Physiology and Pharmacology of Epidurally Administered Drugs

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Chapter

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Katarina Tomulić Brusich, Lara Valenčić and Željka Polonijo

Abstract

In the last few decades, epidural administration of various drugs has gained popularity and widespread clinical acceptance. Epidural administration of local anesthetics and opioids has been considered "state of the art" in acute pain management (thoracic and major abdominal surgery, labor). Its advantage is that it yields profound, long-lasting, dose-dependent analgesia, leaving other sensory and motor functions intact. It facilitates early patient mobilization and ambulation and therefore reduces the risk of postoperative thromboembolism and respiratory complications. The increment in the elderly population caused an increase in musculoskeletal and spine diseases and thus, epidural steroid injections have become highly effective for chronic pain treatment. There are many factors that have an impact on drug physiology and pharmacology in the epidural space and, therefore, can modify epidural anesthesia or the expected effect of another medication. This chapter provides insight into this complex and comprehensive topic to demonstrate a predictable pattern that can provide a safe and accurate guide to clinical practice.

Keywords: epidural space, pharmacology, opioids, local anesthetics, steroids

1. Introduction

Clinical indications for epidural anesthesia and analgesia have expanded over the years. Epidural analgesia is often used as a supplement to general anesthesia for surgical procedures in pediatric and adult patients [1, 2]. It is well tolerated in patients with age-related comorbidities, such as chronic obstructive pulmonary disease, hypertension, coronary artery disease, and renal insufficiency [3, 4]. Elderly patients may benefit from decreased postoperative confusion and delirium associated with regional anesthesia if intraoperative hypotension is avoided [5].

Epidural drug administration provides analgesia in intraoperative, postoperative, peripartum, and end-of-life settings. It can be used as the primary anesthetic for surgery from the mediastinum to the lower limbs. Additionally, epidural techniques are increasingly being used for diagnostic procedures, acute pain therapy, and the management of chronic pain [6]. Epidural anesthesia reduces surgical stress response, the risk of cancer recurrence, the incidence of perioperative thromboembolic events, and, possibly, the morbidity and mortality associated with major surgery [7–9].

Aforesaid is in the ideal setting. However, epidural drug administration and its clinical effect may face many obstacles compared with subarachnoid block, since

epidural space is "virtual" and somewhat different from spinal space. Injection of the drug in a large volume is made into the region where target nerves are entrenched behind barricades and where blood flow inflicts heavy losses on the advancing local anesthetic. Furthermore, the flow of fluids in the epidural space is modified by abdominal and thoracic pressures transmitted through the intervertebral lamina. All mentioned can affect and modify drug pharmacology and clinical effect.

One of the first articles written on epidural drug physiology and pharmacology was by legendary professor Bromage, who set the cornerstone of regional anesthesia [10]. Since then, the principle has remained the same. However, new drugs were reinstated, and many randomized studies have been undertaken for a better understanding of this complex subject.

This chapter provides insight into this complex and comprehensive topic in order to demonstrate a predictable pattern that can provide a safe and accurate guide to clinical practice.

2. "Back to basics"

2.1 Anatomy of epidural space

Before pharmacology issues are discussed, it is important to regard the site of administration and relevant anatomy in some detail. The vertebral column has 7 cervical, 12 thoracic, 5 lumbar, 5 fused sacral, and most commonly, 4 fused coccygeal vertebrae. Vertebral anatomy varies according to each level. The atlas (C1) and the axis (C2) are highly atypical vertebrae, but from C3 downward the vertebrae have a recognizable anterior body, posterolateral pedicles, transverse processes, and posterior laminae, which fuse to form the spinous processes. The spinal canal enclosed within these structures is known as the epidural space. Its central portion is occupied by the dural sac, which contains the anterior and posterior spinal nerve roots, also known as the caudal equina. Between the arachnoid and the pia mater, which is applied to the spinal cord, is cerebrospinal fluid (**Figure 1**) [11].

The epidural space surrounds the dura mater circumferentially and extends from the foramen magnum to the sacrococcygeal ligament. Posteriorly it is bound by the ligament flavum, laterally by the pedicles and the intervertebral foramina, and anteriorly by the posterior longitudinal ligament, respectively [1].

Each intervertebral foramen connects the epidural with the paravertebral space without any barrier. Even within the intervertebral foramen, the epidural space is perforated by a spinal nerve and its duplicated dura sheath. Furthermore, the epidural space is in connection with the paravertebral space and attached anatomical structures. Thus, the epidural space is neither a distinct anatomical compartment nor a homogeneous compartment [12]. Disk herniation (the most common chronic disease of the spine) occurs primarily at weak points in this posterior longitudinal ligament in an area that comprises the anterior epidural space, as opposed to the more clinically relevant posterior epidural space [12].

The epidural space contains adipose tissue, blood vessels, nerve roots, lymphatics, and various haphazard fibrous connections to the ligament flavum, which can have an unpredictable effect on the course of an epidural catheter. The ligament flavum is not uniform from skull to sacrum, nor even within an intervertebral space. The ligament thickness, distance to the dura, and skin-to-dura distance vary with the area of the vertebral canal (1.5–3.0 mm in cervical, 3.0–5.0 mm in thoracic, 5.0–6.0 mm in

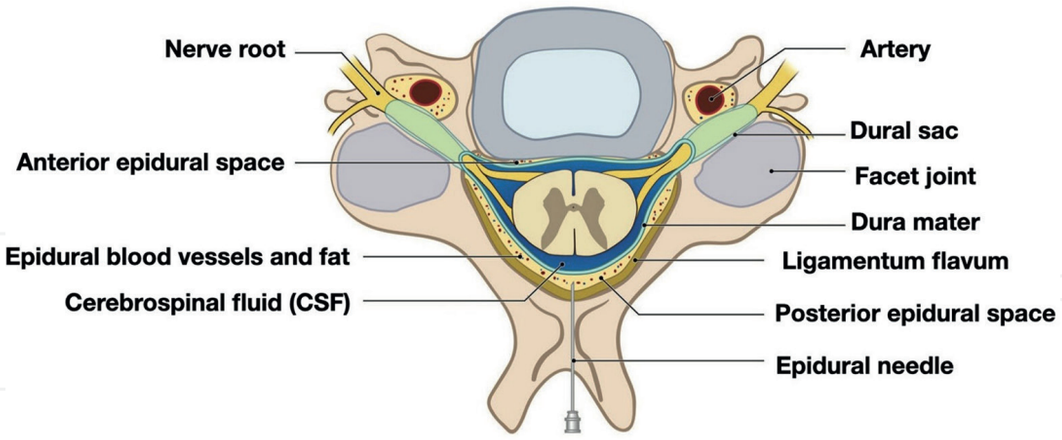

Figure 1.
Anatomy of the spinal cord (cross-sectional view). Notice the close proximity of the posterior epidural space to the subarachnoid space.

lumbar, and 2.0–6.0 mm in caudal level, respectively) [13]. The amount of adipose tissue in the epidural space appears to affect the spread of local anesthetic, but it remains unclear whether epidural fat prolongs nerve block duration by serving as a reservoir or decreases the amount of available drug, thereby slowing onset or both. The reduction of adipose tissue with age is speculated to account in part for the higher levels and faster onset of epidural anesthesia in the elderly [14]. Also, those fat pads under the ligament flavum could further explain the inhomogeneous spread of a local anesthetic and the deviation of epidural catheters. They can influence catheter advancement and may facilitate catheter migration through the intervertebral foramen [15].

Epidural arterial supply arises from anterior and posterior spinal arterial arcades, arising from spinal arteries entering the space through every intervertebral foramen. Its venous drainage is *via* a plexus of valveless veins, which is in the anterior epidural space. The venous plexus receives blood shunted from thoracic and pelvic veins, which means that straining and coughing can transiently engorge them. Because the plexus is valveless, blood from any of the connected systems can flow into the epidural vessels. Therefore, in situations when caval flow is obstructed, as in late pregnancy, the spinal veins are distended and occupy an abnormal absorption of the spinal canal [11, 12].

Aforesaid, the epidural space is irregular and segmental. It is distensible and an injection of fluid tends to distort its dimensions. Rheumatoid arthritis and trauma may affect this relationship and the ability to recognize the relevant anatomy [16]. We think that a picture tells a thousand words (**Figure 2**). With this kind of spine pathology, the epidural administration will probably modify or alter the detection of epidural space, epidural catheter placement, and drug efficacy. Also, we can expect a high incidence of epidural insertion-related complications [11, 12, 15].

2.2 Physiologic effects of epidural blockade

The extent of these physiologic effects depends on the level of placement and the number of spinal segments blocked. In general, high thoracic epidural nerve blocks (i.e., above Th5) and extensive epidural nerve blocks are associated with more profound physiologic changes than nerve blocks with low sensory levels (i.e., below Th10). Spinal anesthesia and epidural anesthesia produce a similar degree of differential sensory blockade. Epidural anesthesia produces a sympathetic block, which

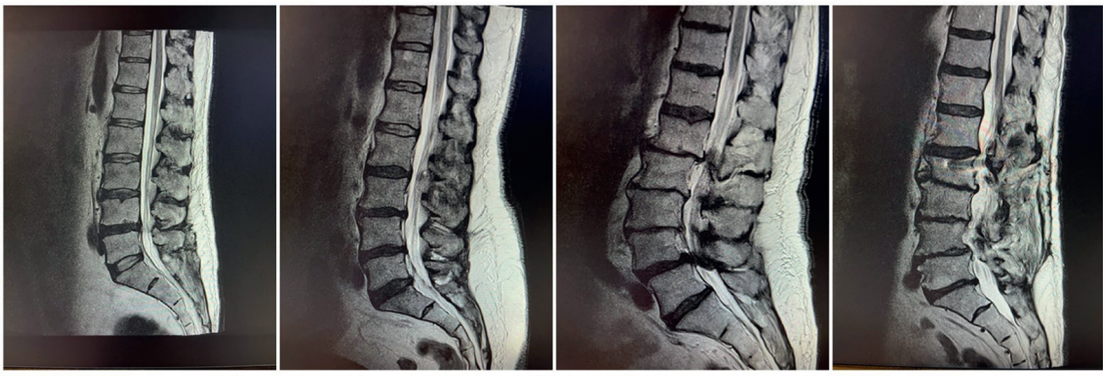

Figure 2.
MRI of the lumbar spine (T2-weighted sagittal) shows mild to severe lumbar pathology (from left to right). Courtesy of Department of Radiology, Clinical Hospital Centre Rijeka.

extends higher than the sensory block, with the lack of motor block, which is characteristic of spinal anesthesia [17].

