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Managing Opioid Risks and Adverse Effects In a Politically Charged Environment

Overview

Moderate-to-severe pain continues to be widely undertreated in outpatient settings, often due to fears of legal and regulatory sanctions, insurance barriers, and adverse outcomes from opioids. Despite the pain-relieving properties of opioid medications, the potential for abuse remains a concern among primary care providers, pain management specialists, and other clinicians who manage patients with pain. The risk of contributing to an opioid use disorder or overdose is omnipresent.

When an opioid is used, clinicians must also find safe and effective ways to manage adverse effects, such as opioid-induced constipation (OIC). As many as 80% of patients taking an opioid medication experience at least one adverse event, which diminishes overall satisfaction and limits a patient's ability to achieve adequate analgesia.

> *Engaging patients through an interdisciplinary approach can help effectively manage pain.*

This includes ensuring patient adherence and making sure each patient understands how to properly take medication(s). Clinicians must be prepared to discuss potential side effects and ways to manage these events, and must address patient concerns regarding the use of opioids. Clinicians should also be familiar with new and emerging analgesic therapies, some of which tout an improved safety profile.

Managing Opioid Risks and Adverse Effects in a Politically Charged Environment will address factors that prevent appropriate and safe opioid management of pain, and will explore the reduction of adverse effects associated with opioids. Increasing clinicians' awareness of evidence-based pain management can improve patient quality of life and satisfaction.

Contents

Target Audience

This education is intended for surgeons, primary care providers, pain management specialists, and other clinicians who are in need of increased knowledge and competence regarding the management of pain.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Recognize the most common adverse effects of opioid therapy
- Discuss the physician- and patient-related barriers associated with under-treatment of pain
- Identify mechanisms of action, safety and efficacy profiles of agents, particularly new and emerging agents that minimize side effects, to guide personalized pain-management plans

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Jeffrey Gudin, MD	*Consultant/Independent Contractor:* Quest Diagnostics, Collegium, Daiichi Sankyo, Depomed, Egalet, Inspirion, Kempharm, Insys, Salix, Shionogi, Teva
Lynn Webster, MD	*Consultant/Independent Contractor:* Alcobra, Daiichi Sankyo, Depomed, Egalet, Elysium, Inspirion, Insys, Kempharm, Pain Therapeutics, Pfizer, Shionogi, Teva

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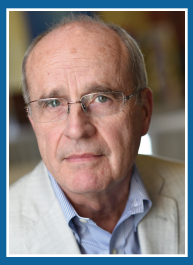
Faculty



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Lynn Webster, MD is a leading pain physician and researcher with a focus on the management of complex pain problems and addiction. Dr. Webster has long been an advocate for patients suffering from chronic pain, and has fought for better education and safer therapies to address the twin crises of chronic pain and addiction in America. He is dedicated to minimizing the potential for harm from pain medications.

Dr. Webster earned his doctorate of medicine from the University of Nebraska and completed his residency in the University of Utah's Department of Anesthesiology. He is board-certified in anesthesiology, pain medicine, and addiction medicine. He lectures extensively and has authored over 300 scientific publications.
Dr. Webster is a senior editor of *Pain Medicine* and former editor of the sections on Neuromodulation and Opioids, Substance Abuse and Addiction. He maintains a loyal base of thousands of followers via the social networks and his blog at www.thepainfultruthbook.com.

Dr. Webster is vice president of Scientific Affairs for PRA, a leading clinical research organization that operates in more than 80 countries. Dr. Webster is a past president of the American Academy of Pain Medicine (AAPM). He is the author of *The Painful Truth: What Chronic Pain Is Really Like and Why It Matters to Each of Us* (Webster Media, LLC) and co-producer of the documentary *It Hurts until You Die*, to be viewed at film festivals and on public television in 2017.

Jeffrey Gudin, MD completed his residency in anesthesiology at the Yale University School of Medicine and his fellowship at the Yale Center for Pain Management. While in New Haven, Dr. Gudin also trained in addiction medicine and directed a substance abuse treatment center. For the last 17 years, Dr. Gudin has been the Director of Pain Management and Palliative Care at Englewood Hospital and Medical Center, a former Mt. Sinai University School of Medicine teaching affiliate in New Jersey. He remains active in teaching and research, and has lectured internationally on a variety of topics in pain management, palliative care, and addiction medicine.

Dr. Gudin has dedicated his career to promoting education in pain management. He attends and has presented at the American Pain Society, American Academy of Pain Management (AAPM), American Academy of Physical Medicine and Rehabilitation, as well as many other national venues. Dr. Gudin serves as a consultant to state medical boards on challenging cases, as well as to industry on novel analgesic products and risk management associated with opioids. He has presented annually at the AAPM Safe Opioid Prescribing Course.

