Association of Lowering Default Pill Counts in Electronic Medical Record Systems With Postoperative Opioid Prescribing After Cardiac Surgery

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HÁSKÓLI ÍSLANDS

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Abstract

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Introduction: Overuse of opioid analgesics and high rates of death related to opioids, referred to as the opioid epidemic, is a major public health crisis in the US. Overprescribing of opioids after surgeries has contributed to this problem. Electronic medical records (EMR) systems can auto-populate a default number of opioids that are prescribed at time of discharge, and this tool can be used to alter prescribing practices. The aim of this study was to examine the association between lowered default pill counts with changed prescribing behaviors after cardiac surgery.

Methods: On May 18 2017, the default number of pills prescribers see in EMRs in the Yale New Haven Health System was lowered from 30 to 12. Patients undergoing coronary artery grafts, valve surgeries, and thoracic aortic aneurysm surgeries were included in this study. Data was gathered and stratified in to two groups: First, one year prior (May 18 2016 to May 17 2017); and second, one year following (from May 18 2017 to May 17 2018) the default change, and actual amount of opioid prescribed was compared between the two groups.

Results: A total of 1741 patient charts were reviewed, 832 before the change and 909 after the change. Significant changes were seen in prescribing practices, where the average amount of opioid prescribed was about 25% lower after the change. This amounted to about 15 fewer pills of 5 mg morphine for each patient. A linear regression model adjusting for other factors determined a prescribing difference of 75.2 MME per prescription ($p < 0.01$). In addition, a significant decrease in opioids prescribed was found for each type of procedure.

Conclusions: Lowering the default opioid pill count in EMRs is a simple, cheap and effective intervention to change prescribing behavior and promote judicious prescribing of opioids after cardiac surgery.

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Abbreviations

BMI	Body mass index
CABG	Coronary artery bypass graft
CDC	Centers for Disease Control and Prevention
CREB	cAMP response element binding protein
DOR	Delta opioid receptor
EMR	Electronic medical record
GIRK	G-protein inwardly rectifying K^+ channel
GPCR	G-protein coupled receptor
GRK	G-protein coupled receptor kinase
KOR	Kappa opioid receptor
MME	Morphine milligram equivalent
MOR	Mu opioid receptor
NAc	Nucleus accumbens
NOP	Nociceptin opioid receptor
OIRD	Opioid-induced respiratory depression
PAG	Periaquaductal gray
PKA	Protein kinase A
RVM	Rostroventral medulla
TAA	Thoracic aortic aneurysm
VTA	Ventral tegmental area
YNHH	Yale New Haven Hospital

Introduction

For thousands of years, opioids have been used for medicinal purposes such as analgesia, sleep and to prevent diarrhea, and recreationally for their euphoric effects. Morphine, the prototypic opioid agonist, is found among other related alkaloids in opium obtained from a species of poppy. Opioids have a dark side, as their addictiveness has for centuries been a problem. (1)

1.1 Pain

An organism's ability to detect pain is essential for its well-being and is important to modulate behavior in a way to avoid possibly life-threatening situations. (2)

Pain can be subdivided into acute pain and chronic (persistent) pain. Acute pain is a normal response to noxious stimuli and results from activation of pain receptors (nociceptors) at sites of tissue damage. Pain transmission pathways display great plasticity, which can lead to enhancement of pain signals, producing hypersensitivity, and resulting in chronic and debilitating pain. (2) The Centers for Disease Control and Prevention (CDC) estimated that in 2016, 20% of US adults had chronic pain (pain on most days or every day for past 6 months), and 8% had high impact chronic pain, defined as pain interfering with work or daily life most days or every day. (3) Pain is one of the top reasons adults seek medical care, (4) and chronic pain has been linked with depression and significantly decreased activity. (5) In addition to emotional and physical burden to individuals, chronic pain is a considerable socioeconomic burden, costing the US hundreds of billions of dollars annually. (6)

Two major classes of nociceptors respond to noxious stimuli, Aδ and C-fibers. The Aδ fibers are myelinated, and mediate acute pain ("fast pain"), while the C-fibers are non-myelinated, and mediate diffuse, poorly localized pain ("slow pain"). The cell bodies of these nociceptors are located in the dorsal root ganglia of the spine for the body, and in the trigeminal ganglion for the face. In the dorsal horn of the spinal cord, the nociceptors synapse on second-order neurons projecting to higher centers of the brain, like the somatosensory cortex and insular cortex, where pain is perceived. Nociceptors do not exclusively communicate with the second-order neuron, carrying sensations to the central nervous system. They are pseudo-unipolar, which means they can send and receive messages from either end of the neuron. Neurogenic inflammation refers to the process where these neurons peripherally release inflammatory peptides, like CGRP and substance P, which leads to heightened pain sensitivity. (2)

The CNS can modulate incoming pain information, by controlling transmission in the dorsal horn. A particularly important system is a descending pathway which inhibits neuronal transmission at the dorsal horn level. The periaqueductal gray (PAG) in the midbrain is a key part of this system. Electrical stimulation of the PAG leads to analgesia (7). The PAG receives input from other parts of the brain, including the cortex, amygdala, and the hypothalamus. PAG neurons project to the rostroventral medulla (RVM), and from there to the dorsal horn via the dorsolateral funiculus of the spinal cord. Analgesia results from inhibition of the ascending nociceptive information at the spinal cord level. (8)

1.2 Opioids

1.2.1 Endogenous opioids

The first endogenous agonists of opioid receptors were found in 1975, two pentapeptides known as enkephalins. (9) They are now known to be a part of a larger family of endogenous opioid peptides, the endorphins (for endogenous morphine). Other endorphins include β-endorphin and dynorphin. (10) A proposed role for endogenous opioids is to inhibit pain during times of stress. Naloxone, a competitive opioid receptor antagonist, reverses this effect, called stress-induced analgesia. (11) This may have an evolutionary role in promoting self-defense during times of a physical threat, thereby increasing likelihood of survival. (12) Interestingly, naloxone reduces placebo analgesia, which indicates the involvement of endogenous opioids. (13)