The nerve fibers vary in their response to LAs based on their diameter and state of myelination. The most susceptible are Aδ nociceptive fibers (which are responsible for autonomic nervous system transmission) resulting in an epidural block in a concentration-dependent manner [18]. The meaning of the aforementioned is that this type of myelinated fiber requires larger LA concentrations because of the myelin sheath, also becomes blocked faster, and recovers faster. On the other hand, small unmyelinated C-fibers (postganglionic fibers in the autonomic nervous system and nerve fibers at the dorsal roots) that are in charge of transmission of visceral dull pain sensation need lower concentrations of LAs because they lack a protective myelin sheath and diffusion barrier, but with the longer necessary time to recover. Based on these findings, differential neural block and sensitivity to LAs are best presented in an epidural block where the main goal is to achieve appropriate anesthesia in a dermatomal distribution of the patient's pain complaints [19]. We can say succinctly that in the epidural block, autonomic fibers (types C and B) are the fastest and easiest blocked nerve fibers, and usually reach higher dermatome levels (2–6 levels) than the sensory block. Myelinated, Aδ nociceptive fibers are the next fibers where the neuronal transmission stops; sensory functions include first temperature (cold), then the pain (pinprick), and finally, touch. The last ones blocked are the proprioception (A-beta, Aβ) and motor fibers (Aα) with a descending dermatomal level [18, 20].

During general anesthesia combined with epidural analgesia, the degree of sedation and minimum alveolar concentration (MAC) sparing effect appear to correlate with the height and level of the sensory nerve block. Also, a thoracic block is associated with a greater sedative effect than the lumbar block and a higher concentration of LAs may contribute to a greater MAC-sparing effect. The addition of opioid adjuvants to the epidural LA solution does not appear to reduce volatile agent requirements any further, although it does contribute to better postoperative pain scores [21].

Cardiovascular and hemodynamic effects are primarily the result of a sympathetic nerve fiber blockade. They include venous and arterial vasodilation, reduced systemic vascular resistance, and changes in chronotropy and inotropy resulting in blood pressure and cardiac output variations. The type and intensity of these changes are related to the level of nerve block, the total number of dermatomes blocked, as well as the type and dose of LA administered. In general, high thoracic nerve blocks can cause marked changes compared with lumbar blocks [22].

Epidural anesthesia may also affect lung function, depending on the level of block. Tidal volume remains unchanged, while vital capacity and forced expiratory volume in 1 s (FEV (1.0)) can be decreased during high thoracic epidural block [23]. However, thoracic epidural anesthesia has benefits in major abdominal and thoracic surgery since it enhances pain relief postoperatively and thus reduces postoperative pulmonary complications [24].

As for the gastrointestinal (GI) system, sympathectomy associated with an epidural block in the mid-to-low thoracic levels results in unopposed vagal tone, which manifests clinically with increased peristalsis, relaxed sphincters, an increase in GI secretions, and, likely, more rapid restoration of GI motility in the postoperative phase [25].

Because renal blood flow is maintained through autoregulation, epidural anesthesia has little effect on renal function in healthy individuals. Compensatory and feedback mechanisms (afferent arteriolar dilation and efferent arteriolar vasoconstriction) ensure constant renal blood flow over a broad range of pressures (50–150 mmHg) [26].

As far as thermoregulation is concerned, hypothermia is primarily due to peripheral vasodilation resulting in heat redistribution from the core to the periphery. In addition, reduced heat production (due to reduced metabolic activity) results in a negative heat balance [25].

Epidural anesthesia reduces the hypercoagulable state in the postoperative period and is associated with a decreased risk of deep vein thrombosis (DVT) and pulmonary embolism. Likewise, it could effectively inhibit central sensitization and reduce the damage of intraoperative stress response to cognitive function [27].

2.3 Basic epidural pharmacology

When drugs are administered neuraxial, it is of crucial importance to understand the pharmacokinetics and pharmacodynamics of the agents employed in order to ensure adequate anesthesia/analgesia as well as safety. In general, neuraxial administered drugs need to reach their primary site of action to work [28]. Absorption to the main target site (i.e., the spinal cord and intrathecal dorsal nerve root as well as local and systemic (re-)distribution) determine the onset and duration of action of epidural and intrathecal drugs.

After injection of epidural drug(s), the drug solution coats the dural sack, spreading up and down in a fairly random fashion. From the epidural space, drugs may go four ways (**Figure 3**):

1. Exit the intervertebral foramina to reach the paraspinous muscle space

2. Distribute into epidural fat. This defines the main influence on epidural drug behavior. The drug forms a reservoir and redistributes gradually, creating a longer effect. The speed of onset is also mainly related to lipid solubility (discussed later in the chapter).

3. Diffuse into ligaments

4. Diffuse across the spinal meninges and into the cerebrospinal fluid (CSF) where the arachnoid is the main meningeal barrier to diffusion. Apart from that, a small minority of drugs will penetrate the systemic circulation and then appear in the CSF after diffusing out of the spinal cord.

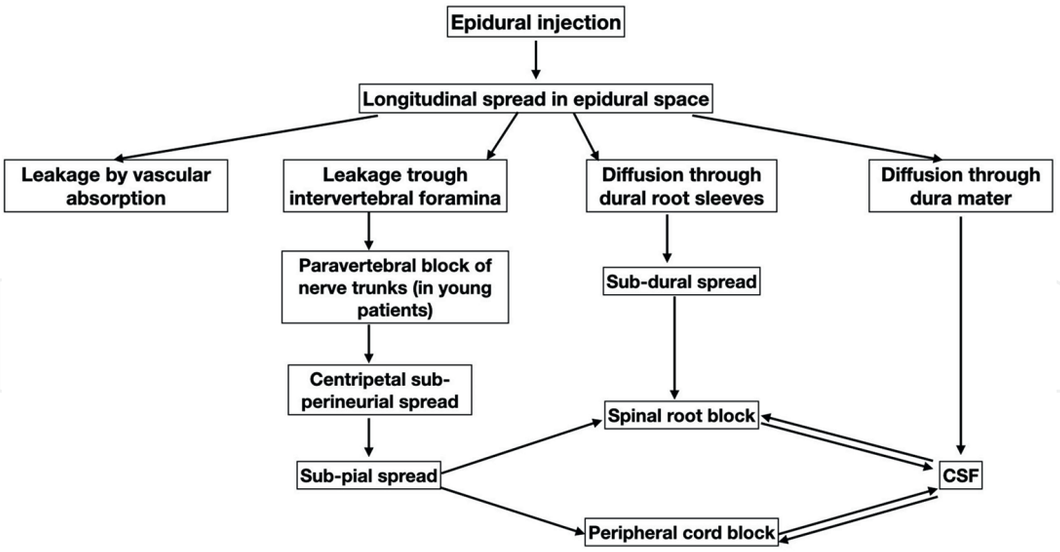

Figure 3.
The fate of an epidural injection; CSF—Cerebrospinal fluid [10].

In the epidural space, diffusion has the main influence on drug absorption and is done according to Fickian principles. The main factors that influence the penetration of an epidurally administered drug into the cerebrospinal fluid (CSF) are as follows:

Dose, volume, and concentration: The dose of LAs necessary for epidural anesthesia or analgesia is a function of the concentration of the solution and the volume injected. The concentration of the drug affects the density of the nerve block; the higher the concentration, the more profound the motor and sensory nerve block. Volume and total LA dose are the variables that affect the degree of spread of the nerve block. A larger volume of the same concentration of LA will block a greater number of nerve segments. However, if the total dose of LA is unchanged, but the concentration is doubled, the volume can be halved to achieve a similar spread of LA. Clinical observations of the spread of epidural analgesia have shown that the extent of the segmental blockade is mainly determined by the mass of the drug injected (the product of volume and concentration) and not by volume alone. Another interesting finding regarding epidural space is that, beyond a certain point, further increase in anesthetic concentration does not consistently reduce the time required for anesthesia to develop, nor produce an improvement in the rather merger quality of motor blockade [29]. These findings reveal an unexpectedly complex relationship between concentration and effect and support the suggestion that epidural blockade is not a simple matter of diffusion from one space to another, but rather of several diffusion pathways (**Figure 3**).

Surface area is largely determined by the volume of the infused drug.

Protein binding determines the free fraction of the drug.

Lipid solubility is defined by the ionization constant (pKa value) of the drug and the pH of the solution.

General guidelines for the administration of epidural drugs state that 1–2 mL of medications should be applied per segment until the target dermatomal level is reached. In the group of patients of lower height, a reduction to 1 mL per segment is recommended [30]. The established term "time to two-segment regression" is defined as the time required for the regression of the sensory block at two dermatomal levels, and it varies depending on the type of applied LA in the epidural block. It requires the repeated application of one-half or one-third of the given initial dose [31].

2.3.1 Epidural pharmacology of local anesthetics (LAs)

For local anesthetics (LAs), the most relevant properties are the ionization constant (pKa value), lipophilicity, and the degree of protein binding. LAs are defined as water-soluble salts of lipid-soluble alkaloids. Their structure consists of three components: a lipophilic aromatic ring, an intermediate ester or amide chain, and a terminal hydrophilic amine group. All mentioned components contribute to distinct properties of the molecule [32]. The aromatic ring as a lipophilic structure improves the liposolubility of the molecule. This characteristic allows diffusion through the myelin sheath and also correlates with potency because a greater dose of LA can enter the neuronal fiber [32, 33].

