



# Utilization of Magnesium for the Treatment of Chronic Pain

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Received 2020 December 21; Accepted 2020 December 28.

## Abstract

**Context:** The International Association for the Study of Pain (IASP) defines chronic pain as pain that persists or recurs for longer than 3 months. Chronic pain has a significant global disease burden with profound effects on health, quality of life, and socioeconomic costs.

**Evidence Acquisition:** Narrative review.

**Results:** There are several treatment options, including pharmacological therapy, physical rehabilitation, psychological therapies, and surgical interventions, for chronic pain management. Magnesium has been FDA-approved for several indications including hypomagnesemia, arrhythmia, prevention of seizures in eclampsia/preeclampsia, and constipation. Magnesium has been used for numerous off-label uses, notably for acute and chronic pain management. The mechanism of magnesium in pain management is primarily through its action as a voltage-gated antagonist of NMDA receptors, which are involved in pain transduction.

**Conclusions:** This narrative review will focus on the current evidence and data surrounding the utilization of magnesium as a treatment option for chronic pain.

**Keywords:** Chronic Pain, Infusion, Intravenous, Magnesium Sulfate, Chronic Regional Pain Syndrome, Peripheral Neuropathy, Abdominal Pain

## 1. Context

The International Association for the Study of Pain (IASP) defines chronic pain as pain that persists or recurs for longer than three months (1-3). In 2012, the IASP formed a task force to develop a new classification of chronic pain for the 11th version of the international classification of diseases (ICD-11), which is expected to go into effect in 2022 (1-3). The new ICD category for chronic pain distinguishes between chronic primary versus secondary pain syndromes (3). Chronic primary pain is a new concept that acknowledges that chronic pain is not just a symptom, but rather a health condition on its own that cannot be better explained by another etiology or condition

(3). Chronic secondary pain is organized into six subcategories: chronic cancer-related pain, chronic postsurgical or posttraumatic pain, chronic neuropathic pain, chronic secondary headache or orofacial pain, chronic secondary visceral pain, and chronic secondary visceral pain (3). The new classification system also offers optional extension codes to document pain severity, temporal course, and evidence of psychosocial factors (3). Chronic pain is complex and involves three main pathways: nociceptive, neuropathic, and central sensitization (4).

## 2. Evidence Acquisition

Narrative review.

### 3. Results

#### 3.1. Magnesium Infusion/Drug Compound

Magnesium is a divalent cation that is obtained from diet, absorbed through intestinal epithelial channels in the gastrointestinal tract, and excreted by the kidney (5). It is an essential electrolyte that is critical for many functions in the human body (6-8). It is a cofactor for more than 300 biochemical enzymes, such as Na<sup>+</sup>/K<sup>+</sup>-ATPase, hexokinase, creatine kinase, protein kinase, and cyclase. It is involved in numerous physiological functions, including energy production, neuromuscular conduction, nucleic acid, and protein synthesis, electrolyte balance, cellular membrane function, glucose metabolism, cardiovascular system regulation, and bone development (5-7). As a calcium channel antagonist, magnesium blocks the N-methyl-D-aspartate (NMDA) receptor in a voltage-dependent manner (5). Magnesium is a cofactor for the ATP-dependent synthesis of glutathione, and thus serves an important role in antioxidant defense (6). Magnesium is also required for the conversion of vitamin D into the active, hormonal form 1,25(OH)<sub>2</sub>D (6).

#### 3.2. Pharmacology for IV Magnesium

Magnesium can be administered via oral, intramuscular, intraosseous, or intravenous (IV) routes, but the focus of this review will be on IV administration (5, 9, 10). As an IV form, magnesium sulfate can be given as an IV push, infusion, or additive to TPN (5). For analgesic management during anesthesia, magnesium is administered intravenously as a 30 - 50 mg/kg bolus of magnesium sulfate as a loading dose and maintained at 6 - 20 mg/kg/h by continuous infusion until the end of surgery or for 4 hours after the initial loading dose (11). Magnesium administered via intravenous (IV) route is absorbed immediately, and the effects are immediate and last for about 30 minutes (12). Most of magnesium is found in bone or intracellularly, and 1 - 2% of total body magnesium is found in the extracellular fluid space, with less than 1% found specifically in serum (6, 12). In serum, 55 - 70% is ionized, 20 - 30% is bound to albumin, and 5 - 15% is complexed with anions (6). Magnesium is filtered and excreted by the kidneys at a rate proportional to the serum concentration (12). A lower dose should be administered in patients with severe renal insufficiency as these patients may be at increased risk for hypermagnesemia or heart block (12). Concomitant use of certain drugs, including aminoglycosides, cyclosporine, digitalis, alcohol, amphotericin B, diuretics, and cisplatin, may induce renal losses of magnesium (12).

