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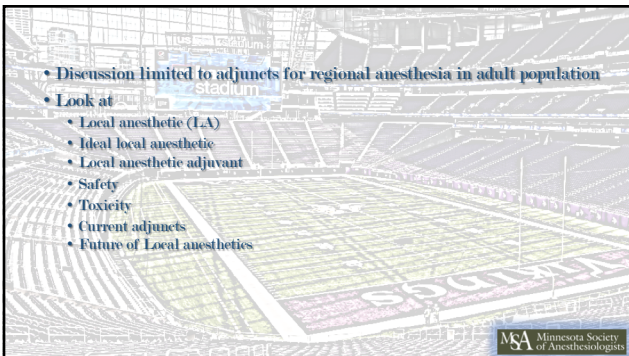
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### Local anesthetic

- An agent that, when applied directly to mucous membranes or when injected about the nerves, produces loss of sensation by inhibiting nerve excitation or conduction.
- A local anesthetic (LA) is a medication that causes reversible absence of pain sensation. When it is used on specific nerve pathways (local anesthetic nerve block), paralysis (loss of muscle power) also can be achieved.



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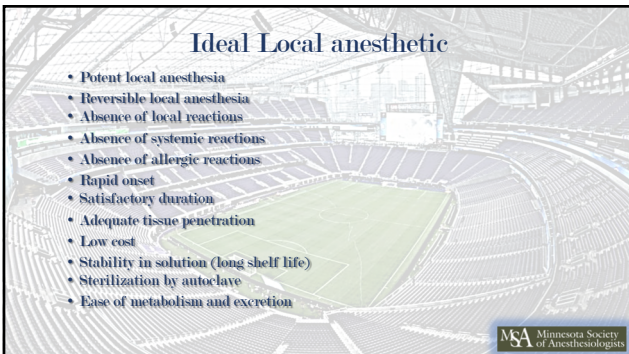
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### Ideal Local anesthetic

- Potent local anesthesia
- Reversible local anesthesia
- Absence of local reactions
- Absence of systemic reactions
- Absence of allergic reactions
- Rapid onset
- Satisfactory duration
- Adequate tissue penetration
- Low cost
- Stability in solution (long shelf life)
- Sterilization by autoclave
- Ease of metabolism and excretion



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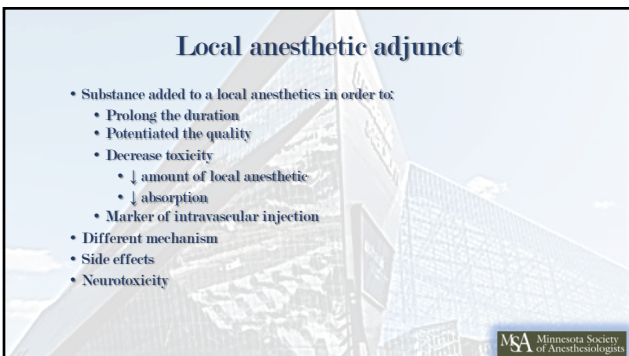
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### Local anesthetic adjunct

- Substance added to a local anesthetics in order to:
  - Prolong the duration
  - Potentiated the quality
- Decrease toxicity
  - ↓ amount of local anesthetic
  - ↓ absorption
- Marker of intravascular injection
- Different mechanism
- Side effects
- Neurotoxicity



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**Safety**

- **Mixing**
  - Drug error
  - Physical alteration
  - Potential for neurotoxicity
  - Contamination

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**Local anesthetics**

- **Mixing of Local Anesthetics**
  - Faster onset of the shorter acting LA = No advantage
  - Longer duration of the longer acting LA
- **More dose**
  - = Longer duration
  - = Higher chance of side effects
  - Rebound pain

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**Local anesthetic toxicity**

- This can be seen in organs of the body that depend upon sodium channels for proper functioning. These include the central nervous system and heart. The CNS is more sensitive to the effects of local anesthetics than the cardiac system and will generally manifest signs/symptoms of toxicity first.
- **Factors in Toxicity**
  - Amount
  - Speed of administration
  - Speed of absorption
  - Affinity for the receptor

