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Abstract: Procedural sedation and analgesia (PSA) in the emergency department (ED) presents a crucial aspect of emergency medicine, enabling the execution of painful or distressing procedures with minimal patient discomfort. This narrative review delineates the pharmacological framework, methodologies, and clinical considerations integral to optimizing PSA, with a particular focus on pediatric and geriatric populations. Through a comprehensive review and analysis of current practices, this work evaluates the pharmacokinetics and pharmacodynamics of widely utilized sedatives and analgesics, including propofol, ketamine, dexmedetomidine, fentanyl, midazolam, etomidate, nitrous oxide, and remimazolam. Special attention is dedicated to the selection criteria based on patient-specific risk factors, procedural requirements, and the management of potential adverse effects. The manuscript also explores innovative sedation techniques and the integration of new pharmacological agents, emphasizing evidence-based approaches to enhance patient safety and outcome. The results underscore the significance of tailored sedation strategies, especially for vulnerable groups such as pediatric and geriatric patients, highlighting the need for meticulous pre-procedural assessment and monitoring to mitigate risks. The conclusions drawn advocate for a nuanced application of PSA, guided by current evidence and clinical guidelines, to improve the quality of care in emergency settings. This research reinforces the imperative for ongoing education, skill development, and the adaptation of new evidence into clinical practice to advance procedural sedation and analgesia in the ED.

Keywords: procedural sedation; emergency medicine; pharmacological management

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1. Introduction

The administration of procedural sedation and analgesia (PSA) in the emergency department (ED) represents a cornerstone of modern emergency medicine, enabling clinicians to perform potentially painful or distressing procedures with minimal patient discomfort and stress while preserving vital physiological functions [1,2]. This practice necessitates a sophisticated understanding of pharmacology to select and administer sedative and analgesic agents that are best suited to the patient's needs and the specific procedural requirements [1,3]. Agents such as propofol, ketamine, dexmedetomidine, fentanyl, midazolam, etomidate, nitrous oxide, and the innovative benzodiazepine remimazolam, each with distinct pharmacokinetic and pharmacodynamic profiles, are judiciously evaluated to ensure their optimal application in procedural sedation [4–10].

Effective PSA in the ED transcends mere pharmacological intervention, requiring a comprehensive patient assessment, strategic planning, and preparation for potential complications. Identifying patient-specific risk factors, including age, existing comorbidities, and physiological reserves, is crucial for customizing sedation strategies that balance efficacy with safety. Such an approach is underscored by clinical guidelines and recommendations that advocate for vigilant monitoring, airway management, and cardiovascular stability throughout the sedation process.

The unique challenges presented by special populations, such as pediatric and geriatric patients, underscore the necessity for tailored sedation approaches. These groups demand careful consideration due to their specific physiological and pharmacological characteristics, which influence drug metabolism, airway management, and susceptibility to adverse reactions. This manuscript explores these nuanced considerations, proposing evidence-based strategies to enhance care for these vulnerable groups within the ED setting.

Furthermore, the introduction of new sedative agents and advancements in sedation techniques highlight the evolving landscape of PSA. Innovations, exemplified by remimazolam, promise to refine sedation practices with potential benefits in safety and effectiveness [11]. Such developments reinforce the importance of evidence-based practice and patient-centered care, integrating new knowledge into clinical protocols to improve procedural sedation outcomes [12].

In conclusion, PSA in the ED encompasses a comprehensive array of pharmacological options, patient care principles, and clinical techniques. This manuscript aims to provide an in-depth overview of the current state of practice, addressing challenges and highlighting innovations in PSA to foster the delivery of safe, effective, and patient-focused care in emergency medicine. Through detailed discussions on pharmacology, patient assessment, monitoring techniques, and considerations for special populations, this work contributes to the advancement of sedation practices in the emergency setting.

2. Pharmacology in PSA

Procedural sedation and analgesia (PSA) is routinely performed in the emergency department to facilitate potentially painful medical procedures by reducing the patient's discomfort, pain and anxiety. PSA typically involves the intravenous administration of sedative or dissociative agents, with or without the concomitant delivery of analgesics [13]. This strategy enables clinicians to perform procedures effectively and requires monitoring the patient closely for potential adverse effects [14].

The ideal medications for PSA have a rapid onset and short duration of action, with a quick recovery of cognitive and physical faculties, maintain haemodynamic and respiratory stability, and have minimal associated risks [15]. To better predict the pharmacokinetic effects, the recommended route of administration is intravenously: most of the drugs used for PSA are injected as single or repeated boluses or as a continuous infusion [16]. Some evidence suggests intranasal administration for drugs such as dexmedetomidine [17].

A combination of drugs is generally required to reach both the hypnotic and analgesic endpoints [18]. The addition of local or regional anesthesia and non-opioid analgesics can help reducing pain levels and the doses of PSA medications needed, as well as decreasing the risk of post-procedural respiratory depression.

There is no clear evidence about which drugs are safer than others; consequently, the type and dose of drug should be chosen and optimized according to both the patient's characteristics and the medications' specific effects and risks [19].

According to the American College of Emergency Physicians Clinical Policies Subcommittee, in patients undergoing PSA in the emergency department, the level A recommendation states that ketamine can be safely administered to children and propofol can be safely administered to children and adults [13].

2.1. Propofol

Introduced in 1975, propofol is an intravenous anesthetic known for its short-acting properties. It is commonly employed to initiate general anesthesia and for sedation in monitored anesthesia scenarios. Furthermore, since 1996, its application has extended to procedural sedation within emergency care settings [20].

Known chemically as 2,6-diisopropylphenol, propofol is an alkylphenol derivative with rapid-action properties. Its formulation in a lipid-based emulsion, comprising soybean oil, glycerol, egg lecithin, and a trace of EDTA (to inhibit bacterial growth), contributes to its distinctive milky hue [21]. A number of different formulations of propofol are currently available.

Propofol, like many anesthetics, acts as an agonist for the γ-aminobutyric acid (GABA) receptors, boasting advantageous pharmacokinetic and pharmacodynamic profiles. Its widespread adoption as an intravenous anesthetic is attributed to these qualities. The drug's strong affinity for GABA receptors plays a significant role in its efficacy in diminishing pain. Moreover, propofol has the effect of dampening sympathetic nerve activity, reducing the effectiveness of the baroreceptor reflex, and promoting the release of nitric oxide, which in turn causes blood vessels to dilate [22,23].

2.1.1. Pharmacokinetics and Pharmacodynamics

The pharmacokinetic profile of propofol is characterized by a fast distribution from the blood into tissues, a rapid metabolic clearance from the blood, and then a slow return of the drug from the peripheral compartment. These processes explain its rapid onset and short duration of action [24].

Intravenous administration is the only suitable route of administration of propofol: oral bioavailability is indeed very low because of a high first-pass effect and high hepatic extraction rate (90%) [25].

After intravenous administration, propofol is bound to the plasma proteins (mostly albumin) and erythrocytes. It is rapidly and extensively distributed to well-perfused tissues, including the brain where propofol easily crosses the blood–brain barrier and causes a rapid loss of consciousness [24]. The speed of induction depends on both patient-related factors (e.g., cardiac output) and the speed of infusion. Equilibrium between blood and brain concentrations is reached after 30 min and redistribution to lean muscle and fat tissue occurs due to the high lipid solubility of propofol. The context-sensitive decrement time for propofol is generally favorable compared with other hypnotics [26]: in the case of a short infusion (3 h), the 80% decrement time is 50 min [27].

The liver is the main site of propofol metabolism, with CYP2B6 and CYP2C9 isoforms being the major catalysts: a maintained hepatic perfusion is thus essential to guarantee an efficient metabolism of propofol. Extrahepatic sites of metabolism, predominantly the kidneys and the small intestines, account for 40% of total propofol clearance [28].

Moreover, 88% of propofol is excreted within 5 days in the urine, while a minimal amount is excreted through exhalation [27].

Propofol is a sedative hypnotic agent which rapidly and reliably causes the loss of consciousness [24].

Propofol's hypnotic effect occurs through potentiation of the effects of the inhibitory neurotransmitter GABA [29]: propofol binds to the b-subunit of the postsynaptic GABA-A receptor, causing inward chloride currents that hyperpolarize the postsynaptic membrane and inhibit neuronal depolarization [27].

Propofol has amnestic properties that mostly affect explicit memory in a dose-dependent manner, but they are not as marked as those of the benzodiazepines [24,27].

Propofol produces anxiolysis in subhypnotic doses: the mechanism involved is not well defined but seems to be related to the inhibition of 5-HT activity in the hippocampus or nitric oxide synthase in the hypothalamus, amygdala, and hippocampus [30].

A significant characteristic of propofol is its antiemetic effect, with low incidence and severity of PONV compared to that associated with other hypnotic drugs. This effect

depends on propofol's interaction with dopaminergic (D2) receptors in the chemoreceptor trigger zone, the inhibition of the limbic system [31], and the 5-HT3 receptors located in the central nervous system [15].

Since propofol has no analgesic properties, it is often combined with opioids during PSA, resulting in a synergistic relationship between sedative and analgesic effects [18].

Propofol decreases cerebral blood flow and the metabolic rate and lowers intracranial pressure, while cerebral autoregulation is preserved [24,32].

Propofol shows extensive effects on both cardiovascular and respiratory systems. It causes a reduction in systemic blood pressure and a decrease in cardiac output, effects that appear to be more pronounced in elderly and physiologically compromised patients. The mechanisms responsible for cardiovascular depression are the propofol-mediated decrease in sympathetic tone and vascular resistance and the inhibition of the physiological baroreflex responses [33].

As to the respiratory system, propofol is a potent ventilatory depressant: it reduces the ventilatory responses to hypercapnia and hypoxia, acting at the central chemoreceptor level [34,35]. Propofol also causes upper airway relaxation and suppresses the upper airway reflexes, therefore changing the pattern of breathing [36].

Although the liver and kidneys are highly involved in propofol metabolism and excretion, no functional changes in these organs have been reported [27].

2.1.2. Dosing Regimen

The administration of propofol can occur through either a bolus or continuous infusion, with its onset speed varying according to the dose administered. The drug's action primarily ceases after a single bolus dose as it rapidly moves from the central nervous system to peripheral tissues. This redistribution process is facilitated by the drug's lipophilic nature [37].

In the context of procedural sedation and analgesia (PSA) for adults, the administration of propofol begins with a slow intravenous injection, starting with an initial loading dose ranging from 0.5 to 1 mg/kg. This is followed by subsequent doses of 0.25 to 0.5 mg/kg, administered intravenously at intervals of one to three minutes, until reaching the desired sedation level [38].

In older adult patients without major comorbidities or hemodynamic instability, propofol, as an ultra-short-acting sedative, is preferred among others to perform PSA.

For this patient category, it's recommended to decrease the dose to 20–60% of what is normally administered to a healthy, young adult. This reduced amount should be administered more gradually, over a period of three to five minutes, starting with an initial bolus not exceeding 0.5 mg/kg. Such precautions are necessary to avoid extended periods of sedation and significant cardiorespiratory depression [39].

For patients experiencing kidney or liver function impairment, there is no need to adjust the propofol dosage [40].