The mechanism of magnesium in pain management is primarily through its action as a voltage-gated antagonist of NMDA receptors, which are involved in pain trans-

duction (11). The NMDA receptor is a membrane voltage-gated ion channel in the central nervous system that allows the entry of sodium and calcium ions, and the outflow of potassium ions (11). At resting state, magnesium blocks the NMDA receptor, inhibiting the entry of calcium ions (11). The release of glutamate and neuropeptides can depolarize the membrane and open the NMDA receptor channel (11). The opening of NMDA receptors and increased intracellular calcium concentrations contribute to central sensitization, which is responsible for pain hypersensitivity and the long-term potentiation of pain (11). By serving as an NMDA receptor antagonist, magnesium can inhibit the induction of central sensitization and end the potentiation of pain (11).

#### 3.3. Migraine

A case-control study comprised of 40 patients presenting with different types of headaches found complete elimination of pain in 32 of 40 patients (80%) within 15 minutes of magnesium infusion (13). Additionally, of the 18 patients whose pain relief persisted for 24 hours, 16 patients (89%) had a low serum magnesium level. These findings support the authors' notion that low serum and brain tissue ionized magnesium levels may play a role in headache symptoms. Similar results were found in another study by Mauskop *et al.* that treated cluster headaches in 22 patients with magnesium infusions (14). 76% of the infusions showed a correlation between a pain relief response and an ionized magnesium level below a certain threshold. However, only 9 out of the 22 (41%) patients enrolled reported clinically significant relief. The authors also note that 2 of these patients who responded to the magnesium therapy also went into spontaneous remission, lowering the actual proportion of patients that received relief from magnesium. A separate prospective study conducted by Ginder *et al.* enrolled 36 patients who presented to the emergency department (ED) with an acute headache (15). Patients were randomized to receive either intravenous prochlorperazine or magnesium sulfate. 90% of the prochlorperazine group reported complete or partial pain relief, while only 56% of the magnesium group reported complete or partial relief. Contrary to previous findings, there was also no difference in ionized magnesium levels between those who responded and those who did not. It was concluded that magnesium infusion was less effective than prochlorperazine, only slightly better than historical placebo effects, and just as effective as oral sumatriptan, meperidine, and dihydroergotamine in treating headaches in the ED. In a separate study investigating magnesium therapy for patients presenting to the ED with an acute benign headache, Frank *et al.* performed a randomized double-blind placebo-controlled trial consisting of 42

patients (16). Interestingly, there was a greater improvement in pain scores in the placebo group than the magnesium group (8 versus 3). There were also more side effects documented in the magnesium group, suggesting IV magnesium therapy is not recommended in patients with acute benign headache.

The results from studies looking at patients with migraine headaches were also discordant. A pilot study by Mauskop *et al.* studied the effectiveness of treating acute migraine attacks with IV magnesium sulfate in 40 consecutive patients (17). Pain relief was reported to last at least 24 hours post-infusion in 18 of 21 patients (86%) who had low serum ionized magnesium levels, while only 3 of 19 patients (16%) reported similar pain relief in those who had high levels of ionized magnesium. The results from this study indicated a very strong relationship between migraine reduction and low ionized magnesium levels, which prompted the need for further investigation. Recently following the publication of these findings, Demirkaya *et al.* carried out a randomized, single-blind, placebo-controlled trial including 30 patients to investigate the efficacy and tolerability of IV magnesium in treating moderate or severe migraine attacks (18). The investigators found a 100% response rate in the magnesium group compared to a 7% response rate in the placebo, with greater pain-free rates in the magnesium group as compared to placebo (87% versus 0%). Albeit a small sample size, the authors concluded magnesium is an efficient, safe, and well-tolerated therapy for acute migraines with a better recurrence rate than reported in large studies looking at other medications.

In the same year, Corbo *et al.* performed a randomized, double-blind, placebo-controlled trial comparing IV metoclopramide plus IV magnesium sulfate or IV metoclopramide plus a placebo of IV saline (19). Pain scores were improved in both groups; however, unexpectedly, the improvement was smaller in the magnesium group than the placebo group (16-point difference on the visual analog scale). The normal functional status following intervention also favored the placebo group. It was determined that the addition of magnesium sulfate attenuates the therapeutic benefit experienced with IV metoclopramide, which may be secondary to countertherapeutic cerebral vasodilatation caused by magnesium. Four years later, Cete *et al.* conducted another randomized, placebo-controlled, double-blind trial with 120 patients to determine the difference in the effectiveness of magnesium sulfate alone or metoclopramide alone as compared to placebo in treating acute migraines (20). Patients receiving placebo required a higher rate of rescue medication; however, in contrast to Corbo *et al.*'s results, IV magnesium and metoclopramide were no more effective than placebo in treating pain from

acute migraine attacks. In 2015, Shahrami *et al.* carried out a double-blind RCT comprised of 70 patients comparing the effects of magnesium sulfate to the combination of dexamethasone/metoclopramide on acute pain relief from migraine headaches (21). Contrary to Cete's findings, the infusion of magnesium sulfate was associated with significantly decreased pain scores at all time intervals as compared to the dexamethasone/metoclopramide group. Though requiring further investigation, the authors state this observation may be a result of dexamethasone decreasing the efficacy of metoclopramide when used in combination.

