The ability to sense pain (nociception) is lifesaving. Without it, tissue trauma would not be detected, potentially resulting in the development of more severe tissue injury and infection. Severe tissue injury and infection can initiate a systemic inflammatory response syndrome that results in multiple organ failure and death. In humans, congenital insensitivity to pain results in extensive tissue damage typified by destruction of the joints, pressure ulcers, and muscle ischemia in addition to self-induced mutilation. Most humans afflicted with this condition die within the first or second decade of life because of overwhelming infections. Therefore, the pain-detecting system has a vital life-sustaining role, and it is the key warning system for alerting an animal to the presence of potential tissue-damaging stimuli, which results in initiation of protective physiologic, somatic motor, and behavioral responses to maintain the integrity of the body.

Typically, most noxious stimuli (mechanical, thermal, chemical, and electrical) are transient, non–tissue-damaging events that generate pain (physiologic pain) by activating high-threshold pain receptors (nociceptors) located on the terminal ends of thinly myelinated or unmyelinated peripheral Aδ and C nerve fibers. A noxious stimulus is transduced into electrical impulses that are transmitted to the dorsal horn of the spinal cord, thereby initiating the release of glutamate from presynaptic nerve terminals. Glutamate activates postsynaptic AMPA and KA receptors. The AMPA and KA receptors are the primary mediators of fast excitatory pain transmission (Figure 1). Sensory processing is subsequently controlled by electrical impulses generated in local spinal cord segmental circuits and by descending tonic and phasic facilitatory and inhibitory influences originating from the brain. If tissue damage occurs despite the activities of this defensive system, changes in pain sensitivity occur that help to protect the animal from and prevent further injury. Severe tissue injury (trauma, surgery, or inflammation) or sustained nociceptive input (trauma) increases glutamate release from the presynaptic nerve terminals and results in increases in neuronal activity of the superficial dorsal horn and removal of Mg²⁺ from NMDARs (named on the basis of the synthetic agonist that activates them). The activation and modulation of NMDARs by the excitatory neurotransmitter glutamate are believed to be key components in the development of central sensitization and secondary hyperalgesia and in the consequent amplification of the pain response. Increases in sensitivity to noxious or non-noxious stimuli (hyper-sensitivity) are recognized as allodynia and hyperalgesia. Allodynia is pain caused by a stimulus that does not normally provoke pain. Depending on the severity and duration of noxious stimuli, allodynia or hyperalgesia may spread from the site of injury (primary hyperalgesia) to surrounding noninjured tissues (secondary hyperalgesia). Primary hyperalgesia can be caused by a reduction in the threshold (peripheral sensitization) of normally high-threshold peripheral nociceptors. Peripheral sensitization is caused by the generation of inflammatory mediators, including prostaglandins, bradykinin, cytokines, neuropeptides, and nerve growth factors (collectively referred to as a sensitizing soup). Many of these sensitizing agents also activate quiescent (so-called silent or sleeping) nociceptors, thereby magnifying the pain response to nonpainful stimuli. Intense or sustained peripheral stimuli can also effect changes in the excitability of neurons located in the dorsal horn of the spinal cord. Temporal summation and cumulative depolarization (ie, wind-up) of impulses transmitted by pain fibers amplify and facilitate neuronal activity in dorsal horn neurons, leading to central sensitization (Figure 1). Clinically, central sensitization contributes to the development of alldynia and hypersensitivity at the site of injury (primary hyperalgesia) and further expands the extent of the painful area to noninjured tissue (secondary hyperalgesia). Peripheral and central sensitizations are responsible for primary and secondary hyperalgesia and contribute to the development of pain memory and catastrophization.