Comparable to the approach in elderly patients, propofol exhibits an increased volume of distribution in individuals with obesity. Consequently, the initial dosage should be calculated based on the patient's adjusted body weight, with subsequent doses finely adjusted to reach the desired sedation level.

Propofol is one of the most widely used medications for pediatric procedural sedation, showing advantages in recovery time compared with other drugs. Evidence suggests propofol has a safety profile similar to alternative sedatives, without excessive concerns for respiratory or cardiovascular adverse events in the pediatric population [41].

2.1.3. Adverse Effects

Owing to propofol's narrow therapeutic index, there is a potentially high risk of adverse events, especially in elderly patients [42].

The most commonly recognized side effects of propofol include bradycardia and hypotension, which are the results of myocardial depression, along with respiratory de-

pression. These effects typically dissipate swiftly and without complications due to the short duration of action of propofol. Nevertheless, hypotension may cause further issues in patients with serious health conditions such as sepsis or cardiac dysfunction or in those suffering from hypovolemia [20]. Respiratory depression often presents as temporary hypoxemia, which can be intensified by the simultaneous use of other sedatives or analgesics. This condition is generally manageable with the application of supplemental oxygen or simple airway adjustment techniques [43].

Another common but minor adverse effect is pain on propofol injection (POPI) due to the irritation of venous adventitia, leading to release of mediators such as kininogen from the kinin cascade. The use of lidocaine or ketamine, as well as the rapid injection of propofol into a large vein, is an appropriate precaution to alleviate POPI [44].

Due to propofol's formulation, it should be noticed that hypersensitivity reactions might occur in patients with reported allergies to egg or soy products.

2.2. Ketamine

Ketamine, recognized for its dissociative, analgesic, and anesthetic properties, is frequently utilized in emergency medicine for both pediatric and adult procedural sedation and analgesia (PSA). It delivers sedation, analgesia, and amnesia while preserving upper airway muscle tone, protective airway reflexes, respiratory drive, and hemodynamic stability [45]. Additionally, ketamine is highly effective for anesthetic induction and maintenance, and it can serve as a supplement to regional or local anesthesia, thereby boosting the efficacy of these anesthetic methods.

In combination with propofol, the sub-dissociative dosing of ketamine can provide adequate analgesia and possibly fewer complications compared with short-acting opioids (e.g., fentanyl).

2.2.1. Pharmacokinetics and Pharmacodynamics

Ketamine is an antagonist of N-methyl-D-aspartate (NMDA) receptors and is structurally related to phencyclidine.

The drug is highly lipid-soluble: this characteristic results in extensive distribution to peripheral sites (including the CNS) as evidenced by its relatively large Vd [15].

Ketamine shows a chiral structure consisting of two optical isomers. The use of S-ketamine is increasing worldwide, since the S(+)-enantiomer has been postulated to be a four times more potent anesthetic and analgesic than the R(−)-enantiomer and approximately two times more effective than the racemic mixture of ketamine [46].

The absorption of ketamine is rapid, as seen though the rate of uptake, and its bioavailability is determined by the route of exposure [45].

Intravenous ketamine has low oral bioavailability due to its extensive first-pass metabolism with conversion to the active metabolite norketamine [15] by cytochrome P450. Ketamine is metabolized via the hepatic system, with a half-life of approximately 45 min [47], and it is primarily eliminated by the kidneys, though unchanged ketamine accounts for only a small percentage in the urine [45].

Like propofol, ketamine is employed as a sedative for brief, painful procedures such as fracture reduction or laceration repair in the emergency department. This usage is due to its quick onset and relatively short effect duration (10–20 min), along with its outstanding sedative and analgesic qualities [21,48].

Ketamine's pharmacological basis is distinct from other agents used for procedural sedation and analgesia. It induces a dissociative state by separating the thalamocortical and limbic systems, effectively blocking the perception of sensory inputs such as pain, sight, and sound [21]. This results in a trance-like state of sensory isolation where patients experience significant analgesia, sedation, and amnesia and yet maintain cardiovascular stability as well as spontaneous breathing and protective airway reflexes. Its unique dissociative properties and partial agonism at opiate mu-receptors allow for the conduct of painful procedures with consistent sedation and patient comfort [49,50]. Additionally,

ketamine interacts with sigma receptors and can reduce central sensitization, the wind-up phenomenon, and the memory of pain, making it useful in managing ongoing or chronic pain [47]. At low doses, ketamine can enhance opioid-induced analgesia and help prevent the development of opioid-induced hyperalgesia and tolerance [51].

2.2.2. Administration

Ketamine can be administered via intravenous (IV) or intramuscular (IM) routes. When given via IV administration, the onset of action occurs rapidly, within 30 to 60 s. In contrast, IM administration leads to an onset of action around 4 min. Regardless of the route, the duration of ketamine's effects typically ranges from 15 to 30 min [47]. The IV route is preferable, especially for adults, because recovery is faster and the emetic effect is lower. The IM route is useful in case of difficulty obtaining an IV access and for patients who are uncooperative or combative (e.g., mentally disabled patients) [49].

The dosing regimen for ketamine varies depending on the desired effects, the patient's age, and any underlying health conditions. Children, who metabolize the drug faster than adults, may require higher or more frequent doses. Conversely, elderly patients typically exhibit lower drug clearance rates and a prolonged duration of action, necessitating reduced dosages to accommodate their altered pharmacokinetics. [15].

Instead of a dose-response continuum observed with all other PSA agents, ketamine dissociation appears at a dosing threshold of approximately 1 to 1.5 mg/kg intravenously or 3 to 4 mg/kg intramuscularly. When given in smaller doses, ketamine causes analgesia and disorientation. Once the dissociative threshold is reached, additional ketamine does not influence the level of sedation, as would be the case with opioids, sedative–hypnotics, or inhalational agents [52].

The initial intravenous (IV) dose of ketamine for procedural sedation in adults typically ranges from 0.5 to 2 mg/kg, and it is administered over a period of 30 to 60 s. Depending on the patient's response and whether other anesthetic or analgesic medications are being used concurrently, subsequent doses ranging from 0.25 to 1 mg/kg may be administered at intervals of every 5 to 10 min [53].

For children, the guidelines recommend administering 4 to 5 mg/kg IM with repeated full or half doses after 5 to 10 min if necessary [52].

Like propofol, no dose adjustments are required for ketamine in patients with impaired kidney or liver function. For obese patients, it is recommended to use AdjBW to determine the initial dosing of ketamine and additional titrated doses as needed to prevent side effects and oversedation [54].

Tonic–clonic movements can occur during the administration of ketamine; however, these movements do not necessarily indicate a need for additional doses of the anesthetic [47].

2.2.3. Ketofol

In the context of PSA, a recently emerging strategy is to combine ketamine and propofol, obtaining the so called "ketofol", to create a synergistic sedation state.

Several small prospective trials have studied this combination, suggesting that it may lead to a more stable procedural sedation state and be well tolerated [55]. In addition to that, the intravenous combination typically allows lower drug dosing compared to that necessary with either propofol or ketamine used as a sole agent, thus reducing the potentially associated adverse risks [13].

Ketofol showed less respiratory adverse effects than propofol alone in emergency department PSA [21]. Similarly, the risk for ketamine-associated nausea and vomiting and emergence reactions are purportedly reduced by the antiemetic and axiolytic properties of propofol [13].

There is not a universally standardized method for mixing or dosing; a frequently used strategy involves combining 10 mg/mL of ketamine with 10 mg/mL of propofol in a 20 mL syringe. The initial dosing for this mixture ranges from 0.375 to 0.5 mg/kg (which

translates to 0.0375 to 0.05 mL/kg). If necessary, half of this initial dose can be administered subsequently.

Ketamine is often preferred over propofol when there is a particular concern about hypotension. It is also favored for patients who have developed a significant tolerance to GABAergic agents, for procedures that last longer than 5–10 min and when it is critical to maintain airway protective reflexes.

2.2.4. Adverse Effects

Ketamine is a useful medication in procedural sedation; however, careful attention should be made in patient selection [53].

The most frequently observed side effects of ketamine encompass emesis, tachycardia, and hypertension, along with emergence reactions. Additional side effects include hypersalivation, transient laryngospasm, elevated intracranial and intraocular pressures, muscular hypertonicity, and random, purposeless movements, which are particularly noted in children [52,56].

Emergence reactions are among the most reported side effects of ketamine, occurring in up to 20% of adults [56]. They have been described as disorientation, vivid dreams and hallucinations, which are often benign and self-limited. Emergence reactions can be promptly and effectively treated with small doses of benzodiazepines such as midazolam or even prevented with midazolam or haloperidol pretreatment [57].

Mild to moderate transient increases in blood pressure, heart rate, and cardiac output are common effects due to ketamine's increase in sympathetic activity [53]. On one hand, this anti-shock effect might be helpful to avoid peri-procedural hypotension; on the other, these cardiovascular changes raise concerns of an elevated mycardial oxygen demand that could potentially exacerbate underlying cardiac disease. Ketamine is included in the American Heart Association (AHA) list of medications that may cause or exacerbate heart failure and has been reported to precipitate myocardial ischemia in the elderly [58,59]. The real incidence of myocardial ischemia after ketamine administration is unknown; however, ketamine avoidance is recommended for patients with known coronary artery disease, older adults with CAD risk factors, or those who are already hypertensive or tachycardic [52].

Laryngospasm, although rare, tends to occur more often in children than in adults. It is usually transient and can typically be improved with bag-mask ventilation. This risk of laryngospasm is higher in patients with anatomical abnormalities of the upper airway, such as tracheal stenosis or tracheomalacia.

Regarding the emetic effects of ketamine, pretreatment with ondansetron or similar antiemetic agents can be effective in preventing the nausea and vomiting associated with its use. Absolute contraindications for ketamine administration are an age younger than 12 months—for the higher risk of airway complications—and known or suspected schizophrenia—due to the risk of the exacerbation of this condition.

Relative contraindications include the following: major procedures stimulating the posterior pharynx (e.g., endoscopy); a history of airway instability, tracheal surgery or tracheal stenosis (possible higher risks of airway complications); active pulmonary infections or disease, including asthma; known or suspected cardiovascular disease (its exacerbation caused by the sympathomimetic properties of ketamine); CNS masses, abnormalities, or hydrocephalus (increased intracranial pressure with ketamine); glaucoma or acute globe injury (increased intraocular pressure with ketamine); and porphyria, thyroid disorder, or medication (enhanced sympathomimetic effect) [52].

Overall, ketamine remains a safe medication option in adults undergoing procedural sedation [53].

2.3. Dexmedetomidine

Dexmedetomidine is a commonly used alternative to propofol for PSA in adults and has demonstrated to be an efficacious and safe adjuvant to other sedative and anes-

thetic medications during surgical procedures and in intensive care units. In this context, dexmedetomidine has shown to consistently reduce opioids, propofol, and benzodiazepines requirements [60].