Another randomized, double-blind, placebo-controlled trial investigated the effectiveness of magnesium sulfate versus placebo in patients controlling for migraine without aura and migraine with aura (22). The results from 120 patients indicated that magnesium was no different than a placebo with respect to pain relief in treating migraines without aura, but magnesium did improve the associated symptoms of photophobia and phonophobia in this group. In contrast, patients with migraines with aura received a statistically significant improvement in pain and all associated symptoms with magnesium therapy as compared to placebo. These findings suggest magnesium infusion is an effective singular therapy for migraine with aura and may be used as an adjunct to treat the associated symptoms in migraines with and without aura.

A separate prospective quasi-experimental study by Baratloo *et al.* allocated 70 patients with acute migraine headache to receive either IV caffeine or IV magnesium sulfate (23). Reduced pain scores were observed in both groups, but the magnesium group exhibited better improvement than the caffeine group at one- and two-hours post-infusion. Though limited by a quasi-randomized design, the outcomes suggest magnesium is superior to caffeine in the short-term management of migraine headaches.

Xu *et al.* conducted the largest observational study to our knowledge concerning the use of IV magnesium in the treatment of status migrainosus to determine which patients have the best response (24). Of 234 patients retrospectively analyzed, 144 (44%) patients that received IV magnesium did not require additional IM rescue medications, averaging a 44% reduction in pain. It was determined that patients with initial lower pain intensity tended to respond better than those with more severe initial pain. Contrary to Bigal *et al.*'s findings, this study did not appreciate a difference in response rate between migraine with and without aura. However, it is important to note the authors acknowledge the presence of an aura is difficult to identify in a chart review analysis. Due to

the subset of patients who responded significantly, minimal risk profile, and cost-effectiveness of IV magnesium therapy, the authors argue magnesium should be the first parental option.

A meta-analysis performed by Choi *et al.* included 5 of the randomized controlled trials discussed above (Frank *et al.*, Cete *et al.*, Ginder *et al.*, Corbo *et al.*, Bigal *et al.*, Demirkaya *et al.*) to determine the overall effectiveness of intravenous magnesium in the treatment of acute migraines in adults (25). The pooled data revealed the number of patients who received headache relief 30 minutes after the infusion was 7% higher in the control groups as compared to the magnesium groups. Patients treated with magnesium also had a 37% higher rate of side-effects or adverse events than controls. However, the heterogeneity of primary and secondary outcomes and different comparison groups prevent the authors from drawing any conclusions about the effectiveness of magnesium infusion for this indication. A separate meta-analysis of randomized controlled trials by Chiu *et al.* investigated 11 studies on the effects of IV magnesium on acute migraines and ten studies on the effects of oral magnesium on migraine prophylaxis (26). Conflicting with Choi *et al.*'s results, the results showed IV magnesium relieved acute migraines within 15 - 45 minutes, 120 minutes, and 24 hours post-infusion with an OR of 0.23, 0.20, 0.25, respectively. Oral magnesium was found to significantly reduce the frequency (OR = 0.20) and intensity (OR = 0.27) of migraines as well. Despite some of the included studies not adopting adequate randomization methods, the authors concluded IV and oral magnesium should be part of a multimodal treatment regimen for migraines. An additional systematic review by Miller *et al.* failed to perform a meta-analysis but analyzed 7 RCTs that used IV magnesium sulfate to treat migraine headaches or benign non-traumatic headaches in the ED (27). The authors were unable to provide a conclusion due to the heterogeneity of comparison groups, the dose of magnesium, and methods and timing of pain assessments, but suggest the evidence indicates potential benefits beyond 1 hour of infusion.

Gertsch *et al.* published a case series of 20 pediatric patients that was the first known study to report on the use of IV magnesium as an acute treatment for headaches in this population (28). Of the 13 adolescents that were treated in the ED, ten were admitted for further headache treatment, and three were discharged. There was a total of 4 reported side effects, including 1 episode of pain, 1 episode of redness, 1 episode of burning, and 1 episode of decreased respiratory rate without a change in oxygenation. The limitations of this study design require further investigation into the effectiveness of treatment for pediatric patients. See [Table 1](#).

### 3.4. Abdominal Pain

Magnesium can reduce the anesthetic and analgesic requirements in the intraoperative and postoperative periods (29-31) and is also associated with an attenuation of catecholamine secretion during surgery (32). Magnesium can be administered intravenously as a bolus dose prior to the induction of general anesthesia and/or as a continuous infusion throughout the surgery (33). In 2013, De Oliveira *et al.* published a meta-analysis of 20 randomized controlled trials studying the effects of perioperative magnesium on postoperative pain; approximately half of these studies involved abdominal surgery (30). Key findings in their analysis were that systemic magnesium administration improved reported pain scores 0 - 4 hours following surgery at rest and with movement, as well as at 24 hours after surgery with movement, and led to a reduction in opioid consumption in the 24 hours after surgery. Their findings supported a recommendation to consider magnesium as an adjunct therapy to reduce postoperative pain; this contradicted a prior systematic review by Lysakowski *et al.* (34) that found no benefit in the use of magnesium to improve postoperative pain (30).

