CNS Drugs (2022) 36:877–896
https://doi.org/10.1007/s40263-022-00936-y

REVIEW ARTICLE

The Options for Neuraxial Drug Administration

Henning Hermanns[1] · Elke M. E. Bos[1] · Mark L. van Zuylen[1] · Markus W. Hollmann[1] · Markus F. Stevens[1]

Accepted: 14 June 2022 / Published online: 15 July 2022
© The Author(s) 2022

Abstract

Neuraxial drug administration, i.e., the injection of drugs into the epidural or intrathecal space to produce anesthesia or analgesia, is a technique developed more than 120 years ago. Today, it still is widely used in daily practice in anesthesiology and in acute and chronic pain therapy. A multitude of different drugs have been introduced for neuraxial injection, only a part of which have obtained official approval for that indication. A broad understanding of the pharmacology of those agents is essential to the clinician to utilize them in a safe and efficient manner. In the present narrative review, we summarize current knowledge on neuraxial anatomy relevant to clinical practice, including pediatric anatomy. Then, we delineate the general pharmacology of neuraxial drug administration, with particular attention to specific aspects of epidural and intrathecal pharmacokinetics and pharmacodynamics. Furthermore, we describe the most common clinical indications for neuraxial drug administration, including the perioperative setting, obstetrics, and chronic pain. Then, we discuss possible neurotoxic effects of neuraxial drugs, and moreover, we detail the specific properties of the most commonly used neuraxial drugs that are relevant to clinicians who employ epidural or intrathecal drug administration, in order to ensure adequate treatment and patient safety in these techniques. Finally, we give a brief overview on new developments in neuraxial drug therapy.

Key Points

Neuraxial drug administration is widely used in anesthesiology and pain therapy.

The neuraxial route is characterized by unique pharmacokinetic and pharmacodynamic properties, and many drugs have been introduced to clinical practice.

A solid understanding of the pharmacology of neuraxially administered drugs is indispensable for anesthesiologists and pain practitioners using these techniques in order to safely and efficiently accomplish anesthesia and analgesia.

In the present review we summarize the pharmacology of the most commonly used neuraxial drugs, the clinical indications, possible neurotoxic effects and new developments in neuraxial drug therapy.

✉ Markus W. Hollmann
m.w.hollmann@amsterdamumc.nl

[1] Department of Anesthesiology, Amsterdam UMC, University of Amsterdam, Meibergdreef 9, Amsterdam, The Netherlands

1 Introduction

Administration of drugs via the epidural or intrathecal route, both of which together are referred to as neuraxial anesthesia, is a technique that is predominantly used by anesthesiologists and pain specialists. Today, more than 120 years after the first spinal anesthesia, performed by August Bier using cocaine [1], neuraxial techniques are an integral part of modern anesthesia concepts.

In the vast majority of cases, local anesthetics are administered to achieve anesthesia or analgesia in a wide variety of settings, comprising surgery, labor pain, acute and chronic pain management, or spasticity [2]. In addition to opioids, which are commonly added to neuraxially administered local anesthetics, or more uncommonly used as the sole neuraxial drug, a large number of other pharmacologic agents have been used. Most of these as adjuvants, such as clonidine, dexmedetomidine, ketamine, or dexamethasone [3]; others as the sole drug, such as ziconotide or baclofen. Based on the proximity to the spinal cord, neurotoxicity limits the use of some agents for intrathecal administration (e.g., ketamine) whereas for others, fast epidural resorption does not outweigh the benefits compared to a direct systemic application. Furthermore, it is important to realize that many of

those drugs have not been approved for neuraxial use, and are hence used off-label, even when clinically established.

The application of medication via the neuraxial route has unique pharmacokinetic and pharmacodynamic characteristics. These are affected by the anatomy of the respective compartments, bypassing the first-pass metabolism and the vicinity of the primary effector sites, next to the general physicochemical properties of the respective drugs.

A profound knowledge on factors that affect the clinical effects of neuraxially injected agents is essential to anesthesiologists or pain specialists to secure efficient and safe use of this technique. In this article, we focus first on the anatomical and pharmacological aspects of neuraxial drug administration, clinical indications, as well as their potential neurotoxicity, and then provide a concise overview on the drugs that are clinically used on a regular basis.

2 Anatomy Relevant to Neuraxial Drug Administration

The epidural space reaches from the skull base to the sacral hiatus and consists predominantly of adipose tissue and abundant vessels, mostly veins. It encircles the spinal canal containing the dural sac and the spinal cord. 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 an anatomical distinct compartment nor a homogenous compartment. The posterior epidural space is traversed by thin fibrous dorsal meningo-vertebral ligaments connecting the dorsal dura to the lamina and ligamenta flava [6]. A dorsal midline structure called plica mediana dorsalis from the dorsal end of the dura to the laminae may compartmentalize the right and left posterior epidural spaces. Although these ligaments should not hinder epidural spread, they can influence catheter advancement and may facilitate catheter migration through the intervertebral foramen [4]. Vice versa, paravertebral catheters can migrate into the epidural space and local anesthetics, if injected with high pressure around the lumbar plexus, can spread into the epidural space [5]. Although this anatomical structure can frequently be seen during epiduroscopy, it rarely completely compartmentalizes the epidural space [6, 7]. To what extent the plica mediana dorsalis is responsible for unilateral and asymmetric epidural spread is unknown. Furthermore, high-definition 7T three-dimensional magnetic resonance imaging reconstruction has recently visualized another hitherto unknown compartmentalization of the epidural space and has been confirmed in cadavers [8]. While the vertebral laminae are closely attached to the dural sac by fibrous tissues, pyramidal-shaped fat pads are found between the laminae under the ligamenta flava. Those fat pads could further explain the inhomogeneous spread of a local anesthetic and the deviation of epidural catheters.

Finally, a significant percentage of patients have ligament flava with a midline gap, as has been demonstrated in three-dimensional magnetic resonance imaging as well as anatomical dissections [9, 10]. These gaps are about 1 mm wide in the midline at the upper border of the lamina and can extend to the lower border of the next lamina. Most frequently, those gaps are seen from C3/4 to T2/3 (60–75%), while between T10/11 and L1/2 they occur in a frequency of 28–35% and are infrequent at lower lumbar levels (0–11%) [9–11]. Thus, these midline gaps connect the epidural space with the retrolaminar compartment and may be responsible for some leakage of local anesthetics. More importantly, these midline gaps may interfere with the "Loss of resistance" that is used by the anesthesiologist to identify the epidural space, facilitating the inadvertent dural tap.

This challenging anatomical composition of the epidural space is properly illustrated by Arendt and Segal "For those who have studied the epidural space, it may seem amazing that epidurals ever work." [12]. Considering these anatomical features, it is not astonishing that epidural spread and intensity vary considerably. Therefore, the success percentage of epidural anesthesia varies between 53 and 87% [13]. Nevertheless, with catheter retraction or new placement the success percentage can be increased to almost 100% [14]. This contradiction of the primary success rate and success rate after top-ups, partial catheter retraction, and a newly placed epidural may be explained by the great variability of the epidural space. It is difficult to place a catheter at the right place, but with replacement of a catheter, retraction of the catheter tip, or added volume a sufficient spread of local anesthetics can be achieved in a very high percentage of cases.

2.1 Pediatric Anatomy

Classically, it was hawked that in babies and neonates the conus medullaris ends at the third lumbar vertebra (L3) or lower in contrast to L1/2 in adults. Furthermore, the dural sac was supposed to ascend from S3–4 in infants to L1–2 in toddlers. More recent ultrasound studies, however, illustrated that even in neonates the median termination of the spinal cord is located at L2 and that a spinal cord descending to mid-L3 or lower is suspicious for a tethered cord [15, 16]. Similarly, the dural sac in infants rarely reaches to a level below S2 [17]. These differences are partially explained by

Table 1 Weight-adapted dose of bupivacaine as suggested by the American Society of Regional Anesthesia and Pain Medicine/European Society of Regional Anaesthesia and Pain Therapy for pediatric spinal anesthesia [19]

Weight (kg)	Bupivacaine dose (mg/kg)
< 5[a]	1
5–15	0.4
> 15	0.3

[a]Also for neonates and premature newborns

different positions of the neuraxis used in the reported literature. While anatomical studies of the neuraxis are classically performed in a prone position, clinical ultrasound studies are conducted with the lumbar vertebral column flexed [18]. Thus, in the same position where the neuraxial blockade is performed. Therefore, the ultrasound investigations are a better representation of the anatomy as it is approached by the anesthesiologist.

Spinal anesthesia is frequently performed in young infants for a variety of reasons: improved hemodynamic stability, less early postoperative apnea, and possibly reduced neurotoxicity of general anesthetics. However, small infants have a relatively higher liquor volume compared with older children or adults. Therefore, the weight-adapted dose is relatively higher in small infants compared with older children (Table 1 [19]). Furthermore, the resorption of local anesthetics from liquor into the systemic circulation in infants is much faster reducing the duration of action of a single-shot spinal anesthesia from about 3 hours in adults to approximately 1 hour in neonates, although the dose per kilogram is much higher in neonates.

3 Pharmacology of Neuraxial Drugs

When drugs are administered neuraxially, 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, neuraxially administered drugs need to reach their primary site of action to work. Absorption to the main target site (i.e., the spinal cord and intrathecal dorsal nerve root [20]) as well as local and systemic (re-)distribution determine the onset and duration of action of epidural and intrathecal drugs. First, the general pharmacological properties and mechanisms of action of the respective drugs apply.

3.1 General Pharmacological Aspects of Neuraxial Drug Administration

For *local anesthetics*, the most relevant properties are the ionization constant (pKa value), lipophilicity, and the degree of protein binding. While the potency of a local anesthetic 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 (increased protein binding is associated with a longer duration of action) [21].

The primary mechanism of action of local anesthetics is the blockade of voltage-gated sodium channels [22]. However, a plethora of different ion channels, receptors, and other molecular targets have been shown to be additional targets of local anesthetics, as shown predominantly from experimental studies on lidocaine [23].

Neuraxial administration of local anesthetics frequently causes hypotension, both with and without adjuvants, and is related to height of the block [24–26] Lower doses of local anesthetics and the addition of synergistic low doses of opioids significantly reduce the risk of hypotension in both epidural and spinal anesthesia [25, 27].

Systemic absorption of local anesthetics may, in large doses, have deleterious effects [28]. Toxic symptoms, mainly neurological and cardiovascular, following an epidural injection are rare [29], but may occur through rapid systemic absorption or an accidental intravascular injection of a local anesthetic [28, 29]. Important in the management of local anesthetic toxicity are the discontinuation of administration of local anesthetics and supportive care. In cases of severe local anesthetic toxicity, the use of intravenous lipid emulsions is recommended [30].

Concerning *opioids*, lipid solubility is the essential determining factor for pharmacological effects after neuraxial application. Hydrophilic opioids such as morphine have a slower onset and a longer duration of action, while lipophilic opioids such as fentanyl produce a rapid onset and shorter duration of action. 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 (delayed) respiratory depression and sedation [31, 32].

The mechanism of action of neuraxial opioids, mediated largely by μ-opioid receptors, is an interplay of local effects within the spinal cord, supraspinal effects due to rostral spread especially for hydrophilic opioids, and systemic effects after absorption of the opioid, primarily from the vasculature in epidural fat tissue. The significance of cerebral or systemic effects is variable as is the extent of segmental

or spinal cord action, and hinge particularly on the physicochemical properties of the respective opioid [33, 34].

Neuraxial administration of opioids causes similar side effects as systemic administration, including sedation, nausea, pruritus, and (delayed) respiratory depression [35]. As with systemic administration, administering neuraxial hydrophilic opioids (e.g., morphine) provides long-lasting analgesia, which is enhanced when given together with a local anesthetic [20]. Neuraxial administration of hydrophilic opioids, which have higher bioavailability and spinal cord selectivity [36], can cause delayed respiratory depression up to 24 hours after intrathecal or epidural administration [37]. It is not yet entirely clear whether this is due to active metabolites (e.g., morphine-6-glucuronide, the active metabolite of morphine, has very strong analgesic properties) or to the rostral migration of the hydrophilic opioid via the cerebrospinal fluid to the brainstem [31].

The incidence of delayed respiratory depression caused by neuraxial hydrophilic opioids seems to be similar to systemic administration [37, 38]. However, it is important to consider the heterogeneity in the reporting studies, both in terms of study populations, dosages administered, and definitions used for delayed respiratory depression [37, 38]. Alongside general pharmacological and drug-specific properties, owing to distinct anatomy, pharmacokinetic mechanisms differ between epidural and spinal routes of administration and account for relevant differences in clinical effects between these two techniques.

