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# Utilization of Intravenous Lidocaine Infusion for the Treatment of Refractory Chronic Pain

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## Abstract

**Context:** Chronic pain accounts for one of the most common reasons patients seek medical care. The financial burden of chronic pain on health care is seen by direct financial cost and resource utilization. Many risk factors may contribute to chronic pain, but there is no definite risk. Managing chronic pain is a balance between maximally alleviating symptoms by utilizing a therapeutic regimen that is safe for long-term use. Currently, non-opioid analgesics, NSAIDs, and opioids are some of the medical treatment options, but these have numerous adverse effects and may not be the best option for long-term use. However, Lidocaine can achieve both central and peripheral analgesic effects with relatively few side effects, which may be an ideal compound for managing chronic pain.

**Evidence Acquisition:** This is a Narrative Review.

**Results:** Infusion of lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide), an amino-amide compound, is emerging as a promising option to fill the therapeutic void for treatment of chronic pain. Numerous studies have outlined dosing protocols for lidocaine infusion for the management of perioperative pain, outlined below. While there are slight variations in these different protocols, they all center around a similar dosing regimen to administer a bolus to reach a rapid steady state, followed by infusion for up to 72 hours to maintain the therapeutic analgesic effects.

**Conclusions:** Lidocaine may be a promising pharmacologic solution with a low side effect profile that provides central and peripheral analgesia. Even though the multifaceted mechanism is not entirely understood yet, lidocaine may be a promising novel remedy in treating chronic pain in various conditions.

**Keywords:** Chronic Pain, Lidocaine, Headache, Fibromyalgia, CRPS, Low Back Pain

## 1. Context

Whether it is accidentally touching a hot stove or a fresh paper cut, pain elicits an unpleasant sensation. Pain serves more than just an unpleasant experience and has been recognized by the American Pain Society as the "fifth vital sign" (1). When a noxious stimulus creates a feeling of pain, it serves as a warning signal to the body (2). This signal can alert a person to potential harm. However, not all pain is considered adaptive (3). When the pain persists

beyond the healing process, it no longer serves a beneficial purpose (4). Furthermore, persistent pain may lead to structural and functional changes within the nervous system that leads to continuous pain generation and chronic pain (4, 5).

Chronic pain accounts for one of the most common reasons individuals seek medical care (6). These visits increase the health care burden both (7). The presence of chronic pain impacts every aspect of a person's abil-

ity to function (8). Chronic pain has been linked to decreased quality of life, increased mobility restrictions, and daily activities (9). There are also reasonably high rates of substance-related disorders among patients with chronic pain, including opioid dependence (10). The increase in opioid dependence secondary to chronic pain can create additional burdens on both the patient and the community through abuse and addiction (7).

Lidocaine, a suitable alternative for treating visceral and central pain, can also be useful where drugs are inefficient or contribute to unpleasant side effects. Intravenous lidocaine can control chronic pain, such as post-operative pain, headaches, neurological malignancies, and back pain (11-14).

### 1.1. Current Medical Management of Chronic Pain

Managing chronic pain is a balance between maximally alleviating symptoms while also utilizing a therapeutic regimen that is safe for long-term use. In 1986, the WHO released an "analgesic ladder" to guide clinical decision-making for cancer-related pain control. This has become a resource for augmenting therapeutic intensity in non-cancer pain (15-17). In this model, the ladder's bottom rung begins with non-opioid treatments, plus adjunctive therapy like antidepressants and anxiolytics for compounding symptoms (16). For pain that outpaces a low-rung analgesic, the next step escalates to opioids like codeine for mild to moderate pain (16). The upper-tier utilizes strong opioids like morphine for moderate to severe pain (16).

The main adverse effects of each medication on the ladder are outlined below, as these must be weighed in the therapeutic decision-making process. Among the non-opioid analgesics, oral NSAIDs carry a risk of gastrointestinal bleeding, renal damage, and cardiovascular effects. Acetaminophen can cause liver toxicity at high doses. The tricyclic antidepressants used as adjunctive therapy for neuropathic pain, like amitriptyline and nortriptyline, carry a risk of QTc prolongation. Anticonvulsants like pregabalin and gabapentin are also effective for neuropathic pain but may cause sedation, peripheral edema and need to be dose-adjusted for renal impairment. Topical NSAIDs carry the lowest side effect profile but are only effective for localized pain (4).

