Current Pain and Headache Reports (2023) 27:65–79
https://doi.org/10.1007/s11916-023-01108-3

CHRONIC PAIN MEDICINE (O VISWANATH, SECTION EDITOR)

ERAS Protocol Options for Perioperative Pain Management of Substance Use Disorder in the Ambulatory Surgical Setting

Nicholas M. Zwolinski[1] · Kaiwal S. Patel[1] · Nalini Vadivelu[1] · Gopal Kodumudi[2] · Alan David Kaye[2,3]

Accepted: 20 March 2023 / Published online: 20 April 2023

Abstract

Even prior to the COVID-19 pandemic, rates of ambulatory surgeries and ambulatory patients presenting with substance use disorder were increasing, and the end of lockdown has further catalyzed the increasing rates of ambulatory patients presenting for surgery with substance use disorder (SUD). Certain subspecialty groups of ambulatory procedures have already established protocols to optimize early recovery after surgery (ERAS), and these groups have subsequently enjoyed improved efficiency and reduced adverse outcomes as a result. In this present investigation, we review the literature as it relates to substance use disorder patients, with a particular focus on pharmacokinetic and pharmacodynamic profiles, and their resulting impact on the acute- or chronic user ambulatory patient. The systematic literature review findings are organized and summarized. We conclude by identifying areas of opportunity for further study, specifically with the aim of developing a dedicated ERAS protocol for substance use disorder patients in the ambulatory surgery setting.

Key Summary Points

- Healthcare in the USA has seen an increase in rates of both substanceuse disorder patients and separately in ambulatory surgery cases.
- Specific perioperative protocols to optimize outcomes for patients whosuffer from substance use disorder have been described in recent years.
- Agents of interest like opioids, cannabis, and amphetamines are thetop three most abused substances in North America.
- A protocol and recommend further work should be done to integrate withconcrete clinical data, in which strategies should be employed to conferbenefits to patient outcomes and hospital quality metrics like those enjoyed byERAS protocol in other settings.

Keywords Substance abuse disorder · Early recovery after surgery (ERAS) · Ambulatory surgery · COVID-19 pandemic

Introduction

Substance abuse in the USA threatens nearly 10% lifetime prevalence rate, and the rate is worsening considerably in this past decade. In 2017, the US Department of Health and Human Services specifically declared that the opioid abuse epidemic was a public health emergency [1]. The numbers have continued to dramatically worsen; the 2020 survey of the National Survey on Drug Use and Health marked the first time using the newer criteria of diagnosing substance use disorders (SUD) by the DSM-5 as opposed to its DSM-4 predecessor. Under these new criteria, the year 2020 saw 14.5% prevalence rate of Americans suffering from SUD [2].

Reviews have already identified the COVID-19 pandemic as the ideal catalyst for this substance abuse epidemic [3], yet there are no signs that this trend is subsiding in congruence with "post-covid" society. Furthermore, the COVID-19 pandemic placed a unique pressure on ambulatory surgery centers to receive higher acuity cases, especially in the immediate post-lockdown era. The United Nations Office on Drugs and Crime annual Drug Use

✉ Alan David Kaye
alan.kaye@lsuhs.edu

[1] Department of Anesthesiology, Yale University School of Medicine, 333, Cedar Street, New Haven, CT 06520, USA

[2] Department of Anesthesiology, LSU School of Medicine, 1542 Tulane Avenue Room 659, New Orleans, LA 70112, USA

[3] Department of Anesthesiology, Louisiana State University Health Sciences Center, 1501 Kings Hwy, Shreveport, LA 71103, USA

Report cites in 2021 that North America continues to represent the highest rates of use for the most popular drugs of abuse (cannabis, opioids, and amphetamines) compared to other regions of the world [4]. This establishes precedent for a new level of acuity and a new level of care that can be expected in the ambulatory setting [5]. The most recent US Ambulatory Surgery Center Market Report valuated the market at USD 34.8 billion in 2021 and projected an annual growth rate of 6% for the remainder of the decade to 2030 [6]. The rising share of ambulatory surgery in the market in the post-COVID era is enough to warrant timely investigation of subpopulations of patients receiving care in this sector.

Providers should expect that this increasing prevalence of substance use disorder will impact their practice, and in the case of surgical patients undergoing anesthesia, it is reasonable to conclude that anesthesiologists will need to adapt their practices to accommodate this swiftly growing subset of the population as they enter under their care. A challenge of pain control in the ambulatory setting in recent years has already been identified [7, 8], and suggestions for opioid optimization and multimodal analgesia have already been posited [9]. The management of chronic pain patients in ambulatory surgery centers has already received increased attention [10], and so it stands to reason that increased attention should also be paid to SUD patients, as these patient populations commonly overlap. Here, we review current practices and then propose specific perioperative protocols to optimize outcomes for patients who suffer from substance use disorder.

Review of ERAS Protocol

Implementation of perioperative protocols for the purpose of optimizing patient recovery is hardly a novel concept. Namely, ERAS (early recovery after surgery) protocols aim to provide a framework for just that reducing postoperative and hospital recovery time with the primary goal of improving patient outcomes. An additional, self-serving aspect of ERAS protocols is that they help to streamline complex surgical procedures, thus optimally migrating them from an inpatient to outpatient surgery setting [11]. ERAS protocols are not usually applicable to any certain patient population in principle; rather, they represent an overall approach to the perioperative patient to optimize convalescence, but they leave the nuanced details of patient care to the discretion of the specific physicians to utilize as appropriate to each case. For this reason, ambulatory procedures are likely the most reliant on ERAS protocols to ensure expedient discharge to home.

For example, recovery after colorectal surgery has enjoyed the implementation of ERAS protocol. They aim for early oral intake and postoperative mobilization and encourage several interventions such as the avoidance of mechanical bowel preparation and modified preoperative oral intake with attention to the nature of current laparoscopic surgical techniques. They also include nutrition counseling for the patient and provider team and implement the start of patient carbohydrate loading 2 h preoperatively. These are all implemented with the recognition that early return of bowel function and mobility, along with adequate post-surgical pain control in the colorectal patient, leads to a decrease in postoperative morbidity and decreases the postoperative length of stay [12].

Many other examples of successful ERAS protocols exist as designed by certain hospital systems and for their unique subset of surgical patients. Patients undergoing gynecologic surgery—a patient population which is often sourced from the ambulatory setting—already enjoy the benefits of ERAS protocol [13]. Recently, gynecological patients under ERAS protocol demonstrated lower intra- and postoperative opioid use, and this correlated to less postoperative staff burden on follow-up visits and calls [14]. It is evident that postoperative pain management is an integral part of all ERAS protocols, specifically highlighting the value of multimodal analgesic therapy [15]. Still, there is a paucity of examples of ERAS protocols in practice as they relate to SUD patients, or which are engineered to consider the growing US population of substance users who present for surgery.

In particular, the volume of ambulatory (same day) surgeries performed in the USA has grown consistently over the past quarter century. This can be attributed to improved technology allowing less invasive surgical procedures as well as improvements in perioperative care. With this rise in ambulatory cases, it is critical that the migration of procedures from an inpatient to outpatient setting does not compromise the quality of care and patient safety.

Patient safety following ambulatory surgery is maintained via strict discharge criteria from the post-anesthesia care unit (PACU). This requires assessment of the patient's mental status, respiratory and cardiovascular function, pain control, level of nausea and vomiting, fluid balance, temperature conservation, and wound sites—in other words, ERAS protocols. When these criteria are not met, the length of PACU stay increases, or else results in an unanticipated hospital admission. This confers an increased cost to the patient to the hospital from the resulting complication.

There are several conditions that are associated with high unplanned admission rates; these include chronic pulmonary disease, congestive heart failure, diabetes mellitus, renal failure, liver disease, peripheral vascular disease, deficiency anemia, depression, and substance abuse. In one study of 6189 patients diagnosed with substance use disorder who underwent non-cardiac ambulatory surgery, 9.7% had an unanticipated hospital readmission within 30 days [16].

Earlier studies on PACU length of stay suggested that postoperative pain and postoperative nausea and vomiting are the two most critical factors for prolonged stay after ambulatory surgery [17]. Among a study of 16,411 surgical patients undergoing ambulatory surgery, the type of surgery, type of anesthesia, and specific adverse events such as excessive pain, postoperative nausea and vomiting, dizziness, drowsiness, and cardiovascular events prolonged stay. Patients receiving general anesthesia had a 50-min longer stay than those receiving monitored anesthesia care. Patients undergoing strabismus, transurethral, or otorhinolaryngological/dental procedures had the longest postoperative stay. A more recent study of 3152 patients showed increased PACU length of stay for intraoperative blood loss, increased volume of infused colloids, female gender, advanced age, longer duration of surgery, intubation, spinal anesthesia, high pain score, and nausea and vomiting [18].

ERAS protocol in the ambulatory setting also aims to reduce unexpected postoperative hospital admissions. In one recent report, the overall incidence of unexpected admissions in a study population of over 200,000 ambulatory surgery candidates was 0.11% [19]. Certain predictive factors were identified which included male gender, ASA physical status of II or III, a prolonged duration of surgery, procedures finishing after 3 pm, postoperative bleeding, excessive pain, nausea and vomiting, and excessive dizziness or drowsiness. Subsets of patients on the ENT, urology, and chronic pain services demonstrated the highest rates of unanticipated admissions.

Substance Abuse

Substance abuse disorders (SUD) present unique challenges in the perioperative planning of ambulatory surgery. Substance abuse is associated with refractory pain, decreased functional status, increased length of stay, increased readmission rates, and increased economic costs. Enhanced recovery after surgery (ERAS) protocols for the general population have been shown to significantly reduce postoperative complications and risk of readmission. At the current moment, there is no ERAS protocol specifically targeting substance abuse disorders. The goal of this review article is to establish recommendations and create an ERAS protocol for these patients. We will focus on specific drugs and the perioperative management required to increase the quality of care of these patients. Substance abuse is seen with prescription drug misuse (PDM) and non-prescription substances [20]. Prescription drug prevalence rates arise from the most misused medication classes: opioids, sedatives, tranquilizers, and stimulants [21].