| AMPA | α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid |
| KA | Kainate |
| NMDA | N-methyl-D-aspartate |
| NMDAR | NMDA receptor |
| PKC | Protein kinase C |
| GABA | γ-aminobutyric acid |
| NSAID | Nonsteroidal anti-inflammatory drug |
substances cause increases in intracellular Ca\(^{2+}\) and Na\(^{+}\) concentrations in the dorsal glutamate and substance P in the C fibers of the dorsal horns of the spinal cord. These lower threshold and spontaneous impulse generation result in persistent release of C fibers become sensitized by inflammatory mediators (peripheral sensitization); the wind-up of the CNS. During somatic and visceral pathologic pain conditions, NMDARs, leading to removal of the Mg\(^{2+}\) block and to the wind-up phenomenon. I, II, III, IV, V, and VI = Various laminae of the dorsal horn of the spinal cord. A8, A6, and C = Sensory nerve fibers. SP = Substance P. GLU = Glutamate. KAR = Kainate receptors. P = Phosphorylation.

Figure 1—Schematic diagram of the structures and processes involved in sensitization and wind-up of the CNS in mammals. During physiologic pain, most NMDARs are blocked by Mg\(^{2+}\). Consequently, there is no postsynaptic cumulative depolarization or wind-up of the CNS. During somatic and visceral pathologic pain conditions, C fibers become sensitized by inflammatory mediators (peripheral sensitization); the lower threshold and spontaneous impulse generation result in persistent release of glutamate and substance P in the C fibers of the dorsal horns of the spinal cord. These substances cause increases in intracellular Ca\(^{2+}\) and Na\(^{+}\) concentrations in the dorsal horn neurons of the spinal cord and trigger the activation of PKC, phosphorylates, and those receptors, including high permeability to cations (Na\(^{+}\) and Ca\(^{2+}\)) once their Mg\(^{2+}\) block has been removed, dependence on glutamate and glycine for efficient activation, and a comparatively prolonged duration of activation (compared with AMPA/KAR receptors) during which the channel remains open.\(^{19}\) Functional NMDARs are formed by the combination of the ubiquitously expressed NR1 subunit with at least 1 of 4 secondary NR2 subunits (type A, B, C, or D) to form functional ligand (glutamate)-activated channels or pores, which carry currents (primarily movement of Ca\(^{2+}\)) that mediate excitatory neurotransmission in the CNS.\(^{25,26}\) The NR2 subunit is essential for the formation of a functional current-conducting channel or pore.\(^{19}\) Regardless of the requirement for the NR1 subunit and the diversity of NMDAR subtypes, the NR2B subunit is believed to play a fundamental role in nociception.\(^{26}\) The presence of the NR2B subunit in the heteromeric NR1/NR2 pore-forming channels of NMDARs is responsible for most of the biophysical and pharmacologic properties of those receptors, such as sensitivity to Mg\(^{2+}\) block, long-term potentiation of transmission, and activity-dependent plasticity.\(^{11,13}\) The importance of the NR2B subunit increased after the discoveries that such subunits were present in the dorsal horn of the spinal cord, in the brain, and on myelinated and unmyelinated peripheral nerves and that the activation of this subunit type was largely responsible for the development and maintenance of inflammatory hyperalgesia.\(^{26,27}\) The NR2D subunits are located only on peripheral nociceptive fibers, and NR2A subunits are poorly sensitive to glutamate.\(^{28}\) Furthermore, pain-related behaviors were not altered in genetically modified (ie, knockout) mice that lack NR2A subunits, compared with those of genetically normal control mice.\(^{25}\) The NR3 subunit is not believed to be important in regard to pain because its coassembling with other subunits (eg, NR1 and NR2) forms channels that are unaffected by glutamate and impermeable to Ca\(^{2+}\). Together, these data suggest that NMDAR antagonists should have analgesic effects and that selective NR2B antagonists that are devoid of notable CNS effects could be developed.

