Regional Anesthesia: How Do We Make It Last?

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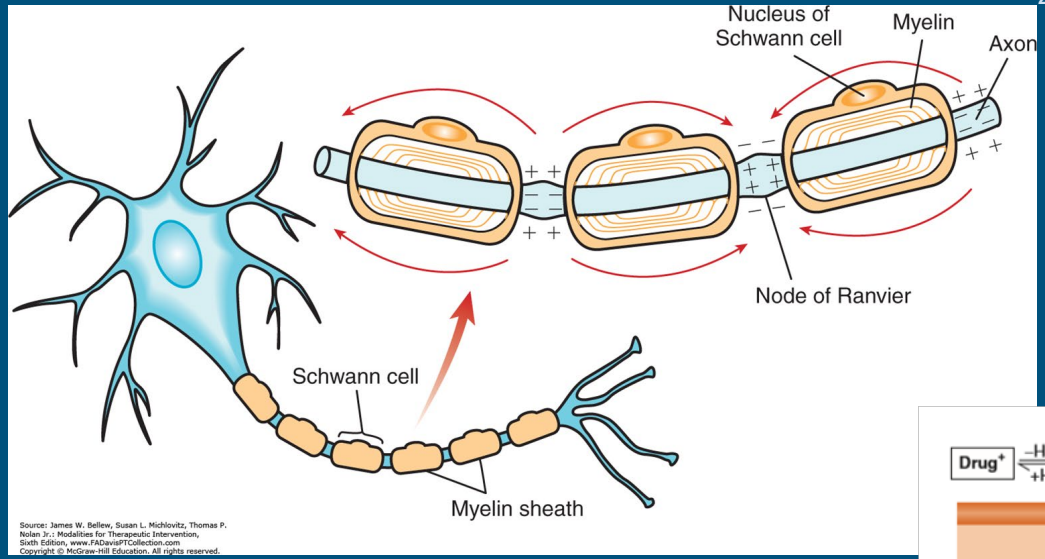
I have no conflicts of interest and nothing to declare

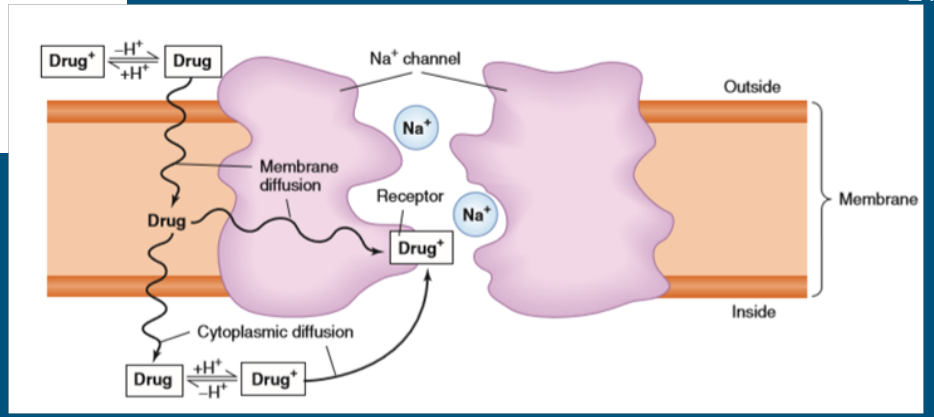
Many of these adjuncts are considered to be off-label use