Dr. Gudin is recognized nationally as a leader in pain management. He is an experienced researcher, consultant, speaker, and speaker trainer. He has collaborated with numerous initiatives to enhance responsible prescribing and the safe use of opioid pain medications

Abstract

The treatment of chronic pain is complex and is made more challenging by the barriers to effective pain management that physicians face. Opioids have been a mainstay of chronic pain management, but they do not provide complete pain relief and are not effective or the right choice in all patients. Barriers to effective pain management with opioids include a political opposition, third-party payer requirements, and legal and cultural issues. These barriers, as well as the bothersome and potentially dangerous adverse effects of opioids, contribute to undertreatment of chronic pain. The use of multimodal therapy (including non-opioid measures) may mitigate adverse effects. In addition, there are now treatments for opioid-induced constipation, the most common and bothersome gastrointestinal adverse effect of this drug class. Numerous opioid and non-opioid molecules/compounds are in development for treating pain. They show promise for providing more complete analgesia and/or having a more favorable safety and tolerability profile. Until these newer therapies are available, clinicians need to understand how to safely prescribe opioids when appropriate.

The body's response to pain is complex, involving various domains, including the medical, psychological, physical/mechanical, and sleep aspects. The domains are interrelated, which also contributes to the complexity of treating pain. Coupled with this are the challenges facing physicians to effectively treat patients with chronic pain. Available analgesics are only partially effective—they do not provide a cure—and they have bothersome and potentially dangerous adverse effects. The approach to the treatment of chronic pain becomes one of managing the condition, much like that used for other chronic conditions, such as diabetes or heart disease. With this approach, the goals of treatment are to help patients learn to live with their pain and to improve their quality of life. Better treatments are needed. Emerging therapies are targeting more effective pain control and lessening or improving bothersome side effects.

Managing Barriers and Risks to Pain Management

In addition to meeting the complex challenges of treating chronic pain, physicians must overcome the barriers to effective management of pain with opioids. The barriers include a politically charged environment, third-party payer requirements, and legal issues. Over the last decade, attitudes toward and expectations of treatment, as well as behaviors and understanding of what pain is, have changed a great deal. Treatment guidelines, such as the recent Centers for Disease Control (CDC) Guidelines for Prescribing Opioids,[1] may differ in their recommendations or their focus for type of patient (e.g., cancer, non-cancer patient with chronic pain), making it difficult to know which guideline or recommendation is best suited for a particular patient. Third-party payer requirements of step therapy and denials of treatment other than an opioid are not useful for resolving the complexities inherent in chronic pain management. Such tactics add to the challenges and may deny patients alternative therapies such as cognitive behavioral therapy, extended physical therapies, or abuse-deterrent formulations of opioids. Finally, legal

sanctions and threats of losing one's medical license because of opioid prescribing within the course of one's practice are barriers physicians face.

Another barrier is the cultural stigmatization of chronic pain and its treatment with opioids. A headline in *The Washington Post* (October 16, 2016)—'The drug industry's answer to opioid addiction: More pills'—suggests that physicians and the pharmaceutical industry are creating greater profit at the expense of patients by developing drugs to either treat addiction or mitigate adverse effects patients may experience. Responses to ads for a drug to treat opioid-induced constipation by comedians, commentators, and political staffers that suggest the ad is intended for people who are addicted or that it fuels addiction are polarizing, may result in some physicians not adequately treating chronic pain or the adverse effects of treatment, and indicate cultural attitudes that must be transformed to improve the management of chronic pain. Physicians who advocate for effective treatment of chronic pain receive communications from patients who feel abandoned by their physicians because their medication has been reduced, resulting in pain so severe that they have thoughts of suicide. The dialogue related to the safe and responsible prescribing of opioids for chronic pain management must continue and include education to overcome political, legal, and cultural barriers.

Positioning Opioid Therapy for Chronic Pain Treatment

The barriers to opioid prescribing impact physician decisions and practices. When considering an opioid for a patient with chronic non-cancer pain, several questions can help to position the need for, as well as the potential adverse consequences of, opioid therapy in a given patient (Table 1).[2,3] Documentation of having investigated and/or tried reasonable alternatives, as well as having performed risk assessments (benefit to harm), is important. One must also document that there is a legitimate medical reason for opioid use. However, there is no legal definition of legitimate medical purpose or standard of care for opioid use.

Table 1.
Questions to consider before prescribing an opioid for a patient with chronic non-cancer pain.[2,3]

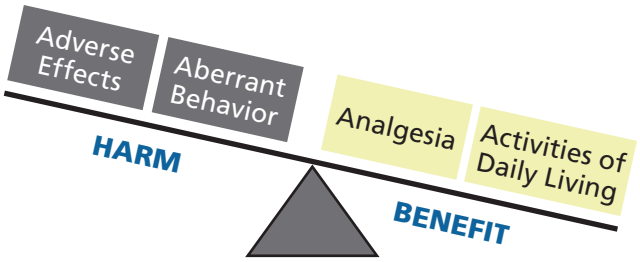
What is conventional practice?
Are there reasonable alternatives?
Is there a relatively high risk of adverse events?
Is the patient likely to be a responsible drug-taker?
Is there a legitimate medical purpose?