In 2017, Haryalchi *et al.* published a randomized, double-blind, placebo-controlled study in which they examined the effects of low-dose magnesium sulfate on postoperative analgesia following total abdominal hysterectomy (TAH) (32). The primary endpoints for this trial were pain scores taken at 0, 6, 12 and 24 hours following surgery using a verbal numeric rating scale (VNRS); secondary endpoints were venous blood levels of endogenous beta-endorphins taken shortly before induction of general anesthesia and at the completion of the surgery analyzed with enzyme-linked immunosorbent assay (ELISA) (32). Beta-endorphins are endogenous opioids secreted by the pituitary gland and have a high affinity for  $\mu$  opioid receptors (32, 35); these stress hormones are released in response to painful stimuli during invasive surgeries, and their levels have been correlated with postoperative pain (36, 37). The study enrolled 40 patients undergoing an elective TAH without a history of prior abdominal surgery, major organ dysfunction, or history of opioid use disorder or prior use of calcium-channel blockers (32). The test group received a continuous infusion of 15 mg/kg/h dissolved in 100 mL of isotonic saline 15 minutes prior to receiving general anesthesia while the control group received an identical volume of isotonic saline. The results of the study showed that the control group had a significantly lower mean VNRS pain rating at completion of the surgery; however, at 6- and 12- hours post-operation, the magnesium group had significantly lower VNRS, and at 24 hours there was no significant difference between the 2 groups (32).

