Prescription opioids are commonly prescribed for the relief of many kinds of pain syndromes, including cancer pain. In order to combat the growing rates of abuse and misuse of prescription opioids, the Centers for Disease Control and Prevention, along with the U.S. Food and Drug Administration and multiple pharmaceutical companies, have implemented many risk mitigation strategies. Abuse-deterrent drug delivery technology and more consistent prescribing of the opioid antagonist, naloxone, are two of the mechanisms of reducing harm in patients on chronic opioid therapy. Abuse-deterrent technology is implemented into different commercially available opioid products with the intent of discouraging manipulation of the opioid or making the use of the manipulated opioid less appealing.

Use of the opioid antagonist, naloxone, for reversal of intentional or unintentional opioid overdose is a safe and effective means to reduce potential risk in patients who are on opioids for pain management. These mechanisms have multiple advantages and limitations that influence their practical use specifically in patients with cancer pain. Patients with cancer pain have unique therapeutic needs and goals, and their balance of treatment risks and benefits differs from that of other kinds of chronic pain disorders. This article provides an overview of the advantages and limitations of these specific harm-reduction strategies and provides guidance on how to practically utilize them when caring for patients with cancer pain.
population. However, no patient population is exempt from potential opioid misuse or opioid-related harm; therefore, risk mitigation strategies should always be considered in the process of creating a comprehensive care plan. This article will focus on two specific harm-reduction efforts, specifically, the use of abuse-deterrent formulations of prescription opioids and the prescription of naloxone for those at increased risk of intentional or unintentional overdose, and their practical implications for use in patients with cancer pain.

**ABUSE-DETERRENT TECHNOLOGY**

The use of extended-release (ER) or long-acting (LA) opioid formulations is very common in clinical practice when treating patients with cancer pain that is not responsive to other, non-opioid analgesics. The use of ER or LA opioids for chronic cancer pain management results in significant benefits over the sole use of immediate-release (IR) formulations, including reduction in overall baseline pain, improved sleep, and convenience of administration [4]. The danger of manipulating ER or LA products for misuse, compared with that of IR products, is that there is often a greater amount of drug in each dosing unit, which greatly increases the risk of overdose when manipulated for misuse. However, this very reason is why the ER and LA formulations are of greater value to those who seek to misuse opioids: a higher dose will likely result in a greater “high.” The challenge health care providers are facing is how to balance the appropriate use of prescription opioids with the risks and consequences that are associated with potential misuse and abuse.

One mechanism that was developed to help mitigate the misuse of prescription opioids is abuse-deterrent technology. Abuse-deterrent technology is utilized with the intent of discouraging manipulation (e.g., crushing, snorting, injecting) of prescription products or making the use of the manipulated product less appealing [5]. The result of using this technology as a method of regulating prescription drug misuse was the production abuse-deterrent formulations (ADFs) of opioids [5]. ADFs include all opioid products that have one or more properties that increase the difficulty of abuse, make abuse less attractive and/or less rewarding [1, 4]. Prior to the use of ADFs, all opioids were susceptible to physical manipulation meant to alter the routes of administration from their intended use [4].

At first glance, these ADFs seem like a wonderful solution to reduce risk, abuse, and addiction. These products give providers a mechanism by which to effectively treat patients with chronic pain while limiting abuse, with the intention to then limit rates of addiction and substance use disorder. Unfortunately, it is not quite that simple. There are clear advantages but also significant limitations to the use of ADFs in clinical practice, and all should be considered carefully when evaluating their role.

**PRACTICAL ADVANTAGES AND LIMITATIONS TO ADFS**

There are multiple mechanisms which by abuse-deterrent technology is utilized. It is important to recognize that opioid products can be abused in multiple ways [1]. Common routes of abuse include swallowing whole, crushing and swallowing, chewing and swallowing, crushing and snorting, crushing and smoking, and dissolving and injecting [1, 4]. The U.S. Food and Drug Administration (FDA) currently categorizes different ADF technology into groups including physical or chemical barriers, agonist-antagonist combinations, aversion technology, delivery system technology, new molecular entities and prodrugs, combinations of these ADFs, and other novel approaches [1]. More descriptive information about each of these categories can be found below. The intent of these technology categories is to reduce the likelihood that the product can be converted into a form that could be snorted or injected, thereby inhibiting some of the most frequently used routes of abuse.