Guidelines from both the American Pain Society/ American Academy of Pain Medicine (APS/AAPM) and the CDC outline principles for prescribing opioid therapy.[1,4] An important step in assessing the appropriateness of an opioid is to perform a benefit-to-harm evaluation defined by the APS/ AAPM, including a history, physical examination, and appropriate diagnostic testing both before and on an ongoing basis during chronic opioid therapy. It is also important to understand the outcomes of opioid treatment, which range from the desired adequate pain relief to the adverse outcomes of pseudo-addiction and addiction (Figure 1).

Under-treatment of pain results in ineffective pain relief. Multiple factors contribute to under-treatment of pain with opioids (Table 2).[5-11] Physician factors are largely related to the barriers surrounding treatment, as well as a lack of training in the use of opioids, including patient selection and titration.[5-10] Patient concerns leading to under-treatment of pain relate to their fears of opioid use, socioeconomic and psychological factors, and lack of knowledge regarding the risks associated with opioids.[5-7,10,11] Other factors involve the lack of communication between physicians and patients, often because of a lack of time, and governmental and public policy related to inadequate reimbursement for options other than opioid analgesics to treat pain.[7,10]

It is important to note that non-opioid pharmacologic treatment options for chronic pain also are limited by their efficacy and adverse events. Gastrointestinal side effects, as well as renal and hepatic toxicity, limit the use of non-steroidal anti-inflammatory drugs.[12] Acetaminophen also is associated with renal and hepatic toxicity.[12,13] The

Figure 2.
The 4 A's as a template for balancing benefit to harm in treating patients with chronic pain.



COX-2 inhibitors may have a better gastrointestinal side-effect profile, but are associated with cardiovascular and cerebrovascular adverse events.[14,15] Determining the right treatment for a given patient is about striking a balance between efficacy and adverse events—benefit and harm.[16] The four A's of this balance are illustrated in Figure 2: analgesia, activities of daily living, adverse effects, and aberrant drug-related behavior.[17,18] Emerging data suggest that many opioid-related suicides classified as unintentional actually are intentional, as patients lose hope that their pain can be controlled. A patient-centered approach to treatment in which the four A's of benefit and harm are documented at each visit, with the goal being that the patient's pain is controlled and the quality of life is improved while adverse effects and behavioral changes are minimized, is best.

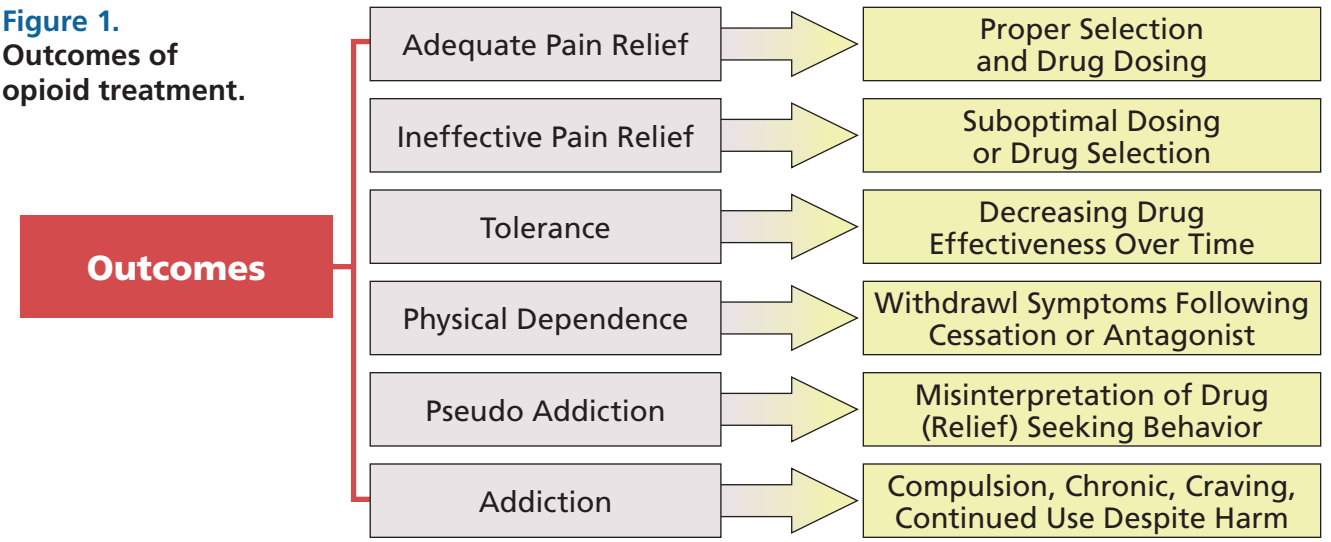
Impact of Opioid-Associated Gastrointestinal Side Effects

The difficult challenge for physicians is to balance analgesia/quality of life with the many potential adverse effects of opioids, which range from bothersome (nausea/vomiting, constipation) to dangerous (respiratory depression, misuse/abuse/addiction); (Table 3).