Similar RCTs were published by Asadollah *et al.* and

**Table 1.** Magnesium Treatment for Migraines

| Author                      | Groups Studied and Intervention   | Results & Findings  | Conclusions  |
|-----------------------------|---|---|--|
| Mauskop et al (1996) (13)   | Case control of patients receiving IV magnesium who had low or high ionized serum magnesium levels  | Complete elimination of pain in 32 of 40 patients (80%) within 15 minutes of magnesium infusion   | Low serum and brain tissue ionized magnesium levels may play a role in headache symptoms   |
| Mauskop et al (1995) (14)   | Case series of patients with cluster headaches receiving IV magnesium   | 76% of the infusions showed a correlation between a pain relief response and an ionized magnesium level below a certain threshold; only 9 out of the 22 (41%) patients enrolled reported clinically significant relief  | Measurements of ionized magnesium may prove useful in identifying patients who may benefit from magnesium treatment  |
| Ginder et al (2000) (15)    | Randomized control trial comparing IV prochlorperazine to IV magnesium for treatment of patients presenting to ED with an acute headache                                | 90% of the prochlorperazine group reported complete or partial pain relief, while only 56% of the magnesium group reported complete or partial relief; there was no difference in ionized magnesium levels between those who responded and those who did not  | Magnesium infusion was less effective than prochlorperazine in treating headaches in the ED  |
| Frank et al (2004) (16)     | Randomized double-blind placebo-controlled trial comparing IV magnesium to placebo in patients presenting to the ED with an acute benign headache                       | Greater improvement in pain scores in the placebo group than the magnesium group; there were more side effects documented in the magnesium group  | IV magnesium therapy is not recommended in patients with acute benign headache   |
| Mauskop et al (1995) (17)   | Pilot study investigating the effectiveness of IV magnesium in treating acute migraine attacks  | Pain relief was reported to last at least 24 hours post-infusion in 18 of 21 patients (86%) who had low serum ionized magnesium levels, while only 3 of 19 patients (16%) reported similar pain relief in those who had high levels of ionized magnesium  | The results indicated a very strong relationship between migraine reduction and low ionized magnesium levels   |
| Demirkaya et al (2001) (18) | Randomized, single-blind, placebo-controlled trial comparing IV magnesium to placebo in moderate to severe migraine attacks   | 100% response rate in the magnesium group compared to a 7% response rate in the placebo, with greater pain-free rates in the magnesium group as compared to placebo (87% versus 0%)   | Magnesium is an efficient, safe, and well-tolerated therapy for acute migraines  |
| Corbo et al (2001) (19)     | Randomized, double-blind, placebo-controlled trial comparing IV metoclopramide plus IV magnesium sulfate or IV metoclopramide plus a placebo of IV saline               | Pain scores were improved in both groups; unexpectedly the improvement was smaller in the magnesium group than the placebo group (16-point difference on the visual analog scale); normal functional status following intervention also favored the placebo group   | Addition of magnesium sulfate attenuates the therapeutic benefit experienced with IV metoclopramide  |
| Cete et al (2005) (20)      | Randomized, placebo-controlled, double-blind trial comparing magnesium sulphate alone or metoclopramide alone as compared to placebo                                    | Patients receiving placebo required a higher rate of rescue medication; no differences in pain scores were seen between the magnesium, metoclopramide, and placebo groups   | IV magnesium and metoclopramide were no more effective than placebo in treating pain from acute migraine attacks   |
| Shahrami et al (2015) (21)  | Double-blind, randomized controlled trial comparing magnesium sulfate to the combination of dexamethasone/metoclopramide  | Magnesium sulfate was associated with significantly decreased pain scores at all time intervals as compared to the dexamethasone/metoclopramide group   | Dexamethasone may decrease the efficacy of metoclopramide when used in combination to treat migraine headaches   |
| Bigal et al (2002) (22)     | Randomized, double-blind, placebo-controlled trial investigated magnesium sulphate vs placebo in patients controlling for migraine without aura and migraine with aura. | Magnesium was no different than placebo with respect to pain relief in treating migraines without aura, but magnesium did improve the associated symptoms of photophobia and phonophobia in this group; patients with migraines with aura received a statistically significant improvement in pain and all associated symptoms with magnesium therapy as compared to placebo. | Magnesium infusion is an effective singular therapy for migraine with aura, and may be used as an adjunct to treat the associated symptoms in migraines with and without aura. |
| Baratloo et al (2017) (23)  | Prospective quasi-experimental study comparing IV caffeine to IV magnesium  | Reduced pain scores were observed in both groups but the magnesium group exhibited better improvement than the caffeine group at one- and two-hour post-infusion  | Magnesium is superior to caffeine in the short term management of migraine headaches   |
| Xu et al (2019) (24)        | Retrospective chart review of patient receiving IV magnesium to treat status migrainosus.   | 144 (44%) patients that received IV magnesium did not require additional IM rescue medications, averaging a 44% reduction in pain; patients with initial lower pain intensity tended to respond better than those with more severe initial pain.  | Magnesium should be the first parental option due to the subset of patients who responded significantly, minimal risk profile and cost effectiveness of therapy.               |
| Choi et al (2014) (25)      | Meta-analysis of 5 RCTs using IV magnesium to treat acute migraines in adults.  | The number of patients who received headache relief 30 minutes after infusion was 7% higher in the control groups as compared to the magnesium groups; patients treated with magnesium also had a 37% higher rate of side-effects or adverse events than controls.  | The authors did not draw any conclusions about the effectiveness of magnesium infusion for this indication.  |
| Chiu et al (2016) (26)      | Meta-analysis of 21 RCTs investigating IV magnesium for acute migraines or oral magnesium for migraine prophylaxis.   | IV magnesium relieved acute migraines within 15 - 45 minutes, 120 minutes, and 24 hours post-infusion with an OR of 0.23, 0.20, 0.25, respectively; oral magnesium was found to significantly reduce the frequency (OR = 0.20) and intensity (OR = 0.27) of migraines.  | IV and oral magnesium should be part of a multimodal treatment regimen for migraines.  |
| Miller et al (2019) (27)    | Systematic review of 7 RCTs that used IV magnesium to treat either migraine headaches or benign non-traumatic headaches in the ED.                                      | The evidence indicates potential benefits of magnesium beyond 1 hour of infusion.   | Unable to provide a conclusion due to the heterogeneity of comparison groups, dose of magnesium, and methods and timing of pain assessments.                                   |
| Gertsch et al (2014) (28)   | Case series describing 20 pediatric patients who received IV magnesium for acute treatment of headaches.  | Of 13 adolescents that were treated in the ED, 10 were admitted for further headache treatment and 3 were discharged; there was a total of 4 reported side effects, including 1 episode of pain, 1 episode of redness, 1 episode of burning, and 1 episode of decreased respiratory rate without change in oxygenation.   | Further investigation into the effectiveness of treatment for pediatric patients is required.  |

Jarhazadeh et al. in 2015 and 2016, respectively, that examined the role of MgSO<sub>4</sub> on postoperative pain and opioid consumption following gynecological surgery, namely abdominal hysterectomy (38, 39). In the study conducted by Asadollah et al., the treatment group received a bolus dose of MgSO<sub>4</sub> 50 mg/kg in 100 mL of isotonic saline shortly before induction of anesthesia followed by a continuous infusion of 8mg/kg/h throughout the surgery, whereas the treatment group in the Jarhazadeh et al. study received a bolus dose of MgSO<sub>4</sub> 50 mg/kg in 500 mL of Ringer's solution following induction of anesthesia and administra-

tion of morphine 5 mg. Both studies utilized visual analog scale (VAS) scores to evaluate postoperative pain; pain was assessed at the end of surgery, 1, 2, 6, and 12 hours after surgery and 30 minutes, 4, 12, and 24 hours after surgery (38, 39). Both studies demonstrated significantly lower mean VAS scores in the first 12 hours following surgery compared to controls; however, at 24 hours, the reported pain level was similar to the control group. Opioid consumption was also measured in both studies and found to be significantly lower in the groups that received MgSO<sub>4</sub> (38, 39). See Table 2.