Objectives

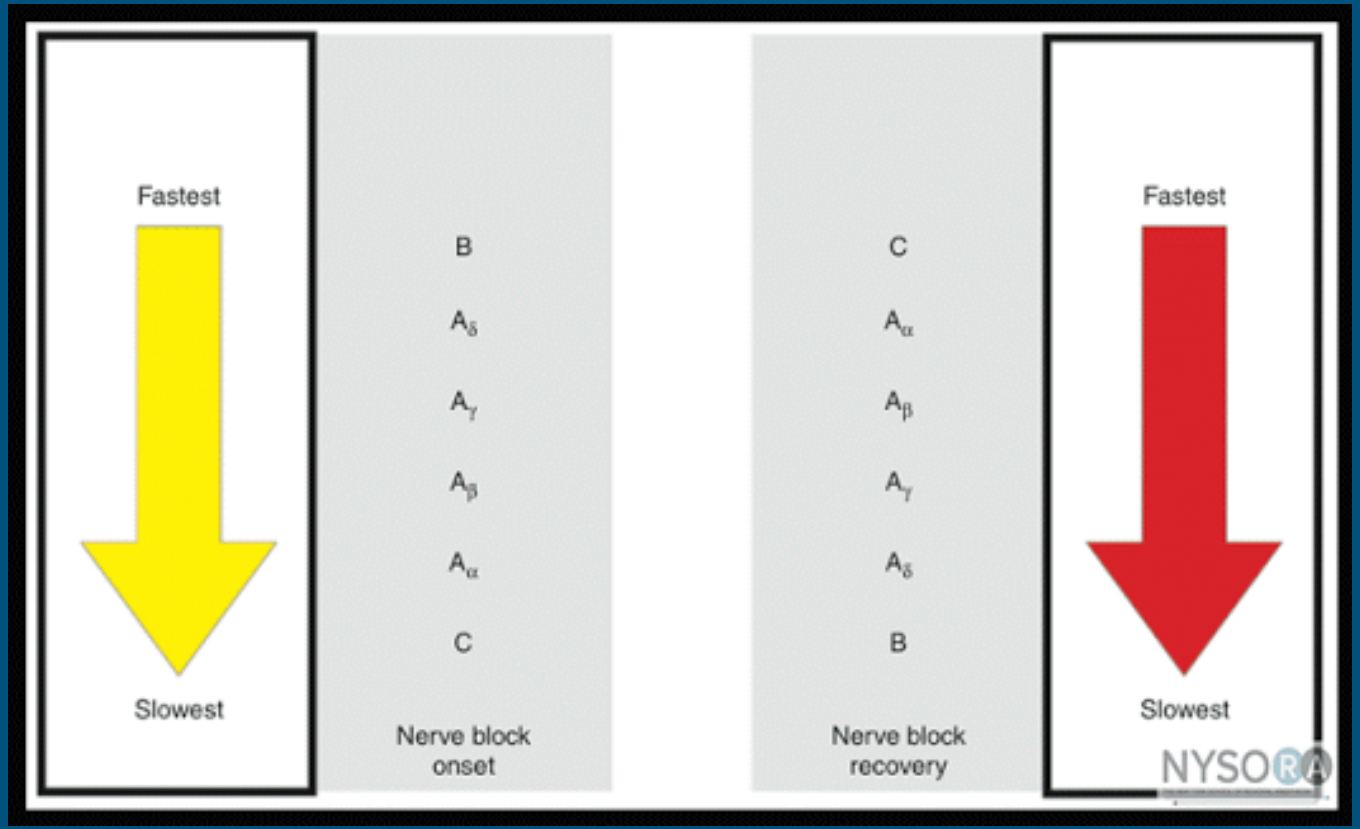
- Understand the basic pharmacology of local anesthetics
- Understand previously used medications and why they are no longer recommended
- Understand currently used medication adjuncts for peripheral nerve blocks
- Understand the future direction of adjuncts for peripheral nerve blocks

Local Anesthetics: How Do They Work Again?





Local Anesthetics: How Do They Work Again?



Local Anesthetics: How Do They Work Again?