NMDAR Antagonists

The critical role of NMDARs in the CNS in learning, memory, cognition, and coordination of motor activity and their importance in animal models of chronic pain syndromes and to the establishment of pain as a disease in affected individuals.\(^{10-13}\) The NMDARs were first identified in the late 1980s, when it was demonstrated that NMDAR antagonists (eg, MK-801 [dizocilpine]) inhibited hyperexcitability in nociceptive neurons of the dorsal horn of the spinal cord.\(^{3,14}\) Since that time, NMDARs have been detected in the brain (where they have been linked to visceral pain hyperexcitability or wind-up, induction of central sensitization, and spinal cord neuronal degeneration is well established.\(^{19}\) Their activation has also been implicated in the development of tolerance to opioid treatment.\(^{19}\) The NMDAR is composed of NR1, NR2 (types A, B, C, and D), and NR3 (types A and B) subunits.\(^{10,23}\) All NMDARs have unique properties that distinguish them from other receptors, including high permeability to cations (Na\(^{+}\) and Ca\(^{2+}\)) once their Mg\(^{2+}\) block has been removed, dependence on glutamate and glycine for efficient activation, and a comparatively prolonged duration of activation (compared with AMPA/KAR receptors) during which the channel remains open.\(^{19}\) Functional NMDARs are formed by the combination of the ubiquitously expressed NR1 subunit with at least 1 of 4 secondary NR2 subunits (type A, B, C, or D) to form functional ligand (glutamate)-activated channels or pores, which carry currents (primarily movement of Ca\(^{2+}\)) that mediate excitatory neurotransmission in the CNS.\(^{25,26}\) The NR2B subunit is essential for the formation of a functional current-conducting channel or pore.\(^{19}\) Regardless of the requirement for the NR1 subunit and the diversity of NMDAR subtypes, the NR2B subunit is believed to play a fundamental role in nociception.\(^{26}\) The presence of the NR2B subunit in the heteromeric NR1/NR2 pore-forming channels of NMDARs is responsible for most of the biophysical and pharmacologic properties of those receptors, such as sensitivity to Mg\(^{2+}\) block, long-term potentiation of transmission, and activity-dependent plasticity.\(^{11,13}\) The importance of the NR2B subunit increased after the discoveries that such subunits were present in the dorsal horn of the spinal cord, in the brain, and on myelinated and unmyelinated peripheral nerves and that the activation of this subunit type was largely responsible for the development and maintenance of inflammatory hyperalgesia.\(^{26,27}\) The NR2D subunits are located only on peripheral nociceptive fibers, and NR2A subunits are poorly sensitive to glutamate.\(^{28}\) Furthermore, pain-related behaviors were not altered in genetically modified (ie, knockout) mice that lack NR2A subunits, compared with those of genetically normal control mice.\(^{25}\) The NR3 subunit is not believed to be important in regard to pain because its coassembling with other subunits (eg, NR1 and NR2) forms channels that are unaffected by glutamate and impermeable to Ca\(^{2+}\). Together, these data suggest that NMDAR antagonists should have analgesic effects and that selective NR2B antagonists that are devoid of notable CNS effects could be developed.
severe acute and chronic pain are well established. Their central role in the development of central and peripheral sensitization has led to the investigational and clinical administration of drugs with diverse pharmacologic properties (including NMDAR-blocking activity), with the goal of improving pain control in various species. However, the development and manufacture of drugs that block only NMDARs have been problematic because of CNS and neurotoxic adverse effects associated with those drugs. Dizocilpine, a non-specific NMDAR antagonist, was one of the first drugs recognized for its potential analgesic effects, but it has never been approved for clinical use in humans because of nervous system-associated adverse effects in clinical patients.28 The dissociative anesthetics, ketamine and tiletamine, are considered to be the most potent of the currently available NMDAR antagonists.29,30 Several opioid analgesics (meperidine, fentanyl, morphine, and codeine) produce NMDAR antagonistic effects in vitro, although only methadone and dextromethorphan inhibit NMDARs at concentrations that overlap with the plasma concentrations that are deemed clinically relevant for drug efficacy.31 Interestingly, long-term opioid administration for the treatment of chronic pain in humans is associated with the development of tolerance and delayed hyperalgesia, a phenomenon now known to be the result of opioid-induced increases in PKC and the activation of NMDARs.30,31 Finally, the infusion of magnesium (although rationalized on the basis that NMDARs are typically blocked by Mg²⁺ ions) is not associated with effective control of pain caused by wind-up and central sensitization.22 Reports of the analgesic effects of magnesium infusion are most likely mistaken assessments of the central muscle relaxant and mild sedative properties of Mg²⁺ ions.32

