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## Review Article

## Opioid use in gynecologic oncology in the age of the opioid epidemic: Part I - Effective opioid use across clinical settings, a society of gynecologic oncology evidence-based review

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## HIGHLIGHTS

- The appropriate role for opioids in pain management varies based on clinical setting
- Opioids remain first line treatment for cancer-related pain
- Consider minimizing opioid use in post-operative and survivorship settings
- Patients should be counseled on expectations for & management of opioid side effects

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## ABSTRACT

As the only oncologists that provide both medical and surgical oncologic care, gynecologic oncologists encounter an exceptionally broad range of indications for prescribing opioids, from management of acute post-operative pain to chronic cancer-related pain to end-of-life care. If we are to balance opioid efficacy, safety and accessibility for our patients, we must be intimately familiar with appropriate clinical use of opioids in a range of settings, and engage in the national conversation around opioid misuse and how associated regulations and legislation may impact us and our patients. This article examines the appropriate use of opioids across the range of clinical settings encountered in gynecologic oncology.

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## 1. Introduction

Opioids are first-line treatment for cancer-related pain [1,2]. The legal and illicit use of opioids has recently entered the national conversation due to the sustained and dramatic increase in opioid-related deaths over the past decade. From 1999 to 2014, more than 165,000 deaths in the United States were attributed to opioid-related overdoses [3]. The broad term opioid misuse refers to any use of opioids for a purpose not consistent with legal or medical guidelines and includes

recreational opioid use and diversion or sale of prescribed opioids for recreational use [4]. Regulatory issues related to opioid prescribing and opioid misuse will be covered in Part II of this article. Recent increased attention to the national issue of misuse must not deter us from using opioids in appropriate clinical settings to treat pain related to cancer and its treatments. Appropriate use of opioids will vary by clinical setting. While comprehensive coverage of non-opioid pharmacologic and non-pharmacologic management of pain are beyond the scope of this paper, both are critically important to effective pain control and covered elsewhere including in the Society of Gynecologic Oncology white paper on palliative care [5]. To illustrate patterns of effective use across clinical settings, this article will utilize the case example of DM, a 47 yo with stage IB1 cervical cancer.

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## 2. Post-operative pain

Case: DM is a 47 yo G2P1 executive assistant with a history of depression, alcohol use disorder in remission and ongoing cigarette use who presented with intermenstrual bleeding. On pelvic exam she had a 3 cm cervical mass with biopsy showing squamous cell carcinoma. Her PET scan was negative for metastatic disease. She underwent a robotic-assisted radical hysterectomy, bilateral salpingectomy and bilateral pelvic lymph node dissection. She is discharged post-operative day number one with a prescription for oxycodone 5 mg tablets (take 1–2 q4–6 h prn; #40) and recommendations to take acetaminophen 1000 mg PO tid, ibuprofen 600 mg PO qid and docusate 100 mg daily.

Final pathology shows a 3.5 cm poorly differentiated squamous cell carcinoma, with lymphovascular space invasion, negative margins, negative parametria, and one of 18 pelvic lymph nodes positive. The patient calls on post-operative day #5 reporting persistent pain. She is not using ibuprofen because it upset her stomach and she is not using acetaminophen because it was not effective, so she is relying primarily on oxycodone, taking 6–8 tablets per day, and is about to run out. She denies fevers, nausea, vomiting or any other worrisome symptoms. She is struggling to move her bowels. The on-call provider authorizes a refill of an additional 40 tabs of 5 mg oxycodone for her to pick up in clinic and she is instructed to address her symptoms further at her clinic visit later in the week.

Opioids have long been the mainstay of pain control in the immediate post-operative period. They can be delivered by oral, intravenous or epidural/intrathecal routes. In the inpatient setting, use of post-operative patient controlled analgesia (PCA) (compared with non-patient controlled opioid administration) is associated with higher opioid consumption, but improved pain control and patient satisfaction [6]. Morphine and hydromorphone are the two most commonly used post-operative parenteral opioids. They are similar with respect to onset (5–6 min) and half-life (2–3 h) [7,8]. However, hydromorphone is much more potent (1.5 mg IV hydromorphone = 10 mg IV morphine) and reaches peak effect more quickly (approximately 20 min versus 90 min). Once patients are able to tolerate oral intake, they can be transitioned to oral opioids, which are available in opioid-only formulations (such as oxycodone or hydromorphone) or in combination with a non-opioid analgesic (such as oxycodone-acetaminophen or hydrocodone-acetaminophen).

