Unconventional Analgesics for Pediatric Pain Management

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Intravenous Lidocaine

Lidocaine is beneficial in the treatment of neuropathic pain states by blocking conduction of sodium channels in peripheral and central neurons, and therefore reducing spontaneous impulse firing.(1,2) Furthermore, the effectiveness of intravenous lidocaine (IVL) in producing analgesia is a predictor of the subsequent efficacy of oral mexiletine both in the treatment of cardiac arrhythmias (3) and in the treatment of neuropathic pain.(4) Although animal studies have shown that intravenous lidocaine alleviates tactile allodynia in rats (5), human studies have found no association between reduction in allodynia and pain relief.(6) Typically, IVL is administered to a target plasma lidocaine level of 2-5 µg/ml.(7,8,9)

There are few reports of the use of lidocaine for treatment of neuropathic pain states in children. Wallace and others (10) used intravenous lidocaine to control pain after anti-GD2 antibody therapy in children with neuroblastoma using IVL at 2 mg/kg over 30 minutes followed by 1 mg/kg/hr. Compared with a morphine infusion (0.05-0.1 mg/kg/hr), lidocaine was associated with improved mobility and decreased supplemental analgesic requirements. Of note, extended use of lidocaine infusions over 4 days was associated with an increased incidence of nausea.

Our clinical experience confirms that lidocaine is useful for treatment of pediatric neuropathic conditions. We routinely employ lidocaine as an adjunct medication for pain syndromes refractory to conventional therapy, such as the pain of mucositis following bone marrow transplantation and refractory cancer pain (11,12), and also in neuropathic pain states such as CRPS-1, CRPS-2, erythromelalgia, and painful neuropathies to predict the efficacy of mexiletine (see below).

Because lidocaine pharmacokinetics are similar in children and adults, dosing schedules for children should correlate reasonably with published experience in adults. Lidocaine plasma levels are readily available in most clinical laboratories, to assure that infusions are delivering an effective dose without producing toxicity. The most accurate way to deliver intravenous lidocaine is by a computerized infusion, a technique utilized in our adult pain clinic, in which our protocol calls for an initiating bolus of lidocaine equal to 1 mg/kg over 5 minutes, with subsequent infusion of lidocaine at a rate of 1 mg/kg/hr. Blood levels are checked every 8 hours and the lidocaine infusion is adjusted to target a blood level between 2-5 µg/ml. Patients with hepatic or renal insufficiency need dose adjustments (halving the dosage of bolus or infusion) to prevent toxicity.

Mexiletine

Originally used as an oral cardiac antiarrhythmic analog of lidocaine, mexiletine is used by most pain treatment centers as an oral analog to lidocaine to treat neuropathic pain. The original antiarrhythmic studies for lidocaine showed that it was a useful predictor for the antiarrhythmic efficacy of mexiletine and tocainide. Tocainide, unfortunately, produces significant toxicity such as blood dyscrasias and interstitial pneumonitis. Mexiletine, on the other hand, is without such toxicity and is much better tolerated. Dejgard and others (13) reported a dose of mexiletine of up to 10 mg/kg daily to treat diabetic neuropathy. Mexiletine was used with at similar doses by Chabal and others in adults to treat peripheral nerve injuries.(14) Chabal commented that most subjects required a daily dose of mexiletine of 10 mg/kg for pain, while the usual range for treatment of cardiac arrhythmias is between 10-15 mg/kg.

A review of the pediatric literature shows no pharmacologic or pharmacokinetic difference in the absorption or metabolism of mexiletine between children and adults. Mexiletine is frequently associated with untoward gastrointestinal side effects, most commonly nausea and vomiting, as

well as sedation, confusion, difficulty concentrating, diploplia, blurred vision, and ataxia, although gradual introduction of the drug and progressive escalation of the dose is ordinarily successful in reducing this side effect, as illustrated in Table 1.

Table 1. Mexiletine dosing schedule for children. Mexiletine is available as 150mg, 200mg, 250mg, and 300mg tablets. The target dose is 10-15 mg/kg.