3.2 Pharmacological Aspects Specific to Epidural Drug Administration

Redistribution from the epidural space through the meninges into the cerebrospinal fluid (CSF) is the major mechanism for epidural drugs to reach the primary target site [39]. Diffusion among the arachnoid mater depends on the concentration gradient, volume (effectuating surface area), lipid solubility, and protein binding of the respective drug. The predominant factor determining CSF bioavailability of epidural drugs is their lipid solubility [40]. Here, hydrophilic drugs such as morphine reach higher spinal bioavailability, while lipophilic drugs such as fentanyl and sufentanil are easily sequestrated to epidural adipose tissue. The overall spinal bioavailability of epidurally administered drugs is low, with a range between approximately 5% and 20% [36, 41–44]. Lipophilic drugs are also readily cleared into the plasma and can hence produce undesired central nervous system side effects. In turn, this clearance rate is dependent on vascularization and local blood flow in the capillary network of the dura mater, which can be lowered by the addition of vasoconstrictors such as epinephrine.

Table 2 Factors affecting the intrathecal spread of local anesthetics

Drug-specific factors	Patient-specific factors	Procedure-specific factors
Baricity	Patient height	Injection speed
Temperature	Position	Injection pressure
Viscosity	Age	Needle orientation
Dosage	Anatomy	Needle approach

3.3 Pharmacological Aspects Specific to Intrathecal Drug Administration

In contrast to epidural drug administration, the rate of diffusion into target tissue after spinal injection is rapid, owing to a high CSF concentration and a short diffusion distance of only a few millimeters [39]. This is reflected by a much smaller dose required to reach similar effects, when compared with an epidural injection. In turn, this accounts for the lower risk of systemic toxicity of the respective drug. Furthermore, the onset of effect is significantly faster than with the epidural route.

In general, and similar to the epidural space, lipophilicity of drugs is the major determinant of intrathecal pharmacokinetics. Further relevant factors affecting CSF distribution are drug volume, baricity, CSF flow rate, and intrathecal residence time [45]. Factors that affect the intrathecal spread of local anesthetics are manifold, as shown in Table 2.

When a drug is injected into the intrathecal space, systemic absorption is considerably slower than after epidural injection, given the latter is significantly more vascularized, permitting rapid uptake. Hence, given there is likewise no relevant local drug metabolism, pharmacological agents that would systemically be rapidly metabolized or distributed, especially hydrophilic drugs can display persisting effects. These factors also explain why, for example, intrathecal morphine can cause delayed respiratory depression due to rostral spread within the subarachnoid space.

4 Clinical Use of Neuraxial Drug Administration

4.1 Perioperative

In the perioperative setting, different methods of neuraxial drug administration can be distinguished: intrathecal drugs, i.e., spinal anesthesia, the administration of epidural drugs, and a combination of these two techniques, i.e., combined-spinal epidural (CSE) procedures. Typical indications for spinal anesthesia include surgical procedures involving the lower abdomen (including cesarean section), pelvis, and lower extremities [46]. In addition to these classic indications,

other options for spinal anesthesia are under investigation, for instance, the use of spinal anesthesia for laparoscopic procedures of the upper abdomen such as laparoscopic cholecystectomy [47] or peritoneal inguinal mesh repairs [48] and for spinal surgeries such as single-level discectomy [49]. In cardiac surgery, the use of a high spinal anesthetic technique in addition to general anesthesia has been reported [50]. Goals of spinal anesthesia for these 'newer' indications comprise possible lower stress responses with a reduction in inflammatory mediators [50], cost effectiveness, less post-operative nausea and vomiting, better post-operative analgesia, quicker recovery, and possibly earlier extubation after cardiac surgery compared with general anesthesia only [51]. However, these advantages are questionable, as negative side effects and complications are reported such as hypotension, urinary retention, post-dural puncture headache, shoulder pain during laparoscopic interventions in awake patients, and the need for conversion to general anesthesia [52]. In conclusion, spinal anesthesia is indicated for surgical procedures involving the lower abdomen, pelvis, and lower extremities and may be an option for other procedures in selected patients with significant risks associated with general anesthesia [52] provided that the surgical procedure and anticipated duration of the procedure are appropriate.

Epidural analgesia is regularly used to provide pain relief for major open abdominal surgeries and thoracotomies [53, 54]. For pain management after major open abdominal surgeries, the use of epidural analgesia has been reported to be superior in terms of decreased pain scores compared with continuous wound infiltration and patient-controlled analgesia with intravenous opioids [55, 56]. However, the historically reported beneficial effects of epidural analgesia on morbidity, mortality, complication rates, return of bowel functioning, and reduced length of hospital stay have been questioned, whereby even higher complication rates (hypotension with consecutive fluid overload, urinary retention) and an increased length of hospital stay have been reported [56]. Other factors such as the avoidance of fluid overload, bowel stimulation, and postoperative rehabilitation programs have led to reduced complications rates also in patients treated with alternatives for epidural analgesia. [55]

Furthermore, with the implementation of minimally invasive surgical methods and an increasing awareness for the more frequently than expected occurring (1:1000-1: 6000 cases) serious complications of epidural analgesia, the overall trend seems to move away from neuraxial blocks in favor of truncal blocks, peripheral nerve blocks, and local anesthetic wound infiltration where possible [54]. In addition, use of epidural anesthesia and peripheral nerve blocks seems to vary in different hospital types and locations. A study evaluating the use of neuraxial anesthesia versus peripheral nerve blocks for total hip and knee arthroplasties from 2006 to 2013 showed a decreasing trend for the use of neuraxial anesthesia in most hospitals toward the end of the study period (2012–2013). However, the contrary applied to rural hospitals, where neuraxial anesthesia was in fact increasing. For peripheral nerve blocks, an increasing trend was seen, with a significantly higher use in total knee arthroplasty compared with total hip arthroplasty, and a strong increase was observed in large teaching hospitals [57].

In cytoreductive surgery and cancer-related abdominal debulking procedures, epidural analgesia remains the gold standard, based on the available literature [54, 58]. However, the coagulation status and occurrence of thrombocytopenia can be a limiting factor in widespread use of this modality in these patients [58].

In conclusion, alternative analgesic techniques, including (among others) continuous wound infiltration and truncal and paravertebral blocks, are increasingly used in surgical procedures with a historical preference for the use of epidural analgesia [56]. Epidural analgesia is no longer a routine choice in enhanced recovery protocols for open intestinal, colon, colorectal, or aortic surgery [55]. Alternative analgesic techniques can be considered; however, some benefits (e.g., statistically significant superior pain relief and improved patient satisfaction) of epidural analgesia provided to patients undergoing major open surgical procedures have been proven [53]. We underscore an individualized perioperative analgesic approach depending on patient and surgical characteristics, as the severity of postoperative pain varies for minimally invasive surgery to major open procedures [58].

4.2 Obstetrics

Epidural analgesia is the gold standard for analgesia in the obstetric setting as efficacy is proven and complications and permanent neurological damage are rare in young and healthy women [56]. In addition to epidural analgesia, other neuraxial techniques can be distinguished, such as single-shot spinal anesthesia and CSE or a dural puncture epidural (DPE) technique.

For labor analgesia, CSE has the fastest onset time of analgesia. Combined-spinal epidural procedures during a cesarean section may offer the advantage of an intraoperative addition of epidural drugs in the case of prolonged surgery or an inadequate surgical block from the intrathecal anesthetic, next to the possibility of postoperative administration of neuraxial opioids and local anesthetics. However, after CSE, a higher incidence of urinary retention, nausea and vomiting, pruritus, and maternal hypotension compared with traditional epidural analgesia was reported [59, 60]. Combined-spinal epidural procedures might be an option in selected patients with a higher likelihood of neuraxial block failure [60]. The DPE technique is a modification of conventional epidural or CSE techniques that involves the intentional puncture of the dura with a spinal needle, without the intrathecal injection of

drugs, next to the placement of an epidural catheter into the epidural space. The drugs administered through the epidural catheter in the epidural space may enter the subarachnoid space by the previous punctured dura. With this theory, it is believed that the DPE technique combines the advantages of both CSE and epidural analgesia while mitigating the disadvantages [61]. However, there is a lack of clear evidence on the benefits and risks of the DPE technique, such that a recommendation for or against its routine use is premature [62].

Regarding the dosage of neuraxial drugs during labor, low-concentration local anesthetic solutions (bupivacaine less than 0.1% or equivalent) are preferred for the initiation and maintenance of labor epidural analgesia, as the quality of analgesia does not seem to be compromised, but lower rates of instrumental vaginal delivery and a shorter duration of second-stage labor were reported for women who received epidural analgesia with a low concentration of local anesthetics [63]. Overall, the use of neuraxial anesthesia for obstetric indications is widely implemented and provides excellent analgesia with minimal risks.

4.3 Chronic Malignant and Non-malignant Pain

Neuraxial techniques may be suitable for treating chronic pain refractory to standard treatments and include epidural or intrathecal drug-delivery systems [56]. The incidence of cancer-related pain is 39% after curative treatment and 55% during anticancer treatment, such as chemotherapy, radiation therapy, and surgery. The incidence of cancer-related pain in advanced, metastatic, or terminal disease is in the order of 66% [58]. Epidural and intrathecal analgesia is reported to be effective with decreased pain intensity [64]. Regarding neuraxial techniques in patients with cancer, there can be specific anatomical considerations to take into account. Vertebral metastases, spinal stenosis, loss of epidural fat in cachexia, and epidural invasion by tumors may complicate administration of neuraxial applied drugs and drug distribution [65]. Non-malignant pain conditions that may benefit from neuraxial drug-delivery systems comprise (among others) failed back surgery syndrome, lumbar post-laminectomy syndrome, complex regional pain syndrome and causalgia (complex regional pain syndrome type 2), phantom limb pain, and plexopathy [66].

To date, the US Food and Drug Administration and European Medicines Agency approve only ziconotide (a neuronal calcium channel blocker) and morphine for an intrathecal infusion for pain management. However, off-label drugs such as hydromorphone, fentanyl, sufentanil, bupivacaine, and clonidine are used in clinical practice, as monotherapies or combined agents [67].

The use of neuraxial techniques in patients with chronic pain, both patients with malignant and non-malignant pain, is often based on expert opinion. It can be considered for patients refractory to conventional pain treatments. Concerns for the use of neuraxial implantable devices in patients with chronic pain for the long-term administration of neuraxial drugs comprise infectious complications, risks of respiratory depression, withdrawal with drug discontinuation or pump malfunction, and the development of tolerance. Careful patient selection and management is important [68]. In a retrospective study evaluating a total of 1001 reports from a database of patients treated with intrathecal drug delivery systems from 2018 to 2019, the top three reasons for adverse reports are infection/erosion (15.7%, $n = 157$), motor stall (12.4%, $n = 125$), and adverse medication reactions (11.8%, $n = 119$). Five deaths were reported in the study period due to bacterial meningitis, spinal epidural hematoma, sepsis after device implant, and two cases of possible opioid overdose. Epidural hematoma ($n = 3$) after intrathecal drug delivery system surgery resulted in death, cauda equina syndrome 36 hours after intrathecal drug delivery system implantation, lower extremity sensory deficits, and residual neurological deficits after surgical evacuation. Granuloma, an intrathecal inflammatory mass, was reported in 19 (1.9%) cases within this analysis. The presentation ranged from an asymptomatic incidental diagnosis on magnetic resonance imaging to new back pain, lack of efficacy, reservoir volume discrepancy, worsening leg weakness, and paralysis-like symptoms. Patients were treated with a device explant ($n = 6$), catheter repositioning ($n = 3$), catheter replacement ($n = 2$), unclear surgical intervention ($n = 2$), termination of neuraxial applied drug [device filled with saline] ($n = 1$), and conservative treatment comprising follow-up imaging ($n = 1$). Neuraxial drug delivery systems may be considered, but possible complications are not negligible. Alternatives for epidural or intrathecal analgesia are sympathetic neurolysis, spinal neurolysis, nerve blocks, or plexus blocks depending of the location of the disease.

5 Neurotoxicity

All local anesthetics are locally neurotoxic depending on their concentration and duration of action. Although clinically neurotoxicity very rarely leads to permanent neural damage, such damage can be devastating. In the 1990s, the introduction of intrathecal microcatheters led to a number of cauda equine syndromes. This led to a large number of experimental studies assessing the mechanism of local anesthetic-induced neurotoxicity. The mechanism identified was mainly apoptosis and in higher concentrations necrosis [69, 70]. In most models, the concentrations inducing apoptosis (or necrosis) are frequently an order of magnitude lower than the concentrations clinically applied epidurally or intrathecally. However, while the concentrations in most models are

kept constant for hours or longer, in the clinical situation, the applied concentration of local anesthetic dilutes within minutes by orders of magnitude. The question of whether one local anesthetic is more or less toxic than another is not answered unequivocally. Most studies find a correlation between potency and neurotoxicity, i.e., equipotent local anesthetic doses induce equitoxic effects [71, 72]. The most prominent apoptotic pathways identified inducing apoptosis are the intrinsic (or mitochondrial) caspase pathway of apoptosis, the PI3K pathway, and the MAPK pathway [69].

