Thesis

The Impact of multimodal analgesia in patients undergoing hysterectomy

submitted by

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Graz, 27.02.2025

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Zusammenfassung

Hintergrund: Im Rahmen dieser Studie haben wir den Einfluss multimodaler Analgesie auf postoperative Ergebnisse (u.a. Komplikationen, Krankenhaus-Aufenthaltsdauer und Einsatz von Opioiden) bei Hysterektomie-Patientinnen untersucht.

Methoden: Unter Verwendung der "Premier Healthcare claims data" wurden N = 1.307.923 erwachsene Patientinnen, die im Zeitraum von 2006 bis 2022 eine elektive Hysterektomie erhielten, in die Studie miteinbezogen. Innerhalb dieser Patientengruppe wurde multimodale Analgesie als die Anwendung von Opioiden in Kombination mit 1, 2 oder >2 nicht-Opioiden Analgetika definiert. Multivariable Regressionsmodelle analysierten die Assoziation zwischen diesen multimodalen Kategorien und definierten Ergebnissen (perioperative Komplikationen (komposit, respiratorisch, kardiovaskulär, gastrointestinal, urogenital, Zentralnervensystem), kumulative Opioidverschreibungsdosis (in morphine milligram equivalents (MME)), Länge des Krankenhausaufenthalts (LOS, in Tagen) und Kosten (in US-Dollar (USD)). Odds Ratios (OR) und 95% Konfidenzintervalle (CI) wurden berichtet.

Resultate: Insgesamt erhielten 84,3 % der Patienten multimodale Analgesie, von denen 58,9 %, 28,0 % und 12,1 % jeweils 1, 2 bzw. ≥ 2 zusätzliche nicht-Opioide Analgetika erhielten. Multivariable Analysen zeigten, dass die Anwendung multimodaler Analgesie bei den Hysterektomie-Patientinnen mit verbesserten postoperativen Ergebnissen, reduziertem Opioidverbrauch und kürzerer Krankenhausaufenthaltsdauer (LOS) assoziiert ist.

Conclusio: Der Einsatz multimodaler Analgesie bei Hysterektomie-Patientinnen hat im Studienzeitraum (2006-2022) signifikant zugenommen, insbesondere die Anwendung zwei oder mehrerer Modalitäten. Die Studie zeigt die wesentlichen Vorteile der multimodalen Analgesie, darunter eine signifikante Reduktion schwerwiegender Komplikationen, einen verminderten Opioid Einsatz sowie eine verkürzte Krankenhausaufenthaltsdauer.

Abstract

Objective: We investigated the association between multimodal analgesia and postoperative outcomes (complications, length of hospital stay (LOS), opioid usage) among patients undergoing hysterectomy.

Methods: Using Premier Healthcare claims data, N = 1,307,923 adult patients undergoing elective hysterectomy (2006-2022) were included in this retrospective cohort study. Within these, multimodal analgesia was defined as opioid use with the addition of 1, 2 or >2 non-opioid analgesic modes. Multivariable regression models measured the associations between these multimodal categories and defined outcomes (perioperative complications, opioid prescription dose (in morphine milligram equivalents (MME)), length of hospital stay (LOS, in days) and cost (in United States dollar (USD)). Odds ratios (OR) and 95% confidence intervals (CI) were reported.

Results: In total, 84,3% of the described patient population received multimodal analgesia of which 58.9%, 28.0% and 13.1% received 1, 2, or >2 additional non-opioid analgesics, respectively. Multivariable analysis indicated that the use of multimodal analgesia among hysterectomy patients included in the study was associated with improved postoperative outcomes, reduced opioid usage, and shorter LOS.

Conclusion: The use of multimodal analgesia in hysterectomy cases significantly increased over the study period, particularly the application of two or more modalities. The study demonstrates substantial benefits of multimodal analgesia, including a significant reduction in serious complications, decreased opioid use, and shorter LOS. These factors may contribute to more effective pain management, optimized opioid use and a reduction in costs, ultimately enhancing patient care.

Previously Published Works

1. Multimodal Analgesia and Outcomes in Hysterectomy Surgery—A Population-Based Analysis
   Published in Journal of Clinical Medicine, *13*(18), September 2024
   Cozowicz, C.; Gerner, H.D.; Zhong, H.; Illescas, A.; Reisinger, L.; Poeran, J.; Liu, J.; Memtsoudis, S.G.

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List of Abbreviations

Abbreviation	Definition
AAPM	American Academy of Pain Medicine
ASA	American Society of Anesthesiologists
ASRA	American Society of Regional Anesthesia and Pain Medicine
cAMP	Cyclic adenosine monophosphate
CI	Confidence Intervals
CNS	Central nervous system
COX-2 inhibitor	cyclooxygenase-2 inhibitor
CPSP	chronic postsurgical pain
CSF	Cerebrospinal fluid
dl	deciliter
DOP	delta (δ)-opioid peptide
EBP	Epidural blood patch
ERAS	Enhanced Recovery After Surgery
FDA	Food and Drug Administration
GDP	Guanosine diphosphate
GI	gastrointestinal
GTP	Guanosine triphosphate
GU	genitourinary
h	hour
ICD	International Classification of Diseases
IQR	Interquartile ranges
kg	Kilogram
KOP	kappa (κ)-opioid peptide
LOS	Length of hospital stay
mg	*Milligramm*
mL	milliliters
MME	Morphine milligram equivalents
MOP	mu (μ)-opioid peptide
NAPQI	N-acetyl-p-benzoquinone imine
NMDA	N-methyl-D-aspartate

NOP	nociceptin
NRS	Numeric Rating Scale
NSAIDs	Non-selective Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
OSA	Obstructive sleep apnea
PAG	Periaqueductal grey matter
PDPH	Post-dural puncture headache
PONV	Postoperative nausea and vomiting
TRAAK	TWIK-related Arachidonic Acid-Stimulated K+ channel
TREK-1	TWIK-related K+ channel 1
TRPM8	transient receptor potential cation channel subfamily M member 8
TRPV1	transient receptor potential cation channel subfamily M member 8
USD	United States dollar
VAS	Visual Analog Scale

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1. Introduction

Hysterectomy for benign indications remains one of the most common surgical procedures in gynecology and is frequently associated with significant postoperative pain. Uncontrolled acute post-operative pain increases the risk for patient dissatisfaction (1), post-operative complications and the development of chronic pain. (2) In order to effectively control post-operative pain, Enhanced Recovery After Surgery (ERAS) protocols strongly recommend a multimodal approach to postoperative analgesia in hysterectomy patients. (3) This concept of achieving analgesia through additive/synergistic effects of different analgesic modes (4) aims to promote a fast recovery, reduce complications and (5) decrease post-operative opioid requirements. (4) Avoiding opioid use within a multimodal analgesia pathway has become increasingly significant in recent years due to unwanted side effects as well as overprescription, especially in post-surgical patients. (6) Relying solely on opioids for post-operative pain relief can lead to adverse effects such as sedation, nausea, and fatigue, while also raising the risk of addiction and resulting in significant financial and social consequences. (6)

This introduction aims to provide a better understanding of key aspects of this study, including relevant anatomy, the steps involved in the various procedures, and the characteristics as well as risk factors of post-hysterectomy pain. A discussion of multimodal analgesia will follow, exploring its role in pain management within this context. Finally, the challenges of managing pain after surgery will be addressed, with particular focus on the issues surrounding opioid overprescription.

1.1. Anatomy of the Uterus

As seen in Figure 1, the uterus is a pear-shaped organ, consisting of the fundus, body and cervix. The fallopian tubes enter the superolateral angle on each side (the cornu), above which lies the fundus. The uterine body narrows to the isthmus, which continues as the cervix. The triangular shaped cavity of the uterus connects with the cervical canal via the internal os and the cervical canal opens into the vagina via the external os. (7)

The uterus can naturally adopt different positions within the pelvis, including anteflexion, retroflexion, anteversion, and retroversion. The angle between the axis of the uterine body and the cervix determines the flexion, while the angle between the axis of the cervix and the axis of the vagina defines the version of the uterus. Anteflexion with anteversion of the uterus is considered the natural position. (8) The anterior surface of the uterine body is related to the uterovesical pouch of peritoneum, whilst the posterior surface is associated with the recto-uterine pouch of Douglas. Laterally, the broad ligament contains the fallopian tubes, ovaries, blood vessels, nerves, and lymphatics. (7)

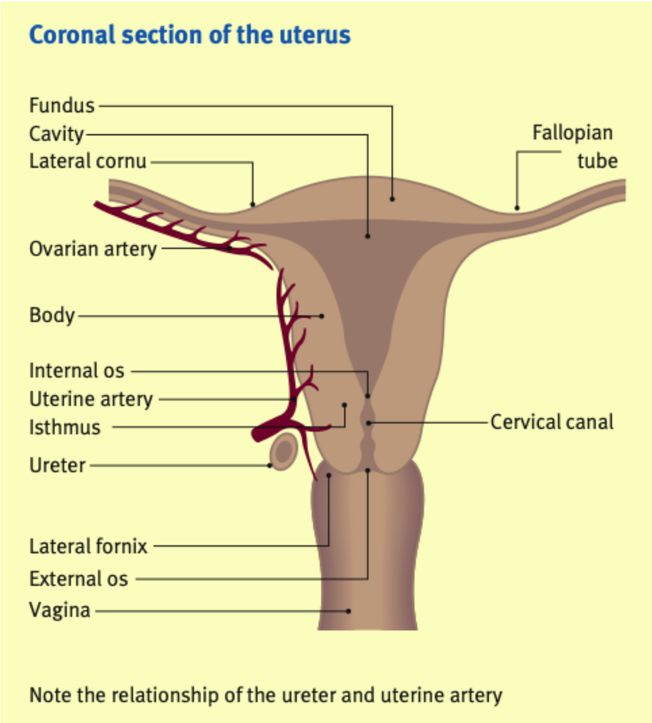

Figure 1. Coronal section of the uterus. (7)

The uterine arteries (Figure 2), which arise from the internal iliac arteries, are the main vascular supply of the uterus. Apart from the broad ligament, they are the only structures that pass superficially to the ureter, which poses a risk of unintentional division during clamping in a hysterectomy. On both sides, the uterine arteries ascend alongside the uterine body and anastomose with the respective ovarian arteries, which arise from the aorta. The uterine veins accompany the arteries until draining into the internal iliac vein, also communicating with the ovarian vein as well as veins of the vagina and bladder via the pelvic venous plexus. (7, 9)

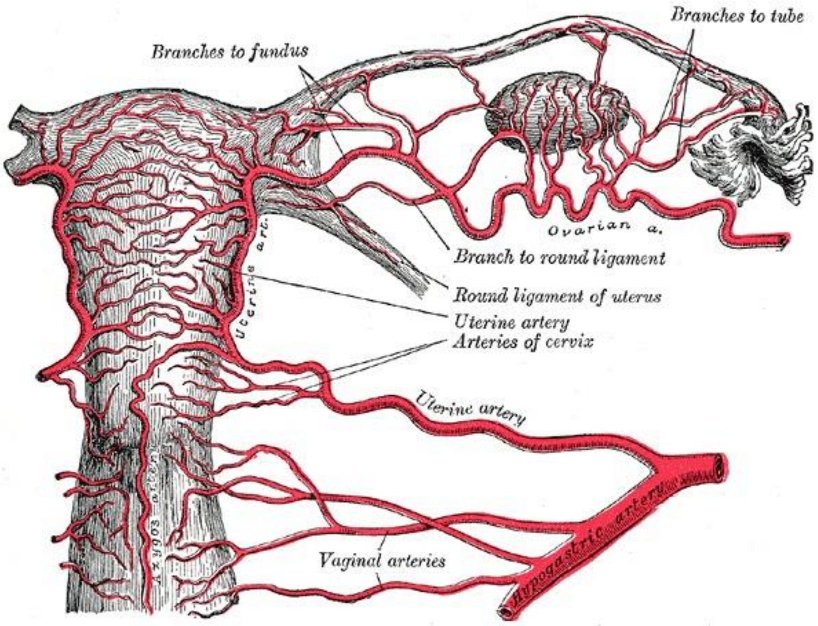

Figure 2. The arteries of the internal organs of generation of the female, seen from behind. (9)

1.2. Hysterectomy

1.2.1. Indications

The term hysterectomy originates from Greek: "hystero", meaning uterus and "ectomy" meaning surgical removal. (10) Although this surgical procedure is recommended for several common gynecologic problems, most hysterectomies are performed for benign indications. In the United States, the most common indications for hysterectomy are uterine fibroids/leiomyomas, abnormal uterine bleeding and endometriosis. (11) Similarly, in Austria, three primary conditions account for 78% of the benign hysterectomies: fibroids/leiomyomas, followed by pelvic organ prolapse and abnormal uterine bleeding. Other common indications include endometrial hyperplasia, adenomyosis, uterine prolapse and cervical intraepithelial neoplasia. (12) Hysterectomies can be total or subtotal as well as with or without the adnexae, depending on the indication.

1.2.2. Routes and Rates

Hysterectomies can be performed via various routes, including abdominal hysterectomy (AH), vaginal hysterectomy (VH), laparoscopic hysterectomy (LH) and robotic-assisted hysterectomy (RH). Laparoscopic hysterectomy is further classified into laparoscopic assisted vaginal hysterectomy (LAVH), total laparoscopic hysterectomy (TLH) and subtotal laparoscopic hysterectomy (STLH). (10) To date, multiple studies have evaluated the advantages and disadvantages of these different approaches to define the most effective surgical route for performing hysterectomy for benign conditions. Evidence shows that abdominal hysterectomy is associated with increased complications, LOS and recovery period compared to both vaginal and laparoscopic hysterectomy. Additionally, non-open procedures are associated with fewer wound/abdominal wall infections due to the absence of a wide abdominal scar. (13) In Austria, the most common approach is vaginal, which accounts for roughly half of all procedures. This is followed by laparoscopic and laparoscopically assisted vaginal hysterectomies and then abdominal hysterectomy. (12) In the United States, although the rate of abdominal hysterectomies continues to decline, it remains the most frequently performed method, followed by laparoscopic and then vaginal procedures. (14)

Whilst hysterectomy rates vary considerably among different regions and countries, they remain one of the most common surgical procedures among women. In Austria, a yearly incidence of 7,747 hysterectomies was reported in 2014. (12) In the United States, hysterectomies are the second most common surgery among women, the most common being childbirth by cesarean delivery. More than 600,000 hysterectomies are performed annually, (15) despite a continuous decline in rates due to medical and hormonal treatments, as well as less invasive surgical options. (12)

1.2.3. Operative Techniques and Complications

Abdominal hysterectomy

Abdominal hysterectomy is performed with the patient lying in the supine position. (16, 17) A longitudinal incision is made in the abdominal wall, which is then deepened through the fascia and peritoneum to expose the pelvic cavity. The pelvic sidewall is explored and the pararectal space is developed to allow identification of the ureter on the medial leaf of the broad ligament. The anterior leaf of the broad ligament is then opened down to the vesicouterine peritoneal reflection, followed by ligation and division of the round ligament. The vesicouterine peritoneal incision is extended and the vesicocervical space exposed via sharp dissection. After confirming the position of the ureter, a plane of dissection is created in the avascular space of Graves. Keeping the ureter under direct visualization, the infundibulopelvic ligament – which contains the ovarian vessels - is clamped, divided and ligated. The bladder is then further mobilized off the cervix and proximal vagina. Next, the uterine vessels are clamped, divided and ligated, followed by the cardinal ligament. The bladder is then sharply dissected off the proximal vagina, followed by palpating the position of the cervix. An anterior colpotomy is performed and clamps are placed along the vaginal fornix. The sacrouterine ligaments are then cut and clamped together with the vaginal wall, and – after excision - the vaginal vault is closed with Z-figure sutures. (16, 17)

Vaginal hysterectomy

Vaginal hysterectomy is performed with the patient lying in lithotomic position and the legs placed in Allen stirrups. After vaginal inspection, adequate traction is achieved by grasping the cervix with two tenacula (anterior and posterior lip, respectively). Following infiltration of the paracervical tissue with dilute vasopressin, (18) a circumferential incision is performed around the cervix at the vaginal fornices. The anterior cul-de-sac is then entered via dissection to separate the vaginal mucosa from the cervical stoma. The bladder is reflected cranially and protected via a right angle or Deaver retractor. Via posterior incision, the posterior cul-de-sac is opened, exposing the peritoneum. After correct identification, the uterosacral and cardinal ligaments – followed by the uterine vessels - are then clamped, cut, and sutured. The broad ligament is then clamped medially, cut and sutured. The fundus of the uterus is then pulled out to expose the round and uteroovarian ligaments as well as the salinges, which are then clamped, cut and ligated, followed by removal of the uterus. The peritoneum is finally tied to the vagina circumferentially and the cuff closed horizontally with a suture. (19)

Total laparoscopic Hysterectomy

After insertion of an intrauterine manipulator, an operative laparoscope is introduced at the umbilical site, and two ancillary trocars are placed laterally to the epigastric arteries in the lower abdominal quadrants. The procedure begins with cauterizing and sectioning the round and infundibulopelvic ligaments. The broad ligament then opens to the uterovesical fold, which is incised to reflect the bladder. Next, the uterine arteries, cardinal ligaments, and uterosacral ligaments are cauterized and transected. A circular colpotomy is performed with a monopolar hook, the uterus is extracted from the vagina, and the vaginal cuff is closed in a single layer. (20)

Complications associated with hysterectomy vary depending on the operative technique used. The main complications can be categorized into infectious, venous thromboembolic, genitourinary (GU) and gastrointestinal (GI) tract injury, bleeding, nerve injury and vaginal cuff dehiscence. (21) Vaginal cuff dehiscence is defined as partial or complete separation of the vaginal cuff edges that were sutured during hysterectomy. This separation can result in evisceration of the bowel, adnexa and omentum, potentially leading to serious complications, including bowel ischemia, bowel necrosis, ileus, bacteremia, peritonitis and sepsis. (22)

According to a study performed by Clarke-Pearson et al, the most common complication following hysterectomy is infection, most commonly occurring in vaginal hysterectomy. Bleeding complications after hysterectomy are generally rare, with estimated blood loss being the highest for abdominal hysterectomy (238-660.5 mL). Vaginal cuff dehiscence is a rare but notable complication, estimated at a rate of roughly 0.39%. This is more common after total laparoscopic hysterectomy - compared to laparoscopic assisted vaginal, abdominal and vaginal hysterectomy. (21)