1.2.2 Opioid receptors

Three types of “classical” opioid receptors in the central nervous system have been defined: mu, kappa, and delta opioid receptors (MOR, KOR and DOR, respectively). Activation of all these receptors has analgesic effects. (14) A fourth opioid receptor, the nociceptin opioid receptor (NOP), shows significant homology with the classical opioid receptors. However, it does not bind morphine derivatives but binds specific endogenous peptides. (15) The MOR is clinically most relevant, and mediates the major pharmacological effects of morphine, like analgesia, respiratory depression, euphoria and physical dependence. (16)

1.2.3 Cellular effects

Opioid receptors are all G-protein coupled receptors (GPCR), linked with a heterotrimeric $G_{i/o}$. Once a ligand binds to the receptor, the trimeric G protein complex dissociates into G_α and $G_{\beta\gamma}$. G_α inhibits adenylyl cyclase and cAMP production inside the cell, and the $G_{\beta\gamma}$ subunit interacts directly with ion channels in the membrane. Inside the neuron, this promotes the opening of G-protein inwardly rectifying K^+ (GIRK) channels and inhibits the opening of Ca^{2+} channels. The result is a hyperpolarization of the cell and reduction of transmitter release, respectively. (14) Even though opioids reduce the firing of neurons, they cause increased activity in certain pathways via disinhibition. Protein Kinase A (PKA) is a cAMP dependent kinase and mediates downstream effects of opioids. Opioid receptor activation leads to decreased amount of intracellular cAMP, which in turn lead to decreased activity of PKA. Less activation of the enzyme leads to decreased ionic conductance and changes in gene expression through less activation of the cAMP response element binding protein (CREB) transcription factor. (17)

1.2.4 Pharmacological effects

Opioids are among the most effective analgesic drugs known. However, The use of opioids has many side effects, including a potentially life-threatening respiratory depression, miosis (pupil constriction), constipation, nausea, suppressed immune function, sedation, euphoria, tolerance and dependence. (18)

Opioids cause analgesia and are extensively used for pain relief. Opioid receptors are widely distributed in the brain, and opioids partly induce analgesia by inhibiting inhibitory (disinhibition), tonically active GABAergic interneurons in the PAG. (8, 19) In accordance, GABAergic neurons within the PAG express MORs. (20) Also, naloxone seems to reverse analgesia induced by PAG stimulation, indicating that PAG stimulation is mediated by endogenous opioids acting at opioid receptors. (21) Other sites of action for opioid analgesia in the brain include the cortex, amygdala, thalamus and hypothalamus. (22)

In addition to increasing activity in this descending pathway, opioids also inhibit transmission of ascending pain pathways, firstly by limiting transmission of nociceptive dorsal horn neurons, (23, 24) and secondly by inhibiting nociceptors in peripheral tissues. (25) Opioid receptors are found in the periphery, where injury and inflammation results in increased synthesis and axonal transport of opioid receptors in the dorsal root ganglion neurons. Inhibition of sensory neuron excitability via activation of these receptors results in analgesia. (26)

Opioids also induce tolerance. When tolerance develops, a larger dose is needed for the same effects. Tolerance does not develop equally for all effects of opioids. For example, tolerance to analgesia and respiratory depression develops faster than tolerance to constipation and miosis. (14) Tolerance limits the use of opioids in chronic pain treatment (27) and contributes to social problems of opioid abuse. On a cellular level, MOR-expressing neurons display reduced responses to opioids following chronic exposure. Like many other GPCRs, MOR exposure to agonists can result in a rapid desensitization and internalization of the receptor. A key event for desensitization is receptor phosphorylation mediated by G-protein coupled receptor kinases (GRKs), followed by binding of arrestins. Receptors bound to arrestin can then be internalized by a clathrin-dependent endocytosis. Following internalization, receptors can be recycled to the cell surface, or degraded in lysosomes. (28) Following long-term exposure, persistent activation of the receptor leads to changes in gene expression, which in turn lead to increased internalization of receptors. With some opioids (e.g. fentanyl) down-regulation of receptors is seen, but not with others (e.g. morphine). Opioid tolerance leads to decreased analgesic effects of opioids, and contributes to a paradoxical opioid-induced hyperalgesia (increased pain sensitivity). (22)

Dependence is seen during long-term administration and has two components: physical and psychological. Physical dependence is a predictable pharmacologic event and is used to describe the experiencing of withdrawal symptoms following sudden discontinuation of opioid administration. Symptoms of opioid withdrawal include anxiety, irritability, nausea, abdominal cramps, and diaphoresis (excessive sweating). Psychological dependence (addiction) is a craving for an opioid, where compulsive drug-seeking behavior is characteristic. Many people addicted to opioids will have some degree of physical dependence, but a person can be physically dependent, without being addicted. (29)

On a cellular level, acute exposure to opioids leads to decreased activity of adenylyl cyclase, but with chronic exposure, adenylyl cyclase activity returns to basal levels. Sudden withdrawal of opioids results in a “superactivation” of adenylyl cyclase which leads to high amounts of intracellular cAMP.

Withdrawal results in increased GABA release in various regions of the brain, probably through these mechanisms. (17)

Opioid-induced respiratory depression (OIRD**)** is the most serious side effect of opioid use. It is the primary cause of death in opioid overdose. (30) Activation of MORs in respiration-controlling neurons in the brainstem causes OIRD. This can cause a slow and irregular breathing rhythm, which can lead to death. (31, 32) The pre-Bötzinger complex in the medulla, involved in the control of respiratory rhythm generation, seems to be an important site of action in OIRD. (32) On a cellular level, opening of GIRK channels following MOR activation is important in mediating OIRD. (33)

1.3 Clinical use of opioid analgesics

Opioids have proven useful to treat acute pain (34) and cancer-related pain. (35) Short term opioid therapy has proven to be effective, but opioid tolerance, dependence and their abuse liability might influence their effectiveness over time. Evidence for the effectiveness of long-term opioid therapy for chronic non-cancer pain is limited, and the CDC recommends the use of other analgesics for chronic pain. (36) Rates of opioid prescribing varies greatly between states. Factors accounting for the variation are unknown, suggesting a lack of consensus regarding opioid prescribing. (37)