Lidocaine (and other local anesthetics) when given intrathecally can lead to transient neurologic symptoms (TNS). The exact mechanism of TNS is hitherto unknown. Nevertheless, there are factors influencing the incidence of TNS. Ropivacaine (levo-) bupivacaine, prilocaine, and procaine have an approximately ten times lower risk than lidocaine of inducing TNS after spinal anesthesia, while mepivacaine and 2-chloroprocaine have similar TNS percentages to lidocaine [73]. Furthermore, the patient position influences the incidence of TNS after spinal anesthesia with lidocaine. While the lithotomy position has an incidence of TNS of about 30–36%, in the position for knee arthroscopy it is about 18–22% and in the supine position only 4–8% [74].

As there are many adjuvants used in clinical practice mixed with local anesthetics to enhance their effect and possibly reduce their dose and concentration, this may be a proper method to further reduce the risk of local anesthetic-induced neurotoxicity. However, a prerequisite would be that those adjuvants are at least not neurotoxic or even neuroprotective. In turn, there is hardly any evidence for clinically relevant neurotoxic effects of neuraxial adjuvants. The frequently used adjuvants have been applied in hundreds or thousands of patients without reports of an increased rate of neurological damage. The only exception is epidural corticosteroids, which led to very infrequent but severe neurological damage that led to a Food and Drug Administration warning in 2014.

Experimentally, opioids have the best record of not being neurotoxic themselves nor enhancing local anesthetic-induced neurotoxicity [75]. In contrast, midazolam, (es) ketamine, corticosteroids epidurally, and recently, dexmedetomidine have been demonstrated to induce neurotoxicity at least in some experimental models [76–86]. As many of the adjuvants described exhibit equally or at least partially analgesia-enhancing and block-enhancing effects when given systemically, the systemic application may be considered instead of the epidural application.

In conclusion, opioids applied epidurally or intrathecally can be considered safe. As neurotoxic effects cannot be excluded for most other adjuvants and the mechanism of action seems to be predominantly due to systemic absorption, we do not believe in the superiority of neuraxial administration.

6 Neuraxial Drugs in Clinical Use

A multitude of drugs have been applied via the epidural or intrathecal route since the introduction of these techniques into the clinic. However, only a few agents have gained approval for this indication (see Table 3). As follows, we detail the most relevant drugs used clinically.

6.1 Local Anesthetics

The use of neuraxial techniques for anesthesia and analgesia typically involves the use of local anesthetics, which may or may not be supplemented by adjuvants. Here, we give a brief overview on the clinically most relevant local anesthetics.

6.1.1 Lidocaine

Lidocaine is a hydrophilic local anesthetic of the amide type and a class Ib anti-arrhythmic agent, with a pKa of 7.8. Because of its anti-arrhythmic properties, lidocaine is also used in the treatment of ventricular arrhythmias [87]. In cardiac muscle fibers, lidocaine inhibits the large transient increase in membrane permeability to sodium during the plateau phase of the action potential. It also increases potassium efflux during the repolarization phase. Excitation conduction in the sinus node and supraventricular areas remains virtually unaffected. Lidocaine slows excitation conduction and produces negative inotropy, negative chronotropy, and hypotension [88].

Lidocaine is mainly used as an intrathecal local anesthetic in ambulatory surgery. The duration of action of lidocaine is relatively short and thus it is not suitable for use in lengthy procedures. It is safe to use as an intravenous analgesic given its favorable properties concerning cardiotoxicity and has the largest therapeutic window among local anesthetics [89–91].

Transient neurologic symptoms in the postoperative period occur more frequently when intrathecal lidocaine is used, compared with bupivacaine, levobupivacaine, or ropivacaine, a notion also confirmed in a recent Cochrane review of 24 trials [73]. Symptoms include non-permanent mild-to-severe gluteal and leg pain that may persist for days.

6.1.2 Bupivacaine

Bupivacaine is a long-acting local anesthetic of the amide type, with a pKa of 8.1. Bupivacaine is completely and biphasically absorbed from the epidural space. Slow absorption is the rate-determining factor in the elimination of bupivacaine. It has a plasma binding of 96%. Clearing of bupivacaine occurs primarily through metabolism in the liver, and it is more sensitive to changes in intrinsic hepatic enzyme function than of blood flow in the liver [92, 93].

Table 3 Synopsis on state of approval of neuraxial drugs

	FDA approval Epidural	FDA approval 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	No
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
Parecoxib	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
NMDA receptor antagonist		
Ketamine	No	No
Esketamine	No	No
Somatostatin agonists		
Octreotide	No	No
Adjuvants		
Adrenergic agonists		
Clonidine	Yes	No
Dexmedetomidine	No	No
Epinephrine	No	No
Epinephrine co-administered with bupivacaine	Yes	No
Epinephrine co-administered with lidocaine	Yes	No
Phenylephrine	No	No
Magnesium sulfate	No	No
Sodium bicarbonate	No	No
Dextran	No	No

FDA US Food and Drug Administration, *GABA* gamma-aminobutyric acid, *NMDA* N-methyl-D-aspartate

After administration, the effect occurs slowly (after more than 10 minutes) and persists for 3–3.5 hours [93]. In low doses, the sensory blockade is more pronounced than the motor blockade. Intrathecal bupivacaine is also available in a hyperbaric and hypobaric solution, which increases the steerability of nerve blocks. Hyperbaric bupivacaine is produced by the addition of glucose to isobaric (plain) bupivacaine, while dilution with distilled water renders bupivacaine hypobaric. The difference in density affects diffusion patterns and distribution after injection into the intrathecal space.

Bupivacaine has strong cardiotoxic properties (e.g., cardiac arrhythmias, myocardial depression) due to slow dissociation from the sodium ion channel [91]. This makes the drug unsuitable for intravenous analgesia.

6.1.3 Levobupivacaine

Levobupivacaine is a long-acting amide-type local anesthetic used in both intrathecal and epidural anesthesia and analgesia with a pKa of 8.1 and is the left-handed enantiomer of bupivacaine with a plasma binding of > 97%. Similar to bupivacaine, it blocks nerve conduction in sensory and motor nerves largely by interacting with voltage-gated sodium channels on the cell membrane, but potassium and calcium channels are also blocked [94, 95]. In addition, levobupivacaine affects stimulus transmission

and conduction in other tissues, with its effects on the cardiovascular system and central nervous system being of great importance to the occurrence of clinical adverse events [94, 95]. Levobupivacaine has similar anesthetic and analgesic effects to bupivacaine [96]. Additionally, the metabolism of levobupivacaine and bupivacaine is similar, with levobupivacaine being extensively metabolized and no unchanged levobupivacaine being found in the urine or feces [94, 95].

After neuraxial administration, there are some studies that showed that plasma concentrations of levobupivacaine were higher than those of bupivacaine [97, 98], although this was not found in other studies [99]. There may be a smaller risk of central nervous system toxicity in levobupivacaine compared with bupivacaine [100, 101]. Furthermore, levobupivacaine may provide a longer motor block than bupivacaine, but the block is not as pronounced [97]. Levobupivacaine has less cardiotoxic properties than bupivacaine, possibly owing to a lower affinity for cardiac sodium channels, although other cardiotoxic pathophysiology also seems to be involved [100–102] The doses at which clinically relevant differences in cardiotoxicity occurred between bupivacaine and levobupivacaine were high enough for central nervous system symptoms to occur [100, 101].

6.1.4 Ropivacaine

Ropivacaine is a long-acting local anesthetic of the amide type that has a pKa of 8.1. It has a chiral center and is available as a pure S-enantiomer. It is less lipid soluble (94%) than (levo-)bupivacaine. All metabolites have a local anesthetic effect, but significantly lower efficacy and a shorter duration of action than ropivacaine [103, 104]. As with bupivacaine, slow absorption is the rate-determining factor for the elimination of ropivacaine. Because ropivacaine has a low-to-moderate intermediate hepatic extraction rate, the elimination rate depends on the free unbound plasma concentration [103, 104].

When ropivacaine was initially marketed it was reported to have better differentiation in terms of sensory/motor blockade than the other local anesthetics; however, several conflicting results have since been reported [105]. Ropivacaine is thought to be safer in regard to toxicity than racemic bupivacaine. When ropivacaine was administered systemically to healthy volunteers, the tolerated maximum dose before cardiovascular or neurological effects occurred was about twice as high as when racemic bupivacaine was used [106, 107]. However, ropivacaine is about 30–50% less potent than racemic bupivacaine and levobupivacaine [108, 109] and it is also approximately two and a half times less lipophilic [110]. Moreover, taking into account some cases of serious complications that have occurred with an accidental intrathecal or intravenous injection of ropivacaine [111, 112], it remains uncertain whether ropivacaine actually has an increased safety profile at equipotent doses and an associated clinically relevant lower cardiotoxicity compared to other local anesthetics.

6.2 Opioids

In most cases, neuraxial opiates are given as adjuvants to long-acting local anesthetics [32, 113]. This provides, among other things, a longer analgesic effect and a reduction in the required local anesthetic dose, therefore reducing the risk of adverse effects. Usually, a lipophilic (e.g., fentanyl, sufentanil) opioid is chosen to prevent any late respiratory depression, although intrathecal morphine is frequently added for post-cesarean section pain relief, owing to its prolonged postoperative analgesic effects [114].

Opioids are, at times, used as the primary neuraxial drug, mainly in cases of severe chronic (palliative) pain where patients have received a spinal catheter for this specific indication [115–117]. We summarize next the clinically most used opioids for neuraxial administration.

6.2.1 Morphine

Neuraxial morphine has a long duration of action with good analgesia because of its hydrophilicity, making it a suitable opioid for single-bolus epidural but mainly spinal administration. However, the duration of action is directly dependent on the dosage chosen, with higher doses dramatically increasing the risk of adverse events [118]. Furthermore, morphine is also administered by continuous infusion through a spinal catheter in patients with severe chronic pain and palliative patients [115, 116].

To ensure adequate long-term analgesia (up to 48 hours), an extended-release epidural morphine containing multivesicular liposomes, giving it a depot function, was marketed to be administered without a local anesthetic. However, a large number of adverse events were observed with the initial dosing recommendations [119–124], which led to the dosing recommendation being adjusted downwards (i.e., $\leq$ 15 mg). This reduced the side effects but also shortened the duration of analgesia [125].

6.2.2 Hydromorphone

The potent hydrophilic opioid hydromorphone is used both epidurally [126] and intrathecally [117]. The analgesic effect of hydromorphone appears similar to that of other opioids when administered neuraxially [127–129], but its onset is

relatively slow. Less delayed respiratory depression than with morphine is reported for hydromorphone, although respiratory depression has been reported up to 4.5 hours after epidural administration [130]. These characteristics made hydromorphone a less favorable opioid for epidural administration compared with for example, fentanyl and sufentanil [36, 131]. Like morphine, intrathecal hydromorphone is used in severe chronic and cancer-related pain [117, 132].

6.2.3 Diamorphine

Diamorphine is a highly lipophilic prodrug with a rapid onset of action. Diamorphine is used both intrathecally [133] and epidurally [134] and appears to have a better risk profile than morphine with less risk of (late) respiratory depression [135]. Although some have suggested that this may be more related to the more variable doses of diamorphine and the fact that there are significantly more studies of neuraxial morphine compared with diamorphine, which could give a biased picture [118]. Additionally, diamorphine is characterized by a longer duration of action than the most commonly used other lipophilic opioids [136]. This is possibly related to diamorphine being metabolized in the spinal cord tissue to active metabolites, which are less lipid soluble than diamorphine and thus less likely to diffuse back into the CSF [137]. Neuraxial diamorphine is only available in the UK.

6.2.4 Fentanyl

Fentanyl is a lipophilic opioid with a rapid onset of action. As with most other lipophilic opioids, it is rapidly distributed to the spinal cord and epidural space and cleared quickly. Therefore, compared with hydrophilic opioids such as morphine, the risk of delayed respiratory depression with neuraxial administration is reduced [31]. The same applies to other side effects such as the risk of sedation [32]. Like most epidural adjuvants, fentanyl has a supra-additive local anesthetic-sparing effect [138]. However, epidurally administered fentanyl is supposed to have a primarily systemic, rather than neuraxial, effect [139].