2.3.1. Mechanism of Action

Dexmedetomidine is a highly selective and potent alpha-2 adrenergic agonist with a dose-dependent effect that ranges from minimal to deep sedation [61]. It acts on presynaptic alpha-2 receptors at the locus coeruleus in the pons to reduce the release of norepinephrine, therefore affecting the activity of the sympathetic nervous system [62]. It also seems to diminish pain perception by means of the modulation of alpha receptors in the spinal cord [60].

Dexmedetomidine has remarkable pharmacological properties including sedation, anxiolysis, and analgesia [60].

Dexmedetomidine induces a distinctive sedative state often compared to natural sleep, known as "arousable sedation" or "cooperative sedation." This state facilitates a smooth transition from sleep to wakefulness, allowing patients to remain cooperative and communicative upon stimulation [63].

The drug's analgesic effect involves multiple mechanisms, including binding to alpha2 receptors in both central and spinal locations. It effectively suppresses pain transmission through the hyperpolarization of interneurons and reduces the release of pronociceptive neurotransmitters such as substance P and glutamate [64].

While dexmedetomidine does cause dose-related sedation, it does not significantly impair memory and cognitive functions [65].

Cardiovascularly, dexmedetomidine produces a biphasic response; it causes hypotension at low plasma concentrations and hypertension at higher ones [66]. The intravenous (IV) loading dose typically results in a transient increase in blood pressure, likely due to vasoconstriction triggered by peripheral α-2B receptor stimulation in vascular smooth muscle. This is accompanied by reflex bradycardia, mediated by a decrease in norepinephrine levels due to baroreceptor reflex activation [67]. After the initial phase, when the plasma concentrations of dexmedetomidine decrease, hypotension typically occurs. This is mainly due to the vasodilatory effects mediated by central α-2A receptors and enhanced vagal activity [68]. Both bradycardia and hypotension can be effectively managed with interventions such as atropine and vasoactive agents. Alternatively, these conditions can be prevented by adjusting the loading dose size or extending the time interval between administrations [66].

Several small trials revealed that the combination of dexmedetomidine with ketamine (1 to 2 mg/kg) can provided effective procedural sedation while minimizing cardiovascular depression [69].

Unlike many other sedatives or anesthetics, dexmedetomidine is notable for causing minimal respiratory depression, even when administered in higher doses. This attribute makes it a preferable choice in scenarios where maintaining respiratory stability is critical. [65]. However, it has been shown to rarely cause apnea and to impair the respiratory responses to hypoxia and hypercapnia [70].

Dexmedetomidine has minimal effect on cerebral hemodynamics, including cerebral blood flow and brain tissue perfusion; however, it may modestly reduce ICP due to its mild cerebral vasoconstriction effects and reduction in cerebral blood volume and in cerebral metabolic rate [71].

Dry mouth is a reported side effect of dexmedetomidine [67].

2.3.2. Pharmacokinetics

Dexmedetomidine pharmacokinetics exhibit significant inter-individual variability. Several factors contribute to these differences, including body size, hepatic impairment, plasma albumin levels, and cardiac output, each playing a substantial role in influencing the drug's pharmacokinetics [66].

Although multiple administration routes for dexmedetomidine have been explored, its registered use remains intravenous. Extravascular methods such as oral or intranasal delivery could be advantageous for uncooperative children or geriatric patients, and these methods help avoid the high peak plasma concentrations typically seen with IV administration.

Additionally, dexmedetomidine exhibits a significant first-pass effect when absorbed through the buccal mucosa, with a bioavailability of approximately 16% [72].

Dexmedetomidine is quickly distributed throughout the body, efficiently crossing both the blood–brain and placental barriers. The drug is primarily metabolized in the liver into inactive metabolites via glucuronidation and hydroxylation processes. The elimination of dexmedetomidine predominantly occurs through the kidneys, accounting for 95% of its clearance, while about 4% is excreted via feces. Less than 1% of the drug is excreted unchanged [66].

2.3.3. Administration

When employed as a sedative, dexmedetomidine is administered via infusion at a rate of 0.2 to 1 mcg/kg/h for both adults and children. Prior to beginning the infusion, a bolus dose of 0.5 to 1 mcg/kg may be administered over a 10 min period. It is important to note that patients with liver disease or those who are obese may require lower starting doses due to altered pharmacokinetics [73]. The onset time of IV dexmedetomidine is 3 to 5 min, while the effects last 15 min [74]. Dexmedetomidine can be administered intranasally at doses of 2 to 3 mcg/kg for the purposes of anxiolysis and sedation, particularly when other routes of administration are not considered ideal. This method can be particularly useful in situations where intravenous access is challenging or in settings requiring less invasive administration techniques.

2.3.4. Contraindications and Monitoring

There are no absolute contraindications to the use of dexmedetomidine. It should be used cautiously in patients with bradycardia and hypotension and with known heart failure as there is level B evidence showing that dexmedetomidine might exacerbate myocardial dysfunction [75].

As with other sedative agents, heart rate and rhythm, blood pressure, pulse oximetry, and the level of sedation require close monitoring [75].

In conclusion, thanks to its short half-life and low respiratory effects, dexmedetomidine can be considered a reasonable choice for PS in the ED [62].

2.4. Fentanyl

Short-acting opioids such as fentanyl, alfentanil, and remifentanil are frequently used either alone or in conjunction with sedatives to facilitate procedural sedation and analgesia (PSA). These opioids are preferred for their rapid onset and brief duration of action, which are ideal for short-term procedures requiring significant pain relief. After being synthesized more than 60 years ago, fentanyl has become the opioid most commonly used intravenously for intraoperative analgesia [76]. This fact has occurred due to its minimal cardiovascular effects, absence of histamine release, relatively short action, and for being easily and inexpensively prepared for the marketplace [77].

Before the widespread availability of propofol and etomidate, fentanyl was often co-administered with midazolam to provide analgesia during procedural sedation and analgesia (PSA) [76]. Despite the introduction of newer, ultra-short-acting agents, this combination remains in use, particularly in settings where these agents are unavailable or when a longer duration of PSA is necessary, such as during gastrointestinal endoscopy [13].

2.4.1. Pharmacology and Pharmacokinetics

Fentanyl is a synthetic potent lipid-soluble opioid. It is a mu-selective opioid agonist that produces analgesia and also has the capability to activate other opioid system receptors like the delta receptors and potentially the kappa receptors [77].

Fentanyl is known for its high potency, being 75 to 125 times stronger than morphine. It has a rapid onset of action, typically within 1 to 3 min, and a relatively short duration of effect, lasting about 30 to 60 min. However, unlike some other opioids and sedatives, fentanyl does not have amnestic properties [77].

Many reports have shown important pharmacokinetic differences between alfentanil, fentanyl, and sufentanil, the first one having the most rapid analgesic onset and time to peak effect as well as the shortest distribution and elimination half-lives. The pharmacokinetic properties of opioid analgesics can be influenced by factors like patient age, plasma protein content, acid–base status, changes in hepatic blood flow, and the administration of competitive drugs but not by renal insufficiency [78].

Fentanyl is highly lipophilic and exhibits strong binding to plasma proteins. It has a considerable volume of distribution, ranging from 3.5 to 8 L/kg, and a high clearance rate of 30 to 72 L/h [79]. When administered as an intravenous bolus, fentanyl is quickly distributed from the plasma to highly vascularized compartments. Subsequently, there is a rapid redistribution from the central nervous system to muscle and fat tissues, accounting for its swift onset and short duration of effect [77].

Fentanyl is hepatically metabolized via the CYP450 enzyme system, specifically CYP3A4, through an N-dealkylation that results in the inactive metabolite norfentanyl. Less than 1% is metabolized by alkyl hydroxylation, N-dealkylation, or amide hydrolysis to the inactive compounds hydroxyfentanyl, hydroxynorfentanyl, and despropionylfentanyl.

Fentanyl has a half-life of 3 to 7 h. Excretion occurs 75% in the urine and 9% in feces [78].

2.4.2. Dosing Regimen

Opioid analgesics are mainly administered using the intravenous route. Still, other techniques of administration, including epidural, intrathecal, transdermal, and intranasal applications, have been demonstrated [77]. Fentanyl is a rapid-acting drug when given via transmucosal or intravenous routes, while the transdermal administration shows a slower onset and a longer duration of effect [80].

When combined with a sedative for procedural sedation and analgesia (PSA), fentanyl is typically administered intravenously at an initial dose of 1 to 1.5 mcg/kg. This dose is then titrated at intervals of 0.5 to 1 mcg/kg every 3 min until the desired level of sedation and analgesia is reached [80]. The general maximum total dose is usually capped at 5 mcg/kg, or approximately 250 mcg, although higher doses may be necessary in certain cases. For obese patients, it is recommended to use adjusted body weight (AdjBW) rather than actual body weight (ABW) for calculating both the initial dose and subsequent titrations to minimize the risk of potential side effects [54].

The commonly used combination of midazolam and fentanyl for procedural sedation is linked to a significant risk of hypoxia and apnea, potentially necessitating airway management and the reversal of the medication's effects [81]. To mitigate the risk of respiratory depression, a cautious dosing strategy involves initially administering midazolam at 0.02 mg/kg, followed by fentanyl at 0.5 mcg/kg, with each dose carefully titrated. It is essential to closely monitor the patient's response prior to each dose. Additionally, older patients or those with hepatic or renal dysfunction may require smaller doses and longer intervals between administrations to safely achieve the desired sedative and analgesic effects.

2.4.3. Contraindications and Adverse Effects

The use of fentanyl is contraindicated in the following situations: patients with respiratory depression or obstructive airway diseases, liver failure, known intolerance or

hypersensitivity to fentanyl or other morphine-like drugs or any components present in the formulation, and MAO use in the previous 14 days [79].

Fentanyl should not be taken concomitantly with CYP3A4 inhibitors, such as macrolide antibiotics or azole antifungal agents because of potential drug interactions. Protease inhibitors and the cessation of a CYP3A4 inducer medication (e.g., carbamazepine, phenytoin) should also be avoided since they might increase fentanyl plasma concentrations, thus facilitating opioid-related adverse effects and cause potentially fatal respiratory depression [78,79].

Respiratory depression is the main side effect of opioids that appears to be potentiated by the coadministration of sedatives.

Like morphine, meperidine, and others, fentanyl produces the typical mu opioid central nervous system actions such as fatigue, sedation, nausea and vomiting, dizziness, and bradycardia (due to a central vagal stimulating action). Fentanyl has fewer hemodynamic effects, and therefore, its use is suggested in the case of hypotension, and the incidence of constipation and pruritus is lower than that caused by morphine and most non-fentanyl mu receptor-stimulating opioids [77].

Elderly patients and those with renal or hepatic dysfunction are at an increased risk of experiencing more prolonged or profound adverse effects from medications. This heightened sensitivity requires careful monitoring and often adjustments in dosage or treatment protocol to safely manage their condition. A reversal drug, naloxone, is available to effectively terminate fentanyl effects when necessary [77].

2.5. Midazolam

Midazolam is the most frequently used benzodiazepine for procedural sedation. It is reported to be two to six times as potent as diazepam [81].

Midazolam might be used alone for anxiolysis; however, as it has no analgesic properties, and it is commonly administered with fentanyl for more profound levels of sedation and analgesia [18].