Enhanced recovery after surgery protocols (ERAS) were initially developed in general surgery, with the goal of using physiologically based management techniques in the perioperative and post-operative period to attenuate the stress response and improve outcomes [9]. A primary component of ERAS protocols is to minimize post-operative opioid use, given opioids' association with ileus, nausea and sedation [10,11]. Retrospective data suggest use of ERAS in the gynecologic oncology population is associated with decreased length of hospital stay and decreased cost [12]. Opioid use is moderated in ERAS protocols by a multimodal analgesia approach, with use of nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, gabapentin and regional anesthesia when indicated (epidural, spinal and/or truncal nerve blocks). Literature from other surgical specialties suggests efforts to minimize post-operative opioid use can begin even prior to surgery, with pre-operative administration of non-opioid analgesics having been shown to decrease post-operative opioid use [13–16]. A study of patients undergoing abdominal hysterectomy demonstrated a 59% reduction in PCA opioid consumption at 24 h in patients treated with peri-operative acetaminophen [17]. Protocols for minimally invasive surgery may differ from those for open surgery, with less use of elements such as regional anesthesia. In one ERAS study, the use of PCA decreased nearly 300% and overall opioid use decreased by 80% in the immediate post-operative period, with no change in pain score versus traditional pain management [18]. The Society of Gynecologic Oncology (SGO) recently embraced this approach with the publication of formal ERAS guidelines [19].

Data from the non-gynecologic surgery literature suggests that overprescription of outpatient post-operative opioids relative to patient utilization is common. Studies of outpatient opioid use after orthopedic and general surgery procedures have found that, on average, only between 19% and 34% of the opioids prescribed were used [20–22] and that the amount of opioids prescribed after a given procedure varied widely by provider [22]. Efforts to start to standardize post-operative opioid prescribing in the general surgery literature have focused on standardizing number of pills prescribed by procedure. Based on evaluation of utilization data, Hill and colleagues made recommendations for standardizing the amount of opioid pills prescribed for five common general surgery procedures (5 for partial mastectomy, 10 for partial mastectomy with sentinel lymph node biopsy, and 15 for laparoscopic cholecystectomy, laparoscopic inguinal hernia repair, and open inguinal hernia repair) [22]. An educational intervention based on those recommendations was associated with a 53% decrease in amount of opioids prescribed after those five general surgery procedures with only one patient in a cohort of 246 patients requiring an opioid refill [23]. Postoperative outpatient opioid utilization patterns have not been described after gynecologic oncology surgery.

Potential morbidity of overprescribing outpatient post-operative opioids includes risk of accidental ingestion of improperly stored unused opioids, risk of diversion of unused opioids (via sale or sharing with friends/family for recreational use) and risk of previously opioid-naïve patients becoming chronic opioid users after surgery. A recent study showed that 5.9% of patients undergoing minor general surgery procedures demonstrated new persistent opioid use after their procedure [24]. The authors of that study advocate that new persistent opioid use after surgery be viewed as a surgical complication.

### 2.1. Case commentary

Constipation is an expected side effect of opioid use and post-operative opioid prescriptions should be accompanied by instructions to use a daily laxative regimen (not a stool softener such as docusate). A generally effective regimen is senna 2 tabs qhs while on opioids, titrate up as needed (to maximum dose of 4 tabs bid) with goal of a daily soft bowel movement [25]. Patients should be instructed that they can safely take up to four senna tablets twice daily and other laxative agents such as polyethylene glycol (Miralax) can be added as needed to achieve a daily soft bowel movement.

This patient may be at increased risk for opioid misuse because of her smoking, depression and prior alcohol use disorder, based on data from non-cancer populations [26]. Some data suggests that cigarette use is also correlated with “chemical coping,” or use of medications including opioids to cope with emotional distress [27]. Presence of risk factors for opioid misuse is not a reason to withhold opioids for post-operative pain, but all patients should be counseled pre-operatively about expectations (i.e. they should not expect to be pain free, focus should be on treating pain to facilitate function) and about using opioids judiciously in addition to non-opioid analgesics.

In this case the patient was prescribed 40 tabs of oxycodone after a minimally invasive surgery. While there is no consensus standard on exactly what is the right amount of opioid to prescribe after gynecologic surgery, this is likely more opioid than most patients will need after minimally invasive surgery. One survey of patients after gynecologic surgery found that after vaginal or laparoscopic surgery, patients were prescribed a mean of 24 tablets of oxycodone or hydromorphone and used a mean of 10 tablets [28]. Another survey of patients after hysterectomy for benign indications similarly found that patients on average used approximately half of the opioids prescribed, with a median amount of unused opioid of 110 oral morphine equivalents [29]. While we may expect this patient to have more pain than the average patient after benign simple hysterectomy, we still likely would not expect her to need 40 tabs of oxycodone. When the patient called reporting having used all 40 tabs in only five days, her provider might

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