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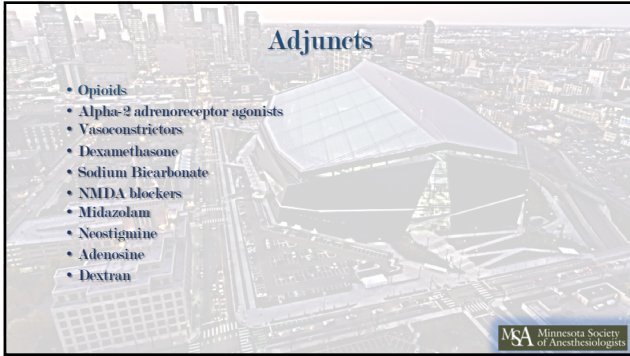
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## Adjuncts

- Opioids
- Alpha-2 adrenoceptor agonists
- Vasopressors
- Dexamethasone
- Sodium Bicarbonate
- NMDA blockers
- Midazolam
- Neostigmine
- Adenosine
- Dextran



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## Opioids

- Applications: Neuraxial, Peripheral
- Profile
  - Effect: inhibitory G protein-coupled receptors that hyperpolarize membranes of afferent sensory neurons
  - Intrathecally, effects are complex:
    - Spinal cord dorsal horn opioid receptor activation
    - Cerebral opioid receptor activation
    - Peripheral and central systemic effects after vascular uptake
  - Side Effects pruritus, nausea, and respiration depression



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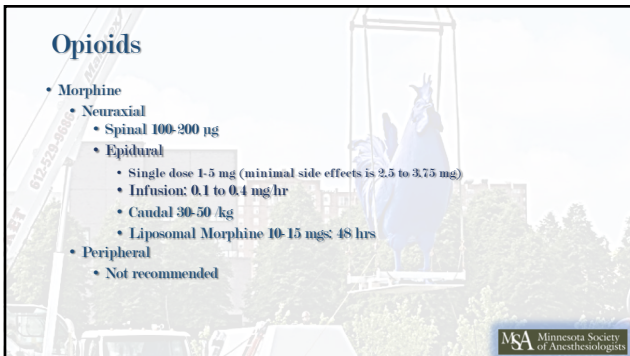
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## Opioids

- Morphine
  - Neuraxial
    - Spinal 100-200 µg
    - Epidural
      - Single dose 1-5 mg (minimal side effects is 2.5 to 3.75 mg)
      - Infusion: 0.1 to 0.4 mg/hr
      - Caudal 30-50 µg
      - Liposomal Morphine 10-15 mgs: 48 hrs
  - Peripheral
    - Not recommended



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### Opioids

- Hydromorphone
  - Neuraxial
    - Spinal 50-100 µg
      - Neurotoxicity profile not clear
    - Epidural
      - Bolus of 0.4 to 1.5 mg
      - Infusion is delivered at rates between 5 and 30 µg/hr.
  - Peripheral
    - Not recommended



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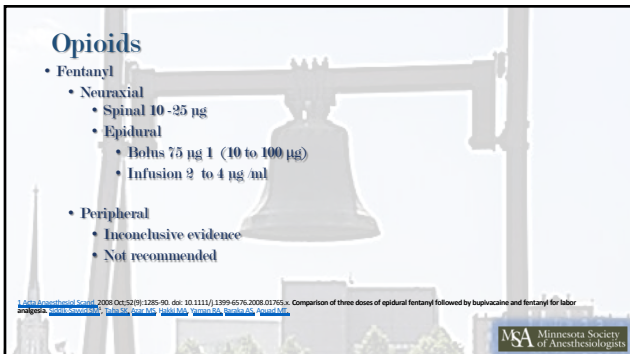
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### Opioids

- Fentanyl
  - Neuraxial
    - Spinal 10 -25 µg
    - Epidural
      - Bolus 75 µg 1 (10 to 100 µg)
      - Infusion 2 to 4 µg/ml
  - Peripheral
    - Inconclusive evidence
    - Not recommended

1. *Am Anesthesiol Soci*. 2008;01:5279-1285-90. doi: 10.1111/j.1395-6576.2008.01765.x. Comparison of three doses of epidural fentanyl followed by bupivacaine and fentanyl for labor analgesia. [pubmed.ncbi.nlm.nih.gov/16464141/](#), [pubmed.ncbi.nlm.nih.gov/16464141/](#), [pubmed.ncbi.nlm.nih.gov/16464141/](#), [pubmed.ncbi.nlm.nih.gov/16464141/](#), [pubmed.ncbi.nlm.nih.gov/16464141/](#), [pubmed.ncbi.nlm.nih.gov/16464141/](#), [pubmed.ncbi.nlm.nih.gov/16464141/](#)