DAY	MORNING	MID-DAY	BED-TIME
1			1 Tablet
2			1 Tablet
3			1 Tablet
4	1 Tablet		1 Tablet
5	1 Tablet		1 Tablet
6	1 Tablet		1 Tablet
7	1 Tablet	1 Tablet	1 Tablet
8	1 Tablet	1 Tablet	1 Tablet
9	1 Tablet	1 Tablet	1 Tablet
10	1 Tablet	1 Tablet	2 Tablets
11	1 Tablet	1 Tablet	2 Tablets
12	1 Tablet	1 Tablet	2 Tablets
13	1 Tablet	1 Tablet	2 Tablets
14	2 Tablets	1 Tablet	2 Tablets
15	2 Tablets	1 Tablet	2 Tablets
16	2 Tablets	1 Tablet	2 Tablets
17	2 Tablets	1 Tablet	2 Tablets
18+	2 Tablets	2 Tablets	2 Tablets

Anticonvulsants

Carbamazepine (Tegretol®)

Carbamazepine is an older anti-epileptic used to treat neuropathic pain via sodium channel blockade. Carbamazepine can be administered in oral (100-200 mg) and suspension formulations (100 mg/5 ml). Recommended dosing schedules for children > 6 years start at 10 mg/kg/day in two divided doses to a usual maintenance dose of 15-30 mg/kg/day in 2-4 divided doses per day. Blood levels (therapeutic 4-12 mcg/ml) can be obtained but do not necessarily correlate with analgesia for neuropathic pain.

Metabolism and adverse effects are significant with carbamazepine. Carbamazepine is hepatically metabolized, limiting its usefulness patients with hepatic insufficiency. Moreover, adverse effects are common including hematologic – aplastic anemia, agranulocytosis; cardiovascular – congestive heart failure, syncope, arrhythmias; central nervous system – sedation, dizziness, fatigue, slurred speech, ataxia; and even hepatitis.(15) A complete blood count should be obtained prior to initiating this antiepileptic and should be repeated every 3-6 months. Although a classic agent for the management of neuropathic pain, carbamazepine is no longer a first line drug, particularly for a child or adult who may have hematologic alterations or hepatic dysfunction.

Sodium Valproate (Depakote®)

Valproic acid is an anti-epileptic drug that has been used to treat neuropathic pain states and associated mood disturbances. The drug also seems effective for management of migraine

headaches, but because of significant side effects, valproate is not usually a first-line agent.

The mechanism of action for valproate is unclear. The drug has a wide spectrum of anticonvulsant applications, therefore multiple mechanisms of action are proposed. Loscher describes at least three mechanisms.(16) Valproate increases GABA synthesis and release, which may partially explain efficacy in treating central pain. Valproate also attenuates neuronal excitation induced by NMDA-type glutamate receptors. NMDA receptors have some correlation with centralization of neuropathic pain states or the "wind-up" phenomenon. Moreover, valproate has direct effects on excitable membranes and acts as a membrane stabilizer, similar to intravenous lidocaine and mexiletine.

Valproate is available in an oral tablet, syrup, and rectal suppository. Dosing starts at 10-15 mg/kg/day to a maximum of 30-60 mg/kg/day. The drug has a half-life in children of 6-18 hours with a peak effect in 4 hours after administration. Plasma concentration does not correlate with toxicity, seizure control, or analgesia. Valproate is protein-bound (80-95%) and metabolized by glucuronidation and other oxidative pathways.

Adverse effects can be significant. Typical toxic effects within the first several months include anorexia, nausea/vomiting, sedation, and weight gain or loss. Valproate may cause hepatotoxicity and hepatic dysfunction in 5-30% of patients. Other less common adverse effects include hyperammonemia, pancreatitis, and platelet dysfunction. For these reasons, valproate is not a first-line agent. Liver function tests should be performed prior to initiation of valproate treatment and then every month for the next 6 months. Symptoms such as malaise, lethargy, gastrointestinal symptoms, and easy bruising may indicate liver dysfunction and lead to immediate laboratory evaluation and discontinuation of the drug. (17)

Gabapentin (Neurontin®)

Gabapentin is a compound that was originally synthesized as a gaba-ergic drug to treat spasticity. It was later found to be more effective as a potent anticonvulsant for treating partial seizures and generalized tonic-clonic seizures.(18,19) At this time, the mechanism of action of this agent is unclear. Gabapentin may enhance extracellular GABA levels by reversing GABA transport in a unique way. The compound does not reduce voltage sensitive sodium channels or affect NMDA receptors. On a biochemical level, gabapentin may inhibit a branched chain amino acid transferase ultimately producing a decreased level of glutamate, an excitatory amino acid that may be important in nerve transmission. Increased activity of glutamate dehydrogenase and glutamic acid decarboxylase has also been noted in gabapentin treated animals, further decreasing levels of glutamate.