2.5.1. Pharmacology

The actions of benzodiazepines such as midazolam are mediated through the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). These drugs bind to the benzodiazepine site on GABA-A receptors, which potentiates the effects of GABA by increasing the frequency of the chloride channel opening, thereby producing a sedating effect, muscle relaxation, anxiolysis, anterograde amnesia, and also an anticonvulsant action.

Midazolam has a rapid onset time of 2 to 3 min, but the effect site concentration peaks only after approximately 13 min [61]. The duration of action is longer than propofol (20 to 80 min) and with a prolonged half-life: for this reason, midazolam is used mainly for shorter procedures but with caution in elderly patients or patients with comorbidities [18].

Midazolam is both a hydrophilic and lipophilic molecule, depending on pH [82], and can easily and quickly penetrate the blood–brain barrier.

2.5.2. Pharmacokinetics

The pharmacokinetic parameters of midazolam are variable and depend on factors such as age, bodyweight, and hepatic and renal function. In the elderly, obese patients, and those with hepatic impairment, midazolam has a reduced clearance and prolonged half-life. Since midazolam is highly protein-bound, hypoalbuminaemia leads to a higher free fraction of midazolam and increased distribution of the drug in the CNS, resulting in a greater sedation effect [15].

Midazolam has limited oral bioavailability, and both in adults and pediatric patients, the drug is approximately 97% bound to plasma proteins, principally albumin.

Its metabolism take place via hepatic CYP450 enzymes and glucuronide conjugation. The 1-hydroxy-midazolam metabolite comprises 60–70% of the biotransformation products

of midazolam, and it is as potent as the parent compound, contributing 10% to the net pharmacologic activity of midazolam.

The amount of midazolam excreted unchanged in the urine when given intravenously is less than 0.5%, with an elimination half-life of 1.5 to 2.5 h. Furthermore, 45% to 57% of the dose is excreted in the urine as the 1-hydroxymethyl midazolam conjugate.

2.5.3. Administration and Dosage

Midazolam can be administered via oral, intranasal, buccal, intravenous, and intramuscular routes. For procedural sedation and analgesia (PSA), it is commonly administered intravenously over 1 to 2 min in doses ranging from 0.02 to 0.03 mg/kg. The total dose needed for adequate sedation varies depending on several factors, including the patient's weight, age, medication tolerance, comorbidities, and the duration of the procedure. Typically, in adults, midazolam is administered in individual doses of 0.5 or 1 mg and is titrated to achieve the desired effect. No single dose should exceed 2.5 mg, and additional doses may be given every 2 to 5 min as needed. Generally, no more than 5 mg of midazolam is required to perform PSA. Sedation usually occurs within 3 to 5 min after IV injection.

For pediatric patients between 1 and 5 months old, the intranasal route is recommended at a dose of 0.2 mg/kg. For children aged 6 months and older, the appropriate dose is about 0.2 to 0.3 mg/kg when administered intranasally [82].

Patients over 65 years of age and those with hepatic or renal dysfunction have a decreased clearance of midazolam. Therefore, they should receive reduced doses (approximately half the dose used in younger patients) and longer dosing intervals and should be monitored for excessive sedation [15].

Patients with cardiovascular diseases should undergo a systematic and careful evaluation of their physical status and cardiac reserve before performing PSA. However, in emergency procedures (e.g., gastroscopy for bleeding), this evaluation might have to be limited. Current practice suggests providing PSA with benzodiazepine (mainly midazolam) and/or propofol and low-dose opioids, especially for minor or major cardiac procedures such as left heart catheterization or coronary stenting, electrical cardioversion, and the implantation of internal defibrillators, pacemakers, or trans-femoral aortic valves [18].

The pharmacokinetics of benzodiazepines, such as their half-life and volume of distribution, tend to increase with body weight. Consequently, the medication and its metabolites are prone to accumulate with repeated doses, potentially leading to adverse effects, particularly oversedation and respiratory depression, especially in obese patients. It is recommended to calculate the initial dose based on the patient's adjusted body weight (AdjBW). Additionally, it is advisable to administer smaller supplemental doses as needed until the desired effect is achieved to minimize the risk of these adverse outcomes [54].

2.5.4. Adverse Effects and Monitoring

The primary drawback of midazolam is the potential for the accumulation of the drug, mostly in adipose tissue, with repeated doses, which can significantly prolong sedation [15].

While midazolam is thought to cause minimal hemodynamic effects, it has the potential to induce the loss of airway reflexes, respiratory depression, and even apnea. Respiratory depression can occur with 0.15 mg/kg with an increased risk when associated with other sedatives or opioids, such as fentanyl [61].

Several studies suggest that the incidence of bradycardia, hypotension, and hypoxia is higher with the use of midazolam/opiates, compared to other sedatives or analgesics for PSA, and can occur primarily in the case of rapid IV administration [14].

Other common adverse effects associated with midazolam include hiccoughs, cough, nausea, vomiting, thrombophlebitis, and pain at the injection site. In elderly patients, it is crucial to be vigilant about the potential for benzodiazepine-induced neurocognitive alterations, which can increase the risk of drowsiness, ataxia, falls, and confusion.

Monitoring is particularly essential for elderly individuals and patients with liver or kidney disease. It is also necessary to monitor for potential drug interactions when midazo-

lam is used in conjunction with medications such as erythromycin, clarithromycin, diltiazem, sertraline, protease inhibitors, rifampin, phenytoin, phenobarbital, carbamazepine, opioids, antipsychotics, and alcohol, all of which can alter the metabolism and effects of midazolam [82].

When necessary, flumazenil is a reversal agent available to terminate the effects of midazolam or other benzodiazepines.

2.6. Etomidate

Etomidate is a short-acting, hypnotic intravenous molecule [83]. It is approved for use in various medical procedures including the induction of general anesthesia, rapid sequence intubation, and short operative procedures such as joint dislocation reductions, tracheal intubation, cardioversion, dilation and curettage, and cervical conization [84,85].

Evidence from several randomized trials and prospective observational studies supports the effectiveness of etomidate as a sedation agent for procedural sedation and analgesia (PSA). These studies also indicate that etomidate is not associated with major complications, highlighting its safety profile for these applications [86].

2.6.1. Pharmacology and Pharmacokinetics

Etomidate, a derivative of imidazole, is structurally distinct from other anesthetic agents. It exerts its anesthetic effects by functioning as a positive allosteric modulator of GABA-A receptors. This action involves direct binding to specific sites on these receptors, enhancing their affinity for the inhibitory neurotransmitter GABA. Through this mechanism, etomidate amplifies GABA-mediated neuronal inhibition, which contributes to its efficacy as an anesthetic [85].

Its action at the level of the reticular-activating system produces anesthesia. Etomidate seems to have disinhibitory effects on the parts of the nervous system that control extrapyramidal motor activity; these effects might explain the incidence of myoclonus during induction with this drug [83].

Etomidate is registered for intravenous use only, although other routes of administration have been investigated for sedative or anxiolytic purposes.

Like most intravenous anesthetics, etomidate is highly protein-bound (77%). As a consequence, in low albumin states (e.g., hepatic or renal insufficiency), more free drug is available and reaches higher concentrations in the brain.

The volumes of distribution are relatively large, likely owing to etomidate's high solubility in fat, and seem to be related to body weight [87].

Etomidate induces unconsciousness within one circulation time. Recovery is rapid as a result of extensive redistribution and rapid metabolism.

Metabolism is primarily hepatic, and ester hydrolysis leads to inactive metabolites. These metabolites are excreted in urine and a small part in bile; less than 2% of etomidate is excreted unchanged [87].

2.6.2. Administration and Dosage Regimen

Etomidate is an intravenous agent that offers several advantages: a simple dose regimen, fast onset of action, short duration of effect, rapid metabolism, low risk of histamine release, and hemodynamic stability on bolus injection [85].

Etomidate has a favorable hemodynamic profile upon induction, causing the minimal depression of blood pressure. This makes it particularly suitable for use in shock trauma patients, those with hypovolemia, or individuals with significant cardiovascular disease [88]. For procedural sedation and analgesia (PSA) in adults, etomidate is administered intravenously over 30 to 60 s at doses of 0.1 to 0.15 mg/kg, which is lower than the dose typically used for rapid sequence intubation. Additional doses of 0.05 mg/kg can be administered approximately every 3 to 5 min as needed [48,89]. The onset of action of etomidate is nearly immediate, and its duration of effect is dose-dependent, with each

0.1 mg/kg providing roughly 100 s of unconsciousness. Therefore, the typical duration regarding usual dosages for adults ranges from 5 to 15 min [83].

Etomidate is primarily excreted by the kidneys, and the risk of toxic reactions may be heightened in patients with renal dysfunction. As elderly patients are more likely to have decreased renal function, it is advisable to use doses at the lower end of the dosing range for this demographic and to monitor kidney function closely [83]. No dosage adjustments are necessary for patients with hepatic impairment.

Similarly to propofol, obese patients require dosing to be based on AdjBW, with additional titrated doses given as needed [54].

2.6.3. Medication Choice

Propofol and etomidate are both favored medications for procedural sedation and analgesia (PSA) in healthy and hemodynamically stable patients due to their safety, effectiveness, and similar times to onset and recovery. However, propofol is known to potentially cause hypotension or decreased cardiac function. For this reason, etomidate is often the preferred choice for patients where hypotension is a particular concern as it tends to maintain greater hemodynamic stability. Nevertheless, etomidate might be responsible for myoclonus (which appears to reduce the rate of procedural success) and dose-dependent adrenal suppression (which may be harmful in patients with critical illness) [89]. Evidence also suggests that etomidate might be more likely associated with post-procedural nausea and vomiting [90].

Etomidate has no analgesic properties and often requires the coadministration of a short-acting opioid (e.g., fentanyl), which increases the risk of respiratory depression [48]. In this setting, the recommendation is not to exceed 0.5 mcg/kg of fentanyl in any single dose when given with etomidate and to keep the total amount of fentanyl to a minimum.

2.6.4. Adverse Effects

Potential side effects of etomidate include myoclonus, adrenal suppression, nausea, and vomiting.

Transient intravenous pain on injection, especially into peripheral and small vessels, is common. Strategies prior to the IV injection of lidocaine can be carried out [83].

Myoclonus, often related to subcortical disinhibition, can occur in up to 80% of patients receiving procedural sedation and analgesia (PSA). The severity of myoclonus can be dose-dependent and ranges from mild and transient to severe enough potentially to disrupt a procedure. However, severe myoclonus is rarely observed during PSA.

When severe myoclonus does occur, the recommended management is the administration of midazolam at doses of 1 to 2 mg intravenously, repeated approximately every 60 s until the myoclonus subsides. Research indicates that pretreatment with agents such as midazolam, dexmedetomidine, fentanyl, propofol, or ketamine can significantly reduce both the incidence and severity of myoclonus following a bolus dose of etomidate. These pretreatments may help stabilize neural activity and prevent the excitatory effects that lead to myoclonus [83,91].

Etomidate, when administered via continuous infusion, is known to cause adrenal insufficiency. However, reductions in plasma cortisol concentrations have also been observed in patients receiving even a single induction dose [92]. The clinical significance of these transient reductions in cortisol during procedural sedation and analgesia (PSA) with etomidate remains uncertain, and to date, no complications related to adrenal suppression have been definitively reported in such scenarios [93–95].