1.3. Post-operative pain

1.3.1. Mechanism of pain

Pain is one of the most prevalent symptoms in medicine, estimated to affect more than 20% of the global population. (23) To effectively diagnose, interpret and treat pain in patients, it is essential to understand its underlying mechanisms, as well as its psychological and emotional dimensions. According to the International Association for the Study of Pain revision of 2020, pain is defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.” (24)

Nociceptors are at the core of pain perception, as they are responsible for detecting potentially harmful stimuli—whether thermal, mechanical, or chemical—that reach a threshold indicative of injury. This triggers a cascade of signaling pathways, transmitting pain signals from the dorsal horn of the spinal cord to the brain via ascending tracts such as the spinothalamic and spinoreticulothalamic pathways, relaying pain information to the thalamus and brainstem, respectively. Pain perception is not localized to a single area of the brain. (25) Instead, it results from activation of a distributed group of structures, some of which are more involved in the sensory-discriminative aspects of pain, such as the localization and intensity of the sensation (e.g., the somatosensory cortex), while others are implicated in the affective and emotional dimensions of pain (e.g., the anterior cingulate cortex and insular cortex). This chapter aims to provide a deeper understanding of the mechanisms underlying pain, its neural pathways, and the various factors that contribute to its perception. (26)

Nociceptors and Pain Transduction

Nociceptors are peripheral nerve fibers located in tissues such as the skin, joints, viscera, muscles and bone. They can be categorized into two major types based on their structure and function: A-delta fibers and C fibers. A-delta fibers are medium-diameter, myelinated nerves that transmit acute, well-localized "fast" pain, while C fibers are small-diameter, unmyelinated nerves responsible for transmitting poorly localized, diffuse "slow" pain. A-delta fibers are further divided into Type I and Type II. Type I are primarily activated by mechanical and chemical stimuli, with less sensitivity to heat (activating at temperatures above 50°C). Type II A-delta nociceptors, on the other hand, have a much lower heat threshold, but a very high mechanical threshold. Most C fibers are activated by both mechanical and thermal stimuli. (26)

The various nociceptor subtypes each have distinct sets of transduction molecules that allow them to detect different types of stimuli. For instance, heat-sensitive afferents typically express TRPV1 (transient receptor potential cation channel subfamily V member 1) and most cold-sensitive afferents express TRPM8 (transient receptor potential cation channel subfamily M member 8). In addition to these receptors, nociceptor fibers also express a variety of voltage-gated sodium channels (such as NaV 1.8 and 1.9) and potassium channels (such as TWIK-related Arachidonic Acid-Stimulated K+ (TRAAK) and TWIK-related K+ channel 1 (TREK-1)), which regulate excitability and/or contribute to action potential propagation. (26)

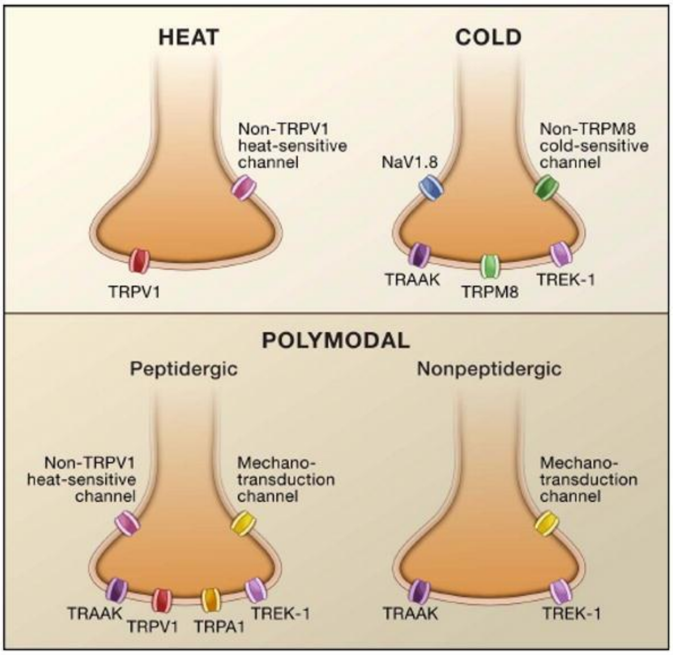

Figure 3. Nociceptor diversity. (26)

When noxious stimuli reach a threshold indicative of injury, the damaged tissue releases various chemical mediators—including substance P, histamine, nerve growth factor and arachidonic acid—that, in turn, stimulate an action potential in the nerve fibers through transducer channels like transient receptor potential channels. The noxious information is then transmitted to projection neurons within the dorsal horn of the spinal cord. The dorsal horn is organized into distinct layers known as laminae, (27) with the subsets of primary afferent fibers targeting spinal neurons within specific laminae. For example, peptidergic C fibers (Figure 4, shown in red) and Aδ fibers (Figure 4, shown in purple) synapse in lamina I, while non-peptidergic C fibers (Figure 4, shown in blue) target interneurons in lamina II. Aβ fibers, carrying innocuous input, synapse on PKCγ-expressing interneurons (Figure 4, shown in orange) in the ventral part of lamina II. (26)

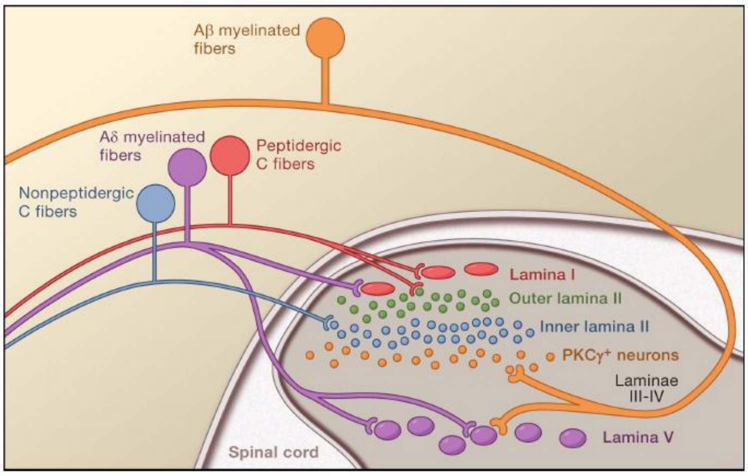

Figure 4. Connections between primary afferent fibers and the spinal cord. (26)

<u>Pain Pathway</u>

A subset of projection neurons in the dorsal horn relays information to the somatosensory cortex via the thalamus, where it contributes to the perception of pain location and intensity (sensory-discriminative aspects). Other projection neurons connect with the cingulate and insular cortices through pathways involving the brainstem's parabrachial nucleus and the amygdala, influencing the emotional and affective aspects of the pain experience. Additionally, this ascending pain information engages neurons in the rostral ventral medulla and midbrain periaqueductal gray matter, which regulate spinal cord output through descending feedback systems. (26)

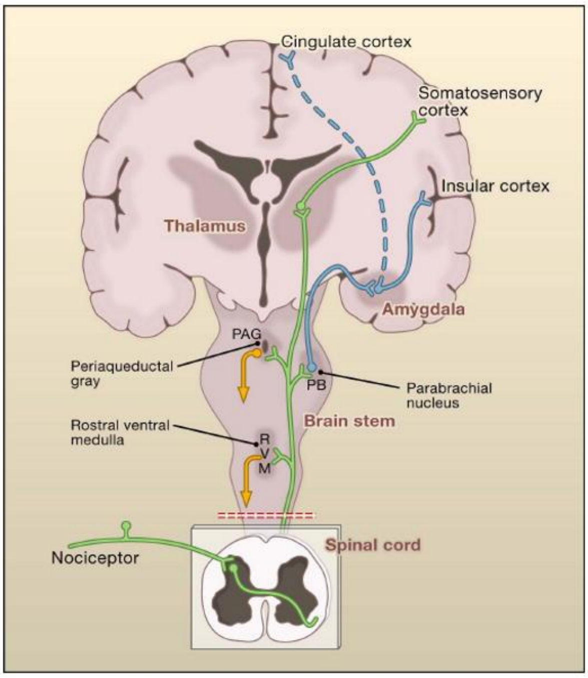

Figure 5. Anatomy of the pain pathway. (26)

Additionally, many psychological factors play a significant role in pain perception. For example, focusing attention on the painful sensation and its source can amplify the pain experience. Patients with conditions such as somatic preoccupation or hypochondriasis often become hyper-attuned to bodily sensations, which can heighten their perception of pain. In addition, cognitive factors such as how the individual appraises the meaning of the sensation, along with emotional responses, expectations, and coping strategies, all provide feedback that can influence how pain is experienced and interpreted. (28)

Due to its complex, subjective, and multifaceted nature, pain is challenging to measure accurately in a clinical setting. For acute pain, simple tools like the Visual Analog Scale (VAS) and Numeric Rating Scale (NRS) are commonly used to assess pain intensity. For chronic pain, multidimensional assessment tools such as the McGill Pain Questionnaire and the Brief Pain Inventory are often employed to capture the broader aspects of pain experience. (29, 30)

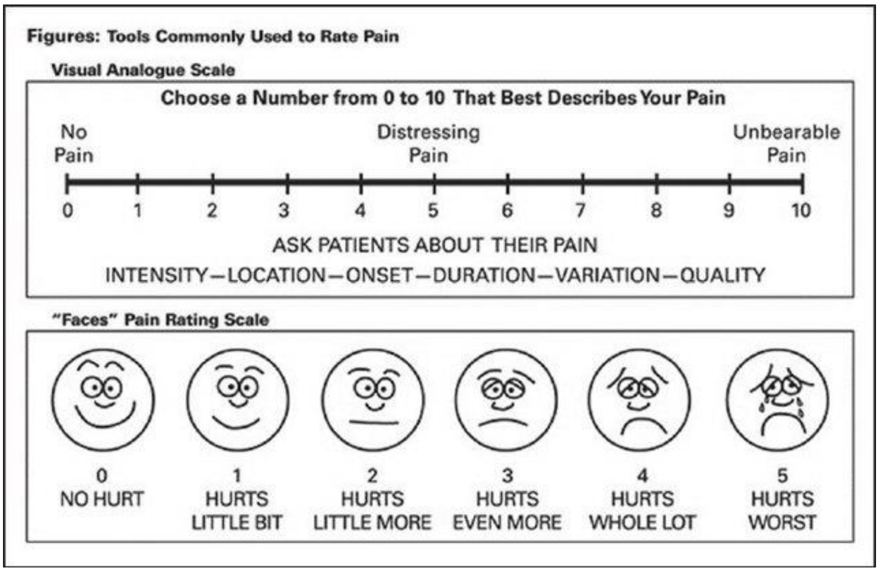

Figure 6. Tools Commonly Used to Rate Pain. (31)

1.3.2. Pain following hysterectomy

Post-hysterectomy pain can be considerable, and evidence indicates that the chosen surgical approach can significantly impact this outcome. Non-open procedures are associated with reduced postoperative pain compared to abdominal hysterectomy. Compared to vaginal hysterectomy, patients who have undergone laparoscopic hysterectomy experience significantly less postoperative pain and show a decreased analgesic requirement. Several factors may explain this reduction in postoperative pain. For example, vaginal hysterectomy often involves significant downward traction on the uterus, unlike laparoscopic techniques. Furthermore, laparoscopic hysterectomy uses electrosurgical devices for coagulation and dissection, while vaginal hysterectomy relies on traditional techniques with clamps, scissors and knot tying. Finally, total laparoscopic hysterectomy allows for a more natural positioning of the lower limbs compared to vaginal surgery. (20)

That being said, total laparoscopic hysterectomy may result in pain due to various perioperative predicaments, such as pneumoperitoneum, stretching of the abdominal cavity, residual blood in the cavity and dissection of the pelvic region. Additionally, patients undergoing total laparoscopic hysterectomy may receive less pain medication, as its laparoscopic approach is often perceived as less painful compared to more invasive major surgeries. (32)

Regarding the location of postoperative pain, most patients who underwent total laparoscopic hysterectomy primarily reported perineal pain, in addition to abdominal (visceral and incisional) pain and shoulder pain. Incisional and visceral pains were most intense the first 30 minutes after surgery, followed by a gradual decrease. For the first 72 hours postop, visceral pain dominated over incisional pain. Shoulder pain, on the other hand, was less severe on the day of surgery and increased to maximum severity at 24 hours post-surgery. (32) Abdominal hysterectomy patients most frequently described pain surrounding the abdominal scar, followed by groin pain with the majority of the patient population indicating neuropathic pain. (33)

1.3.3. Chronic Pain Development

According to the 11th revision of the International Classification of Diseases (ICD-11), chronic postsurgical pain (CPSP) is defined as pain that develops or worsens after surgery or tissue injury, persists for at least three months beyond the expected healing period, and is localized to the surgical site or projected onto the corresponding innervation area, excluding other causes like pre-existing conditions or malignancy. It may present with neuropathic pain characteristics and is distinguished from pain caused by accidental trauma. (34) CPSP can occur as a complication of any surgical procedure, with incidence rates ranging from 5% to 85%, depending on the type of surgery. (35) The mechanism of CPSP seems to be multifactorial, with several risk factors identified. Early recognition of these factors can help with risk stratification and the development of preventive treatment strategies. These include patient-related factors such as younger age, female sex, psychological factors (e.g., fear and anxiety), smoking, and poor social support, as well as surgery-related factors such as the type of procedure, duration, complications, and postoperative pain severity. Importantly to the current discussion, anesthesiologic factors, including the type of anesthesia and pain management, have also been implicated. (34)

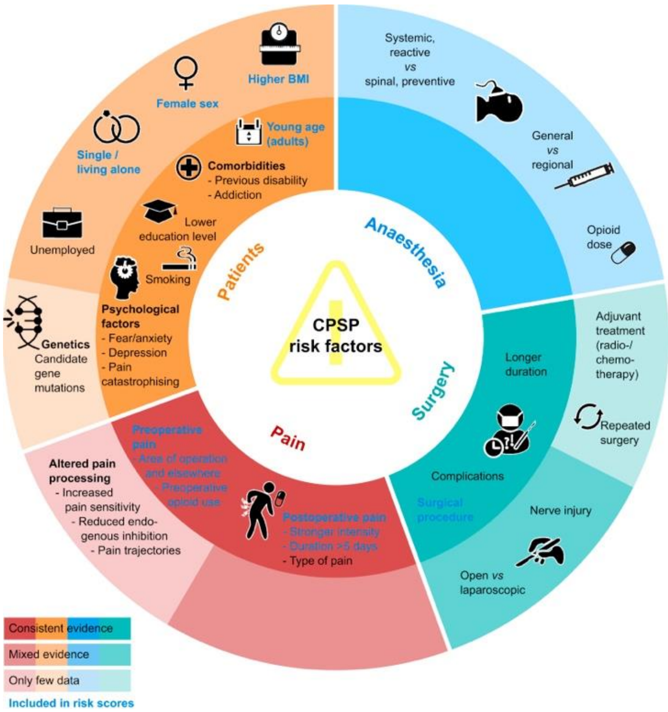

Figure 7. CPSP risk factors. (34)

Regarding chronic pain following hysterectomy, most studies report frequencies in the range of 10-50%. In a nation-wide study based on data from the Danish Hysterectomy Database, Brandsborg and Nikolajsen concluded that 31.9% of patients had pain 12-15 months after hysterectomy. (36) Pinto et al. concluded that 50% of patients presented with CPSP four months following hysterectomy. The most common locations were the pelvic region, followed by the abdominal scar and vagina. Of the patients with CPSP, the majority (51.6%) perceived it daily and 19.4% several times a week. The experienced pain seemed to interfere in a variety of domains - mainly mood, enjoyment of life, general activity and work. The average pain intensity was 3 and the worst pain intensity was 4 on the 0 to 10 NRS. (37)

Although the exact cause of chronic pain following hysterectomy is not fully understood, several risk factors have been identified. The most common include type of hysterectomy, pre-existing pain elsewhere, preoperative pelvic pain, psychological factors and acute postoperative pain. (38) The frequency of chronic postsurgical pain was highest after open abdominal hysterectomy (25-26%) (39, 40), followed by laparoscopic hysterectomy (20-31%) (39, 41, 42) and vaginal hysterectomy (12-18%). (41, 42)

Pinto et al. aimed to further examine the combined role of sociodemographic, clinical, and psychological risk factors for CPSP development four months after hysterectomy for benign diseases. (37) In addition to established demographic and clinical predictors (as mentioned above), they focused on three psychological models: emotional distress, illness perception, and coping strategies. The patient's individual illness perceptions are explained by the Common-Sense Self-Regulation Model, which suggests that, in the context of illness, patients develop individual cognitive and emotional representations of their condition. For example, the affective response to the condition addressed by the hysterectomy predicted CPSP. When applying the illness perception model, presurgical emotional representations of the surgical condition (i.e., emotional reactions to the illness leading to the hysterectomy) emerged as significant predictors of CPSP. This suggests that specific emotional responses to the illness, such as depression, anger or fear, may influence pain outcomes. In the emotional distress and coping strategies model, presurgical anxiety and catastrophizing emerged as significant predictors of CPSP, respectively. These results suggest that screening patients for emotional distress, illness perceptions, and pain coping strategies, along with implementing appropriate presurgical interventions (eg, cognitive pain coping techniques, cognitive behavioral therapy, relaxation strategies, etc.) may offer a promising approach for prevening CPSP in patients following hysterectomy. (37)

1.4. Multimodal Analgesia

1.4.1. Definition

Multimodal analgesia is defined as the combined use of two or more analgesic modes that target different pathways within the nociceptive system. (43) This synergistic effect allows for lower doses of each individual drug, while preserving overall efficacy. (44, 45) In theory, this should translate to improved analgesia while reducing opioid-related side effects. (46) As mentioned above, ERAS protocols and many other guidelines focus heavily on the utility of multimodal analgesia with opioid-sparing techniques. Rather than achieving opioid-free anesthesia, the aim is a balanced multimodal regimen with opioids limited to the minimum necessary. (47) The systemic analgesics available for pain management can be broadly categorized into classical non-opioid analgesics, adjuvant analgesics and local infiltration analgesia. The following paragraphs will provide a more detailed explanation of each individual analgesic modality, offering a clearer understanding of their mechanisms, advantages, and disadvantages. The multimodal analgesic agents included in this study are Ketamine, Non-selective Nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol/acetaminophen, cyclooxygenase-2 (COX-2) inhibitors, steroids, gabapentin/pregabalin and neuraxial anesthesia. Other less common analgesics – such as N-methyl-D-aspartate (NMDA) antagonists, magnesium, alpha-2 agonists, clonidine and dexmedetomidine – are outside the scope of this review.