The intermediary chain categorizes LAs into esters or amides with their characteristics (**Table 1**) [33].

While the potency of LAs is related to its lipid solubility (those with higher lipid solubility more easily permeate neuronal membranes), the speed of onset predominantly depends on the pKa (a lower pKa would effectuate a higher speed of onset), and the duration of action is significantly influenced by the degree of protein binding, more precisely on alpha-1-glycoprotein (increased protein binding is associated with a longer duration of action and lower bioavailability [18, 34]). The LA base is stable in a solution as a hydrochloride salt (a weak base). At the time of injection, LAs are in the ionized, quaternary, water-soluble state and not able to diffuse through the myelin sheath. So, the time of onset of anesthesia is directly related to the proportion of molecules that convert from quaternary to the tertiary, lipid-soluble, non-ionized structure when they are exposed to the physiologic pH of 7.4.

That is determined using the ionization constant (pKa) for the LAs, and it is presented and calculated using the Henderson-Hasselbach equation for weak bases [18, 32, 33]:

$$\log\left(\frac{non-ionized}{ionized}\,form\right) = pKa - pH \tag{1}$$

At normal and physiological pH of 7.4, 50% of LAs exist in a tertiary, lipid-soluble non-ionized form, and 50% are in the quaternary, a water-soluble ionized form; only 50% of molecules can diffuse through both the epineurium and the neuronal membrane. When the pKa of the LA is close to the physiological pH, the onset of action is the fastest due to the optimal ratio of non-ionized and ionized fractions. Acidosis in the surrounding tissue (such as infection) increases the ionized fraction of the LAs, making them water-soluble with no diffusion capacity through the myelin sheath. Once the molecule reaches the tertiary form in the axoplasm of the neuron, the amine gains a hydrogen ion and, now ionized and in a quaternary form again, it is responsible for the actual blockade of the VGSC. So, in conclusion, the equilibrium between quaternary and tertiary forms lies in the pH of the tissues and the pKa of the anesthetics [33]. An optimal anesthetic uptake and activity require a relatively low pH at the site of action [35].

2.3.2 Epidural pharmacology of opioids

Concerning opioids, lipid solubility is the essential determining factor for pharmacological effects after neuraxial application. Generally speaking, opioids

Classification	pKa	Relative potency*	Onset	Duration (min)	Maximum single dose (mg)	Epidural administration
ESTERS						
Procaine	8.9	1	Slow	45–60	500	No
2-Chloroprocaine	8.7	2	Rapid	30–45	600	Yes
Tetracaine	8.5	8	Slow	60–180	100 (only topical)	No
AMIDES						
Lidocaine	7.9	2	Rapid	60–120	300	Yes
Etidocaine	7.7	2	Slow	240–480	300	Yes
Prilocaine	7.9	2	Slow	60–120	400	Yes
Mepivacaine	7.6	2	Slow	90–180	300	Yes
Bupivacaine	8.1	8	Slow	240–480	175	Yes
Levobupivacaine	8.1	8	Slow	240–480	175	Yes
Ropivacaine	8.1	6	Slow	240–480	200	Yes

** Relative potency varies based on the route of administration.*

Table 1.
Classification of LAs with their main characteristics.

are lipid-soluble weak bases that are highly bound to the proteins and are ionized at physiologic pH. The variations in protein binding affinity are the main reason for the different speeds of transfer across the cellular membrane [36, 37]. Hydrophilic opioids such as morphine have a slower onset and a longer duration of action, while lipophilic opioids such as fentanyl and sufentanil produce a rapid onset and shorter duration of action. Lipophilic opioids tend to accumulate in fat-rich tissues such as epidural fat and white matter of the spinal cord, resulting in smaller concentrations in cerebrospinal fluid (CSF). They have less bioavailability, a large volume of distribution, and a larger initial volume in the central compartment compared with more hydrophilic molecules such as morphine [38–41]. Neuraxial lipophilic opioids have a more rapid distribution and clearance from the spinal cord and epidural space than hydrophilic opioids, resulting in a lower rate of respiratory depression and sedation [42, 43].

Elimination of epidurally administered opioids varies related to the molecular weight of the drugs and is dependent on the speed at which opioids spread in the rostral direction. Their mechanism of action is dose-dependent. In small doses, they show spinal effects, whereas in higher doses, they are responsible for supraspinal analgesia and can have pronounced systemic side effects [38–40].

It appears that the systemic absorption of drugs from the epidural space follows a two-compartment model. The rapid disappearance phase is believed to be related to uptake by rapidly equilibrating tissues (i.e., tissues that have high vascular perfusion). The slower phase of disappearance is mainly the function of the particular compound and the half-life of the drug. LAs appear in the venous blood within a few minutes of epidural injection and rises to a maximum in 10–30 minutes, depending upon the diffusion characteristics of the drug concerned [44]. Lipophilic drugs are also readily cleared into the plasma and can hence produce undesired side effects in the central

nervous system. The degree of absorption depends on the dose and the presence or absence of vasoconstriction in the epidural solution. Very large doses may cause sufficiently high blood levels to produce a toxic reaction [45].

2.3.3 Other factors that may affect epidural block onset

Height is very poorly correlated with epidural dose requirements except for extremely tall or short patients [30, 46].

Weight: There is little correlation between the spread of analgesia and the weight of the patient. However, in morbidly obese patients, there may be compression of the epidural space related to increased intra-abdominal pressure and, therefore, a higher nerve block may be attained with a given dose of LA [46].

Age: With advancing age, the LA dose required to attain a specific nerve block is reduced. Greater spread in the elderly may be related to the reduced size of the intervertebral foramina, which theoretically limits the regress of LAs from the epidural space. Decreased epidural fat, which allows more of the drug to bathe the nerves, and changes in the compliance of the epidural space may lead to enhanced cranial spread and prolonged duration of the block [47]. This results in a possible need for up to 40% less volume of administrated epidural medications in elderly patients [48].

Pregnancy: Dose requirements at term are reduced by about one-third to one-half. Two reasons may be responsible: First, the pregnant uterus causes a partial occlusion of the inferior vena cava at term, and the proportion of the venous returns from the legs, and pelvis is diverted into the internal vertebral plexus. This results in the enlargement of the extradural veins and the reduction of the remaining volume in the epidural space [49]. Second, pregnancy causes increased sensitivity to both LAs and general anesthetics. The possible mechanism is attributed to elevated levels of progesterone and endogenous endorphins, which leads to increased permeability of membranes and blood vessels [50].

Blood flow: The natural factors that impair blood flow in the epidural space such as age, arteriosclerosis, and diabetes increase the spread of analgesia, but they do not carry with them the tendency for a more profound block. Additionally, arterial hypertension may prolong blockade, but its effects on the quality of blockade have not been sufficiently investigated [51].

Epidural catheter positioning: Epidural block height is affected primarily by the level of injection. In the cervical region, drugs administered in the epidural space mostly spread caudally, while in the midthoracic region (level of Th2–Th6), the expansion is equally cranial and caudal. By administering the epidural drugs in the lower thoracic region (Th6-L1), the spread is only cranial. After a lumbar epidural, the spread is more cranial than caudal with a delay in the onset of anesthesia at the L5-S1 segments because of the larger size of these nerve roots. The position of the patient on the bed does not affect the spread of the medications in the epidural space, regardless of whether the patient is in a sitting or lateral position [30, 31, 48].

In summary, the onset of epidural blockade is relatively slow, due to the fact that administered drugs have to pass several diffusion barriers. The result depends upon interaction of many different factors discussed above. The epidural blockade is indeed a complex process, which takes place at many different sites, including spinal roots, nerve trunks, and the spinal cord itself. There are still many gaps in our knowledge of the fundamental process of epidural action, which requires further investigations, careful experimental design, and examination of direct and indirect evidence from clinical and laboratory sources due to the fact that many variables are not susceptible

to direct measurement. It is very difficult to meet all the specified criteria, and much of the proposed research did not acquire ethical committee approval. This is probably the reason why the majority of the literature on basic epidural pharmacology is of an older date.

3. Epidural administration of local anesthetics

Epidural anesthesia has gained great importance due to its safety, especially when using local (LAs) anesthetics in combination with opioids that have become commonplace for relief of pain. Synthetic opioids can, thereby, increase the effectiveness of anesthetics, leading to the main goal of epidural medication administration, which is the patient's maximum pain relief [52].

3.1 Nerve anatomy and physiology

The main role of LAs is to inhibit action potential in nociceptive fibers and block the transmission of pain impulses. The abovementioned effect is achieved by suppressing action potentials in excitable tissues by blocking voltage-gated sodium (Na+) channels (VGSC) [18].

Surgical incision creates trauma to the affected tissue, activating in that way nociceptors, leading to, in the literature, the so-called "inflammatory soup." Nociceptors are the free endings of one form of myelinated A fibers called A-delta (Aδ) fibers that can be found in the skin, muscles, joints, bones, and viscera. Every stimulation of nociceptors (like surgical incision) results in depolarization with activation of Na + channels—a structure that is composed of a large pore-forming alpha (α) subunit associated with one or two beta (β) subunits. The α subunit has four domains (I–IV), each containing six segments (S1–S6). The segments S5 and S6 form the channel, such as the short loops of amino acids that link them. The voltage-sensitive region is S4 in each domain containing positively charged arginine or lysine amino acids. Looped domains III and IV are meritorious for gate inactivation (**Figure 4**) [18].

Normally, these channels can exist in three states: resting, open, and inactivated. During the rest, entry of Na + ions is denied, and the channel is in a non-conductive state. This makes a membrane potential of approximately −70 mV. Stimulation of the channel, the great influx of Na + ions occurs, and the S4 segments open by outward spiral rotation, initiating depolarization. Following the sudden change in membrane voltage, the Na + channel assumes an inactivated state. The Na + channel inactivation and efflux of potassium (K+) ions restore the electrochemical gradients and depolarize the nerve back to its resting state [18, 53].