**Physical or chemical barriers [1]:**

- Physical barriers: prevent crushing, chewing, cutting, grinding, or opening of the dosage form.
- Chemical barriers: gelling agents that help resist extraction using common solvents like water, simulated biological media, alcohol, or other organic solvents.
- Physical and chemical barriers limit drug release following mechanical manipulation, or change the physical form of a drug, rendering it less amenable to abuse.

**Agonist-antagonist combinations [1]:**

- An opioid antagonist can be added to interfere with, reduce, or defeat the euphoria associated with abuse. The antagonist can be sequestered and released only upon manipulation of the product.
- For example, a drug product can be formulated such that the substance that acts as an antagonist is not clinically active when the product is swallowed but becomes active if the product is crushed and injected or snorted.

**Aversion technology [1]:**

- Substances can be added to the product to produce an unpleasant effect if the dosage form is manipulated or is used at a higher dosage than directed.
- For example, the formulation can include a substance irritating to the nasal mucosa if ground and snorted.

**Delivery system technology [1]:**

- Certain drug release designs or the method of drug delivery can offer resistance to abuse.
- For example, sustained-release depot injectable formulation or a subcutaneous implant may be more difficult to manipulate.

Combinations [1] of these technologies refers to the use of two or more of the above-mentioned methods combined to deter abuse. And the category of novel approaches [1] encompasses any means or technologies that are not captured in the previous categories.

The use of these ADF technologies was shown in clinical studies to demonstrate significant reduction in various abuse-related parameters and indicators [6], as well as a decrease in intentional and unintentional overdose events [6]. What is important to remember is that many of these studies look at abuse of a single product or two products at most. What these studies have failed to depict is that the reduction in abuse of a single product does not carry across the entire class of opioid medications. A study by Cicero and colleagues showed that...
The use of ADF technology alone is not enough to simply imply that a drug product is abuse deterrent, but it does not mean abuse-proof. Although the intent of ADF technology is to limit the abuse potential, there is a caveat with all individual products, such as Oxycontin. Additionally, there are other limitations of ADFs that are important to highlight.

As new ADFs are brought to market, they are available first as branded products and are markedly more expensive than the generic, non-abuse-deterrent formulations that are currently on the market [6]. This can be a barrier for patients without insurance, but also for those with insurance, as companies are hesitant to spend more money on a drug that is available more cheaply. However, as more third-party payers include ADFs in covered formularies, patients may not have to pay as much out of pocket for these medications [6].

It is also important to understand that ADF technology simply implies that a drug product is abuse deterrent, but it does not mean abuse-proof. Although the intent of ADF technology is to limit the abuse potential, there is a caveat with all ADF products brought to market that abuse is still possible. No ADF product on the market can prevent abuse or misuse by simply swallowing more than the prescribed number of dose units. The use of ADF technology alone is not enough to cease all abuse of prescription opioids, which is a deeply rooted concern across the U.S. More importantly, an opioid that is produced with ADF technology does not make the drug product any less addictive, which is a common misconception by many users. Misuse of ADF opioids can result in addiction in the same way that non-ADF opioids can, and they should not be considered a “safer” alternative to generic opioids. Although there are many commercially available products that use abuse-deterrent technology, only eight of those products have received FDA abuse-deterrent labeling. A comprehensive list of the commercially available, FDA-approved products with abuse-deterrent labeling, the available formulation, and their specific abuse-deterrent mechanism can be found in Table 1.

### Table 1. Commercially available products that have U.S. Food and Drug Administration-approved labeling describing abuse-deterrent properties using ADF technology