Escalation to opioid therapy also must be used with caution. Opioids act as agonists on the mu, delta, and kappa opioid receptors to produce analgesia, and side effects include sedation, nausea/vomiting, and decreased gastrointestinal motility leading to constipation (18). Of greatest concern, opioids can also result in fatal respiratory depression, dependence, tolerance, and opioid use

disorder (18). A study in 2014 identified that 34.6% of patients received opioid prescriptions from two providers, 14.2% of patients from 3 providers, and 11.9% of patients from four or more providers, which highlights that prescription opioids have played a large role in the progression of the opioid epidemic (15, 19).

Despite the widespread use of opioids, studies have found opioids can be counterproductive for managing chronic pain. Over time, opioids increase the levels of circulating cytokines like interleukin 6, interleukin 1B, and tumor necrosis factor, which results in paradoxical hyperalgesia (15). Neuronal plasticity in the spinal column, medulla, and hippocampus further contributes to this hyperalgesia (1). In addition to the numerous adverse effects outlined above, this physiologic finding underscores the need for alternative therapies for chronic pain that are safe and effective for long-term use.

## 2. Evidence Acquisition

This is a Narrative Review.

## 3. Results

### 3.1. Infusion/Drug Compound

Infusion of lidocaine (2-(diethylamino)-N-(2,6-dimethylphenyl)acetamide), an amino-amide compound, is emerging as a promising option to fill the therapeutic void for treatment of chronic pain (20, 21). Lidocaine was originally used in 1943 to treat neuropathic burn pain and has since gained a wide spectrum of uses (1). Because of its action at voltage-gated sodium channels, lidocaine is a class 1b antiarrhythmic used to manage pulseless ventricular tachycardia and ventricular fibrillation (22). Lidocaine also stabilizes the myocardium by decreasing intracellular sodium and calcium and is therefore protective in states of ischemia (20). In pain control, lidocaine is classically considered a local anesthetic but is now becoming more widely used for systemic analgesia. Some conditions responsive to lidocaine infusion include fibromyalgia, diabetic neuropathy, complex regional pain syndrome, opioid refractory cancer pain, SCI pain, and postherpetic neuralgia (1). Patients receiving lidocaine infusion for perioperative analgesia have demonstrated improved outcomes with less dependence on opioids for pain control, decreased nausea, decreased ileus rates, and shorter hospital stay duration (23-25).

Numerous studies have outlined dosing protocols for lidocaine infusion for the management of perioperative pain, outlined below. While there are slight variations in

these different protocols, they all center around a similar dosing regimen to administer a bolus to reach a rapid steady state, followed by infusion for up to 72 hours to maintain the therapeutic analgesic effects. See [Table 1](#).

The dosing patterns outlined above help prevent lidocaine toxicity, which occurs at plasma concentrations greater than 5-8  $\mu\text{g/mL}$  (20). Some of the common presenting symptoms of toxicity include perioral paresthesia, metallic taste, tinnitus, and other neurological symptoms such as confusion and seizure (20). Patients receiving lidocaine infusion should be monitored to develop any of these symptoms, with subsequent discontinuation of their infusion if toxicity is suspected.

### 3.2. Mechanism of Action and Pharmacology

#### 3.2.1. Pharmacokinetics and Half-Life

Lidocaine is a weak base with low water solubility that distributes systemically to the brain, kidneys, and heart before reaching less vascularized structures like the skin, skeletal muscle, and adipose tissue (20). It circulates with 60-80% bound to albumin and  $\alpha$ -1 acid glycoprotein and has a volume of distribution of 91 L  $\text{kg}^{-1}$  (20). Plasma clearance of systemic lidocaine is about 10-14 mL  $\text{kg}^{-1} \text{min}^{-1}$  (1, 20). Lidocaine equilibrates across the blood-brain barrier in about 15 minutes to produce central anesthetic effects (20). The half-life of bolus-dose lidocaine is about 1.5-2 hours, but this increases up to 3 hours in obese patients and is progressively prolonged with continuous infusion, reaching up to 6.9 hours in a 48-hour infusion (20).