3.2 Selection of LAs

The epidural anesthesia is produced by the diffusion of LAs through the dura mater achieving their effects on nerve roots and in paravertebral space passing through the intervertebral foramina [32]. Commonly used LAs for an epidural block can be divided into short-, intermediate-, and long-acting (**Table 1**). The time required to achieve peak performance varies on the type, dose, and volume of LA, which is administered into the epidural space. The time to onset of epidural block after injection of LAs can usually be detected within 5–10 minutes [20, 32].

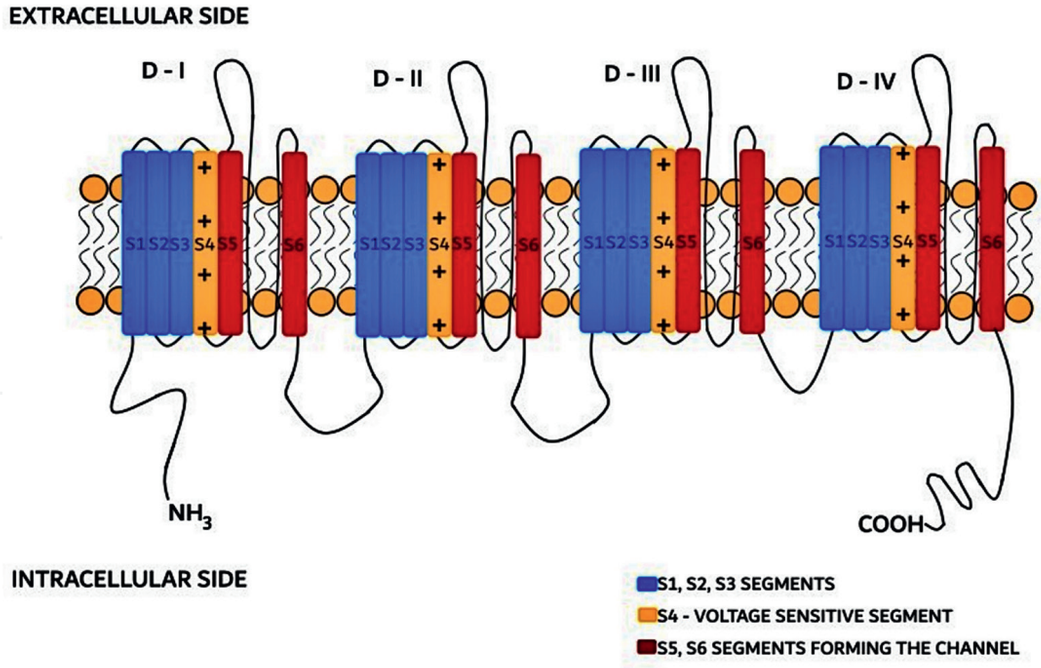

Figure 4.
Structure of voltage-gated sodium (Na+) channel (VGSC) with main subunits and segments. **Legend:** *Blue—S1, S2, S3 segments, yellow—voltage-sensitive segment S4, red—S5,6 segments forming the channel.*

The most common application of short-acting ester LA, 2-chloroprocaine is neuraxial anesthesia because of its short duration. The United States Food and Drug Administration (FDA) recently approved 2-chloroprocaine for providing neuraxial anesthesia for adults undergoing short-duration abdominal and lower extremity surgery. Throughout the world, 2-chloroprocaine is used off-label when the fast onset of epidural anesthesia is indicated, like in obstetric settings, for the need for an emergency cesarean section, but it is pregnancy category C. Its high pKa of 8.7 is an exception to the abovementioned rule of faster onset of LAs when they are closer to physiological pH. The 2-chloroprocaine has a very low risk for systemic toxicity because it is rapidly hydrolyzed by pseudocholinesterase, so it can be administrated in higher doses and have a faster onset, regardless of pKa [54].

Lidocaine is the intermediate-acting LA that is used commonly for surgical anesthesia *via* the epidural route. It is classified as an amide LA agent and also a class Ib antiarrhythmic agent on the Vaughan-Williams classification. Usually, it is combined with epinephrine, so the duration of action can be extended up to 60%. Lidocaine has a pKa of 7.7, meaning that approximately 25% of molecules will be able to diffuse through the myelin sheath, so it has a more rapid onset of action than other LAs with higher pKa (except 2-chloroprocaine). For the epidural block, it is usually used in a 1–2% concentration in a plain form or, more often, with a 1 per 200,000 epinephrine [55].

Long-acting LAs used for epidural blocks are bupivacaine, levobupivacaine, and ropivacaine. Because of the long duration of action, for many years, bupivacaine has been used as the first LA of choice for an epidural block. Today, the doses of this amide LA used for an epidural block are associated with a higher risk for cardiac toxicity because of its interaction with cardiac Na + channels, such as central nervous system (CNS) toxicity with an unwanted postoperative motor blockade. Due to the aforementioned and the need for a smaller dose and volume, bupivacaine is the ideal

choice for spinal anesthesia [32, 56]. It has a higher pKa than other local anesthetics and consequently a slower onset of anesthesia. It can be prepared in three different concentrations: 0.25%, 0.5%, and 0.75%. A concentration of 0.5% is the most suitable for surgical anesthesia and epidural block. Accidentally injected intravenously, 0.75% bupivacaine has been associated with refractory cardiac arrest, and it is no longer recommended for epidural block [48]. Levobupivacaine, the S (−)-enantiomer and racemic sibling of bupivacaine, has similar characteristics as bupivacaine but with less pronounced cardiotoxic effects. Equal doses of levobupivacaine and bupivacaine can provide similar onset and duration of anesthesia (up to 6–8 hours) but with fewer life-threatening side effects and a better safety profile with levobupivacaine [57]. Likewise, levobupivacaine and ropivacaine also present a long-acting, amide LA that is enantiomerically pure (S-enantiomer) with properties and efficacy similar to bupivacaine. Because of its low lipid solubility, ropivacaine has a lower potency than bupivacaine but with a higher affinity for Aδ and C fibers than those controlling motor functions like Aβ, so it can easily produce the earlier mentioned differential block. Ropivacaine is less cardiotoxic than equal concentrations of racemic bupivacaine, and it has a significantly higher threshold for CNS toxicity [58, 59]. Ropivacaine offers an advantage concerning cardiotoxicity when applied and compared with bupivacaine, but with a marginal advantage in a differential block and with a higher market price. The duration of anesthesia for all long-acting anesthetics is between 6 and 8 hours [48].

In conclusion, levobupivacaine is imposed as the safest and most suitable long-acting LA for use in the epidural block.

3.3 Adverse effects of local anesthetics

Improper handling of LAs can lead to both systemic and local toxic effects [18].

3.3.1 Local anesthetic systemic toxicity (LAST)

This life-threatening event is most often the result of the intravascular application of LA (e.g., unintentional epidural vein cannulation during catheter placement) or in less common situations as a result of excessive concentration after LA absorption at the injection site. The extent of this effect depends on the dose of the LA, the site of application, and the fact whether a vasoconstrictor such as epinephrin was included in the solution. The most common consequences are visible in the CNS and cardiovascular system. High plasma concentrations of LAs lead to the blockade of cortical inhibitory pathways by interrupting neuronal depolarization. In the clinical picture, the abovementioned are manifested in the early phase as dizziness, tinnitus, perioral paresthesia and tingling, audio-visual disturbances, agitation, and confusion of patient. As concentrations get higher, generalized seizures appear with the further possibility of a state of consciousness disturbances, coma, and respiratory arrest. Simultaneously, in the cardiovascular system, rhythm disturbances are the most likely disorders as a consequence of a direct blockade of myocardial Na + channels leading to prolonged PR, QRS, and ST intervals. That can manifest as re-entry tachy- and bradyarrhythmias with hypotension, and eventually, cardiac arrest, which most often results in asystole [31, 60, 61].

When long-acting anesthetics are desired, it is better to use levobupivacaine or ropivacaine because of their higher threshold for CNS and cardiovascular complications, such as lower vasodilatory properties and slower systemic absorption. Maximal

	Epidural	Intrathecal
Absorption into target site	Rate of diffusion into CSF is slower, and depends on Fick principles: - Volume (surface area of available meninges) - Concentration - Lipophilicity (pH, pKa) - Protein binding and free fraction - CSF flow rate/turbulence	Rate of diffusion into target tissue is rapid: High CSF concentration Short diffusion distance (2–4 mm)
Local distribution	Epidural spaces are irregular, segmental, and the injected material encircles the dural sack	Depends on basicity (density of inject ate relative to CSF)
Systemic distribution	Two competent model: rapid early distribution (into epidural fat) and then slowly back out	Slow absorption; increased half life The more lipophilic the drug, the faster it is cleared from the CSF
Metabolism and elimination	Normal mechanism prevails (liver and kidney). However, because of the hemodynamic effect of spinal (anesthetic) drugs, the perfusion of liver and kidneys may be decreased, which could delay clearance.	

Table 2.
Epidural vs. intrathecal drug administration [30].

single doses of each local anesthetic must be respected (**Table 2**). This condition must be treated timely, including airway maintenance, suppression of seizure activity, and hemodynamic support with preparation for possible cardiopulmonary resuscitation [61]. Lipid emulsion (20%) therapy should be started according to the American Society of Regional Anesthesia (ASRA) guidelines, as follows:

For a patient over 70 kilograms—a rapid 100 mL bolus of emulsion over 2–3 minutes followed by another 200–250 mL over 15–20 minutes [19].

For patients below 70 kilograms—an initial loading dose of 1.5 mL/kg over 2–3 minutes, followed by a continuous infusion of 0.25 mL/kg/min for a minimum of 10 minutes after restoring circulatory stability [19].

The recommended dosing limit is 12 mL/kg for repeated bolus doses [62].