The most remarkable clinical feature of gabapentin is its few and infrequent side-effects or dose limiting factors. In fact, it is safe to say that of the many agents described in this chapter for the management of pain, none has a more benign side effect or toxicity profile.

Gabapentin is not protein bound; therefore, distribution is not affected by alterations in hepatic function. Gabapentin is not metabolized, and therefore does not induce hepatic enzymes. Gabapentin elimination is entirely by renal excretion. Dosage must therefore be adjusted proportionally to the reduction in creatinine clearance.

Side effects are predominately limited to the central nervous system: somnolence, dizziness, ataxia, nystagmus and tremor. These effects are dose related and are usually minor.

Dosage for adults ranges from 300 mg/day to 5600 mg/day. Gabapentin has a biological half-life of 5-9 hours and therefore is typically prescribed on a three times a day schedule. Higher dosages (for example, >20 mg/kg/day) require more frequent administration because

gastrointestinal absorption depends upon an L-amino acid transporter in the gastrointestinal tract that may become saturated at higher gabapentin dosages, producing diarrhea.

The use of gabapentin has been well described in the pediatric literature, using doses from 5-30 mg/kg for the management of seizure disorders.(20,21) Behavioral side effects of gabapentin have been described in children consisting of intensification of baseline behaviors including tantrums, hyperactivity, oppositional behavior, fighting, and increased anger.(22) A disinhibition theory similar to one seen with benzodiazepine therapy has been postulated as the cause.

Gabapentin has been unambiguously found to be beneficial in treating chronic neuropathic pain syndromes in adults. Mellick (23) described the use of gabapentin in complex regional pain syndrome type I, in which significant pain relief and possible reversal of the disease process was found. Controlled studies by Robotham (24) for postherpetic neuralgia and Backonja (25) for neuropathy secondary to diabetes mellitus also suggest efficacy of treatment in these neuropathic pain conditions. Backonja additionally found that gabapentin therapy had a positive effect on mood.

In the treatment of pain in the pediatric population, reports are few, limited mostly to case reports and small series. (26) Since the initiation of use of gabapentin, however, its clinical utility has far outpaced the published data. In part, this may be due to the relative paucity of agents useful in neuropathic pain, and the significant side effects of these agents. In our clinic, gabapentin is frequently used as a first or second line agent for the treatment of neuropathic pain, initially at 10mg/kg and gradually escalating over several weeks to a maximum of 50mg/kg. The daily dosage may be titrated up to 70 mg/kg/day depending on clinical response and side effects. (27)

Tricyclic Antidepressants

Depression and other psychological symptoms such as anxiety and anger accompany many chronic pain conditions. Originally, chronic pain patients were treated for depression and coincidentally found significant pain relief independent of the mood altering affect of antidepressant medication. Subsequent studies by Max (28i) and others (29,30) showed statistically significant relief in treating neuropathic pain syndromes.

Antidepressants therefore have multiple uses in pain medicine. These agents are used to treat depression, anxiety, sleep disturbance, and, of course, pain.

All tricyclic antidepressants that have been tested have equal efficacy at therapeutic dosages. While most antidepressants take 4-6 weeks to reach their full antidepressant effect, the onset of analgesic effect is less clear, but is almost certainly much shorter than that for the antidepressant effect.

The pharmacology of tricyclic antidepressants is well defined. The mechanism of action of tricyclic antidepressants is the reuptake inhibition of serotonin and norepinephrine from synaptic junctions in the central nervous system. Each TCA has varying degrees of effect on serotonin and norepinephrine levels, depending upon whether the drug is a primary or tertiary amine.

Tricyclic antidepressants have a high first pass metabolism by the liver after absorption from the gastrointestinal tract. They are highly protein bound in plasma to alpha-1 acid glycoprotein. Tricyclic antidepressants are lipophilic molecules, therefore accumulate in the body's fat stores; biologic half-lives are quite long (1-4 days).

In patients, there is wide plasma TCA level variability due to genetic polymorphism. TCAs are metabolized by P450 2D6. The biochemical activity of the drug metabolizing isozyme

cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7-10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants when given usual doses. Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma level of the TCA).