ERAS protocols for control of pain in patients with history substance abuse are truly a challenge. There has been more research in opioid abuse compared to other commonly abused substances. It has been seen in ERAS that early multimodal therapy for analgesia provides significant benefits over the use of opioids alone for post-surgical pain. Hydrocodone and oxycodone are two of the most common prescription opioids that are associated with abuse, diversion, and overdose in the US [22].

Ideal multimodal analgesic regimens for patients with history of substance use disorder are still being determined. Due to the several classes of substances abused and the paucity of research in pre-existing non-opioid SUD patients, there has been difficulty in designing an effective multimodal analgesic therapy in this population.

Substance use disorder leads to chronic diseases of the brain [23]. It has been shown that these patients need specialized treatment modalities such as cognitive behavioral therapy and may additionally require pharmaceutical synergistic treatment with agents such as buprenorphine, methadone, and naltrexone in cases of opioid use disorder [24].

Several non-opioid analgesics have been used in multimodal analgesia in ERAS protocols and have shown to decrease PONV as well as decrease pain in patients undergoing surgery. These non-opioid adjuvants include gabapentin, lidocaine, pregabalin, ketamine, and acetaminophen as well as regional anesthesia. For patients with substance abuse, the ERAS protocols must be modified with considerations according to the types of substances abused to provide safe anesthesia and pain control in ambulatory surgery patients.

Opioids in the Perioperative Setting

Morphine and Other Strong Opioids

Up to 60% of opioids misused in the USA are deviations from original prescriptions written by legitimate medical prescribers, whereas the additional sources are from close relations or illicit drug dealers [25]. When substance users first utilize the opiate, it triggers mesolimbic activation of opioid receptors in the brain and is the primary mechanism by which a substance user's reward system is reinforced. Acutely, activated dopaminergic pathways induce a sense of analgesia and euphoria originating in the ventral tegmental area of the midbrain, eventually communicating to the nucleus accumbens to release dopamine to generate pleasure. This process is akin to the reward process that humans experience when engaging in basic life-preserving functions like eating or sex. Ancillary pathways such as the endogenous opioidergic and GABA-ergic systems also play roles in these motivating pathways, many through interactions by mu-opioid and GABA-ergic interneurons [26]. Eventual

inactivation of the opioid moiety either by the liver or kidney eventually leads to elimination of the metabolites by the kidney or, in some combination by feces, in a relatively direct manner.

For patients on chronic opioid therapy, tolerability of the drug class is usually dictated by the gastrointestinal side effects. These include effects such as nausea, vomiting, and constipation. Opioid-induced constipation is the most experienced and is the most impactful on daily quality of life and can be a barrier to discharge for an ambulatory patient as previously discussed [27]. Other side effects such as dizziness, somnolence, and urinary retention have been identified as well as various hormonal disturbances. Respiratory depression is the most feared complication; however, in properly monitored settings, the actual incidence is quite low [28].

For these reasons, morphine and its closely related analogues are highly useful in the perioperative period for managing acute surgical pain. Substances like morphine, fentanyl, and hydromorphone afford significant pain relief and minimized risk of adverse effects when given in a properly monitored setting, even when dose adjusting for CKD and ESRD patients [28]. In fact, when considering CKD patients for ambulatory surgery, the use of opioids should not be a deterrent to surgical candidacy, as literature shows that these patients with chronic pain have higher rates of undertreated pain, either by way of an abundance of caution or by frank unfamiliarity with the agents by non-pain specialists [29]. In the peri-surgical setting, eventual transition to oral morphine derivatives such as oxycodone or long-acting contemporaries allows for expedient disposition of post-surgical patients to home to convalesce in a monitored, outpatient setting.

In contrast to a monitored healthcare setting, the use of opioids in the absence of acute pain only reinforces the pleasure pathway without utilizing the intended purpose of analgesia. This scenario highlights the recreational environment wherein opiate habituation is present. As this reward system is repeatedly triggered, it compounds beyond the simple pleasure drive. As substance users progress into the chronic stage, they develop a physiologic need for additional dosing to achieve the same (remembered) effect, thus developing physiologic *opioid tolerance*. Insidiously, this physiologic dependence also bolsters a negative reinforcement schema should the user abstain, since the resulting withdrawal symptoms are highly unpleasant to experience thereby rendering the user with *opioid dependence*. Finally, higher-order and executive functioning of the prefrontal cortex—which normally exercises inhibitory capacity over the mesolimbic system—suffers from decreased mu receptor sensitivity, thus modulating the glutamate and GABA pathways, thus reducing the user's ability to inhibit compulsory urges [30]. Eventually, the phenotypical expression of compulsive, drug-seeking behaviors resulting from this pathophysiology is the hallmark of chronic opioid addiction [31]. While this overall pathogenesis is well-studied and demonstrated across all persons and the pharmacokinetic and pharmacodynamic profiles of agents remain unchanged, it is important to note that variations do exist within the population, thus offering one likely explanation as to why certain patients are more susceptible to developing opioid use disorder compared to other genotypic or environmental variants.

One pharmacokinetic (PK) factor of particular importance is the rate of administration of the drug, which has implications for the substance users and their chosen source. In short, faster administration achieves higher plasma levels and thus greater drug effect, greater opioid agonism, and thus a more robust drug reward [32]. In principle, this confers a reduction in risk of abuse potential when extended-release formulations are used [33]. Additionally, absorption rate is a PK parameter that is potentially extorted by substance users, namely, by manipulation of the agent. For example, crushing a morphine (or ER) morphine tablet and ingesting it have been shown to manipulate time to maximum plasma concentration and thus correlate to the peak effect and euphoric reward of the drug [34]. This explains the wide variety of prescription and illicit opioid substances that are available to users depending on the desired effects, although the overall pharmacological principles remain the same. In sum, the overall impact of chronic opioid use on the ambulatory patient is increased opioid need compared to their naïve counterpart, more intense noxious sensation of untreated pain, and a dose-dependent reliance on a steady supply of equipotent oral morphine equivalents (OMEs) to stave off withdrawal symptoms.

Methadone

Additional pharmacological and physiologic parameters are considered when reviewing certain synthetic opioid agents. For example, methadone confers the benefit of being a full-opioid agent with rapid effect, yet the maximum effect can take up to 5 days [35]. It demonstrates a high degree of tissue redistribution due to its lipophilic nature, and so it affords a long duration of action by releasing slowly back into plasma circulation. This has been demonstrated as wide variability in terms of drug half-life up to 65 h. Further, analgesia begins within 30 min of ingestion, and duration can last up to 6 h [36]. It exerts additional antagonistic action on NMDA receptors and inhibition of serotonin reuptake at the synaptic junction [37]. It can be taken via a daily regimen and is therefore favored for controlled opioid dependence weaning programs, as its profile tends to subvert the undesired withdrawal effects.

When a patient presents to preoperative clinic on methadone, they are usually a chronic methadone patient for the purposes of opioid weaning therapy protocol. Treatment regimens for patients are highly individualized, and therefore,

titration for discontinuation can vary based on providers. A general guideline is a gradual 10–25% reduction of dosage stepwise every 2 to 3 days (or longer if the case warrants, as no difference in withdrawal symptoms was found in one study between a 5- and 10-day weaning protocol [38]), with the goal of reaching a daily dose of 10–15 mg. This patient can be considered optimized pre-surgically for postoperative pain, and further weaning to discontinuation can be considered if appropriate. At any point, withdrawal symptoms during taper can be easily treated with an immediate-release methadone dose to help reduce taper intensity. In cases of surgical emergency, methadone may be reversed as other full-opioid agonists with naloxone. It is important to note that redosing may be necessary and patients should be monitored closely for re-narcotization, warranting an additional dose, as naloxone has a half-life of 30 min, much shorter than that of methadone [39].

Buprenorphine

As a partial agonist of the mu-opioid receptor, the benefit of buprenorphine is that it suppresses both withdrawal symptoms and physiological craving responses. Its peculiar drug profile is what lends itself to be categorized as an "atypical" opiate. It is also a drug that is often encountered within the patient population as a chronic phenotype rather than an acute, abuse-potential drug. This property of partial agonism induces a ceiling effect for any unwanted mu-opioid receptor-mediated side effects [40]. Despite the partial agonism at the mu-receptor, its binding profile to the receptor itself is of higher affinity than most full-opioid antagonists. This allows the buprenorphine molecule to bind tightly to the receptor and prevent or displace the binding of the full-opioid antagonists [41].

This is a property that is exploited for the purposes of blunting euphoric effect or otherwise physiologic reward response if/should a full-opioid dose be taken. However, this high affinity property also allows buprenorphine to precipitate withdrawal in individuals if they are physiologically dependent; thus, these withdrawal symptoms are often coaxed to surface prior to administration of buprenorphine, as the emergence of withdrawal symptoms correlates to a time of greater receptor availability. The molecule exhibits great potency, slow dissociation from its target receptor, and a relatively long half-life. Sublingual, oral, and even implantable administration routes exist, although the adverse effect profile of above 50% leaves much to be desired [42, 43].

Related to these complexities, patients on chronic buprenorphine therapy have been the subject of many recent studies as they pertain to perioperative pain control. In 2019, a comprehensive clinical practice advisory for perioperative management of these patients was published, clarifying recommendations and guidelines throughout the perioperative period. Advisements were developed from a committee meta-review on this patient population; however, the systematic review revealed little in the way of randomized controlled trials or higher levels of evidence. As such, these recommendations mainly represent GRADE level 4 or level 5 evidence [44], meaning that they represent conclusions drawn from mainly case series, case studies, or observational studies without control groups. Still, the recommendations represent a significant leap in progress for management of these patients.