3.3.2 Local tissue toxicity

All LAs possess nerve and muscle toxicity that can be, in a rare number of cases, clinically apparent. As the dose of LA gets higher, so as the duration of exposure, some local reactions such as nerve ischemia and nerve vulnerability are possible, and must be recognized promptly [48].

4. Epidural administration of opioids

One of the main priorities in current anesthesia practice is perioperative pain management, due to the fact that inadequately treated pain is associated with increased morbidity, mortality, protracted recovery, and delayed discharge from the hospital. The main group of medications used for the treatment of acute and chronic pain is opioids, which achieves their effect by binding to opioid receptors [36, 37, 63]. Opioids can be endogenous (i.e., enkephalins, endorphins, and endomorphins dynorphins) and exogenous (morphine, heroin, meperidine, fentanyl, and many others). Endogenous opioids are peptides that are expressed in pain pathways and packaged in

core vesicles and transported to axon terminals during which they are broken down into smaller, more specific peptides, which eventually bind to the opioid receptors [37]. Exogenous opioids are derived from the opium poppy plant, more specifically alkaloid morphine, which can be processed to produce heroin and other synthetic opioids, and codeine and thebaine, which are used to produce drugs such as oxycodone, hydrocodone, and hydromorphone. The basic opioid molecule is morphine and most of the opioids that are used today in anesthesiology share its structural features and are made by complex alterations of the morphine molecule [36, 37, 63].

4.1 Opioid receptors

Opioid receptors, which are responsible for the main pharmacological effect of opioids, are a G-protein-coupled family of receptors. They have seven transmembrane portions; intra- and extracellular loops, extracellular N terminus, and intracellular C terminus. Opioid agonists bind to the receptor and activate the three subunits of the G-protein. The effects produced are mostly inhibitory, and they lead to the hyperpolarization of the cell and reduction of its excitability (**Figure 5**) [36, 37, 63, 64].

Four main types of opioid receptors have been identified—mu (μ), kappa (κ), delta (δ) opioid receptors (mu—MOR, kappa—KOR, and delta—DOR), and nociceptin (NOR) receptors. Other types of receptors that are proposed to exist are epsilon (ε) receptor, zeta (ζ) receptor, and a binding site called lambda (λ). Sigma (σ) receptors are not considered opioid receptors anymore but target sites for phencyclidine (PCP) and are responsible for psychomimetic effects, dysphoria, and depression (**Table 3**) [36, 37, 63, 64].

Opioid receptors are localized in and outside of the central nervous system (CNS). In the CNS, they are mainly located in the dorsal horn of the spinal cord and the cerebral cortex, thalamus, area postrema, the limbic system and the periaqueductal gray region, locus ceruleus, rostral ventral medulla, and peripheral afferent nerves. Outside of the CNS, they can be found in many other tissues such as the

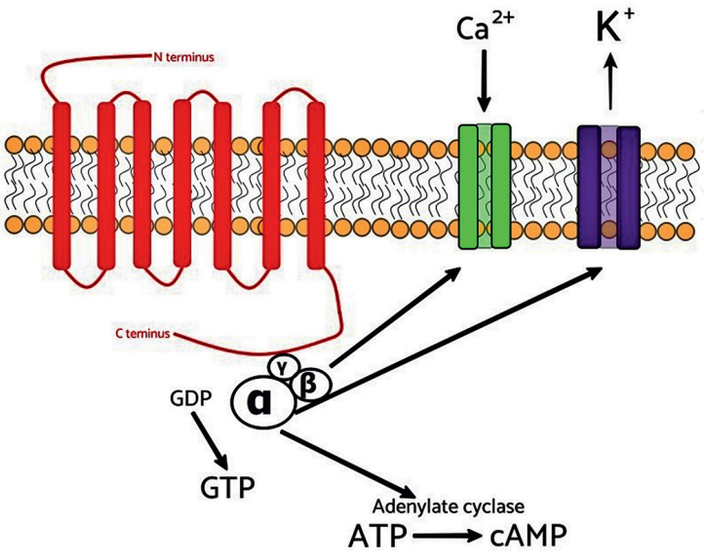

Figure 5.
Structure of opioid receptor: Seven transmembrane portions, intra- and extracellular loops, extracellular N terminus, and intracellular C terminus. Opioid agonists bind to the receptor and activate three subunits of the G-protein. Production of cAMP decreases by inhibition of adenylyl cyclase, Ca2+ influx decreases by the closing of voltage-sensitive calcium channels, and K+ efflux increases.

Opioid receptor	Prototype agonist	Location	Effects
Mu (μ) receptors (MOR)	Morphine	Central nervous system Cerebral cortex Amygdala Periaqueductal gray Basal ganglia	Supraspinal analgesia Euphoria Sedation ↓Respiration ↓Gastrointestinal movements Physical addiction Miosis Pruritus Anorexia Vasodilatation
Kappa (κ) receptors (KOR)	Ketocyclazocine	Diencephalic areas Limbic areas Spinal cord Brain stem	Spinal analgesia Sedation Dysphoria Dependence Dyspnea ↓Respiration
Delta (δ) receptors (DOR)	Delta-alanine-delta-leucine-enkephalin	Brain	Analgesia ↓Gastrointestinal movements
Nociceptin receptors (NOR)	Nociceptin/orphanin	Central nervous system	Analgesia Hyperalgesia

Table 3.
Types of opioid receptors [36, 37, 63–65].

gastrointestinal or biliary, and some of the actions of the agonists of these receptors outside of the CNS account for the adverse effects of opioids [36, 37, 63, 64].

Opioids are classified by their actions on opioid receptors as agonists, mixed agonists-antagonists, partial agonists, and antagonists [36, 37, 63].

Opioid agonists in the spinal cord inhibit the release of substance P from sensory neurons of the dorsal horn, changing the transfer of painful stimuli to the brain. In the brain stem, they modulate nociceptive transfer in the dorsal horn through descending inhibitory pathways. They change the response to pain in the forebrain and also induce activity in reward structures in the brain. Therefore, opioids provide analgesia by attenuation of peripheral nociceptive stimuli and by changing our central response to it. Agonists of MOR receptors mostly treat pain sensations carried by unmyelinated C fibers. Other sensations such as touch and temperature are not affected. With larger doses administered, they also produce drowsiness and sleep, but they do not affect responsiveness and amnesia. Through cough centers in the medulla, they produce antitussic effects, but also can sometimes produce a paradoxical increase in coughing after usage as an intravenous induction agent [36, 37, 63–65].

4.2 Adverse effects and metabolism of opioids

One of the most frequent and significant adverse effects of opioids is depression of ventilation. Opioids alter the ventilatory response to carbon dioxide in arterial blood, and they depress the hypoxic drive to breathing and diminish the ventilation drive in the patient. This effect is greater in patients who receive high dosages of opioids, are older, use other central nervous system depressants, and have renal or hepatic insufficiency [36, 37, 63–66].

Also, opioids produce vasodilatation by decreasing the central vasomotor tone in the brainstem and by directly acting on the blood vessels. They affect both preload and afterload. In older, hypertensive patients or patients with congestive heart failure, opioids can lead to significant hypotension [36, 37, 63, 64].

One of the most often associated adverse effects of opioid administration is nausea and vomiting, by stimulating the trigger zone in the area postrema in the fourth ventricle of the brain and pruritus, by weakening inhibition of itching by neurons of the dorsal horn in the medulla. These effects are the result of the rostral spread of opioids, meaning that more hydrophilic opioids tend to have these adverse effects when administered epidurally [36, 37, 41, 63–65].

Opioids affect the gastrointestinal system in a way that they cause tonic contractions of smooth muscles and decrease peristaltic, which can lead to the postoperative development of ileus. They can also lead to urinary retention by decrease in bladder detrusor tone and increase in urinary sphincter tone. This can be more pronounced in male patients when opioids are given epidurally or inthrathecally [36, 37, 41, 63–66].

The use of opioids in obstetric patients may affect neonates. It may inhibit or enhance the progress of labor. Also, possible is neonatal morbidity because of vascular reabsorption of drugs and possible transfer to the placenta and the fetus, which can lead to respiratory depression in neonates, neurological depression, and other side effects [66].

Opioids can produce alterations in body temperature, most likely by interacting with opioid receptors in the spinal cord and possibly by migration of the drug into the hypothalamus. Administration of epidural sufentanil decreases shivering and may induce hypothermia [66].

Opioids may also lead to different types of cardiac dysrhythmias and may lead to damage to the spinal cord (motor and sensory dysfunction), most likely due to the effect of opioid preservatives or additives, which leads to vasoconstriction and spinal cord ischemia [66].

All of these side effects are mediated *via* opioid receptors, and their treatment are opioid receptor antagonists such as naloxone. Administration of a pure antagonist may lead to the end of analgetic effects, and if this effect should be maintained, an opioid agonist/antagonist can be administered. Antiemetics are useful in treating nausea and vomiting, such as transdermal scopolamine patches in those receiving epidural morphine or droperidol in the epidural infusion [66, 67].

4.3 Types of opioids and elected representatives

By their origin, opioids are classified as follows:

1. Naturally occurring opioids:

   a. benzylisoquinolines (papaverine)

   b. phenanthrenes (morphine, codeine, oxycodone, hydrocodone)

2. Semi-synthetics: morphine derivatives with simple or complex changes

3. Synthetic opioids:

a. morphinan derivatives (i.e., levorphanol)

b. diphenyl or methadone derivatives (i.e., methadone)

c. benzomorphans (i.e., pentazocine, phenazocine)

d. phenylpiperidine derivatives (meperidine, fentanyl, sufentanil, remifentanil, alfentanil)

Tramadol is an atypical opioid, a partial agonist that also has central GABA, serotonergic, and catecholamine activity [36, 37, 63, 64].

4.3.1 Morphine

Morphine is considered a prototype opioid substance against which all others are evaluated (**Figure 6**). It consists of a benzene ring with two hydroxyl groups (a phenolic at the third position and an alcohol at the sixth position and the nitrogen atom). Both of these can be converted to ethers or esters. Many of the opioids that are used today in anesthesiology share their structural features, and also many of the semi-synthetic ones are created by modifications of morphine molecule [36, 37, 43–45].