1.3.1 Pain and opioid use after surgery

Postoperative pain management requires balancing of two important concerns: Providing adequate analgesia and minimizing risk of chronic opioid use after surgery. Adequate perioperative pain management is important for patient satisfaction, functional recovery and enhancing outcomes, (38) and a large 2016 study showed that reliance on opioids for perioperative analgesia is still widespread. (39) Acute pain after surgery is very common, and in most cases it is self-limiting. However, in some cases the pain persists and becomes chronic. (40, 41) The intensity of acute postoperative pain has been associated with the development of chronic pain, (42, 43) which is defined as a state of pain owing to surgery, at least 2 or 3 months after the surgery. (44) Around 10-50% of individuals with acute postoperative pain later suffer from chronic pain, (43) which makes it the most common post-operative complication. (41) 2-10% of these patients will then suffer from severe pain, with functional impairment. (43) It is therefore not surprising that surgeries have been associated with an increased risk of opioid dependency among opioid-naïve patients. (45) This should be taken seriously, because overprescribing of opioids postoperatively has played a part in the opioid epidemic, and larger initial doses of opioids are associated with a higher risk of long-term opioid use. (46, 47)

Risk of chronic opioid use among opioid-naïve patients after surgery varies between different kinds of surgeries. For example, total knee arthroplasty is a much stronger risk factor than a cesarean section. (45) Other risk factors include lower household income, comorbidities (e.g. diabetes), a history of alcohol or drug abuse and use of benzodiazepines and antidepressants preoperatively. (45, 48) Age over 50 has been associated with chronic opioid use after surgeries, (45) but in an older population (over 65) a younger age is associated with chronic use. (48)

Opioid prescribing varies between surgeries, which may be appropriate because the level of pain for different surgeries is variable. Thoracic, abdominal and orthopedic surgeries, as well as a longer duration of surgery, have been identified as predictors of post-operative pain. (49) Most heart surgeries are performed via median sternotomy, and post-sternotomy pain is a common complication of cardiac surgery. (50) A recent study of over 15,000 opioid-naive patients revealed that opioid prescribing after cardiac surgeries is similar to general surgery prescribing, but substantially less than after orthopedic surgery or neurosurgery. (51) This is consistent with another large study (52) that found prescribing to be relatively very high after spine surgery and arthroplasty.

1.4 Opioid addiction

Addiction is an important and serious risk that follows long-term opioid use. (53) Identifying the risk factors when prescribing opioids for chronic pain may therefore be important to evaluate the safety of opioid use. Addiction has many negative consequences, both for the addicted and society. Patients with a diagnosed opioid use disorder have higher rates of many comorbidities, like hepatitis, mental illnesses, pancreatitis, and some infections. They utilize medical services more than people who do not abuse opioids. (54) In addition to the increased health care costs, opioid addiction imposes great costs to society because of productivity loss and spending on law enforcement. (55)

1.4.1 Physiological basis

Addiction can be defined as a continued use of a substance, despite having negative consequences (56). Opioids have great addiction potential because they cause a feeling of euphoria by activating dopaminergic pathways via MORs from the ventral tegmental area (VTA) in the midbrain. More specifically, opioids reduce the level of GABAergic inhibition, increasing the firing of VTA dopaminergic neurons. (57) The nucleus accumbens (NAc), among other structures like the limbic system and the cortex, receives dopaminergic input from the VTA. Opioids, like other addictive drugs, increase the concentration of dopamine within the NAc. (58) Naturally rewarding stimuli, like food and sex, also increases dopamine release in the NAc. (59) Normally, midbrain dopamine systems process reward information for modulating future behavior. The function of these dopaminergic neurons is to evaluate environmental stimuli and ascribe motivational value to these stimuli, and to signal the presence or absence of rewards. (60) This is important to survival, because animals need to learn under which circumstances they can achieve vital goals, like obtaining food. Achieving these goals is rewarding. (58) Normally, responses to rewards are dependent on predictability (reward prediction error). That means that these dopamine neurons are activated when an outcome is better than expected and when the outcome is worse than expected, their firing is depressed. (60) With repeated use, the motivational value of drug-using will be pronounced, and humans and animals will seek to use the drug in preference to other goals. (58) The memory of previous drug experiences can be strong and lead to craving of the drug. Associative learning is important in addiction, because environmental stimuli paired with previous drug use acquires a motivational value, leading to the expectation of the drug and memories of previously experienced euphoria, which lead to craving. Craving can be intense and long lasting, and may lead to relapse after prolonged periods of abstinence. (61) In addition to the euphoric effects, long term opioid use causes physical dependence, resulting in aversive abstinence symptoms when abruptly discontinued, and pain relive in itself is rewarding. (62)

1.4.2 Risk factors

The use of opioids for chronic pain can result in addiction, (53) especially for susceptible individuals. Up to 25% of patients receiving opioid therapy in a primary care setting are addicted to opioids. (63) Other identified opioid addiction risk factors include a history of substance abuse, mental health disorders, psychological stress, functionally impairing pain, greater opioid supply, younger age, poor social support, and a white race. (63-65) There also seems to be a genetic factor involved in opioid use disorder like other substance use disorders. Opioid addiction susceptibility seems to be among the most heritable among substance use disorders. First-degree relatives of addicts are at greater risk, but this is probably also in part due to shared environmental factors. (66)

1.5 US opioid epidemic

Opioid addiction has been a rising problem since the 1990s. Globally, the prevalence of opioid use disorders substantially increased from 1990 to 2016. (67) By 2016, opioid use disorder was the 15th leading cause of years of life lost due to premature death in the US, after being the 52nd leading cause in 1990. (68) The extensive overuse of opioid drugs worldwide, especially in the US, is referred to as the opioid epidemic and is a major public health challenge. A study of a large US sample from 2012-2013 estimated that around 4% of the adult US population (over 10 million people) misused prescription opioids. (69) In a 20 year period from 1999-2018, opioids were involved in 446,032 deaths in the US, averaging over 20,000 deaths a year. (70)