| Generic drug                  | Brand name of ADF | Formulation | ADF technology used                                                                 |
|------------------------------|-------------------|-------------|-------------------------------------------------------------------------------------|
| Hydrocodone                  | Hysingla ER [3, 11] | ER tablet   | Physiochemical technology: intended to make the tablet more difficult to manipulate for misuse and abuse |
| Morphine                     | Arymo ER [3, 12]  | ER tablet   | Physiochemical technology: formulated with inactive ingredients to make the tablet more difficult to manipulate for misuse and abuse |
| Morphine                     | Morphabond ER [3, 13] | ER tablet   | Physiochemical technology: formulated with inactive ingredients to make the tablet more difficult to manipulate for misuse and abuse |
| Morphine/naltrexone          | Embeda [3, 14]    | ER capsule  | Agonist/antagonist combination: formulated with a sequestered opioid antagonist (naloxone) which is released with manipulation by crushing |
| Oxycodone/naloxone           | Targiniq ER [3, 15] | ER tablet   | Agonist/antagonist combination: formulated with a sequestered opioid antagonist (naloxone) which is released with manipulation by crushing |
| Oxycodone                    | Roxybond [3, 16]  | IR tablet   | Physiochemical technology: formulated with inactive ingredients to make the tablet more difficult to manipulate for misuse and abuse |
| Oxycodone                    | Oxycontin [3, 17] | ER tablet   | Physiochemical technology: formulated with inactive ingredients to make the tablet more difficult to manipulate for misuse and abuse |
| Oxycodone                    | Xtampza ER [3, 18] | ER capsule  | Physiochemical technology: contains microspheres formulated with inactive ingredients to make the tablet more difficult to manipulate for misuse and abuse |

Abbreviations: ADF, abuse-deterrent formulation; ER, extended release; IR, immediate release.

Naloxone use in the setting of opioid overdose reversal is a relatively safe and effective treatment. The most notable adverse effect of naloxone use is the precipitation of severe opioid withdrawal [9]. Abrupt reversal of opioid effects in a person who is physically dependent on opioids has been shown to increase the risk of severe withdrawal symptoms. Naloxone can be used to reverse opioid effects in patients who have been administered opioids for pain management. The increasing rate of opioid-related overdose deaths has led to the increasing use of naloxone in the community [8]. Naloxone is available in different routes of administration, including intravenous, intramuscular, and intranasal, with growing popularity of the intranasal formulation in the community.

**Naloxone: Risk Mitigation Strategy**

An alternative method of risk mitigation related to the opioid crisis is providing the use of naloxone for the reversal of intentional as well as unintentional opioid overdose. Numerous societies and guidelines have adapted to advocate for naloxone to be used as a harm-reduction strategy [8] for patients with a history of opioid use disorder as well as those on prescription opioids for pain management. The increasing rate of opioid-related overdose deaths has led to the increasing use of naloxone in the community [8]. Naloxone is available in different routes of administration, including intravenous, intramuscular, and intranasal, with growing popularity of the intranasal formulation in the community.

Naloxone use in the setting of opioid overdose reversal is a relatively safe and effective treatment. The most notable adverse effect of naloxone use is the precipitation of severe opioid withdrawal [9]. Abrupt reversal of opioid effects in a person who is physically dependent on opioids has been shown to
precipitate acute withdrawal syndrome which includes symptoms such as body aches, fever, sweating, runny nose, piloerection, weakness, shivering, nervousness, restlessness, diarrhea, nausea and vomiting, abdominal cramps, increased blood pressure, and tachycardia [9].

**Controversy of Naloxone Use in Patients with Cancer**

Although the use of naloxone as a means of harm-reduction for those at high risk of overdose has been well studied and widely accepted, there is some controversy surrounding the use of naloxone in patients who have life-limiting illnesses, including cancer. Patients who are diagnosed with a life-limiting condition pose a very specific challenge for health care providers to balance the risks and benefits of opioid use for symptom management. An important question to address in this patient population is, Are the risk mitigation strategies used in the general population easily translatable to those who have a life-limiting disease? The answer may not be as clear as one would hope.

Pain is one of the most common symptoms associated with a cancer diagnosis and can have negative impact on a person’s functional status and quality of life [10]. Pain occurs in 20% to 50% of patients with cancer, and roughly 80% of patients with advanced-stage cancer have moderate to severe pain [10]. Additionally, the use of opioid medications for the relief of moderate to severe cancer pain is considered necessary for most patients at some point during the disease process [10]. Patients with cancer pain can be on opioid medications for long periods of time, and their medications are often titrated to specific indications. The implementation of naloxone prescribing in this subpopulation of patients is likely to have much greater risk or harm than benefit in the setting of suspected opioid intoxication because of reasons discussed above.