Several drugs (eg, memantine and amantadine) that have been approved for other clinical uses are now considered to be reasonably effective NMDAR antagonists.33-35 At present, attempts are being made to develop and market NR2B subunit-specific NMDAR antagonists (eg, ifenprodil, besoconprodil, and eliprodil) with the hope of eliminating or minimizing CNS adverse effects while retaining the analgesic activity of this type of drug (Appendix).31,32 Regardless of these efforts, a great deal of controversy presently exists regarding the efficacy and usefulness of NMDAR antagonists for the clinical treatment of acute pain in humans and other animals. Data supporting claims of pain relief in humans are highly variable, and in many instances, analgesic efficacy has been difficult to substantiate unless the NMDAR antagonist was administered in conjunction with other analgesic drugs, particularly opioids.9 Potential reasons for poor efficacy when NMDAR antagonists are administered alone are not immediately apparent but are likely related to the dependence of these agents on the development of wind-up or central sensitization, administration of an inadequate dose or inappropriate dosing regimen, and the high variability in affinities for the various NR2 receptor subtypes (particularly the NR2B receptor subtype). Current opinion suggests that NMDAR antagonists may be most effective as analgesics when used to treat severe acute or chronic pain that has wind-up or central sensitization as a major component and that more effective pain relief can be achieved by their administration as preemptive and multimodal therapy.36-38 Others have suggested that non-NMDARs have an exclusive role in the maintenance of dorsal horn neuron activation early after surgical incision.39 This would indicate that cerebral NMDARs have a greater role in development of hyperalgesia after surgery than spinal cord NMDARs, which is in agreement with findings of a previous clinical study40 in humans.

**Specific NMDAR Antagonist Drugs**

Ketamine hydrochloride (an aryl-cyclohexylamine congener of phencyclidine) is a popular injectable dissociative anesthetic agent that is used to provide short-term anesthesia in humans and other animals; it is a noncompetitive NMDAR antagonist.9 Tiletamine, like ketamine, is also a congener of phencyclidine and an NMDAR antagonist. Tiletamine is commercially available in combination with zolazepam hydrochloride (CI-744), which is a benzodiazepine derivative with potent muscle relaxant and anticonvulsant effects.39 Ketamine is rapidly distributed after IV administration and has been administered IV, IM, SC, epidurally, intraperitoneally, and orally to achieve anesthesia or as an adjunct to other anesthetic agents.39-41 Studies in humans and other animals have revealed that ketamine administered IV or epidurally produces anesthetic-sparing effects; furthermore, in humans, ketamine appears to provide analgesia for the treatment of severe acute or chronic pain when administered in subanesthetic doses. Ketamine acts both centrally and peripherally at multiple receptor sites, including NMDA, opioid, AMPA, KA, and GABA-A receptors.32 In humans and other animals, a single IV or IM bolus of ketamine is associated with effective short-acting (duration of 1 to 2 hours) pain relief, whereas infusion following a loading dose is associated with analgesia of longer duration and opioid-sparing effects.42,43 Subcutaneous administration of ketamine has the advantage of relatively slow absorption into the bloodstream, low peak blood concentrations, and reduced CNS effects.44 Oral administration of ketamine produces few adverse effects and may be more effective than SC administration of the drug.45,46 In a recent review, it has been suggested that the analgesic efficacy of ketamine was moderate to weak at best and that ketamine should be considered a third-line option after other treatments had proven ineffective.47 Additional clinical studies in animals are needed to define the analgesic effects, doses, routes of administration, and efficacy of ketamine and the tiletamine-zolazepam drug combination when administered in subanesthetic doses to animals.