The incidence of postoperative nausea and vomiting (PONV) is noted to be higher when etomidate is used for both the induction and maintenance of anesthesia, especially in short procedures [83]. This is a consideration that may influence the choice of anesthetic in settings where PONV is a particular concern.

Despite these considerations, etomidate's brief duration of action is associated with a reduced risk of adverse respiratory events, making it a generally safe option for PSA. There

have been no serious complications reported with its use. Nonetheless, clinicians must always be prepared to support the patient's airway and breathing in case of respiratory compromise during its administration.

2.7. Nitrous Oxide

Nitrous oxide (N_2O), commonly known as "laughing gas," is an analgesic and anxiolytic agent that induces CNS depression and euphoria, yet it has minimal impact on respiratory function. As an ultra-short-acting agent, it features an immediate onset of action and quick recovery due to its low blood solubility, providing effective analgesia, anxiolysis, and sedation. This rapid onset and recovery make it a popular choice for various medical settings [96].

Nitrous oxide is versatile, used for general anesthesia, procedural sedation, and dental anesthesia—particularly in pediatric care. It is also employed to manage severe pain, proving especially useful in obstetrical wards or emergency departments, where its potent analgesic properties can significantly ease patient discomfort [96].

Although generally safe for children and found to be effective in various settings, studies indicate that nitrous oxide may not always provide adequate analgesia for more intensely painful procedures, such as fracture reduction. This limitation suggests that while N_2O can be beneficial for many situations, alternative or supplemental analgesics may be necessary for procedures involving more significant pain.

2.7.1. Pharmacology and Pharmacokinetics

Nitrous oxide (N_2O) is an odorless, colorless, non-flammable gas and stands as the least potent inhalational anesthetic available. To reach one minimum alveolar concentration (MAC)—a standard measure of anesthetic potency—it requires a concentration of 104%, which is practically unachievable. Therefore, it is often administered in combination with more potent and volatile anesthetics to enhance its efficacy.

The mechanisms of action for nitrous oxide are diverse, involving multiple supraspinal and spinal sites. Its anesthetic effects are primarily mediated through the non-competitive inhibition of NMDA receptors in the central nervous system. For its analgesic effects, which are comparable to those of morphine, nitrous oxide facilitates the release of endogenous opioids that act on opioid receptors, providing significant pain relief. Additionally, the activation of GABA-A receptors contributes to its anxiolytic properties, helping to reduce anxiety.

Beyond these effects, nitrous oxide uniquely stimulates central sympathetic activity, which helps maintain blood pressure, systemic vascular resistance, and cardiac output. It also promotes increased cerebral blood flow and consequently can raise intracranial pressure. These hemodynamic and cerebral effects make nitrous oxide a versatile tool in medical anesthesia, though they also necessitate caution in patients with conditions affected by changes in blood flow or intracranial pressure [97].

Compared to other anesthetic agents, nitrous oxide (N_2O) is noted for its minimal effects on the respiratory and cardiovascular systems. While it does lead to a decrease in tidal volume and an increase in respiratory rate, it largely preserves overall minute ventilation, ensuring that the total volume of air breathed per minute does not decrease significantly. This makes it a safer option in terms of maintaining respiratory function during anesthesia. In terms of its impact on the cardiovascular system, nitrous oxide can cause direct myocardial depression. However, this potential negative effect is typically offset by its ability to stimulate sympathetic nervous system activity. The resultant sympathetic stimulation tends to counterbalance the myocardial depression, resulting in a minimal net effect on cardiac function. This dual action allows nitrous oxide to maintain more stable hemodynamics compared to other anesthetics that may cause a more significant suppression of heart function. Another distinct characteristic of nitrous oxide is that unlike many other volatile anesthetics, it lacks muscle relaxation properties. This absence can be a

consideration in surgeries or procedures where muscle relaxation is required; in such cases, additional agents would be necessary to achieve this effect [98].

The pharmacokinetic properties of nitrous oxide (N_2O) are notably efficient, making it a unique agent among inhaled anesthetics. After inhalation, N_2O is rapidly absorbed through the alveoli, with its onset of action occurring within 2 to 5 min [99]. This swift absorption is due to its rapid diffusion across the alveolar basement membranes, a feature that distinguishes it from other gases. One significant effect of nitrous oxide's rapid absorption is the "second gas effect." As N_2O quickly exits the alveoli, it causes an increased concentration of the remaining alveolar gases. This increased concentration accelerates the uptake of N_2O into the blood and speeds up the onset of anesthesia, enhancing the overall efficiency of the anesthetic process. Regarding metabolism, nitrous oxide undergoes a unique pathway where it is metabolized through reduction by anaerobic bacteria located in the gut. However, this metabolic process is minimal, and the vast majority of N_2O is eliminated unchanged via the lungs. This direct exhalation through the respiratory system contributes to its quick elimination from the body, allowing for a rapid recovery from its effects [96].

2.7.2. Administration

Nitrous oxide administration occurs via inhalation using a simple face mask, laryngeal mask airway, or an endotracheal tube.

For surgical procedural sedation and analgesia (PSA) and dental procedures, nitrous oxide (N_2O) is typically administered in combination with oxygen to ensure safety and efficacy. The usual practice involves initially providing the patient with 100% oxygen at the beginning of the procedure to saturate their system with oxygen. Subsequently, the flow of oxygen is reduced, while the concentration of nitrous oxide is gradually increased to the desired level. It is important to note that there are no standard therapeutic levels for the use of nitrous oxide, but its concentration in the gas mix should generally not exceed 50% to avoid potential side effects and ensure sufficient oxygenation [100]. The typical flow rate of the gas mixture ranges from 5 to 6 L per minute, which is comfortable for most patients.

However, the use of nitrous oxide is contraindicated in certain conditions due to specific risks. These include the following:

- Chronic obstructive pulmonary disease (COPD), where decreased respiratory function could be further compromised;
- Severe emotional disturbances or drug-related dependencies, which could exacerbate underlying conditions;
- The first trimester of pregnancy, due to potential risks to fetal development;
- Patients undergoing treatment with bleomycin sulfate as N_2O can potentially exacerbate pulmonary toxicity;
- Recent tympanic membrane graft surgery as the gas can expand in enclosed spaces, causing pressure effects;
- MTHFR (methylenetetrahydrofolate reductase) deficiency as N_2O can inactivate B12 and exacerbate symptoms of this genetic disorder [96].

No specific information about dose adjustments for patients with renal or hepatic impairment is available.

2.7.3. Adverse Effects

The use of nitrous oxide (N_2O), while generally safe, is associated with several potential adverse effects that require careful management to prevent complications:

Diffusion Hypoxia: This occurs after the discontinuation of N_2O, when the concentration gradient between the gases in the lung alveoli and the bloodstream rapidly reverses. This can lead to a quick dilution of oxygen in the alveoli, resulting in hypoxia. To counteract this effect, it is recommended to administer 100% oxygen immediately following the cessation of nitrous oxide.

Respiratory Depression: Although N_2O has minimal direct respiratory effects, it can enhance the respiratory depressant effects of other sedatives, hypnotics, or opioids if they are used concurrently. This potentiation requires the careful monitoring and adjustment of dosages when combining these agents [96].

Subacute Myeloneuropathy: Chronic abuse or prolonged exposure to nitrous oxide can lead to a severe but potentially reversible form of myeloneuropathy. This condition is characterized by axonal sensorimotor neuropathy and is a significant risk primarily for individuals who misuse N_2O [101].

Nausea and Vomiting: Nitrous oxide is associated with a higher risk of postoperative nausea and vomiting (PONV) compared to some other anesthetic agents. This risk can be mitigated with the use of prophylactic anti-emetics administered before or during the use of nitrous oxide.

Hyperhomocysteinemia: N_2O can irreversibly oxidize the cobalt atom in vitamin B12, leading to a reduction in the activity of B12-dependent enzymes, such as methionine synthase. This effect can result in elevated homocysteine levels in the blood and may contribute to the development of megaloblastic anemia [96].

2.8. Remimazolam

Remimazolam is a novel short-acting benzodiazepine approved for intravenous procedural sedation and general anesthesia [102]. In particular, remimazolam is indicated for the induction and maintenance of PS in adults undergoing procedures lasting 30 min or less.

Compared to other benzodiazepines, it offers several advantages that make it a promising sedative for a broad spectrum of patients, including those who are critically ill. Its fast onset and short, predictable duration of sedative action allow for precise control over sedation levels, which is particularly valuable in settings requiring rapid adjustments to patient responsiveness, such as procedural sedation or intensive care. Additionally, remimazolam has a short recovery time, meaning patients can awaken more quickly once sedation is discontinued. This feature is beneficial in both medical procedures and critical care, where rapid patient assessments and mobilization may be necessary. Importantly, remimazolam shows rare accumulation in the body after long-term infusion, a significant advantage in critically ill patients who may require extended periods of sedation. Compared to other benzodiazepines, remimazolam is associated with less serious side effects. This safety profile, coupled with its effective sedative properties, supports its use in a wide range of clinical settings, enhancing patient care by providing effective and manageable sedation with fewer complications [102].

2.8.1. Chemical Structure

Remimazolam is a novel drug within the benzodiazepine class, designed by combining properties from two well-known anesthetic agents: midazolam and remifentanil. This innovative approach aims to leverage the strengths of each drug to create a more effective and manageable sedative. The chemical structure of remimazolam is similar to that of midazolam, but it has been specifically modified to allow for an organ-independent metabolism. This modification means that remimazolam is metabolized by tissue esterases rather than relying on liver enzymes for its breakdown and elimination. This feature is particularly beneficial as it allows for consistent and predictable pharmacokinetics, regardless of variations in liver function, which can be especially important in patients with impaired hepatic function or the elderly. The design of remimazolam ensures that it has a rapid onset and a short duration of action, similar to remifentanil, yet maintains the sedative and anxiolytic properties typical of midazolam. This organ-independent metabolism reduces the risk of drug accumulation and side effects, making remimazolam an advantageous option for sedation in a wide range of medical settings, including surgeries and intensive care units where varying degrees of liver function can affect drug efficacy and safety.

It is an ultra-short-acting drug, with a faster recovery compared to midazolam [103] that achieves peak sedation within 3 to 3.5 min after IV administration; this characteristic makes remimazolam desirable for use during short procedures.

Like other benzodiazepines, remimazolam exerts its therapeutic action by potentiating the effect of gamma-aminobutyric acid on GABA-A receptors, the main inhibitory neurotransmitter receptors in the mammalian brain, as a positive allosteric modulator.

2.8.2. Pharmacokinetics and Pharmacodynamics

Remimazolam is rapidly distributed upon intravenous administration, and it is >91% protein-bound in plasma, primarily to serum albumin. Following intravenous administration, its distribution half-life is 0.5–2 min, and the terminal elimination half-life is 37–53 min.

Remimazolam does not appear to undergo biotransformation via hepatic cytochrome P450 enzymes, nor does it induce or inhibit these enzymes. Thus, clinically significant metabolic drug interactions are unlikely [102].