The other setting in which naloxone can be beneficial to prescribe to patients with cancer pain is if there is a history of or risk of abuse of the patient’s medications by a family member or friend who is frequently in the home or has access to the medications. Although it may be controversial to utilize naloxone on a patient battling cancer, there is more evidence for use in someone without a serious illness, who misuses opioids with no therapeutic indication and experiences an intentional or unintentional overdose. The presence of opioid medications in the home increases the risk of misuse, abuse, or overdose by family members and friends simply because of access. The patient and prescriber should explore prescribing naloxone for this specific purpose after determining the potential for harm on a case-by-case basis.

**Disclosures**

The author indicated no financial relationships.

### References

1. Center for Drug Evaluation and Research. Abuse-Deterrent Opioids – Evaluation and Labeling: Guidance for Industry. Rockville, MD: Center for Drug Evaluation and Research, Food and Drug Administration, U.S. Department of Health and Human Services; April 2015.

2. Dowell D, Haegerich TM, Chou R. CDC Guideline for prescribing opioids for chronic pain – United States, 2016. JAMA 2016;315:1624–1645.

3. Abuse-deterrent opioid analgesics. U.S Food and Drug Administration website. https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/abuse-deterrent-opioid-analgesics. Updated April 16, 2018. Accessed April 15, 2019.

4. Fudin J, Bettinger JJ, Raouf M. Expanding the pharmacist’s role in prevention opioid abuse: Understanding abuse-deterrent formulations and identifying risks [continuing education course]. Power-Pak CE website. https://www.powerpak.com/course/preamble/115940. Published December 22, 2017. Accessed April 15, 2019.

5. Lee Y, Brown DL, Chen HY. Current impact and application of abuse-deterrent opioid formulations in clinical practice. Pain Physician 2017;20:E1003–E1023.

6. Simon K, Worthy SL, Barnes MC et al. Abuse-deterrent formulations: Transitioning the pharmaceutical market to improve public health and safety. Ther Adv Drug Saf 2015;6:67–79.

7. Cicero TJ, Ellis MS, Suratt HL. Effect of abuse-deterrent formulation of OxyContin. N Engl J Med 2012;367:187–189.

8. Dunne RB. Prescribing naloxone for opioid overdose intervention. Pain Manag 2018;8:197–208.

9. NARCAN Nasal Spray, naloxone hydrochloride [package insert]. RADNO, PA: Adapt Pharma; 2017.

10. PDQ Supportive and Palliative Care Editorial Board. PDQ Cancer Pain – Health Professional Version. Bethesda, MD: National Cancer Institute; March 6, 2019. https://www.cancer.gov/about-cancer/treatment/side-effects/pain/pain-hp-pdq. Accessed April 17, 2019.

11. Hysingla ER – hydrocodone bitartrate tablet, extended release [prescribing information]. Stamford, CT: Purdue Pharma; 2018. http://app.purduepharma.com/xmlpublishing/pi.aspx?id=h. Accessed April 15, 2019.

12. Amaryo ER – morphine sulfate tablet, film coated, extended release [prescribing information]. Wayne, PA: Egalet US; 2018. https://dailymed.nlm.nih.gov/dailymed/druginfo.cfm?setid=e60552c9-06ce-4790-95e7-aad4df12b2a. Accessed April 15, 2019.

13. Morphabond ER – morphine sulfate extended release tablet [prescribing information]. Basking Ridge, NJ: Daiichi Sankyo; 2018. http://dsi.com/about-cancer/treatment/side-effects/pain/pain-hp-pdq. Accessed April 14, 2019.

14. Embeda (morphine sulfate and naltrexone hydrochloride) extended-release capsules [prescribing information]. New York, NY: Pfizer Laboratories;
For Further Reading:
Judith A. Paice. Risk Assessment and Monitoring of Patients with Cancer Receiving Opioid Therapy. *The Oncologist* 2019;24:1294–1298; first published on May 22, 2019.

Implications for Practice:
Throughout the trajectory of cancer care, opioid use is often indicated, and, in fact, it may be unethical to limit or prohibit the use of opioids when pain is severe. Oncologists face the significant challenge of providing cancer pain control that is safe and effective, while limiting individual risk for abuse or overdose and keeping the community free of diverted substances. Most oncology providers report inadequate training in chronic pain principles and in managing addiction. Risk assessment and mitigation measures can be incorporated within oncology care to enhance effective pain management while reducing the potential for harm.