In short, the advisory board recommended: (1) continuation of buprenorphine therapy in the pre- and perioperative setting; (2) continuation of buprenorphine therapy in the postoperative period with (3) adjunct analgesia almost always appropriate for these patients (including opiate and non-opiate multimodal analgesics); (4) specific confirmation that it is almost always appropriate to supplement postoperative pain control with full mu-opioid receptor agents such as hydromorphone, morphine, or fentanyl; and (5) discharge from hospital with appropriate equianalgesic dose of buprenorphine, or otherwise full mu agonists with appropriate outpatient monitoring [45]. It bears repeating that the level 4 and level 5 evidence strength are further proof that more high-fidelity studies of these patient populations need to be conducted in order to further optimize perioperative pain management.

Non-Opioid Agents in the Perioperative Setting

NSAIDS

NSAIDS decrease PONV as well as postoperative opioid requirement [46]. There is synergy between NSAIDS, acetaminophen, and dexamethasone when given together with regard to decreasing pain postoperatively [47]. Both opioid reduction and decrease of pain are seen when COX-2 selective inhibitors (COXIBs) are given as an analgesic adjuvant. This has been seen in an RCT of laparoscopic cholecystectomy receiving Cox inhibitors [48]. Recent meta-analyses and Cochrane reviews reveal only low-certainty evidence as to their efficacy, namely, that they have shown to reduce postoperative pain, PONV, and postoperative opioid use. Furthermore, in cancer surgery patients, NSAIDs have been shown to improve disease-free and overall survival rates (mainly through perioperative use of ketorolac) [49].

One classically cited contraindication to perioperative NSAID use is the concern for bleeding. Previously, very little data existed on NSAID impact on postoperative bleeding outcomes [50]. A systematic review and meta-analysis conducted and published by the *Journal of American*

College of Surgery reported that out of 151,000 patients, no significant difference was found between NSAID and non-NSAID groups regarding hematoma, take-backs for bleeding, or blood transfusion administration. This indicates that NSAIDs are unlikely to be the definitive cause of postoperative bleeding complications [51].

Acetaminophen

Acetaminophen works in synergy with NSAIDS and decreases opioid consumption. The exact mechanism remains elusive, though current hypotheses indicate a central nervous system inhibition of the prostaglandin signaling pathway [52]. The greatest effect of acetaminophen is observed when given in conjunction with NSAIDs and is scheduled before surgery and every 6 h following as congruent with current ERAS 2020 guidelines [53]. Discussion regarding cost of IV versus oral modalities is ongoing and is relegated to individual healthcare organizations as dictated by resource availability.

Studies consistently show benefit for management of mild to moderate postoperative pain. It is well-tolerated and has a favorable side effect profile with minimal drug-drug interactions [54]. However, the relative ubiquity of acetaminophen in both IV and oral formulations makes its clinical benefit obscured. One recent meta-analysis among cesarean section patients receiving neuraxial anesthesia and IV acetaminophen reported no significant benefit and that the use of long acting neuraxial opioids may render IV acetaminophen obsolete. However, it does note that as neuraxial analgesia weans, the oral formulation becomes more effective [55]. In patients undergoing cardiac surgery, one study reported a benefit of IV acetaminophen administration in the form of reduced incidence of AKI [56]. Generally, ERAS application of acetaminophen is widely applied to cases such as thoracic/lung surgery, open laparotomy, total hip and knee arthroplasties, cesarean sections, and even in liver transplantation [57].

Gabapentinoids

Gabapentinoids have recently seen increased utility in the substance abuse space. A 2020 randomized control trial of alcohol use disorder patients who received gabapentin demonstrated a significant increase in rates of total abstinence and/or reduced drinking when compared to placebo. This effect was more intensely observed among patients who had more significant withdrawal symptoms [58]. This highlights the similarity of mechanism of action with the substance in question: the drug class binds to voltage-sensitive calcium channels at the alpha-2-delta-1 site of the GABA receptor, the same moiety affected in alcoholism [59].

Anti-epileptic drugs gabapentin and pregabalin have been used for the treatment of chronic pain. A randomized control trial has shown a decrease in the use of tramadol after hysterectomy after the use of gabapentin [60]. A similar decrease in the use of opioid medication within the first 24 h after receiving gabapentin has also been demonstrated in multiple surgical subpopulations [61, 62]. Thus, gabapentinoids previously were thought to be a useful tool at the disposal of the ERAS anesthesiologist in attenuating narcotic need during and after procedures [63]. However, a recent meta-analysis of perioperative gabapentin across 281 studies showed no clinically significant difference in acute, subacute, or chronic pain management across the perioperative period. Secondary findings included slightly lower nausea and vomiting incidence, however greater risk of visual disturbance and dizziness seen with gabapentin use [64]. Editorial review of this meta-analysis by *Anesthesiology* in 2020 posited whether the diminished evidence of benefit and increased evidence of harm warrant a shift in the perioperative paradigm[65]. The authors further point out that the FDA identified that the French Society of Anesthesiology no longer recommends the routine use of gabapentin in the perioperative period [66]. In short, the value of gabapentinoids in the perioperative period is most evident in patients who are chronic pain patients already on a gabapentin regimen; however, the initiation in a naïve patient is likely not beneficial.

NMDA Receptor Antagonists

Ketamine is the prototypical drug of abuse in this category [66]. Its merit as an intraoperative adjunct to analgesia and anesthesia is well-studied. In a meta-analysis by Laskowski et al. in 2011, including 4701 total patients, the use of ketamine was associated with decrease in pain control as seen by VAS scores, decreased opioid requirements postoperatively, and lengthened time to first rescue analgesic. Typical clinical application occurs in the form of an IV bolus for induction and/or a maintenance infusion for the purposes of adjunct anesthesia and analgesia. The typical adverse effect is a risk of post-ketamine emergence agitation akin to emergence delirium [67]. An increase in neuropsychiatric side effects was also noted [68]. This coincides with the added therapeutic benefit of inducing dissociative anesthesia and mood-controlling and mood-reinforcing properties [69]. Such properties have earned ketamine (and its enantiomer esketamine) increased focus in recent years as an emerging psychotherapeutic [70], yet these same properties prime the agent for abuse potential. Since ketamine works as a non-competitive antagonist of the NMDA receptor, it targets the neural effects of endogenous glutamate, a major excitatory neurotransmitter [71]. This induces a reward effect, and along with its metabolite derivative methoxetamine, the agent has been demonstrated to serve as a reinforcing

stimulus, which potentiates the risk of self-administration and eventually abuse [72]. Acute ketamine use, in addition to a dissociative anesthetic and amnestic state, mimics a cardiovascular stimulant by inducing symptoms such as tachycardia and hypertension [73], though these symptoms have been observed to be transient and linked to the drug's plasma half-life of 2–4 h [74].

Chronic users of ketamine present with more characteristic symptoms. Most notable are the schizophreinoid symptoms of dopamine positive and negative findings like visual and auditory hallucinations and detachment, delusion, and amotivation, respectively [75]. Related to its unique mechanism of action in contrast to other psychostimulants and opioids, ketamine is thought to activate central dopamine release, which results in chronic feedback inhibition of dopaminergic release by the nucleus accumbens [76]. This also indicates a potential for negative reinforcing effects synonymous with withdrawal symptoms, essentially encouraging continued use to avoid a slew of uncomfortable withdrawal symptoms [77]. Studies also show that chronic users endorse greater rates of abdominal and urinary symptoms and suggest that ketamine may cause suprapubic pain, dysuria, and hematuria [78]. It has been suggested that the effects are due to the direct metabolism and excretion of ketamine and metabolites (norketamine, methoxetamine), eventually causing renal toxicity [79]. Literature is sparse about chronic ketamine abuse treatment; however, some emerging treatments also suggest acute reversal of dependency which may prove useful in the intraoperative setting. Iatrogenic inhibition of glutamatergic pathways with agents such as lamotrigine has been shown to reduce both the dosage and frequency of daily ketamine needs by chronic users [80]. Most chronic effects of ketamine use are psychogenic in nature, and there is scarcity in modalities to treat or reverse this state. However, ketamine psychotherapy is currently proving to be a promising approach to the treatment of substance abuse disorder when the agent is not ketamine [81], and so the clinical use of ketamine in and of itself may prove to be beneficial for the substance abuse patient, although more research is needed in this area.

Cannabis

According to the National Conference of State legislatures as of 9 November 2022, 37 US states, 3 territories, and the District of Columbia allow medial use of cannabis products. Furthermore, 21 states, 2 territories, and the District of Columbia have legislative measures allowing and regulating for non-medical (recreational) use [82]. Cannabis use at a recreational capacity is expected to see increased rates across the USA as legalization trends continue. Cannabis is an agent that is widely sought after for its well-known neurological and cognitive effects [83]. It has been previously suggested that regular users of cannabis experience acute effects (depending on route of administration). For example, patients who smoke cannabis have been observed to experience airway inflammation and mucosal injury, with increased reactive upper airway symptoms [84]. Independent of route, cannabis consumption triggers tachycardia and has been somewhat implicated in precipitating myocardial events [83, 85]. Endogenous cannabinoid receptor (CB) types 1 and 2 have been observed to be expressed in the liver, fat, muscle, and brain, whereas selectively CB type 2 receptors are found in myocytes, the spleen, and immune cells [83]. Pharmacological modulation of CB-2 receptors has demonstrated a cardioprotective and immunomodulating role [86]. Perioperative effects of self-reported cannabis use were studied in a small group of endoscopy patients ($n=46$), and no statistically significant difference was found in anesthetic agent requirements between users and non-users [87].