In addition, certain drugs inhibit the activity of this isozyme and make normal metabolizers resemble poor metabolizers. An individual who is stable on a given dose of TCA may become abruptly toxic when given one of these inhibiting drugs as concomitant therapy. The drugs that inhibit cytochrome P450 2D6 include some that are not metabolized by the enzyme (quinidine; cimetidine) and many that are substrates for P450 2D6 (many other antidepressants, phenothiazines, and the type 1C antiarrhythmics propafenone and flecainide). While all the selective serotonin reuptake inhibitors (SSRIs), e.g., fluoxetine, sertraline, and paroxetine, inhibit P450 2D6, they may vary in the extent of inhibition. The extent to which SSRI-TCA interactions may pose clinical problems will depend on the degree of inhibition and the pharmacokinetics of the SSRI involved. Nevertheless, caution is indicated in the coadministration of TCAs with any of the SSRIs and in switching from one class to the other. Of particular importance, sufficient time must elapse before initiating TCA treatment in a patient being withdrawn from fluoxetine, given the long half-life of the parent and active metabolite (at least 5 weeks may be necessary).

Typical side effects of TCAs are dose-related and include:

- Antihistaminic (H1 and H2): sedation and increased gastric pH
- Antimuscarinic: dry mouth (xerostomia), impaired visual accommodation, urinary retention, and constipation
- Alpha-adrenergic blockade: orthostatic hypotension
- Appetite stimulation: weight gain
- Quinidine-like effect: QRS widening, prolonged QTc. As early as 1990 in "The Medical Letter" and as recently as 1997, reports of the sudden death of children have raised concerns of life threatening arrhythmias.(31,32) Sudden deaths in TCA-treated children may be idiosyncratic. Desipramine and imipramine in particular seem to produce greater changes in baseline EKG, specifically increased QRS duration.

Amitriptyline

$CHCH_2CH_2N(CH_3)_2$

Nortriptyline

$CHCH_2CH_2NHCH_3$

Desiprimine

$CHCH_2CH_2NHCH_3$

Protriptyline

H $CHCH_2CH_2NHCH_3$
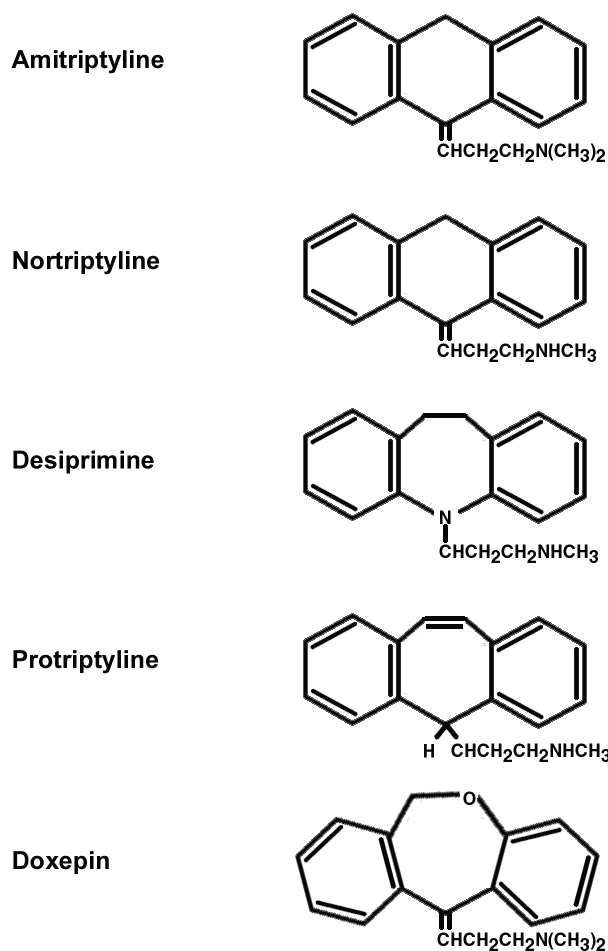
Doxepin

$CHCH_2CH_2N(CH_3)_2$

Figure 1. *The chemical structures of commonly prescribed tricyclic antidepressants.*

Amitriptyline (Elavil®)

Collins (33) retrospectively described eight children, ages 5-17 years, in whom intravenous amitriptyline was effective in treating neuropathic pain, depression, sleep disturbance, and as an adjuvant for opioid analgesia. The calculation of initial intravenous dosage for 'amitriptyline naïve" children was 0.2mg/kg/day, with ultimate doses of 0.05-2.4 mg/kg/day given intravenously. Side effects in addition to those listed above included dysphoria, which might have been secondary to concurrent opioids, and extrapyramidal effects that resolved with diphenhydramine.