In 1995, the American Pain Society suggested that pain should be regarded as a "5th vital sign" which was a big step towards promoting excessive opioid use. (71, 72) This was based on beliefs that pain was being undertreated, and misbeliefs that therapeutic use of opioids only rarely resulted in addiction. (73, 74) In 2001 the Joint Commission, which accredits US hospitals, published pain management standards where pain was considered a 5th vital sign in the hospital's care of patients. By 2004, this phrase had been deleted from the standards manual. (75) Following new standards in pain treatment, US pharmaceutical companies extensively marketed opioids, talking down the euphoric and addictive effects of opioids. A very notable example is Purdue Pharma's marketing of OxyContin. (76) Oxycontin was introduced in 1996, emerging timely to fuel the epidemic. Between 1996 and 2001, Purdue Pharma paid 5000 healthcare workers to attend speaker training conferences, and sponsored 20.000 pain education programs. (77) Sales grew from $48 million to over $1 billion between 1996 and 2000, and by 2004 it was a major drug of abuse in the US. In 2001 alone, Purdue Pharma spent over $200 million in the promotion of Oxycontin. (78) Following the role of OxyContin is the US opioid epidemic, Purdue Pharma filed for bankruptcy in 2019 after over 2600 lawsuits. (79)

These new standards contributed to greatly increased prescriptions and overprescribing of opioid analgesics. From 1997 through 2002, the medical use and abuse of common analgesic opioids (morphine, hydromorphone, fentanyl and oxycodone) increased markedly. (80) Between 1997 and 2005, long-term opioid therapy for chronic non-cancer pain was substantially more frequent, despite a lack of evidence for its effectiveness. (81) This trend continued, and from 2002 to 2010, there was a substantial increase in opioid analgesic prescriptions, though there was a slight decrease between 2011 and 2013. Rates of opioid abuse and opioid related deaths followed this trend, indicating a strong association between the availability of opioid analgesics and related adverse outcomes. (82) From 2012 to 2017, prescription rates continued to lower, and fewer physicians wrote high-risk initial prescriptions. (83, 84) However, overdose deaths continued to rise, and since the late 1990s the rate of opioid overdose deaths has risen in three waves.

While the increased rate of opioid related deaths from the late 1990s until 2010 was mostly driven by prescription opioids, a second wave began around 2010 with substantial increases in overdose deaths involving heroin. (85) Heroin is pharmacologically similar to morphine, and prescription opioids may serve as gateway drugs towards the use of illicit opioids, such as heroin. The majority of heroin users report to have previously used prescription opioids non-medically. (86) Actions taken by federal agencies and pharmaceutical companies to reduce inappropriate opioid prescribing may have forced some prescription opioid dependent people to find a cheaper alternative, like heroin. Since 2013, a third wave of overdose deaths involving synthetic opioids, primarily illicit fentanyl and its derivatives, has been driving opioid-related deaths. (87, 88) Fentanyl is approximately 75-100-fold more potent than morphine. (89) In 2017, drug overdose deaths in the US were over 70.000, and approximately two thirds of those were due to opioids, which means over 100 people died per day in the US because of an opioid overdose. From 2017 to 2018 there was a decline in overdose deaths (4.1%), but the age-adjusted rate was still more than 3 times higher than in 1999. (88, 90)

1.6 Opioid overprescribing after surgeries

Overprescribing of opioids fueled the opioid epidemic, so finding ways to reduce opioid prescriptions may be important in battling the epidemic. Opioid prescribing after minor surgeries in the US increased over time from 2004 to 2012, (91) and comparison studies have revealed that physicians in the US seem to rely more on opioids postoperatively than colleagues in other countries, like the Netherlands, Japan and France. (72) A large 2016 study reviewed over 18,000 patients who underwent surgery requiring an inpatient hospital stay longer than 24 hours. Findings of the study indicated that 45% of patients who used no opioids on the last day of their hospital stay, still received an opioid prescription upon discharge, indicating that over-prescription of opioids is common. (92) However, since 2012 the rates of initial prescriptions for opioid-naïve patients have gradually been declining. CDC guidelines from 2016 discouraging opioid use for chronic pain had a considerable impact. (83) Careful opioid prescribing is important because prescription opioids have potential for misuse and can act as a gateway for illegitimate opioid use. Also, excess pills can be diverted to friends or family, sold illegally, or stolen, contributing to opioid misuse. (72, 93) Studies have shown that prescribed opioids among US patients who undergo surgery are frequently unused and undisposed, suggesting that opioids have been overprescribed. (94) Because larger initial opioid doses are associated with a higher risk of long-term use (46, 47) decreasing the initial opioid doses after surgery may decrease the risk of opioid dependency. Reducing the risk of opioid dependency is very important, because opioid addiction is costly for individuals and society. (55)

1.6.1 Using EMRs to change prescribing behaviors

Many strategies have been developed to change prescribing practices, like educating health care professionals on opioid prescribing (95), guidelines to prescribing (36) and prescription drug monitoring programs. (96) Even though opioid prescribing has been declining since 2010, it remains alarmingly high, indicating that further action needs to be taken. (84) A potential way to improve prescribing behaviors is through the use of computerized provider order entry systems within electronic medical record (EMR) systems. Prescribing patterns can be changed by setting prescribing limits for opioid-naïve patients (97), or by altering the default number of pills seen in an EMR. (98) When opioids are prescribed through an EMR, the system can auto-populate a default number of pills to prescribe. Changing the default number may affect prescription behaviors by altering prescriber beliefs of the amount of opioid needed, and studies have shown that prescribers are influenced by the default number. (99) The prescriber can increase or decrease the amount prescribed if they think it is necessary. Having to actively increase the amount is similar in concept to an "opt out" strategy to change behavior, which has for example successfully been used to increase the number of organ donors, where people automatically are listed as donors and have to actively opt out. (100) An active choice mechanism also has been used to increase the rates of influenza vaccination, where physicians are prompted by an EMR alert to actively choose to accept or cancel vaccine orders for eligible patients. (101)

