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## Review Article

## Ongoing strategies and updates on pain management in gynecologic oncology patients

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## HIGHLIGHTS

- Gynecologic oncology patients experience disease and treatment related acute pain.
- The goal of treatment should be to maximize function and minimize side effects.
- Consider adjunct medications and neuraxial/local analgesia to minimize opioids.
- A multidisciplinary approach should be considered in the treatment of chronic pain.

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## ABSTRACT

The opioid crisis in the United States has been declared a public health emergency. Various governmental agencies, cancer care organizations and the Centers for Disease Control and Prevention have issued guidelines in hopes of managing this crisis. Curbing over-prescription of opioids by medical professionals has been a central theme in many of these guidelines. Gynecologic oncologists encounter patients with a variety of pain sources, including acute pain secondary to the underlying malignancy or surgical procedures as well as chronic pain related to the malignancy and the sequelae of treatments rendered. In this review, we discuss the various etiologies of pain experienced by gynecologic oncology patients and discuss modalities frequently used to treat this pain. We highlight strategies to reduce the number of opioids prescribed and focus on incorporating non-opioid pain relief management principles in this review. We also discuss the mechanisms and etiology of various types of pain, with a focus on multimodal treatment strategies including preoperative counseling, strategies to identify individuals at risk of developing opioid dependence, and the role of symptom management and palliative care teams. Finally, we provide a blueprint for gynecologic oncology practices to develop their practice-specific pain management contracts to engage patients in a meaningful conversation around the addictive potential of opioids.

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## 1. Introduction

In the 1990s, multiple organizations including the American Pain Society and the Institute of Medicine began to identify pain management as an important component of patient care [1]. By 2001, the Joint Commission released standards addressing pain management and encouraged systematic assessment and treatment of pain [2]. Over the past fifteen years, the number of opioid prescriptions in the United States has increased dramatically as physicians have attempted to follow these recommendations [3]. By 2012, 259 million prescriptions for opioid medications were prescribed by American physicians [3,4]. Over the past twenty-year time period, the number of opioid overdose deaths has risen four-fold [5]. In 2017, ninety-one Americans die every day from an opioid overdose and the majority of these overdoses involved prescription medications [5].

With the recent awareness of the opioid epidemic in the United States, various state legislatures, the federal government, the Centers for Disease Control and Prevention (CDC) and numerous cancer organizations have entered into the discussion regarding physician opioid prescribing practices. Many of these entities, including the CDC and National Academy of Sciences, recommend limiting the use of opioids in the management of chronic pain [6,7]. Additionally studies have suggested that limiting the prescription of opioids in the treatment of acute pain may prevent patients from becoming long term opioid users and a recent study revealed that over 10% of opioid-naïve cancer patients undergoing primary treatment with curative intent were using opioids at one year [8]. Acute pain is typically described as pain lasting less than three months [6]. Once pain has persisted for three or more months, it is considered chronic pain [6]. The conversion of acute pain to chronic pain is poorly understood but the designation between the two is important since the pathophysiology may be different and the current treatment guidelines put forth by the CDC and National Comprehensive Cancer Network (NCCN) differentiate between the two entities [6,7,9].

Gynecologic oncologists encounter patients with a variety of pain sources, including acute and chronic pain [10]. Our patients may experience acute pain due to disease burden or cancer treatments [10]. Gynecologic oncology patients frequently have higher rates of moderate to severe pain and opioid use than patients diagnosed with other cancers [10,11]. Moreover, patients living longer, with or without active disease, frequently develop chronic pain either as a result of previous treatments or disease burden. Thus, all gynecologic oncologists should be familiar with pharmacologic and non-pharmacologic methods of treating both acute and chronic pain. In this review, we discuss the various etiologies of pain experienced by gynecologic oncology patients and discuss modalities frequently used to treat this pain, with a focus on incorporating non-opioid pain relief strategies.

## 2. Acute pain

Over two-thirds of advanced stage cancer patients experience severe pain and up to half of these patients report that their pain is poorly controlled [12,13]. Gynecologic Oncology patients are no different and may experience acute pain as a result of disease burden or cancer treatment.