While children may be rapid metabolizers of amitriptyline, and therefore require twice-daily dosing schedule, a single daily dose is usually first used until a side effect profile is established for individual patients. The most prominent and consistent side effect is somnolence; therefore, the daily dose is generally given before bedtime. A recommended initial dosage is 0.05 mg/kg/day, escalating over a period of 3-4 weeks to approximately 0.5-1 mg/kg/day is generally sufficient for pain management, although higher doses have been used in the past for mood elevation. Amitriptyline may also be parenterally administered as an intramuscular injection using about one-third to one-half the oral dose. The intramuscular preparation presently marketed may also be administered intravenously over a period of 2 hours, to mimic the absorption of an intramuscular injection.

The utility of routine measurement of plasma drug levels in pain management is dubious, because no correlation has been shown between plasma drug levels and analgesia. However, plasma levels may identify a rapid or slow metabolizer, confirm patient/parent compliance with prescription, and optimization of dosage prior to discontinuation of trial.(34)

Nortriptyline (Pamelor®)

Nortriptyline is a compound with virtually identical pharmacology to amitriptyline, but because of the demethylation of the terminal amide group, the side effect profile is superior to amitriptyline, particularly in regards to its sedative and antimuscarinic effects.

While published experience with nortriptyline is lacking in pediatrics, experience shows that it is equally effective, and preferable when daytime somnolence limits the use of amitriptyline.

Desiprimine (Norpramin®)

Desipramine has been reported to be associated with sudden death in several pediatric cases; therefore, its use has been abandoned for the management of pain in children.

Selective Serotonin Reuptake Inhibitors (SSRI's)

While most useful to treat clinical signs of depression complicating the management of chronic pain, most SSRIs are less effective as specific analgesics than TCAs, although Sindrup, et al. found some benefit in using paroxetine (Paxil®) to treat diabetic neuropathies, especially when patients could not tolerate the side-effects of tricyclic antidepressants.(35) The notable exception to the absence of analgesic properties with this newest class of antidepressants is venlafaxine.

Venlafaxine (Effexor®)

Venlafaxine is a novel SSRI chemically unrelated to other SSRIs but chemically similar to the opioid tramadol (Ultram®) (Figure 1).(36)
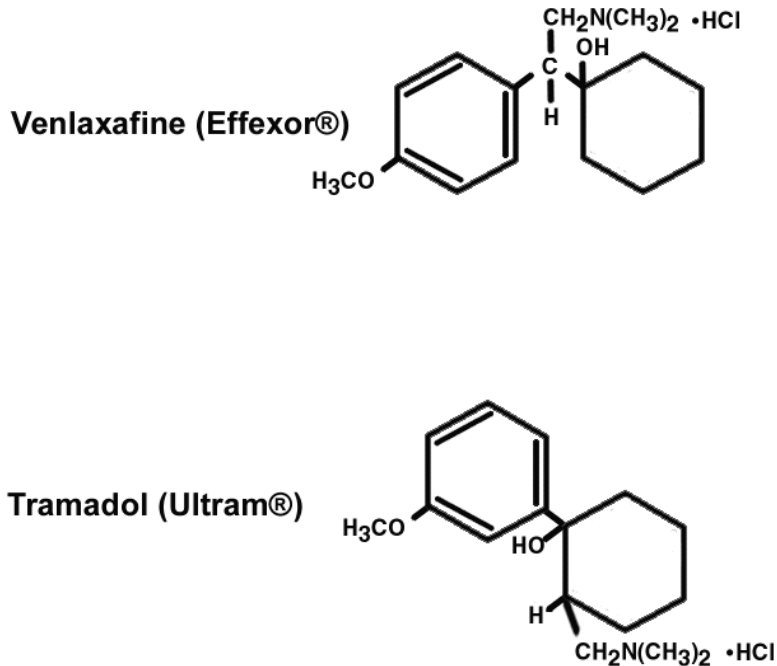
Figure 2. *The chemical structures of venlafaxine and tramadol demonstrating the chemical similarity between these two antidepressant and analgesic substances, respectively.*

The mechanism of the antidepressant action of venlafaxine in humans is believed to be the same as with other SSRIs, associated with its potentiation of neurotransmitter activity in the CNS as with other SSRIs: preclinical studies have shown that venlafaxine and its active metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.