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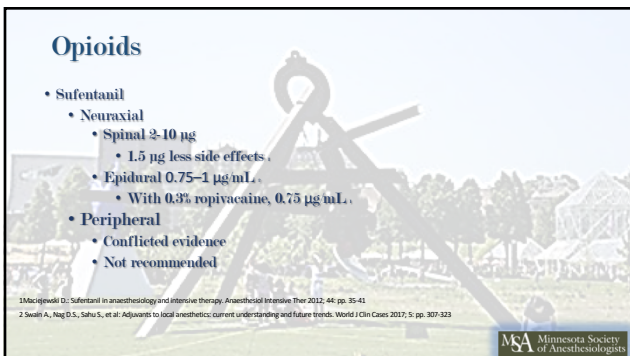
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### Opioids

- Sufentanil
  - Neuraxial
    - Spinal 2-10 µg
      - 1.5 µg less side effects.
    - Epidural 0.75-1 µg/mL
      - With 0.3% ropivacaine, 0.75 µg/mL.
  - Peripheral
    - Conflicted evidence
    - Not recommended

1. *McGraw Hill*. Sufentanil in anesthesiology and intensive therapy. *Anesthesiol Intensive Ther* 2012; 44: pp. 35-41

2. *Swaffin A, Nag D.S., Sahu S., et al.* Adjuncts to local anesthetics: current understanding and future trends. *World J Clin Cases* 2017; 5: pp. 307-323



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### Opioids

- **Buprenorphine**
  - **Neuraxial**
    - Spinal 75-100 µg
    - Epidural 150-300 µg
  - **Peripheral**
    - 300 µg
    - Prolong block, mainly in upper extremity, increase PONV
    - Block from long-acting LA is prolonged by approximately 6 hours
    - Neurotoxicity at high doses, in rats

1. Smith A, Nag B, Chiu S, et al. Advances in local anesthetics: current understanding and future trends. World J Clin Cases 2017; 9: 307-323




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### Opioids

- **Tramadol**
  - **Neuraxial**
    - Spinal 10-50 µg variable
    - Epidural 1-2 mg/kg Helpful in obstetrics and abdominal surgery
  - **Peripheral**
    - Minimal block prolongation, prevalence of side effects
    - Not recommended




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### Alpha-2 adrenoceptor agonists

- Applications: Neuraxial, Peripheral
- Profile
  - Effect
    - Neuraxial acts apparently by hyperpolarization through potassium channels.
    - Peripheral works hyperpolarizing cation channels, which leads to prolonged analgesic duration
  - Side effects: Hypotension, bradycardia, dry mouth, and sedation. : Thoracic

1. Bhatti S, Balamandran A, Beek D.R, et al. Chloride prolongation of bupivacaine analgesia after sciatic nerve block in rats is mediated via the hyperpolarization-activated cation current, not by alpha-2 adrenoceptors. Anesthesiology 2004; 101: pp. 488-494




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### Alpha-2 adrenoceptor agonists

- Clonidine
  - Neuraxial
    - Spinal 15-40 µg
    - Epidural Sensory + motor
      - Single bolus doses of 75-80 mcg
      - Infusion rates of 25-50 µg/hr
      - Caudal 2 µg/kg Minimal side effects
  - Peripheral
    - 0.5 µg/kg up to 150 mcg
    - Extend Sensory and Analgesic time
    - Side effects
    - Presentation: vial 1000 µg

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### Alpha-2 adrenoceptor agonists

- Dexmedetomidine
  - Neuraxial
    - Spinal 5-10 µg
      - Prolonged sensory block by 150 min
    - Epidural 1 µg/kg
  - Peripheral
    - 0.75-2 µg/kg
      - Brachial plexus: Extend duration 284 min
      - Less neurotoxicity in sciatic nerve

1. Abdallah F.W., and Bruhl R. Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. *Br J Anaesth* 2013; 110: pp. 915-920

2. Kozdzy R., Palahniuk R.J., and Cumming M.O. Spinal cord blood flow following subarachnoid tetracaine. *Can Anaesth Soc J* 1985; 32: pp. 23-29

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### Epinephrine

- Applications
- Profile
  - Effect
    - Vasoconstrictive properties of epinephrine prevent systemic reabsorption and therefore allow it to prolong the nerve blockade
    - Direct action on  $\alpha$ -2 adrenergic receptors at the spine level
  - Concerns
    - Compromise to endoneurial blood flow and potential increase in neurotoxicity in animal diabetic models
    - There are no human data supporting this theory
    - No decrease in nerve blood supply when epinephrine concentration > 1:400,000 (2.5 µg/mL).