It has a very slow onset time, is almost completely ionized at physiologic pH, has very low lipid solubility and high protein binding, and is rapidly conjugated with glucuronic acid. Therefore, it has a prolonged latency to peak effect, and it slowly penetrates the CNS. The non-alkalized form of morphine crosses the blood-brain barrier much easily. When given intrathecally or epidurally, it also has a slower onset and longer duration of action compared with more lipophilic opioids [36, 37, 43–45, 63, 64].

Its slow onset can lead to the stacking of doses in patients with severe pain. Since morphine is a high histamine releaser, it can cause hypotension, bronchospasm, and direct respiratory depression. Decreased sympathetic nervous system tone can lead to other already described side effects such as nausea, vomiting, pruritus, constipation, and miosis [36, 37, 43–45, 63, 64].

4.3.2 Methadone

Methadone is considered the best treatment option for opioid addicts since it has long-acting pharmacokinetics and a very rare development of withdrawal syndrome. It also acts as an NMDA receptor antagonist resulting in attenuated opioid tolerance and can be used in the treatment of severe neuropathic and opioid-resistant pain due to serotonin and norepinephrine reuptake inhibition. It has high lipid solubility (analgesic action 4–8 hours) and a very long elimination phase with a long half-life (up to 150 hours). It is considered to be a good analgesic alternative for patients with morphine allergies since it is unrelated to standard opioids in structure. It can be used epidurally with relatively fewer side effects than morphine. However, its use is still considered off-label [36, 37, 43, 45, 63, 64, 68, 69].

4.3.3 Fentanyl

Fentanyl can be administered in multiple ways; intravenously, through the skin, mucous membranes, lungs, and nasally, and also intrathecally and epidurally. It is

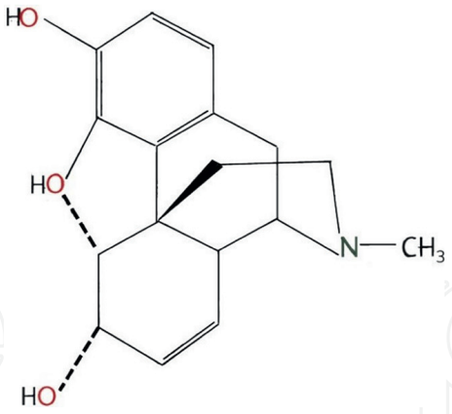

Figure 6.
Structure of the morphine molecule: A benzene ring with two hydroxyl groups (a phenolic at the third position and an alcohol at the sixth position and the nitrogen atom).

the oldest synthetic piperidine agonist and much more potent than morphine (80 times). It is highly lipophilic and binds strongly to proteins in the plasma (around 80%). The first-pass effect is mostly mediated by the lungs. It is primarily a MOR opioid agonist, and through this effect, it increases the pain threshold. Its duration of action is related to redistribution in highly vascular structures. It is metabolized in the liver and excreted *via* the kidneys, and it can be detected in urine 48 hours after administration [36, 37, 45, 63, 64, 70].

4.3.4 Alfentanil

Alfentanil has a short terminal half-life after an intravenous bolus injection because it has a high diffusibility fraction and quickly reaches peak effect concentrations. It is lipophilic and has one-fourth or one-tenth the potency of fentanyl. A very high proportion of the drug is uncharged at physiologic pH. The effects of alfentanil are mediated through mu-opioid receptors, but cause more significant respiratory depression than fentanyl [36, 37, 45, 63, 64].

4.3.5 Sufentanil

Sufentanil is the most potent opioid used in modern anesthesia (5–10 times more potent than fentanyl). It has a smaller volume of distribution and a terminal half-life between fentanyl and alfentanil. Like other fentanyl analogues, it is lipophilic. It has minimal cardiovascular side effects, preserving cardiac output and oxygen balance of the myocardium. It causes much harsher respiratory depression and rigidity of muscles compared with fentanyl [36, 37, 45, 63, 64, 70, 71].

4.3.6 Remifentanil

Remifentanil is the shortest acting synthetic opioid available because it is very quickly hydrolyzed by tissue and plasma esterases. It has a short latency to peak effect and has a rapid effect. It is twice more potent as fentanyl and 100–200 times more potent than morphine. It does not accumulate in the tissues, and its duration of action does not increase with the duration of administration [36, 37, 45, 63, 64, 70].

4.3.7 Hydromorphone

Hydromorphone has been used epidurally in thoracic, abdominal, and pelvic surgery, post-Cesarean section, and post-laminectomy syndrome. It is a lipophilic agent that has a faster onset of analgesia than morphine and a longer duration of action than fentanyl. Also, it has fewer side effects than morphine [44, 72].

4.3.8 Oxycodone

Oxycodone has high bioavailability, faster analgesia onset, and less histamine release than morphine, but a much shorter duration of action. It has liposolubility similar to morphine. Some studies show that epidural administration of oxycodone has better analgetic outcomes than oxycodone given intravenously. However, its epidural administration has not been approved by the FDA [42, 45, 73, 74].

4.3.9 Naloxone

Naloxone is an opioid antagonist that binds to opioid receptors competitively, and it can reverse all effects of opioids if there is ongoing opioid therapy. Mostly, it is used to reverse opioid-induced ventilator depression. It is rapidly metabolized in the liver, has a high clearance, and mostly has a significantly shorter action than that opioid whose effect it has to reverse [36, 37, 63, 64].

4.3.10 Nalbuphine, buprenorphine, pentazocine, and butorphanol

Nalbuphine, buprenorphine, pentazocine, and butorphanol are partial agonist-antagonists that bind to opioid receptors. Buprenorphine is a kappa receptor antagonist and mu receptor agonist, while others listed are kappa receptor partial agonists and competitive mu antagonists. They are efficient in relieving mild and moderate pain and have less effect on ventilatory depression in patients (**Table 4**) [36, 37, 63, 64].

When different opioids are selected, one has to keep in mind how quickly the desired effect should be achieved, how long it must continue for, should the desired effect be quickly modified, and is there a need to completely avoid the adverse effects. Also, the route of administration is very important to achieve a steady state and achieve the desired effects.

5. Epidural steroid injection (ESI)

Corticosteroids are very attractive as drugs for many musculoskeletal diseases because of their potent anti-inflammatory effect. Epidural steroid injection (ESI) is widely used to treat various back pain conditions such as herniated intervertebral disc and spinal stenosis [75].

Initially, it was thought that the radicular pain was due to a compression of the nerve secondary to degenerative disc disease. However, recent studies show that inflammation plays a major role in the evolution of radiculopathy [76]. Clinically, a large herniation of an intervertebral disc associated with significant neural compression may be asymptomatic, whereas severe radicular pain may exist without

Opioid type	pKa	Unionized at 7,4 pH (%)	Plasma protein bound (%)	Octanol/ water partition coefficient	Receptor affinity	FDA approved for epidural
Morphine	8,0	23	20–40	1,4	μ +++ κ + δ	Yes
Methadone	9,2	1	85–90	117	μ +++ κ δ	No
Fentanyl	8,4	9	84	813	μ +++ κ δ	No
Alfentanil	6,5	90	92	145	μ +++ κ δ	NA
Sufentanil	8,0	20	93	1778	μ +++ κ + δ +	Yes
Remifentanil	7,1	68	80	17,9	μ +++ κ δ	NA
Hydromorphone	8,2		20	1,3	μ +++ κ δ	No
Oxycodone	8,5		45	0,7	μ ++ κ δ	NA

Table 4.
Opioid physicochemical and pharmacokinetic properties. The octanol/water partition coefficient is a measure between the lipophilicity and hydrophilicity of a substance (value >1 = substance more soluble in fat-like solvents; < 1 = more soluble in water [36, 42–47].

detectable root compression. Also, the size or shape of herniation and its eventual change do not correlate with clinical presentation or course [77]. The leak of the nucleus pulpous of the disc causes the release of several neuropeptides such as substance P, vasoactive intestinal peptide, calcitonin gene-related peptide and also nitric oxide, tumor necrosis factor α, metalloproteinases, and the production of hyperalgesic prostaglandins, thromboxanes, and leukotrienes. These cytokines activate immune cells and cause the attraction of lymphocytes, macrophages, and fibroblasts, leading to ischemia and inflammation. These biological components sensitize free nerve endings and adjacent nerve roots or dorsal root ganglions, producing back pain [78].

Corticosteroids belong to the class of steroid hormones produced by the cortex of the adrenal gland and are involved in several physiological regulatory mechanisms. They achieve the effect by the abolition of the rate-limiting step by the enzyme phospholipase A2 (PLA2) to liberate arachidonic acid from cell membranes. Arachidonic acid then leads to the upregulation of the cyclooxygenase and lipoxygenase enzymes, achieving the physiological effect by reducing intraneural edema, venous congestion, ischemia, and pain through the production of hyperalgesic prostaglandins,

thromboxanes, and leukotrienes [78]. They are classified into glucocorticoids and mineralocorticoids. Glucocorticoids participate in the metabolism of carbohydrates, fats, and proteins with their anti-inflammatory action as is mentioned above. In epidural injection, glucocorticoids are routinely used and treated as epidural steroids. Current evidence suggests that more soluble glucocorticoids have a shorter duration of systemic effect than less soluble glucocorticoids [79]. On the other hand, mineralocorticoids play a role in the regulation of water and electrolytes in the body. In **Table 5**, physiochemical properties of corticosteroids are displayed.

Patients suffering from back pain with a radicular component due to herniated nucleus pulposus benefit the most from epidural steroid injection (ESI). The contraindications for ESI include local infection, systemic infection, allergy to injectate, and potentially bleeding disorders or anticoagulation. Contraindications for steroid injections can also expand to certain medical conditions, such as poorly controlled diabetes, hypertension, or congestive heart failure [80].