However, it should be known that the breadth of literature regarding chronic use of cannabis as it relates to anesthesia has not definitively shown significant increased risk of any major adverse perioperative events and at best merely suggests a possible increased risk of sudden cardiac death [85, 87]. While cannabinoid-induced tachycardia from acute use implies arrhythmogenic properties, the suggested mechanism of vasodilation leading to reflex tachycardia makes its primary role in arrhythmogenicity dubious [88]. Furthermore, chronic cannabis use has been associated with low baseline heart rate and near resolution of orthostatic hypotension, along with a blunting of both sympathetic and parasympathetic activity [89]. Further investigations of case reports or case series have implicated cannabis as the cause for more severe cardiovascular sequela, atrial fibrillation, ventricular tachycardia in young patients, and in one case fatal ventricular fibrillation [90–92]. The poor power of these reports, along with author speculation of alternative mechanisms, makes the perioperative cardiovascular effects unclear at best [93]. Furthermore, a randomized control study of low-dose oral cannabinoid along with very low-dose ethanol (essentially mimicking the pharmacologic milieu of recreational use) did not show a significant change in physiological response or cognitive function [94]. Clearly, the effects of acute and chronic cannabis use in patients can be complex, but literature fails to demonstrate robust evidence of increased risk of adverse events. This highlights potential for additional areas of investigation, especially as perioperative healthcare can reasonably expect that recreational cannabis use will only become more frequent and more common, especially among the ambulatory population.

Benzodiazepines and Barbiturates

Associated with perioperative delirium, and especially in the elderly patient, benzodiazepines are a relic of perioperative anxiolysis and are generally no longer utilized in

the surgical period unless specific indications exist. The American Geriatrics Society recommends minimization of benzodiazepines for older surgical patients to prevent delirium [95]. Interestingly, most general anesthetics and benzodiazepines are known to positively modulate GABA-a receptors to change neuronal activity in the brain, benzodiazepines were further studied and found to exhibit additional membrane binding sites, and thus, the allosteric mechanism of benzodiazepines is implicated in the side effect profile of the drug class [96, 97].

In general, recent studies demonstrate a lack of benefit to benzodiazepine administration, particularly among patients above the age of 50 years and age dependent (however, it is noted that current administration practices already limit benzodiazepine usage with patients 65 and older) [98]. Furthermore, patients who are previously benzodiazepine naïve and were prescribed perioperative benzodiazepines demonstrated a risk of developing persistent benzodiazepine use at an incidence rate of 1 in 5 [99]. Newer literature explores the possible benefit of replacing benzodiazepine anxiolysis in the perioperative setting with that of cannabis [100]. Still, current novelty and controlled substance management makes studies limited, and more data are needed to establish this change.

Like benzodiazepines, barbituates are known to interface with GABA-A receptors and induce several effects including sedation, anxiolysis, and hypnosis. Agents like phenobarbital are clinically popular for its anti-epileptic properties and more specifically for alcohol withdrawal prophylaxis [97, 101]. It is rare for perioperative patients in the ERAS setting to present on a chronic home barbiturate regimen. Still, clinical awareness of GABA modulation effects in conjunction with general anesthetics during surgery should be noted. Appropriate attenuation of MAC, accounting for patient age and adiposity, is an important factor to include when determining an anesthetic plan aimed at minimizing recovery time.

Alpha-2 Agonists

Agents like dexmedetomidine and clonidine have been implicated in various perioperative pharmacological properties such as anti-nociception, anxiolysis, nausea prophylaxis, anti-inflammation, and renal protection. Central pain modulatory pathways involving alpha-2 receptors associated with peripheral c-fiber signal transduction are the main mechanism of supraspinal and spinal anti-nociceptive effects [102]. Further review and meta-analysis identify dexmedetomidine to be a highly selective alpha-2 agonist with broad perioperative effects, including inhibition of endogenous adrenocorticoid release, decreased blood glucose, modulation of interleukin signaling, and improvement of natural killer, B cell, and CD4+ T cell ratios in addition to the previously mentioned benefits [103]. Modulation of neuroinflammation following spinal or brain injury by dexmedetomidine has also been studied [104].

The impact of clonidine and dexmedetomidine on postoperative pain and morphine requirements postoperatively has been studied. Findings included that both dexmedetomidine and clonidine decreased morphine requirements postoperatively as well as decreased PONV. However, one study found that patients who received clonidine had a higher rate of hypotension intraoperatively and postoperatively, while those who used dexmedetomidine were seen to have bradycardia [46].

Additional studies have demonstrated the perioperative use of dexmedetomidine for post-surgical pain. Dexmedetomidine administered at the end of the procedure offered better hemodynamic stability and improved pain response in comparison to ropivacaine. It also demonstrated early discharge from PACU and improved postoperative outcomes when used as part of ERAS protocol [105]. Still, certain subpopulations of surgical patients have not demonstrated significant benefit: a small, randomized study of lateral thoracotomy patients receiving dexmedetomidine infusions did not enjoy decreased analgesic requirements within the perioperative 72 h; however, it did result in decreased intraoperative opioid consumption and improved postoperative sleep quality [106]. In sum, utilization of either a perioperative bolus and/or a continuous infusion of 0.3–1.0 mcg/kg/h (most commonly 0.5 mcg/kg/h) in the meta-analysis by Wang et al. showed the abundance of benefit as described above and indicate the impressive potential for dexmedetomidine in the ERAS space [103].

Inhaled Solvents

Inhaled solvents represent a wide range of surfactants, propellants, and other diverse agents that are commonly found in household aerosolized or propelled products [107]. They are generally categorized into three subgroups by agent type: group I includes volatile solvents, fuels, and anesthetics; group II represents nitrous oxide; and group III includes volatile alkyl nitrates. These agents produce a quick and reliable high with rapid dissipation while boasting minimal negative withdrawal effects [108]. The sought-after CNS excitation and psychoactive effects are thus easily accessible and readily abused on their own, or they can also be utilized as carriers for other target drugs which do not readily vaporize at room temperatures so that they may be inhaled. Inhaled solvents represent some of the most abused substances in the USA within the last decade, specifically among adolescent population, although trends typically decrease somewhat into adulthood [109].

One prototypical example is the toxic difluoroethane which is commonly found in compressed air canisters for electronic cleaning. It is thought to exert its effect by stimulating GABA receptors but also by possible inhibition of NMDA receptors [110]. For this reason, volatile anesthetics most readily resemble the effects of acute alcohol intoxication [111]. The acute effects are thus an initial high or "rush" followed by lightheadedness and transient prefrontal cortex-mediated disinhibition and impulsivity. This effect can last several minutes but can be extended by repeat inhalation. Increasing doses can result in slurred speech, dizziness, visual disturbances, and ataxia. Prolonged and chronic use can stimulate visual hallucinations and time distortion [112]. While these effects are sometimes sought after, chronic users are more likely to report a mixed positive–negative or even noxious experience [113].

The pattern of acute versus chronic users can be organized as such, however with one exceptional morbidity and mortality risk which is present at any use regardless of frequency. The aptly named "sudden sniffing death syndrome" was attributed to as much as 22% of inhalant abuser deaths on their initial use of the substance and is thus the leading cause of death among all inhalant abusers [114]. It is postulated that the hydrocarbons, as well as other inhalants, sensitize the myocardium to epinephrine by stabilizing the cell membrane to depolarization. Since individual myocardial cell responses exist in the way that electrical impulses and sensitization is propagated, the net result is a disorganized electrical conductance circuit that increases the risk of sudden fatal arrhythmias [110]. These arrhythmias can occur even at physiological levels of circulating epinephrine; however, endogenous surges from a threat stimulus notably increase the risk. Most other side effects of inhalant abuse are relegated to chronic users and have general CNS declination symptoms such as loss of brain mass and visual or sensorineural hearing loss. Additional cases of cardiomyopathy, toxic hepatitis, and distal renal tubular acidosis have also been cited [108].

In summary, the acute effects of these agents are transient in nature and would likely have marginal effect on ambulatory substance use patients. However, care should be given to those in whom providers suspect chronic use phenotypes, as their GABA and NMDA receptor activation pathways may be effectively altered like that of a chronic alcohol user.

Neuraxial Anesthesia

Patients with chronic pain and substance abuse require greater analgesic doses. Intrathecal morphine that has been tried in laparoscopic colorectal surgery showed a shorter hospital length of stay for the intrathecal group in an RCT of intrathecal morphine compared to epidural analgesia. There was also early return to mobility and better postoperative pain control in the intrathecal group [115]. This could be an area of research for patients with pre-existing chronic pain and substance abuse for pain control undergoing laparoscopic surgery. However, in an open abdominal surgery gastrectomy RCT in 2014, this was not the case: the intrathecal group demonstrated opposite results suggesting inadequate pain control in the postoperative period for open cases [116].

Thoracic epidural analgesia has been effective in both open and laparoscopic abdominal surgeries, and faster return to bowel function and minimization of narcotic use has been observed [117]. A meta-analysis of postoperative pain control showed excellent efficacy with epidural analgesia compared to parenteral opioids[118]. Faster return of bowel function was again shown in patients with epidural analgesia in a 2016 Cochrane review [119]. However, there have been conflicting reports on patient length of stay with epidural analgesia in open procedures and laparoscopic procedures in patients who received epidurals [120, 121]. Understandably, neuraxial anesthesia remains a useful tool in the ERAS perioperative pathways, provided that the patient is an appropriate surgical candidate for this modality.

Regional Anesthetic Techniques

Thoracolumbar nerves are anesthetized in TAP blocks mostly done with the use of ultrasound between the transverse abdominis muscles and the internal oblique muscles [122]. A decrease in 24-h morphine requirement in patients undergoing laparoscopic surgery was noted in a randomized control trial but demonstrated an increase in PONV [123]. Generally, TAP blocks in abdominal surgery have not been associated with increased risk of PONV [124]. Studies for TAP blocks in the most common ambulatory setting (labor and delivery) remain conflicted. In one study of cesarean section patients in 2020, the combination of intrathecal morphine with TAP block using lysosomal bupivacaine and bupivacaine HCl has afforded opioid-reducing benefit [125]. However, as recently as 2021, an RCT of TAP block with or without intrathecal morphine demonstrated non-inferior post-opioid consumption through 72 h, with the additional benefit of reduced pruritus and more favorable safety profiles when intrathecal morphine is not administered [126]. Investigation of quadratus lumborum blocks in parturients who have received intrathecal morphine demonstrated no additional analgesic benefit [127]. Similar non-inferior or otherwise non-significant benefit was concluded from a RCT of ambulatory total laparoscopic hysterectomy patients receiving TAP blocks [128].