Table 2.
Factors contributing to under-treatment of pain.[5-11]

■ Physician Related — Fear of disciplinary action/prosecution — Potential for abuse — Lack of training in opioid use/titration	■ Patient Related — Fear of addiction, tolerance — Fear of side effects — Socioeconomic, psychological factors — Lack of knowledge
■ Communication between physician and patient	■ Governmental and public policy on payment for opioids

Figure 1.
Outcomes of opioid treatment.



The product labeling for extended-release opioids has a warning regarding adrenal insufficiency. Opioids, as well as pain, stress, age, sleep, and diet, affect the pituitary-hypothalamic-gonadal axis and may cause endocrinopathy. The fear of adverse effects, fear of regulatory sanctions, major guidelines that indicate opioids are not effective for chronic pain, and difficult-to-manage patients with significant chronic pain contribute to more referrals of patients to pain treatment centers. While opioids are not an appropriate choice for all patients, they are perhaps the only choice that can treat severe levels of pain in a subset of patients.

One finding from a study that evaluated the importance to physicians and patients of side effects with opioid treatment relative to pain relief was that physicians usually underestimated the extent of side effects experienced by patients; nearly all patients (96% of those with chronic, 92% of those with acute pain) reported experiencing at least one side effect while receiving an opioid, whereas physician-estimated incidence rates were much lower (50% of patients reported nausea compared with 25% to 29% of physicians).[19] The study employed adaptive conjoint analysis (ACA) to determine the trade-offs physicians and patients were willing to make regarding benefit (pain relief) and risk (five side effects).[19] Opioid side effects and not pain relief explained the majority of variance for preference for both patients and physicians, with nausea and vomiting the major determinants of medication preference.[19]

The burden with opioid-associated gastrointestinal side effects is multifaceted.[20] For the patient, gastrointestinal side effects are not only bothersome and worrisome, but they also impair work and daily activities and have a negative effect on health-related quality of life. For physicians, they limit dose titration, challenging the balance between pain relief and tolerability, thereby presenting a barrier to optimal pain management and possibly becoming a cause of medical complications. The economic burden is evidenced by prolongation of hospital stays and recovery, increased healthcare resource utilization, and higher costs both for inpatients and outpatients.[20] A far preferable strategy is, therefore, to prevent opioid-associated gastrointestinal side effects rather than treat them once they have occurred.

Opioid-Induced Constipation

Opioid-induced constipation (OIC) is a common and burdensome gastrointestinal side effect that may affect patients' daily activities and quality of life.[19] An international working group of basic science and clinical experts in pain medicine, palliative care, gastroenterology, and gut neurobiology proposed the following definition of OIC, which considers the change in bowel habits from before opioid initiation (baseline) recorded over ≥7 days: "a change when initiating opioid therapy from baseline bowel habits that is characterized by any of the following – reduced bowel movement frequency; development or worsening of straining to pass bowel movements; a sense of incomplete rectal evacuation; harder stool consistency."[21] The group considers the definition a staring point and acknowledges the need for future psychometric evaluations. AAPM incorporated a working definition of OIC into the Bowel Function Index assessment tool in order to provide guidance as to when to give consideration to prescribing medication for OIC (score of ≥30 points on the Bowel Function Index).[22,23]

Table 3.
Adverse effects of opioid treatment.

■ Nausea/Vomiting	■ Endocrine Effects
■ Constipation	■ Tolerance
■ Pruritus	■ Misuse/Abuse/Addiction
■ Ileus, Urinary Retention	■ Diversion
■ Sedation	■ Hyperalgesia
■ Drug:Drug Interactions	■ Respiratory Depression

The reported incidence of OIC varies widely, with up to 95% of patients reporting OIC.[24] A pooled analysis of 15 randomized, placebo-controlled studies of step 3 opioids reported that 80% of patients experienced at least one adverse event and 41% reported constipation.[25] The incidence of constipation was double that in a multinational internet-based survey of patients with chronic pain who were taking daily oral opioids and laxatives (n=322): constipation, the most prevalent opioid-induced adverse event, was reported by 81% of patients, 45% reported <3 bowel movements per week, and 58% reported straining to pass a bowel movement.[26] Another survey of 2,055 persons found that 57% had experienced constipation, and 33% indicated it was the most bothersome adverse event with opioid treatment.[27]