1. Effects of local anesthesia on nerve blood flow: studies using lidocaine with and without epinephrine. *Myers RB, Heckman HM Anesthesiology*. 1989 Nov; 71(5):717-62.

2. Kozdzy R., Palahniuk R.J., and Cumming M.O. Spinal cord blood flow following subarachnoid tetracaine. *Can Anaesth Soc J* 1985; 32: pp. 23-29

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## Epinephrine

- Neuraxial
  - Spinal 100-600 µg All Lidocaine, Bupivacaine (Less extend), Tetracaine
  - Epidural: Response based on vasoconstriction properties of LA:
    - 50% duration increase: Lidocaine, Mepivacaine, and Chloroprocaine
    - Moderate increase: Bupivacaine, levobupivacaine, and etidocaine
    - Minimal effect: Ropivacaine (Vasoconstrictor)
- Epinephrine also serves as a marker of intravenous injection of local anesthetic. An increase in heart rate of 20 bpm or greater and/or an increase in systolic blood pressure of 15 mmHg or greater after a dose of 10 to 15 mg of epinephrine should raise a suspicion of intravascular injection.




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## Epinephrine

- Neuraxial
  - Spinal 100-200 µg (Up to 600)
    - Lidocaine, Tetracaine > Bupivacaine
  - Epidural 1-5 mg
  - Caudal anesthesia in doses of 0.5 mg/kg
- Peripheral
  - Mainly lidocaine and mepivacaine\*

\*Kirksey M.A., Haskins S.C., Cheng J., et al: Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: a systematic Qualitative review. PloS One 2015; 10: pp. e0137312




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## Phenylephrine

- Neuraxial
  - Spinal 2-5 mgs prolongs Lidocaine and Tetracaine
    - 5 mgs for Tetracaine (Risk of Transient Neurological Symptoms)
  - Epidural do not reduce peak blood levels of LA




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## Dexamethasone

- **Effect:**
  - Most effective adjuvant for prolonging block duration with minimal side-effects
  - Potent glucocorticoid with anti-inflammatory properties .
  - Prolonged analgesia postoperatively on a completely separate mechanism compared to its intrinsic anti-inflammatory properties .
  - Analgesic effects can be attributed to its systemic involvement especially when administered intravenously as an antiemetic.

1 Tordor M N, Fan L, Kolesnikov S, et al: Adjuvant dexamethasone with bupivacaine prolongs the duration of interscalene block: a prospective randomized trial. J Anesth 2011, 25: pp. 704-709  
 2 Knapcz D L, Lacouture P G, Wu D, et al: The dose response and effects of dexamethasone on bupivacaine microcapsules for intercostal blockade (T9 to T11) in healthy volunteers. Anesth Analg 2003, 96: pp. 576-582  
 3 Liu J, Richman K A, Grodzday S R, et al: Is there a dose response of dexamethasone as adjuvant for supraclavicular brachial plexus nerve block? A prospective randomized double-blinded clinical study. J Clin Anesth 2015, 27: pp. 237-242




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## Dexamethasone

- Supraclavicular brachial Plexus Superior to dexmedetomidine, without the risks of hypotension or sedation
- Block duration increase, depending on the type of LA:
  - ~2-3 hours when added to a medium-acting LA.
  - up to 10 hours when added to a long-acting drug
- A recent meta-analysis suggests that percutaneous administration of dexamethasone is more effective than intravenous administration, by, on average, 4 hours, in prolonging analgesia by long-acting LA .
- There is a theoretical risk of neurotoxicity with increasing doses.