Still, there exist many other regional anesthetic techniques that can decrease postoperative pain and improve patient recovery. These include upper extremity, lower extremity, truncal/abdominal blocks, and lower

extremity blocks [129–131]. Application to ambulatory orthopedic and/or cosmetic procedures is readily apparent in these circumstances.

Alcohol

According to the 2019 National Survey on Drug Use and Health, 14.5 million people ages 12 and older had alcohol use disorder (AUD) in 2019. The large prevalence has many consequences including emergencies and deaths in the USA as well as the economic burden in the USA totaling $249 billion per year. For the human body, alcohol use, whether acute or chronic, poses many physiological implications that can be challenging for an anesthesiologist to manage in the perioperative setting.

Acute alcohol intoxication is a clinical condition following the ingestion of large amounts of alcohol. Clinical manifestations involve different organs including behavioral, cardiac, gastrointestinal, pulmonary, neurological, and metabolic. Symptoms are usually related to blood alcohol concentration (BAC). As the BAC increases, level of consciousness ranges from altered perception of the environment, to slurred speech, to coma, and death. In the perioperative setting, this will impair the ability to obtain informed consent.

Metabolic alterations of acute alcohol ingestion include hypoglycemia, lactic acidosis, hypokalemia, hypomagnesemia, hypoalbuminemia, hypocalcemia, and hypophosphatemia. Cardiovascular effects include tachycardia, peripheral vasodilation, and volume depletion leading to hypothermia and hypotension. Holiday heart syndrome is a colloquialization of such cardiovascular effects that can be characterized by atrial or ventricular tachyarrhythmias and new onset atrial fibrillation. Acute alcohol intoxication can result in respiratory depression and decreased airway sensitivity increasing the risk of aspiration and pneumonia. The gastrointestinal effects include nausea, vomiting, diarrhea, gastritis, peptic ulcers, and pancreatitis [132]. Since acute intoxication with alcohol closely resembles the mechanism of action for most sedating anesthetics (namely, at the central GABA receptors), anesthetic requirement is relatively decreased.

This contrasts with chronic alcohol users, who will develop tolerance and thus require more anesthetic compared to their sober counterpart. Additional concerns include vitamin B1 and thiamine deficiencies, cardiac arrhythmias, alcohol-induced diastolic cardiomyopathy, liver dysfunction, and sensitivity to fluid shifts. Endorphin release is also diminished in chronic AUD patients, and so analgesic dosing may need adjustment [133].

It is estimated that one in five surgical patients suffer from AUD [134]. Effects of alcohol intoxication are so vast and represent such a high fraction of the patient population in the ambulatory setting regardless of timing of ingestion that certain protocolizations of care by larger organizations have already occurred [135].

Specific anesthetic implications for acutely intoxicated patients in the ambulatory setting are as follows:

- Delay surgery if not urgent/emergent.
- BAC value varies and is therefore not a clinically useful value to obtain [136].
- Remain vigilant for cross-tolerance of alcohol with most sedating anesthetics [137].
- Assess for volume status and treat as indicated.
- Preoperative labs including complete blood count, liver function studies, and electrolyte panel may be necessary given nutritional status.
- Perioperative vitamin B1 and thiamine supplementation may be beneficial.
- Consider an electrocardiogram and echocardiography to assess cardiovascular function.
- Maintain normothermia: acutely intoxicated patients are more prone to hypothermia which poses increased infection risk.
- Patients may have increased PONV, and so a transdermal scopolamine patch 30 min prior to incision, with dexamethasone at induction, and ondansetron prior to emergence may be used in concert (adapted from [138]).

Conclusion

Even before the pandemic, the healthcare in the USA saw an increase in rates of both substance use disorder patients and separately in ambulatory surgery cases. The COVID-19 pandemic highlighted the importance of focus in these areas and catalyzed the rates of both populations. Here, a systematic literature review shows that a wealth of pharmacological and clinical precedent exists for the development of ERAS protocol for ambulatory surgery patients who concurrently suffer from substance use disorder. Agents of interest like opioids, cannabis, and amphetamines are the top three most abused substances in North America, and much is known about their pharmacokinetic and dynamic profiles with respect to the perioperative setting. NMDA antagonists and alpha 2 agonists are also well-researched. The utilization of gabapentinoids has fallen in recent years, owing to mounting evidence of lack of benefit. Opportunities remain to further solidify clinical guidelines for atypical opioids, with buprenorphine as a specific example. In summary, the richness of literature on this subject sets a precedent for developing a comprehensive ERAS protocol for substance use disorder patients in the ambulatory setting. Here, we establish a basis for developing such a protocol and recommend further work be done to integrate with concrete clinical data. Finally, implementation of

this protocol is expected to confer benefits to patient outcomes and hospital quality metrics like those enjoyed by ERAS protocol in other settings.

Author Contribution Study concept and design: NMZ KP NV GK ADK analysis and interpretation of data: NMZ KP NV GK ADK drafting of the manuscript: NMZ KP NV GK ADK critical revision of the manuscript for important intellectual content: NMZ KP NV GK ADK statistical analysis: NMZ KP NV GK ADK.

Data Availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

References

1. Ignaszewski MJ. The epidemiology of drug abuse. Supp Art J Clin Pharmacol. 2021;2021:10–7. https://doi.org/10.1002/jcph.1937.
2. SAMHSA. Highlights for the 2020 national survey on drug use and health. 2020.
3. Ornell F, Moura HF, Scherer JN, Pechansky F, Kessler FHP, von Diemen L. The COVID-19 pandemic and its impact on substance use: Implications for prevention and treatment. Psychiatry Res 2020;289:113096. https://doi.org/10.1016/J.PSYCHRES.2020.113096.
4. United Nations Office On Drugs and Crime. Booklet 2 - Global overview: drug demand drug supply. World Drug Report. 2021;2021(2):109.
5. ASCs in 2021: a year in review. 2022. https://www.beckersasc.com/asc-transactions-and-valuation-issues/ascs-in-2021-a-year-in-review.html. Accessed 9 Nov 2022.
6. Grand View Research. U.S. ambulatory surgery centers market size share & trends analysis report by application (orthopedics, pain management/spinal injections), by ownership, by center type, by region and segment forecasts, 2022 - 2030. Grand View Research 2022:1–66. https://www.grandviewresearch.com/industry-analysis/us-ambulatory-surgery-centers-market-report. Accessed 9 Nov 2022.
7. Jones MR, Petro JA, Novitch MB, Faruki AA, Bice JB, Viswanath O, et al. Regional catheters for outpatient surgery—a comprehensive review. Curr Pain Headache Rep. 2019;23:1–9. https://doi.org/10.1007/S11916-019-0762-4/TABLES/1.
8. Kaye AD, Renschler JS, Cramer KD, Klein KE, Granier AL, Hart BM, et al. The role of clinical pharmacology in enhanced recovery after surgery protocols: a comprehensive review. Anaesthesiol Intensive Ther. 2020;52:154–64. https://doi.org/10.5114/AIT.2020.95020.
9. Vadivelu N, Kai AM, Kodumudi V, Berger JM. Challenges of pain control and the role of the ambulatory pain specialist in the outpatient surgery setting. J Pain Res. 2016;9:425–35. https://doi.org/10.2147/JPR.S86579.
10. Charipova K, Gress KL, Urits I, Viswanath O, Kaye AD. Maximization of non-opioid multimodal analgesia in ambulatory surgery centers. Cureus 2020;12. https://doi.org/10.7759/CUREUS.10407.
11. Joshi GP. Enhanced recovery pathways for ambulatory surgery. Curr Opin Anaesthesiol. 2020;33:711–7. https://doi.org/10.1097/ACO.0000000000000923.
12. Simpson JC, Bao X, Agarwala A. Pain management in enhanced recovery after surgery (ERAS) protocols opioid analgesia and side effects. Clin Colon Rectal Surg. 2019;32:121–8. https://doi.org/10.1055/s-0038-1676477.
13. Kallen AN. ACOG Committee Opinion No. 750: Perioperative pathways: Enhanced recovery after surgery. Obstet Gynecol 2018;132:E120–30. https://doi.org/10.1097/AOG.0000000000002818.
14. Levytska K, Yu Z, Wally M, Odum S, Hsu JR, Seymour R, et al. Enhanced recovery after surgery (ERAS) protocol is associated with lower post-operative opioid use and a reduced office burden after minimally invasive surgery. Gynecol Oncol. 2022;166:471–5. https://doi.org/10.1016/J.YGYNO.2022.06.020.
15. Beaumont WR. Morpheus and the underworld-interventions to reduce the risks of opioid use after surgery: ORADEs, dependence, cancer progression, and anastomotic leakage. J Gastrointest Surg. 2019;23:1240–9. https://doi.org/10.1007/s11605-019-04167-3.
16. Teja B, Raub D, Friedrich S, Rostin P, Patrocínio MD, Schneider JC, et al. Incidence, prediction, and causes of unplanned 30-day hospital admission after ambulatory procedures. Anesth Analg. 2020;131:497–507. https://doi.org/10.1213/ANE.0000000000004852.
17. Chung F, Mezei G. Factors contributing to a prolonged stay after ambulatory surgery. Anesth Analg. 1999;89:1352–9. https://doi.org/10.1097/00000539-199912000-00004.
18. Junger A, Klasen J, Benson M, Sciuk G, Hartmann B, Sticher J, et al. Factors determining length of stay of surgical day-case patients. Eur J Anaesthesiol. 2001;18:314–21. https://doi.org/10.1046/J.0265-0215.2000.00837.X.
19. Melton MS, Li YJ, Pollard R, Chen Z, Hunting J, Hopkins T, et al. Unplanned hospital admission after ambulatory surgery: a retrospective, single cohort study. Can J Anesth. 2021;68:30–41. https://doi.org/10.1007/S12630-020-01822-1/TABLES/3.
20. Schepis TS, Teter CJ, McCabe SE. Prescription drug use, misuse and related substance use disorder symptoms vary by educational status and attainment in U.S. adolescents and young adults. Drug Alcohol Depend 2018;189:172–7. https://doi.org/10.1016/J.DRUGALCDEP.2018.05.017.
21. Hedden SL, Kennet J, Lipari R, Medley G, Tice P, P Copello EA, et al. Key substance use and mental health indicators in the United States: Results from the 2015 national survey on drug use and health. 2016.
22. Cata JP, Bugada D, De Andrés J. Opioid-less perioperative care. Minerva Anestesiol 2017;83:315–20. https://doi.org/10.23736/S0375-9393.16.11698-0.
23. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. N Engl J Med. 2016;374:363. https://doi.org/10.1056/NEJMRA1511480.
24. Bryson EO. The perioperative management of patients maintained on medications used to manage opioid addiction. Curr Opin Anaesthesiol. 2014;27:359–64. https://doi.org/10.1097/ACO.0000000000000052.
25. Manchikanti Laxmaiah, Standiford Helm 2nd BFJWJVPJS-GMVB. Opioid epidemic in the United States health policy review. Pain Physician 2012. https://pubmed.ncbi.nlm.nih.gov/22786464/. Accessed 17 Oct 2022.
26. Johnson SW, North RA. Opioids excite dopamine neurons by hyperpolarization of local interneurons. 1992.
27. SIAARTI Recommendations for chronic noncancer pain. Minerva Anestesiologica 2006;72(11):859–80 - Minerva Medica - Journals. https://www.minervamedica.it/en/journals/minerva-anestesiologica/article.php?cod=R02Y2006N11A0859. Accessed 9 Nov 2022.