1.4.2. Agents

Classical Nonopioid Drugs

NSAIDs and COX-2 inhibitors

Non-selective NSAIDs and COX-2 inhibitors (e.g., celecoxib) are widely used drugs with anti-inflammatory, antipyretic and analgesic properties. Common non-selective NSAIDs include acetylsalicylic acid (Aspirin), diclofenac, ibuprofen, indomethacin and naproxen. Both exert their effects via inhibition of the enzyme cyclo-oxygenase (COX), which is required to convert arachidonic acid into thromboxanes, prostaglandins and prostacyclins – "pain-producing chemicals". (48) The cyclooxygenase isoenzymes COX-1 and COX-2 play different roles throughout the body. COX-1, which is constitutively expressed throughout the body, is important for maintaining gastrointestinal mucosa, kidney function and platelet aggregation. COX-2, on the other hand, is not constitutively expressed, but rather induced during inflammatory responses. Most NSAIDs are nonselective, inhibiting both COX-1 and COX-2. COX-2 inhibitors selectively inhibit COX-2, leading to different adverse effects. (49)

NSAIDs are mainly available as oral tablets, but can also be administered as topical NSAIDs, which can be useful for pain related to soft-tissue injuries or osteoarthritis. (50) Additionally, NSAIDs can be administered parenterally, such as IV ibuprofen as a 30-minute infusion to manage pain and reduce fever. The dosages for the most common over-the-counter NSAIDs are as follows: ibuprofen, in 200 mg tablets, can be taken as 1 to 2 tablets every 4 to 6 hours, with a daily limit of 1200 mg. Aspirin, in 325 mg tablets, is generally taken as 1 to 2 tablets every 4 hours, with a daily limit of 4000 mg. (51)

The most prominent side effects of NSAIDs affect the gastric mucosa, renal and cardiovascular system. Gastric side effects - such as gastritis, erosions and ulcerations - are related to the inhibition of COX-1, the prime mediator for maintaining gastric mucosal integrity. Due to its COX-1 specificity, the use of COX-2 selective NSAIDs should offer a lower-risk alternative. (49) Inhibition of COX-1 and COX-2, which facilitate the production of prostaglandins important for renal hemodynamics, can lead to nephrotoxic effects in patients with renal dysfunction, such as acute renal dysfunction, fluid/electrolyte disorders or renal papillary necrosis. (52) Cardiovascular adverse effects, including myocardial infarction, thromboembolic events and atrial fibrillation, can also be increased with NSAID use – most commonly with diclofenac. (53) NSAIDs are contraindicated in patients with NSAID or salicylate hypersensitivity, patients who have undergone coronary artery bypass graft surgery, pregnant patients in the third trimester and patients with impaired kidney function. (51)

Acetaminophen/Paracetamol

Acetaminophen - also known as N-acetyl-para-aminophenol or paracetamol in many countries - is one of the older and most used medications in the world, containing analgesic and antipyretic properties. While the exact mechanism of action remains unclear, its therapeutic targets are thought to include the COX pathway in the central nervous system (CNS), more specifically a central splice variant of COX-1, referred to as COX-3. The reduction of the COX pathway seems to inhibit prostaglandin synthesis in the CNS, leading to its effects. Other therapeutic targets include the descending serotonergic pathways in the CNS, the endogenous opioid system, the nitric oxide synthase and the endocannabinoid system. (54, 55)

Acetaminophen can be administered via oral, rectal or IV route. It is rapidly and efficiently absorbed orally from the gastrointestinal tract, with peak plasma concentration achieved within 30-60 minutes. Intravenous administration of acetaminophen results in immediate and higher peak plasma concentrations. Rectal administration bypasses first-pass metabolism, which is preferred for unconscious patients and children. (56) In adults and adolescents (≥13 years old) with a body weight of ≥50kg, the recommended dose of acetaminophen is 1000mg every 6 hours (or 650mg every 4 hours), with a maximum daily dose of 4000mg. In adults and adolescents with a body weight <50kg and children aged 2 to 12, the recommended dose is 12.5 mg/kg every 4 hours (or 15 mg/kg every 6 hours),

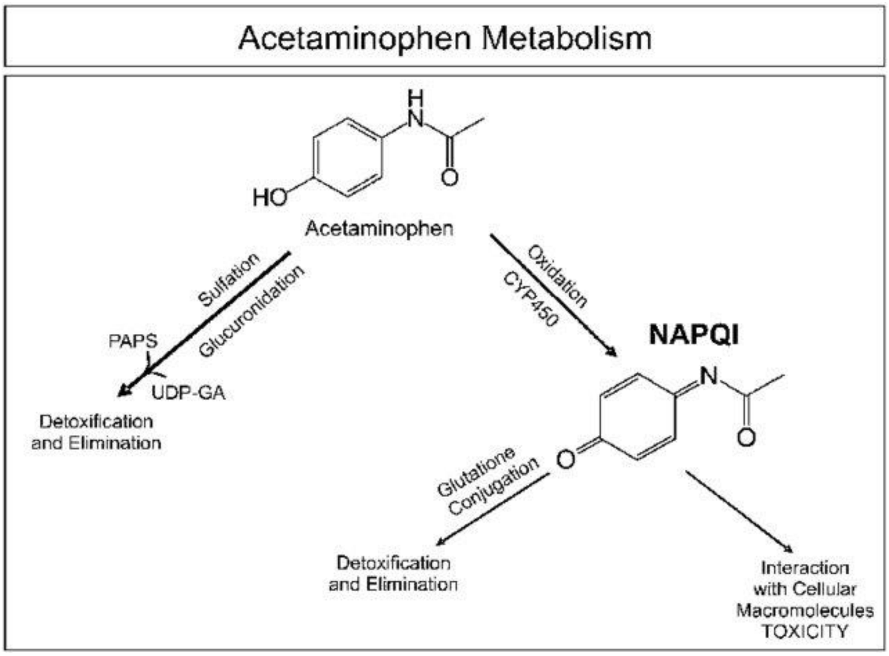

Figure 8. Acetaminophen Metabolism. (58)

with a maximum daily dose of 75mg/kg. (57)

As seen in Figure 8, acetaminophen is primarily metabolized hepatically via first-order kinetics, using three distinct pathways – conjugation with glucuronide, conjugation with sulfate, and oxidation by the cytochrome P450 enzyme system (mainly CYP2E1). This last pathway includes the formation of a reactive intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI). Most metabolites are then excreted in the urine. (58, 59)

One of the most important potential side effects of acetaminophen is hepatotoxicity, caused by NAPQI. Toxicity can be due to overdose, or preexisting liver damage. Acetaminophen is therefore contraindicated in cases of active liver disease or severe hepatic impairment.

There are several systematic reviews supporting the effectiveness of acetaminophen combined with another nonopioid adjunct, such as an NSAID or COX-2 inhibitor, to enhance postoperative pain relief and reduce opioid consumption. (60, 61) A combination of NSAID and acetaminophen is more effective than either drug alone, (60) and the ERAS guidelines for postoperative care in gynecologic/oncologic surgery recommend that both be administered in combination regularly to all patients unless contraindications exist. (4)

<u>Adjuvant Analgesics</u>

Glucocorticoids/dexamethasone

Corticosteroids, synthetic analogues of the natural steroid hormones produced in the adrenal cortex, possess both glucocorticoid and mineralocorticoid properties, similar to the endogenous hormones. Glucocorticoids are mainly involved in metabolism with primarily anti-inflammatory, immunosuppressive, anti-proliferative and vasoconstrictive effects. (62)

The majority of the anti-inflammatory and immunosuppressive actions are mediated by their interaction with the cytosolic glucocorticoid receptor. Upon binding, the receptor trans-locates into the nucleus, where it modulates gene transcription to either induce or repress gene transcription in inflammatory leukocytes. This results in either the up-regulation of anti-inflammatory genes or down-regulation of inflammatory genes. (63)

Glucocorticoids also exert significant antiemetic effects - dexamethasone and methyprednisolone are routinely used to prevent and treat postoperative nausea and vomiting (PONV). The analgesic effects of glucocorticoids - thought to result from the inhibition of COX-2 and phospholipase enzymes – and their role as a components of multimodal analgesia have been studied for many years. However, the precise mechanisms and extent of their role remain not fully understood. In a meta-analysis of randomized controlled trials, De Oliveira Jr. et al found that – in addition to beneficial effects on PONV - intermediate-dose dexamethasone (0.11 to 0.2 mg/kg) reduced postoperative pain (early and late pain, both at rest and at movement) and had opioid-sparing effects. The clinical implication is that, since lower doses of dexamethasone are routinely given during anesthesia induction to prevent PONV, increasing the dose to an intermediate level may offer the added benefit of improved postoperative analgesia. (64)

Glucocorticoids can affect many systems in the body, which is reflected in their well-known side effects, including osteoporosis, adrenal suppression, Cushingoid features, diabetes/hyperglycemia, myopathy, glaucoma, cataracts and immunosuppression. However, these side effects are more commonly associated with chronic or high-dose use. (65)

Common concerns about perioperative dexamethasone administration include potentially impaired wound healing and the risk of hyperglycaemia. While chronic steroid use may impair wound healing in susceptible individuals, acute high-dose systemic corticosteroid use likely has no clinically significant effect on wound healing. (66) In terms of hyperglycaemia, a recent retrospective study examining patients with and without diabetes who underwent orthopedic surgery found that perioperative dexamethasone was associated with a transient increase in hyperglycaemia risk. However, it was also linked to a shorter LOS, suggesting that the benefits of dexamethasone may likely outweigh the risks of transient hyperglycaemia. (67)

Gabapentinoids

Gabapentin, initially introduced as an antiepileptic drug in 1993, is Food and Drug Administration (FDA)-approved for the management of partial seizures (in adults and pediatric patients ≥3 years of age), postherpetic neuralgia, neuropathic pain and restless leg syndrome. (68)

The mechanism of action of gabapentin, which freely passes the blood-brain barrier, is likely mediated by binding to the 21 subunits of the presynaptic voltage-gated calcium channels, which are up-regulated in the dorsal root ganglia and spinal cord after surgical trauma. Inhibition of calcium influx via these channels subsequently inhibits the release of excitatory neurotransmitters from activated nociceptors, inhibits ascending pain transmission and activates descending inhibitory pathways – ultimately preventing hyperalgesia and central sensitization. (69, 70) Peak plasma levels are reached approximately 3 hours after ingesting a 300 mg capsule. Gabapentin is not metabolized and is excreted unchanged in the urine, with an elimination half-life of 5 to 9 hours. (70)

Gabapentin was initially enthusiastically implemented for off-label use in perioperative pain management, supported by numerous studies suggesting its analgesic effects reducing acute postoperative pain and opioid consumption – however largely lacking data on adverse effects and risks. Recent critical studies have led to a reversal in its use, highlighting significant risks. Due to the rich expression of the $\alpha_2\delta$ subunit of voltage-gated calcium channels in the cerebellum and hippocampus, gabapentin can cause dizziness, visual disturbances and sedation. (69) More concerning, when combined with opioids, gabapentinoids exacerbate respiratory risks, leading to greater postoperative respiratory depression and the requirement of non-invasive ventilation or naloxone use. (71, 72) In the general population, concomitant gabapentinoid and opioid use significantly increases the risk of opioid-related death. In response to these findings, the FDA has issued warnings about the adverse respiratory effects of gabapentinoids. Multimodal analgesia relies on favourable pharmacodynamic interactions, where the benefits of combination therapy should outweigh the risks—an approach that is now questioned regarding the broad perioperative use of gabapentinoids. (69) However, the 2019 update of the ERAS guidelines for perioperative care in gynecologic/oncology surgery continues to recommend the routine pre-emptive administration of gabapentin, among other analgesics, to reduce pain and opioid requirements. (6)

Ketamine

Ketamine – a NMDA antagonist - is a dissociative anesthetic agent, first used as a general anesthetic in the 1960s. Its analgesic use in subanesthetic concentrations for managing acute pain and sparing postoperative opioids has surged in recent years. (73) While its mechanisms of action are complex, ketamine essentially acts on glutamate binding sites, NMDA receptors, and non-NMDA receptors (e.g. μ-opioid, muscarinic, monoaminergic, γ-aminobutyric acid receptors). (74) The antagonism of the NMDA receptor is responsible for specific amnesic and psychosensory effects, analgesia and neuroprotection.

At lower doses (0.1 mg/kg slow bolus, followed by a 0.1 mg/kg/h infusion), ketamine exerts anti-hyperalgesic effects, while at higher doses (0.5–1 mg/kg bolus), it acts as an anesthetic and analgesic. (73) The state of anesthesia induced by ketamine – known as "dissociative anesthesia" – is different from other anesthetic drugs (e.g., propofol, benzodiazepines, etc.). During "dissociative anesthesia", while sensory information may reach cortical receiving areas, it fails to be perceived in some association areas. (75) Additionally, ketamine can exert psychodyleptic effects – such as impression of unreality, depersonalization or hallucinations – most commonly during the "awakening phase". (76) Finally, antidepressive properties of ketamine have been described – partially due to the implication of NMDA receptors in depression state. (75) Multiple studies have supported these antidepressive properties - for example, DiazGranados et al showed an improvement in suicidal ideation in patients with treatment-resistant major depressive disorder within 40 minutes of a ketamine infusion, remaining improved for up to four hours post-infusion. (77)

Due to its high liposolubility, ketamine is distributed extensively. It is mainly metabolized (80%) into the active metabolite norketamine, which is further transformed into 6-hydroxy-norketamine followed by excretion into the bile and urine after glucuronoconjugation. Given intravenously, ketamine reaches its receptors very quickly with a transfer half-life of < 1 minute. Additionally, it can be administered intramuscularly, intrarectally, orally or intranasally. Oral bioavailability however is limited due to the hepatic metabolism. (75, 78) According to the consensus guidelines from the American Society of Regional Anesthesia and Pain Medicine (ASRA), the American Academy of Pain Medicine (AAPM), and the

American Society of Anesthesiologists (ASA), the recommended subanesthetic dose of ketamine bolus should not exceed 0.35 mg/kg, and infusions for acute pain generally should not exceed 1 mg/kg/h in settings without intensive monitoring. (73) As a rule of thumb, lower doses should be preferred over higher doses. O'Neill and Lirk (2022) recommend starting with a lower dose (0.1 to 0.15 mg/kg as a bolus, 0.1 mg/kg/h as an infusion) and gradually titrating upwards, with the primary aim of avoiding side effects. (79)

Patients that could benefit from subanesthetic ketamine in the acute pain setting include those undergoing surgery in which the expected postoperative pain is severe. (80) On the other hand, perioperative ketamine use has not been shown to provide benefits for patients undergoing procedures with expected mild pain. (73) Additionally, studies suggest at least a mild benefit of subanesthetic ketamine in opioid-tolerant or -dependent patients presenting for surgery or during acute exacerbations of chronic pain conditions. (81) Ketamine also remains an attractive option for those at an increased risk for opioid-related respiratory depression (e.g., obstructive sleep apnea (OSA)) – due to the resulting reduction of opioid consumption. (82)

The benefits of ketamine as a component of multimodal analgesia were assessed in four recent meta-analyses. These concluded that the addition of ketamine was associated with a small but significant reduction in pain scores, a moderate decrease in the requirement of opioids in all 4 meta-analyses, and a lower incidence of postoperative nausea and vomiting during the initial postoperative period in 3 of the 4. (80, 83-85) None of the 4 meta-analyses reported increased sedation with use of ketamine, and only one found an increase in neuropsychiatric adverse effects with ketamine (eg, hallucinations, nightmares). (80)

The main contraindications for ketamine use are typically related to its anesthetic use at high doses, while clinical studies on subanesthetic use offer limited guidance on specific contraindications. According to the ASRA, AAPM and ASA, evidence suggests that ketamine should be avoided in individuals with poorly controlled cardiovascular disease, active psychosis, severe liver disease (e.g., cirrhosis), elevated intracranial pressure, elevated intraocular pressure, and pregnant individuals. (73)

Neuraxial anesthesia

Neuraxial anesthesia techniques, including intrathecal (spinal), epidural, and combined spinal-epidural modalities, are widely used to manage postoperative pain and, in some cases, to provide anesthesia during surgery. (86) Epidural anesthesia is particularly favoured in many ERAS protocols for open surgeries due to its effectiveness in reducing opioid use and mitigating the body's stress response to surgery by inhibiting sympathetic nerve activity—key elements of the ERAS strategy.