Endogenous opioids modulate pain-related signaling along the nociceptive neuroaxis and bind to receptors throughout the central and peripheral nervous systems.[28] The analgesic effects of opioids are mediated by central μ-opioid receptors, whereas constipation is mediated largely by peripheral μ-opioid receptors in the gastrointestinal tract that modulate physiologic processes from the lower esophageal sphincter to the rectum. Among the mechanisms contributing to OIC are that opioids increase fluid absorption and decrease secretion of electrolytes and water into the intestinal lumen and they innervate nerves in the gut, inhibiting gut motility.[29] Peripherally acting μ-opioid receptor antagonists (PAMORAs) reverse these gastrointestinal effects of opioid analgesics, and are, therefore, useful for the treatment of OIC.

Several prescriptive treatments for OIC are now available, most of which are PAMORAs (Table 4).[28,29] Lubiprostone is the only approved OIC treatment that activates the chloride channel in the gut as its mechanism of action. It is administered orally and is approved also for chronic idiopathic constipation, and irritable bowel syndrome-associated constipation in women. Methylnaltrexone was first approved for subcutaneous administration, as its oral bioavailability is low. An oral formulation is now available that was shown to result in a spontaneous bowel movement (defined as no laxative use in previous 24 hours) within 4 hours of dosing 27% of the time in patients with chronic non-cancer pain and OIC. Nalemedine is another PAMORA that was approved in early 2017 for the treatment of OIC in adults with chronic non-cancer pain, but is not marketed as of the date of this publication.

Table 4.
Therapies approved by the Food and Drug Administration for the treatment of opioid-induced constipation in adult patients with chronic non-cancer pain.

	Lubiprostone	Methyl Naltrexone	Naloxegol	Naldemedine
Mechanism of Action	Chloride channel activator	PAMORA	PAMORA	PAMORA
Route of Administration	Oral	Subcutaneous, Oral	Oral	Oral
Recommended Daily Dose	48 mcg (in 2 divided doses)	Subcutaneous: 8, 12 mg (0.15 mg/kg) Oral: 450 mg (3 tablets)	25 mg, 12.5 mg	0.2 mg with/without food
Indications	OIC, CIC, IBS-C	OIC (Subcutaneous: advanced disease patients receiving palliative care and insufficient response to laxative therapy)	OIC	OIC

Abbreviations: CIC = chronic idiopathic constipation; IBS-C = irritable bowel syndrome-associated constipation; OIC = opioid-induced constipation; PAMORA = peripherally acting μ-opioid receptor antagonist.

Emerging Therapies for the Treatment of Pain

Considerable research is ongoing to identify compounds/molecules that are effective analgesics with improved safety and tolerability, as well as formulations to deter abuse. Table 5 summarizes some of those emerging therapies under investigation, while Figure 3 illustrates abuse deterrent formulations either in use or under investigation.

One approach to abuse deterrent formulations is to alter the properties of the capsule or tablet. For example, the capsule/tablet may have a hard coating that renders it difficult to crush or split or its physicochemical properties are altered by creating a copolymer that becomes gummy and does not dissolve in water or alcohol. Another approach is by using a prodrug, for example, benzhydrocodone (a combination of hydrocodone and benzoic acid), which is being developed as an immediate-release oral formulation to deter against non-oral routes of abuse. The discovery of new chemical entities such as NKTR 181 affects both the benefits and risks of opioids. It is a long-acting, selective μ-opioid agonist that provides pain relief without the inherent rapid onset euphoria, as it has low permeability across the blood-brain barrier, slowing its rate of entry into the brain and attenuating euphoria [Nektar R&D Information]. A human abuse potential study found significantly lower abuse potential with NKTR 181 compared with oxycodone.

Opioid Drugs

Other opioid and opioid-like therapies provide relief of pain, but are associated with fewer adverse effects. A combination of a sustained release agonist (oxycodone) and a sustained release antagonist (naloxone) also affects the benefits and risks of opioids. Naloxone blocks the μ-opioid receptors in the gut, thereby mitigating opioid-induced constipation. Overseas, the combination was shown to provide effective relief of non-cancer pain and to significantly improve bowel function, as measured by an improvement in the bowel function index, an increase in the number of complete spontaneous bowel movements, and a decrease in laxative use.[30]