28. Coluzzi F, Caputi FF, Billeci D, Pastore AL, Candeletti S, Rocco M, et al. Safe use of opioids in chronic kidney disease and hemodialysis patients: tips and tricks for non-pain specialists. Ther Clin Risk Manag. 2020;16:821. https://doi.org/10.2147/TCRM.S262843.
29. Bailie GR, Mason NA, Bragg-Gresham JL, Gillespie BW, Young EW. Analgesic prescription patterns among hemodialysis patients in the DOPPS: Potential for underprescription. Kidney Int. 2004;65:2419–25. https://doi.org/10.1111/J.1523-1755.2004.00658.X.
30. Maher CE, Martin TJ, Childers SR. Mechanisms of mu opioid receptor/G-protein desensitization in brain by chronic heroin administration. Life Sci. 2005;77:1140–54. https://doi.org/10.1016/J.LFS.2005.03.004.
31. Kosten TR, George TP. The neurobiology of opioid dependence: Implications for treatment. Sci Pract Perspect. 2002;1:13. https://doi.org/10.1151/SPP021113.
32. Abreu ME, Bigelow GE, Fleisher L, Walsh SL. Effect of intravenous injection speed on responses to cocaine and hydromorphone in humans. Psychopharmacologia. 2001;154:76–84. https://doi.org/10.1007/s002130000624.
33. Shram MJ, Sathyan G, Khanna S, Tudor IC, Nath R, Thipphawong J, et al. Evaluation of the abuse potential of extended release hydromorphone versus immediate release hydromorphone. J Clin Psychopharmacol. 2010;30:25–33. https://doi.org/10.1097/JCP.0B013E3181C8F088.
34. Vaughn B, Brown C, Lawler J, Lindhardt K, Niebler G, Dayno J. The relationship between the pharmacokinetics of morphine abuse-deterrent, extended-release, injection-molded tablets and pharmacodynamic outcomes in oral and intranasal human abuse potential studies. J Pain. 2017;18:S35. https://doi.org/10.1016/J.JPAIN.2017.02.130.
35. The American Society of Health-System Pharmacists. Archived from 2015. "Methadone hydrochloride." American Society of Health-System Pharmacists 2015.
36. Brown R, Kraus C, Fleming M, Reddy S. Methadone: Applied pharmacology and use as adjunctive treatment in chronic pain. Postgrad Med J. 2004;80:654–9. https://doi.org/10.1136/PGMJ.2004.022988.
37. Elefritz JL, Murphy CV, Papadimos TJ, Lyaker MR. Methadone analgesia in the critically ill. J Crit Care. 2016;34:84–8. https://doi.org/10.1016/J.JCRC.2016.03.023.
38. Berens RJ, Meyer MT, Mikhailov TA, Colpaert KD, Czarnecki ML, Ghanayem NS, et al. A prospective evaluation of opioid weaning in opioid-dependent pediatric critical care patients. Anesth Analg. 2006;102:1045–50. https://doi.org/10.1213/01.ANE.0000202395.94542.3E.
39. Fainsinger R, Schoeller T, Bruera E. Methadone in the management of cancer pain: a review. Pain. 1993;52:137–47. https://doi.org/10.1016/0304-3959(93)90125-9.
40. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE. Clinical pharmacology of buprenorphine: Ceiling effects at high doses. Clin Pharmacol Ther. 1994;55:569–80. https://doi.org/10.1038/CLPT.1994.71.
41. Strain EC, Walsh SL, Bigelow GE. Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine. Psychopharmacology. 2002;159:161–6. https://doi.org/10.1007/S002130100920.
42. Ling W, Casadonte P, Bigelow G, Kampman KM, Patkar A, Bailey GL, et al. Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial. JAMA. 2010;304:1576–83. https://doi.org/10.1001/JAMA.2010.1427.
43. Coe MA, Lofwall MR, Walsh SL. Buprenorphine pharmacology review: Ipdate on transmucosal and long-acting formulations. J Addict Med. 2019;13:93. https://doi.org/10.1097/ADM.0000000000000457.
44. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336:924–6. https://doi.org/10.1136/BMJ.39489.470347.AD.
45. Goel A, Azargive S, Weissman JS, Shanthanna H, Hanlon JG, Samman B, et al. Perioperative Pain and Addiction Interdisciplinary Network (PAIN) clinical practice advisory for perioperative management of buprenorphine: results of a modified Delphi process. BJA: British J Anaesthesia 2019;123:e333. https://doi.org/10.1016/J.BJA.2019.03.044.
46. Blaudszun G, Lysakowski C, Elia N, Tramèr MR. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: Systematic review and meta-analysis of randomized controlled trials. Anesthesiology. 2012;116:1312–22. https://doi.org/10.1097/ALN.0B013E31825681CB.
47. Ong CKS, 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;110:1170–9. https://doi.org/10.1213/ANE.0B013E3181CF9281.
48. Gan TJ, Joshi GP, Zhao SZ, Hanna DB, Cheung RY, Chen C. Presurgical intravenous parecoxib sodium and follow-up oral valdecoxib for pain management after laparoscopic cholecystectomy surgery reduces opioid requirements and opioid-related adverse effects. Acta Anaesthesiol Scand. 2004;48:1194–207. https://doi.org/10.1111/J.1399-6576.2004.00495.X.
49. Shaji S, Smith C, Forget P. Perioperative NSAIDs and long-term outcomes after cancer surgery: a systematic review and meta-analysis. Curr Oncol Rep 2021;23. https://doi.org/10.1007/S11912-021-01133-8.
50. Klifto KM, Elhelali A, Payne RM, Cooney CM, Manahan MA, Rosson GD. Perioperative systemic nonsteroidal anti-inflammatory drugs (NSAIDs) in women undergoing breast surgery. Cochrane Database Syst Rev 2021;11. https://doi.org/10.1002/14651858.CD013290.PUB2.
51. Bongiovanni T, Lancaster E, Ledesma Y, Whitaker E, Steinman MA, Allen IE, et al. Systematic review and meta-analysis of the association between non-steroidal anti-inflammatory drugs and operative bleeding in the perioperative period. J Am Coll Surg. 2021;232:765-790.e1. https://doi.org/10.1016/J.JAMCOLLSURG.2021.01.005.
52. Hemmings HC Jr, Egan TD. Section II: Nervous system, introduction. Pharmacol Physiol Anesthesia. Elsevier; 2019:144. https://doi.org/10.1016/B978-0-323-48110-6.00057-0.
53. Tubog TD. Overview of multimodal analgesia initiated in the perioperative setting. J Perioper Pract. 2021;31:191–8. https://doi.org/10.1177/1750458920928843.
54. Smith HS. Perioperative intravenous acetaminophen and NSAIDs. Pain Med. 2011;12:961–81. https://doi.org/10.1111/J.1526-4637.2011.01141.X.
55. Felder L, Riegel M, Quist-Nelson J, Berghella V. Perioperative intravenous acetaminophen and postcesarean pain control: a systematic review and meta-analysis of randomized controlled trials. Am J Obstet Gynecol MFM 2021;3. https://doi.org/10.1016/J.AJOGMF.2021.100338.
56. Young AM, Strobel RJ, Rotar EP, Kleiman A, McNeil JS, Teman NR, et al. Perioperative acetaminophen is associated with reduced acute kidney injury after cardiac surgery. J Thorac Cardiovasc Surg. 2022. https://doi.org/10.1016/J.JTCVS.2022.09.005.
57. Brustia R, Monsel A, Skurzak S, Schiffer E, Carrier FM, Patrono D, et al. Guidelines for perioperative care for liver transplantation: Enhanced Recovery After Surgery (ERAS) recommendations. Transplantation. 2022;106:552–61. https://doi.org/10.1097/TP.0000000000003808.
58. Anton RF, Latham P, Voronin K, Book S, Hoffman M, Prisciandaro J, et al. Efficacy of Gabapentin for the treatment of alcohol use disorder in patients with alcohol withdrawal symptoms: a randomized clinical trial. JAMA Intern Med. 2020;180:728–36. https://doi.org/10.1001/JAMAINTERNMED.2020.0249.

