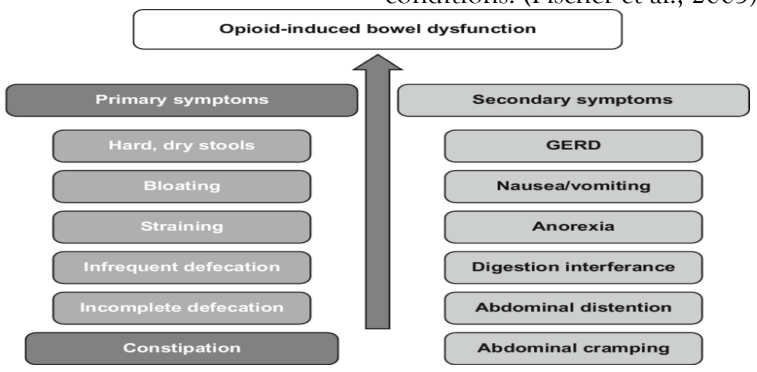

Figure 3: Opioid-Induced Bowel Dysfunction Primary and Secondary Symptoms

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This **figure 3** illustrates the symptoms associated with opioid-induced bowel dysfunction. It divides the symptoms into primary and secondary categories. Primary symptoms include issues directly related to bowel function, such as hard, dry stools, bloating, and straining. Secondary symptoms are related complications like nausea, anorexia, and abdominal distention. These symptoms highlight the negative gastrointestinal effects opioids can have on patients, particularly those on long-term opioid therapy.

It has been seen that the clinical benefits of new mu-opioid receptor antagonists are diminished by the failure to penetrate the blood-brain barrier, leading to a decrease in the ability to compete with endogenous agonists and the associated opioid-withdrawal symptoms. An example of such a drug is naloxegol, a pegylated analogue of naloxone. Naloxegol is a pegylated drug developed by Nektar Therapeutics and later licensed to and marketed by AstraZeneca designed to be highly affine to P-glycoprotein transporter. This change limits the compound to the peripheral circulation, excluding the potential disruptive effects on centrally mediated analgesia or initiating opioid withdrawal (Chey et al., 2014). Several phase-3 studies have demonstrated that naloxegol is safe, well tolerated, and effective in resolving constipation related to chronic non-cancer pain without interfering with the pain reducing effects of opioids (Chey et al., 2014; Tack et al., 2015; Webster et al., 2014). There are comparatively small amounts of pharmacokinetic information surrounding the possible impact of naloxegol on opioid metabolism, as the compound is itself a hypersensitive substrate of the hepatic enzyme CYP3A (Yu et al., 2019).

2. Discussion:

The rising threat to public health posed by opioid misuse, particularly opioid related addiction, overdose and dependence, has deepened academic interest in non-opioid options to manage pain. Traditionally, morphine and oxycodone have been the main pharmacologic solution to moderate to severe pain; however, their abuse potential, as well as negative sequelae including tolerance and constipation, warrants the exploration of safer, yet equally effective alternatives. In this review, therefore, the necessity to develop and popularize non-opioid pharmacological treatment, especially against the background of the current opioid crisis, is emphasized (Volkow et al., 2019).

A variety of possible agents such as antidepressants, anticonvulsants, and non-steroidal anti-inflammatory drugs (NSAIDs) offer hope to treat chronic pain without the risk of liability that opioids present. There is evidence that tricyclic antidepressants and selective noradrenaline reuptake inhibitors (SNRI) are effective in neuropathic pain, but clinical response is inconsistent. At the same time, nerve-associated pain is typically managed with anticonvulsants like gabapentin and pregabalin which have adverse-effect profiles that may limit their long-term applicability. Use of NSAIDs is still rife but its extended use is linked to gastrointestinal mucosa irritation and renal complications (Martinez et al., 2017).