Some opioid-like compounds may agonize cell membranes differently, resulting in analgesic efficacy with less adverse effects. Examples are tramadol, which stimulates the μ-opioid receptor and is a selective serotonin reuptake inhibitor (SSRI), and tapentadol, which also stimulates the μ-opioid receptor and is a serotonin-norepinephrine reuptake inhibitor.[31,32] Tapentadol extended release is approved for the treatment of diabetic peripheral neuropathy.[33] An opioid-like molecule under investigation, cebranopadol is a μ-opioid receptor agonist, as well as a nociceptin/orphanin FQ peptide receptor (NOP) agonist, which is a more recently identified opioid-like receptor [Grünenthal Press Release 2016].[34] Activation of the NOP receptor is effective against neuropathic, inflammatory, and visceral pain, with low risk of respiratory depression and addiction, while μ-opioid receptor activation is effective against nociceptive pain. Thus, the combined receptor agonist activity appears to provide analgesic efficacy across a broad pain spectrum (chronic cancer, osteoarthritis, low back pain, diabetic peripheral neuropathy), with reduced risk of adverse effects.

Research suggests that opioid-induced analgesia results from μ-opioid receptor signaling via the G-protein channel, whereas adverse effects such as constipation and respiratory depression are conferred downstream of μ-opioid receptor activation via the ß-arrestin channel.[35,36] Based on these findings and using computational methodology, researchers have identified 'biased' opioid agonist ligands, including TRV130 and PZM21, that provide analgesia equivalent to morphine without the associated adverse effects of respiratory depression or constipation.

A new class of drugs that target the peripheral kappa opioid receptor, the κ-opioid receptor agonists (KORAs), are hydrophilic tetrapeptides that penetrate the blood-brain barrier poorly [Cara Therapeutics R&D Information, 2017]. Activation of the central κ-receptor is associated with dysphoria and hallucinations, but in the periphery, activating κ-receptors have anti-nociceptive, anti-inflammatory, and antipruritic effects. Among the first KORAs in development is CR845, which has shown analgesic and antipruritic effects without the usual opioid

adverse effects and abuse/dependence potential in phase 2 studies of acute postoperative pain, chronic pain, and pruritus [Cara Therapeutics R&D Information, 2017; Cara Therapeutics Press Release, 2017]. Both intravenous and oral formulations are being studied.

Non-Opioid Drugs

Several classes of non-opioid drugs marketed for other indications, such as alpha-2-adrenergic agonists, N-methyl-D-aspartate (NMDA) receptor antagonists, and gabapentanoids, are now being used for the treatment of chronic pain (Table 5).

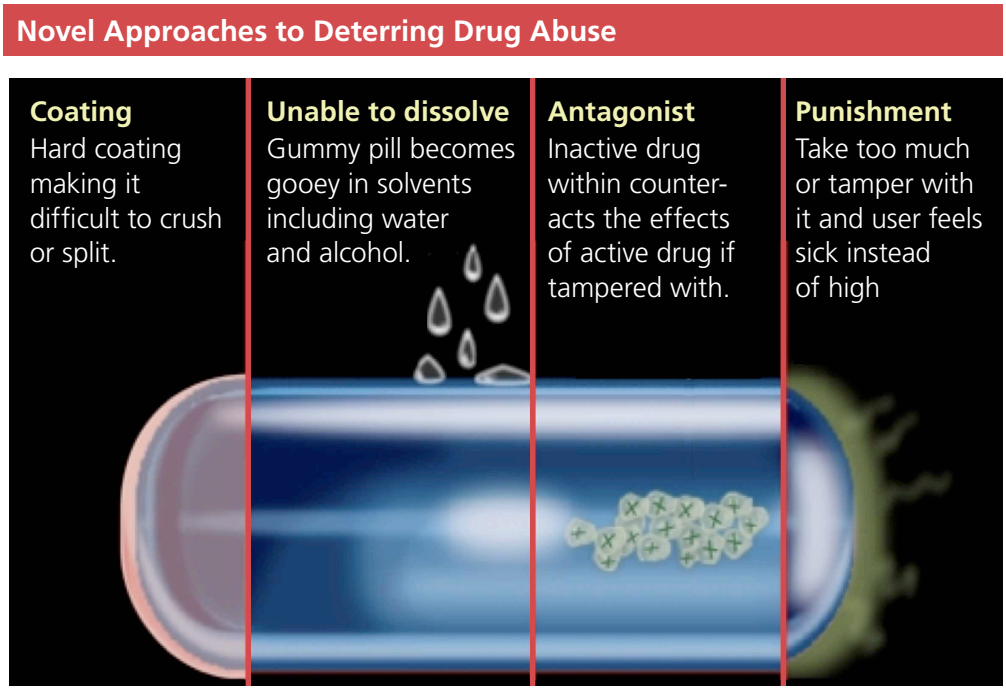
Table 5.
Emerging analgesic compounds/molecules that may demonstrate improved efficacy, safety, and tolerability.