The origins of spinal anesthesia date back to 1898 when the German surgeon August Bier performed the first operation using a spinal block with cocaine, after testing it on himself and his assistant. (87) Despite experiencing post-dural puncture headaches (PDPH), Bier's technique quickly spread across Europe and reached America within a few years. (88) Epidural anesthesia emerged in 1901 using a caudal approach, but lumbar epidurals, as we know them today, were not developed until 1921. (89)

In spinal anesthesia, a needle is inserted through the dura mater to inject the anesthetic into the intrathecal space, where it mixes with the cerebrospinal fluid (CSF). This technique is typically performed between the third and fourth lumbar vertebrae to avoid injury to the conus medullaris, the terminal end of the spinal cord (Figure 9). Epidural anesthesia, on the other hand, involves injecting local anesthetics into the epidural space, which surrounds the dura and extends the length of the spinal canal. The procedure can be done at lumbar or thoracic levels, and often includes the insertion of a catheter to allow for continuous drug delivery. The area affected by spinal anesthesia corresponds to the nerve roots that exit the spinal canal at the injection site, usually at the lumbar or low thoracic level. Epidural anesthesia provides a broader area of analgesia, and the addition of neuraxial opioids can further enhance the effect. The combined spinal-epidural technique allows for both methods to be utilized together in a single procedure, with an intrathecal injection followed by catheter placement in the epidural space. (86)

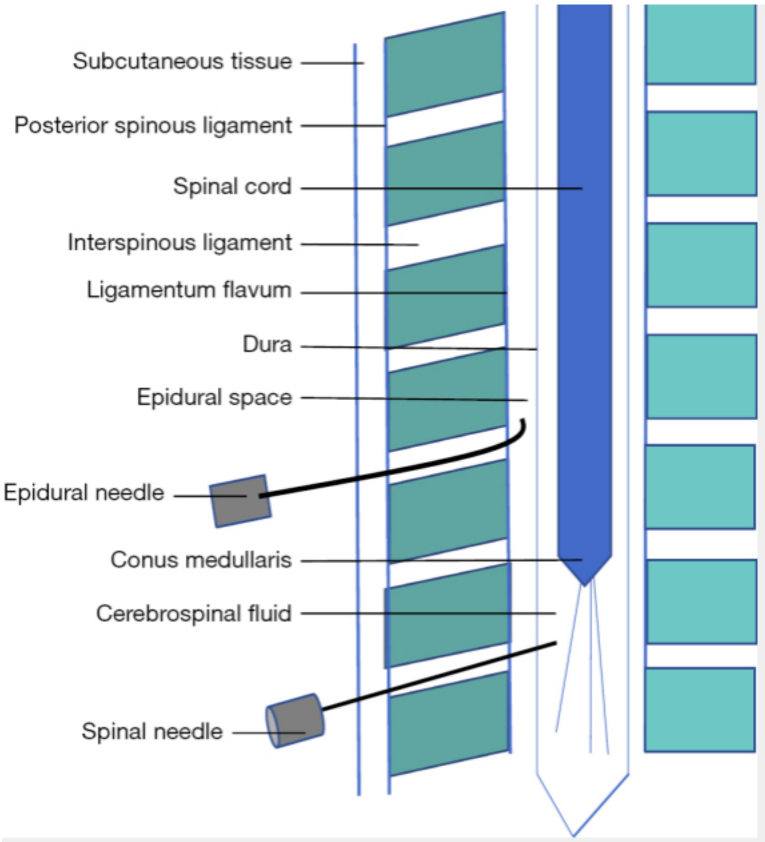

Figure 9. Schematic diagram for placement of epidural and spinal neuraxial blocks. (86)

Absolute contraindications to neuraxial anesthesia include patient refusal, local infection at the injection site, allergies to anesthetic agents, elevated intracranial pressure, and significant, untreated hypovolemia. Many previously considered "absolute" contraindications are now viewed as relative, including conditions such as coagulopathy, sepsis, demyelinating neurological diseases, and fixed cardiac output states (e.g., aortic stenosis). (2,4) In such cases, a careful assessment of the risks and benefits is necessary before proceeding. (88, 90)

Minor and relatively common complications of a neuraxial block include block failure, itchiness, urinary retention, shivering, and hypotension. PDPH is another frequent complication, occurring in approximately 1 in 200 to 1 in 500 cases. It results from CSF leakage through a puncture site in the dura mater, which can cause a drop in CSF pressure and result in headache and other symptoms. For patients who do not respond to conservative treatments—such as simple analgesics, hydration, and caffeine (91)—an epidural blood patch (EBP) may be required. EBP involves the injection of the patient's own blood into the epidural space, aiming to seal the dural puncture and halt the CSF leak. (92) Serious complications are rare but can include nerve injury, which can be caused by direct trauma, vertebral canal hematomas, or infections such as epidural abscess, meningitis, or arachnoiditis. Drug errors can also lead to significant complications: incorrect dosing can cause total spinal anaesthesia and wrong route administration can cause nerve injury. (86)

Local anesthetics used in neuraxial blocks can be administered as a single dose, intermittent boluses, or continuous infusions to achieve analgesia and anesthesia for perioperative pain management. These anesthetics may be hypobaric, isobaric, or hyperbaric relative to the CSF. (88) The addition of adjuncts to the local anesthetic can further influence its speed of onset, duration of action and density of the block. These additives include opioids, alpha-2-agonists, ketamine and sodium bicarbonate. (93) Opioids can be used in combination with local anaesthetics or as sole agents to provide postoperative analgesia, which will be further discussed in the following chapter. Their mechanism of action varies depending on the route of administration. When delivered intrathecally, opioids primarily act at the dorsal horn of the spinal cord, reducing the propagation of nociceptive action potentials. As the opioid spreads toward the brain, it also modulates descending inhibitory pain pathwys. Additionally, it is absorbed systemically into the blood stream. In the epidural space, the primary mechanism of action is through systemic absorption, although some opioid may also diffuse into the intrathecal space. The physical properties of the drug also influence their mechanism of action. (86) Lipophilic opioids, such as fentanyl and sufentanil, (93) diffuse quickly into the intrathecal space and bind to receptors in the dorsal horn, resulting in a rapid but short-lasting effect. In contrast, hydrophilic opioids like morphine have a slower onset of action because they do not bind as quickly to the dorsal horn. Because of this, a greater portion of the drug is free to move up the CSF, which explains the delayed respiratory depression with morphine compared to fentanyl, for example. (93, 94) Alpha-2 agonists (clonidine, dexmedetomidine) have been shown to prolong duration of block and improve postoperative pain relief, though they may cause hypotension, bradycardia, and sedation. (93, 94) Ketamine, which also acts at the dorsal horn of the spinal cord at NMDA receptors, can speed up the onset and prolong analgesia, but may cause sedation and headache. (94) Sodium bicarbonate, mostly utilized with lidocaine in the epidural space, can accelerate its onset by increasing the unionised drug portion, which is able to diffuse to it intraneural site of action. (94) The addition of vasoconstrictors such as adrenaline can reduce systemic absorption and extend the duration of action, particularly when combined with shorter acting local anesthetics, such as lidocaine. (86)

1.4.3. Opioids

Evidence suggests that the opium poppy (*Papaver somniferum*) has been used for its medicinal properties as far back as 3000 BC. In 1806, the German chemist Friedrich Sertürner isolated morphine from opium, marking the beginning of modern opioid pharmacology. (95) While morphine is the most well-known alkaloid derived from *P. somniferum*, four primary alkaloids can be extracted from the plant: morphine, codeine, papaverine, and thebaine. Following Sertürner's discovery, chemical modifications of these basic opiate alkaloids led to the development of a variety of semi-synthetic opioids. These include drugs such as diamorphine (heroin), dihydrocodeine, buprenorphine, nalbuphine, naloxone, and oxycodone. In the 20th century, numerous synthetic opioids were also created, either intentionally or by chance. These synthetic opioids can be categorized into four chemical classes: morphinan derivatives (e.g., levorphanol, butorphanol), diphenylheptane derivatives (e.g., methadone, propoxyphene), benzomorphan derivatives (e.g., pentazocine, phenazocine), and phenylpiperidine derivatives (e.g., pethidine, alfentanil, fentanyl, sufentanil, and remifentanil). (95)

Opioids have traditionally been a mainstay analgesic treatment for managing perioperative acute pain, and their role in anesthesia practice remains unquestioned. However, we struggle with basic unresolved issues such as optimal dosing, duration of therapy and opioid therapy tailored for optimal individual outcome. (96)

1.4.3.1.Classification and Opioid receptors

Opioids can be classified based on their effects at opioid receptors as agonists (e.g., morphine), partial agonists (e.g., buprenorphine), or antagonists (e.g., naloxone). (97) Additionally, they can be categorized by specific opioid receptors through which they exert their effects. There are three primary opioid receptors— mu (μ)-opioid peptide (MOP), delta (δ)-opioid peptide (DOP), and kappa (κ)-opioid peptide (KOP)— all of which are G-protein-coupled and widely distributed in the central nervous system. (98, 99) Following the identification of these receptors, several endogenous ligands were discovered, derived from three pro-hormone precursors: proenkephalin (which produces met-enkephalin and leu-enkephalin, acting on the DOP receptor), prodynorphin (which generates dynorphins A and B, targeting the KOP receptor), and pro-opiomelanocortin, which produces β-endorphin, an agonist at the MOP receptor, but also interacts with all three receptors. (98, 100) In addition, the nociceptin (NOP) receptor, activated by its endogenous ligand nociceptin/orphanin FQ (N/OFQ), is distinct from the classical opioid receptors, as it does not bind naloxone, leading some to classify it as a non-opioid receptor. (99)

When an opioid agonist binds to a G-protein-coupled opioid receptor, it causes the α subunit of the G-protein to exchange its bound guanosine diphosphate (GDP) for guanosine triphosphate (GTP). This causes the α-GTP subunit to dissociate from the βγ complex, both of which then interact with target proteins. For classical opioid agonists, this leads to inhibition of adenylyl cyclase, reducing intracellular cyclic adenosine monophosphate (cAMP) levels. The complexes also interact with ion channels, increasing potassium conductance and inhibiting calcium conductance. The overall result is a decrease in cAMP, cell hyperpolarization, and reduced neurotransmitter release in neurons. (97)

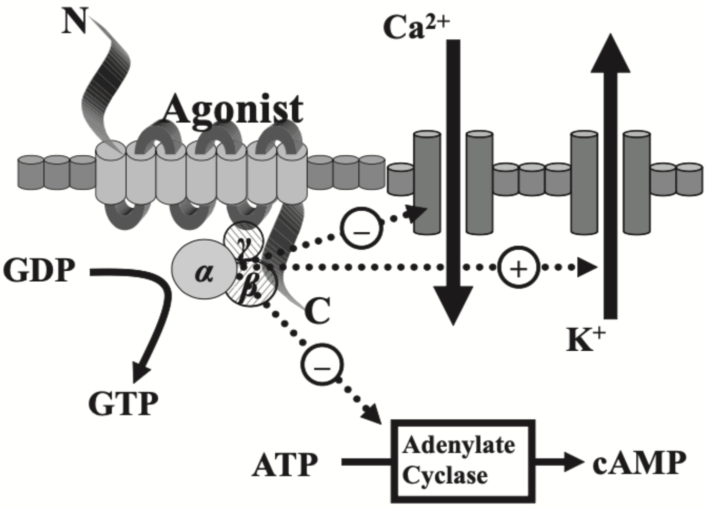

Figure 10. Intracellular changes occuring following the binding of an opioid agonist to a G-protein-coupled opioid receptor. (94)

1.4.3.2.Analgesic effects

Opioid receptors are widely distributed throughout the CNS and in peripheral tissues of both neural and non-neural origin. Within the CNS, high concentrations of opioid receptors are found in the periaqueductal grey matter (PAG), locus coeruleus, and rostral ventral medulla, as well as in the substantia gelatinosa of the dorsal horn. The activation of MOP receptors in the midbrain is considered a central mechanism of opioid-induced analgesia. MOP agonists exert their effects by indirectly stimulating descending inhibitory pathways that influence regions like the PAG and the nucleus reticularis paragigantocellularis. This activation of descending inhibitory neurons in turn increases neural activity in the nucleus raphe magnus. This heightened neuronal traffic enhances the release of 5-hydroxytryptamine (serotonin) and enkephalin, both of which activate pain-modulating neurons that directly synapse with the substantia gelatinosa in the dorsal horn. The overall result is a reduction in nociceptive (pain-related) signaling from the periphery to the thalamus. In addition to these central mechanisms, opioids can directly inhibit nociceptive transmission at the level of the substantia gelatinosa in the dorsal horn and in peripheral nociceptive afferent neurons - further reducing the transmission of pain signals from the periphery. (97)

1.4.3.3.Common clinical opioids

All opioids used in clinical practice primarily act at the mu opioid (MOP) receptor, though some also interact with other opioid or non-opioid receptors. MOP receptor agonism is responsible for most of their analgesic effects but also contributes to common side effects, including sedation, euphoria (leading to abuse potential), respiratory depression, and effects on cardiovascular stability. Morphine, for example, can cause histamine release, lowering blood pressure and systemic vascular resistance. Other side effects of opioids include constipation, nausea, vomiting, urinary retention, pruritus, miosis, and muscular rigidity. (97)

Morphine acts as a MOP receptor agonist and also targets DOP and KOP receptors. It is commonly given orally or intravenously but can also be administered via various other routes. Due to its low lipid solubility, morphine crosses the blood-brain barrier slowly, resulting in a delayed onset of action, even with IV administration. Oral morphine is subject to significant first-pass metabolism, reducing its bioavailability by 40–60%. It is primarily metabolized by glucuronidation, producing active metabolites, such as morphine-6-glucuronide, which can be more potent and longer-lasting than morphine itself. With a half-life of around 150 minutes in healthy individuals, morphine often requires frequent dosing to maintain effective pain relief. (97)

Alfentanil, fentanyl, and remifentanil are all MOP receptor agonists, differing from morphine mainly in their pharmacokinetics. Alfentanil and fentanyl are highly lipid-soluble, leading to a faster onset of action than morphine. However, prolonged administration can cause these drugs to be stored in fat, resulting in a delayed recovery through slow release back into the bloodstream and renal excretion. In contrast, remifentanil, though more lipid-soluble than morphine, is rapidly metabolized by non-specific esterases in blood and tissues, allowing for quick clearance without an increased context sensitive half-life. This makes remifentanil ideal for use in surgery and intensive care, where quick clearance of the drug is beneficial. (97)

Oxycodone is a potent semi-synthetic opioid derived from thebaine, acting on both MOP and KOP receptors to produce its analgesic effects. In addition to its high oral bioavailability, Oxycodone is available in time-release formulations, allowing for convenient twice-daily dosing. (101)

In contrast, buprenorphine, a partial MOP receptor agonist, offers a different pharmacological profile. It provides effective pain relief at lower plasma concentrations via its interaction with the MOP receptor but may cause anti-analgesic effects at higher doses due to its interactions with KOP and NOP receptors. Buprenorphine's ability to be delivered via transdermal patches, along with its reduced risk of respiratory depression and overdosing compared to pure MOP agonists, makes it a valuable option in chronic pain management. (97) Partial agonism leads to a ceiling effect that makes buprenorphine a valuable tool for maintenance therapy in patients suffering from opioid use disorder (OUD).

Tramadol and methadone are additional commonly prescribed opioid receptor agonists that also act on non-opioid sites. Tramadol, a phenylpiperidine derivative of codeine, not only acts on MOP receptors but also modulates serotonin and norepinephrine reuptake, contributing to its analgesic effects. While tramadol shares many side effects with other MOP agonists, it tends to cause less respiratory depression and fewer gastrointestinal issues. However, it can increase the risk of seizures, particularly when combined with other drugs that affect serotonin and norepinephrine levels. (97)

Methadone is known for its limited first-pass metabolism, high bioavailability, and lower potential for euphoria. It is commonly used as an oral substitute for individuals with opioid use disorder. In addition to its role in addiction treatment, methadone is also used for chronic pain, where its potential antagonism at the NMDA receptor may help manage neuropathic and rebound pain. (97) Methadone has undergone a resurgence within the field of anesthesia as well, where it’s long half-life and favourable side effect profile has led to increased use for the management of post-operative pain, especially within the population of patients undergoing major spine surgery.

In some settings, such as in patients with severe respiratory depression or altered consciousness, opioid effects may need to be reversed. Naloxone and naltrexone can reverse opioid effects by acting as antagonists at the MOP, KOP, and DOP receptors. However, they do not bind to the NOP receptor, so they do not affect the action of NOP agonists or partial agonists. (97)

1.4.3.4.The Opioid crisis

In today's opioid-conscious environment, it's easy to overlook the underlying issue that sparked the opioid crisis: poorly managed pain. (102) Factors initially intended to address this pain – such as the inclusion of pain as the fifth vital sign, aggressive pain management standards, the influence of profit-driven pharmaceutical companies and widespread overprescribing – along with the belief that medicinal opioids carried little risk of addiction, all played significant roles in the prevalent the opioid crisis. (103) According to the U.S. Centers for Disease Control and Prevention, roughly 250,000 people died in the United States from overdosing on prescription opioids from 1999 to 2019. (104)

High rates of persistent postoperative opioid prescribing have been observed in previously opioid-naïve patients across nearly all surgical cohorts. (105-108) While some of this persistent prescribing may be linked to non-surgical factors, (109) studies using claims data with non-surgical control groups have found significantly higher rates of opioid use among patients undergoing surgery. This suggests that surgery, and the associated postoperative prescribing, is a key factor driving the initiation of long-term opioid use. (107, 108) Additional risk factors for prolonged opioid use or opioid misuse include history of opioid use, substance use disorder, smoking, psychiatric comorbidities (particularly anxiety and depression), additional medical comorbidities (higher Elixhauser comorbidities index), younger age and history of chronic pain. (110)

While approximately 50,000 Americans lose their lives to opioid overdoses each year, (111) the crisis has expanded beyond U.S. borders, with Canada and parts of Europe now facing similar challenges. In a retrospective study analyzing opioid use and misuse proxies in the Netherlands between 2008 and 2017, Kalkman et al. found that opioid prescriptions nearly doubled over the 10-year period. (96) Concurrently, the authors observed an increase in the incidence of hospital admissions related to prescription opioid intoxication, in the proportion of patients receiving addiction care for prescription opioid use disorder while prescription opioid-related mortality also increased. (96)

According to a 2018 report by the International Narcotics Control Board, the United States is the world's largest consumer of opioids, with 40,240 daily dosages per million inhabitants daily. Germany ranks second with 28,862, followed by Canada with 26,029 dosages. As mentioned above, the opioid crisis in the United States stems from influential reports that downplayed the risks of opioids, aggressive pharmaceutical marketing, the increase of "pill mills" (clinics or pharmacies that improperly dispense opioids), and shifting attitudes toward pain management. (112, 113) In contrast, many European countries, including Austria, prohibit direct-to-consumer pharmaceutical marketing and have stricter prescription regulations. These structural differences in healthcare systems and regulatory frameworks have helped Austria avoid the opioid crisis that has severely impacted North America. Nonetheless, Austrian healthcare systems must remain vigilant as opioid misuse and overprescribing are growing global concerns, emphasizing the importance of maintaining a balanced approach to opioid use by minimizing overprescription while avoiding the complete eradication of opioids, which remain essential for effective acute and perioperative pain management.