#### 3.2.2. Mechanisms of Action to Decrease Pain

The most well-documented mechanism of action of lidocaine is the non-selective inhibition of sodium channels to dampen the excitability of neurons and decrease the rate of action potentials (1, 17, 26, 27). Because intravenous lidocaine can achieve a therapeutic effect at a much lower concentration than what is needed to block a peripheral nerve, the mechanism of lidocaine is more complex than simple sodium channel blockade. It likely is a synergistic effect of the multiple mechanisms outlined below (20).

In addition to blocking sodium channels, lidocaine can interact with voltage-gated potassium channels to affect tonic firing neurons (20). Lidocaine also increases intracellular calcium, which modifies T-type calcium channels involved in pain signaling (20). Inhibition of voltage-gated hyperpolarization-activated cyclic nucleotide channels (HCN) in the brain, spinal cord, and dorsal root ganglia inhibits the normally excitatory inward current of cations (20, 27). Synergistically, lidocaine can amplify the inhibitory effects of glycine channels through allosteric regulation to further tone down the pain response (27). Another site of action is ligand-gated ionotropic glutamate

receptors, where lidocaine reduces the presynaptic release of excitatory glutamate (27). By decreasing activation of the kainic acid ionotropic glutamate receptors, lidocaine reduces gene expression of the cytokines interleukin-1 $\beta$ , interleukin-6, and tumor necrosis factor-6 $\alpha$  that normally promote inflammation and damage to endothelium (23, 27). Additionally, lidocaine can increase natural killer cell activity and augment cell-mediated immunity to promote a strong immune response against potential pathogens (20).

On a more macroscopic level, each of these mechanisms described above helps to decrease excitability and diminish neuronal transpain signals' neuronal transmission of pain signals. Lidocaine prevents depolarization of damaged and dysfunctional nerves that are implicated in chronic pain (17). Additionally, lidocaine decreases transmission through A-delta and C neural pain fibers, which decreases visceral pain (1). Lidocaine can achieve both central and peripheral analgesic effects with relatively few side effects, making it an ideal compound for the management of chronic pain.

#### 3.3. Headache

Chronic daily headache (CDH) is a descriptive term that encompasses many different headaches that occur at least fifteen days per month for three months or more. CDH includes chronic tension-type headache, chronic migraine headache, new daily persistent headache, medication overuse headache, and hemicrania continua (28). In a retrospective survey of patients with CDH associated with medication overuse ( $n=71$ ), lidocaine infusion at 2 mg/min for a minimum of 7 days to a maximum of 14 days resulted in successful withdrawal from the implicated analgesic medication in 97% of patients. Moreover, at the 6-month follow-up, 20% of patients reported that their headache was less severe, and 51% of patients no longer were experiencing chronic daily headaches. Notably, only mild side effects (seen in 21% of patients) occurred, such as nausea and hypotension - and they did not lead to the discontinuation of treatment (29).

The efficacy of intravenous lidocaine is corroborated by another retrospective survey conducted by Hand *et al.* of 19 patients with CDH, all taking codeine or another narcotic. Hand *et al.* found lidocaine infusion resulted in remission of symptoms in four individuals and a more manageable pattern of headache in six individuals at the six-month mark. Since complications and adverse effects were minimal, the study found lidocaine to be safe for managing severe, intractable CDH (30). Similarly, Kaube *et al.* reported that, in 19 patients with CDH, IV lidocaine infusions (2 mg/min) for two days resulted in a discontinuation of pain in 26% of patients and a 50% or greater im-

**Table 1.** Bolus Dose, Infusion Rate, and Notes about Lidocaine Infusion

Bolus dose (mg kg <sup>-1</sup> )	Infusion Rate (2 mg kg <sup>-1</sup> h <sup>-1</sup> )	Special Notes	Citation
1-2	1-2	Administer bolus over 1 minute, and don't exceed 100mg bolus dose	3
2	0.5-3	1-2 mg kg <sup>-1</sup> h <sup>-1</sup> is the most common dosing range for continuous infusion	3
1-2	1-2	50% dose reduction every six hours to prevent toxicity	8
0-1.5	1.5-3	-	10
1	0.5-1	Discontinue infusion on postoperative day 2	10

provement in pain for 42% of patients (31). Marmura et al. found in a retrospective chart review of 68 patients with CDH and chronic cluster headache (CCH) lidocaine infusions resulted in a 4-point decrease in headache severity, from 7.9 to 3.9.