1 97. Choi S, Rodseth R, McCartney C J. Effects of dexamethasone as a local anesthetic adjuvant for brachial plexus block: a systematic review and meta-analysis of randomized trials. Br J Anaesth. 2014;112:427-439  
 2 Chong MA, Berbenetz NM, Lin C, Singh S. Peri-neural versus intravenous dexamethasone as an adjuvant for peripheral nerve blocks: a systematic review and meta-analysis. Reg Anesth Pain Med. 2017;42:1139-1215




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## Sodium Bicarbonate

- **Effect:**
  - Theoretically an increase the amount of unionized local anesthetic hastening the onset of the block
  - The alkalinized anesthetic has demonstrated a marginal increase in speed of onset at select perineural sites including interscalene and three of the seven minor nerves of the upper extremity
  - Available data suggest that there are no clinical advantages for carbonated solutions .
- Currently no recommended

1 Bokesch P M, Raymond S A, and Strichartz G R.: Dependence of lidocaine potency on pH and PCO<sub>2</sub>. Anesth Analg 1987, 66: pp. 9-17




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### NMDA blockers

- Applications: Neuraxial
- Profile
  - Effect
    - Neuraxial acts by inhibiting nociceptive impulses at the dorsal horn of the spinal cord, and blocks the sympathetic outflow;
    - Intrathecal and epidural ketamine have both been shown to speed up the onset of motor and sensory blocks, but it also decreased the duration of motor blockade\*
  - Side effects: Hallucinations, drowsiness, and nausea, mainly with peripheral nerve blocks

\* Swain A., Nag D.S., Sahu S., et al: Adjuvants to local anesthetics: current understanding and future trends. World J Clin Cases 2017; 9: pp. 307-323




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### NMDA

- Ketamine
  - Neuraxial
    - Spinal 100-200 µg
    - Epidural 1-5 mg
    - caudal anesthesia in doses of 0.5 mg/kg
  - Peripheral
    - Not recommended\*

\* Kirby M.A., Haskins S.C., Cheng J., et al: Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: a systematic qualitative review. PLoS One 2015; 10: pp. e0137312




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### NMDA

- Magnesium sulfate
  - Prolong intravenous and intrathecal analgesia
  - Enhance the effect of lidocaine in Aβ fibers but not in C fibers
  - Neurotoxicity still to be determined
- Peripheral
  - Synergistic effect seen in femoral, interscalene, and axillary blocks
  - 200 mg interscalene 2 to 3 times increase in nausea 12 h postoperatively, but not at 150 mg

1. Ballard N.S., Ortiz J., and Flores R.A.: Additives to local anesthetics for peripheral nerve blocks: evidence, limitations, and recommendations. Am J Heal Pharm 2014; 71: pp. 373-385  
2. Brummett C., and Williams S.: Additives to local anesthetics for peripheral nerve blockade. Int Anesthesiol Clin 2011; 49: pp. 1-11




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### Midazolam

- Applications
- Profile
  - Effect
    - Indirect agonist at  $\gamma$ -aminobutyric acid-A (GABA-A) receptors
    - Prolonged postoperative analgesia
  - Concerns: Intrathecal and epidural midazolam caused irreversible sensory neurotoxicity

1 Ballard N.S., Ortiz J., and Flores R.A.: Additives to local anesthetics for peripheral nerve blocks: evidence, limitations, and recommendations. Am J Heal Pharm 2014; 71: pp. 373-385  
2 Yilmaz E., Hough K., Gebhart G., et al: Mechanisms underlying midazolam-induced peripheral nerve block and neurotoxicity. Reg Anesth Pain Med 2014; 39: pp. 525-533




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### Neostigmine

- Profile
  - Effect
    - Increase Ach in the synaptic cleft.
    - Does not prolong block duration.
    - Intrathecal neurotoxicity at 50  $\mu\text{g/kg}$  single dose and 10  $\mu\text{g/kg}$  multidose.
    - Epidural: Has shown labor analgesia before local anesthetic.
    - Side Effects: Nausea and gastrointestinal distress.
  - Currently no recommended

1 Kirksey M.A., Hawkins S.C., Cheng J., et al: Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: a systematic Qualitative review. PLoS One 2015; 10: pp. e0137312  
2 Demirel E., Ugur H.C., Dolgun H., et al: The neurotoxic effects of intrathecal midazolam and neostigmine. 2006; 34: pp. 218-223  
3 Rosenthal F., Laroche-Therme P.M., and Mercier-Fastier V.: Epidural administration of neostigmine and doxidine to induce labor analgesia: evaluation of efficacy and local anesthetic-sparing effect. Anesthesiology 2005; 102: pp. 1205-1210