1.4.3.5.Opioids after hysterectomy

In the United States, roughly 82% of women undergoing benign hysterectomy are prescribed opioids perioperatively. (114) This is further corroborated by a national study on perioperative opioid prescriptions, which found that surgeons performing hysterectomies ranked among the top four physician groups for opioid prescriptions. (115) There is considerable variation in perioperative opioid dispensing practices, with doses ranging from 50 to 300 MME. (116) To address this, several best practice guidelines have been developed, primarily aimed at reducing opioid use in the perioperative setting. (116, 117) For example, Reagan et al. recommended that opioid-naïve women undergoing pelvic reconstructive surgery, with no pain comorbidities, should be prescribed no more than 112.5 MME of opioids. (118) However, a recent meta-analysis on perioperative opioid dispensing after benign hysterectomy revealed that the average perioperative opioid dose dispensed was 143.5 MME, highlighting a concerning trend of overprescription among gynecologic surgeons. (117-119)

Hessami et al. further explored opioid prescribing by hysterectomy approach and found that abdominal hysterectomy was associated with the highest dose of dispensed perioperative opioids, followed by laparoscopic and vaginal approaches. (119) This difference is likely due to the reduced postoperative pain and quicker recovery times linked to minimally invasive procedures, generally resulting in fewer opioid prescriptions. (116, 120, 121) Despite this plausible explanation, a nationwide trend analysis from 2004 to 2014 showed a significant increase in perioperative opioid prescriptions for hysterectomy in the U.S., (122) even as minimally invasive hysterectomy rates were on the rise. Moreover, while opioid doses for minimally invasive hysterectomies were lower than those for abdominal procedures, they still exceeded the recommended limits. (118)

While the overall incidence of persistent opioid use after benign hysterectomy was 5%, the route of hysterectomy did not significantly predict the likelihood of ongoing opioid use. Additionally, several risk factors associated with a higher risk of persistent opioid use after benign hysterectomy have been identified. These include younger age, smoking, alcohol use, back pain and fibromyalgia. (119) These findings emphasize the need for stricter, standardized guidelines for opioid prescribing in gynecologic surgery to minimize the risk of overprescription and subsequent opioid dependence.

The data on opioid dispensing following hysterectomy in Austria is limited, likely due to the fact that it is almost non-existent. A recent comparative cohort study conducted across two tertiary care centers—one in Canada and the other in Austria—revealed significant differences in opioid and non-opioid analgesics administered both intraoperatively and postoperatively. Specifically, the Austrian cohort received significantly higher MME during surgery compared to the Canadian cohort, whereas the Austrian cohort received significantly lower MME in the post-anesthesia care unit compared to their Canadian counterparts. The authors hypothesize that these differences may be attributed not only to variations in surgical techniques (open vs. minimally invasive) but also to cultural differences in attitudes toward postoperative opioid use. In Austria, the longer average hospital stay, driven in part by hospital billing policies and traditions, appears to facilitate a reduction—or even elimination—of opioid prescriptions at discharge following hysterectomy. Furthermore, many patients in Austria show a preference for minimizing or avoiding opioid-based pain medications, potentially influenced by the widespread awareness of the opioid crisis in North America. (123)

1.4.4. Enhanced Recovery after surgery (ERAS)

ERAS is an evidence-based multimodal, multidisciplinary approach aiming to improve the care of surgical patients, ultimately resulting in improved recovery with decreased complications, shorter hospital stay and reduced surgery-related costs. (124) ERAS protocols generally include four components - prehabilitation, preoperative, intraoperative and postoperative - all containing multiple elements aimed at reducing stress and improving the body's stress response. (5) Key elements include patient education, bowel management, venous thromboembolism prophylaxis, antimicrobial prophylaxis, standard anesthetic protocols, fluid management, postoperative analgesia and nutrition - creating a comprehensive approach to stress reduction throughout the surgical process. (125)

In the postoperative setting, the ERAS guidelines for perioperative care in gynecologic/oncologic surgery strongly recommend several key practices with high level evidence. (4, 6) These include prophylaxis against thromboembolism via compression stockings and intermittent pneumatic compression, as well as extended prophylaxis (28 days) for patients after laparotomy. The guidelines also emphasize the importance of perioperative nutritional care, recommending the initiation of a regular diet within the first 24 hours after surgery, as well as postoperative glucose control. ERAS elements that reduce metabolic stress should be considered, to reduce insulin resistance and the development of hyperglycemia. This also entails maintaining blood glucose levels (< 180-200 mg/dl) and treatment of levels above this range to improve perioperative outcomes. (4, 6)

Another critical element within the postoperative component is the management of postoperative pain through multimodal analgesia. The guidelines recommend the adoption of a multimodal approach to analgesia, including use of NSAIDs/acetaminophen, gabapentin and dexamethasone, unless contraindications exist. (4) Effective control of post-operative pain allows achievement of other ERAS targets, such as early mobilization and postoperative nutrition whilst reducing the need for opiates. More specifically, the guidelines recommend a multimodal analgesia strategy in patients undergoing gynecologic surgery – with the goal of reducing post-operative opioid requirements. Post-operatively, patients who can tolerate a diet should be given oral opioids rather than intravenously.

Acetaminophen and NSAIDs should be administered in combination, unless contraindicated. Additionally, gabapentin may be considered as part of the pain management regimen. A recent systematic review found that preemptive administration of gabapentin in patients undergoing abdominal hysterectomy was effective in reducing postoperative pain, opioid consumption, while the optimal dosing and timing of administration remains to be determined. However, recent evidence has challenged previously emphasized benefits of gabapentin use in the surgical setting and raised concerns for adverse effects when routinely used for perioperative pain management. (69, 126)

Furthermore, intrathecal morphine and paracervical nerve blocks have been utilized to promote early discharge as part of enhanced recovery pathways, particularly for vaginal hysterectomy, though studies are mixed regarding their effectiveness. (4, 127) In the 2019 update of ERAS recommendations for perioperative care in gynecologic/oncologic surgery, reducing opioid use with a multimodal post-operative analgesic protocol is further emphasized. Additional techniques, such as incisional injection of bupivacaine, can decrease the need for systemic medications. (6) The final ERAS guidelines for postoperative care in gynecologic/oncologic surgery include short-term use (<24h) of urinary catheters, avoiding routine peritoneal drainage and early mobilization within 24 hours of surgery. (4)

2. Methods:

2.1. Data Source, Study Design and Study Sample

After institutional review board approval (Hospital for Special Surgery, New York, New York; IRB #2012-050), we extracted data from the Premier Healthcare claims dataset (Premier Healthcare Solutions, Inc., Charlotte, NC;). The requirement for written informed consent was waived given the de-identified nature of the data.

Adult patients undergoing hysterectomy procedures from 2006 to 2022 were included in this retrospective cohort study. Hysterectomy procedures were identified using International Classification of Diseases, Ninth and Tenth revision (ICD-9/10) and Current Procedural Terminology (CPT) codes as shown in Appendix 1.

From a total of 1.393.962 records, we excluded unknown sex (n=516), unknown discharge status (n=1533), patients without documented opioid use (n=70,635), and cases with opioid utilization above the 95th percentile (to exclude outliers, n=13,355).

2.2. Study Variables

The main exposure of interest was the use of multimodal analgesia, which was further categorized into three groups: opioid use with the addition of 1, 2 or >2 non-opioid analgesic modes. Non-opioid analgesic modes included ketamine, NSAIDs, paracetamol/acetaminophen, COX-2 inhibitors, steroids (>1 dose of use on the day of or the day after surgery), gabapentin/pregabalin, or neuraxial anesthesia. The use of multimodal analgesia components was identified from billing codes, which have been published previously. (128) Outcomes of interest were opioid prescription, LOS (measured in days), cost (measured in 2022 USD) and perioperative complications. Complications included a composite and individual analysis of respiratory, cardiac, gastrointestinal, genitourinary, and CNS complications. ICD-9 and ICD-10 diagnosis codes were used to define all perioperative complications as seen in Appendix 2. Opioid utilization during hospitalization was based on billing for opioids (opioid type and dosage were billed by day in Premier) and then was converted into oral MME.

Patient-related variables included age, sex and race/ethnicity. Additionally, variables describing history of OSA, substance abuse, chronic pain conditions, psychiatric conditions and opioid abuse were included. The severity of comorbidities was assessed using the Elixhauser Comorbidity index, categorized as 0, 1, 2 and 3+. Procedure-level variables showed the year in which surgery was performed, and type of anesthesia (general, neuraxial) used. Healthcare-level variables included insurance type (commercial, Medicaid, Medicare, uninsured, other), hospital location (urban, rural), hospital size (less than 300, 300 to 499, greater than or equal to 500 beds), and hospital teaching status.

2.3. Statistical Analysis

A descriptive analysis was conducted for all study variables, stratified based on the number of multimodal analgesia methods used. Categorical variables were summarized as counts and percentages, while continuous variables reported as median and interquartile ranges (IQR). Given the large sample size, univariable differences between groups are more likely to achieve statistical significance - therefore, standardized differences were used rather than p-values. A standardized difference of ≥0.1 (or 10%) was considered indicative of a meaningful difference in the distribution of covariates between groups.

To compare associations between the multimodal analgesia categories and binary outcomes (e.g. composite complications, individual complications), multivariable multilevel logistic regression models were used. The results were reported as OR with 95% CI. These models were adjusted for a set of a priori-determined covariates, including age, race, gender, Elixhauser Comorbidity Index, year of surgery, hospital location, bed size, and teaching status - as previously described.

Associations between the use of multimodal analgesia categories (classified as opioid-only, 1, 2, or >2 non-opioid analgesics) and continuous outcomes (opioid utilization, LOS, and cost) were assessed using generalized linear models. These models were adjusted for the same covariates used in the logistic regression models. The results were presented as least square means differences relative to the reference group, along with 95% CIs. Additionally, for opioid utilization, we further adjusted for factors such as substance use/abuse (including smoking), chronic pain conditions, psychiatric comorbidities, and opioid use disorder due to their known association with opioid consumption. The LOS outcome was modeled exclusively using data from the inpatient cohort. Statistical significance was set at a p-value threshold of <0.01. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

Among a patient population of 1,307,923 adult women undergoing hysterectomy surgery in the time from January 2006 to December 2022, we found that 84.3% (N = 1,102,812) received multimodal analgesia. Of these, 58.9% (N = 649,471) received one, 28.0% (N = 308,579) received two and 13.1% (N = 144,762) received more than two additional non-opioid analgesics.

The use of multimodal analgesia was slightly increased in patients with a higher comorbidity burden and a history of substance abuse. On the other hand, utilization of multimodal analgesia was lower in older patients, those on Medicare, and patients receiving general anesthesia. The use of >2 analgesic modes was more common in teaching hospitals, while non-teaching hospitals more frequently used a lower number of analgesic modalities. The most used multimodal components were acetaminophen and NSAIDs, followed by gabapentin and neuraxial anesthesia. (Table 1)

Trend analysis showed that utilizing three or more non-opioid analgesic modalities in addition to opioids has risen steadily from an incidence of 1.03% in 2006 to 39.57% in 2022. Simultaneously, the addition of just one non-opioid analgesic modality to opioid analgesia decreased from 61.72% in 2006 to 18.84% in 2022. Additionally, a significant decrease in the use of opioid-only analgesia was noted from 25.31% in 2006 to 5.14% in 2022. (Figure 11)

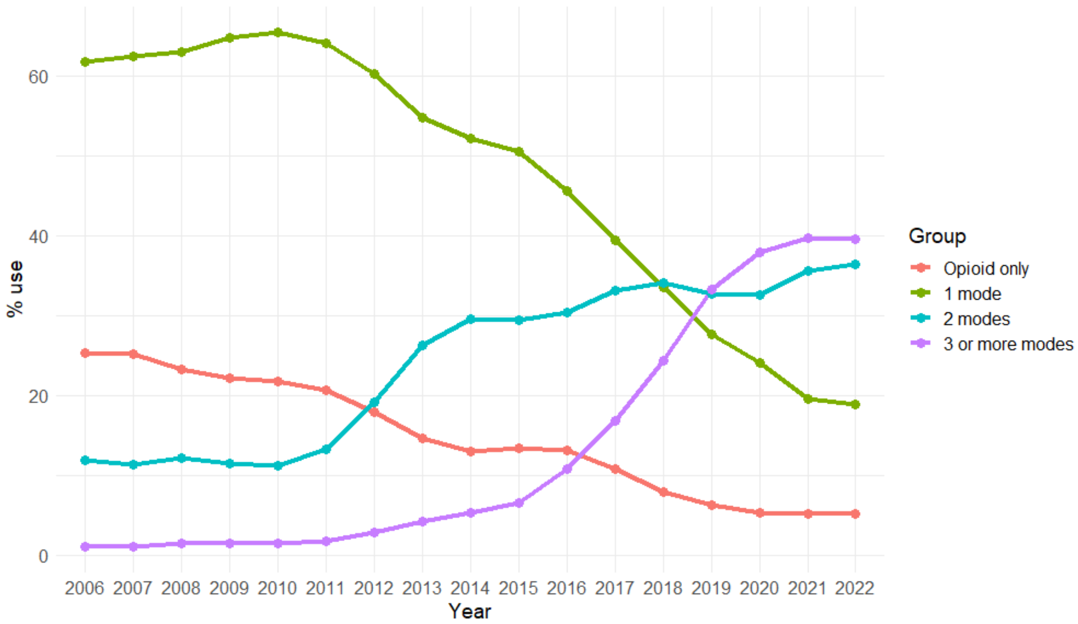

Figure 11. Trends of multimodal analgesia among hysterotomy cases over study time.

In unadjusted outcomes stratified by multimodal groups, patients receiving multimodal analgesia had a lower incidence of the composite outcome for any complication - more specifically respiratory, cardiac and genitourinary complications. Furthermore, opioid use was lower among those receiving multimodal analgesia. (Table 2)

This pattern became more evident in adjusted models. (Table 3) Multimodal analgesia, categorized into four groups (1, 2, or ≥3 additional non-opioid analgesics versus opioid-only) was consistently linked to a decrease in the likelihood of any complication (OR 0.66 CI 0.64;0.68 / OR 0.63 CI 0.61;0.66 / OR 0.65 CI 0.62;0.67). Increasing the number of analgesic modalities did not further reduce the odds of complication. Specifically, the addition of 1, 2 or ≥3 non-opioid analgesics showed a decrease in respiratory complications (OR 0.60 CI 0.57;0.63 / OR 0.60 CI 0.56; 0.64 / OR 0.64 CI 0.60; 0.69), cardiac complications (OR 0.71 CI 0.68, 0.75 / OR 0.69 CI 0.65, 0.73 / OR 0.66 CI 0.62, 0.71), and genitourinary complications (OR 0.65 CI 0.62, 0.68 / OR 0.58 CI 0.55, 0.61 / OR 0.61 CI 0.57, 0.66) respectively; all $p<0.001$. A reduction of gastrointestinal complications was only seen with the addition of one non-opioid analgesic modality (OR 0.81 CI 0.74, 0.90). No effects were found regarding the occurrence of central nervous system complications.

A decrease of LOS by 0.52 days (CI 0.54; 0.51), 0.49 days (CI 0.51; 0.47) and 0.40 days (CI 0.43; 0.38), respectively, was observed with the gradual use of multimodal analgesia compared to opioids only. Additionally, costs were reduced by -765 USD (CI -817; -714) and -479 USD (CI -539; -419) with the addition of 1 or 2 non-opioid modalities. A small - non-significant - increase in cost of 79 USD (CI 2; 156), was revealed among those receiving >2 non-opioid analgesic modalities. Total opioid consumption was progressively reduced as additional non-opioid analgesics were used, with reductions of -9.51 mg (CI: -11.16; -7.86), -15.29 mg (CI: -17.21; -13.37), and -29.35 mg (CI: -31.79; -26.91), respectively. (Table 3)

4. Discussion

In this retrospective cohort study, we analyzed data from 1.3 million women who underwent hysterectomy surgery between 2006 and 2022, focusing on the impact of multimodal analgesia within post-operative pain management. Hysterectomy for benign indication is among the most common gynecological procedures and can be associated with significant pain, underscoring the need to optimize post-operative analgesia. Inadequate pain management following gynecologic surgery is a significant contributor to postoperative complications, prolonged recovery, and increased opioid consumption. (3, 129) Therefore, ERAS guidelines, including those specific to gynecological procedures, strongly recommend the routine use of multimodal analgesia to minimize opioid use, promote faster recovery, and reduce complications. (6) The reduction in opioid use is particularly important given the risks associated with opioid misuse, their adverse effects, and the financial burden they can place on healthcare systems. The goal of multimodal analgesia is to simultaneously target multiple pain pathways by combining different analgesic medications and techniques, achieving both additive and synergistic effects while reducing complications. (3) However, the clinical impact of multimodal analgesia in hysterectomies remains poorly understood, and pharmacologic strategies to enhance pain management in this patient population have yet to be thoroughly explored. (130)

This study evaluated the impact of multimodal analgesia on perioperative outcomes, including complications, opioid prescription doses, LOS and healthcare costs, in patients undergoing hysterectomy. The findings demonstrate that multimodal analgesia significantly improves these outcomes, supporting its integration into standard practices. Specifically, the odds of experiencing any postoperative complication were reduced by 35% in patients receiving multimodal analgesia. Respiratory and genitourinary complications each decreased by approximately 40%, while cardiac complications were reduced by 30%. However, no significant effect was observed on CNS complications. Additionally, multimodal analgesia was associated with reduced LOS, lower total opioid consumption, and decreased healthcare costs. Cost reductions were most notable with the addition of one or two non-opioid modalities, with no further savings observed beyond two modalities.

Trend analysis over the last two decades further highlighted substantial changes in perioperative pain management practices for hysterectomies. The use of more than two non-opioid analgesic modalities increased dramatically, from 1.03% in 2006 to 39.57% in 2022, while reliance on only one non-opioid modality in combination with opioids declined sharply, from 61.72% to 18.84%. These trends reflect a growing integration of multimodal approaches, aligning with evidence of their effectiveness in improving patient outcomes and reducing healthcare burdens. (6)

With the increasing emphasis on opioid-sparing analgesia in postoperative pain management and its inclusion in many clinical guidelines, there has been growing interest in multimodal analgesia, (131) although evidence specific to postoperative pain management in gynecological surgeries, particularly hysterectomies, remains limited.