That venlafaxine is analgesia is seen in studies in animals that show that venlafaxine is effective in reversing chronic neuropathic pain secondary to thermal hyperalgesia, and additionally is effective in treating the hyperalgesia of neuropathic pain due to chronic sciatic nerve constriction injury in rats.(37)

Venlafaxine-induced antinociception is significantly inhibited by naloxone, nor-BNI and naltrindole but not by beta-FNA or naloxonazine, implying involvement of kappa1- and delta-opioid mechanisms. When adrenergic and serotoninergic antagonists are used, yohimbine but not phentolamine or metergoline, decreased antinociception elicited by venlafaxine, implying a clear alpha2- and a minor alpha1-adrenergic mechanism of antinociception. Therefore, the antinociceptive effect of venlafaxine is mainly influenced by the kappa- and delta-opioid receptor subtypes combined with the alpha2-adrenergic receptor. These results suggest a potential use of venlafaxine in the management of some pain syndromes. However, further research is needed in order to establish both the exact clinical indications and the effective doses of venlafaxine when prescribed for neuropathic pain. (38)

Spinal Alpha-Agonists

Clonidine (Duraclon Injection®)

Recent studies using clonidine in central and peripheral blockade show that it is co-analgesic when used with either local anesthetics or opioids in epidural, intrathecal, or peripheral blocks.(39,40,41) Clonidine is thought to have applications in the treatment of chronic pain, particularly neuropathic pain. Finally, intrathecal administration of clonidine has been shown to reduce intractable muscle spasms in patients with spinal cord injuries.

Alpha-2 receptors are located on primary afferent terminals (both peripheral and spinal endings) in the superficial laminae of the dorsal horn of the spinal cord, and within several brainstem nuclei. The analgesic effect of clonidine may be at all three sites, with each site's relative contribution to its analgesic effect being unclear. Most studies support a direct and primary spinal analgesic action of clonidine. Supportive data for this conclusion are the facts that the relative potency of epidural clonidine to intravenous clonidine is 2:1, clonidine has a lipophilicity similar to fentanyl, the duration of analgesia of epidural clonidine is 3-5 hours, and that intrathecal administration of clonidine results in a peak effect within 30-60 minutes and has duration of up to 6 hours.

Clonidine increases the release of acetylcholine at the dorsal horn. This enhances sensory and motor block of C and A-delta fibers by local anesthetics by increasing potassium conductance.

Adverse effects of clonidine include:

- Dose dependent decrease in blood pressure. Action at the nucleus tractus solitarius and locus coeruleus decrease peripheral sympathetic tone. Further action at the lateral reticular nucleus causes hypotension and an antiarrythmogenic action. Neuraxial administration inhibits sympathetic preganglionic neurons in the spinal cord, and heart rate may decrease secondary to a depression in atrioventricular nodal conduction.
- Sedation. This side effect is localized to the activity in the locus coeruleus. The sedation is dose dependent between 50-900 μg regardless of route of administration. Clonidine has a rapid onset of sedation within 20 minutes. In adults, an infusion of epidural clonidine of 30 μg per hour does not produce more sedation than epidural placebo or epidural morphine.
- Endocrine depression. Clonidine reduces but does not suppress neurohormonal secretion.
- Sudden cessation of clonidine treatment, regardless of the route of administration and including after prolonged epidural administration, has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor, accompanied or followed by a rapid rise in blood pressure.

Clonidine alone does not induce respiratory depression nor potentiate respiratory depression from opioids.