ESI utilizes the principle of delivering steroids directly to the source of the problem to create higher local concentrations. There are three most common routes for epidural steroid administration: the caudal route, the interlaminar approach, and the transforaminal approach [81]. Each of these routes has benefits, risks, and concerns regarding the efficacy of ESI. The caudal and interlaminar approach can lead to wide fluctuations in results due to an inability to deliver medication to the target area, and the drug spread can be affected by the presence or absence of epidural ligaments and scarring (post-surgical). In transforaminal injections, flow is set toward the anterior and lateral epidural space, while in the caudal and interlaminar route, flow is predominantly into the posterior epidural space and, therefore, away from probable sites of inflammation. Post-surgical patients cause problems due to loss of normal anatomy, landmarks, scarring, and poor flow within the space. Therefore, fluoroscopic-guided procedures enhance safety and improve the accuracy of placing the steroid at or nearer the site of the pathology [82].

Common ESI complications include hypothalamic-pituitary-adrenal (HPA) axis suppression, adrenal insufficiency, iatrogenic Cushing's syndrome, hyperglycemia, osteoporosis, and immunological or infectious diseases. The type of corticosteroid also affects the severity of complications. It is reported that HPA axis suppression was more likely with longer-acting insoluble corticosteroid formulations such as methylprednisolone or triamcinolone than betamethasone and dexamethasone [79]. The HPA axis suppression is observed in all patients who receive ESI and serves as an indicator of an ESI limitation. The recovery curve of HPA function after ESI is similar to that of the elimination of epidurally injected steroids and represents a dose-response relationship, which provides important information about the minimal dosage of epidural steroids [83]. However, the incidence of complications related to epidural steroids is not high, and most of them are not serious.

Risks associated with the needle placement or with injectate include infection (more common in immunocompromised patients and can include epidural abscess and meningitis) and bleeding (epidural hematoma occurs in ~0.02% of procedures). Several cases of spinal cord ischemia after ESI have been reported since they were first described [84]. The current hypothesis is that this is due to a particulate steroid suspension being injected into a small artery, which then causes the development of an anterior spinal artery syndrome.

The corticosteroids for ESI are divided into **particulate** (triamcinolone and methylprednisolone) and **non-particulate** (dexamethasone and betamethasone) formulations. There have been no serious complications attributed to the use of

Name	Glucocorticoid potency (anti-inflammatory potency)	Mineralocorticoid potency (Na + retaining potency)	Duration of action (t1/2) (h)	Equivalent dose (mg)	Particulate or non-particulate	Particle size (mcg)
Hydrocortisone (cortisol)	1	1	8	20	P	Not studied
Prednisolone	4	0.8	16–36	5	P	Not studied
Methylprednisolone	5–7.5	0.5	18–40	4	P	<7.6
Triamcinolone	5	0	12–36	4	P	0.5–100
Dexamethasone	25–80	0	36–54	0.75	Non-P	<7.6
Betamethasone	25–30	0	36–54	0.75	P	0.5–100

Table 5.
Physicochemical properties of corticosteroids [85].

non-particulate steroids (dexamethasone). There is evidence that only dexamethasone and methylprednisolone have particles consistently smaller than a red blood cell (7.5–7.8 μm) but that methylprednisolone tended to aggregate and pack densely with a possible propensity to cause emboli and block a small arteriole, whereas dexamethasone did not (**Table 5**). It is also important to note that dexamethasone is a water-soluble preparation, whereas methylprednisolone is a suspension. Therefore, dexamethasone is generally considered safer as it is water-soluble and does not aggregate and pack densely and, for practical purposes, is considered non-particulate in the field of chronic pain management [85]. Recent literature documents that there is no significant difference in pain relief at any point between non-particulate and particulate steroids. There are recommendations that non-particulate steroid preparations should be considered as first-line agents when performing ESI [86, 87]. However, further studies are necessary to compare corticosteroid preparations.

Unfortunately, there is no definitive consensus regarding the optimal interval and dosage of ESI. Also, little information concerning recommendations or practice guidelines is available to date. Significant differences were observed in the selection and dose of steroids as well as in the ESI interval. It is mostly attributed to physician preference, who should be aware of the possibility of repeated ESI [88]. We should bear in mind that repeated ESIs within 3 months provide cumulative effects [89]. An appropriate interval between ESIs should be decided based on the average duration of HPA axis suppression after ESI without affecting the physiological restoration. Multiple ESIs using particulate steroids require a sufficient interval of about 3–4 weeks due to a long-lasting HPA axis suppression, while non-particulate steroids require shorter periods. The World Institute of Pain (WIP) Benelux working group recommended that the number of ESIs should be adjusted according to the clinical response, suggesting that a 2-week interval for additional ESI may be appropriate for proper evaluation and minimization of endocrine side effects, and the lowest effective dose should be used for ESI (40 mg for methylprednisolone, 10 to 20 mg for triamcinolone, and 10 mg for dexamethasone) [90].

In the future, determining the optimal steroid dose, duration, and interval for ESIs is essential to develop a treatment protocol with minimal complications without compromising the treatment's effectiveness.

6. Adjuvants for epidural administration

In the last few decades, several non-anesthetic applications for epidural procedures have emerged. Epidural catheter infusion techniques of analgesics are being used increasingly for pain control at the end of life in both children and adults, including those with cancer-related pain [91]. In addition to opioids, which are commonly added to epidurally administered local anesthetics, a large number of other pharmacologic agents have been used. Most of these are administered as adjuvants, such as clonidine and dexmedetomidine, while ketamine and neostigmine are still under investigation and are not part of routine clinical practice. Others can be administered as the sole drug, such as antineoplastic drugs (i.e., methotrexate for primary CNS lymphoma) or antibiotics (for ventriculitis or post-neurosurgical infections) [92].

A broad understanding of the pharmacology of those agents is essential for the clinician to utilize them safely and efficiently. Furthermore, it is important to realize that many of those drugs have not been approved for epidural use and are hence used

off-label, even when clinically established [93]. **Table 2** reveals the list of Food and Drug Administration (FDA)-approved neuraxial drugs.

6.1 Alpha-adrenergic receptor agonists

Alpha-adrenergic receptor agonists are added to neuraxial drugs for several reasons: reducing local anesthetic clearance and distribution from the epidural and spinal space, an intrinsic analgesic effect, and a local anesthetic-sparing property [94]. In this way, complications and side effects associated with the use of epidural local anesthetics and/or opioids can potentially be reduced. Clonidine and dexmedetomidine are the two most important representatives that can cause dose-dependent side effects (sedation, hypotension, and bradycardia) [95]. Therefore, it is important to make a clear risk-benefit assessment before administering any of these drugs neuraxially.

6.1.1 Clonidine

Clonidine exerts a direct analgesic effect by binding to α2-adrenoceptors in the spinal cord, leading to presynaptic inhibition of Aδ and C-fiber transmitter release. Neuraxial administration of clonidine has a dose-sparing effect on local anesthetics and local anesthetics combined with an opioid, which could reduce the incidence of adverse events [96]. It can produce local vasoconstriction, decreasing the vascular clearance of the local anesthetic around neural structures. It is also a highly lipophilic substance and therefore exerts systemic absorption, with redistribution to more peripheral sites of action [97]. Therefore, adequate hemodynamic monitoring is necessary when administering clonidine to patients.

6.1.2 Dexmedetomidine

Dexmedetomidine is a selective central α2-adrenergic agonist with sedative properties and works similar to clonidine. When administered as a neuraxial adjuvant, it reduces the required local anesthetic dose and prolongs and potentiates postoperative analgesia [98]. Although the FDA has not approved dexmedetomidine as an adjuvant in neuraxial blocks, it is widely used and is still in use in anesthesia practice as an adjuvant in regional anesthesia for both epidural and intrathecal modalities. In several studies, 1–2 μg/kg of dexmedetomidine along with bupivacaine for caudal epidural block led to prolonged analgesia without significant side effects [99, 100]. Also, dexmedetomidine during labor epidural analgesia demonstrated good maternal satisfaction without deleterious effects on uteroplacental circulation and newborns' outcomes [101]. Nevertheless, there is still insufficient safety data to support the use of neuraxial dexmedetomidine in the clinical setting.

6.1.3 Adrenaline (epinephrine)

Adrenaline (epinephrine) is used both epidurally and intrathecally to enhance the duration and intensity of neuraxial drugs. It causes vasoconstriction of blood vessels, which reduces neuraxial clearance [94]. Low intrathecal doses (less than 100 μg) led to prolonged sensory and motor block duration but were associated with a greater incidence of hypotension or PONV [102]. Also, neuraxial adrenaline can potentially

exacerbate local anesthetic-induced neurotoxic damage in patients whose spinal cord circulation is compromised (such as can occur with diabetes mellitus or arteriosclerosis) [103]. Based on a systematic review, the beneficial effects of adding epidural epinephrine to a local anesthetic remain uncertain [104].

6.2 Miscellaneous adjuvants commonly used via epidural route

6.2.1 Ketamine

Ketamine is a selective, non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, with analgesic and anti-hyperalgesic effects. The side effects of ketamine include psychological and mild sympathomimetic effects. There is still no conclusive evidence that epidural ketamine is superior to intravenous administration [105, 106]. Although a systematic review showed a statistically significant, but probably clinically irrelevant, minimal reduction in pain scores when epidural ketamine was used in conjunction with opioids [107].

6.2.2 Magnesium

Magnesium is an NMDA receptor antagonist and regulates the influx of calcium into cells, both resulting in an analgesic effect. Due to the fact that magnesium does not cross the blood-brain barrier easily, it is also used neuraxially [108]. Systematic reviews have shown that epidural administration of magnesium prolongs the time to the first analgesic rescue medication, provides a minimal difference in early pain scores at rest after intrathecal use, and provides a 30% reduction in cumulative morphine use in the first 24 h after surgery [108, 109]. In animal studies, neuraxial magnesium has a neurotoxic potential [110], but to date, no optimal epidural magnesium doses in humans have been established. This should raise caution when one is considering administrating magnesium neuraxial.