- ***Duration of Action***: Determined by *protein binding and lipid solubility[9]
  - Drugs with high affinity for protein and lipids = firm attachment to those substances
  - Local anesthetic receptor on the neural membrane is composed of protein
  - Site of injection: speed of absorption changes based on location
    - Local anesthetics cause vasodilation (except cocaine and ropivacaine)
- Onset of Action: Determined by ionization[9]
  - Charged form will not penetrate membranes well
  - Dreaded pKa (Lower pKa = faster onset; except chloroprocaine which is concentration based)
- Potency: Determined by the lipid solubility of the local anesthetic[9]
  - Axolemma and myelin sheath are composed of lipids (i.e. lipid soluble drugs can pass easily through the nerve membrane)
  - Increased lipid solubility correlates with increased protein binding
    - Also correlates with increased likelihood of cardiac toxicity (bupivacaine)

Local Anesthetics: How Do They Work Again

Characteristic	Drug	Common Name	Relative Potency	Onset	Duration (min)
Low potency; short duration of action	Procaine	Novocaine	1	Slow	60-90
	Chloroprocaine	Nesacaine	1	Fast	30-60
Intermediate potency; intermediate - long duration of action	Mepivacaine	Carbocaine	2	Fast	120-240
	Prilocaine	Citanest	2	Fast	120-240
	Lidocaine	Xylocaine	2	Fast	90-200
High potency; long duration of action	Tetracaine	Pontocaine	8	Slow	180-600
	Bupivacaine	Marcaine, Sensorcaine	9	Intermediate	180-600
	Etidocaine	Duranest	6	Fast	180-600
	Ropivacaine	Naropin	10	Slow	180-600

Local Anesthetics: How Do They Work Again?

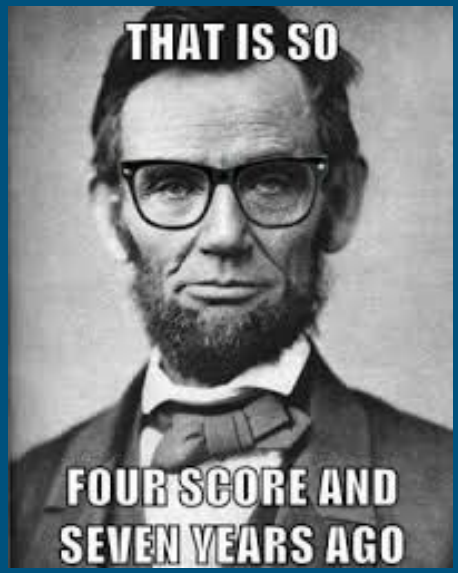
Manufacturers' Recommended Single-Injection Max Dose (mg/kg) [9]

Chloroprocaine	11 / (14)
Lidocaine	4 / (7)
Mepivacaine	4 / (7)
Prilocaine	7 / (8.5)
Bupivacaine	2.5 / (3.2)
Etidocaine	6 / (8)
Ropivacaine	3 / (3.5)

*Drug alone / (drug with epinephrine)

History of Local Anesthetic Adjuncts

- Adenosine
  - No additional benefit[19]
- Dextran
  - Needs high powered studies; currently inconclusive for any benefit[19]
- Fentanyl
  - No benefit when compared to other routes[19]
- Hydromorphone
  - No benefit when compared to other routes[19]
- Ketamine
  - No benefit when compared to other routes[19]
  - Unacceptably high incidence of adverse effects (psychotomimetic)[19]



History of Local Anesthetic Adjuncts

- Midazolam
  - Neurotoxic in animal models[19]
  - Not recommended for use[19]
- Morphine
  - No benefit when compared to other routes[19]
- Neostigmine
  - No benefit[19]
  - Causes adverse side effects that increase with increased doses[19]
  - Neurotoxic when injected perineural[19]
- Sufentanil
  - No benefit when compared to other routes[19]
  - Increased side effect profile[19]

Current Local Anesthetic Adjuncts

- Alpha 2 adrenoreceptor agonists
  - Clonidine
  - Dexmedetomidine
- Buprenorphine
- Epinephrine
- Liposomal Bupivacaine
- Steroid

Clonidine

- Mechanism of action: α-2 receptor agonist; hyperpolarization of nucleotide gated cation channels[19]
- Dosing: 0.5µg/kg (max 150µg)[19]
- Wide range of results[19]
  - One meta analysis showed duration was prolonged by 2 hours
  - Best used with intermediate acting local anesthetics
  - Upper extremity blocks had more success than lower extremity blocks
  - Adverse effects increased with increased doses
- More extensive research needs to be completed before routine use is recommended[19]