A 2017 systematic review by Blanton et al. evaluated non-opioid therapies for patients undergoing vaginal and laparoscopic hysterectomy, (132) however, this review excluded abdominal hysterectomies and did not address the role of opioids, anesthetics, or surgical technique. The study focused exclusively on non-opioid pharmacologic therapies, whereas our study takes a broader approach by exploring the use of opioids alongside additional multimodal strategies. Similarly, Lirk et al. examined the effects of analgesic, anesthetic, and surgical techniques on postoperative pain following hysterectomies and developed the PROSPECT (PROcedure-SPECific postoperative pain managemenT) guidelines. (133) These recommendations highlight a multimodal approach, incorporating acetaminophen and NSAIDs to reduce opioid use, dexamethasone to minimize analgesic requirements and serve as an antiemetic, with opioids reserved for rescue medication. Our findings align with those of Lirk et al. in demonstrating the benefits of multimodal analgesia in reducing postoperative opioid requirements. However, their study focused on laparoscopic hysterectomy and did not address other common surgical methods, such as abdominal and vaginal hysterectomy, which may require different pain management strategies. (134)

Other studies have explored preemptive multimodal analgesia in hysterectomies. For instance, Shultz investigated its effects on patients undergoing robotic-assisted hysterectomy. (135) The preoperative regimen included 200 mg of celecoxib twice daily for two days, followed by 400 mg one hour before surgery. Intraoperatively, 250–300 mg of ropivacaine was administered through vaginal mucosa injection, an intraperitoneal bath, and pre-incisional skin and fascia injections. Shultz concluded that preemptive multimodal analgesia significantly reduced postoperative opioid requirements, enabling earlier discharge without compromising patient safety or comfort. (135) Similarly, Taumberger et al. demonstrated that local preemptive analgesia using a paracervical block led to reduced postoperative pain scores and lower opioid consumption in patients undergoing vaginal hysterectomy. (136) While these studies primarily focused on pre- and intraoperative pain management using COX-2 inhibitors and local anesthetics, this study incorporates a broader range of multimodal strategies to enhance postoperative pain control across various surgical methods. Our study builds upon this existing research by incorporating a wider range of multimodal analgesic agents (ketamine, NSAIDs, paracetamol, COX-2 inhibitors, steroids, gabapentin, neuraxial anesthesia) across different surgical approaches, as shown in the appendix. This broader scope allows for a more comprehensive understanding of pain management in hysterectomies.

Our findings indicate that the use of multimodal analgesia in a large cohort of hysterectomy patients was associated with a significant reduction in serious adverse events, including respiratory, cardiac and genitourinary complications. Pain itself can trigger a range of harmful physiological responses, such as adrenergic activation with catecholamine release, inflammatory mediator activation and disturbances in hemodynamics, cardiac function and respiratory status. (137) As a result, inadequate pain control is linked to increased perioperative morbidity with elevated risks of cardiac and pulmonary complications. (79, 138-141) Thus, it is reasonable to assume that multimodal analgesia, by addressing multiple pain pathways, may help alleviate postoperative stress and mitigate the adverse effects of pain, ultimately contributing to faster recovery. Additionally, poorly managed acute postoperative pain remains one of the strongest predictors of chronic postsurgical pain, which affects 10% to 60% of surgical patients. (142, 143) Acute postoperative pain is also linked to generalized complications, such as postoperative cognitive decline, delirium, and sleep disturbances (144), as well as surgical complications, including surgical site and urinary tract infections, increased 30-day infection rates, and higher readmission rates. (145-147) Chronic postsurgical pain further exacerbates these issues, leading to delayed recovery, reduced satisfaction, and, in some cases, regret about undergoing surgery. (148, 149)

Our data also revealed a reduction in LOS among patients receiving multimodal analgesia, which is consistent with findings from studies on radical laparoscopic gynecological cancer surgeries, where multimodal strategies led to lower pain scores, less time to mobilization, and fewer severe complications. (119)

Additionally, our findings showed that multimodal analgesia in postoperative pain management for hysterectomy patients was associated with a significant reduction in opioid prescriptions. In recent years, the opioid crisis has driven a shift in anesthetic practices, sparking interest in "opioid-free anesthesia." The impact of this epidemic, including immense human and economic burdens, has influenced practitioner behavior, sometimes leading to a shift—consciously or unconsciously—toward a mindset aimed at eradicating opioids entirely, both intraoperatively and postoperatively. (150) However, in the absence of equipotent alternatives, opioids remain essential for perioperative pain management based on their undisputed analgesic efficacy. (151, 152) While the goal of minimizing excessive opioid use is both valid and appropriate, the complete eradication of opioids, as Shanthanna et al. have noted, lacks sufficient evidence to support its safety or efficacy. (131, 132) Opioid sparing, which aims to reduce reliance on opioids without eliminating them, should not be conflated with opioid absence. The history of overprescribing opioids for chronic pain should not drive a reactionary approach that withholds these medications from patients experiencing acute perioperative pain. Although it is well-known that excessive opioid use has serious adverse effects that must be addressed, a complete absence of opioids can also result in unintended negative outcomes. (150)

Optimal postoperative analgesia requires a balanced approach, utilizing available tools tailored to individual patient needs. This involves developing regimens that ensure effective pain relief promoting faster recovery and long-term benefits. (153) By integrating such strategies into clinical practice, we can achieve effective pain management while navigating the risks of both opioid overuse and inadequate analgesia.

Given the substantial opioid prescribing patterns among hysterectomy surgeons in the U.S. - with prescriptions for laparoscopic hysterectomies often exceeding actual postoperative pain requirements by a factor of four (154, 155) – there is a critical need to expand the use of multimodal anesthesia in this setting. Additionally, a nationwide analysis reported a notable increase in perioperative opioid prescriptions for hysterectomies between 2004 and 2014, despite the rise of minimally invasive surgical techniques. (156) With the Society of Gynecologic Oncology advocating for limited opioid use, multimodal analgesia may play a pivotal role in perioperative strategies that balance effective pain management with minimizing excess opioid use. (117-119)

In this national cohort of hysterectomies, we observed an incremental decrease in opioid prescription with the incorporation of more multimodal analgesia techniques. Similar opioid-sparing effects have been demonstrated with multimodal approaches in laparoscopic hysterectomies and cesaeran deliveries. (157) However, earlier studies lacked sufficient power to draw definitive conclusions regarding patient safety and complication risk. (134)

Our findings strengthen the evidence that multimodal analgesia improves postoperative outcomes while reducing opioid consumption in hysterectomy patients. By targeting multiple pain pathways simultaneously, multimodal strategies enhance analgesic effects and minimize side effects. (44, 45) From a clinical perspective, these results support the integration of multimodal analgesia as a standard approach for post-hysterectomy pain management.

5. Conclusion

Hysterectomy surgery for benign indications remains one of the most common gynecological procedures, often associated with significant postoperative pain. As mentioned above, poorly managed pain following gynecologic surgery contributes significantly to postoperative complications, prolonged recovery, and increased opioid consumption. (3, 129) In this study, we analyzed a large national sample of hysterectomy patients, focusing on the impact of multimodal analgesia in post-operative pain management. By targeting multiple pain pathways simultaneously, multimodal strategies produce synergistic and additive effects, (4) enhancing analgesia while reducing side effects. (46)

Our study suggests that the use of multimodal analgesia in hysterectomy patients was associated with substantial benefits, ultimately contributing to improved perioperative outcomes. These benefits included a significant decrease in serious postoperative complications – including respiratory, cardiac and genitourinary - by at least 30%, accompanied by a reduction in LOS and healthcare costs.

Furthermore, we observed a significant reduction in opioid prescriptions with the incorporation of multimodal analgesia, highlighting a safer and more effective strategy for managing acute pain while minimizing the risks associated with excessive opioid use. In the context of the ongoing opioid crisis and its serious adverse effects, multimodal analgesia aims to improve postoperative outcomes while reducing reliance on opioids. The primary goal is not to completely eliminate opioids but to establish a more balanced and safer approach to managing acute pain, mitigating the risks of opioid use.

While more evidence is needed, our study supports the growing body of research suggesting that multimodal analgesia improves postoperative outcomes and reduces opioid consumption in hysterectomy patients. A multimodal approach contributes to faster recovery and shorter hospital stays, which may offer a cost-effective solution. Integrating these strategies into clinical guidelines for hysterectomy patients, as well as other surgical procedures, could help standardize and promote optimal pain management across various surgical practices.

6. Strengths and limitations

This study is subject to several limitations due to its reliance on observational data. While efforts were made to adjust for baseline differences between groups (eg, age, race, insurance type – see Table 1), the lack of randomization introduces the possibility of residual confounding, where unmeasured variables could still influence the outcomes. As a result, the findings should be interpreted as associations rather than definitive causal relationships, requiring careful consideration along with established scientific evidence. Additionally, the use of billing data, which is primarily designed for administrative purposes, means the analysis lacks detailed clinical information, such as the timing of medication administration or patient-reported pain scores.

Despite these constraints, the study has several notable strengths. The large sample size of over 1.3 million hysterectomy patients enhances the statistical power, allowing for the detection of meaningful associations across diverse patient populations. Additionally, the study's inclusion of a wide range of outcomes, such as specific complications (respiratory, cardiac, genitourinary), opioid consumption, LOS, and cost, provides a well-rounded assessment of multimodal analgesia's impact. The multimodal analgesia categories allow for the identification of dose-response relationships, strengthening the study's conclusions. Moreover, the economic analysis adds a practical perspective, showcasing the cost-saving potential of multimodal strategies. With a study period spanning from 2006 to 2022, this research also reflects evolving trends in pain management.

7. Bibliography

1. Myles P.S. WB, Jones K et al. Validity and reliability of a postoperative quality of recovery score: the QoR-40. Br J Anaesth. 2000;84(1):11-5.
2. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008;101(1):77-86.
3. Nelson G, Bakkum-Gamez J, Kalogera E, Glaser G, Altman A, Meyer LA, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer. 2019;29(4):651-68.
4. Nelson G AA, Nick A, Meyer LA, Ramirez PT, Achtari C, Antrobus J, Huang J, Scott M, Wijk L, Acheson N, Ljungqvist O, Dowdy SC. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations--Part II. Gynecol Oncol. 2016;140(2):323-32.
5. Bogani G SG, Ferrandina G, Gallotta V, DI Donato V, Ditto A, Pinelli C, Casarin J, Ghezzi F, Scambia G, Raspagliesi F. Enhanced recovery after surgery (ERAS) in gynecology oncology. Eur J Surg Oncol. 2021;47(5):952-9.
6. Nelson G B-GJ, Kalogera E, Glaser G, Altman A, Meyer LA, Taylor JS, Iniesta M, Lasala J, Mena G, Scott M, Gillis C, Elias K, Wijk L, Huang J, Nygren J, Ljungqvist O, Ramirez PT, Dowdy SC. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer. 2019;29(4):651-68.
7. Ellis H. Anatomy of the uterus. Anaesthesia & Intensive Care Medicine. 2011;12(3):99-101.
8. Nizić D PM, Kos I, Šimunović Marko. Flexion and version of the uterus on pelvic ultrasound examination. Acta Med Croatica. 2014;68(3):311-5.
9. Gray H. Anatomy of the human body. Philadelphia: Lea & Febiger; 1918.
10. Papadopoulos MS TA, Miliaras DE. Hysterectomy-current methods and alternatives for benign indications. Obstet Gynecol Int. 2010.
11. Wright JD HT, Tsui J, et al. Nationwide trends in the performance of inpatient hysterectomy in the United States. Obstet Gynecol Int. 2013;122(2.1):233-41.
12. Edler KM TK, Fülöp G, Reinstadler E, Neunteufel W, Reif P, Laky R, Aigmüller T. Rates and Routes of Hysterectomy for Benign Indications in Austria 2002-2014. Geburtshilfe Frauenheilkd. 2017;77(5):482-6.
13. Pickett CM SD, Mol BWJ, Nieboer TE, Johnson N, Bonestroo T, Aarts JWM. Surgical approach to hysterectomy for benign gynaecological disease. Cochrane Database of Systematic Reviews. 2023(8).
14. Jinhyung Lee P, Kristofer Jennings, PhD2, Mostafa A. Borahay, MD3, Ana M. Rodriguez, MD3, Gokhan S. Kilic, MD3, Russell R. Snyder, MD3, and Pooja R. Patel, MD3,*. Trends in the National Distribution of Laparoscopic Hysterectomies from 2003–2010. J Minim Invasive Gynecol. 2014;21(4):656-61.
15. Harvey SV PR, Landy R, Wentzensen N, Clarke MA. Trends and predictors of hysterectomy prevalence among women in the United States. Am J Obstet Gynecol. 2022;227(4):611.e1-.e12.

16. I. K. Basic Principle and Step-by-Step Procedure of Abdominal Hysterectomy: Part 2. Surg J (N Y). 2018;5(1):11-21.
17. Lippincott. Total Abdominal Hysterectomy | Atlas of Gynecologic Surgery 2013 [Te Linde's Atlas of Gynecologic Surgery provides clear and detailed descriptions of the steps involved in performing today's key gynecological surgery procedures, including total abdominal hysterectomy. Learn more at http://bookpromos.lww.com/gynecologic...]. Available from: https://www.youtube.com/watch?v=pzpTsiJSQ3U&t=130s.
18. Hospital BaWs. https://www.youtube.com/watch?v=tbSWFwfZQyI 2022 [cited 2024 November 1].
19. Pillarisetty LS MH. Vaginal Hysterectomy. StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
20. Ghezzi F US, Cromi A, Siesto G, Serati M, Bogani G, Bolis P. Postoperative pain after laparoscopic and vaginal hysterectomy for benign gynecologic disease: a randomized trial. 2010;203(2):118.e1-8.
21. Clarke-Pearson DL GE. Complications of hysterectomy. Obstet Gynecol Int. 2013;121(3):654-73.
22. Baran Vardar BM. Vaginal cuff dehiscence: report of two cases. Radiology Case Reports. 2021;16(8):2231-5.
23. Cao B, Xu Q, Shi Y, Zhao R, Li H, Zheng J, et al. Pathology of pain and its implications for therapeutic interventions. Signal Transduct Target Ther. 2024;9(1):155.
24. Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976-82.
25. Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. Eur J Pain. 2005;9(4):463-84.
26. Basbaum AI, Bautista DM, Scherrer G, Julius D. Cellular and molecular mechanisms of pain. Cell. 2009;139(2):267-84.
27. Jessell TM, Kandel ER, Schwartz JH. Principles of neural science: McGraw-Hill, Health Professions Division; 2000.
28. Hansen GR, Streltzer J. The psychology of pain. Emerg Med Clin North Am. 2005;23(2):339-48.
29. Younger J, McCue R, Mackey S. Pain outcomes: a brief review of instruments and techniques. Curr Pain Headache Rep. 2009;13(1):39-43.
30. Farrar JT, Berlin JA, Strom BL. Clinically important changes in acute pain outcome measures: a validation study. J Pain Symptom Manage. 2003;25(5):406-11.
31. Ghaderi F, Banakar S, Rostami S. Effect of pre-cooling injection site on pain perception in pediatric dentistry: "A randomized clinical trial". Dent Res J (Isfahan). 2013;10(6):790-4.
32. Choi JB KK, Song MK, Seok S, Kim YH, Kim JE. . Pain Characteristics after Total Laparoscopic Hysterectomy. Int J Med Sci. 2016;13(8):562-8.
33. Beyaz SG ÖH, Ergönenç T, Palabıyık O, Tuna AT, Kaya B, Erkorkmaz Ü, Akdemir N. Chronic postsurgical pain and neuropathic symptoms after abdominal hysterectomy: A silent epidemic. Medicine (Baltimore). 2016;95(33):e4484.

34. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain - update on incidence, risk factors and preventive treatment options. BJA Educ. 2022;22(5):190-6.
35. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008;101(1):77-86.
36. Brandsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS. Risk factors for chronic pain after hysterectomy: a nationwide questionnaire and database study. Anesthesiology. 2007;106(5):1003-12.
37. Pinto PR, McIntyre T, Nogueira-Silva C, Almeida A, Araujo-Soares V. Risk factors for persistent postsurgical pain in women undergoing hysterectomy due to benign causes: a prospective predictive study. J Pain. 2012;13(11):1045-57.
38. Brandsborg B, Nikolajsen L. Chronic pain after hysterectomy. Curr Opin Anaesthesiol. 2018;31(3):268-73.
39. Montes A, Roca G, Sabate S, Lao JI, Navarro A, Cantillo J, et al. Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and Thoracotomy: A Two-year Multicenter Cohort Study. Anesthesiology. 2015;122(5):1123-41.
40. Bouman EA, Theunissen M, Bons SA, van Mook WN, Gramke HF, van Kleef M, et al. Reduced incidence of chronic postsurgical pain after epidural analgesia for abdominal surgery. Pain Pract. 2014;14(2):E76-84.
41. Han C, Ge Z, Jiang W, Zhao H, Ma T. Incidence and risk factors of chronic pain following hysterectomy among Southern Jiangsu Chinese Women. BMC Anesthesiol. 2017;17(1):103.
42. Pokkinen SM, Nieminen K, Yli-Hankala A, Kalliomaki ML. Persistent posthysterectomy pain: A prospective, observational study. Eur J Anaesthesiol. 2015;32(10):718-24.
43. Manworren RCB. Multimodal Pain Management and the Future of a Personalized Medicine Approach to Pain. AORN Journal. 2015;101(3):307-18.
44. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol. 2009;22(5):588-93.
45. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993;77(5):1048-56.
46. Buvanendran A, Kroin JS. Useful adjuvants for postoperative pain management. Best Pract Res Clin Anaesthesiol. 2007;21(1):31-49.
47. Lirk P, Rathmell JP. Opioid-free anaesthesia: Con: it is too early to adopt opioid-free anaesthesia today. Eur J Anaesthesiol. 2019;36(4):250-4.
48. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231(25):232-5.
49. Chaiamnuay S, Allison JJ, Curtis JR. Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. Am J Health Syst Pharm. 2006;63(19):1837-51.
50. Barkin RL. Topical Nonsteroidal Anti-Inflammatory Drugs: The Importance of Drug, Delivery, and Therapeutic Outcome. Am J Ther. 2015;22(5):388-407.
51. Ghlichloo I, Gerriets V. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). StatPearls. Treasure Island (FL)2025.

52. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med. 1999;106(5B):13S-24S.
53. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: an update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci. 2013;16(5):821-47.
54. Klinger-Gratz PP, Ralvenius WT, Neumann E, Kato A, Nyilas R, Lele Z, et al. Acetaminophen Relieves Inflammatory Pain through CB(1) Cannabinoid Receptors in the Rostral Ventromedial Medulla. J Neurosci. 2018;38(2):322-34.
55. Oscier CD, Milner QJ. Peri-operative use of paracetamol. Anaesthesia. 2009;64(1):65-72.
56. Mahajan L, Mittal V, Gupta R, Chhabra H, Vidhan J, Kaur A. Study to Compare the Effect of Oral, Rectal, and Intravenous Infusion of Paracetamol for Postoperative Analgesia in Women Undergoing Cesarean Section Under Spinal Anesthesia. Anesth Essays Res. 2017;11(3):594-8.
57. Gerriets V, Anderson J, Patel P, Nappe TM. Acetaminophen. StatPearls. Treasure Island (FL)2024.
58. Li Y, Hong X, Liang L, Wang X, Ladd-Acosta C. Association between acetaminophen metabolites and CYP2E1 DNA methylation level in neonate cord blood in the Boston Birth Cohort. Clin Epigenetics. 2023;15(1):132.
59. Moyer AM, Fridley BL, Jenkins GD, Batzler AJ, Pelleymounter LL, Kalari KR, et al. Acetaminophen-NAPQI hepatotoxicity: a cell line model system genome-wide association study. Toxicol Sci. 2011;120(1):33-41.
60. Ong CK, Seymour RA, Lirk P, Merry AF. Combining paracetamol (acetaminophen) with nonsteroidal antiinflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg. 2010;110(4):1170-9.
61. Martinez V, Beloeil H, Marret E, Fletcher D, Ravaud P, Trinquart L. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. Br J Anaesth. 2017;118(1):22-31.
62. Hodgens A, Sharman T. Corticosteroids. StatPearls. Treasure Island (FL)2025.
63. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol. 2011;335(1):2-13.
64. De Oliveira GS, Jr., Almeida MD, Benzon HT, McCarthy RJ. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115(3):575-88.
65. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED, Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30.
66. Wang AS, Armstrong EJ, Armstrong AW. Corticosteroids and wound healing: clinical considerations in the perioperative period. Am J Surg. 2013;206(3):410-7.
67. Herbst RA, Telford OT, Hunting J, Bullock WM, Manning E, Hong BD, et al. The Effects of Perioperative Dexamethasone on Glycemic Control and Postoperative Outcomes. Endocr Pract. 2020;26(2):218-25.

68. Yasaei R, Katta S, Patel P, Saadabadi A. Gabapentin. StatPearls. Treasure Island (FL)2025.
69. Kharasch ED, Clark JD, Kheterpal S. Perioperative Gabapentinoids: Deflating the Bubble. Anesthesiology. 2020;133(2):251-4.
70. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg. 2007;104(6):1545-56, table of contents.
71. Deljou A, Hedrick SJ, Portner ER, Schroeder DR, Hooten WM, Sprung J, et al. Pattern of perioperative gabapentinoid use and risk for postoperative naloxone administration. Br J Anaesth. 2018;120(4):798-806.
72. Ohnuma T, Krishnamoorthy V, Ellis AR, Yan R, Ray ND, Hsia HL, et al. Association 'Between Gabapentinoids on the Day of Colorectal Surgery and Adverse Postoperative Respiratory Outcomes. Ann Surg. 2019;270(6):e65-e7.
73. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456-66.
74. Maher DP, Chen L, Mao J. Intravenous Ketamine Infusions for Neuropathic Pain Management: A Promising Therapy in Need of Optimization. Anesth Analg. 2017;124(2):661-74.
75. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19(6):370-80.
76. Bowdle TA, Radant AD, Cowley DS, Kharasch ED, Strassman RJ, Roy-Byrne PP. Psychedelic effects of ketamine in healthy volunteers: relationship to steady-state plasma concentrations. Anesthesiology. 1998;88(1):82-8.
77. DiazGranados N, Ibrahim LA, Brutsche NE, Ameli R, Henter ID, Luckenbaugh DA, et al. Rapid resolution of suicidal ideation after a single infusion of an N-methyl-D-aspartate antagonist in patients with treatment-resistant major depressive disorder. J Clin Psychiatry. 2010;71(12):1605-11.
78. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. Br J Anaesth. 1981;53(1):27-30.
79. O'Neill A, Lirk P. Multimodal Analgesia. Anesthesiol Clin. 2022;40(3):455-68.
80. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth. 2011;58(10):911-23.
81. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010;113(3):639-46.
82. Mulier JP. Perioperative opioids aggravate obstructive breathing in sleep apnea syndrome: mechanisms and alternative anesthesia strategies. Curr Opin Anaesthesiol. 2016;29(1):129-33.
83. Wang L, Johnston B, Kaushal A, Cheng D, Zhu F, Martin J. Ketamine added to morphine or hydromorphone patient-controlled analgesia for acute postoperative pain in

adults: a systematic review and meta-analysis of randomized trials. Can J Anaesth. 2016;63(3):311-25.
84. Assouline B, Tramer MR, Kreienbuhl L, Elia N. Benefit and harm of adding ketamine to an opioid in a patient-controlled analgesia device for the control of postoperative pain: systematic review and meta-analyses of randomized controlled trials with trial sequential analyses. Pain. 2016;157(12):2854-64.
85. Pendi A, Field R, Farhan SD, Eichler M, Bederman SS. Perioperative Ketamine for Analgesia in Spine Surgery: A Meta-analysis of Randomized Controlled Trials. Spine (Phila Pa 1976). 2018;43(5):E299-E307.
86. Agarwala R, Morrison B. Neuraxial anaesthesia and its role in enhanced recovery after surgery: a narrative review. Digestive Medicine Research. 2022;5.
87. Wulf HF. The centennial of spinal anesthesia. Anesthesiology. 1998;89(2):500-6.
88. Chin A, van Zundert A. Spinal Anesthesia. In: Hadzic A, editor. Hadzic's Textbook of Regional Anesthesia and Acute Pain Management, 2e. New York, NY: McGraw-Hill Education; 2017.
89. Mandabach MG. The history of epidural anesthesia. 2000;25.
90. Avila Hernandez AN, Hendrix JM, Singh P. Epidural Anesthesia. StatPearls. Treasure Island (FL): StatPearls Publishing
Copyright © 2024, StatPearls Publishing LLC.; 2024.
91. Cook TM, Counsell D, Wildsmith JA, Royal College of Anaesthetists Third National Audit P. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth. 2009;102(2):179-90.
92. Shin HY. Recent update on epidural blood patch. Anesth Pain Med (Seoul). 2022;17(1):12-23.
93. Emelife PI, Eng MR, Menard BL, Myers AS, Cornett EM, Urman RD, et al. Adjunct medications for peripheral and neuraxial anesthesia. Best Pract Res Clin Anaesthesiol. 2018;32(2):83-99.
94. Theunis van Zyl GK. An Update on Effective Management of the Postdural Puncture Headache [Tutorial]. 2021 [Available from: https://resources.wfsahq.org/atotw/an-update-on-effective-management-of-the-postdural-puncture-headache/.
95. Blakemore PR, White JD. Morphine, the Proteus of organic molecules. Chem Commun (Camb). 2002(11):1159-68.
96. Kalkman GA, Kramers C, van Dongen RT, van den Brink W, Schellekens A. Trends in use and misuse of opioids in the Netherlands: a retrospective, multi-source database study. Lancet Public Health. 2019;4(10):e498-e505.
97. Pathan H, Williams J. Basic opioid pharmacology: an update. Br J Pain. 2012;6(1):11-6.
98. McDonald J, Lambert D. Opioid receptors. BJA Education. 2014;15(5):219-24.
99. Dhawan BN, Cesselin F, Raghubir R, Reisine T, Bradley PB, Portoghese PS, et al. International Union of Pharmacology. XII. Classification of opioid receptors. Pharmacol Rev. 1996;48(4):567-92.
100. Corbett AD, Henderson G, McKnight AT, Paterson SJ. 75 years of opioid research: the exciting but vain quest for the Holy Grail. Br J Pharmacol. 2006;147 Suppl 1(Suppl 1):S153-62.

101. Nielsen CK, Ross FB, Lotfipour S, Saini KS, Edwards SR, Smith MT. Oxycodone and morphine have distinctly different pharmacological profiles: radioligand binding and behavioural studies in two rat models of neuropathic pain. Pain. 2007;132(3):289-300.
102. Kharasch ED AM, Clark JD. Rational Perioperative Opioid Management in the Era of the Opioid Crisis. Anesthesiology. 2020;132(4):603-5.
103. Use. PMatOEBSaIBaRoPO. Phillips JK FM, Bonnie RJ, editor. Washington, D.C: The National Academies Press; 2017.
104. Centers for Disease Control and Prevention NCfIPaC. Understanding drug overdoses and deaths 2022 [November 26, 2024]. Available from: https://www.cdc.gov/drugoverdose/epidemic/index.html.
105. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ. 2014;348:g1251.
106. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Arch Intern Med. 2012;172(5):425-30.
107. Sun EC, Darnall BD, Baker LC, Mackey S. Incidence of and Risk Factors for Chronic Opioid Use Among Opioid-Naive Patients in the Postoperative Period. JAMA Intern Med. 2016;176(9):1286-93.
108. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, et al. New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults. JAMA Surg. 2017;152(6):e170504.
109. Callinan CE, Neuman MD, Lacy KE, Gabison C, Ashburn MA. The Initiation of Chronic Opioids: A Survey of Chronic Pain Patients. J Pain. 2017;18(4):360-5.
110. Larach DB HJ, Brummett CM. Perioperative Opioids, the Opioid Crisis, and the Anesthesiologist. . Anesthesiology. 2022;136(4):594-608.
111. Scholl L SP, Kariisa M, Wilson N, Baldwin G. Drug and Opioid-Involved Overdose Deaths - United States, 2013-2017. MMWR Morb Mortal Wkly Rep. 2018;67(5152):1419-27.
112. Helmerhorst GT, Teunis T, Janssen SJ, Ring D. An epidemic of the use, misuse and overdose of opioids and deaths due to overdose, in the United States and Canada: is Europe next? Bone Joint J. 2017;99-B(7):856-64.
113. Lyapustina T, Rutkow L, Chang HY, Daubresse M, Ramji AF, Faul M, et al. Effect of a "pill mill" law on opioid prescribing and utilization: The case of Texas. Drug Alcohol Depend. 2016;159:190-7.
114. Wong M, Vogell A, Wright K, Isaacson K, Loring M, Morris S. Opioid use after laparoscopic hysterectomy: prescriptions, patient use, and a predictive calculator. Am J Obstet Gynecol. 2019;220(3):259 e1- e11.
115. Howard R KB, Brummett C, Waljee J, Englesbe M, Telem D. Prevalence and Prescribers of Preoperative Opioid Prescriptions in the US, 2008-2019. JAMA Netw Open. 2022;5(2).
116. Johnson CM, Makai GEH. A Systematic Review of Perioperative Opioid Management for Minimally Invasive Hysterectomy. J Minim Invasive Gynecol. 2019;26(2):233-43.

117. Kim CH, Lefkowits C, Holschneider C, Bixel K, Pothuri B. Managing opioid use in the acute surgical setting: A society of gynecologic oncology clinical practice statement. Gynecol Oncol. 2020;157(3):563-9.
118. Reagan KML, Boyles SH, Brueseke TJ, Linder BJ, Willis-Gray MG, Cichowski SB, et al. Postoperative Opioid Prescribing After Female Pelvic Medicine and Reconstructive Surgery. Female Pelvic Med Reconstr Surg. 2021;27(11):643-53.
119. Hessami K WJ, Frost A, AlAshqar A, Arian SE, Gough E, Borahay MA. Perioperative opioid dispensing and persistent use after benign hysterectomy: a systematic review and meta-analysis. Am J Obstet Gynecol. 2023;229(1):23-32.e3.
120. Olsson JH, Ellstrom M, Hahlin M. A randomised prospective trial comparing laparoscopic and abdominal hysterectomy. Br J Obstet Gynaecol. 1996;103(4):345-50.
121. Garry R, Fountain J, Mason S, Hawe J, Napp V, Abbott J, et al. The eVALuate study: two parallel randomised trials, one comparing laparoscopic with abdominal hysterectomy, the other comparing laparoscopic with vaginal hysterectomy. BMJ. 2004;328(7432):129.
122. Thompson JC, Komesu YM, Qeadan F, Jeppson PC, Cichowski SB, Rogers RG, et al. Trends in patient procurement of postoperative opioids and route of hysterectomy in the United States from 2004 through 2014. Am J Obstet Gynecol. 2018;219(5):484 e1- e11.
123. Schiefer J, Marschalek J, Djuric D, Benlolo S, Shore EM, Lefebvre G, et al. Postoperative Opioid Administration and Prescription Practices Following Hysterectomy in Two Tertiary Care Centres: A Comparative Cohort Study between Canada and Austria. J Clin Med. 2024;13(20).
124. Ljungqvist O SM, Fearon KC. Enhanced Recovery After Surgery: A Review. JAMA Surg. 2017;152(3):292-8.
125. Altman AD RM, Armbrust R, Fawcett WJ, Nihira M, Jones CN, Tamussino K, Sehouli J, Dowdy SC, Nelson G. Guidelines for vulvar and vaginal surgery: Enhanced Recovery After Surgery Society recommendations. Am J Obstet Gynecol. 2020;223(4):475-85.
126. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, et al. Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain: A Systematic Review and Meta-analysis. Anesthesiology. 2020;133(2):265-79.
127. Alayed N AN, Tan X, Tulandi T. Preemptive use of gabapentin in abdominal hysterectomy: a systematic review and meta-analysis. Obstet Gynecol. 2014;123 (6):1221-9.
128. Memtsoudis SG, Poeran J, Zubizarreta N, Cozowicz C, Morwald EE, Mariano ER, et al. Association of Multimodal Pain Management Strategies with Perioperative Outcomes and Resource Utilization: A Population-based Study. Anesthesiology. 2018;128(5):891-902.
129. Dong W, An B, Wang Y, Cui X, Gan J. Effect of multimodal analgesia on gynecological cancer patients after radical resection. Am J Transl Res. 2021;13(4):2686-93.
130. Castro-Alves LJ, Oliveira de Medeiros AC, Neves SP, Carneiro de Albuquerque CL, Modolo NS, De Azevedo VL, et al. Perioperative Duloxetine to Improve Postoperative Recovery After Abdominal Hysterectomy: A Prospective, Randomized, Double-Blinded, Placebo-Controlled Study. Anesth Analg. 2016;122(1):98-104.

131. Marks JL, Ata B, Tulandi T. Systematic review and metaanalysis of intraperitoneal instillation of local anesthetics for reduction of pain after gynecologic laparoscopy. J Minim Invasive Gynecol. 2012;19(5):545-53.
132. Blanton E, Lamvu G, Patanwala I, Barron KI, Witzeman K, Tu FF, et al. Non-opioid pain management in benign minimally invasive hysterectomy: A systematic review. Am J Obstet Gynecol. 2017;216(6):557-67.
133. Lirk P, Thiry J, Bonnet MP, Joshi GP, Bonnet F, Group PW. Pain management after laparoscopic hysterectomy: systematic review of literature and PROSPECT recommendations. Reg Anesth Pain Med. 2019;44(4):425-36.
134. Lirk P, Thiry J, Bonnet MP, Joshi GP, Bonnet F. Pain management after laparoscopic hysterectomy: systematic review of literature and PROSPECT recommendations. Reg Anesth Pain Med. 2019;44(4):425-36.
135. Shultz TM. Preemptive multimodal analgesia facilitates same-day discharge following robot-assisted hysterectomy. J Robot Surg. 2012;6(2):115-23.
136. Taumberger N, Schutz AM, Jeitler K, Siebenhofer A, Simonis H, Bornemann-Cimenti H, et al. Preemptive local analgesia at vaginal hysterectomy: a systematic review. Int Urogynecol J. 2022;33(9):2357-66.
137. Cozowicz C, Zhong H, Poeran J, Illescas A, Liu J, Poultsides LA, et al. The impact of multimodal analgesia in coronary artery bypass graft surgery-a population-based analysis. J Thorac Cardiovasc Surg. 2023.
138. Beattie WS, Badner NH, Choi P. Epidural analgesia reduces postoperative myocardial infarction: a meta-analysis. Anesth Analg. 2001;93(4):853-8.
139. Beattie WS, Badner NH, Choi PT. Meta-analysis demonstrates statistically significant reduction in postoperative myocardial infarction with the use of thoracic epidural analgesia. Anesth Analg. 2003;97(3):919-20.
140. Popping DM, Elia N, Marret E, Remy C, Tramer MR. Protective effects of epidural analgesia on pulmonary complications after abdominal and thoracic surgery: a meta-analysis. Arch Surg. 2008;143(10):990-9; discussion 1000.
141. Singh N, Sidawy AN, Dezee K, Neville RF, Weiswasser J, Arora S, et al. The effects of the type of anesthesia on outcomes of lower extremity infrainguinal bypass. J Vasc Surg. 2006;44(5):964-8; discussion 8-70.
142. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology. 2000;93(4):1123-33.
143. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet. 2019;393(10180):1537-46.
144. Wu CL, Rowlingson AJ, Partin AW, Kalish MA, Courpas GE, Walsh PC, et al. Correlation of postoperative pain to quality of recovery in the immediate postoperative period. Reg Anesth Pain Med. 2005;30(6):516-22.
145. van Boekel RLM, Warle MC, Nielen RGC, Vissers KCP, van der Sande R, Bronkhorst EM, et al. Relationship Between Postoperative Pain and Overall 30-Day Complications in a Broad Surgical Population: An Observational Study. Ann Surg. 2019;269(5):856-65.
146. Albers KI, van Helden EV, Dahan A, Martini CH, Bruintjes MHD, Scheffer GJ, et al. Early postoperative pain after laparoscopic donor nephrectomy predicts 30-day

postoperative infectious complications: a pooled analysis of randomized controlled trials. Pain. 2020;161(7):1565-70.
147. Hernandez-Boussard T, Graham LA, Desai K, Wahl TS, Aucoin E, Richman JS, et al. The Fifth Vital Sign: Postoperative Pain Predicts 30-day Readmissions and Subsequent Emergency Department Visits. Ann Surg. 2017;266(3):516-24.
148. Willingham M, Rangrass G, Curcuru C, Ben Abdallah A, Wildes TS, McKinnon S, et al. Association between postoperative complications and lingering post-surgical pain: an observational cohort study. Br J Anaesth. 2020;124(2):214-21.
149. Berkowitz R, Vu J, Brummett C, Waljee J, Englesbe M, Howard R. The Impact of Complications and Pain on Patient Satisfaction. Ann Surg. 2021;273(6):1127-34.
150. Kharasch ED, Clark JD. Opioid-free Anesthesia: Time to Regain Our Balance. Anesthesiology. 2021;134(4):509-14.
151. Larach DB, Hah JM, Brummett CM. Perioperative Opioids, the Opioid Crisis, and the Anesthesiologist. Anesthesiology. 2022;136(4):594-608.
152. Kharasch ED, Avram MJ, Clark JD. Rational Perioperative Opioid Management in the Era of the Opioid Crisis. Anesthesiology. 2020;132(4):603-5.
153. Kharasch ED, Brunt LM. Perioperative Opioids and Public Health. Anesthesiology. 2016;124(4):960-5.
154. Howard R, Kenney B, Brummett C, Waljee J, Englesbe M, Telem D. Prevalence and Prescribers of Preoperative Opioid Prescriptions in the US, 2008-2019. JAMA network open. 2022;5(2):e2147897.
155. Wong M, Vogell A, Wright K, Isaacson K, Loring M, Morris S. Opioid use after laparoscopic hysterectomy: prescriptions, patient use, and a predictive calculator. Am J Obstet Gynecol. 2019;220(3):259.e1-.e11.
156. Thompson JC, Komesu YM, Qeadan F, Jeppson PC, Cichowski SB, Rogers RG, et al. Trends in patient procurement of postoperative opioids and route of hysterectomy in the United States from 2004 through 2014. Am J Obstet Gynecol. 2018;219(5):484.e1-.e11.
157. Anyaehie KB, Duryea E, Wang J, Echebelem C, Macias D, Sunna M, et al. Multimodal opioid-sparing pain management for emergent cesarean delivery under general anesthesia: a quality improvement project. BMC Anesthesiol. 2022;22(1):239.