Methadone and dextromethorphan are opioid derivatives. Methadone is a mu opioid agonist with analgesic potency similar to that of morphine, whereas dextromethorphan is the D-isomer of codeine and acts as an antitussive. Both drugs are weak, noncompetitive NMDAR antagonists. Results of experimental stud-
ies\textsuperscript{9,39,41} have suggested that these drugs decrease NMDA-mediated hyperexcitability and wind-up in dorsal horn neurons, thereby helping to prevent the development of central sensitization. In clinical studies\textsuperscript{73,77} in humans, methadone and dextromethorphan have been associated with quantifiable analgesic effects following oral, IV, or IM administration. Compared with ketamine and high-affinity NMDAR-blocking drugs (eg, dizocilpine), adverse effects associated with methadone and dextromethorphan are rare. Only methadone has clinical potential as a mixed opioid agonist-NMDA antagonist because parenteral formulations of dextromethorphan are currently unavailable and administration of oral preparations does not result in clinically useful analgesic effects. Methadone is considered an optimal choice for treatment of pain in human patients with cancer because of its high oral bioavailability, rapid onset, and time to peak analgesic effect and the relatively long duration of activity that allows for long intervals between doses.\textsuperscript{5,10}

Tramadol, a weak mu opioid agonist, is a centrally acting analgesic that is effective in the management of moderate to severe acute postoperative pain in humans and is well tolerated by patients.\textsuperscript{68} Tramadol inhibits norepinephrine and serotonin reuptake and also has opioid activity. These complementary actions enhance analgesic efficacy and improve the drug’s tolerability profile. Interestingly, tramadol is efficacious in the treatment of allodynia.\textsuperscript{69} Also, tramadol has been reported to inhibit NMDARs at clinically relevant concentrations and GABA receptors at high concentration. The inhibitory effect of tramadol on NMDARs may contribute to its efficacy in the treatment of allodynia or hyperalgesia. The potential for convulsant adverse effects (as a result of the inhibition of GABA receptors) occurs when large doses are administered.\textsuperscript{69}

Gabapentin, an anticonvulsant, has antihyperalgesic effects when administered to humans with neuropathic pain.\textsuperscript{69,70} Gabapentin does not have activity at GABA receptors but does interfere with glutamatergic neurotransmission.\textsuperscript{2,3,15} Recent studies\textsuperscript{2,3,15} have revealed that gabapentin interacts with and modifies NMDAR activity; its action may be PKC dependent and may rely on the state of phosphorylation of the NMDAR channels.\textsuperscript{71} Other proposed mechanisms include binding to the \(\alpha_\delta\) subunit of the voltage-dependent \(\mathrm{Ca}^{2+}\) channel and interference with \(\mathrm{Na}^+\) entry through presynaptic NMDAR channels.\textsuperscript{71,77} Although consensus regarding the mechanism by which gabapentin induces analgesia has not yet been reached, gabapentin has been used successfully in clinical trials to achieve a significant reduction in pain in the early or late postoperative period in humans.\textsuperscript{72,43,13}

Acamprosate is prescribed as treatment for alcoholism and alcoholic relapse.\textsuperscript{85,86} The duration of action of each of those drugs is long and highly variable.\textsuperscript{97,98} Although all 3 drugs have the potential to bind to NMDARs and thereby induce analgesia, only amantadine has been associated with analgesic activity in randomized and masked human clinical studies.\textsuperscript{5,10} To our knowledge, no studies have investigated the pharmacokinetics or analgesic efficacy of any of these drugs in animals with naturally occurring pain. Although results from animal and human studies are encouraging, undesirable drug effects have hampered the widespread use of high-affinity NMDAR antagonists (eg, dizocilpine) as analgesics.\textsuperscript{71} In humans with chronic pain, low-affinity NMDAR antagonists (eg, ketamine) have been reported to be associated with sedation, hallucinations, muscle rigidity, seizures, respiratory depression, excessive salivation, nausea, and vomiting. Furthermore, SC injection of ketamine induces inflammation at the site of injection.\textsuperscript{88} Despite potential adverse effects, there is evidence that administration of low doses of ketamine results in clinically relevant analgesic effects without notable adverse effects.\textsuperscript{86,90} Similarly, the adverse effects associated with methadone and dextromethorphan are dose dependent, and no or minimal adverse effects have been reported following oral administration of these drugs to human patients.\textsuperscript{99} Parenteral administration of methadone, however, has produced sedation and respiratory depression in humans.\textsuperscript{90} Minimal adverse effects of gabapentin have been reported, including sedation, nausea, and vomiting.\textsuperscript{78,11,45} Potential adverse effects after administration of excessive doses of amantidine, memantine, and acamprosate in humans include tachycardia, hypertension, respiratory distress, renal dysfunction, and gastrointestinal tract disturbances.\textsuperscript{69,38}