Dexmedetomidine

- Mechanism of action: α-2 receptor agonist (7 times more selective than clonidine); hyperpolarization of nucleotide gated cation channels[19]
- Dosing: 1-2μg/kg[13,19]
  - Lower dose = less side effects
- Increased duration of motor block, and prolonged time to first request for analgesia for brachial plexus blocks[19]
- Increased duration of sensory block by 3 hours and reduction of pain scores for 4 hours[18]
- Low incidence of adverse effects, can see hypotension/bradycardia as seen with IV administration[19]

Buprenorphine

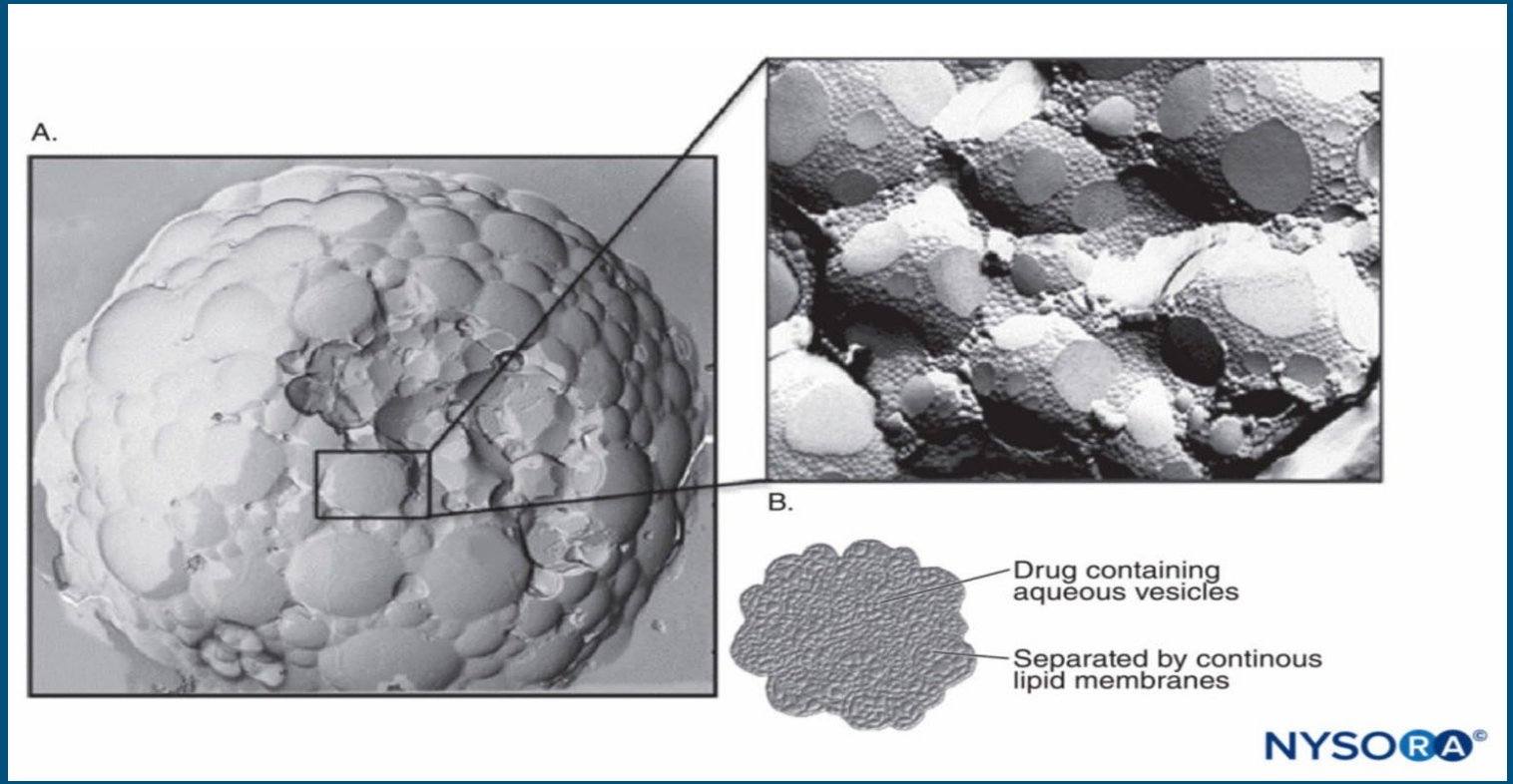
- Mechanism of action: decreased potassium conduction and increased calcium conduction; inhibits release of Substance P[14]
  - Substance P is a proinflammatory polypeptide secreted by nerves and inflammatory cells that is thought to be involved in the synaptic transmission of pain
- Dosing: 0.3mg or 0.3µg/kg[19]
- Duration of action prolonged 1.5- to 3-fold for brachial plexus and sciatic nerve blocks[9, 14, 19]
  - Some studies included epinephrine + buprenorphine
  - Perineural addition extended block longer than IM
  - Increased risk of PONV, no other adverse effects increased
    - Recommended to provide polymodal antiemetics