Moreover, the treatment was well-tolerated with no adverse events that required discontinuation of infusions (32). IV lidocaine may also be a therapeutic option for chronic daily headache secondary to acoustic neuroma resection. Previous studies have shown that headaches are a frequent postoperative complication of resection, occurring in around 50% of patients, and are particularly difficult to treat. A case report by Schere and Silberstein presents a 47-year-old male patient, whose IV lidocaine treatment of post-acoustic neuroma resection headache was successful (33). The potential for this form of treatment is further bolstered by the findings of a case series conducted by Mooney et al. focused on adolescents and young adults. The study, conducted at Seattle Children's Hospital, shows that the use of lidocaine infusions on pediatric patients with chronic headache and other refractory chronic pain conditions was well-tolerated and resulted in reductions in self-reported pain scores without the presence of any serious side effects (34).

Even in rare forms of primary headache, the administration of intravenous lidocaine has yielded beneficial results. In a case series of four patients with short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), Matharu et al. reported that lidocaine infused at 1mg/min – 3 mg/min reduced or completely suppressed headache attacks during the duration of infusion (35). Similarly, Weng et al. examined various treatment modalities for two uncommon headache syndromes: SUNCT and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA). Their work found intravenous lidocaine infusions to be highly efficacious in reducing attacks. Intravenous lidocaine was used in 15 SUNCT patients, resulting in a reduction of 100% of attacks and 9 SUNA patients, resulting in a reduction of 88% (8 of 9 cases) of attacks.

Conversely, intravenous dihydroergotamine, an agent

that has been used to treat intractable migraines and cluster headaches, did not reduce attacks in either SUNCT or SUNA patients. In terms of SUNCT patients, 50% did see a reduction in attacks with greater occipital nerve injections, although this method had no reliable effect on SUNA patients. Furthermore, sumatriptan, high-flow oxygen, placebo-controlled indomethacin injections, dihydroergotamine, and corticosteroids offered little to no help in both SUNCT and SUNA cases (36).

The inefficacy of intravenous dihydroergotamine in particular, though, has also been demonstrated by a case series of 24 patients diagnosed with chronic SUNA or SUNCT and co-existent chronic migraine and CCH. When treated with IV dihydroergotamine, 5 of the patients experienced a significant worsening of their SUNA or SUNCT, 2 developed new-onset SUNA, 16 experienced no benefit, and one patient reported a slight improvement in symptoms. However, it is worth noting that intravenous lidocaine was efficacious in providing relief for the exacerbated symptoms of those seven patients who experienced new or worsening SUNCT/SUNA syndromes due to the intravenous dihydroergotamine treatment (37).

Despite successful responses to IV lidocaine in patients with various forms of refractory chronic headache types, cardiovascular and neurological side effects remain a potential concern. Lidocaine is hepatically metabolized via the cytochrome P450 3A4 enzyme, and factors such as liver dysfunction, drug-drug interactions, and CYP3A4 genetic polymorphisms can all alter serum levels (38). Digala et al. present the case of a 52-year-old woman receiving IV lidocaine infusions for the treatment of refractory hemicrania continua on several medications, including gabapentin, metformin, sertraline, and trazodone. After initially responding well to the infusions, the patient developed nystagmus, syncope, and bradycardia before asystole occurred with significantly elevated lidocaine concentrations (16 mcg/mL). Although the patient recovered after a few days, this case highlights the importance of using IV lidocaine judiciously, especially when a patient is on several medications, a few of which are metabolized by the CYP3A4 enzyme (39). Lidocaine levels should be monitored



carefully and should remain within the therapeutic range as levels beyond 10mcg/mL, as seen in this patient, are associated with ventricular arrhythmias (40). See Table 2.