**Therapeutic Approaches**

Preemptive analgesia is based on the premise that administration of appropriate analgesic treatment prior to introduction of pain-initiating events (including intraoperative and postoperative noxious inputs) may inhibit or block sensitization and therefore block development of acute pain and decrease exacerbations of chronic pain.\textsuperscript{100} Efficacious preemptive analgesia is based on knowing or anticipating the principle mechanisms responsible for pain (ie, mechanism-based treatment).\textsuperscript{3,10} Prevention or reduction of central sensitization can be achieved by blocking NMDARs before or soon after pain is established.\textsuperscript{10,100} Development of hyperalgesia and allodynia can be inhibited by decreasing NMDAR activity, thereby reducing the cascade of events that are characteristic of central sensitization.\textsuperscript{10} It has been suggested that the concept and clinical application of the term preemptive analgesia are too restrictive because they do not incorporate the administration of analgesic interventions after the surgical incision, which may also act to decrease central sensitization and postoperative pain intensity.\textsuperscript{20} It is further suggested that the term preventive analgesia has greater clinical relevance because the goal is to prevent central sensitization that develops throughout the periopera-
tive period and not just that brought about by a surgical incision.11,105

Single-modality drug therapy is rarely effective for the treatment of severe pain because peripheral and central sensitization originate from activation of multiple molecular signaling mechanisms, including NMDARs, and are exaggerated by the release of other factors, including substance P, prostaglandins, and adenosine.101,105 Balancing the application of different treatments, each aimed at decreasing signs of pain in a different manner, can be successful in most clinical situations.19,21,105 Multimodal or balanced analgesia is the combination of analgesic drugs that act via different or similar mechanisms with the aim of improving analgesic efficacy while decreasing individual drug dosages and treatment-associated adverse effects.32,42,105 Other goals include a reduction in total analgesic drug consumption and extension of analgesic activity beyond the duration of action of each of the individual drugs that are combined. The NMDAR antagonists can be combined with opioids or with opioids and NSAIDs.107,114 The main advantage of these drug combinations is that their respective mechanisms of action are different; complementary; and, oftentimes, supra-additive (synergistic), consequently decreasing drug doses and treatment-associated adverse effects.109,110,170 For example, opioid analgesics (eg, morphine and hydromorphone) and NSAIDs (carprofen, meloxicam, and deraconex) can be combined with the NMDAR antagonist ketamine to provide analgesia intraoperatively and during the perioperative period. Opioids can act at peripheral opioid receptors but are believed to achieve most of their analgesic effects by activating opioid receptors at presynaptic sites in neurons of the dorsal horn of the spinal cord.108 The predominant action of opioids is to block the initial response of nociceptive neurons to noxious stimuli, but they are relatively ineffective for preventing wind-up and central sensitization. In contrast, NMDAR antagonists have little effect presynaptically and do not prevent development of initial pain but do reduce wind-up and central sensitization. Morphine-ketamine synergism is most likely explained by the inhibition of presynaptic afferent transmission secondary to reduced transmitter release and postsynaptic NMDAR blockade.111 From the results of some studies,9,18,110 it has been postulated that the combination of low doses of ketamine with opioids may be beneficial during long-term opioid treatment of chronic pain because it decreases opioid-induced tolerance and the potential for development of opioid-induced hyperalgesia secondary to opioid-induced increases in serum PKC activity. The effects of ketamine should therefore be considered both antihyperalgesic and antiallodynic, rather than analgesic.21,42,114,122