With regards to the pediatric literature, most studies have been performed using clonidine in combination with a bupivacaine epidural analgesia in the acute pain setting. Motsch (xli) studied a group of 40 children undergoing minor surgical procedures. He found that combined caudal analgesia with bupivacaine and clonidine (5 μg/kg) was superior to local anesthetic alone, as determined by both duration and intensity of analgesia. However, children had decreased blood pressure and sedation for the first three postoperative hours. This observed effect is consistent with the known duration of epidural clonidine in adults.   Other authors have studied caudal analgesia using bupivacaine and clonidine, 1-2 μg/kg, with bupivacaine. This dose of clonidine

was seen to decrease mean arterial pressure but not to cause bradycardia or respiratory depression. (42,43,44)

The experience in adult cancer patients with intractable pain suggests an initial dose of 30-150 μg followed by a continuous infusion of 8-400 μg/day. Extrapolation from experience in adults and our unpublished clinical experience suggests an initial dose of epidural clonidine of 1-2 μg/kg should also be appropriate either in the subarachnoid or epidural spaces, followed by an infusion of local anesthetic and clonidine at 0.02-0.1 μg/kg/hr, titrating as needed to a maximum of 0.2 μg/kg/hr, while observing for undesired hemodynamic effects or sedation.

Table 2. Summary of unconventional analgesics useful in the management of pain in children.

Drug	Indications and Uses	Pediatric Dosing	Toxicity and Notes
Lidocaine	· Neuropathic pain · Refractory visceral pain	150 µg/kg/hr	· Measure plasma level every 8-12 hr and maintain 2-5 µg/ml
Mexiletine	· See Lidocaine	See Table 1	· See Table 1
Carbamazepine	· Neuropathic pain · Migraine prophylaxis	15-30 mg/kg	· Blood dyscrasias · Monitor plasma level and periodic CBC
Valproate	· Neuropathic pain · Migraine prophylaxis · Mood lability	10-60 mg/kg	· Blood dyscrasias; hepatotoxicity · Dose divided BID. Monitor plasma level and periodic CBC and LFT
Gabapentin	· Neuropathic pain · Migraine prophylaxis	5-30 mg/kg	· Dose divided TID or QID. Escalate dose over several weeks to target dose
Amitriptyline Nortriptyline Imipramine	· Neuropathic pain · Migraine prophylaxis	0.05-2 mg/kg	· Escalate dose over several weeks to target dose. Dose given h.s. Obtain screening ECG prior to use: contraindicated in prolonged QT_c

Drug	Indications and Uses	Pediatric Dosing	Toxicity and Notes
Venlafaxine	· Chronic pain with depression · Neuropathic pain	1-2 mg/kg	· Dose divided BID or TID · Caution when used with TCAs or other SSRIs because of reported arrhythmias
Clonidine	· Neuropathic pain · Visceral pain · Postoperative pain	0.05-0.2 µg/kg/hr	· By continuous epidural infusion · May produce hypotension, bradycardia, somnolence

Capsaicin

Capsaicin is the chemical substance in chili peppers that creates their spiciness and heat. In 1997, a gene that encoded for a receptor specific for capsaicinoids was identified. The capsaicin-gated vanilloid receptor 1 (VR1) is a fatty acid receptor present only on C fibers, that when activated produces desensitization or degeneration of the sensory afferent. This phenomenon has led to the use of capsaicin for the management of chronic pain states, particularly those associated with burning cutaneous dysesthesias and mechanical allodynia. However, there are some conditions for which capsaicin is ineffective, such as peripheral neuropathy associated with the acquired immune deficiency syndrome (AIDS) and neuropathic pain associated with nerve injury. Overall, outcome studies show that the "number needed to treat" (NNT) with capsaicin varies from 2.5 in painful diabetic neuropathy, to 5.9 in other disorders. This is not an impressively effective treatment modality, and the inconvenience of the necessity to spread a cream over a large affected body surface.