### 3.4. Fibromyalgia

The American College of Rheumatology defines fibromyalgia (FM) as a widespread chronic pain syndrome confirmed by the Widespread Pain Index (WPI) and somatic Symptom Severity (SS) scale with associated fatigue, sleep disturbances, psychological distress, and impaired quality of life (41). Sorensen et al. conducted a double-blind cohort study that evaluated the effects of intravenous ketamine infusion and lidocaine infusion on FM patients with central sensitization and secondary hyperalgesia and observed complete pain relief from ketamine infusion with moderate pain control with lidocaine infusion (42). In contrast, Koppert et al. investigated the pain mechanism in FM from multiple pain models and observed mechanical hyperalgesia, a peripheral excitation of  $A\delta$  and C-nociceptor, particularly sensitive low-concentration of lidocaine (43). These findings supported the idea that intravenous lidocaine infusion may provide moderate to significant pain relief in FM's various pain states.

Several studies demonstrated the efficacy of intravenous lidocaine infusion in FM syndrome beyond an initial treatment or brief series of treatments. Schafranski et al. evaluated 23 patients in Brazil with FM who received five consecutive daily infusions of lidocaine (administered in 500 mL of 0.9% saline solution over two hours) and observed a significant improvement after the fifth infusion with decreased pain scores and Fibromyalgia Impact Questionnaire (FIQ) scores (44). This finding is supported by Vlainich et al., who observed a decrease in both hyperalgesia and pain intensity after four weeks of intravenous lidocaine infusion with amitriptyline; no significant findings were reported for amitriptyline alone (45). In a case series reported by Marks et al., three patients with FM had pain relief after starting on intravenous lidocaine infusion. They made the recommendation to start infusion at 5 mg/kg over a 1-hour infusion rate with close cardiac monitoring (41). Wilderman et al. performed a retrospect chart review to evaluate the effects of increasing lidocaine dose starting at 5 mg/kg of body weight, 7.5 mg/kg, and 7.5 mg/kg + 2.5 g of magnesium sulfate and reported the escalating dose of intravenous lidocaine to 7.5 mg/kg (with or without magnesium sulfate) could safely and effectively reduce pain with pain relief up to 17 days (46).

### 3.5. Low Back Pain

Low back pain is a common pain condition with various etiologies ranging from acute injuries, musculoskeletal

abnormalities, and neoplasms. A series of pharmacological tests can help identify the different pain categories in chronic low back pain (CLBP). Sørensen et al. conducted a single-blind placebo-controlled study to evaluate the pharmacological test and observed intravenous morphine with fentanyl epidural and intravenous lidocaine with a local anesthetic epidural had a 50% pain reduction in nociceptive pain and neuropathic pain, respectively (47). The systemic administration of local anesthetics in neuropathic pain has been shown to provide clinical anesthesia and pain relief, which was supported by Dunbar et al., who conducted a two-experimental study that evaluated the analgesic mechanism of epidural steroids in reducing pain associated with degenerative spinal disease (48). There are a few scenarios where intravenous lidocaine infusion may not provide adequate pain relief for refractory pain. For instance, a case report by Watanabe et al. discussed the additional use of the bilateral intrathecal neurolytic block to provide pain control for a patient with advance sigmoid colon cancer (49). While there is increasing evidence that validates the use of intravenous lidocaine infusion for low back pain and chronic pain in general, the analgesic mechanism of lidocaine remains unclear. More research is warranted to better understand the long-term efficacy and resultant symptomatic relief from the treatment.

### 3.6. Complex Regional Pain Syndrome

Complex regional pain syndrome (CRPS) refers to a chronic pain condition marked by a steady deterioration of regional pain without the presence of dermatomal distribution. Until recently, the therapeutics options for CRPS include systemic and local administration of lidocaine (50). This finding was based on prior clinical studies and animal models of neuropathic pain that demonstrated the selectivity of lidocaine on voltage-gated sodium channels on primary nociceptive afferent fibers and inhibition of repetitive depolarization of dorsal root ganglia pain transmission neurons (50, 51).