**Table 2.** Magnesium Treatment for Abdominal Pain

| Author                               | Groups Studied and Intervention  | Results and Findings  | Conclusions   |
|--------------------------------------|--|---|---|
| Asadollah <i>et al.</i> (2015) (38)  | 30 patients undergoing hysterectomy and/or myomectomy randomized to bolus dose of MgSO <sub>4</sub> 50 mg/kg followed by continuous infusion MgSO <sub>4</sub> 8 mg/kg/h or placebo. | Decreased pain score and opioid consumption at 30 minutes, 2, 4 and 12 hours in MgSO <sub>4</sub> group. Pain scores were similar between groups at 24 hours.   | MgSO <sub>4</sub> may be an effective adjuvant therapy for the treatment of acute postoperative abdominal pain. MgSO <sub>4</sub> likely reduces the need for opioid medications in the acute postoperative period. |
| Haryalchi <i>et al.</i> (2017) (32)  | 40 patients undergoing elective total abdominal hysterectomy randomized to low dose continuous infusion MgSO <sub>4</sub> 15 mg/kg/h or placebo.                                     | Decreased pain score at 6 and 12 hours, no difference between groups at 24 hours. Decreased 24 hours opioid consumption in MgSO <sub>4</sub> group.   | MgSO <sub>4</sub> may be an effective adjuvant therapy for the treatment of acute postoperative abdominal pain. MgSO <sub>4</sub> likely reduces the need for opioid medications in the acute postoperative period. |
| Jarahzadeh <i>et al.</i> (2016) (39) | 60 patients undergoing abdominal hysterectomy randomized to bolus dose of MgSO <sub>4</sub> 50 mg/kg or placebo.   | Decreased pain score immediately after surgery, 1, 2, 6 and 12 hours after surgery in MgSO <sub>4</sub> group. Decreased opioid consumption at 1, 2, 6, 12 hours after surgery in MgSO <sub>4</sub> group | MgSO <sub>4</sub> may be an effective adjuvant therapy for the treatment of acute postoperative abdominal pain. MgSO <sub>4</sub> may reduce the need for opioid medications in the acute postoperative period.     |

### 3.5. Peripheral Neuropathy

Oxaliplatin is a platinum compound that is included in the FOLFOX (leucovorin, fluorouracil, oxaliplatin) chemotherapy regimen in the treatment of colorectal cancer and is associated with a stocking-glove distribution neuropathy, in addition to, an acute neuropathy characterized by muscle cramps and cold intolerance (40, 41). A combination of calcium and magnesium (CaMg) are often administered prior to and after FOLFOX therapy to prevent or improve CIPN despite inconsistent evidence of a beneficial effect (41). In a phase III RCT conducted by Loprinzi *et al.*, they set out to determine if CaMg was effective at reducing oxaliplatin-induced neurotoxicity (41). They enrolled 353 patients with a diagnosis of colon cancer receiving FOLFOX therapy and randomized them to 1 of 3 groups: intravenous Ca/Mg 1g/1g before and after oxaliplatin, placebo before and after oxaliplatin, or Ca/Mg 1g/1g before oxaliplatin and placebo after. Neurotoxicity was evaluated using the sensory scale of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy-Induced Peripheral Neuropathy 20 tool. Based on their findings, they determined there was no evidence to suggest that CaMg was beneficial in reducing cumulative neurotoxicity, as there were no significant differences between the 3 study groups (41). This trial was 1 of 5 trials included in a systematic review by Jordan *et al.* evaluating the evidence for the use of CaMg infusions in the prevention of oxaliplatin-induced PN in which the authors concluded that CaMg infusions provided a “nonbeneficial effect (42)”. As stated by Loprinzi *et al.*, the benefits seen with CaMg infusion are largely supported by the findings of 2 retrospective studies (43, 44), as well as, a prospective trial (40) that was terminated early (41).

Kim *et al.* conducted a randomized, double-blind, uncontrolled trial to study the effects of MgSO<sub>4</sub> infusion versus ketamine infusion on 30 patients with severe, refractory postherpetic neuralgia (PHN) (45). Patients were randomized to receive either MgSO<sub>4</sub> 30 mg/kg/h or ketamine 1 mg/kg/h in a total of 3 sessions with VAS pain scores taken prior to treatment and two weeks following the third treatment; patients also completed the Doleur Neuropathique 4 (DN4) questionnaire at baseline and at the final visit. The results showed a significant decrease in VAS score for both groups at two weeks compared to baseline, and although the ketamine group registered a greater improvement in pain reduction, it was found to be an insignificant difference. Their results supported the use of magnesium sulfate as an alternative treatment to alleviate symptoms of PHN particularly cold allodynia, although limitations of the study include lack of a placebo group, small sample size, and limited follow-up period (45). Pickering *et al.* designed a study evaluating the effects of ketamine given in combination with MgSO<sub>4</sub> in patients with neuropathic pain (46). Twenty patients were enrolled in this randomized, double-blind, crossover, placebo-controlled study in which they received one infusion of either ketamine/MgSO<sub>4</sub>, ketamine alone, or placebo every 35 days in a random sequence; data were obtained using a number of instruments to assess neuropathic pain, anxiety, and depression, and sleep quality five weeks after treatment. The primary outcome (daily pain intensity in the 35 days following infusion) was determined not to be significantly different between the three groups, and no significant differences were found in the secondary outcomes. Although these findings showed a benefit of neither ketamine combined with MgSO<sub>4</sub> nor ketamine alone compared to placebo, factors such as a low sample size