Epinephrine

- Proposed mechanism of action: constricts vessels in surrounding area[19]
  - Some antinociceptive properties through α-2 agonism
- Dosing: 0.5-1µg/kg or 5-10µg/mL[19]
- Does not prolong the duration to the same extent with all locals[19]
  - Best with short and intermediate acting local anesthetics
  - Recent study showed no longer than 60 minutes extra[21]
- Can increase the risk for neurotoxicity[3]
  - Current recommendations are against use of epinephrine unless ultrasound is unavailable or tip of needle is not visualized

Liposomal Bupivacaine

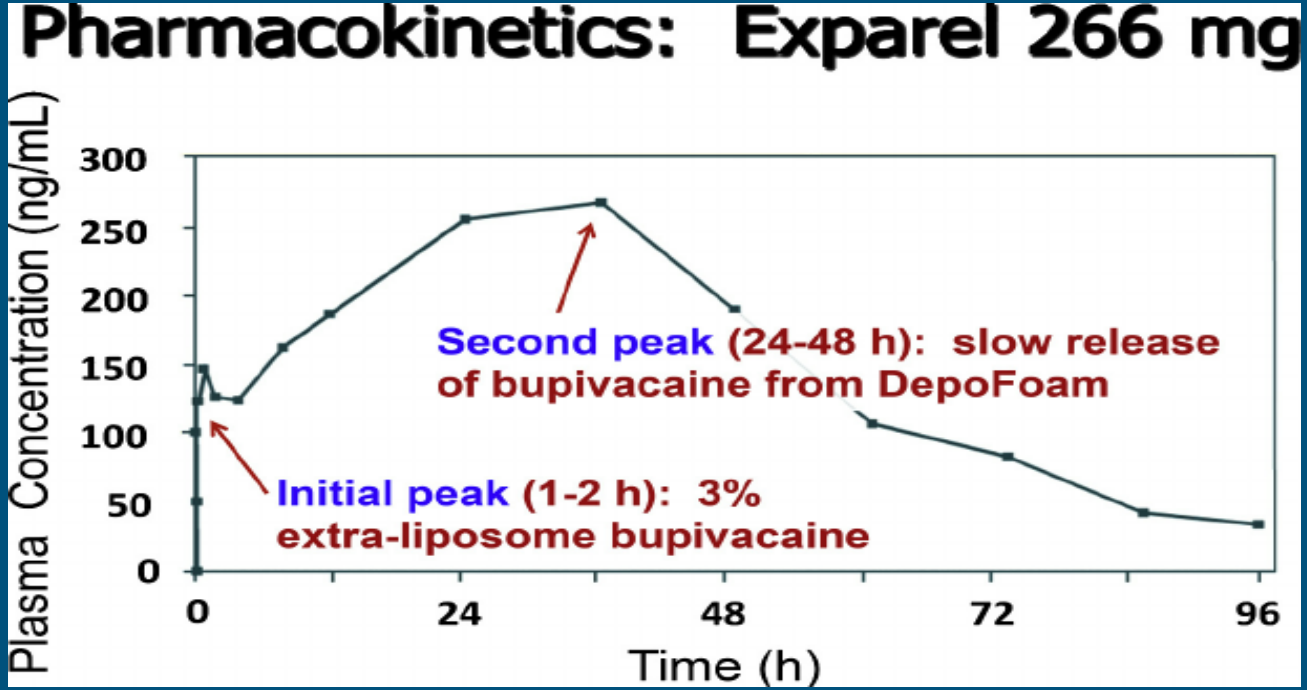
Bupivacaine encapsulated in DepoFoam



Liposomal Bupivacaine

- Mechanism of action: microscopic lipid vesicles ranging in size from 0.02-40 µm act as reservoirs for drugs with low bioavailability[19]
- FDA approved for hemorrhoidectomy, bunionectomy, fascial plane blocks and recently interscalene nerve blocks[11]
  - Dentistry as well
- Mixed results of efficacy depending on the study you read[11]
  - Some state no statistical difference in outcome
  - Some state 1st day specifically a reduction in opioid use
  - Some state up to 72 hours of relief
  - Detected in plasma up to 96 (infiltration)-120 (interscalene) hours after injection
- Potential side effects[11]
  - Avoid additional local anesthetic for 72 hours*
  - Nausea, vomiting or constipation
  - Always risk of local anesthetic side effects

Liposomal Bupivacaine



Liposomal Bupivacaine

Administration:

- Comes in a 10 or 20mL vial at 1.3% concentration (max dose is 20mL or 266mg for infiltration; 10mL or 133mg for brachial plexus blocks)[11]
- Not verified for use in <18yoa[11]
- Dilution with sterile saline up to 300mL[11]
  - May also *admix* bupivacaine HCl- do not exceed 1:2 (bupi HCL:liposomal bupi)