Chronic application of capsaicin leads to depletion of substance P from cutaneous C fibers, and ultimately degeneration of C fibers, thus some degree of analgesia. However, acute cutaneous application of capsaicin produces a complex sensation that changes in intensity and quality as a function of time and is characterized by sting, prick, burn and pain. The painful sensations and inconvenience associated with acute application of capsaicin to affected skin clearly limits its usefulness in pediatric pain medicine. Furthermore, there are no published reports of the use of capsaicin in children.
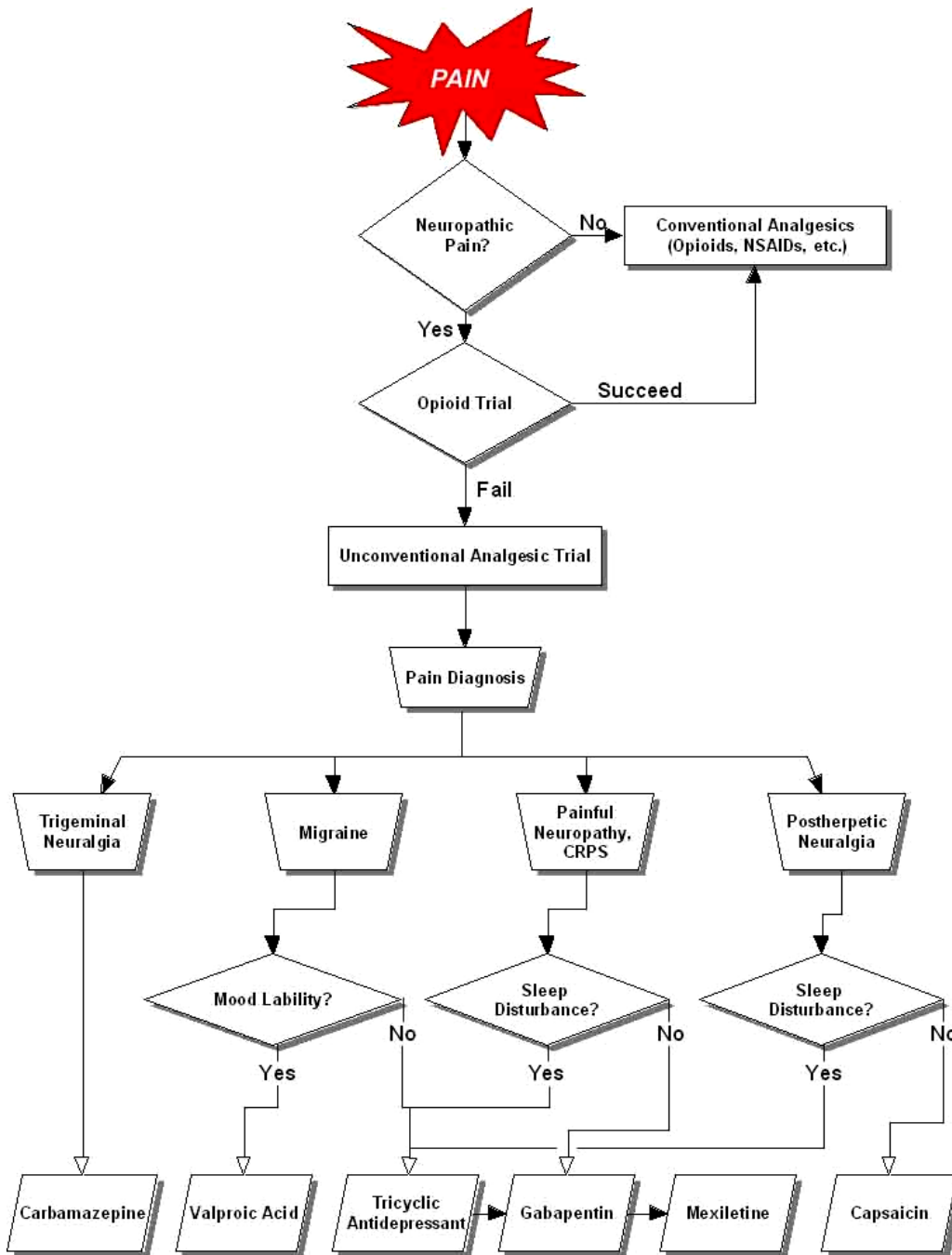
Figure 3. *An algorithm for pharmacologic management of neuropathic pain syndromes.*

Conclusions

Nociceptive pain may be adequately treated with conventional opioid and nonopioid analgesics, however many neuropathic pain states are refractory to conventional analgesics. For these conditions, use of a number of drugs not traditionally considered analgesics, and not developed by the pharmaceutical industry for their analgesic properties is effective. These drugs are

effective by virtue of their membrane stabilizing effects or their additive or synergistic enhancement of endogenous modulation of nociception in the central nervous system.

We are entering an era of new analgesic drug development by the pharmaceutical industry, and it is likely that in the next decade new compounds will be added to our armamentarium to fight pain in novel molecular ways. As our understanding of the molecular mechanisms of pain evolves, the category of unconventional analgesics will certainly expand.

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