must be considered when interpreting these results (46). See [Table 3](#).

### 3.6. Complex Regional Pain Syndrome

Collins et al. conducted a pilot randomized clinical trial comprised of 10 patients with type 1 complex regional pain syndrome (CRPS) (47). Eight patients were randomized to receive 70 mg/kg magnesium sulfate intravenous (IV) infusions over the course of 5 days, while two patients received a NaCl 0.9% placebo infusion. Pain scores using an 11-point Box scale and McGill Pain Questionnaire were significantly reduced at all time points in the group receiving magnesium. Impairment level and quality of life measures were also significantly improved at 12 weeks post-infusion in the magnesium group, while the improvement in McGill sensory subscale was only appreciated at 1-week post-infusion. However, the magnesium group did not show improvement in skin sensitivity or functional limitations. The improvement in pain, impairment, and quality of life suggested magnesium may play a beneficial role in treating CRPS with little to no side effects, which prompted the initiation of a large-scale trial. This subsequent double-blind placebo-controlled trial enrolled 56 patients with chronic type 1 CRPS and administered either MgSO<sub>4</sub> 70 mg/kg or placebo of NaCl 0.9% (48).

In 2019, Niconchuk et al. reported a case of a 29-year-old pregnant female with chronic regional pain syndrome and an indwelling spinal cord stimulator who presented for induction of preterm labor due to preeclampsia (49). The patient reported dramatic, complete resolution of her CRPS-associated pain while receiving peripartum intravenous magnesium therapy, which returned shortly after the cessation of magnesium infusion. Her reported analgesia was initially presumed to be secondary to the epidural that was placed; however, the alleviation of pain continued over 24 hours after the epidural was discontinued and mirrored the magnesium infusion. Additionally, the patient had failed previous attempts of epidural sympathetic blockade, supporting the theory that her CRPS-related analgesia was actually a result of the magnesium infusion. Importantly, this case used a 6 g loading dose followed by a 2 g/h maintenance infusion for the duration of labor and for 24 hours postpartum, which is a significantly higher dose previously used in human trials of magnesium therapy for CRPS. Unfortunately, the therapeutic benefit was not seen past the window of acute treatment, limiting its clinical application. See [Table 4](#).

### 3.7. Other Conditions

Yousef and Al-Deeb (50) conducted a randomized controlled double-blinded study of 80 patients to investigate the efficacy of I.V. magnesium treating chronic lower

back pain with a neuropathic component (50). All study participants received gabapentin, amitriptyline, and celecoxib. In the intervention cohort, participants received two weeks of daily infusions of magnesium daily, followed by four weeks, twice-daily dosing, of oral magnesium capsules. The capsules contained 400 mg of magnesium oxide and 100 mg of magnesium gluconate. The study reported significant improvement in pain and lumbar spine range of motion at 6 months in those receiving magnesium. The only reported adverse event was mild diarrhea in four patients (50). The study offered initial evidence for the efficacy of magnesium in the treatment of neuropathic lower back pain, suggesting that additional studies are warranted to define further magnesium's role in the treatment of chronic lower back pain.

A retrospective chart review of 74 patients diagnosed with fibromyalgia investigated the efficacy of lidocaine infusions, with and without magnesium sulfate, in immediate and prolonged pain management (51). Post-infusion, pain was measured immediately by an 11-point numerical rating scale (NRS). The study found that those who received infusions of 7.5 mg/kg of lidocaine with and without 2.5 g of adjunct magnesium sulfate had a greater mean reduction in their immediate post-treatment pain than those who received an infusion of 5 mg/kg of lidocaine. Moreover, patients who received an infusion of 7.5 mg/kg of lidocaine, regardless of the magnesium adjunct, endorsed a longer mean duration of symptomatic improvement; however, this was evaluated subjectively by chart review. The authors noted that there was a non-significant trend towards the cohort that received magnesium having better outcomes (51). See [Table 5](#).

## 4. Conclusions

Chronic pain affects health, quality of life, and has high socio-economic costs. There are many medical options for chronic pain management, including pharmacological therapy, physical rehabilitation, psychological therapies, and surgery. Magnesium is FDA-approved for many indications including hypomagnesemia, arrhythmia, eclampsia/preeclampsia seizure prevention, and constipation. Magnesium was used for various off-label applications, including acute and chronic pain management.