A single-blind placebo-controlled study conducted by Scrivani et al. evaluated the effectiveness of intravenous phentolamine and lidocaine on chronic neurogenic facial pain and observed no pain relief with the infusion of phentolamine compared to the favorable analgesic response after a single infusion of lidocaine (52). Similar findings were observed in Wallace et al., who investigated the effects of intravenous lidocaine infusion with diphenhydramine on pain and neurosensory thresholds within areas with prominent allodynia (53). Results from the study revealed decreased pain scores to cool stimuli and spontaneous pain and an increased to hot pain threshold from 44.7°C to 47.9°C (53). This finding supported

**Table 2.** A summary of Noteworthy Studies on IV Lidocaine Infusion for Refractory Chronic Headache

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions
<b>Williams et al. (2003) (3)</b>	71 patients with CDH associated with analgesic medication overuse received lidocaine infusion at 2 mg/min for a minimum of 7 days to a maximum of 14 days.	Successful withdrawal from the implicated analgesic medication in 97% of patients. 51% reported they no longer were experiencing chronic daily headaches and 20% reported that their headache was less severe.	IV lidocaine seems to be an effective option for individuals with CDH secondary to medication overuse. Larger controlled studies are needed to definitively establish the efficacy of lidocaine.
<b>Hand et al. (2000) (4)</b>	19 patients with CDH, all taking codeine or another narcotic agent received lidocaine infusion at 2 mg/min for 9 hours up to 12 days.	At the 6 month mark, 4 individuals had remission of symptoms while 6 individuals had a more manageable pattern of headache.	IV lidocaine is useful in the management of intractable CDH secondary to narcotic overuse. As this was a retrospective study primarily aimed at analyzing the safety of lidocaine, its results are intended to pave the way for randomized, placebo-controlled trials.
<b>Kaube et al. (1994) (5)</b>	19 patients with CDH received IV lidocaine infusions at 2mg/min for 2 days.	Discontinuation of pain in 26% of patients and a 50% or greater improvement in pain for 42% of patients.	In individuals who have refractory CDH, these results suggest that IV lidocaine can be effective in reducing or eliminating pain. This study is not blinded and does not serve as a trial of lidocaine; further research would be beneficial in providing support for the efficacy of IV lidocaine.
<b>Marmura et al. (2009) (6)</b>	68 patients with CDH and CCH received IV lidocaine infusions at 1mg/min for first the 4 hours, then 2mg/min up to 4mg/min based on patient's response for 2 to 15 days.	4 point decrease in headache severity, from 7.9 to 3.9, on headache rating scale.	IV lidocaine appears to be a safe and effective option for reducing the severity of headache pain in patients with CDH and CCH. Further research is required to better understand the sole effect of lidocaine (by removing concomitant medications). Additionally, work with lower doses and shorter lengths of infusions should be done to analyze efficacious treatment in less recalcitrant, more common populations.
<b>Weng et al. (2018) (10)</b>	15 SUNCT patients and 9 SUNA patients, received IV lidocaine infusions.	Reduction of 100% of attacks in SUNCT patients and 88% of attacks in SUNA patients.	These results suggest that IV lidocaine infusions can be highly efficacious in reducing attacks in the two distinct and rare conditions SUNCT and SUNA - and offers directions for new work to help treat these difficult conditions.
<b>Matharu et al. (2004) (9)</b>	4 patients with SUNCT received IV lidocaine infusions at 1mg/min - 3mg/min.	Reduced or completely suppressed headache attacks during the duration of infusion.	IV lidocaine infusions are useful for the acute management of SUNCT symptoms but did not provide lasting pain relief after infusions were stopped. Randomized, double-blind, placebo-controlled trials are needed to confirm the utility of IV lidocaine.
<b>Schere et al. (2009) (7)</b>	Male patient with post-acoustic neuroma resection headache received IV lidocaine infusions at 1mg/min - 3mg/min.	1 year post lidocaine infusion, headache frequency reduced to once every two weeks.	IV lidocaine may be a potential treatment option for individuals with chronic headache secondary to a post-acoustic neuroma resection. More studies are needed to determine whether lidocaine can be effectively used in this patient population.
<b>Mooney et al. (2014) (8)</b>	15 Adolescents and young adults with chronic headache and other refractory chronic pain conditions received IV lidocaine infusions at 40-60 mcg/kg/minute for 2 or 6 hours repeated at an interval of 4 weeks.	Mean reduction in pain scores of 1.7 for individuals with chronic headache and a statistically significant improvement in scores when the pain intensity was 6 or more to begin with.	IV lidocaine appears to be effective in reducing pain levels in young adults with chronic headache and other refractory chronic pain conditions particularly when the initial pain is worse. RCTs will be needed to definitively establish the effectiveness of this treatment modality in the pediatric population.
<b>Digala et al. (2020) (13)</b>	Female patient with intractable hemicrania continua received IV lidocaine infusions at 1mg/min on day 1 and 2 mg/min on day 2.	On day 3 the patient experienced pulseless electrical activity and asystole. Lidocaine levels found to be 16 mcg/mL.	IV lidocaine must be used cautiously, especially when a patient is taking several other medications, as drug-drug interactions can occur. Elevated lidocaine levels, as seen in this patient, are associated with ventricular arrhythmias and cardiac arrest.
<b>Lambru et al. (2015) (11)</b>	24 patients diagnosed with chronic SUNA or SUNCT and co-existent chronic migraine and CCH received IV dihydroergotamine.	5 of the patients experienced a significant worsening of their SUNA or SUNCT, 2 developed new onset SUNA. IV lidocaine successfully suppressed the exacerbations induced by IV dihydroergotamine.	IV dihydroergotamine appears to have no benefit in SUNCT/SUNA and may exacerbate symptoms. IV lidocaine, however, was efficacious in providing relief for the 7 patients that experienced new or worsening symptoms.