Evidence suggests that 10-15 pills are sufficient after most surgical operations. Hill et al. found that 15 pills for an initial prescription would satisfy over 80% of patients after common general surgeries. (102) Rodgers et al. had similar results when looking at opioid usage following outpatient upper extremity surgery, where around 80% used 15 pills or less. (103) Lowering the default pill count to a reasonable number has been demonstrated to result in a lower quantity of opioids prescribed. Chiu et al. found that lowering the default pill count from 30 to 12 decreased the median number of pills prescribed in an outpatient setting from 30 to 20, suggesting that prescribers used the default number as a guideline. Also, the mean number of opioid pills prescribed decreased 5.2 pills, or 34.4 morphine milligram equivalents (MME). (98) Two recent studies looked at the effect of the implementation of default pill counts in a system without a prior default. They found that prescribing patterns became more predictable, with more prescriptions at the default level, without significant differences in total opioids prescribed. (99, 104) Another study demonstrated a decrease in pills and MME prescribed for inpatient discharge patients after replacing a functionality that auto-populated the maximum dispense units with a default pill count. (105)

Decreased opioid prescriptions after surgery do not seem to impact patient pain control or satisfaction. Chiu et al. found no significant difference in refill rates before and after the change, (98) consistent with a recent study with over 26,000 opioid-naïve patients receiving opioids after surgery. A smaller initial prescription was not associated with a higher probability of a refill, even for major surgeries like bariatric surgery or a hysterectomy. (106) A study on the association between decreased post-surgical opioid prescribing after an educational intervention with patient satisfaction found no difference in the mean clinician satisfaction. (107) A recent study found that patients receiving more pills were likelier to use more, but those who received less were not more likely to take all of the pills prescribed or get a refill. (108)

Changing the default number of opioid pills prescribers see in the EMR may be a cheap and effective way to battle opioid overprescribing and therefore lower risks of opioid dependency and overdose. This may also have a positive effect on the crisis of opioid overdose in the US, making fewer pills available for diversion. Additionally, smaller opioid prescriptions after surgeries do not seem to diminish patient satisfaction or increase the likelihood of refills. It has been demonstrated that these interventions can affect prescribing patterns in an outpatient setting. (98) However, the impact that this strategy has on prescribing in an inpatient setting after invasive surgery, like cardiac surgery, has yet to be determined.

2 Study aim

The aim of this study was to analyze the association of lowering default opioid pill counts seen by prescribers in an EMR with postoperative opioid prescribing after cardiac surgery.

3 Methods and materials

3.1 Study group and design

This study was a multicenter, retrospective chart review of patients undergoing cardiac surgery in the Yale New Haven Health System from May 18 2016 to May 18 2018. The procedures selected for review were coronary artery bypass grafts, thoracic aortic aneurysm repairs and valve surgeries, as they comprise the majority of open heart surgeries performed. The Yale University Institutional Review Board approved the study, with need for informed consent waived.

On May 18 2017, the multihospital Yale New Haven Health System in Connecticut, USA, which includes five hospitals and multiple outpatient care centers, changed the default number of opioid pills prescribers see in EMRs from 30 to 12 pills. This applied to all medication containing codeine, hydrocodone, hydromorphone hydrochloride, morphine sulfate, oxycodone or tramadol hydrochloride. The Epic EMR system (Hyperspace 2015 IU2; Epic Systems Corporation) was used throughout the health system. This default only served as a guideline, and prescibers could change the amount prescribed. Surgeons were given an educational session on the default change, and the opioid epidemic and ways to reduce overprescribing of opioids.

Data on basic patient demographics (age, sex, race, BMI), with information on the type of surgery by CPT code, performing surgeon and hospital was collected. Information on patient history of substance abuse and chronic pain was also gathered from diagnostic codes, since these conditions can influence the effectiveness of opioid analgesia. Different drug formulations and types of opioids were standardized by conversion to morphine milligram equivalents (MME). This was based on conversion factors published by the Centers for Disease Control and Prevention (CDC). (36)

A total of 1946 of the selected procedures were performed in the study period in the Yale New Haven Health System. These were performed in two hospitals, Bridgeport Hospital and Yale New Haven Hospital (YNHH), making this a multicenter study. Thirteen different surgeons performed the operations before the default change, while 10 of them operated after the change. 179 patients were omitted from the data because it was unknown in which hospital they were operated. 26 patients with large MME values were removed as outliers, so the final number of patients used in the analysis were 1741. A value was considered to be an outlier if the absolute value of its z-score was over 3 (over 3 standard deviations from the mean). Of the 1741 patients, 832 were operated in the first period (from May 18 2016 to May 17 2017), and 909 in the second period (from May 18 2017 to May 17 2018).

3.2 Statistical analysis

For comparison of categorical variables, the chi-square test was used, and Welch‘s t-test or Wilcoxon‘s rank sum test were used for comparison of continuous variables, based on normality. For evaluation of the change in MME prescribed before and after the default change, a multiple linear regression model was used. Changes in MME after the default change stratified by type of surgery were evaluated with Wilcoxons rank sum test. A p-value of <0.05 was considered significant. All statistical analysis and calculations was performed using the statistical software R (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria).

4 Results

4.1 Study group demographics

A total of 1741 patient charts were reviewed. Of those, 832 were operated in the first period (from May 18 2016 to May 17 2017), and 909 in the second period (from May 18 2017 to May 17 2018). Table 1 displays the basic demographics of the two groups. Mean age was about 66 years, and the majority of patients were white (82%) and male (70%). The groups were similar with regards to age, gender, BMI, race, types of procedures and history of substance abuse. However, having a history of chronic pain was significantly more prevalent for patients in the second group (30.9% vs 21.6%, p < 0.01).

Table 1. Comparison of demographic features between the two groups before and after the EMR default change.