6.2.3 Midazolam

Midazolam is a benzodiazepine and is an indirect agonist of gamma-aminobutyric acid (GABA) receptors in the spinal cord. It causes neural inhibition by facilitating the influx of chloride into cells. Epidural administration of midazolam as an adjuvant to local anesthetic in a postoperative continuous infusion increases analgesic and sedative effects and also reduces nausea and vomiting [111, 112]. However, midazolam appears to exacerbate the neurotoxic properties of local anesthetics [113], and therefore, it is questionable if midazolam is appropriate and safe for administration *via* the neuraxial route.

6.2.4 Neostigmine

Neostigmine, a quaternary ammonium salt, is an indirectly acting parasympathomimetic. Inhibition of cholinesterase prolongs and enhances the effect of acetylcholine on muscarinic and nicotinic receptors. Adding neostigmine to epidural morphine increases the time for administration of the first analgesic rescue medication, but total opioid consumption does not change [114, 115]. Neuraxial neostigmine has multiple side effects, including hypotension, sedation, and especially nausea and vomiting, but it does not appear to cause neurotoxicity [115].

	FDA approval	Epidural	Intrathecal
Local anesthetics	Lidocaine	Yes	Yes
	Bupivacaine	Yes	Yes
	Levobupivacaine	Yes	No
	Ropivacaine	Yes	No
	Mepivacaine	Yes	No
	Chloroprocaine	Yes	Yes
	Tetracaine	No	No
Opioids	Morphine	Yes	Yes
	Sufentanil	Yes	Yes
	Fentanyl	No	Yes
	Hydromorphone	No	No
	Buprenorphine	No	No
	Diamorphine	No	No
	Tramadol	No	No
	Methadone	No	No
	Meperidine	No	No
	Levorphanol	No	No
	Butorphanol	No	No
	Oxymorphone	No	No
	Pentazocine	No	No
Calcium channel antagonists	Ziconotide	No	Yes
	Gabapentin	No	No
	Verapamil	No	No
GABA agonists	Baclofen	No	Yes
	Muscimol	No	No
	Midazolam	No	No
Cyclooxygenase inhibitors	Ketorolac	No	No
	Aspirin	No	No
	Perecoxib	No	No
	Lornoxicam	No	No
Cholinergic agonists	Neostigmine	No	No
Adenosine agonists	Adenosine	No	No
Dopamine antagonists	Droperidol	No	No
Corticosteroids	Methylprednisolone	No	No
	Hydrocortisone	No	No
	Triamcinolone	No	No
	Betamethasone	No	No
	Dexamethasone	No	No

	FDA approval	Epidural	Intrathecal
NMDA receptor antagonists	Ketamine	No	No
	Esketamine	No	No
Somatostatin agonists	Octreotide	No	No
Adrenergic agonists	Clonidine	Yes	No
	Dexmedetomidine	No	No
	Adrenaline (epinephrine)	No	No
	Epinephrine co-administered with bupivacaine	Yes	No
	Epinephrine co-administered with lidocaine	Yes	No
	Phenylephrine	No	No
Adjuvants	Magnesium sulfate	No	No
	Sodium bicarbonate	No	No
	Dextran	No	No

Table 6.
FDA US Food and Drug Administration, GABA gamma-aminobutyric acid, NMDA N-methyl-D-aspartate [91].

The use of adjuvants with LAs has been practiced for many years and remains the subject of much interest. Many anesthesiologists advocate their use since their nomination with LAs allows the reduction in doses of both classes of drugs, thus lessening the likelihood of side effects attributed to each. Although the evidence for significant benefit is limited (i.e., clonidine or adrenaline), other adjuvants have been found to be effective but at the expense of frequent side effects (i.e., neostigmine). At this point, only the role of NMDA receptor antagonists seems favorable, and further studies are awaited. Furthermore, many of those drugs have not been approved for neuraxial use and are hence used off-label, partially due to the lack of large clinical trials. Therefore, it is important to make a clear risk-benefit assessment before epidural administration of any of these drugs (**Table 6**).

7. Future perspectives

In addition to the currently approved drugs for neuraxial administration, a whole range of new drugs has been approved for other indications or routes of administration, but are still used off-label for spinal or epidural injections.

As for local anesthetics are concerned, some of the old agents have been reinforced, such as **2-chloroprocaine** [116] and **prilocaine** [117]. Both of them are used for short-duration spinal anesthesia and have a promising place in day-case surgery. However, both of them are still not approved for epidural administration (**Table 1**). Also, novel long-lasting LAs have been developed. **Tonicaine (n-β-phenylethyl lidocaine)** [118] and **n-butyl-tetracaine** [119], derivatives of lidocaine and tetracaine, produce prolonged sensory blockade, which lasts longer than motor blockade, and the onset of action is significantly slower than with the original agent. Another LA that has shown promise as a long-acting agent is **n-butyl amino-benzoate** (BAB) [120, 121]. A single epidural or peripheral nerve block using BAB has provided pain relief for up

to 14 weeks, and it has been used successfully in the management of excruciating pain associated with advanced malignancy. It provides good and long-lasting analgesia combined with a low incidence of motor blockade. Future studies are required to establish the safety of these LAs.

A variety of **animal toxins** such as tetrodotoxin (a naturally occurring toxin of the puffer fish fugu), ProTx-II peptide (from the venom of the tarantula), or omega-conotoxin (from the venom of piscivorous marine snails) specifically block voltage-sensitive calcium channels in a way similar to LAs [122, 123], but their clinical use is still limited due to considerable systemic toxicity.

Some previously established drugs have been found to have LAs effects: **Sameridine** and **pethidine** are compounds with LA and opioid actions, which have been used successfully as intrathecal agents in human studies. The duration of a sensory blockade is similar to that of lidocaine, but analgesia is more prolonged and without side effects such as respiratory depression [124, 125]. **Tricyclic antidepressants** (such as amitriptyline) share several properties, both physical and pharmacological, with LAs. They share a common mechanism of action with both blocking neuronal sodium channels in a use-dependent manner, although tricyclic antidepressants also affect numerous other neurotransmitters including serotonin, glutamate, adenosine, and acetylcholine [126].

Additionally, **advances in delivery systems** have been made. The liposomal delivery system has been developed in an attempt to prolong the duration of action of administered LAs without the need for adjuvant drugs, nerve sheath catheters or pumps. Liposomes are microscopic lipid vesicles (0.02–40 μm) that act as a reservoir of drugs. They prevent redistribution from the site of injection to other tissues, due to the fact that a very small fraction of the drug is bioavailable and therefore, decreases the risk of systemic toxicity. Work in animal models and in humans has shown that the release of liposomal-encapsulated LAs and morphine occurs more slowly than with standard preparations of either drug, resulting in a prolonged analgesic effect without an increase in the time to onset of analgesia [127, 128]. Improved pain scores and decreased opioid consumption have been demonstrated for up to 48 h after lower abdominal surgery, hip arthroplasty, and Cesarean section [129–131]. The safety of liposomal preparations is yet to be fully established. There are concerns regarding the potential neurotoxicity of the liposomes and a risk for liposomal breakdown, resulting in the rapid release of large amounts of free drugs [132]. Hopefully, in the future, these delivery systems should provide the clinician with both an extended range and a choice in the degree of prolongation of the action of each agent.

8. Conclusion

Epidural anesthesia and analgesia often present as a supplement to general anesthesia for surgical procedures in pediatric and adult patients. Medications administrated in epidural space provide analgesia in intraoperative, postoperative, peripartum, and end-of-life settings with a special benefit in a group of elderly patients and those with different comorbidities. Special caution is required during the procedure since the epidural space is "virtual" with anatomical relationships and possible spine pathology that makes the epidural space irregular and segmental, and can affect the spread of the medications and their final drug efficacy. The main goal of the epidural blockade is to produce a quality sensory block with the lack of motor

block. However, autonomic fibers are more susceptible to blockade and reach 2–6 dermatomal levels higher than the sensory block, resulting in cardiovascular and hemodynamic changes that affect almost all organ systems, respectively.

Drugs administrated in the epidural space pass their way to the site of action by diffusion into the CSF through the spinal meninges and are influenced by dose, volume, and concentration of the drug, surface area, protein binding, and lipid solubility, respectively. LAs in a combination with opioids are the most common epidural administrated drugs. LAs inhibit action potential in nociceptive fibers and block the transmission of pain impulses by blocking VGSC. By duration of action, they are classified into the short-, intermediate-, and long-acting groups. On the other hand, opioids are lipid-soluble weak bases that are highly bound to the proteins and are ionized at physiologic pH. They bind to four main types of opioid receptors mainly located in the dorsal horn of the spinal cord, each having their prototype agonist producing the clinical effect. Special caution must be set on their adverse effects with an emphasis on the life-threatening event called local anesthetic systemic toxicity (LAST) and opioid-related depression of the ventilation, that must be treated timely.

New treatment techniques for patients suffering from back pain syndrome include epidural steroid injection (ESI) with corticosteroid administration into the epidural space having an anti-inflammatory effect. Corticosteroids can have a severity of complications. Therefore, a 2-week interval for additional ESI is suggested. Dexamethasone is considered generally safer than methylprednisolone, but further studies are necessary. In addition to the mentioned drugs, many other drugs can help in achieving a successful epidural block, such as adjuvants. However, many of them have not been approved for epidural use and hence are used off-label, even when clinically established. Additionally, new LAs, animal toxins, and liposomal delivery systems have been developed in an attempt to provide clinically effective epidural block.

Since epidural blockade is a complex process, which takes place at many different sites, further investigations are required to fill the gaps in our knowledge of the fundamental process of epidural action. The majority of variables involved in epidural drug efficacy are not susceptible to direct measurement. Therefore, careful experimental design and examination of direct and indirect evidence from clinical and laboratory sources are needed for better clarification.

Conflict of interest

The authors declare no conflict of interest.

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