Remimazolam is susceptible to non-specific tissue esterases, and it is rapidly metabolized into its pharmacologically inactive metabolite CNS-7054 [103], which has a 300-fold smaller affinity for GABA-A receptors compared to the parent drug.

In healthy subjects, about 80% of the administered dose is excreted in the urine as CNS-7054.

No significant effects on the PR interval and QRS duration or on cardiac repolarization were demonstrated during PSA and anesthesia [104]. Also, no clinical effects on heart rate, blood pressure, and respiratory rate were seen [102].

2.8.3. Administration

For procedural sedation in adults, the administration for remimazolam is IV at the dose of 5 mg over 1 min; for maintenance, supplemental doses of 2.5 mg should be administered over a 15 s time period after at least two minutes.

For the initial dose, in ASA class III and IV patients, the recommendation is to administer it in a range from 2.5 mg to 5 mg IV over 1 min based on the clinical condition, followed by 1.25 mg to 2.5 mg following necessity, to maintain PSA [105].

Liver dysfunction can result in elevated serum levels of remimazolam. Therefore, patients with severe hepatic impairment should be carefully titrated to effect.

The pharmacokinetics of remimazolam appear to be stable across different populations, indicating its wide applicability in clinical settings. Studies have shown no significant differences in the pharmacokinetics of remimazolam between healthy individuals and patients with end-stage renal disease. This finding is particularly important because it suggests that remimazolam can be safely used in patients with varying degrees of renal impairment without the need for dose adjustment. This attribute makes remimazolam a versatile sedative as it reduces concerns about the accumulation of the drug and its metabolites in patients whose renal function is compromised. Despite the general stability in its pharmacokinetics across different ages, ASA classes, sexes, and races, it is still recommended to use lower doses of remimazolam infusion for specific patient groups who are considered more vulnerable, such as the fragile elderly or patients with significant systemic diseases (ASA class 3 and above). This cautious approach is advised to manage potential risks and ensure safety, even though the drug's pharmacokinetics itself may not vary with these factors [102].

2.8.4. Adverse Effects

Remimazolam offers several advantages due to its minimal impact on cardiovascular and respiratory systems, making it an appealing option for sedation, especially in medically complex or fragile patients. It is associated with a low risk of causing hypotension or respiratory depression, which are common concerns with other sedative agents. Additionally,

the stability in blood pressure and heart rate during its use underscores its safety profile, particularly in settings where cardiovascular stability is crucial.

Another benefit of remimazolam is its lack of severe injection site pain, a common side effect with some other sedatives like propofol. Interestingly, pretreatment with remimazolam has been shown to reduce both the incidence and intensity of propofol-induced injection pain, enhancing patient comfort when these drugs are used in combination.

The pharmacokinetics of remimazolam are also advantageous. Due to its organ-independent metabolism—primarily through hydrolysis by tissue esterases rather than the liver or kidneys—it exhibits predictable first-order pharmacokinetics. This means that the effect of remimazolam is directly proportional to the dose administered, allowing precise control over sedation levels without concern for cumulative effects or prolonged sedation, even with long-term infusions or higher doses. This dose-dependent and predictable duration of sedation allows clinicians to tailor sedation levels closely to patient needs, ensuring safety and efficacy throughout medical procedures [106].

Remimazolam does not cause of fatal or severe adverse effects during the infusion phase, and if needed, its effects can be reversed by flumazenil (Table 1).

Table 1. Summary of pharmacological agents used in procedural sedation in the emergency department.

Drug	Dosage	Route	Indications	Special Considerations
Propofol	0.5 to 1 mg/kg IV	IV	General sedation, anesthesia induction	Monitor for hypotension
Ketamine	0.5 to 2 mg/kg IV	IV/IM	Sedation, pain management	Monitor for emergence reactions
Dexmedetomidine	0.2 to 1 mcg/kg/h IV	IV	Sedation, ICU use	Caution in hepatic impairment
Fentanyl	1 to 1.5 mcg/kg IV	IV	Pain relief, sedation	Use adjusted body weight in obese
Midazolam	0.02 to 0.03 mg/kg IV	IV/IM/nasal	Anxiolysis, sedation	Reduced dose in elderly
Etomidate	0.1 to 0.15 mg/kg IV	IV	Anesthesia induction, short procedures	Monitor kidney function, risk of myoclonus
Nitrous Oxide	Inhalation, varies	Inhaled	Sedation, analgesia, dental procedures	Minimal respiratory impact
Remimazolam	2.5 to 5 mg, IV	IV	Sedation, critically ill patients	Minimal cardiovascular and respiratory effects, dose-dependent

3. Techniques and Monitoring in Procedural Sedation and Analgesia

Procedural sedation and analgesia (PSA) in the emergency department must always be conducted under the direct supervision of an ED practitioner who is readily available and proficient in managing emergency situations, including airway management and resuscitative maneuvers, to ensure the highest level of patient safety and care.

Sedation and analgesia comprise a continuum of states, ranging from minimal sedation (anxiolysis) through general anesthesia. However, it is not always possible to maintain patients at a pre-determined sedation depth.

Sedation levels [1,2,107] can be divided into (Table 2) the following:

- Minimal: This entails a drug-induced state of diminished anxiety, during which patients are conscious and respond purposefully to verbal commands or light tactile stimulation. Cognitive function and coordination may be impaired, and ventilatory and cardiovascular functions are unaffected. In the emergency department, this level is most often achieved through inhaled mixtures of nitrous oxide and oxygen.
- Moderate: This entails a drug-induced state of depressed consciousness, during which patients retain the ability to respond purposefully to verbal commands or light tactile stimulation. During moderate sedation, no interventions are normally required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained. Event amnesia will frequently occur under moderate sedation levels. In the emergency department this level is most often achieved using a combination of opioids and benzodiazepines.
- Deep: This entails a drug-induced state of depressed consciousness, during which patients are not easily aroused and may respond only to noxious stimuli. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be

inadequate. Cardiovascular function is usually maintained. Nonetheless, deep sedation carries the risk for the loss of airway patency, the depression of protective airway reflexes and of the respiratory centers, and the depression of the cardiovascular system.

Table 2. Levels of sedation.

Level of Sedation	Consciousness and Responsiveness	Airways and Ventilation	Cardiovascular System
Minimal	Patient is conscious Response to verbal stimuli	Preserved	Unaffected
Moderate	Depressed Response to verbal or tactile stimuli	Preserved	Usually unaffected
Deep	Depressed Response to repeated or painful stimuli	May require assistance	Affected

However, to more accurately assess and manage the depth of sedation, implementing standardized sedation scales such as the Richmond Agitation–Sedation Scale (RASS) and the Sedation–Agitation Scale (SAS) is crucial. These scales provide a consistent method to quantify sedation levels, allowing healthcare providers to tailor sedation more precisely to individual patient needs and to swiftly recognize and address any deviations from the intended sedation depth, thus enhancing patient safety during procedural sedation (Table 3).

Table 3. RASS and SAS scale.

RASS Score	RASS Description	SAS Score	SAS Description
+4	Combative	7	Dangerous agitation
+3	Very agitated	6	Very agitated
+2	Agitated	5	Agitated
+1	Restless	4	Calm and cooperative
0	Alert and calm	3	Sedated
−1	Drowsy	2	Very sedated
−2	Light sedation	1	Unarousable
−3	Moderate sedation		
−4	Deep sedation		
−5	Unarousable		

A further separate sedation category is defined by dissociative sedation, a trancelike cataleptic state characterized by profound analgesia and amnesia, with the retention of protective airway reflexes, spontaneous respiration, and cardiovascular system stability. In the emergency department, this level is most often achieved through the use of ketamine [1–3].

The initial drug dose should be determined after having performed a careful pre-sedation assessment of the patient's status. Further titration of the selected drug(s) to optimal effect is critical to safely achieving the established sedation endpoint, thereby minimizing the risk of inadvertent over-sedation.

Whenever feasible, a pre-sedation assessment should be conducted, and it should comprise a focused medical history, physical examination with airway evaluation to rapidly identify a potentially difficult airway, a review of comorbidities, medications and allergies, and an inquiry about previous sedation, anesthesia, and surgery history.

The pre-sedation assessment will allow one to identify possible risks that will lead to a modification of the perioperative care in order to reduce the likelihood of adverse events and develop an appropriate sedation plan [4–7].

The pre-sedation assessment should be focused on risk identification, risk stratification, risk modification (where possible), and residual risk communication, expressed as an appropriate risk management plan [5].

Many sedation guidelines reference the American Society of Anesthesiologists (ASA) physical status classification system as a basis for risk stratification. However, the ASA score, which was initially devised exclusively for adult patients, was never intended as a risk predictor, and there is increasing evidence that scoring using the ASA classification within and between disciplines can be inconsistent [8–10,108].

The ASA physical status classification system was devised in order to offer clinicians a simple categorization of a patient's physiological status and allows one to divide patients into five classes, from ASA1 being the typical healthy patient to ASA5 being a moribund patient who is not expected to survive without the operation. A further level was added later on, the ASA6, which corresponds to a brain-dead patient whose organs are being removed for donor purposes [109,110].

The ASA classification on its own is, however, not a predictor of operative risk, and a careful pre-sedation assessment remains fundamental.

Rather than age or ASA status, some guidelines use red flags (e.g., for increased risk of failed sedation, risk for airway obstruction, risk of failure to provide effective manual ventilation, or for other adverse outcomes) as a prompt for clinicians to consider referral to different providers [111].

Some red flags for potential complications during PSA, which should be identified during the pre-sedation assessment, include risk factors such as trauma, a decreased level of consciousness, extreme obesity (BMI > 95% for age and sex), pregnancy, or bowel motility dysfunction (Table 4).

Table 4. Red Flags and Management Tips for each condition.

Red Flag	Management Tips
Severe comorbidities	Assess overall risk and consider consultation with specialists.
Trauma	Ensure stabilization of trauma areas and monitor closely.
Decreased level of consciousness	Verify airway management resources are immediately available.
Pregnancy	Assess gestational age and potential impacts of sedation.
Obesity	Calculate dosages based on ideal body weight, monitor respiratory status closely.
Bowel motility dysfunction	Evaluate for signs of bowel obstruction or severe constipation before sedation.
Recent alcohol consumption	Consider delaying sedation if possible, monitor for respiratory depression.
Recent substance use	Evaluate for withdrawal risk and interactions with sedative agents.
Potential difficult ventilation, or airway management	Prepare for advanced airway management techniques and equipment.

In these cases, a careful evaluation should be carried out before the administration of sedatives, and preference should be given to a lighter level of sedation or the administration of agents with less risk of depressing protective airway reflexes.

One of the main worries when performing PSA is the need to reduce the probability of pulmonary aspiration of gastric contents. The depression of upper airway reflexes which occurs during anesthesia is indeed a major risk factor for the development of aspiration pneumonia.

The level of sedation that one aims for during PSA is generally moderate to deep sedation. Therefore, the majority of patients maintain respiratory effort and the protection of airway reflexes at these depths of sedation [2]. However, shifting to deeper levels of sedation may occur with some patients.