    - Example: 0.5% Bupi HCl: max 133mg (26mL) with 20mL liposomal bupivacaine
  - Wait at least 20 minutes after lidocaine infiltration to administer
- Do not mix liposomal bupivacaine with anything except the above mentioned[11]
  - Possibility of reducing the efficacy of DepoFoam to encapsulate bupivacaine

Steroid (Dexamethasone)

- Mechanism of action: Current theory- local action on nerve fibers[19]
  - Not the same as it's anti-inflammatory effect
- Dosing: 4, 8, & 10mg all used; no dose-response relationship noted[7]
- 37% increase in prolongation of upper and lower extremity blocks when used with ropivacaine[5]
  - Decreased pain for 24 hours
- A meta-analysis showed reduction of pain scores at 2, 6 and 12 hours and reduced pain medication intake for 24 hours[4]
- Some studies have shown no statistical difference between intravenous and perineural administration[8]
  - Cochrane review showed perineural prolonged sensory block 3 more hours; no difference in pain intensity/pain medications taken[15]

Future Local Anesthetic Adjuncts

- Bupivacaine-collagen implant
- Liposomal adjuncts
- Magnesium
- SABER-bupivacaine
- Tramadol - old & new

Bupivacaine-Collagen Implant

- Mechanism of Action: Collagen matrix that is biodegradable and fully resorbable, impregnated with bupivacaine that is released as the collagen is degraded[11]
- Dosing: Currently varying concentrations[11]
  - Bi-phasic peaks such as that with liposomal bupivacaine
  - Initial research shows 30 minutes to 20 hours
- One study showed decreased pain scores at 24 & 48 hours with no change in opioid intake and another showed no change in pain scores but opioid intake was reduced[11]
  - More studies needed!
- Side effects: Constipation, nausea & headache[11]