8. Tables

Table 1. Baseline characteristics stratified by multimodal groups; each multimodal group is compared separately with the opioid-only group.

		Multimodal					
	Opioid-only	**1 mode**	**Stdiff**	**2 modes**	**Stdiff**	**>2 modes**	**Stdiff**
	N=200,052	N=649,471		N=308,579		N=144,762	
Age, median [IQR]	48 [41.1, 59.9]	45.1 [39, 52.4]	-0.3	45 [38, 52.9]	-0.33	44.7 [36.9, 54.6]	-0.31
Race, n (%)							
Black	30,292 (15.1)	94,903 (14.5)	-0.02	46790 (15.1)	<0.01	26283 (18.1)	0.08
Other	39,651 (19.7)	114,842 (17.6)	-0.06	55087 (17.8)	-0.05	22948 (15.8)	-0.1
White	130,961 (65.2)	443,127 (67.9)	0.06	207457 (67.1)	0.04	95582 (66.0)	0.02
Insurance, n (%)			0.22		0.22		0.24
Commercial	124,528 (62.0)	451,696 (69.2)		202,136 (65.3)		86,796 (59.9)	
Medicaid	22,835 (11.4)	80,029 (12.3)		49,614 (16.0)		27,805 (19.2)	
Medicare	40,617 (20.2)	77,402 (11.9)		39,092 (12.6)		21,301 (14.7)	
Uninsured	5764 (2.9)	18,881 (2.9)		7999 (2.6)		4283 (3.0)	
Unknown	7160 (3.6)	24,864 (3.8)		10,493 (3.4)		4628 (3.2)	
Inpatient/ outpatient, n (%)			-0.1		-0.1		0.06
Inpatient	143,079 (71.2)	433,476 (66.4)		205,441 (66.4)		107,018 (73.9)	
Outpatient	57,825 (28.8)	219,396 (33.6)		103,893 (33.6)		37,795 (26.1)	
General anesthesia, n (%)	169,508 (84.4)	549,005 (84.1)	-0.03	234,946 (76.0)	-0.33	95,309 (65.8)	-0.58
Elixhauser comorbidity group, n (%)			0.18		0.12		0.27
0	129723 (64.6)	455,374 (69.7)		195,770 (63.3)		75,067 (51.8)	
1	32755 (16.3)	109,647 (16.8)		60,494 (19.6)		33,106 (22.9)	
2	19810 (9.9)	52,858 (8.1)		31,351 (10.1)		20,110 (13.9)	
3	18616 (9.3)	34,993 (5.4)		21,719 (7.0)		16,530 (11.4)	
Sleep apnea, n (%)	4361 (2.2)	10,869 (1.7)	-0.04	6732 (2.2)	<.01	4646 (3.2)	0.06
Substance abuse, n (%)	24323 (12.1)	86,390 (13.2)	0.04	44,193 (14.3)	0.06	26,159 (18.1)	0.17
Chronic pain	48688 (24.2)	108,550 (16.6)	-0.19	52,110 (16.8)	-0.18	25,960 (17.9)	-0.16
Psychiatric, n (%)	24741 (12.3)	82,118 (12.6)	0.01	39,573 (12.8)	0.01	18,658 (12.9)	0.02
Opioid abuse, n (%)	170 (0.1)	625 (0.1)	<0.01	562 (0.2)	0.03	574 (0.4)	0.06
Urban/ Rural, n (%)			0.07		0.08		0.03
Rural	17501 (8.7)	71,336 (10.9)		34,775 (11.2)		13,899 (9.6)	
Urban	183403 (91.3)	581,536 (89.1)		274,559 (88.8)		130,914 (90.4)	
Hospital Size, n (%)							
Large	73566 (36.6)	200,558 (30.7)	-0.13	109,264 (35.3)	-0.03	59,044 (40.8)	0.09
Medium	68461 (34.1)	230,322 (35.3)	0.03	107,828 (34.9)	0.02	47,390 (32.7)	-0.03
Small	58877 (29.3)	221,992 (34.0)	0.1	92,242 (29.8)	0.01	38,379 (26.5)	-0.06

Teaching hospital, n (%)			-0.05		0.1		0.32
No	114276 (56.9)	386,814 (59.2)		159,842 (51.7)		59,751 (41.3)	
Yes	86628 (43.1)	266,058 (40.8)		149,492 (48.3)		85,062 (58.7)	
Use of multimodal components, n (%)							
Gabapentin	-	5500 (0.8)		25,924 (8.4)		86,137 (59.5)	
Steroid	-	2835 (0.4)		8866 (2.9)		10,356 (7.2)	
Ketamine	-	3245 (0.5)		17,725 (5.7)		44,896 (31.0)	
NSAID	-	558,994 (85.6)		285,111 (92.2)		126,480 (87.3)	
Cox2	-	3456 (0.5)		9034 (2.9)		49,178 (34.0)	
Acetaminophen	-	72,041 (11.0)		233,878 (75.6)		133,243 (92.0)	
Neuraxial	-	5669 (0.9)		29,817 (9.6)		26,452 (18.3)	
*Stdiff: Multimodal groups were compared to opioid use only group. An absolute standardized difference of 0.1 (or 10%) generally indicates a meaningful difference in covariate distribution between groups.							

Table 2. Outcomes stratified by multimodal groups

	Opioid only	**1 mode**	**2 modes**	**3 or more modes**
	N=200,052	**N=649,471**	**N=308,579**	**N=144,762**
Composite outcome for complication, n (%)	8661 (4.3)	13,979 (2.1)	7694 (2.5)	4915 (3.4)
Respiratory	2998 (1.5)	4006 (0.6)	2330 (0.8)	1615 (1.1)
Gastrointestinal	626 (0.3)	1274 (0.2)	571 (0.2)	263 (0.2)
Genitourinary	3653 (1.8)	5446 (0.8)	2442 (0.8)	1374 (0.9)
Central nervous system	345 (0.2)	600 (0.1)	373 (0.1)	288 (0.2)
Cardiac	2489 (1.2)	4425 (0.7)	2948 (1.0)	2104 (1.5)
Total opioid use, median [IQR]	237 [124, 412]	226 [130, 385]	202 [114, 360]	173 [96, 315]
Adjusted cost, median [IQR]	9683 [6950, 13,494]	9033 [6758, 12,210]	9515 [7083, 13,041]	10,280 [7638, 14,485]
	N=143,079	**N=433,476**	**N= 205,441**	**N=107,018**
Length of stay for inpatient cohort, median [IQR]	2, [2, 3]	2 [1, 3]	2 [2, 3]	2 [2, 3]

Table 3. Adjusted outcomes

Multivariable logistic regression[a]	**Odds Ratio (95% CIs)**	**p-value**
Composite complications		
1 mode vs opioid only	0.66(0.64,0.68)	<.001

2 modes vs opioid only	0.63(0.61,0.66)	<.001
3 modes vs opioid only	0.65(0.62,0.67)	<.001
Respiratory complications		
1 mode vs opioid only	0.6(0.57,0.63)	<.001
2 modes vs opioid only	0.6(0.56,0.64)	<.001
3 modes vs opioid only	0.64(0.6,0.69)	<.001
Cardiac complications		
1 mode vs opioid only	0.71(0.68,0.75)	<.001
2 modes vs opioid only	0.69(0.65,0.73)	<.001
3 modes vs opioid only	0.66(0.62,0.71)	<.001
Gastrointestinal complications		
1 mode vs opioid only	0.81(0.74,0.9)	<.001
2 modes vs opioid only	0.93(0.83,1.05)	0.242
3 modes vs opioid only	1.08(0.92,1.28)	0.360
Genitourinary complications		
1 mode vs opioid only	0.65(0.62,0.68)	<.001
2 modes vs opioid only	0.58(0.55,0.61)	<.001
3 modes vs opioid only	0.61(0.57,0.66)	<.001
Central nervous system complications		
1 mode vs opioid only	0.9(0.79,1.03)	0.143
2 modes vs opioid only	0.93(0.79,1.09)	0.359
3 modes vs opioid only	0.99(0.82,1.19)	0.890
Generalized linear model[b]	**Least square means (95% CIs)**	**p-value**
Length of stay for inpatient in days		
1 mode vs opioid only	-0.52 (-0.54, -0.51)	<.001
2 modes vs opioid only	-0.49 (-0.51, -0.47)	<.001
3 modes vs opioid only	-0.40 (-0.43, -0.38)	<.001
Adjusted cost in US-dollars		
1 mode vs opioid only	-765 (-817, -714)	<.001
2 modes vs opioid only	-479 (-539, -419)	<.001
3 modes vs opioid only	79 (2, 156)	0.042
Total opioid consumption		
1 mode vs opioid only	-9.51 (-11.16, -7.86)	<.001
2 modes vs opioid only	-15.29 (-17.21, -13.37)	<.001

3 modes vs opioid only	-29.35 (-31.79, -26.91)	<.001

a. Multiple logistic regression models were run to compare associations between the use of multimodal analgesia categories for all binary outcomes (composite complication, and individual complications). Odds ratios (OR) and 95% CIs were reported. Models were adjusted a priori-determined covariates, including age, race, gender Elixhauser Comorbidity index group, year of surgery, hospital location, bed size, and hospital teaching status, as described previously.

b. A generalized linear model was applied to compare associations between the use of multimodal analgesia categories (categorized as opioid-only, 1, 2 or >2 non-opioid analgesic modes) and continuous outcomes (Opioid utilization, inpatient length of stay, and cost) adjusting the same covariates in the logistic regression model. Estimates were presented as least square means differences compared with the reference group along with 95% CIs. For opioid utilization outcome, we additionally adjusted for history of substance use/abuse (including smoking), chronic pain conditions, psychiatric comorbidity variables, and opioid use disorder given their association with opioid use.

9. Appendix

Appendix 1: Identifying hysterectomy procedures based on International Classification of Diseases 9th (ICD-9) and 10th (ICD-10) Revision procedure codes and The Current Procedural Terminology (CPT) codes

ICD-9	**Description**
68.0x	Hysterotomy
68.3x	Subtotal abdominal hysterectomy
68.4x	Total abdominal hysterectomy
68.5x	Vaginal hysterectomy
68.6x	Radical abdominal hysterectomy
68.7x	Radical vaginal hysterectomy
68.8x	Pelvic evisceration
68.9x	Other and unspecified hysterectomy
ICD-10	
0U54xxx	Destruction of Uterine Supporting Structure
0U55xxx	Destruction of Fallopian Tube, Right
0U56xxx	Destruction of Fallopian Tube, Left
0U57xxx	Destruction of Fallopian Tubes, Bilateral
0U59xxx	Destruction of Uterus
0U94xxx	Drainage of Uterine Supporting Structure
0U95xxx	Drainage of Fallopian Tube, Right
0U96xxx	Drainage of Fallopian Tube, Left
0U97xxx	Drainage of Fallopian Tubes, Bilateral
0U99xxx	Drainage of Uterus
0UB4xxx	Excision of Uterine Supporting Structure
0UB5xxx	Excision of Fallopian Tube, Right
0UB6xxx	Excision of Fallopian Tube, Left
0UB7xxx	Excision of Fallopian Tubes, Bilateral
0UB9xxx	Excision of Uterus
0UC4xxx	Extirpation of Uterine Supporting Structure
0UC5xxx	Extirpation of Fallopian Tube, Right
0UC6xxx	Extirpation of Fallopian Tube, Left
0UC7xxx	Extirpation of Fallopian Tubes, Bilateral
0UN4xxx	Release of Uterine Supporting Structure
0UN5xxx	Release of Fallopian Tube, Right
0UN6xxx	Release of Fallopian Tube, Left
0UN7xxx	Release of Fallopian Tubes, Bilateral
0UN9xxx	Release Uterus
0UT2xxx	Resection of Bilateral Ovaries
0UT4xxx	Resection of Uterine Supporting Structure
0UT5xxx	Resection of Fallopian Tube, Right
0UT6xxx	Resection of Fallopian Tube, Left
0UT7xxx	Resection of Fallopian Tubes, Bilateral

0UT9xxx	Resection of Uterus
0UTCxxx	Resection of Cervix
CPT	
58150	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s)
58152	Total abdominal hysterectomy (corpus and cervix), with or without removal of tube(s), with or without removal of ovary(s)
58180	The provider removes the uterus via an abdominal incision. The provider may also removes the fallopian tubes and ovaries.
58200	The provider removes the uterus and cervix and may also remove the fallopian tubes and ovaries, all through via an abdominal incision. The provider removes the upper one–third of the vaginal canal and some of the pelvic and para–aortic lymph nodes.
58210	The provider removes the uterus and cervix including the parametrium via an abdominal incision, known as a radical abdominal hysterectomy. The provider may also remove all or part of the vagina, all the pelvic lymph nodes on the right and left side, and biopsy a few of the para aortic lymph nodes. The provider may remove part or all of the fallopian tubes and ovaries.
58240	The provider performs pelvic exenteration on patients who have had a recurrence of cancer of the cervix after they have had radiation therapy or patients who have stage IV cancer, and the tumor is in the bladder and rectum. There is no standard procedure, and organs and tissues that the provider removes depend on where the cancer is located and the stage. In a total exenteration, the provider removes the uterus, tubes, ovaries, parametrial tissue, bladder, rectum, vagina, urethra, and part of the levator ani muscles. In an anterior exenteration, the provider does not remove the rectum. In a posterior exenteration, the provider does not remove the bladder and urethra. He may also resect part of the anus, urethra, and part of the vulva.
58260	In this procedure, the provider surgically removes the uterus and cervix only using a vaginal approach, known as a vaginal hysterectomy. The uterus is normal in size, which means it weighs 250 g or less.
58262	In this procedure, the provider surgically removes the uterus, cervix, fallopian tubes, and ovaries using a vaginal approach, known as a vaginal hysterectomy. The uterus is normal in size, which means it weighs 250 g or less.
58263	In this procedure, the provider surgically removes the uterus, cervix, fallopian tubes, and ovaries using a vaginal approach, known as a vaginal hysterectomy. Because the patient has small bowel prolapsing into the vaginal canal, called an enterocele, he also repairs this area. The uterus is normal in size, which means it weighs 250 g or less.
58267	In this procedure, the provider surgically removes the uterus and cervix only using a vaginal approach, known as a vaginal hysterectomy. The patient also has stress urinary incontinence which requires the suspension of the urethra. The uterus is normal in size, which means it

	weighs 250 g or less, and the provider may use an endoscope during the procedure.
58270	In this procedure, the provider surgically removes the uterus and cervix only using a vaginal approach, known as a vaginal hysterectomy. The provider also repairs a small bowel prolapse into the vaginal canal. The uterus is normal in size, which means it weighs 250 grams or less.
58275	In this procedure, the provider surgically removes the uterus and the cervix using a vaginal approach, known as a vaginal hysterectomy. The provider also partially or completely excises the vagina.
58280	The provider surgically removes the uterus and the cervix using a vaginal approach, known as a vaginal hysterectomy. The provider also partially or completely excises the vagina and repairs a small bowel prolapse into the vaginal canal.
58285	the provider removes the uterus, fallopian tubes and ovaries, the parametrium, which includes the uterosacral, cardinal, broad, and round ligaments, and the upper one third of the vagina. This procedure treats cervical cancer.
58290	the physician surgically removes the uterus and cervix only using a vaginal approach. The uterus is larger than normal, usually due to the presence of fibroids, which means it weighs more than 250 g.
58291	the physician surgically removes the uterus, cervix, the fallopian tubes, and ovaries using a vaginal approach. The uterus is larger than normal usually due to the presence of fibroids, which means it weighs more than 250 g.
58292	the physician surgically removes the uterus, cervix, the fallopian tubes and ovaries using a vaginal approach. Because the patient has small bowel prolapse into the vaginal canal, the provider also repairs this area. The uterus is larger than normal usually due to the presence of fibroids, which means it weighs more than 250 grams.
58294	the physician surgically removes the uterus and cervix only using a vaginal approach. Because the patient has small bowel prolapsing into the vaginal canal, this area is repaired. The uterus is larger than normal usually due to the presence of fibroids, which means it weighs more than 250 grams.

Appendix 2: Identifying perioperative complications based on International Classification of Diseases 9th (ICD-9) and 10th (ICD-10) Revision procedure codes

	ICD-9	**ICD-10**
Respiratory	518.5, 518.52, 518.51, 518.53, 518.82, 786.09, 799.02, 799.01, 518.81, 518.84	J95.2, J80, R09.02, R09.01, J95.821, J96.00, J96.01, J96.02, J96.90, J96.91, J96.92, J96.20, J96.21, J96.22, J95.822
Cardiac		
Gastrointestinal	584, N17	E879.1, V45.11, Z99.2
Genitourinary	997.4	K91.3, K91.8
CNS	997.01,780.09,780.97,799.2, 293	G97.81, G97.82,R41.82, R40.0, R40.1, F06.8, R45, F05, F6, F53