Pre-procedural fasting cannot be considered routinely applicable in the ED. The American College of Emergency Physicians (ACEP) does not consider recent food intake as a contraindication for PSA in the ED [6]. Previous studies, which studied the incidence of aspiration during ED PSA, concluded that routine fasting is not mandatory prior to procedural sedation and analgesia in the emergency department [13,112]. There is therefore

no clear evidence that non-compliance with elective fasting guidance increases the risk of aspiration or other adverse events during procedural sedation in the emergency department. Nonetheless, emergency clinicians should always weigh the possible risks of sedating nonfasted patients with the benefits of and necessity for completing the procedure.

The clinician should therefore undertake a risk assessment, taking into account dynamic risk factors for aspiration (such as alcohol ingestion), established risk factors (such as obesity, pregnancy, and known bowel dysfunctions), the proposed sedation agent, and the procedure to be performed [1].

Another critical sedation-related risk is the failure to maintain a patent airway and the need to support or assist inadequate spontaneous ventilation, particularly when there is an inadvertent transition towards deeper levels of sedation and unconsciousness [1]. The pre-sedation assessment should therefore focus on specific ways to predict airway and breathing-related risks.

Different risk factors have been identified as predictors of a difficult airways.

A study published in 2000 observed an incidence of difficult mask ventilation (DMV) in 5% of the patients in a general adult population. This study also recognized five criteria as independent factors for a DMV (age older than 55 yr, body mass index > 26 kg/m^2, beard, lack of teeth, and history of snoring), and the presence of two of these risk factors indicated a high likelihood of DMV (sensitivity, 0.72; specificity, 0.73) [113].

Another study evidenced that DMV is more common in obese patients, and predictors for a difficult mask ventilation include a reduced mandibular protrusion, a higher Mallampati score [114], and a greater neck circumference [115].

Another useful tool to predict difficult airways is the DIFFMASK score, proposed by Lundstrøm et al., which allows one to predict difficult facemask ventilation during general anesthesia using ten independent criteria (sex, age, BMI, a history of previous difficult tracheal intubation, thyromental distance, Mallampati score, the presence of a beard, a history of sleep apnea or snoring, and neck radiation changes) [116].

The clinician performing PSA should be able to rescue a patient who becomes inadvertently over-sedated and, where necessary, maintain an airway and establish satisfactory ventilation and oxygenation through alternative supportive oxygenation and ventilation techniques should tracheal intubation fail and bag-mask ventilation prove difficult or impossible.

Monitoring

Respiratory depression and hemodynamic instability are considered the most common and important adverse events of PSA.

PSA providers must therefore be well trained in recognizing and treating life-threatening complications that may arise during sedation and should be proficient in antidote administration (i.e., flumazenil, naloxone), advanced airway management, IV cannulation, and cardiac arrest management (advanced life support) [6,13]. Advanced airway equipment, resuscitative medications, and vascular access supplies should be easily accessible when performing PSA.

The main risks for complications linked with moderate sedation and analgesia are dependent on the drugs used, which may lead to problems on the cardiovascular or respiratory systems. These complications may be prevented when detected and treated in a timely manner, and this is why monitoring is of fundamental importance during procedural sedation and analgesia.

Patient monitoring should include the following:

- The monitoring of ventilation, oxygenation, and gas exchanges.

This is usually assessed through clinical signs, capnography, and pulse oximetry.

Expired carbon dioxide monitoring is valuable to diagnose the simple presence or absence of respirations, airway obstruction, or respiratory depression.

Multiple studies showed that the use of continuous end-tidal carbon dioxide monitoring (i.e., capnography) is associated with a reduced frequency of hypoxemic events

when compared to monitoring without capnography, so end-tidal carbon dioxide (ETCO2) monitoring has been demonstrated to be useful in the early recognition of hypoventilation and providing advanced warning of hypoxic events [6,7,117–121]. In patients receiving supplemental oxygen, capnography facilitates the recognition of apnea or airway obstruction several minutes before the situation would be detected just by pulse oximetry [12,13]. Abnormalities in capnography, however, are frequently transient and have not been shown to be related to adverse outcome or the requirement for intervention, and it is important to note that the exact value of expired carbon dioxide is less important than the simple assessment of continuous respiratory gas exchange.

In 2012, the Royal College of Anaesthetists and the College of Emergency Medicine published new guidelines in the UK, which included a recommendation for the routine use of ETCO2 monitoring on all patients undergoing procedural sedation in the ED [19].

Capnography should be available for minimal and moderate sedation and is strongly advised for moderate sedation in both adults and children and in ASA 3 or ASA 4 patients [1].

Oxygen supplementation in both moderate and severe sedation can be useful in order to prevent any possible adverse effect. The use of oxygen during procedural sedation is encouraged especially for at-risk patient groups (e.g., ischaemic heart disease) and those undergoing deep sedation procedures (an increased risk of short periods of apnea) [2]. Previous guidelines express a consensus on the possibility to administer supplemental oxygen during moderate procedural sedation/analgesia unless specifically contraindicated for a particular patient or procedure [6,19].

It is, however, important to note that although oxygen supplementation during PSA reduces hypoxemia rates, it can obscure the identification of other adverse effects such as hypoventilation and upper respiratory tract obstruction [122].

- The monitoring of the cardiovascular system.

This is usually assessed through repeated non-invasive measures of blood pressure (5 min interval), and a continuous monitoring of heart rate; continuous electrocardiographic monitoring may be useful when performing moderate sedation in patients with clinically significant cardiovascular disease or those who are undergoing procedures where dysrhythmias are anticipated.

- The monitoring of the patient's level of consciousness.

This is usually monitored during PSA by clinical observation, which is performed by judging a sedated patient's response to increasing levels of stimulation [123]. Monitoring the depth of sedation, typically by assessing the patient's response to verbal commands or stimulation, will allow one to detect whether the patient is experiencing a deeper than intended sedation. The loss of patient response to stimulation or verbal commands indicates that the loss of airway reflexes and respiratory and/or cardiovascular depression are likely, and sedation should be lightened accordingly.

As the risk of adverse events increases with the depth of sedation induced, the frequent monitoring of the level of consciousness is recommended. The most frequently cited scales for sedation and responsiveness monitoring are the Observer's Assessment of Alertness/Sedation Scale, the Richmond Agitation–Sedation Scale, and the Ramsay Sedation Scale [124,125].

The monitoring of verbal response may be difficult in some special populations, for example, small children and patients with intellectual disabilities or language difficulties. Devices for the monitoring of the depth of anesthesia (like the processed electroencephalogram-based depth of anesthesia monitoring devices) provide an alternative method to monitor the level of consciousness that can be used in addition to clinical observation. Research suggests that depth of anesthesia monitors may reduce intraoperative awareness and may predict anesthesia outcomes in specific high-risk populations and should be used as the main form of sedation assessment in adult patients who are in deep levels of sedations and for which subjective sedation assessments are unobtainable in these patients. Supplemental

technologies to monitor the depth of sedation are, however, not currently advised for procedural sedation and analgesia in the setting of the emergency department when clinical observation can allow the appreciation of the depth of sedation [126–128].

Following procedural sedation and analgesia, monitoring should be continued until the patient has reached back a baseline level of consciousness and is no longer at risk for the compromission of airway patency and cardiorespiratory depression [6].

4. Special Populations Considerations

Higher-risk age groups for procedural sedation and analgesia include both pediatric patients and elderly patients (Table 5).

Table 5. Specificity of the geriatric and pediatric populations.

The Elderly Patient	The Pediatric Patient
Risk factors: - comorbidities - polymedication - increased sensitivity to sedatives - limited physiological reserve	Risk factors: - uncooperative behavior - different anatomy - slower drug clearance - limited physiological reserve
Possible complications: - cardiovascular or respiratory disfunction - drug interactions - deeper than intended sedation	Possible complications: - deeper than intended sedation - drug-induced loss of airway patency - difficult airway management
Precautions: - pre-sedation assessment - pre-oxygenation - smaller boluses - increased redosing interval - proper monitoring	Precautions: - pre-sedation assessment - assessing cognitive and developmental status of the patient - airway assessment - availability of proper equipment adapted to pediatric patients.

Emergency physicians must recognize these higher-risk patients and proceed with sedation only if their level of expertise and experience justifies doing so.

4.1. Geriatric Population

Elderly patients are more likely to be at risk from sedation given that they often have many have comorbidities, increased sensitivity to sedatives, and limited physiological reserve.

Elderly patients are more at risk during procedural sedation and analgesia because they are more prone to cardiorespiratory decompensation when given sedative or analgesic drugs.

The elderlies are usually more sensitive to many drugs than younger patients and generally require lower milligram-per-kilogram doses to reach the same depth of sedation of younger patients. Elderly patients have an increased variability in drug response and decreased requirements for most anesthetic drugs. Elderly patients have an increased redosing interval, and the cautious administration of sedation will help reduce the risks associated with sedation in the elderly.

When performing procedural sedation in an elderly patient, due care needs to be exercised in relation to drug choice, dosage, and interactions (analgesics, sedatives, and the patient's regular medications) as well as the need to take into account the often delayed onset time for sedation agents in this group. This group of patients are much more likely to have comorbidities which impact their respiratory and cardiovascular functional reserves, and these factors, as well as the patient's regular medications, need to be considered during PS decision making, especially when considering fluid and oxygen supplementation [2].

When investigating whether the elderlies (>75 y.o) actually constitute a high-risk population, a prevalence of adverse events of 2.6% in the population studied was detected,

without adverse outcomes. The main adverse events were respiratory complications (hypoxemia and apnea) and cardiovascular problems, such as hypotension [42]. According to these results, the prevention of adverse events in the elderly may include the administration of a smaller drug bolus, as well as quality pre-oxygenation which could help in protecting most apneic patients from hypoxemia.

When taking the appropriate precautions adjusted for the age of the population, several further studies had different findings for what concerns the relationship between increased age and increased risk of adverse events (mainly linked to respiratory and cardiovascular events), with studies failing to demonstrate a statistically significant incidence of complication rates in patients of at least 65 years of age when corrected doses of sedatives are administered [7,129,130].

In summary, important precautions to be adopted in the geriatric population include the following: a careful pre-sedation assessment taking into consideration possible drug interactions and notable comorbidities, the administration of smaller doses of sedatives with an increased redosing interval, proper monitoring, and preoxygenation to avoid hypoxemia in the case of apnea.

4.2. Pediatric Population

Sedation in children is often administered to relieve pain and anxiety as well as to modify behavior (e.g., immobility) to allow the safe completion of a procedure. A child's ability to control his or her own behavior to cooperate for a procedure depends both on his or her chronologic age and cognitive/emotional development.

Patients of the pediatric population possess physiological and anatomical considerations that demand supplementary knowledge and skills.

Infants and children under 6 months of age are at higher risk from sedation procedures because of slower drug clearance, decreased protein binding, increased drug passage across the blood–brain barrier, and a lower ratio of lean to total body mass [131,132].

Children under 6 years of age are not only at a higher risk for sedation-related adverse events than an older cohort due to the sedating medications' effect on the respiratory drive, airway patency, and protective airway reflexes [133,134], but because they are less mature and less cooperative, this group is also more at risk of deeper than intended sedation [135–137].