Liposomal Adjuncts

- Duration of Action: Extended duration of action due to liposomes surrounding medication[16]
- Animal studies showing positive results for both liposomal dexamethasone and liposomal dexmedetomidine when added with liposomal bupivacaine[16]
  - Increased block 2.9-fold
  - Duration of time increased 16.2 +/- 3.5 hours
    - Single adjunct addition extended 8-10 hours
  - Decreased tissue inflammation as well
- *Addition of unencapsulated adjuvants prolong duration by 25 +/- 6.3 hours[16]
  - Accompanied with systemic side effects

Magnesium

- Mechanism of action: NMDA receptor antagonist, voltage-gated calcium channel inhibition[19]
- Doubled the analgesic effect of lidocaine interscalene block with 500mg MgSO4 in one study[19]
  - Has been shown to add ~2 hours to bupivacaine/epinephrine ISB
  - *Study completed outside of U.S.[1]
- Lack of well defined neurotoxicity studies; therefore, it is currently not recommended for routine use[19]
- Side effects: bradycardia, hypotension, sedation, headache[19]

SABER-Bupivacaine

- Sucrose Acetate Isobutyrate Extended Release-Bupivacaine[11]
- Mechanism of Action: bioerodable injectable depot system (able to deliver drugs over days to 3 months)[11]
  - Linear pharmacokinetics; location of block can disrupt how long medication lasts
- One study showed this medication decreased pain up to 3 days[11]
- Again, more studies necessary before approval[11]

Tramadol

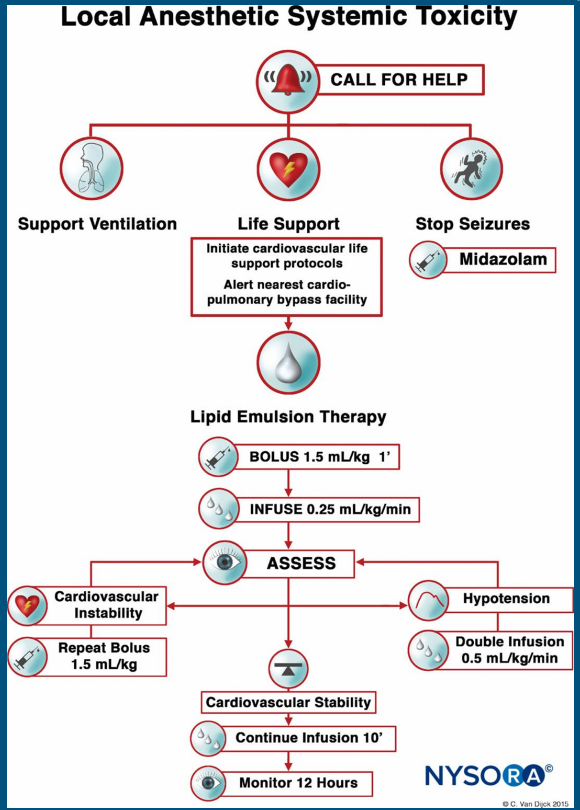
- Proposed mechanism of action: some inhibition of voltage gated potassium and sodium channels[10]
- Previously contradictory results[17]
- 2017 meta-analysis of brachial plexus blocks +/- tramadol[17]
  - 100mg prolonged sensory block by 61.5 minutes for axillary block (not ISB or SCB)
  - 100mg prolonged motor block by 65.6 minutes
  - 100mg prolonged analgesia by 125.5 minutes
  - Did not increase chance of adverse effects
- Likely more research to come- not yet recommended for routine use

LAST but not least….

Know your signs/symptoms of Local Anesthetic Systemic Toxicity (LAST)[12]:

- Vertigo
- Tinnitus
- Ominous Feelings
- Circumoral numbness
- Garrulousness
- Tremors
- Myoclonic Jerks
- Convulsions
- Coma
- Cardiovascular Collapse

Treatment of LAST



Any Questions?

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