Opioids	Non-Opioids
Abuse Deterrent Formulations (prodrug agonist/ antagonist, delivery systems, aversive therapies, combination agents)	Alpha-2-Adrenergic Agonists (clonidine, dexmedetomidine)
Slow-Entry Opioids (NKTR 181)	NMDA Receptor Antagonists (ketamine, dextromethorphan, magnesium)
Opioid-Like Molecules (cebranopadol, tramadol tapentadol)	Gabapentanoid Compounds
'Biased' Opioid Compounds (TRV 130, PZM 21)	Novel NSAIDs
Kappa Opioid Receptor Agonists (CR 845)	NGF Antagonists (TrkA inhibitors)
	Glial Cell Modulators
	Cannabinoids

Abbreviations: NMDA = N-methyl-D-aspartate; NSAIDs = non-steroidal anti-inflammatory drugs; NGF = nerve growth factor.

Figure 3.
Abuse deterrent opioid formulations in practice or under investigation.

- Physicochemical
  - PEO
- Agonist/antagonist
  - Naloxone, Naltrexone
- Prodrug
  - Benzhydrocodone
- Delivery Systems
  - Depots, implants
- Combination agents
- Aversive therapies
- New Chemical entities
  - NKTR-181 slow entry opioid

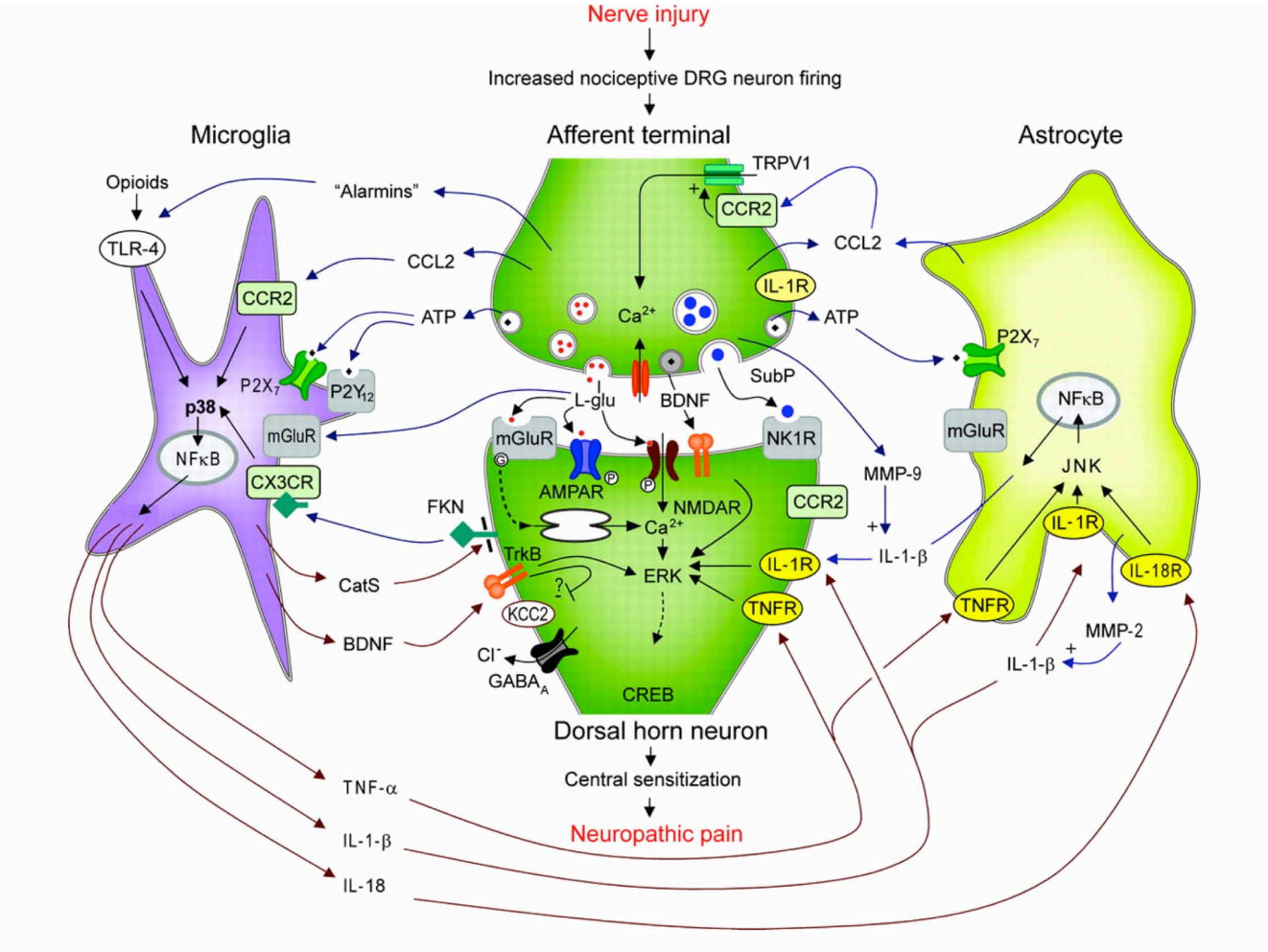


Inflammation, angiogenesis, nerve growth, and pain are interconnected processes.[37] Nerve growth factor (NGF) belongs to a family of molecules known as neurotrophins, target-derived proteins that regulate the survival, development, and function of subsets of sensory and sympathetic neurons, and neurotrophins bind to tropomyosin-related kinase (Trk) receptors.[38] NGF plays a role in both acute and chronic inflammatory pain, preferentially binding to the TrkA receptor. It sensitizes peripheral nerves and may stimulate blood vessel and nerve growth in structures that are not normally innervated, such as articular cartilage, as well as possibly leading in turn to sensory nerves, releasing neuropeptides that augment inflammation. Research has shown that therapies that target the NGF-TrkA-signaling pathway have significant analgesic efficacy, including difficult-to-treat chronic pain states, such as rheumatoid and osteoarthritis.[38,39]

It is now appreciated that glial cells, as well as neurons and their interactions, contribute to chronic pain, as glial cells modulate neuronal excitability following injury and disease.[40] Three types of glial cells are implicated in the development and maintenance of chronic pain: microglia and astrocytes in the central nervous system and satellite glial cells in the dorsal root and trigeminal ganglia. Glial mediators modulate excitatory and inhibitory synaptic transmission at pre-, post-, and extra-synaptic sites (Figure 4).

Accumulating evidence indicates that cannabinoids impact normal inhibitory pathways and pathophysiological processes that influence

Figure 4.
Complex nociceptive response and multi-mechanistic interactions.