59. Maneuf YP, Luo ZD, Lee K. α2δ and the mechanism of action of gabapentin in the treatment of pain. Semin Cell Dev Biol. 2006;17:565–70. https://doi.org/10.1016/J.SEMCDB.2006.09.003.
60. Turan A, Karamanlioğlu B, Memiş D, Usar P, Pamukçu Z, Türe M. The analgesic effects of gabapentin after total abdominal hysterectomy. Anesth Analg. 2004;98:1370–3. https://doi.org/10.1213/01.ANE.0000108964.70485.B2.
61. Sen H, Sizlan A, Yanarates O, Emirkadi H, Ozkan S, Dagli G, et al. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesth Analg. 2009;109:1645–50. https://doi.org/10.1213/ANE.0B013E3181B65EA0.
62. Rai AS, Khan JS, Dhaliwal J, Busse JW, Choi S, Devereaux PJ, et al. Preoperative pregabalin or gabapentin for acute and chronic postoperative pain among patients undergoing breast cancer surgery: a systematic review and meta-analysis of randomized controlled trials. J Plast Reconstr Aesthet Surg. 2017;70:1317–28. https://doi.org/10.1016/J.BJPS.2017.05.054.
63. Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. JAMA Surg. 2017;152:691–7. https://doi.org/10.1001/JAMASURG.2017.0898.
64. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, et al. Perioperative use of gabapentinoids for the management of postoperative acute paina systematic review and meta-analysis. Anesthesiology. 2020;133:265–79. https://doi.org/10.1097/ALN.0000000000003428.
65. Kharasch ED, Clark JD, Kheterpal S. Perioperative gabapentinoidsdeflating the bubble. Anesthesiology. 2020;133:251–4. https://doi.org/10.1097/ALN.0000000000003394.
66. FDA in Brief: FDA requires new warnings for gabapentinoids about risk of respiratory depression | FDA. 2019. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-requires-new-warnings-gabapentinoids-about-risk-respiratory-depression. Accessed 26 Dece 2022.
67. Avidan MS, Maybrier HR, Abdallah A Ben, Jacobsohn E, Vlisides PE, Pryor KO, et al. Intraoperative ketamine does not affect postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. Lancet 2017;390:267. https://doi.org/10.1016/S0140-6736(17)31467-8.
68. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth. 2011;58:911–23. https://doi.org/10.1007/S12630-011-9560-0.
69. Coyle CM, Laws KR. The use of ketamine as an antidepressant: a systematic review and meta-analysis. Hum Psychopharmacol Clin Exp. 2015;30:152–63. https://doi.org/10.1002/HUP.2475.
70. Bahji A, Vazquez GH, Zarate CA. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;278:542. https://doi.org/10.1016/J.JAD.2020.09.071.
71. Aan Het Rot M, Zarate CA, Charney DS, Mathew SJ. Ketamine for depression: Where do we go from here? Biol Psychiatry 2012;72:537. https://doi.org/10.1016/J.BIOPSYCH.2012.05.003.
72. Botanas CJ, De La Peña JB, Dela Peña IJ, Tampus R, Yoon R, Kim HJ, et al. Methoxetamine, a ketamine derivative, produced conditioned place preference and was self-administered by rats: Evidence of its abuse potential. Pharmacol Biochem Behav. 2015;133:31–6. https://doi.org/10.1016/J.PBB.2015.03.007.
73. Gable RS. Acute toxic effects of club drugs. J Psychoactive Drugs. 2004;36:303–13. https://doi.org/10.1080/02791072.2004.10400031.
74. Copeland J, Dillon P. The health and psycho-social consequences of ketamine use. Int J Drug Policy. 2005;16:122–31. https://doi.org/10.1016/J.DRUGPO.2004.12.003.
75. Powers AR, Gancsos MG, Finn ES, Morgan PT, Corlett PR. Ketamine-induced hallucinations. Psychopathology. 2015;48:376–85. https://doi.org/10.1159/000438675.
76. Liu Y, Lin D, Wu B, Zhou W. Ketamine abuse potential and use disorder. Brain Res Bull. 2016;126:68–73. https://doi.org/10.1016/J.BRAINRESBULL.2016.05.016.
77. Chen WY, Huang MC, Lin SK. Gender differences in subjective discontinuation symptoms associated with ketamine use. Subst Abuse Treat Prev Policy. 2014;9:1–7. https://doi.org/10.1186/1747-597X-9-39/TABLES/3.
78. Yek J, Sundaram P, Aydin H, Kuo T, Ng LG. The clinical presentation and diagnosis of ketamine-associated urinary tract dysfunction in Singapore. Singapore Med J 2015;56:660–5. https://doi.org/10.11622/SMEDJ.2015185.
79. Hills CE, Jin T, Siamantouras E, LiuIssac IKK, Jefferson KP, Squires PE. Special K and a loss of cell-to-cell adhesion in proximal tubule-derived epithelial cells: modulation of the adherens junction complex by ketamine. PLoS One 2013;8. https://doi.org/10.1371/JOURNAL.PONE.0071819.
80. Huang MC, Chen LY, Chen CK, Lin SK. Potential benefit of lamotrigine in managing ketamine use disorder. Med Hypotheses. 2016;87:97–100. https://doi.org/10.1016/J.MEHY.2015.11.011.
81. Dakwar E, Anerella C, Hart CL, Levin FR, Mathew SJ, Nunes EV. Therapeutic infusions of ketamine: do the psychoactive effects matter? Drug Alcohol Depend. 2014;136:153–7. https://doi.org/10.1016/J.DRUGALCDEP.2013.12.019.
82. State Medical Cannabis Laws. 2023. https://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx. Accessed 11 Nov 2022.
83. Goyal H, Awad HH, Ghali JK. Role of cannabis in cardiovascular disorders. J Thorac Dis 2017;9:2079. https://doi.org/10.21037/JTD.2017.06.104.
84. Bryson EO, Frost EAM. The perioperative implications of tobacco, marijuana, and other inhaled toxins. Int Anesthesiol Clin. 2011;49:103–18. https://doi.org/10.1097/AIA.0B013E3181DD4F53.
85. Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S, et al. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012;307:173–81. https://doi.org/10.1001/JAMA.2011.1961.
86. Steffens S, Pacher P. Targeting cannabinoid receptor CB(2) in cardiovascular disorders: Promises and controversies. Br J Pharmacol. 2012;167:313–23. https://doi.org/10.1111/J.1476-5381.2012.02042.X.
87. King DD, Stewart SA, Collins-Yoder A, Fleckner T, Price LL. Anesthesia for patients who self-report cannabis (marijuana) use before esophagogastroduodenoscopy: a retrospective review. AANA J. 2021;89:205.
88. Franz CA, Frishman WH. Marijuana use and cardiovascular disease. Cardiol Rev. 2016;24:158–62. https://doi.org/10.1097/CRD.0000000000000103.
89. Jones RT. Cardiovascular system effects of marijuana. J Clin Pharmacol 2002;42. https://doi.org/10.1002/J.1552-4604.2002.TB06004.X.
90. Casier I, Vanduynhoven P, Haine S, Vrints C, Jorens PG. Is recent cannabis use associated with acute coronary syndromes? An illustrative case series. Acta Cardiol. 2014;69:131–6. https://doi.org/10.1080/AC.69.2.3017293.
91. Sánchez Lázaro IJ, Almenar Bonet L, José Sancho-Tello M, Martínez-Dolz L. Ventricular tachycardia due to marijuana use in a heart transplant patient. Rev Esp Cardiol. 2009;62:459–61. https://doi.org/10.1016/S1885-5857(09)71679-2.
92. Korantzopoulos P, Liu T, Papaioannides D, Li G, Goudevenos JA. Atrial fibrillation and marijuana smoking. Int J Clin Pract. 2008;62:308–13. https://doi.org/10.1111/J.1742-1241.2007.01505.X.
93. Baranchuk A, Johri AM, Simpson CS, Methot M, Redfearn DP. Ventricular fibrillation triggered by marijuana use in a patient with ischemic cardiomyopathy: a case report. Cases J 2008;1. https://doi.org/10.1186/1757-1626-1-373.
94. Ballard ME, De Wit H. Combined effects of acute, very-low-dose ethanol and delta(9)-tetrahydrocannabinol in healthy human volunteers.