6.2.5 Sufentanil

Sufentanil, like fentanyl, is a lipophilic opioid with a rapid onset of action. Distribution to, and clearance from, the spinal cord and epidural space is similar to fentanyl, resulting in fewer side effects than hydrophilic opioids [140]. Sufentanil has a local anesthetic-sparing effect, lacking an additional effect when administered epidurally compared with systemically [141, 142]. Sufentanil is highly potent, with respiratory depression occurring even at relatively low intrathecal doses [143].

6.3 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 [144, 145]. Through the local anesthetic-sparing effect, complications and side effects associated with the use of epidural local anesthetics and/or opioids can potentially be reduced.

Concerning the side effects of those agents, dexmedetomidine and clonidine can cause sedation, hypotension, and bradycardia, among other things, with the extent of the side effects being dose dependent [146]. When clonidine is administered at the thoracic level (compared with the lumbar level), as with morphine, the systemic side effects increase, possibly reflecting rostral spread [42]. Dexmedetomidine has a high incidence of sedation [147] and bradycardia [148]. It is therefore important to make a clear risk-benefit assessment before administering any of these drugs neuraxially.

6.3.1 Clonidine

Clonidine has supposedly a predominantly spinal site of action, suggesting that clonidine may be better administered neuraxially than systemically for its analgesic effect [144, 149]. It exerts its direct analgesic effect by binding to α_2-adrenoceptors in the spinal cord, leading to a presynaptic inhibition of Aδ and C-fiber transmitter release. Clinically, however, it is still a matter of discussion whether systemic clonidine is analgesic [150]. Because it is a highly lipophilic substance, there is also systemic absorption, with redistribution to more peripheral sites of action [151]. Neuraxial administration of clonidine has a dose-sparing effect on local anesthetics and local anesthetics combined with an opioid [152–154], which could reduce the incidence of adverse events. Interestingly, orally and intravenously administered clonidine also prolongs the anesthetic effect of intrathecal local anesthetics [155–158]. Intrathecal clonidine prolongs a sensory block by approximately 130 minutes and a motor block by about 45 minutes [159]. To date, it is not entirely understood what causes the local anesthetic-sparing effect. In vitro, clonidine blocks Aδ and C-fiber conduction and increases potassium conductance in isolated neurons and enhances the local anesthetic nerve conduction blockade, suggesting a direct effect of clonidine on neural transmission. Additionally, clonidine can produce local vasoconstriction, decreasing the vascular clearance of the local anesthetic around neural structures. Finally, clonidine may enhance the peripheral or spinal blockade by synergism, even when given systemically [42]. Low epidural doses of clonidine may cause significant hypotension [42, 153, 160]; therefore, adequate hemodynamic monitoring is necessary when administering clonidine to patients.

6.3.2 Dexmedetomidine

Dexmedetomidine is a selective central α_2-adrenergic agonist with sedative properties and works in a similar manner to clonidine. Like clonidine, when administered as a neuraxial adjuvant it reduces the required local anesthetic dose and prolongs and potentiates post-operative analgesia [161]. The sensory and motor block doubles when intrathecal dexmedetomidine is used [162]. Intravenously administered dexmedetomidine also prolongs the anesthetic effect of intrathecal local anesthetics [155, 156, 163]. Similarly, the most common side effects of dexmedetomidine are hypotension and bradycardia [161]. To date, there is no solid evidence to exclude a neurotoxic effect of neuraxial dexmedetomidine, thus neuraxial administration should be used with caution [164].

6.3.3 Epinephrine

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 [145, 165]. Intrathecal administration was thought to have also a direct analgesic effect through binding to α_2-adrenoceptors in the spinal cord; however, this has not been confirmed [166]. The fear of serious side effects due to the strong vasoconstrictive effects of epinephrine that could lead to spinal cord ischemia appears unfounded at clinically relevant doses (0–200 µg) [167]. Neuraxial epinephrine 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) [167, 168]. Based on a systematic review, the beneficial effects of adding epidural epinephrine to a local anesthetic remain uncertain [169].

7 Miscellaneous Adjuvants Commonly Used

7.1 Dexamethasone

Dexamethasone is a water-soluble steroid with analgesic, anti-inflammatory, and anti-emetic properties and has been studied as an intrathecal and epidural adjuvant to local anesthetics [170–172]. Dexamethasone is believed to have a combined analgesic and local anesthetic-sparing effect, with minimal side effects [173]. To date, however, there have been no well-conducted comparative studies of neuraxial dexamethasone as a neuraxial adjuvant compared to other, more common, neuraxial adjuvants. Likewise, epidurally administered dexamethasone has most likely no added value compared to its intravenous administration [174]. Epidural dexamethasone at a high dose (≥15 mg) is associated with transient adrenal suppression [175], neurotoxicity has not been adequately ruled out [176, 177], and neuraxial pharmacokinetic properties have not been adequately studied [178]. Dexamethasone is included in the Food and Drug Administration warning about deleterious effects of epidural steroids.

7.2 Ketamine

Ketamine is a selective, non-competitive *N*-methyl-D-aspartate receptor antagonist, with analgesic and anti-hyperalgesic effects. The side effects of ketamine include psychological and mild sympathomimetic effects [179]. To date, there is no conclusive evidence that epidural ketamine is superior to intravenous administration [180, 181], 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 [182]. Ketamine is also administered intrathecally, with a minimal improvement in outcomes (i.e., time to first analgesia request, onset time of the sensory and motor block, duration of the sensory and motor block) as shown in a recent systematic review, thus its clinical value seems limited [183]. Furthermore, evidence supports the neurotoxic effects of neuraxial ketamine, particularly when preservatives are used [80, 183–185].

7.3 Magnesium

Magnesium is an *N*-methyl-D-aspartate receptor antagonist and regulates the influx of calcium into cells, both resulting in an analgesic effect. Magnesium is frequently used intravenously. Because magnesium does not cross the blood–brain barrier easily, it is also used neuraxially [186]. Systematic reviews have shown that epidural administration of magnesium prolongs the time to the first analgesic rescue medication, provides 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 (i.e., average 6 mg less morphine use in 24 h) [186, 187]. Other acute pain-related outcomes showed no differences [186]. Side effects associated with magnesium, such as hypotension, bradycardia, or sedation, were not observed [186, 187]. However, the minimally observed analgesic effect of neuraxial magnesium as an adjuvant must be contrasted with a safety profile that has not been adequately studied. Neuraxial magnesium has a neurotoxic potential based on animal studies and some case reports where supra-therapeutic doses of neuraxial magnesium were administered [82–85]. To date, no optimal intrathecal or epidural magnesium doses are known, which should lead to even more caution [186].

7.4 Midazolam

Midazolam is a benzodiazepine and is an indirect agonist of gamma-aminobutyric acid A receptors in the spinal cord. It causes neural inhibition by facilitating the influx of chloride into cells. Neuraxial administration of midazolam as an adjuvant to local anesthetics appears to have some analgesic effect and might also lead to reduced nausea and vomiting [188–190]. The most commonly described side effects of neuraxial midazolam are sedation and hypotension, although those are rare when the lowest clinically effective dose is chosen [190]. In animal studies, neuraxial midazolam has been associated with neurotoxicity [76–78], although more recent studies have failed to show neurotoxic properties [191, 192] and the quality of animal studies associating neuraxial midazolam with neurotoxicity is currently questioned. [193] Midazolam appears to exacerbate the neurotoxic properties of lidocaine [79] and because all local anesthetics are neurotoxic [72], it is debatable whether midazolam should be given in combination with local anesthetics via the neuraxial route. These features should lead to vigilance among clinicians.

7.5 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. Intrathecal administration of neostigmine appears to prolong the duration of postoperative analgesia and sensory and motor blocks [194, 195]. The significant increase in the motor block (from approximately 160 minutes to roughly 220 minutes) combined with common side effects such as nausea and vomiting has resulted in the use of intrathecal neostigmine not being recommended [196]. Adding neostigmine to epidural morphine increases the time to administration of the first analgesic rescue medication, but total opioid consumption does not change [195, 197]. Neuraxial neostigmine has multiple side effects, including hypotension, sedation, and especially nausea and vomiting [195, 196, 198]. Neuraxial neostigmine does not appear to cause neurotoxicity [79, 199–201].

7.6 Ziconotide

Ziconotide is a synthetic analog of a peptide from the venom of the sea snail *Conus magus*. It blocks selectively the N-type voltage-gated calcium channel. Ziconotide inhibits calcium influx into the primary nociceptive afferent pathways that terminate in the superficial layers of the dorsal horn of the spinal cord. This inhibits the release of neurotransmitters, including substance P, and thus spinal pain signals [202–204]. Ziconotide is solely used intrathecally in the treatment of severe chronic pain when pain control with spinally administered morphine and potentially other agents is insufficiently effective or is no longer possible because of side effects [205, 206]. It has dose-dependent psychiatric and central nervous system side effects [204, 206, 207] and a narrow therapeutic window [206].

Table 4 Investigational neuraxial drugs

Drugs not approved for neuraxial use with limited clinical evidence	Experimental drugs
Gabapentin [220]	Substance P-saporin [221]
Adenosine [222]	CGX-1160 [223]
Ketorolac [224]	Xen2174 [225]
Calcitonin [226]	Contulakin-G [227]
Octreotide [228]	Muscimol [229]
HTX-011 [230]	
Resiniferatoxin [231]	
Droperidol [113]	

NMDA N-methyl-D-aspartate

7.7 Baclofen

Baclofen is an intrathecally administered, centrally acting muscle relaxant with a spinal site of action. Baclofen inhibits monosynaptic and polysynaptic reflex transmission in the afferent terminal nerves at the spinal level, probably through stimulation of gamma-aminobutyric acid B receptors, which inhibit the release of glutamic and aspartic acid. It has an anti-nociceptive effect [208–210]. In neurological disorders associated with spasms of the skeletal muscles, intrathecal baclofen not only affects reflex muscle contractions, but also produces a decrease in the intensity of painful spasms and clonus [211, 212]. Baclofen suppresses the central nervous system as a whole; this results in sedation and cardiovascular and respiratory depression [210, 213]. Abrupt cessation can lead to life-threatening withdrawal symptoms [210].

8 New Developments in Neuraxial Drug Administration

In addition to the currently approved drugs for neuraxial administration, a plethora of agents have been approved for other indications/routes of administration but are used off-label for spinal or epidural injections. With respect to local anesthetics, possible future innovations may comprise the use of agents that have hitherto not been used neuraxially on a large scale, such as liposomal bupivacaine, butamben,

or mepivacaine [3, 214, 215]. Furthermore, novel sodium channel blockers such as neosaxitoxin [216] or modality-selective blocking agents could possibly gain interest for neuraxial administration in the future [217].

Concerning opioids, numerous agents that are not approved for neuraxial administration have been used off-label in daily clinical practice, amongst others buprenorphine (which exerts also a local anesthetic-like effect [218]), tramadol, pethidine, methadone, or diamorphine [65]. Their effectiveness has incidentally been described, the safety profiles of those drugs have, however, never been investigated in larger clinical trials.

Beyond local anesthetics, opioids, and drugs that have been initially introduced for other indications or routes of application, there is ongoing research on the development of new neuraxial agents, especially for spinal application in the management of pain (see Table 4). Those efforts also comprise new methods of action such as gene-based approaches using viral vectors, plasmids, or interfering RNAs [20, 219]. Given the large need for new agents with favorable effectiveness and a good safety profile, especially in chronic pain, the development of targeted non-neurotoxic medications that can be administered via the spinal and/or epidural route is highly desirable, and ongoing research should be encouraged.

9 Conclusions

The use of neuraxial drugs to produce anesthesia and/or analgesia is invariably of great interest and clinical relevance. Compared to systemic application, the neuraxial route is characterized by unique pharmacokinetic and pharmacodynamic properties. However, a solid comprehension of the pharmacology of neuraxially administered drugs is indispensable for anesthesiologists and pain practitioners using these techniques in order to safely and efficiently accomplish anesthesia and analgesia.

However, despite extensive use, the amount of approved medications for intrathecal and epidural use remains limited, especially for adjuvants. Hence, there is ongoing off-label use in clinical practice on a regular base. To ensure both patient safety but also legal safety for healthcare givers, a joint effort by practitioners, researchers, pharmaceutical industry, and authorities should be advocated in order to aid the risk-benefit analysis.

In addition to the already approved and/or clinically established drugs, new compounds are under investigation that could potentially increase the armamentarium of neuraxial drug therapy with a favorable risk/benefit relationship. Hence, further experimental and clinical research for neuraxial therapy should be strongly encouraged.