nociception.[41,42] Neurotransmission via the endocannabinoid system, comprised of cannabinoid receptors (CB1, CB2), their endogenous ligands, and enzymes for their biosynthesis and degradation, is increasingly appreciated as a regulator of pain perception and modulation. The brain produces a number of compounds, including anandamide and N-arachidonoyldopamine (NADA), with submicromolar affinity for cannabinoid receptors that function to suppress pain sensitivity. Cannabinoids putatively promote analgesia through the CB1 and CB2 receptors, but may increase pain via the transient receptor potential vanilloid 1 receptor (TRPV1). Novel agonists and antagonists of the endocannabinoid system with receptor subtype selectivity are in development. They should provide a greater understanding of the physiological role of the endocannabinoid system in different pathologies.

Conclusions

There are many formidable barriers to treating chronic pain. Treatment plans for patients should be personalized and patient centered. Alternative therapies should be considered before opioids, and when opioids are prescribed, their potential benefits must outweigh their potential harm. The use of multimodal techniques may complement the partial efficacy that may occur with opioids. In those patients for whom opioids do not help, clinicians need to have an exit strategy. While opioids remain a mainstay for the treatment of severe chronic pain for a select population, newer therapies that are better tolerated with a more favorable adverse effect profile are needed. A number of novel opioid and adjuvant analgesics currently in development may change the landscape for chronic pain management. They show promise for improved safety and tolerability profiles, as well as higher patient satisfaction, and may have improved analgesic efficacy. Until these newer therapies are available, clinicians need to understand how to use opioids with fewest adverse effects.

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Post-Test

In order to receive credit, please complete the online CME/CE post-test and evaluation form at www.rockpointe.com/ManagingOpioids. The post-test questions are listed below for your reference and convenience, and are identical to the post-test you will find online.

However, to receive credit you must complete the online form at: www.rockpointe.com/ManagingOpioids. If you are experiencing problems or have any questions, please email contact@rockpointe-pcme.com.

1 Patients are usually willing to sacrifice pain relief for a reduction in adverse effects?

A. True

B. False

2 What best describes the clinical definition of OIC?

A. Fewer than 2 spontaneous bowel movements per week

B. Fewer than 5 complete bowel movements per week

C. Change bowel habits after initiating opioid therapy

D. Development of hemorrhoids after starting opioid therapy

3 The primary purpose of a clinical definition of OIC is to:

A. Define OIC as a disease

B. Help determine when prescriptive therapies should be considered

C. Improve communication between PCPs and gastroenterologists

D. Help patients understand risk of chronic opioid therapy

4 The incidence of nausea associated with the use of opioids for acute pain is approximately:

A. 10%

B. 20%

C. 40%

D. 60%

E. 75%

5 Analgesics of the Future include:

A. Novel opioid-like molecules

B. Glial cell modulators

C. NGF inhibitors

D. Alpha-2 adrenergic agonists

E. All of the above