Variable	Before n = 832	After n = 909	p-value
Female gender	239 (28.7%)	262 (28.8%)	0.99
Age, years (SD)	66.4 (±13.8)	66.8 (±12.2)	0.80
BMI, kg/m^2 (SD)	30.1 (±6.0)	30.1 (±6.2)	0.65
Race, No. (%)			0.15
Asian	16 (1.9%)	17 (1.9%)	
Black	65 (7.8%)	59 (6.5%)	
Hispanic	50 (6.0%)	72 (7.9%)	
Unknown	7 (0.8%)	17 (1.9%)	
White	694 (83.4%)	744 (81.8%)	
Hospital, No. (%)			0.11
Bridgeport Hospital	141 (16.9%)	182 (20.0%)	
YNHH	691 (83.1%)	727 (80.0%)	
History of chronic pain, No. (%)	180 (21.6%)	275 (30.3%)	< 0.01
History of substance abuse, No. (%)	60 (7.2%)	66 (7.3%)	1.0
Type of procedure, No. (%)			0.68
Coronary artery grafts	412 (49.5%)	441 (48.5%)	
Thoracic aortic aneurysms	122 (14.7%)	125 (13.8%)	
Valve surgery	298 (35.8%)	343 (37.7%)	
MME, mean (SD)	307.2 (±221.9)	233.3 (±203.9)	< 0.01
MME, median (IQR)	240 (150 to 450)	225 (90 to 300)	

4.2 Prescribing changes

A significant decrease in the mean MME prescribed after the selected cardiac surgeries was detected after the default change. Figure 1 displays the monthly average MME prescribed from May 2016 to May 2018. The average MME prescribed for the first group was 307.2 (see table 1) but for the second group the average MME prescribed dropped to 233.3, a difference of 73,9 MME (24,1%). The median MME prescribed also dropped from 240 to 225, a difference of 15 MME (6.25%).

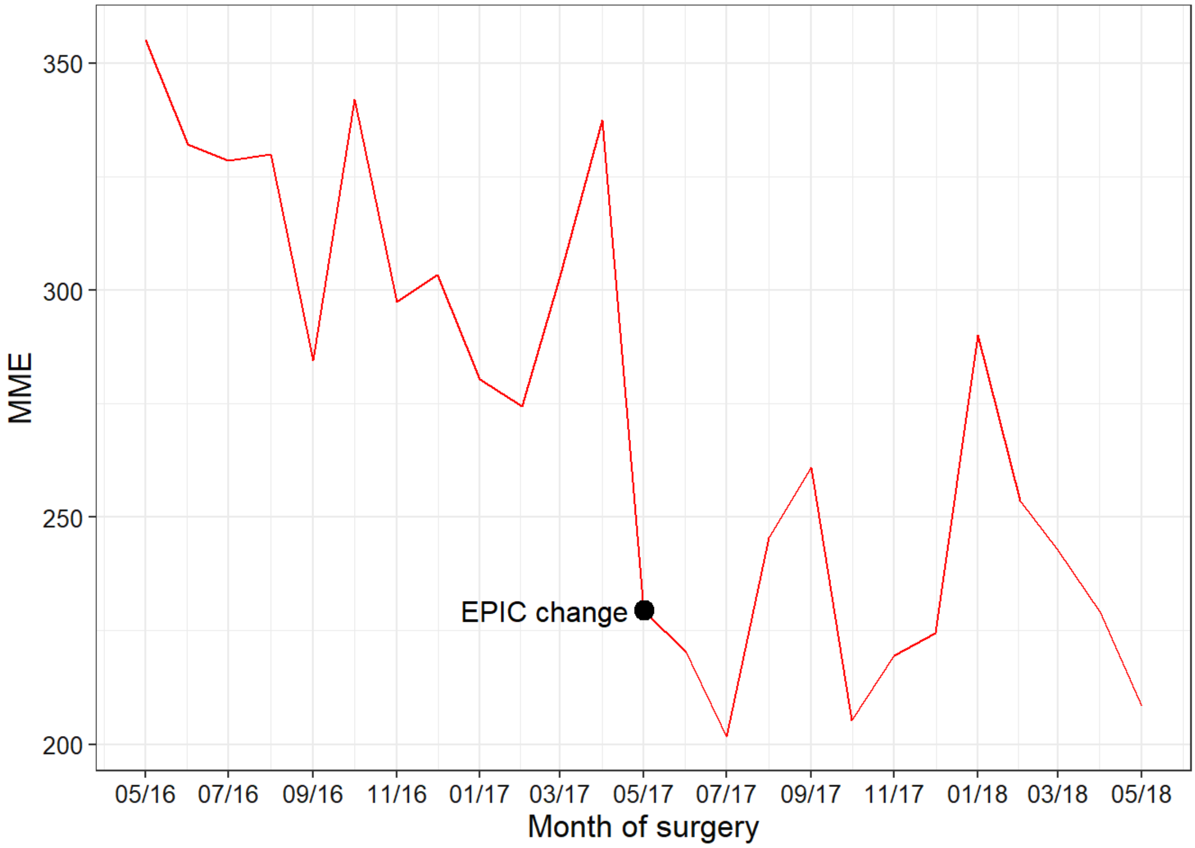

Figure 1. Line graph displaying the average monthly opioid prescribing after cardiac surgery at YNHH, May 2016 - May 2018

A multivariable linear regression model was constructed to adjust for other factors (table 2). When controlling for other factors, the mean MME prescribed was 75.2 lower (95% CI -95.0 to -55.4) after the default change. Other variables affecting prescribing included patient history of substance abuse and chronic pain, which were associated with higher opioid prescriptions, while age had an inverse association. Patients undergoing coronary artery bypass grafts received higher doses compared to the other groups. Also, patients undergoing surgery at YNHH were prescribed a higher amount than patients at Bridgeport Hospital.