Declarations

Funding No funding was received for the preparation of this article. Open access publication was funded by the Netherlands Transformative Agreement.

Conflicts of interest/competing interests The authors have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author contributions All authors were involved in the design of the review article, literature research, and writing and editing of the manuscript.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

References

1. Bier A. Versuche über Cocainisirung des Rückenmarkes. Deutsche Zeitschrift f Chirurgie. 1899;51:361–9.
2. van Zuylen ML, Ten Hoope W, Bos E, Hermanides J, Stevens MF, Hollmann MW. Safety of epidural drugs: a narrative review. Expert Opin Drug Saf. 2019;18(7):591–601.
3. Prabhakar A, Lambert T, Kaye RJ, Gaignard SM, Ragusa J, Wheat S, et al. Adjuvants in clinical regional anesthesia practice: a comprehensive review. Best Pract Res Clin Anaesthesiol. 2019;33(4):415–23.
4. Motamed C, Farhat F, Remerand F, Stephanazzi J, Laplanche A, Jayr C. An analysis of postoperative epidural analgesia failure by computed tomography epidurography. Anesth Analg. 2006;103(4):1026–32.
5. Gadsden JC, Lindenmuth DM, Hadzic A, Xu D, Somasundarum L, Flisinski KA. Lumbar plexus block using high-pressure injection leads to contralateral and epidural spread. Anesthesiology. 2008;109(4):683–8.
6. Ginosar Y, Davidson EM. Plica mediana dorsalis: unilateral epidural anesthesia and the use of bilateral double epidural catheter technique. Anesthesiology. 2016;125(1):220.

7. Savolaine ER, Pandya JB, Greenblatt SH, Conover SR. Anatomy of the human lumbar epidural space: new insights using CT-epidurography. Anesthesiology. 1988;68(2):217–20.
8. Boezaart AP, Prats-Galino A, Nin OC, Carrera A, Barberan J, Escobar JM, et al. The posterior lumbar epidural space: three-dimensional reconstruction of high-resolution MRI: real and potential epidural spaces and their content in vivo. Pain Med. 2019;20(9):1687–96.
9. Lirk P, Colvin J, Steger B, Colvin HP, Keller C, Rieder J, et al. Incidence of lower thoracic ligamentum flavum midline gaps. Br J Anaesth. 2005;94(6):852–5.
10. Reina MA, Lirk P, Puigdellivol-Sanchez A, Mavar M, Prats-Galino A. Human lumbar ligamentum flavum anatomy for epidural anesthesia: reviewing a 3D MR-based interactive model and postmortem samples. Anesth Analg. 2016;122(3):903–7.
11. Lirk P, Kolbitsch C, Putz G, Colvin J, Colvin HP, Lorenz I, et al. Cervical and high thoracic ligamentum flavum frequently fails to fuse in the midline. Anesthesiology. 2003;99(6):1387–90.
12. Arendt K, Segal S. Why epidurals do not always work. Rev Obstet Gynecol. 2008;1(2):49–55.
13. Hermanides J, Hollmann MW, Stevens MF, Lirk P. Failed epidural: causes and management. Br J Anaesth. 2012;109(2):144–54.
14. Pan PH, Bogard TD, Owen MD. Incidence and characteristics of failures in obstetric neuraxial analgesia and anesthesia: a retrospective analysis of 19,259 deliveries. Int J Obstet Anesth. 2004;13(4):227–33.
15. Asil K, Yaldiz M. Conus medullaris levels on ultrasonography in term newborns: normal levels and dermatological findings. J Korean Neurosurg Soc. 2018;61(6):731–6.
16. Willschke H, Bosenberg A, Marhofer P, Willschke J, Schwindt J, Weintraud M, et al. Epidural catheter placement in neonates: sonoanatomy and feasibility of ultrasonographic guidance in term and preterm neonates. Reg Anesth Pain Med. 2007;32(1):34–40.
17. Shin SK, Hong JY, Kim WO, Koo BN, Kim JE, Kil HK. Ultrasound evaluation of the sacral area and comparison of sacral interspinous and hiatal approach for caudal block in children. Anesthesiology. 2009;111(5):1135–40.
18. van Schoor A, Bosman MC, Bosenberg AT. The value of Tuffier's line for neonatal neuraxial procedures. Clin Anat. 2014;27(3):370–5.
19. Suresh S, Ecoffey C, Bosenberg A, Lonnqvist PA, de Oliveira Jr GS, de Leon CO, et al. The European Society of Regional Anaesthesia and Pain Therapy/American Society of Regional Anesthesia and Pain Medicine recommendations on local anesthetics and adjuvants dosage in pediatric regional anesthesia. Reg Anesth Pain Med. 2018;43(2):211–6.
20. Yaksh TL, Fisher CJ, Hockman TM, Wiese AJ. Current and future issues in the development of spinal agents for the management of pain. Curr Neuropharmacol. 2017;15(2):232–59.
21. Lirk P, Picardi S, Hollmann MW. Local anaesthetics: 10 essentials. Eur J Anaesthesiol. 2014;31(11):575–85.
22. Lirk P, Hollmann MW, Strichartz G. The science of local anesthesia: basic research, clinical application, and future directions. Anesth Analg. 2018;126(4):1381–92.
23. Hermanns H, Hollmann MW, Stevens MF, Lirk P, Brandenburger T, Piegeler T, et al. Molecular mechanisms of action of systemic lidocaine in acute and chronic pain: a narrative review. Br J Anaesth. 2019;123(3):335–49.
24. Block BMLS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003;290(18):2455–63.
25. Pöpping DMEN, Van Aken HK, Marret E, Schug SA, Kranke P, Wenk M, Tramèr MR. Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials. Ann Surg. 2014;259(6):1056–67.
26. Hu J, Zhang C, Yan J, Wang R, Wang Y, Xu M. Sufentanil and bupivacaine combination versus bupivacaine alone for spinal anesthesia during cesarean delivery: a meta-analysis of randomized trials. PLoS ONE. 2016;11(3): e0152605.
27. Pöpping DM, Elia N, Wenk M, Tramèr MR. Combination of a reduced dose of an intrathecal local anesthetic with a small dose of an opioid: a meta-analysis of randomized trials. Pain. 2013;154(8):1383–90.
28. Gitman M, Barrington MJ. Local anesthetic systemic toxicity: a review of recent case reports and registries. Reg Anesth Pain Med. 2018;43(2):124–30.
29. Brown DLRD, Hall JA, Leicht CH, Schroeder DR, Offord KP. Regional anesthesia and local anesthetic-induced systemic toxicity: seizure frequency and accompanying cardiovascular changes. Anesth Analg. 1995;81(2):321–8.
30. Harvey M, Cave G. Lipid emulsion in local anesthetic toxicity. Curr Opin Anaesthesiol. 2017;30(5):632–8.
31. Congedo E, Sgreccia M, De Cosmo G. New drugs for epidural analgesia. Curr Drug Targets. 2009;10(8):696–706.
32. Bujedo BM, Santos SG, Azpiazu AU. A review of epidural and intrathecal opioids used in the management of postoperative pain. J Opioid Manag. 2012;8(3):177–92.
33. Bernards CM. Epidural, cerebrospinal fluid, and plasma pharmacokinetics of epidural opioids (part 2): effect of epinephrine. Anesthesiology. 2003;99:466–75.
34. Berger AS, Goldschneider KR. The role of neuraxial opioids in pediatric practice. Clin J Pain. 2019;35(6):497–500.
35. Jannuzzi RG. Nalbuphine for treatment of opioid-induced pruritus: a systematic review of literature. Clin J Pain. 2016;32(1):87–93.
36. Bujedo BM. Spinal opioid bioavailability in postoperative pain. Pain Pract. 2014;14(4):350–64.
37. Sultan P, Gutierrez MC, Carvalho B. Neuraxial morphine and respiratory depression: finding the right balance. Drugs. 2011;71(14):1807–19.
38. Koning MV, Klimek M, Rijs K, Stolker RJ, Heesen MA. Intrathecal hydrophilic opioids for abdominal surgery: a meta-analysis, meta-regression, and trial sequential analysis. Br J Anaesth. 2020;125(3):358–72.
39. Bernards CM. Recent insights into the pharmacokinetics of spinal opioids and the relevance to opioid selection. Curr Opin Anaesthesiol. 2004;17(5):441–7.
40. Burm AG. Clinical pharmacokinetics of epidural and spinal anaesthesia. Clin Pharmacokinet. 1989;16(5):283–311.
41. Hansdottir V, Woestenborghs R, Nordberg G. The cerebrospinal fluid and plasma pharmacokinetics of sufentanil after thoracic or lumbar epidural administration. Anesth Anal. 1995;80(4):724–9.
42. Eisenach JC, De Kock M, Klimscha W. alpha(2)-adrenergic agonists for regional anesthesia: a clinical review of clonidine (1984–1995). Anesthesiology. 1996;85(3):655–74.
43. Clement R, Malinovsky JM, Le Corre P, Dollo G, Chevanne F, Le Verge R. Cerebrospinal fluid bioavailability and pharmacokinetics of bupivacaine and lidocaine after intrathecal and epidural administrations in rabbits using microdialysis. J Pharmacol Exp Ther. 1999;289(2):1015–21.
44. Rose FX, Estebe JP, Ratajczak M, Wodey E, Chevanne F, Dollo G, et al. Epidural, intrathecal pharmacokinetics, and intrathecal bioavailability of ropivacaine. Anesth Analg. 2007;105(3):859–67.
45. Pope JE, Deer TR, Amirdelfan K, McRoberts WP, Azeem N. The pharmacology of spinal opioids and ziconotide for the treatment of non-cancer pain. Curr Neuropharmacol. 2017;15(2):206–16.
46. Olawin AM, Das JM. Spinal anesthesia. Treasure Island: StatPearls Publishing; 2021.