Recent literature on pain management has pointed out the emergence of a number of new therapies. Of these, monoclonal antibodies and cannabinoid-based interventions are attracting more and more scholarly interest and clinical prominence due to their potentially safe and effective outcomes. Eptinezumab is a monoclonal antibody designated to prevent migraine that demonstrated strong efficacy in various randomized controlled trials. Similarly, the use of botulinum toxin as a method of chronic pain management has been successful, although their expensive nature can limit their wide application in clinical medicine. CBD has shown promise in the context of decreasing opioid consumption and dependence, thus a safer alternative in the case of certain patients (Raffa et al. 2010).

One strategy that is currently popular is combination therapy where opioids are administered in combination with non-opioid analgesics or adjuvants to increase their efficacy and to mitigate the adverse effects associated with opioids including constipation and dependence. An example of this is HTX-011, which is an NSAID (meloxicam) combined with a local anesthetic (bupivacaine) showing increasing attention, and which could offer significant reductions in postoperative pain with relatively low doses, as they can offer effects on inflammation and localized pain simultaneously (Espinosa-Juarez et al., 2016).

The emerging development of abuse-sensitive opioids (ADO) is an important breakthrough in reducing

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opioid abuse. ADO formulations such as OxyContin and Hysingla ER prevent abuse channels normally used (e.g., crushing and parenteral administration) and so limit overdose potential. However, the ability of such formulations to reduce the wider opioid epidemic is yet to be firmly determined, with overall rates of opioid misuse still on the rise (Cicero et al., 2015).

A second approach to managing opioid-related morbidity is to introduce peripherally-selective MOR antagonists, including regents such as naloxegol that reduce opioid-related side effects, such as constipation, without sacrificing analgesic efficacy. This modality is a clinically significant intervention in patients with opioid-induced bowel dysfunction, a painful condition seen in long-term opioid treatment (Fischer et al., 2005).

The present debate continues to highlight an enthusiasm on personalized pain management that is combining a pharmacological practice with non-pharmacological interventions like cognitive-behavioral therapy (CBT), and physical therapy. A patient-centered integrative paradigm, respecting individual patient needs and aimed at reducing the risk that comes with opioids, has emerged as essential to the achievement of therapeutic efficacy. The modern pain-management environment indicates significant improvements, but the future of the clinically indicated superiority of non-opioid choices, specifically those targeting the reduction of opioids, is not that secure without an array of future studies. Future developments in the field of formulations and combinations in pharmacological treatment show promise to ensure safer and more effective pain management in the future.

3. Conclusion

Pain management has been reshaped in the last several years, with a stronger emphasis on reducing opioid dependence as concerns about addiction, misuse, and toxicity surfaced abundantly. Despite opioids being the most effective form of severe pain treatment, its associated dangers, namely, dependence, tolerance, and overdose, have increased the search of alternative treatment methods. There is some evidence that non-opioid pharmacotherapies can be used to replace or supplement opioid regimens; these include antidepressants, anticonvulsants, topical preparations, and newer agents such as monoclonal antibodies and cannabinoids. Combination therapy, where opioids are used together with non-opioid substances, has, therefore, become a viable means of enhancing the analgesic effect and reducing the unpleasant effects of opioids. This intervention has the promise of improving the outcomes of opioid complications by allowing lower dosages to provide adequate analgesia. Additional treatment alternatives, such as cognitive-behavioral and physical therapies, have also been critical to pain management and have allowed customized, combined care. Despite significant advances, many non-opioid interventions still need rigorous clinical testing to establish a uniform effectiveness, especially in maximizing drug combinations, reducing dependence and side effects. At the same time, pharmacokinetic innovations in the form of peripherally selective μ-opioid receptor antagonists and abuse-deterrent formulations present the future options in the mediation of safe pain management. Finally, an interdisciplinary, individualized approach that combines pharmacologic interventions and non-pharmacologic treatments is necessary to maximize the effectiveness of individuals with chronic pain.

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