Pharmacol Biochem Behav. 2011;97:627–31. https://doi.org/10.1016/J.PBB.2010.11.013.
95. Finkelstein A, Taubman S. Randomize evaluations to improve health care delivery. Science. 1979;2015(347):720–2. https://doi.org/10.1126/SCIENCE.AAA2362.
96. Olsen RW. GABAA receptor: Positive and negative allosteric modulators. Neuropharmacology. 2018;136:10–22. https://doi.org/10.1016/J.NEUROPHARM.2018.01.036.
97. Kim JJ, Gharpure A, Teng J, Zhuang Y, Howard RJ, Zhu S, et al. Shared structural mechanisms of general anaesthetics and benzodiazepines. Nature. 2020;585:303–8. https://doi.org/10.1038/S41586-020-2654-5.
98. Lei VJ, Navathe AS, Seki SM, Neuman MD. Perioperative benzodiazepine administration among older surgical patients. Br J Anaesth. 2021;127:e69-71. https://doi.org/10.1016/J.BJA.2021.05.016.
99. Wright JD, Cogan JC, Huang Y, Tergas AI, St. Clair CM, Hou JY, et al. Association of new perioperative benzodiazepine use with persistent benzodiazepine use. JAMA Netw Open 2021;4. https://doi.org/10.1001/JAMANETWORKOPEN.2021.12478.
100. Stewart C, Fong Y. Perioperative cannabis as a potential solution for reducing opioid and benzodiazepine dependence. JAMA Surg. 2021;156:181–90. https://doi.org/10.1001/JAMASURG.2020.5545.
101. Löscher W, Rogawski MA. How theories evolved concerning the mechanism of action of barbiturates. Epilepsia. 2012;53(Suppl 8):12–25. https://doi.org/10.1111/EPI.12025.
102. Zhang SJ, Lai G, Griffis CA, Schiltz M, Aroke EN. α2-Adrenergic receptor agonist, an attractive but underused eras component in improving fast-track recovery and surgical outcomes. AANA J. 2021;89:529–37.
103. Wang K, Wu M, Xu J, Wu C, Zhang B, Wang G, et al. Effects of dexmedetomidine on perioperative stress, inflammation, and immune function: Systematic review and meta-analysis. Br J Anaesth. 2019;123:777–94. https://doi.org/10.1016/J.BJA.2019.07.027.
104. Gao J, Sun Z, Xiao Z, Du Q, Niu X, Wang G, et al. Dexmedetomidine modulates neuroinflammation and improves outcome via alpha2-adrenergic receptor signaling after rat spinal cord injury. Br J Anaesth. 2019;123:827–38. https://doi.org/10.1016/J.BJA.2019.08.026.
105. Kaye AD, Chernobylsky DJ, Thakur P, Siddaiah H, Kaye RJ, Eng LK, et al. Dexmedetomidine in enhanced recovery after surgery (ERAS) protocols for postoperative pain. Curr Pain Headache Rep 2020;24. https://doi.org/10.1007/S11916-020-00853-Z.
106. Mao Y, Sun X, Si L, Chen L, Liu X, Zhang Z, et al. Perioperative dexmedetomidine fails to improve postoperative analgesic consumption and postoperative recovery in patients undergoing lateral thoracotomy for thoracic esophageal cancer: a randomized, double-blind, placebo-controlled trial. Pain Res Manag 2020;2020. https://doi.org/10.1155/2020/4145893.
107. Marsolek MR, White NC, Litovitz TL. Inhalant abuse: Monitoring trends by using poison control data, 1993–2008. Pediatrics. 2010;125:906–13. https://doi.org/10.1542/PEDS.2009-2080.
108. Williams JF, Storck M, Joffe A, Behnke M, Knight JR, Kokotailo PK, et al. Inhalant abuse. Pediatrics. 2007;119:1009–17. https://doi.org/10.1542/PEDS.2007-0470.
109. Levari E, Stefani M, Ferrucci R, Negri A, Corazza O. The dangerous use of inhalants among teens: a case report. Emerg Trends Drugs Addictions Health 2021;1:100006. https://doi.org/10.1016/J.ETDAH.2021.100006.
110. Tormoehlen LM, Tekulve KJ, Nañagas KA. Hydrocarbon toxicity: a review. Clin Toxicol. 2014;52:479–89. https://doi.org/10.3109/15563650.2014.923904.
111. Kann L, Kinchen S, Shanklin SL, Flint KH, Hawkins J, Harris WA, et al. Youth risk behavior surveillance - United States, 2013. MMWR Surveill Summ. 2014;63:1–168.
112. Cruz SL, Domínguez M. Misusing volatile substances for their hallucinatory effects: a qualitative pilot study with Mexican teenagers and a pharmacological discussion of their hallucinations. Subst Use Misuse. 2011;46:84–94. https://doi.org/10.3109/10826084.2011.580222.
113. Garland EL, Howard MO. Phenomenology of adolescent inhalant intoxication. Exp Clin Psychopharmacol. 2010;18:498–509. https://doi.org/10.1037/A0021737.
114. Balster RL. Neural basis of inhalant abuse. Drug Alcohol Depend. 1998;51:207–14. https://doi.org/10.1016/S0376-8716(98)00078-7.
115. Virlos I, Clements D, Beynon J, Ratnalikar V, Khot U. Short-term outcomes with intrathecal versus epidural analgesia in laparoscopic colorectal surgery. Br J Surg. 2010;97:1401–6. https://doi.org/10.1002/BJS.7127.
116. Lee JH, Park JH, Kil HK, Choi SH, Noh SH, Koo BN. Efficacy of intrathecal morphine combined with intravenous analgesia versus thoracic epidural analgesia after gastrectomy. Yonsei Med J. 2014;55:1106–14. https://doi.org/10.3349/YMJ.2014.55.4.1106.
117. Lassen K, Soop M, Nygren J, Cox PBW, Hendry PO, Spies C, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced recovery after surgery (ERAS) group recommendations. Arch Surg. 2009;144:961–9. https://doi.org/10.1001/ARCHSURG.2009.170.
118. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003;290:2455–63. https://doi.org/10.1001/JAMA.290.18.2455.
119. Guay J, Nishimori M, Kopp SL. Epidural local anesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, vomiting, and pain after abdominal surgery: a cochrane review. Anesth Analg. 2016;123:1591–602. https://doi.org/10.1213/ANE.0000000000001628.
120. Khan SA, Khokhar HA, Nasr ARH, Carton E, El-Masry S. Effect of epidural analgesia on bowel function in laparoscopic colorectal surgery: a systematic review and meta-analysis. Surg Endosc. 2013;27:2581–91. https://doi.org/10.1007/S00464-013-2794-X.
121. Hübner M, Blanc C, Roulin D, Winiker M, Gander S, Demartines N. Randomized clinical trial on epidural versus patient-controlled analgesia for laparoscopic colorectal surgery within an enhanced recovery pathway. Ann Surg. 2015;261:648–53. https://doi.org/10.1097/SLA.0000000000000838.
122. Charlton S, Cyna AM, Middleton P, Griffiths JD. Perioperative transversus abdominis plane (TAP) blocks for analgesia after abdominal surgery. Cochrane Database Syst Rev. 2010. https://doi.org/10.1002/14651858.CD007705.PUB2.
123. Walter CJ, Maxwell-Armstrong C, Pinkney TD, Conaghan PJ, Bedforth N, Gornall CB, et al. A randomised controlled trial of the efficacy of ultrasound-guided transversus abdominis plane (TAP) block in laparoscopic colorectal surgery. Surg Endosc. 2013;27:2366–72. https://doi.org/10.1007/S00464-013-2791-0.
124. Johns N, O'Neill S, Ventham NT, Barron F, Brady RR, Daniel T. Clinical effectiveness of transversus abdominis plane (TAP) block in abdominal surgery: a systematic review and meta-analysis. Colorectal Dis 2012;14. https://doi.org/10.1111/J.1463-1318.2012.03104.X.
125. Nedeljkovic SS, Kett A, Vallejo MC, Horn JL, Carvalho B, Bao X, et al. Transversus abdominis plane block with liposomal bupivacaine for pain after cesarean delivery in a multicenter, randomized, double-blind, controlled trial. Anesth Analg. 2020;131:1830–9. https://doi.org/10.1213/ANE.0000000000005075.
126. Habib AS, Nedeljkovic SS, Horn JL, Smiley RM, Kett AG, Vallejo MC, et al. Randomized trial of transversus abdominis plane block with liposomal bupivacaine after cesarean delivery with or without intrathecal morphine. J Clin Anesth 2021;75. https://doi.org/10.1016/J.JCLINANE.2021.110527.

127. Tan HS, Taylor C, Weikel D, Barton K, Habib AS. Quadratus lumborum block for postoperative analgesia after cesarean delivery: a systematic review with meta-analysis and trial-sequential analysis. J Clin Anesth 2020;67. https://doi.org/10.1016/J.JCLINANE.2020.110003.
128. Calle GA, Lõpez CC, Sánchez E, De Los Ríos JF, Vásquez EM, Serna E, et al. Transversus abdominis plane block after ambulatory total laparoscopic hysterectomy: Randomized controlled trial. Acta Obstet Gynecol Scand. 2014;93:345–50. https://doi.org/10.1111/AOGS.12351.
129. Ardon AE, Prasad A, McClain RL, Melton MS, Nielsen KC, Greengrass R. Regional anesthesia for ambulatory anesthesiologists. Anesthesiol Clin. 2019;37:265–87. https://doi.org/10.1016/J.ANCLIN.2019.01.005.
130. Jones MR, Novitch MB, Sen S, Hernandez N, De Haan JB, Budish RA, et al. Upper extremity regional anesthesia techniques: a comprehensive review for clinical anesthesiologists. Best Pract Res Clin Anaesthesiol. 2020;34:e13-29. https://doi.org/10.1016/J.BPA.2019.07.005.
131. Kang C, Hwang DS, Song JH, Lee GS, Lee JK, Hwang SJ, et al. Clinical analyses of ultrasound-guided nerve block in lower-extremity surgery: a retrospective study. J Orthop Surg (Hong Kong) 2021;29. https://doi.org/10.1177/2309499021989102.
132. Vonghia L, Leggio L, Ferrulli A, Bertini M, Gasbarrini G, Addolorato G, et al. Acute alcohol intoxication. Eur J Intern Med. 2008;19:561–7. https://doi.org/10.1016/J.EJIM.2007.06.033.
133. Spies C, Eggers V, Szabo G, Lau A, Von Dossow V, Schoenfeld H, et al. Intervention at the level of the neuroendocrine-immune axis and postoperative pneumonia rate in long-term alcoholics. Am J Respir Crit Care Med. 2006;174:408–14. https://doi.org/10.1164/RCCM.200506-907OC.
134. Egholm JWM, Pedersen B, Møller AM, Adami J, Juhl CB, Tønnesen H. Perioperative alcohol cessation intervention for postoperative complications. Cochrane Database Syst Rev 2018;11. https://doi.org/10.1002/14651858.CD008343.PUB3.
135. Spies CD, Rommelspacher H. Alcohol withdrawal in the surgical patient: Prevention and treatment. Anesth Analg. 1999;88:946–54. https://doi.org/10.1097/00000539-199904000-00050.
136. Dilley JE, Nicholson ER, Fischer SM, Zimmer R, Froehlich JC. Alcohol drinking and blood alcohol concentration revisited. Alcohol Clin Exp Res. 2018;42:260–9. https://doi.org/10.1111/ACER.13549.
137. Heilig M, Egli M, Crabbe JC, Becker HC. Acute withdrawal, protracted abstinence and negative affect in alcoholism: Are they linked? Addict Biol. 2010;15:169–84. https://doi.org/10.1111/J.1369-1600.2009.00194.X.
138. Ungur AL, Neumann T, Borchers F, Spies C. Perioperative management of alcohol withdrawal syndrome. Visc Med. 2020;36:160–6. https://doi.org/10.1159/000507595.