47. Longo MA, Cavalheiro BT, de Oliveira Filho GR. Laparoscopic cholecystectomy under neuraxial anesthesia compared with general anesthesia: systematic review and meta-analyses. J Clin Anesth. 2017;41:48–54.
48. Hajibandeh S, Hajibandeh S, Mobarak S, Bhattacharya P, Mobarak D, Satyadas T. Meta-analysis of spinal anesthesia versus general anesthesia during laparoscopic total extraperitoneal repair of inguinal hernia. Surg Laparosc Endosc Percutan Tech. 2020;30(4):371–80.
49. Erbas YC, Pusat S, Yilmaz E, Bengisun ZK, Erdogan E. Posterior lumbar stabilization surgery under spinal anesthesia for high-risk patients with degenerative spondylolisthesis, spinal stenosis and lumbar compression fracture. Turk Neurosurg. 2015;25(5):771–5.
50. Lee TW, Kowalski S, Falk K, Maguire D, Freed DH, Hay-Glass KT. High spinal anesthesia enhances anti-inflammatory responses in patients undergoing coronary artery bypass graft surgery and aortic valve replacement: randomized pilot study. PLoS ONE. 2016;11(3): e0149942.
51. Hanada S, Kurosawa A, Randall B, Van Der Horst T, Ueda K. Impact of high spinal anesthesia technique on fast-track strategy in cardiac surgery: retrospective study. Reg Anesth Pain Med. 2020;45(1):22–6.
52. Vadhanan P. Recent updates in spinal anesthesia: a narrative review. Asian J Anesthesiol. 2021;59(2):41–50.
53. Bachman SA, Lundberg J, Herrick M. Avoid suboptimal perioperative analgesia during major surgery by enhancing thoracic epidural catheter placement and hemodynamic performance. Reg Anesth Pain Med. 2021;46(6):532–4.
54. Bos EME, Schut ME, de Quelerij M, Kalkman CJ, Hollmann MW, Lirk P. Trends in practice and safety measures of epidural analgesia: report of a national survey. Acta Anaesthesiol Scand. 2018;62(10):1466–72.
55. Hughes MJ, Ventham NT, McNally S, Harrison E, Wigmore S. Analgesia after open abdominal surgery in the setting of enhanced recovery surgery: a systematic review and meta-analysis. JAMA Surg. 2014;149(12):1224–30.
56. Bos EME, Hollmann MW, Lirk P. Safety and efficacy of epidural analgesia. Curr Opin Anaesthesiol. 2017;30(6):736–42.
57. Zeltsman M, Dozier J, Vaghjiani RG, Poch A, Eguchi T, Pedoto A, et al. Decreasing use of epidural analgesia with increasing minimally invasive lobectomy: impact on postoperative morbidity. Lung Cancer. 2020;139:68–72.
58. Patel K, Shergill S, Vadivelu N, Rajput K. Analgesia for gynecologic oncologic surgeries: a narrative review. Curr Pain Headache Rep. 2022;26(1):1–13.
59. Simmons SW, Cyna AM, Dennis AT, Hughes D. Combined spinal-epidural versus epidural analgesia in labour. Cochrane Database Syst Rev. 2007;18(3): CD003401.
60. Guasch E, Brogly N, Gilsanz F. Combined spinal epidural for labour analgesia and caesarean section: indications and recommendations. Curr Opin Anaesthesiol. 2020;33(3):284–90.
61. Yin H, Tong X, Huang H. Dural puncture epidural versus conventional epidural analgesia for labor: a systematic review and meta-analysis of randomized controlled studies. J Anesth. 2022;36(3):413–27.
62. Heesen M, Rijs K, Rossaint R, Klimek M. Dural puncture epidural versus conventional epidural block for labor analgesia: a systematic review of randomized controlled trials. Int J Obstet Anesth. 2019;40:24–31.
63. Kocarev M, Khalid F, Khatoon F, Fernando R. Neuraxial labor analgesia: a focused narrative review of the 2017 literature. Curr Opin Anaesthesiol. 2018;31(3):251–7.
64. Hattori S, Takarada J, Yokota M. The role of interventional pain treatment in gynecologic cancer: neurolysis and spinal analgesia: 14AP8-6. Eur J Anaesthesiol. 2013;30:225.
65. Farquhar-Smith P, Chapman S. Neuraxial (epidural and intrathecal) opioids for intractable pain. Br J Pain. 2012;6(1):25–35.
66. Di Napoli R, Esposito G, Cascella M. Intrathecal catheter. Treasure Island: StatPearls; 2022.
67. Capozza MA, Triarico S, Mastrangelo S, Attina G, Maurizi P, Ruggiero A. Narrative review of intrathecal drug delivery (IDD): indications, devices and potential complications. Ann Transl Med. 2021;9(2):186.
68. Chalil A, Staudt MD, Harland TA, Leimer EM, Bhullar R, Argoff CE. A safety review of approved intrathecal analgesics for chronic pain management. Expert Opin Drug Saf. 2021;20(4):439–51.
69. Verlinde MHM, Stevens MF, Hermanns H, Werdehausen R, Lirk P. Local anesthetic-induced neurotoxicity. Int J Mol Sci. 2016;17(3):339.
70. Werdehausen R, Braun S, Essmann F, Schulze-Osthoff K, Walczak H, Lipfert P, et al. Lidocaine induces apoptosis via the mitochondrial pathway independently of death receptor signaling. Anesthesiology. 2007;107(1):136–43.
71. Lirk P, Haller I, Colvin HP, Lang L, Tomaselli B, Klimaschewski L, et al. In vitro, inhibition of mitogen-activated protein kinase pathways protects against bupivacaine- and ropivacaine-induced neurotoxicity. Anesth Analg. 2008;106(5):1456–64 (**table of contents**).
72. Werdehausen R, Fazeli S, Braun S, Hermanns H, Essmann F, Hollmann MW, et al. Apoptosis induction by different local anaesthetics in a neuroblastoma cell line. Br J Anaesth. 2009;103(5):711–8.
73. Forget P, Borovac JA, Thackeray EM, Pace NL. Transient neurological symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics in adult surgical patients: a network meta-analysis. Cochrane Database Syst Rev. 2019;12(12): CD003006.
74. Pollock JE. Neurotoxicity of intrathecal local anaesthetics and transient neurological symptoms. Best Pract Res Clin Anaesthesiol. 2003;17(3):471–84.
75. Westin BD, Walker SM, Deumens R, Grafe M, Yaksh TL. Validation of a preclinical spinal safety model: effects of intrathecal morphine in the neonatal rat. Anesthesiology. 2010;113(1):183–99.
76. Bozkurt P, Tunali Y, Kaya G, Okar I. Histological changes following epidural injection of midazolam in the neonatal rabbit. Paediatr Anaesth. 1997;7(5):385–9.
77. Ugur B, Basaloglu K, Yurtseven T, Ates U, Aydin ON, Ozenc D, et al. Neurotoxicity with single dose intrathecal midazolam administration. Eur J Anaesthesiol. 2005;22(12):907–12.
78. Stevens MF, Werdehausen R, Gaza N, Hermanns H, Kremer D, Bauer I, et al. Midazolam activates the intrinsic pathway of apoptosis independent of benzodiazepine and death receptor signaling. Reg Anesth Pain Med. 2011;36(4):343–9.
79. Werdehausen R, Braun S, Hermanns H, Kremer D, Kury P, Hollmann MW, et al. The influence of adjuvants used in regional anesthesia on lidocaine-induced neurotoxicity in vitro. Reg Anesth Pain Med. 2011;36(5):436–43.
80. Vranken JH, Troost D, de Haan P, Pennings FA, van der Vegt MH, Dijkgraaf MG, et al. Severe toxic damage to the rabbit spinal cord after intrathecal administration of preservative-free S(+)-ketamine. Anesthesiology. 2006;105(4):813–8.
81. Rijsdijk M, van Wijck AJ, Kalkman CJ, Meulenhoff PC, Grafe MR, Steinauer J, et al. Safety assessment and pharmacokinetics

of intrathecal methylprednisolone acetate in dogs. Anesthesiology. 2012;116(1):170–81.
82. Ozdogan L, Sastim H, Ornek D, Postaci A, Ayerden T, Dikmen B. Neurotoxic effects of intrathecal magnesium sulphate. Braz J Anesthesiol. 2013;63(1):139–43.
83. Saeki H, Matsumoto M, Kaneko S, Tsuruta S, Cui YJ, Ohtake K, et al. Is intrathecal magnesium sulfate safe and protective against ischemic spinal cord injury in rabbits? Anesth Analg. 2004;99(6):1805–12 (**table of contents**).
84. Goodman EJ, Haas AJ, Kantor GS. Inadvertent administration of magnesium sulfate through the epidural catheter: report and analysis of a drug error. Int J Obstet Anesth. 2006;15(1):63–7.
85. Dror A, Henriksen E. Accidental epidural magnesium sulfate injection. Anesth Analg. 1987;66(10):1020–1.
86. Yu ZY, Geng J, Li ZQ, Sun YB, Wang SL, Masters J, et al. Dexmedetomidine enhances ropivacaine-induced sciatic nerve injury in diabetic rats. Br J Anaesth. 2019;122(1):141–9.
87. Khan SU, Winnicka L, Saleem MA, Rahman H, Rehman N. Amiodarone, lidocaine, magnesium or placebo in shock refractory ventricular arrhythmia: a Bayesian network meta-analysis. Heart Lung. 2017;46(6):417–24.
88. Pitkanen M, Feldman HS, Arthur GR, Covino BG. Chronotropic and inotropic effects of ropivacaine, bupivacaine, and lidocaine in the spontaneously beating and electrically paced isolated, perfused rabbit heart. Reg Anesth. 1992;17(4):183–92.
89. Beaussier M, Delbos A, Maurice-Szamburski A, Ecoffey C, Mercadal L. Perioperative use of intravenous lidocaine. Drugs. 2018;78(12):1229–46.
90. Harrison DCSJ, Morrow AG. The antiarrhythmic properties of lidocaine and procaine amide: clinical and physiologic studies of their cardiovascular effects in man. Circulation. 1963;28(4):486–91.
91. Wolfe JWBJ. Local anesthetic systemic toxicity: update on mechanisms and treatment. Curr Opin Anaesthesiol. 2011;24(5):561–6.
92. farmacotherapeutischkompas.nl. Bupivacaine information. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/b/bupivacaine. Accessed Mar 2022.
93. medicines.org.uk. Bupivacaine information. https://www.medicines.org.uk/emc/product/6591/smpc. Accessed Mar 2022.
94. farmacotherapeutischkompas.nl. Levobupivacaine information. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/l/levobupivacaine. Accessed Mar 2022.
95. medicines.org.uk. Levobupivacaine Information from medicines.org.uk. https://www.medicines.org.uk/emc/product/329/smpc. Accessed Mar 2022.
96. Foster RH, Markham A. Levobupivacaine. Drugs. 2000;59(3):551–79.
97. Faccenda KA, Simpson AM, Henderson DJ, Smith D, McGrady EM, Morrison LM. A comparison of levobupivacaine 0.5% and racemic bupivacaine 0.5% for extradural anesthesia for caesarean section. Reg Anesth Pain Med. 2003;28(5):394–400.
98. Kopacz DJ, Allen HW, Thompson GE. A comparison of epidural levobupivacaine 0.75% with racemic bupivacaine for lower abdominal surgery. Anesth Analg. 2000;90(3):642–8.
99. Bader AM, Tsen LC, Camann WR, Nephew E, Datta S. Clinical effects and maternal and fetal plasma concentrations of 0.5% epidural levobupivacaine versus bupivacaine for cesarean delivery. Anesthesiology. 1999;90(6):1596–601.
100. Bardsley HGR, Baker H, Watson N, Nimmo W. A comparison of the cardiovascular effects of levobupivacaine and rac-bupivacaine following intravenous administration to healthy volunteers. Br J Clin Pharmacol. 1998;46(3):245–9.
101. Gristwood RW, Greaves JL. Levobupivacaine: a new safer long acting local anaesthetic agent. Expert Opin Investig Drugs. 1999;8(6):861–76.
102. Heppolette CAA, Brunnen D, Bampoe S, Odor PM. Clinical pharmacokinetics and pharmacodynamics of levobupivacaine. Clin Pharmacokinet. 2020;59(6):715–45.
103. farmacotherapeutischkompas.nl. Ropivacaine information. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/r/ropivacaine. Accessed Mar 2022.
104. medicines.org.uk. Ropivacaine information. https://www.medicines.org.uk/emc/product/9686/smpc. Accessed Mar 2022.
105. Casati APM. Bupivacaine, levobupivacaine and ropivacaine: are they clinically different? Best Pract Res Clin Anaesthesiol. 2005;19(2):247–68.
106. Knudsen K, Beckman Suurkula M, Blomberg S, Sjovall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth. 1997;78(5):507–14.
107. Scott DB, Lee A, Fagan D, Bowler GM, Bloomfield P, Lundh R. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg. 1989;69(5):563–9.
108. McDonald SB, Liu SS, Kopacz DJ, Stephenson CA. Hyperbaric spinal ropivacaine: a comparison to bupivacaine in volunteers. Anesthesiology. 1999;90(4):971–7.
109. Lee YY, Ngan Kee WD, Fong SY, Liu JT, Gin T. The median effective dose of bupivacaine, levobupivacaine, and ropivacaine after intrathecal injection in lower limb surgery. Anesth Analg. 2009;109(4):1331–4.
110. Taylor A, McLeod G. Basic pharmacology of local anaesthetics. BJA Educ. 2020;20(2):34–41.
111. Abouleish EI, Elias M, Nelson C. Ropivacaine-induced seizure after extradural anaesthesia. Br J Anaesth. 1998;80(6):843–4.
112. Jiang X, Huang W, Lin X. Ropivacaine-induced cardiac arrest and paraplegia after epidural anesthesia. Minerva Anestesiol. 2012;78(11):1309–10.
113. Guay J, Kopp S. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev. 2016;1: CD005059.
114. Sultan P, Halpern SH, Pushpanathan E, Patel S, Carvalho B. The effect of intrathecal morphine dose on outcomes after elective cesarean delivery: a meta-analysis. Anesth Analg. 2016;123(1):154–64.
115. Sukul VV. Intrathecal pain therapy for the management of chronic noncancer pain. Neurosurg Clin N Am. 2019;30(2):195–201.
116. Mastenbroek TC, Kramp-Hendriks BJ, Kallewaard JW, Vonk JM. Multimodal intrathecal analgesia in refractory cancer pain. Scand J Pain. 2017;14:39–43.
117. Ma K, Jin Y, Wang L, Feng ZY, Song T, Yang XQ, et al. Intrathecal delivery of hydromorphone vs morphine for refractory cancer pain: a multicenter, randomized, single-blind, controlled noninferiority trial. Pain. 2020;161(11):2502–10.
118. Sharawi N, Carvalho B, Habib AS, Blake L, Mhyre JM, Sultan P. A systematic review evaluating neuraxial morphine and diamorphine-associated respiratory depression after cesarean delivery. Anesth Analg. 2018;127(6):1385–95.
119. Gambling D, Hughes T, Martin G, Horton W, Manvelian G. A comparison of Depodur, a novel, single-dose extended-release epidural morphine, with standard epidural morphine for pain relief after lower abdominal surgery. Anesth Analg. 2005;100(4):1065–74.
120. Viscusi ER. Emerging techniques in the management of acute pain: epidural analgesia. Anesth Analg. 2005;101(5 Suppl.):S23–9.