The pre-sedation risk assessment should, in addition to the items already covered for the adult population, include any history of comorbidities, congenital anomalies, and malformations, which could pose a risk for airway management and the cardiovascular stability, and consideration should be given to the preparation of parents and family to the sedation/analgesia.

It is also important to identify children who could be at a higher risk of laryngospasm or children at risk of airway obstruction (in the case of obstructive sleep apnea or sleep-disordered breathing) and syndromes associated with airway difficulties [1]. A focused airway examination for large and potentially obstructive tonsils (most common, 2–6 years) or anatomic airway abnormalities that might increase the potential for airway obstruction is of foremost importance to ensure the safety of the procedure.

As the American Society of Anesthesiologists (ASA) physical status classification system was devised for adult patients, the NICE guidelines have been created for pediatric patients [138].

According to the NICE guidelines, pediatric patients of corresponding ASA grade 3 and above and infants (including neonates) are at greater risk for complications during sedation, and therefore, the advice of a specialist should be sought when considering PSA in this special population [19].

Similarly to the adult population, guidelines for pediatric PSA agree on the fact that procedural sedation may be safely administered to pediatric patients in the ED who have had recent oral intake [139]. Once again, the risk benefit ratio of performing PSA in nonfasted patients should also be weighed before starting the procedure.

No additional monitoring equipment is specifically required in the pediatric population. Capnography should be considered for all pediatric patients undergoing PSA as it may allow one to detect hypoventilation and apnea earlier than pulse oximetry and/or clinical assessment alone [12,13]. This might be especially useful in the pediatric population which may not have the same respiratory reserve as the adult population and in which deterioration may occur more rapidly.

Practitioners performing PSA in the pediatric population must be able to recognize the various levels of sedation and have the skills and age- and size-appropriate equipment necessary to provide appropriate cardiopulmonary support if needed.

In summary, important precautions to be adopted in the pediatric population include the following: a careful pre-sedation assessment taking into consideration the psychological and developmental status of the patient as well as conditions which put the infant more at risk for a difficult airway, the choice of drug and its dose based on the age of the patient, and the availability of proper equipment adapted to pediatric patients. Moreover, when considering PSA in the emergency department for children younger than 6 months old and children with corresponding ASA scores higher than 2, specialist advice and assistance is needed.

5. Collaboration in Procedural Sedation and Analgesia

As the fields of application of procedural sedation continue to expand, the imperative of a mandatory collaboration and the adequate training of all practitioners, regardless of their educational background, becomes extremely evident. In accordance with the latest guidelines promulgated by the American Society of Anesthesiologists in 2018 [6], the need for a multidisciplinary teamwork focused on patient evaluation, preparation, monitoring, and recovery support is crucial for the successful implementation of a high-quality sedation process.

However, the goal of a tailored procedural sedation adequate for the needs of the patient still remains far from the current reality: concerns over the safety of sedation procedures keep emerging, highlighting the absence of a standardized curriculum. Many of the complications that emerged in past surveys [140,141] were mostly related to adverse drug responses, in particular in pediatric sedation [142], for which the spectrum of available drugs is extremely narrow; the majority of adverse response's complications could be avoided if detected and treated in a timely manner. That is only achievable with the presence of an individual responsible for the patient's monitoring.

Therefore, cooperation among different healthcare specialists who have received formal training is imperative for optimal outcomes. Recent reviews spanning nursing [143], anesthesiology, emergency medicine [144], and pediatric emergency medicine underscore the necessity of a multidisciplinary standard in procedural sedation, especially for those procedures conducted outside of the operating room [142]. Thus, the escalating demand for such procedures driven by the increased utilization of diagnostic tools and procedural treatment methods requires a new approach to specialist training [145].

A crucial step to decrease sedation-related adverse events includes a globally unified approach and precise decision-making criteria for involving an anesthesiologist. Sedation is nowadays used for an ample range of procedures in various specialties, many of which are performed by non-anesthesiologists, such as dental care, cardiology, gastroenterology [146], and emergency medicine. The techniques used in these different fields are effective for most of the patients. However, the limitations of setting, comorbidities, and advanced/multiple drug use suggest the absolute need of a specialized and adequately trained individual responsible for monitoring the patient [147].

As the depth of sedation increases, the essential requirement of strict monitoring follows: according to the previously cited Guidelines of the American Society of Anesthesiologists [6], the recommendations for patient evaluation consider the monitoring of the level of consciousness, of respiratory and ventilation, and of hemodynamic functions and the contemporaneous recording of multiple parameters.

Many hospitals and institutions have decided to adopt a more conservative attitude towards the implementation of procedural sedation practices to minimize the perceived risk [144]. However, sedation-related events, especially airway events, are common but rarely result in an adverse outcome. Elderly patients, deeply sedated with short-acting agents, are particularly at risk [130]. Understanding the mechanisms of actions of sedatives will remain crucial, alongside a global data contribution for developing a unified and targeted sedation practice [148].

Moreover, emphasis should be placed on shared decision making between specialists and patients to determine the intervention of an anesthesiologist for high-risk patients. The provision of a patient advice leaflet [149] describing the procedure and informing both the patient and their caregivers has proven to be a valuable communication tool.

6. Future Perspectives in Procedural Sedation and Analgesia

As the demand for minimally invasive interventions continues to rise, the future of PSA is unfolding with unprecedented opportunities and challenges. The advancements made in the development of novel drugs such as remimazolam and the introduction of innovative monitoring technologies, such as capnography, is bringing forth a paradigm shift in the domain of procedural sedation, emphasizing the need for an international discussion on the future of its training and certification, particularly in the case of non-planned situations.

In the realm of emerging drugs, remimazolam emerges as a potential game-changer in PSA practices. Its distinct pharmacokinetic profile and rapid onset of action present a promising alternative to traditional sedatives, aiming to optimize patient experience and procedural efficiency. Recent clinical trials and findings shed light on this benzodiazepine's efficacy and safety in diverse procedural settings, igniting discourse on its integration into standard PSA protocols. It distinguishes itself from other intravenous hypnotic agents, like propofol, due to its minimal propensity for causing cardiovascular depression, respiratory depression, and injection pain [150] in line with other benzodiazepines' adverse effects. The benzodiazepine antagonist flumazenil could be used to treat adverse events [105,150], not only reverting the effects of remimazolam but also contributing to expedited recovery times.

Most of remimazolam's clinical trials in procedural sedation, primarily performed in colonoscopy, upper gastrointestinal endoscopy, and bronchoscopy settings (a single report of a trial in hysteroscopy is present), demonstrate how in 70% of the procedures, an adequate level of sedation was achieved with a rapid onset and offset of sedation [105]. Given its efficacy profile, it emerges as a potentially valuable drug for high-risk patients, thanks to its low impact on cardiovascular and respiratory systems [105]. Moreover, remimazolam does not require dose adjustments in subjects with hepatic or renal impairment [151]. The effect of higher concomitant doses of fentanyl with remimazolam is still unclear [150].

Within the sphere of advancements in monitoring technologies for procedural sedation and analgesia, real-time monitoring has become a cornerstone in ensuring heightened precision and safety during sedation procedures. Cutting-edge technologies, including advanced sedation monitors and capnography, play pivotal roles in constantly assessing patient vitals and sedation depth. As we navigate through this technological frontier, the integration of improved monitoring not only enhances patient outcomes but also reshapes the very fabric of PSA practices. According to recent reviews and trials, the incidence of composite adverse events was reduced with the addition of capnography monitoring: this was mostly due to the significant reduction in mild and severe oxygen desaturation events, which may have helped to avoid the need for assisted ventilation [152,153]. Capnography use, nonetheless, was not associated with shorter recovery time in the ED [154].

Delving into the prospect of personalized medicine within the domain of procedural sedation and analgesia opens a new dimension to patient care. The concept revolves around tailoring sedation approaches based on individual patient characteristics, acknowledging the inherent variability in responses to sedative agents. Genetic factors, medical history, and other patient-specific variables play integral roles in influencing the efficacy and safety of

sedation. This personalized approach seeks to move beyond the one-size-fits-all paradigm, aiming to optimize sedation outcomes by aligning pharmacological interventions with the unique biological makeup of each patient. Ongoing research and developments in personalized medicine offer glimpses into a future where PSA practices are finely tuned to accommodate the diversity of patient profiles and settings [12].

In this evolving landscape regarding procedural sedation practice, the necessity for healthcare professionals to keep up with these innovations becomes evident. Training programs need to be recalibrated in order to incorporate the nuances of administering new drugs and implement advanced monitoring tools effectively.

What emerges, from recent surveys and reviews [155,156], is the absence of a clearly defined training pathway in all the medical specialties that should be able to manage PSA and its possible complications: all practitioners are required to be able to manage a scenario corresponding to two levels of sedation deeper than the programmed one for the procedure in order to buffer for unexpected complications. While anesthesiologists and nurse anesthetists administer anesthesia within the boundaries of the operating room, practitioners offering sedation beyond the OR setting, such as those in emergency medicine, may find a suitably trained Physician's assistant (PA) to be a cost-effective alternative for the majority of simple procedural sedation instances, allowing anesthesiologists and intensivists to focus their expertise on patients with more demanding medical needs.

The integration of critical incidence simulation in training regimens further enhances the preparedness of healthcare providers by offering realistic scenarios for refining skills in a controlled environment [156]. Simultaneously, considerations for adapting certification requirements emphasize the need for healthcare professionals to demonstrate proficiency in the application of these novel interventions.

7. Conclusions

In conclusion, the comprehensive examination of procedural sedation and analgesia (PSA) within the emergency department (ED) underscores the critical importance of this practice in facilitating a wide range of medical procedures by minimizing patient discomfort and enhancing the overall quality of care. The manuscript has highlighted the nuanced pharmacological landscape of PSA, detailing the selection, application, and potential complications associated with key sedative and analgesic agents including propofol, ketamine, dexmedetomidine, fentanyl, midazolam, etomidate, nitrous oxide, and the novel agent remimazolam. Special attention was given to the tailored approaches required for managing pediatric and geriatric populations, acknowledging their unique physiological and pharmacological considerations.

The findings reinforce the necessity of an individualized approach to PSA, rooted in a thorough pre-procedural assessment, vigilant monitoring, and readiness to address complications. This approach ensures patient safety while achieving the desired sedative and analgesic effects. Furthermore, the manuscript underscores the dynamic nature of PSA practice, driven by ongoing research and the integration of new pharmacological agents, which promise to enhance sedation safety and efficacy.

Emerging from this review is a clear mandate for emergency medicine practitioners to stay abreast of current guidelines, evidence-based practices, and advances in pharmacology. Continuous education and skill development are imperative for integrating new knowledge into clinical protocols, thereby advancing PSA practices in the ED.

Ultimately, this work advocates for the judicious application of procedural sedation and analgesia as a cornerstone of patient-centered care in emergency settings. By embracing evidence-based strategies, emergency practitioners can improve patient outcomes, reduce the psychological impact of emergency procedures, and uphold the highest standards of care in the fast-paced ED environment.

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