Table 2. Linear regression analysis estimating the MME prescribed

Variable	Estimate (95% CI)	p-value
Study period		
Before default change	1 [Reference]	
After default change	-75.2 (-95 to -55.4)	< 0.01
Sex		
Female	1 [Reference]	
Male	9.49 (-12.8 to 31.8)	0.404
Age	-1.45 (-2.25 to -0.65)	< 0.01
Race		
White	1 [Reference]	
Asian	-35.2 (-107 to 37.1)	0.340
Black	-28.4 (-67.7 to 11.0)	0.157
Hispanic	16.3 (-23.3 to 55.8)	0.420
Unkown	-6.69 (-91.1 to 77.8)	0.876
History of substance abuse	75.2 (36.2 to 114.0)	< 0.01
History of chronic pain	35.2 (12.3 to 58.1)	< 0.01
Procedure type		
Coronary artery grafts	1 [Reference]	
Valve surgery	-33.1 (-55.3 to -10.9)	< 0.01
Thoracic aortic aneurysms	-58.70 (-89.6 to -27.9)	< 0.01
Hospital		
YNHH	1 [Reference]	
Bridgeport Hospital	-51.3 (-77.2 to -25.5)	< 0.01

4.3 Prescribing change by procedure

For all three types of procedures, a significant change in prescribing practices was found (table 3). The change in mean prescriptions was higher for coronary artery bypass grafts (CABG) and valve surgeries than for thoracic aortic aneurysms (TAA) surgeries. The change in median prescribed was largest for CABG, but none for TAA surgeries. Prescribing after CABG before the default change was significantly higher than both for valve surgery ($p < 0.01$) and TAA surgeries ($p < 0.01$). After the change, there was still a significant difference between CABG and valve surgeries ($p < 0.01$), but not between CABG and TAA surgeries ($p = 0.26$). A linear regression model was also built for each type of surgery (supplement tables 4-6). Changes in MME after the default change were significant for all procedures.

Table 3. Prescribing changes stratified for type of surgery

Prescribing changes	Coronary artery grafts (n = 853)	Valve surgery (n = 641)	Thoracic aortic aneurysms (n = 247)
Mean MME before	324.3	299.1	268.9
Mean MME after	251.4	215.2	219.0
Change in mean MME (p-value)	-72.9 (<0.01)	-83.9 (<0.01)	-49.9 (<0.01)
Median MME before (IQR)	300 (207.5 to 450)	225 (150 to 400)	225 (200 to 300)
Median MME after (IQR)	225 (120 to 360)	180 (90 to 240)	225 (90 to 300)
Change in median MME	-75	-45	0

5 Discussion

In this study, we found that lowering the default number of pills prescribers see in an elcetronic medical record system substantially reduced the amount of opioids prescribed after the most common types of cardiac surgeries. The mean morphine milligram equivalent (MME) prescribed was 73.9 lower after the change, dropping from 307.2 to 233.3, while the median dropped from 240 to 225. After adjusting for other factors, the difference in mean MME prescribed was found to be -75.2 (95% CI -95.0 to -55.4). These changes were essentially cost-free and easy to implement.

5.1 Prescribing changes

Lowering the default number of opioid pills prescribers see was very effective in lowering the mean and median amount of opioids prescribed. The change in prescribing behaviors was seen immediately after the default change and remained relatively steady over the 12 months time. The change in prescribing was higher after adjustment with linear regression. This is mostly due to the significantly higher ratio of patients with a history of chronic pain in the second group. Since people with a history of chronic pain are probably more likely to be opioid tolerant, it may increase the odds of receiving higher prescriptions. The drop of an average 73.9 MME is about 15 fewer pills of 5 mg morphine, or 10 fewer pills of 5 mg oxycodone per patient. For all operations, about 43,500 more MME was prescribed before vs. after the change. This translates to about 8700 morphine pills, or 5800 oxycodone pills of 5 mg strength.

These results are similar to the ones Chiu et al. (98) found in a different patient population in the same medical system. They studied outpatients, and established that these changes were associated with a decline in the amount of opioids prescribed in that setting. The population in this study underwent a more invasive procedure and received a higher amount of analgesics, but the relative change was similar compared to outpatient prescribing. These results show that prescibers were influenced by the default pill count, and add to literature on the use of EMR tools to impact prescriber behaviour. No other studies on lowering the default pill count were found, but some recent studies have looked at the effects of implementing a default in systems without a prior default. They find that prescribing becomes more predictable with increased number of prescriptions at the default level, without great changes in amounts prescribed. (99, 104) This study further supports the idea of using lower defaults in attempt to lower prescriptions, with the ultimate goal of reducing addiction rates. In addition, this is a simple and virtually cost-free intervention, requiring only a change in computer programming.

5.2 Changes for types of procedures

The three most common types of cardiac surgeries were chosen for analysis. A significant decrease in the mean MME prescribed was found for all three types of cardiac surgeries (table 3). Mean MME prescribed after TAA surgeries was lower than for the others before the change, making less room for a significant decrease. Relatively, MME decreased the most for valve surgeries (28.1%). Mean prescriptions were significantly higher for CABG than for both valve and TAA surgeries before the change, but the reason for this relative high prescribing after CABG is unclear. In the post-change group, prescribing after CABG was significantly higher than after valve surgeries, but was no longer significantly higher than after TAA surgeries. A significant decrease in MME was detected for each type of surgery using a linear regression model (supplement tables 4-6). The linear models revealed some differences between types of surgeries. In the whole group, a lower age was associated with a higher prescription, but that impact was detected with statistical significance only in the CABG subgroup. A history of substance abuse had significant impact on prescriptions (associated with higher MME prescribed) in the CABG and valve surgery groups, but not in the TAA surgery group. A history of chronic pain was also associated with a higher MME prescribed in the whole group, but only significantly for CABG. However, the sizes of the groups differed, with more people undergoing CABG (n = 853) than valve or TAA surgeries (n = 641 and n = 247, respectively). This may affect the statistical power of the analysis.

5.3 Applications

Lowering defaults may have an impact where other measures have not proven to be successful. Another way to affect prescibing behavior via EMRs is setting prescribing limits. Statewide limits in opioid prescribing for opioid-naïve patients with acute pain have been set in many states. Most are relatively new, from 2016 or later, and set the limits to 7 days supply of opioids. (97) However, early results are disappointing, indicating an association with only minor changes in prescribing patterns. (109) Such limiting laws have been more successful in some states than others, especially where extra measures are taken to enforce them. For example, one study showed a 22% reduction with a 5-day limit, with an addition of an EMR alert when prescribers set the opioid amount above the limit. (110) Another study found no significant differences in prescriptions associated with state limits in 11 states. (111) A suggested reason for this is that the limits are not restrictive enough because most prescriptions for acute pain are already lower than the limits, (109) because they are set to greater amounts than most patients need. (102) Other reasons may be that most limits only apply to days of supply without specifying a maximum daily dosage, and possible non-compliance of providers. (109) For states that have not had marked success with these regulations, a lower default setting in an EMR may possibly help change prescribing patterns. Lowering the EMR defaults encourages use for far less than 7 days, applies to the total opioid dosage, not only day supply, and forces providers to actively increase the dosage if they choose to prescribe a greater amount.