121. Sumida S, Lesley MR, Hanna MN, Murphy JD, Kumar K, Wu CL. Meta-analysis of the effect of extended-release epidural morphine versus intravenous patient-controlled analgesia on respiratory depression. J Opioid Manag. 2009;5(5):301–5.
122. Vaughan C. Development and implementation of a process to ensure safe use of morphine sulfate extended-release liposome injection. Am J Health Syst Pharm. 2008;65(5):458–61.
123. Hartrick CT, Hartrick KA. Extended-release epidural morphine (DepoDur): review and safety analysis. Expert Rev Neurother. 2008;8(11):1641–8.
124. Hartrick CT, Martin G, Kantor G, Koncelik J, Manvelian G. Evaluation of a single-dose, extended-release epidural morphine formulation for pain after knee arthroplasty. J Bone Jt Surg Am. 2006;88(2):273–81.
125. Alam M, Hartrick CT. Extended-release epidural morphine (DepoDur): an old drug with a new profile. Pain Pract. 2005;5(4):349–53.
126. Liu SS, Bieltz M, Wukovits B, John RS. Prospective survey of patient-controlled epidural analgesia with bupivacaine and hydromorphone in 3736 postoperative orthopedic patients. Reg Anesth Pain Med. 2010;35(4):351–4.
127. Parker EOBG, Bartel SJ, et al. Effects of epinephrine on epidural fentanyl, sufentanil and hydromorphone for postoperative pain. Anesthesiology. 1985;63(3A):A235.
128. Chaplan SR, Duncan SR, Brodsky JB, Brose WG. Morphine and hydromorphone epidural analgesia: a prospective, randomized comparison. Anesthesiology. 1992;77(6):1090–4.
129. Drakeford MK, Pettine KA, Brookshire L, Ebert F. Spinal narcotics for postoperative analgesia in total joint arthroplasty: a prospective study. J Bone Jt Surg Am. 1991;73(3):424–8.
130. Wust HJ, Bromage PR. Delayed respiratory arrest after epidural hydromorphone. Anaesthesia. 1987;42(4):404–6.
131. O'Reilly-Shah V, Lynde GC. Determination of ED50 and time to effectiveness for intrathecal hydromorphone in laboring patients using Dixon's up-and-down sequential allocation method. BMC Anesthesiol. 2018;18(1):140.
132. Anderson VC, Cooke B, Burchiel KJ. Intrathecal hydromorphone for chronic nonmalignant pain: a retrospective study. Pain Med. 2001;2(4):287–97.
133. Roofthooft E, Joshi GP, Rawal N, Van de Velde M. PROSPECT guideline for elective caesarean section: updated systematic review and procedure-specific postoperative pain management recommendations. Anaesthesia. 2021;76(5):665–80.
134. McLeod GA, Munishankar B, Columb MO. Is the clinical efficacy of epidural diamorphine concentration-dependent when used as analgesia for labour? Br J Anaesth. 2005;94(2):229–33.
135. Husaini SW, Russell IF. Intrathecal diamorphine compared with morphine for postoperative analgesia after caesarean section under spinal anaesthesia. Br J Anaesth. 1998;81(2):135–9.
136. Vaughan DJ, Ahmad N, Lillywhite NK, Lewis N, Thomas D, Robinson PN. Choice of opioid for initiation of combined spinal epidural analgesia in labour: fentanyl or diamorphine. Br J Anaesth. 2001;86(4):567–9.
137. Cowan CM, Kendall JB, Barclay PM, Wilkes RG. Comparison of intrathecal fentanyl and diamorphine in addition to bupivacaine for caesarean section under spinal anaesthesia. Br J Anaesth. 2002;89(3):452–8.
138. Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for cesarean section. BMC Anesthesiol. 2005;5(1):5.
139. Glass PS, Estok P, Ginsberg B, Goldberg JS, Sladen RN. Use of patient-controlled analgesia to compare the efficacy of epidural to intravenous fentanyl administration. Anesth Analg. 1992;74(3):345–51.
140. Bujedo BM. Current evidence for spinal opioid selection in postoperative pain. Korean J Pain. 2014;27(3):200–9.
141. Geller E, Chrubasik J, Graf R, Chrubasik S, Schulte-Monting J. A randomized double-blind comparison of epidural sufentanil versus intravenous sufentanil or epidural fentanyl analgesia after major abdominal surgery. Anesth Analg. 1993;76(6):1243–50.
142. Swenson JD, Hullander RM, Bready RJ, Leivers D. A comparison of patient controlled epidural analgesia with sufentanil by the lumbar versus thoracic route after thoracotomy. Anesth Analg. 1994;78(2):215–8.
143. Fournier R, Gamulin Z, Van Gessel E. Respiratory depression after 5 micrograms of intrathecal sufentanil. Anesth Analg. 1998;87(6):1377–8.
144. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia: a clinical review of clonidine (1984–1995). Anesthesiology. 1996;85(3):665–74.
145. Niemi G, Breivik H. Epinephrine markedly improves thoracic epidural analgesia produced by a small-dose infusion of ropivacaine, fentanyl, and epinephrine after major surgery: a randomized, double-blinded crossover study with and without epinephrine. Anesth Analg. 2002;94(6):1598–605.
146. De Kock M, Wiederkher P, Laghmiche A, Scholtes JL. Epidural clonidine used as the sole analgesic agent during and after abdominal surgery: a dose-response study. Anesthesiology. 1997;86(2):285–92.
147. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to bupivacaine. J Anaesthesiol Clin Pharmacol. 2011;27(3):339–43.
148. Niu X-Y, Ding X-B, Guo T, Chen M-H, Fu S-K, Li Q. Effects of intravenous and intrathecal dexmedetomidine in spinal anesthesia: a meta-analysis. CNS Neurosci Ther. 2013;19(11):897–904.
149. Bernard J-M. Comparison of intravenous and epidural clonidine for postoperative patient-controlled analgesia. Anesth Analg. 1995;81(4):706–12.
150. Turan A, Babazade R, Kurz A, Devereaux PJ, Zimmerman NM, Hutcherson MT, et al. Clonidine does not reduce pain or opioid consumption after noncardiac surgery. Anesth Analg. 2016;123(3):749–57.
151. Jarrott B, Conway EL, Maccarrone C, Lewis SJ. Clonidine: understanding its disposition, sites and mechanism of action. Clin Exp Pharmacol Physiol. 1987;14(5):471–9.
152. Rockemann MG, Seeling W, Brinkmann A, Goertz AW, Hauber N, Junge J, et al. Analgesic and hemodynamic effects of epidural clonidine, clonidine/morphine, and morphine after pancreatic surgery: a double-blind study. Anesth Analg. 1995;80(5):869–74.
153. Milligan KR, Convery PN, Weir P, Quinn P, Connolly D. The efficacy and safety of epidural infusions of levobupivacaine with and without clonidine for postoperative pain relief in patients undergoing total hip replacement. Anesth Analg. 2000;91(2):393–7.
154. Farmery AD, Wilson-MacDonald J. The analgesic effect of epidural clonidine after spinal surgery: a randomized placebo-controlled trial. Anesth Analg. 2009;108(2):631–4.
155. Whizar-Lugo V, Gómez-Ramírez IA, Cisneros-Corral R, Martínez-Gallegos N. Intravenous dexmedetomidine vs. intravenous clonidine to prolong bupivacaine spinal anesthesia: a double blind study. Anestesia Mexico. 2007;19(3):143–6.
156. Reddy VS, Shaik NA, Donthu B, Reddy Sannala VK, Jangam V. Intravenous dexmedetomidine versus clonidine for prolongation of bupivacaine spinal anesthesia and analgesia: a randomized double-blind study. J Anaesthesiol Clin Pharmacol. 2013;29(3):342–7.
157. Rhee K, Kang K, Kim J, Jeon Y. Intravenous clonidine prolongs bupivacaine spinal anesthesia. Acta Anaesthesiol Scand. 2003;47(8):1001–5.

158. Dziubdziela W, Jałowiecki P, Kawecki P. Prolongation of bupivacaine spinal anaesthesia by oral and intramuscular clonidine. Wiad Lek. 2003;56(11–12):520–6.
159. Crespo S, Dangelser G, Haller G. Intrathecal clonidine as an adjuvant for neuraxial anaesthesia during caesarean delivery: a systematic review and meta-analysis of randomised trials. Int J Obstet Anesth. 2017;32:64–76.
160. Dobrydnjov I, Axelsson K, Gupta A, Lundin A, Holmstrom B, Granath B. Improved analgesia with clonidine when added to local anesthetic during combined spinal-epidural anesthesia for hip arthroplasty: a double-blind, randomized and placebo-controlled study. Acta Anaesthesiol Scand. 2005;49(4):538–45.
161. Solanki SL, Goyal VK. Neuraxial dexmedetomidine: wonder drug or simply harmful. Anesth Pain Med. 2015;5(2): e22651-e.
162. Shen QH, Li HF, Zhou XY, Yuan XZ, Lu YP. Dexmedetomidine as an adjuvant for single spinal anesthesia in patients undergoing cesarean section: a system review and meta-analysis. J Int Med Res. 2020;48(5):300060520913423.
163. Kaya FN, Yavascaoglu B, Turker G, Yildirim A, Gurbet A, Mogol EB, et al. Intravenous dexmedetomidine, but not midazolam, prolongs bupivacaine spinal anesthesia. Can J Anaesth. 2010;57(1):39–45.
164. Paramasivan A, Lopez-Olivo MA, Foong TW, Tan YW, Yap APA. Intrathecal dexmedetomidine and postoperative pain: a systematic review and meta-analysis of randomized controlled trials. Eur J Pain. 2020;24(7):1215–27.
165. Curatolo M, Petersen-Felix S, Arendt-Nielsen L, Zbinden AM. Epidural epinephrine and clonidine: segmental analgesia and effects on different pain modalities. Anesthesiology. 1997;87(4):785–94.
166. de Oliveira Jr. GS, Balliu B, Nader A, McCarthy RJ. Dose-ranging effects of intrathecal epinephrine on anesthesia/analgesia: a meta-analysis and metaregression of randomized controlled trials. Reg Anesth Pain Med. 2012;37(4):423–32.
167. Neal JM. Effects of epinephrine in local anesthetics on the central and peripheral nervous systems: neurotoxicity and neural blood flow. Reg Anesth Pain Med. 2003;28(2):124–34.
168. Hashimoto K, Hampl KF, Nakamura Y, Bollen AW, Feiner J, Drasner K. Epinephrine increases the neurotoxic potential of intrathecally administered lidocaine in the rat. Anesthesiology. 2001;94(5):876–81.
169. Tschopp C, Tramer MR, Schneider A, Zaarour M, Elia N. Benefit and harm of adding epinephrine to a local anesthetic for neuraxial and locoregional anesthesia: a meta-analysis of randomized controlled trials with trial sequential analyses. Anesth Analg. 2018;127(1):228–39.
170. Fan Z, Ma J, Kuang M, Zhang L, Han B, Yang B, et al. The efficacy of dexamethasone reducing postoperative pain and emesis after total knee arthroplasty: a systematic review and meta-analysis. Int J Surg. 2018;52:149–55.
171. Waldron NH, Jones CA, Gan TJ, Allen TK, Habib AS. Impact of perioperative dexamethasone on postoperative analgesia and side-effects: systematic review and meta-analysis. Br J Anaesth. 2013;110(2):191–200.
172. Allen TK, Jones CA, Habib AS. Dexamethasone for the prophylaxis of postoperative nausea and vomiting associated with neuraxial morphine administration: a systematic review and meta-analysis. Anesth Analg. 2012;114(4):813–22.
173. Khafagy HF, Refaat AI, El-sabae HH, Youssif MA. Efficacy of epidural dexamethasone versus fentanyl on postoperative analgesia. J Anesth. 2010;24(4):531–6.
174. Srinivasan B, Karnawat R, Mohammed S, Chaudhary B, Ratnawat A, Kothari SK. Comparison of caudal and intravenous dexamethasone as adjuvants for caudal epidural block: a double blinded randomised controlled trial. Indian J Anaesth. 2016;60(12):948–54.
175. Maillefert JF, Aho S, Huguenin MC, Chatard C, Peere T, Marquignon MF, et al. Systemic effects of epidural dexamethasone injections. Rev Rhum Engl Ed. 1995;62(6):429–32.
176. Kroin JS, Schaefer RB, Penn RD. Chronic intrathecal administration of dexamethasone sodium phosphate: pharmacokinetics and neurotoxicity in an animal model. Neurosurgery. 2000;46(1):178–82 (**discussion 82–3**).
177. Williams BA, Hough KA, Tsui BY, Ibinson JW, Gold MS, Gebhart GF. Neurotoxicity of adjuvants used in perineural anesthesia and analgesia in comparison with ropivacaine. Reg Anesth Pain Med. 2011;36(3):225–30.
178. Lee MS, Moon HS. Safety of epidural steroids: a review. Anesth Pain Med. 2021;16(1):16–27.
179. Olofsen E, Sigtermans M, Noppers I, Niesters M, Mooren R, Bauer M, et al. The dose-dependent effect of S(+)-ketamine on cardiac output in healthy volunteers and complex regional pain syndrome type 1 chronic pain patients. Anesth Analg. 2012;115(3):536–46.
180. Tena B, Gomar C, Rios J. Perioperative epidural or intravenous ketamine does not improve the effectiveness of thoracic epidural analgesia for acute and chronic pain after thoracotomy. Clin J Pain. 2014;30(6):490–500.
181. Xie H, Wang X, Liu G, Wang G. Analgesic effects and pharmacokinetics of a low dose of ketamine preoperatively administered epidurally or intravenously. Clin J Pain. 2003;19(5):317–22.
182. Subramaniam K, Subramaniam B, Steinbrook RA. Ketamine as adjuvant analgesic to opioids: a quantitative and qualitative systematic review. Anesth Analg. 2004;99(2):482–95 (**table of contents**).
183. Sohnen S, Dowling O, Shore-Lesserson L. Single dose perioperative intrathecal ketamine as an adjuvant to intrathecal bupivacaine: a systematic review and meta-analysis of adult human randomized controlled trials. J Clin Anesth. 2021;73: 110331.
184. Vranken JH, Troost D, Wegener JT, Kruis MR, van der Vegt MH. Neuropathological findings after continuous intrathecal administration of S(+)-ketamine for the management of neuropathic cancer pain. Pain. 2005;117(1–2):231–5.
185. Yip KW, Mao X, Au PY, Hedley DW, Chow S, Dalili S, et al. Benzethonium chloride: a novel anticancer agent identified by using a cell-based small-molecule screen. Clin Cancer Res. 2006;12(18):5557–69.
186. Albrecht E, Kirkham KR, Liu SS, Brull R. The analgesic efficacy and safety of neuraxial magnesium sulphate: a quantitative review. Anaesthesia. 2013;68(2):190–202.
187. Pascual-Ramírez J, Gil-Trujillo S, Alcantarilla C. Intrathecal magnesium as analgesic adjuvant for spinal anesthesia: a meta-analysis of randomized trials. Minerva Anestesiol. 2013;79(6):667–78.
188. Nishiyama T, Matsukawa T, Hanaoka K. Continuous epidural administration of midazolam and bupivacaine for postoperative analgesia. Acta Anaesthesiol Scand. 1999;43(5):568–72.
189. Nishiyama T, Matsukawa T, Hanaoka K. Effects of adding midazolam on the postoperative epidural analgesia with two different doses of bupivacaine. J Clin Anesth. 2002;14(2):92–7.
190. Ho KM, Ismail H. Use of intrathecal midazolam to improve perioperative analgesia: a meta-analysis. Anaesth Intensive Care. 2008;36(3):365–73.
191. Johansen MJ, Gradert TL, Satterfield WC, Baze WB, Hildebrand K, Trissel L, et al. Safety of continuous intrathecal midazolam infusion in the sheep model. Anesth Analg. 2004;98(6):1528–35.
192. Tucker AP, Lai C, Nadeson R, Goodchild CS. Intrathecal midazolam I: a cohort study investigating safety. Anesth Analg. 2004;98(6):1512–20.