### 2.1. Acute cancer pain

#### 2.1.1. Mechanism

Mechanisms through which cancer produces pain are incompletely understood. Likely mechanisms include tissue destruction or stimulation of cytokine secretion leading to pain. Local tissue destruction occurs secondary to tumor production of proteases resulting in the breakdown of adjoining tissues allowing cancer to expand into neighboring tissues [14,15]. Pain is not always proportional to tumor burden as different types of cancers can cause differing levels of local tissue destruction and can stimulate production of varying amounts of pain modulators [16]. In the cancer microenvironment, there is signaling and

communication between neoplastic cells, the immune system and the peripheral and central nervous systems [16–19]. Substances produced by cancer cells stimulate immune cell migration and nerve growth into the tumor [19–21]. Once lymphocytes and other immune cells have infiltrated a tumor, they produce substances leading to further tissue damage and secrete neuromodulators [16,22]. These neuromodulators lead to sensitization and activation of peripheral afferent neurons, and overexpression of nociceptive mediators in the spinal cord [16]. All of these changes lead to increased pain signaling in cancer patients.

With complex crosstalk between the nervous system and cancer, there will likely neither be one pathway we can target to treat cancer pain, nor a “one size fits all” treatment strategy for controlling cancer pain. Additionally, many cancer patients have high levels of anxiety and depression following their diagnosis and these co-existing conditions are associated with higher levels of pain [23–28]. Because pain is a “result of a complex interaction” with physical, psychological, and social components [29], individual pain management plans for gynecologic oncology patients should involve multiple disciplines with multimodal treatment strategies including pharmacologic and non-pharmacologic interventions.

#### 2.1.2. Management strategies

Due to the ethics of studying pain in cancer patients, studies evaluating the treatment of pain in this patient population are limited and rarely offer level I evidence. Thus, treatment guidelines are often derived from historical and anecdotal practices and treatment of non-cancer pain rather than data from clinical trials.

**2.1.2.1. Opioids.** There have been few good studies examining the use of opioids in the treatment of acute cancer pain, especially comparing them to non-opioid modalities [30,31]. In a systematic review evaluating the effectiveness of opioids for cancer pain, Koyyalagunta et al. evaluated fifteen studies and found “there is no concrete evidence of the effectiveness and safety of opioids in cancer pain” [31]. A recent Cochrane review examined the use of all opioids in cancer pain and came to the conclusion that “the amount and quality of evidence around the use of opioids for treating cancer pain is disappointingly low” [32]. Nonetheless, the authors conclude that oxycodone “should” decrease cancer pain to mild or no pain within 14 days [32]. Despite the dearth of evidence, oncology experts and health organizations worldwide recommend opioids as first-line treatment for cancer pain. According to the World Health Organization (WHO) analgesic ladder, first published in 1986, opioids are the cornerstone of the treatment of cancer pain [33]. The NCCN confirms the role of opioids in their guidelines for the treatment of cancer pain stating that opioids should be used upfront for moderate to severe pain and non-opioid pain medications are recommended as adjuncts to opioids [9]. The European Association for Palliative Care advises that the “skilled use of opioids is crucial to the relief of cancer pain” [30].

Based on these guidelines and years of experience with opioid use, there is clearly a role for these medications in the management of acute cancer pain. However, the use of opioids in treatment of cancer pain is associated with significant side-effects (somnolence, dry mouth, anorexia and constipation) [34,35]) and concern for development of opioid dependence and abuse [8]. It is therefore critical that future studies focus on the role of alternative pharmacologic and non-pharmacologic modalities to treat acute cancer pain. In the interim, providers should constantly evaluate the severity of acute pain and judiciously prescribe opioids along with adjunctive treatment options (Fig. 1).

**2.1.2.2. Non-opioid medications.** The WHO ladder recommends treating mild cancer-associated pain with non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen [33]. The ladder also indicates that these medications can be used in conjunction with opioids for the treatment of moderate to severe cancer associated pain [33]. Two recent

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