Some may be worried that lower prescriptions may result in untreated pain. Sufficient post-operative analgesia is important for patient satisfaction and for enhancing outcomes (38), so it is reasonable to question if this kind of intervention increases the odds of untreated pain. This study does not take on that question, but Chiu et al. (98) found that refill rates did not change, indicating that the intervention did not leave more people with untreated pain. This does not have to be surprising given that 10-15 pills are enough to treat most people‘s post-surgical pain. (102, 103) Another study found no association between lower prescriptions and lower patient-reported clinician satisfaction. (107)

Lowering opioid prescriptions is important, but other measures are necessary to battle the epidemic. Even though opioid prescriptions have been declining in the US since 2010, (83, 84) opioid overdose deaths continued to rise from 2010 to 2017. This rise is due to the use of illicit opioids, (87) possibly reflecting opioid dependent people who can't get their supply from physicians anymore because of tightened prescribing regulations and increased prescriber awareness. Other interventions, like increasing the availability of addiction treatments and using abuse-deterrent formulations are therefore important. (112) However, the magnitude of initial prescribing is associated with a higher risk of opioid dependancy (47), so promoting safe prescribing of opioids, especially for opioid-naïve patients, may be important to lower the rates of opioid dependency.

5.4 Limitations

This study had some limitations. First, it only shows the effects of such changes in a single health system, from surgeries performed by only 13 surgeons. Therefore, they may not be applicable to other health systems. State-limits for opioid prescribing have shown variable results, and maybe this kind of intervention will be more effective in some states or health systems than others. However, YNHH is a tertiary medical center, while Bridgeport Hospital is more community based, which gives this study a more diverse study population.

Secondly, increasing practitioner awareness of the opioid epidemic and other interventions to change prescribing practices may have played a role in the decrease seen after the change. Opioid prescribing in the US has been declining since for the last 10 years (83, 84) and a slight downward trend may be seen in the 12 months prior to the change. However, the decrease in prescribing was seen immediately after the change, indicating that it is attributable to the default change. Laws limiting the prescribing of opioids for first-time outpatient use became effective in Connecticut on July 1st 2016. They limited prescribing to a 7-day supply, with a 5-day limit for minors added in July 2017. (97) This may have affected prescribers to some extent, but these limiting laws have not proven to be very effective and a 7 day limit is not very restrictive, and is more than most people get prescribed for acute pain. (109) Prescribers also took part in an educational session during general surgery grand rounds at the time the new default took effect, which may have influenced prescribing rates.

5.5 Conclusions

It is important to reverse a culture of overprescribing to battle the national crisis of the opioid epidemic. Lowering the default opioid pill count seen in EMRs is an effective, simple and low-cost intervention to help promote judicious opioid prescribing after the most common types of cardiac surgeries.

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Supplement

Table 4. Linear regression estimating MME for CAGB patients

Variable	Estimate (95% CI)	p-value
Study period		
Before	1 [Reference]	
After	74.50 (-103.0 to -45.9)	< 0.01
Sex		
Female	1 [Reference]	
Male	15.70 (-19.7 to 51.1)	0.384
Age	-2.78 (-4.22 to -1.34)	< 0.01
Race		
White	1 [Reference]	
Asian	-45.50 (-142.0 to 51.6)	0.358
Black	-26.80 (-86.7 to 33.0)	0.379
Hispanic	13.30 (-38.6 to 65.2)	0.615
Unknown	25.10 (-80.1 to 130.0)	0.640
History of substance abuse	68.80 (8.82 to 129.0)	0.025
History of chronic pain	32.60 (-2.01 to 63.2)	0.037
Hospital		
YNHH	1 [Reference]	
Bridgeport Hospital	-52.80 (-86.6 to -19.0)	< 0.01

Table 5. Linear regression estimating MME for valve surgery patients

Variable	Estimate (95% CI)	p-value
Study period		
Before	1 [Reference]	
After	-87.10 (-122.0 to -52.4)	< 0.01
Sex		
Female	1 [Reference]	
Male	-6.950 (-42.1 to 28.2)	0.698
Age	-0.588 (-1.77 to 0.59)	0.328

Race		
White	1 [Reference]	
Asian	-14.90 (-141.0 to 112.0)	0.817
Black	-21.80 (-88.0 to 44.4)	0.518
Hispanic	29.60 (-41.6 to 101.0)	0.415
Unknown	-93.70 (-270.0 to 83.0)	0.298
History of substance abuse	98.90 (35.7 to 162.0)	< 0.01
History of chronic pain	42.60 (-0.942 to 86.2)	0.055
Hospital		
YNHH	1 [Reference]	
Bridgeport Hospital	-64.70 (-110.0 to -19.5)	< 0.01

Table 6. Linear regression estimating MME for TAA surgery patients

Variable	Estimate (95% CI)	p-value
Study period		
Before	1 [Reference]	
After	-46.90 (-90.1 to -3.65)	0.033
Sex		
Female	1 [Reference]	
Male	46.10 (-3.07 to 95.2)	0.066
Age	-1.06 (-2.71 to 0.587)	0.206
Race		
White	1 [Reference]	
Asian	-109.0 (-345.0 to 128.0)	0.366
Black	-44.70 (-124.0 to 34.2)	0.265
Hispanic	-62.70 (-204.0 to 78.2)	0.381
Unknown	19.20 (-218.0 to 256.0)	0.873
History of substance abuse	-6.13 (-93.9 to 81.6)	0.891
History of chronic pain	30.40 (-25.8 to 86.5)	0.288
Hospital		
YNHH	1 [Reference]	
Bridgeport Hospital	142.00 (20.6 to 264.0)	0.022