193. Yaksh TL, Allen JW. Preclinical insights into the implementation of intrathecal midazolam: a cautionary tale. Anesth Analg. 2004;98(6):1509–11.
194. Lauretti GR, de Oliveira R, Reis MP, Juliao MC, Pereira NL. Study of three different doses of epidural neostigmine coadministered with lidocaine for postoperative analgesia. Anesthesiology. 1999;90(6):1534–8.
195. Lauretti GR. The evolution of spinal/epidural neostigmine in clinical application: thoughts after two decades. Saudi J Anaesth. 2015;9(1):71–81.
196. Poddar RK, Gosavi CP. Analgesic effects of intrathecal neostigmine. Eur J Anaesthesiol. 2003;20(12):984.
197. Omais M, Lauretti GR, Paccola CA. Epidural morphine and neostigmine for postoperative analgesia after orthopedic surgery. Anesth Analg. 2002;95(6):1698–701 (**table of contents**).
198. Hood DD, Eisenach JC, Tuttle R. Phase I safety assessment of intrathecal neostigmine methylsulfate in humans. Anesthesiology. 1995;82(2):331–43.
199. Hood DD, Eisenach JC, Tong C, Tommasi E, Yaksh TL. Cardiorespiratory and spinal cord blood flow effects of intrathecal neostigmine methylsulfate, clonidine, and their combination in sheep. Anesthesiology. 1995;82(2):428–35.
200. Yaksh TL, Grafe MR, Malkmus S, Rathbun ML, Eisenach JC. Studies on the safety of chronically administered intrathecal neostigmine methylsulfate in rats and dogs. Anesthesiology. 1995;82(2):412–27.
201. Gurun MS, Leinbach R, Moore L, Lee CS, Owen MD, Eisenach JC. Studies on the safety of glucose and paraben-containing neostigmine for intrathecal administration. Anesth Analg. 1997;85(2):317–23.
202. Bowersox SS, Gadbois T, Singh T, Pettus M, Wang YX, Luther RR. Selective N-type neuronal voltage-sensitive calcium channel blocker, SNX-111, produces spinal antinociception in rat models of acute, persistent and neuropathic pain. J Pharmacol Exp Ther. 1996;279(3):1243–9.
203. Brose WG, Gutlove DP, Luther RR, Bowersox SS, McGuire D. Use of intrathecal SNX-111, a novel, N-type, voltage-sensitive, calcium channel blocker, in the management of intractable brachial plexus avulsion pain. Clin J Pain. 1997;13(3):256–9.
204. Atanassoff PG, Hartmannsgruber MW, Thrasher J, Wermeling D, Longton W, Gaeta R, et al. Ziconotide, a new N-type calcium channel blocker, administered intrathecally for acute postoperative pain. Reg Anesth Pain Med. 2000;25(3):274–8.
205. Staats PS, Yearwood T, Charapata SG, Presley RW, Wallace MS, Byas-Smith M, et al. Intrathecal ziconotide in the treatment of refractory pain in patients with cancer or AIDS: a randomized controlled trial. JAMA. 2004;291(1):63–70.
206. Brookes ME, Eldabe S, Batterham A. Ziconotide monotherapy: a systematic review of randomised controlled trials. Curr Neuropharmacol. 2017;15(2):217–31.
207. Penn RD, Paice JA. Adverse effects associated with the intrathecal administration of ziconotide. Pain. 2000;85(1–2):291–6.
208. Slonimski M, Abram SE, Zuniga RE. Intrathecal baclofen in pain management. Reg Anesth Pain Med. 2004;29(3):269–76.
209. Zuniga RE, Schlicht CR, Abram SE. Intrathecal baclofen is analgesic in patients with chronic pain. Anesthesiology. 2000;92(3):876–80.
210. Farmacotherapeuthisch kompas. Baclofen. 2022. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/b/baclofen. Accessed 5 Feb 2022.
211. Hasnat MJ, Rice JE. Intrathecal baclofen for treating spasticity in children with cerebral palsy. Cochrane Database Syst Rev. 2015;11: CD004552.
212. Creamer M, Cloud G, Kossmehl P, Yochelson M, Francisco GE, Ward AB, et al. Intrathecal baclofen therapy versus conventional medical management for severe poststroke spasticity: results from a multicentre, randomised, controlled, open-label trial (SISTERS). J Neurol Neurosurg Psychiatry. 2018;89(6):642.
213. Kolaski K, Logan LR. A review of the complications of intrathecal baclofen in patients with cerebral palsy. NeuroRehabilitation. 2007;22(5):383–95.
214. Wiles MD, Nathanson MH. Local anaesthetics and adjuvants: future developments. Anaesthesia. 2010;65(Suppl. 1):22–37.
215. Farzanegan B, Zangi M, Saeedi K, Khalili A, Rajabi M, Jahangirifard A, et al. Effect of adding magnesium sulphate to epidural bupivacaine and morphine on post-thoracotomy pain management: a randomized, double-blind, clinical trial. Basic Clin Pharmacol Toxicol. 2018;123(5):602–6.
216. Lobo K, Donado C, Cornelissen L, Kim J, Ortiz R, Peake RW, et al. A phase 1, dose-escalation, double-blind, block-randomized, controlled trial of safety and efficacy of neosaxitoxin alone and in combination with 0.2% bupivacaine, with and without epinephrine, for cutaneous anesthesia. Anesthesiology. 2015;123(4):873–85.
217. Jablonski S, Lirk P. Future in regional anesthesia and pain medicine: the pharmacological view. Minerva Anestesiol. 2021;87(3):351–7.
218. Leffler A, Frank G, Kistner K, Niedermirtl F, Koppert W, Reeh PW, et al. Local anesthetic-like inhibition of voltage-gated Na(+) channels by the partial mu-opioid receptor agonist buprenorphine. Anesthesiology. 2012;116(6):1335–46.
219. Lawson EF, Wallace MS. Current developments in intraspinal agents for cancer and noncancer pain. Curr Pain Headache Rep. 2010;14(1):8–16.
220. Rauck R, Coffey RJ, Schultz DM, Wallace MS, Webster LR, McCarville SE, et al. Intrathecal gabapentin to treat chronic intractable noncancer pain. Anesthesiology. 2013;119(3):675–86.
221. Brown DC, Agnello K. Intrathecal substance P-saporin in the dog: efficacy in bone cancer pain. Anesthesiology. 2013;119(5):1178–85.
222. Eisenach JC, Rauck RL, Curry R. Intrathecal, but not intravenous adenosine reduces allodynia in patients with neuropathic pain. Pain. 2003;105(1–2):65–70.
223. Kern SE, Allen J, Wagstaff J, Shafer SL, Yaksh T. The pharmacokinetics of the conopeptide contulakin-G (CGX-1160) after intrathecal administration: an analysis of data from studies in beagles. Anesth Analg. 2007;104(6):1514–20 (**table of contents**).
224. Lauretti GR, Righeti CC, Mattos AL. Intrathecal ketorolac enhances intrathecal morphine analgesia following total knee arthroplasty. J Anaesthesiol Clin Pharmacol. 2013;29(4):503–8.
225. Okkerse P, Hay JL, Sitsen E, Dahan A, Klaassen E, Houghton W, et al. Pharmacokinetics and pharmacodynamics of intrathecally administered Xen2174, a synthetic conopeptide with norepinephrine reuptake inhibitor and analgesic properties. Br J Clin Pharmacol. 2017;83(4):751–63.
226. Gabopoulou Z, Vadalouca A, Velmachou K, Karanastasi C, Van Zundert A. Epidural calcitonin: does it provide better postoperative analgesia? An analysis of the haemodynamic, endocrine, and nociceptive responses of salmon calcitonin and opioids in epidural anesthesia for hip arthroplasty surgery. Pain Pract. 2002;2(4):326–31.
227. Martin L, Ibrahim M, Gomez K, Yu J, Cai S, Chew LA, et al. Conotoxin contulakin-G engages a neurotensin receptor 2/R-type calcium channel (Cav2.3) pathway to mediate spinal antinociception. Pain. 2021. https://doi.org/10.1097/j.pain.0000000000002561.
228. Deer TR, Kim CK, Bowman RG 2nd, Stewart CD, Norris M, Khan Y, et al. The use of continuous intrathecal infusion of octreotide in patients with chronic pain of noncancer origin: an evaluation of side-effects and toxicity in a prospective double-blind fashion. Neuromodulation. 2005;8(3):171–5.

229. Hosseini M, Karami Z, Yousefifard M, Janzadeh A, Zamani E, Nasirinezhad F. Simultaneous intrathecal injection of muscimol and endomorphin-1 alleviates neuropathic pain in rat model of spinal cord injury. Brain Behav. 2020;10(5): e01576.
230. Cornett EM, Turpin MAC, Busby M, Pham AD, Kallurkar A, Brondeel KC, et al. HTX-011 (bupivacaine and meloxicam) for the prevention of postoperative pain: clinical considerations. Pain Manag. 2021;11(4):347–56.
231. de Almeida AS, Bernardes LB, Trevisan G. TRP channels in cancer pain. Eur J Pharmacol. 2021;904: 174185.