Schwartzman et al., who evaluated the effects from 5-day continuous intravenous lidocaine infusion (2 g lidocaine in 250 mL of 5% dextrose) in CRPS patients with severe refractory pain and observed a significant decrease in me-

chanical and thermal allodynia after one month with moderate improvements remained after six months (50). This finding, along with other studies, supported the potential long-term pain relief from chronic intravenous lidocaine

infusion for chronic pain management in CRPS. However, a randomized, double-blind study conducted by Kim *et al.* reports a short-term pain control after pain relief at the four-week follow-up was not observed even after four consecutive lidocaine infusions (54).

Overall, most studies conclude that there are minimal, nonspecific adverse effects associated with intravenous lidocaine infusion, including nausea, fatigue, bradycardia, and hypotension (50). However, a case report by Leong *et al.* described a 44-year-old male with CRPS who developed sudden onset of mood changes, severe anxiety, and psychotic reactions shortly after receiving lidocaine infusion (55). This finding is believed to be secondary to patients with a predominant affective component or limbically augmented pain syndrome that may not respond to lidocaine infusion or develop behavioral disturbances (55). While studies support the use of intravenous lidocaine infusion for refractory pain management in CRPS, there is a need for additional randomized multicentered clinical trials with a larger sample size and longer follow-up period to make further conclusions (50, 54, 55).

#### 4. Conclusions

A significant percentage of the population suffers from chronic pain, and the drugs patients take may be sub-optimal for long-term use. Lidocaine may be a promising pharmacological approach with a low side-effect profile offering central and peripheral analgesia. Lidocaine is also associated with significantly reduced chronic daily headaches. Intravenous infusions showed mild to substantial relief for fibromyalgia pain and complex regional pain syndrome (CRPS), and low back pain. Although the multifaceted mechanism is not yet fully known, lidocaine can be a promising novel treatment in treating chronic pain under different conditions.

#### Footnotes

**Authors' Contribution:** Study concept and design: JT JWJ AP AT SK analysis and interpretation of data: AD FI GV EMC drafting of the manuscript: ADK OV IU critical revision of the manuscript for important intellectual content: JT JWJ AP AT SK statistical analysis: AD FI GV EMC ADK OV IU.

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