Magnesium's pain control function is mainly through its action as a voltage-gated antagonist of NMDA receptors involved in pain transduction. Magnesium is the fourth most abundant mineral in the body, with the highest concentration (60%) in bone, although this content decreases with age. Magnesium sulfate may be treated as an IV drive, infusion, or TPN additive. Magnesium's pain control function is mainly through its action as a voltage-gated antag-

**Table 3.** Magnesium Treatment for Peripheral Neuropathy

| Author                       | Groups Studied and Intervention   | Results & Findings  | Conclusions   |
|------------------------------|---|---|---|
| Kim et al. (2015) (45)       | 30 patients with refractory PHN randomized to MgSO <sub>4</sub> 30 mg/kg/h or ketamine 1 mg/kg/h in a total of 3 sessions   | Decrease in VAS score for both groups at 2 weeks compared to baseline                                   | Ketamine and MgSO <sub>4</sub> are effective at reducing pain in PHN                      |
| Loprinzi et al. (2014) (41)  | 353 patients receiving FOLFOX therapy randomized to: intravenous Ca/Mg 1g/1g before and after oxaliplatin, placebo before and after oxaliplatin, or Ca/Mg 1g/1g before oxaliplatin and placebo after. | No significant differences between the 3 groups at reducing cumulative neurotoxicity.                   | CaMg is not effective at preventing oxaliplatin-induced neuropathy.                       |
| Pickering et al. (2020) (46) | 20 patients with neuropathic pain receiving ketamine/MgSO <sub>4</sub> , ketamine alone, and placebo at 35-day intervals.   | No significant differences between the 3 groups in reducing daily pain intensity or secondary measures. | Ketamine/MgSO <sub>4</sub> failed to improve pain intensity and other secondary measures. |

**Table 4.** Magnesium Treatment for Complex Regional Pain Syndrome

| Author                      | Groups Studied and Intervention  | Results & Findings   | Conclusions   |
|-----------------------------|--|--|---|
| Collins et al (2009) (47)   | Pilot study comparing IV magnesium sulphate infusion to placebo NaCl 0.9% infusion.                          | Pain scores were significantly reduced at all time points in the group receiving magnesium; impairment level and QOL measures were also significantly improved at 12 weeks post-infusion in the magnesium group, while the improvement in sensory subscale was only appreciated at 1-week post-infusion; magnesium group did not show improvement in skin sensitivity or functional limitations. | Magnesium may play a beneficial role in treating CRPS with little to no side effects.                     |
| Fischer et al (2013) (48)   | Double-blind placebo-controlled trial compared IV magnesium sulphate infusion to placebo NaCl 0.9% infusion. | No significant difference in Box-11 pain scores and impairment scores between the magnesium group and placebo group at different time points.  | IV therapy of magnesium has no additional benefit in treating chronic type 1 CRPS as compared to placebo. |
| Niconchuk et al (2019) (49) | Case report of a female with chronic CRPS who received peripartum IV magnesium for preeclampsia.             | Complete resolution of CRPS-related pain during magnesium infusion.  | The first case report to describe CRPS-associated pain relief while on peripartum magnesium therapy.      |

**Table 5.** Magnesium Treatment for Other Pain Conditions

| Author                       | Groups studied                                     | Intervention  | Efficacy  |
|------------------------------|--|---|---|
| Yousef AA et al. (2013) (50) | Lower back pain with neuropathic component, N = 80 | IV Magnesium sulfate (1g/day for 1st 2 weeks), oral magnesium 500 mg twice daily for weeks 3 - 6)                         | Reduction of 37% in 11-point NRS, improved lumbar range of motion at 6 months.  |
| Wilderman et al. (2019) (51) | Fibromyalgia, N = 74                               | IV infusions of one of the following: lidocaine 5 mg/kg; lidocaine 7.5 mg/kg; lidocaine 7.5 mg/kg + 1 g magnesium sulfate | Significant reduction in 11-point NRS with Lidocaine 7.5 mg/kg immediately post-treatment. Non-significant, positive trend with adjunct magnesium |

onist of NMDA receptors involved in pain transduction. Mixed trials and case reports of using magnesium to treat migraines. Further research is required to confirm the effectiveness of magnesium in treating migraines.

cal analysis: IU, JWJ, AA, LF, AA, BW, VO, EMC, ADK, FI, GV, HL, OV.

**Conflict of Interests:** None.

**Funding/Support:** None.

## Footnotes

**Authors' Contribution:** Study concept and design: IU, JWJ, AA, LF, AA, BW; Analysis and interpretation of data: VO, , ADK, FI, GV, HL, OV; Drafting of the manuscript: IU, JWJ, AA, LF, AA, BW; Critical revision of the manuscript for important intellectual content: VO, EMC, ADK, FI, GV, , OV; Statisti-

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