Noted advantages of therapeutic strategies involving opioids and NMDAR antagonists are enhanced analgesic efficacy, prolonged duration, the prevention of opioid tolerance, and decreased occurrence of adverse effects.111 Most NSAIDs achieve their anti-inflammatory and analgesic effects via inhibition of cyclooxygenase, thereby decreasing the production of prostaglandins (ie, prostaglandin E2).111 Prostaglandin production at a peripheral site of injury is known to play a key role in the development of peripheral sensitization; its production in the CNS following traumatic injury leads to sensitization of NMDARs.112 Thus, synergy between NSAIDs and NMDAR antagonists may occur because of reductions in the peripheral nervous system and CNS prostaglandin production as a result of inhibition of cyclooxygenase activity and NMDAR antagonism.113 There is also evidence that hyperalgesia depends to some extent on cyclooxygenase and subsequent central prostaglandin production triggered by NMDAR activation. Although it is evident that combining drugs that act via different mechanisms of action can be successful, low drug dosages must be strictly adhered to so that the potential for additive or synergistic drug adverse effects can be minimized.

Without doubt, the activation of NMDARs is a key factor in the development of severe acute pain and chronic pain syndromes because of their pivotal role in the development of hyperexcitability of nociceptive neurons in the dorsal horn of the spinal cord and the development of central sensitization. Central sensitization can be recognized clinically as signs of pain that become progressively more severe, that originate from outside the area of primary tissue injury, and that are difficult to treat with single (unimodal) therapy. Central sensitization results in alldynia and secondary hyperalgesia. The NMDAR antagonists are represented by a variety of drugs with diverse clinical uses and differing affinities for the NMDARs. Their administration should be considered in conjunction with other first-line analgesics (eg, opioids and NSAIDs) as part of a comprehensive multimodal approach to the treatment of pain in animals.

References


50. Scheller M, Buller J, Hertle I, et al. Ketamine blocks currents through mammalian nicotinic acetylcholine receptor channels by interaction with both the open and the closed state. Anesth Analg 1996;83:830–836.


Appendix
N-methyl-D-aspartate receptor antagonists that are available for clinical use in dogs and cats and their doses.33-41,a,b

<table>
<thead>
<tr>
<th>NMDAR antagonist</th>
<th>Dogs</th>
<th>Cats</th>
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<tbody>
<tr>
<td>Ketamine</td>
<td>For mild to moderate pain: 0.1–1.0 mg/kg, IV, IM, or SC; q 8 h For moderate to severe pain: 0.5–4.0 mg/kg, IV, IM, or SC; q 8 h 0.01 mg/kg/min* via constant rate infusion 2–10 mg/kg, PO, q 6–8 h 2.5 mg/kg, epidural injection</td>
<td>For mild to moderate pain: 0.1–1.0 mg/kg, IV, IM, or SC; q 8 h For moderate to severe pain: 0.5–4 mg/kg, IV, IM, or SC; q 8 h 0.01 mg/kg/min* via constant rate infusion 2–10 mg/kg, PO, q 8 h</td>
</tr>
<tr>
<td>Drugs that may be combined with ketamine</td>
<td>Morphine</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Morphine</td>
<td>0.1–1.0 mg/kg, IV, IM, SC</td>
<td>25–75 µg/kg/min* via constant rate infusion</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>0.05–1 mg/kg, IM, SC</td>
<td>25–75 µg/kg/min* via constant rate infusion 0.05–0.1 mg/kg, IM or IV, q 4–6 h</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2.2 mg/kg; IV, IM, SC</td>
<td>2.2 mg/kg; IV, IM, SC, or PO; q 12 h</td>
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<tr>
<td>Carprofen</td>
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<td>Deracoxib</td>
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<td>Methadone</td>
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<td>Gabapentin</td>
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<td>Dextromethorphan</td>
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<td>Amitriptyline</td>
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<td>Tramadol</td>
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<tr>
<td>Acamprosate or memantine</td>
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*Greater infusion dosages have been suggested. NA = Not available.