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### Adenosine

- Effect:
  - Work on Adenosine receptors both central and peripherally.
  - No benefit proven in humans
- No benefits seen therefore not recommended




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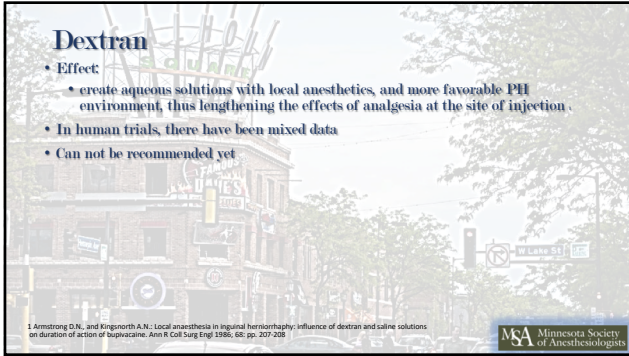
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**Dextran**

- Effect:
  - create aqueous solutions with local anesthetics, and more favorable PH environment, thus lengthening the effects of analgesia at the site of injection .
- In human trials, there have been mixed data
- Can not be recommended yet

1 Armitrong D.K., and Kingnorth A.N.: Local anesthesia in inguinal herniorrhaphy: influence of dextran and saline solutions on duration of action of bupivacaine. Ann R Coll Surg Engl 1986; 68: pp. 267-269




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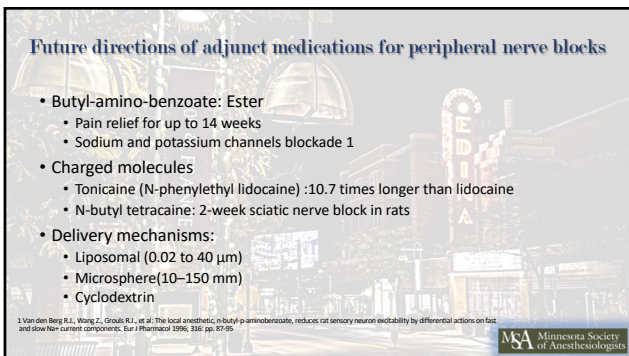
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**Future directions of adjunct medications for peripheral nerve blocks**

- Butyl-amino-benzoate: Ester
  - Pain relief for up to 14 weeks
  - Sodium and potassium channels blockade 1
- Charged molecules
  - Tonicaine (N-phenylethyl lidocaine) :10.7 times longer than lidocaine
  - N-butyl tetracaine: 2-week sciatic nerve block in rats
- Delivery mechanisms:
  - Liposomal (0,02 to 40 μm)
  - Microsphere(10–150 mm)
  - Cyclodextrin

1 Van den Berg R.J., Wang Z., Grouls R.J., et al.: The local anesthetic, n-butyl-p-aminobenzoate, reduces rat sensory neuron excitability by differential actions on fast and slow Na<sup>+</sup> current components. Eur J Pharmacol 1996; 292: pp. 87-95




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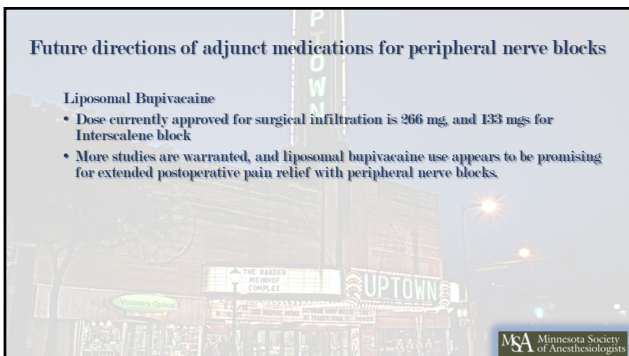
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**Future directions of adjunct medications for peripheral nerve blocks**

**Liposomal Bupivacaine**

- Dose currently approved for surgical infiltration is 266 mg, and E33 mgs for Interscalene block
- More studies are warranted, and liposomal bupivacaine use appears to be promising for extended postoperative pain relief with peripheral nerve blocks.




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