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SUMMARY WITH CRITICAL APPRAISAL

Magnesium as an Alternative or Adjunct to Opioids for Migraine and Chronic Pain: A Review of the Clinical Effectiveness and Guidelines

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Context and Policy Issues

Migraine and chronic pain are common disorders and can result in considerable disability.[1] According to the World Health Organization, migraine is ranked 19th with respect to health disorders causing life lived with disability. The lifetime prevalence of migraine in Canada has been estimated to be 24% in women and 9% in men. Chronic pain is defined as pain that persists for greater than three months.[2] Chronic pain is associated with a variety of disorders such as chronic low back pain, chronic complex regional pain syndrome (CPRS), fibromyalgia and neuropathy. Estimates of the prevalence of chronic pain in Canada vary between 16% and 40%.[3] The variability may be due to differences in the definitions used for chronic pain, sample populations surveyed, and the survey methodologies.[3]

Treatment for migraine can be divided into two broad categories: acute treatment for migraine attacks and prophylactic treatment to reduce the frequency of migraine attacks.[3,4] Treatment of any type of pain is complex and the best options for treatment still remain unresolved. Increasingly, opioids are being used for the alleviation of pain.[5] However, long term use of opioids can lead to addiction, development of tolerance, and resistance of chronic pain to opioid analgesia. In addition, it is associated with side-effects such as chronic constipation, dizziness, consciousness disorders, and cognitive impairment.[5] Hence other modalities for managing pain are needed. Magnesium plays an important physiological role and affects a number of processes. It is the fourth most abundant cation in the body,[6] and is involved in regulation of protein synthesis, energy production, cell growth, and RNA and DNA synthesis.[6] Magnesium modulates ion transport by pumps, carriers and channels and can impact signal transduction.[6] Magnesium acts as a N-methyl-D-aspartate (NMDA) receptor antagonist and blocks the NMDA receptor, resulting in its analgesic effect.[5,6] Activation of the NMDA receptor plays a role in central sensitization and is associated with spontaneous pain and increased reaction to peripheral stimuli.[6,7] As magnesium appears to have an analgesic effect there is growing interest in investigating whether magnesium can be used as an alternative or as an adjunct to opioids for controlling pain.

The purpose of this report is to review the clinical effectiveness of magnesium as an analgesic for the treatment of adult patients with migraine or chronic pain. Additionally, this report aims to review evidence-based guidelines regarding the use of magnesium as an analgesic for the treatment of adult patients with migraine or chronic pain.

Research Question

1. What is the clinical effectiveness of magnesium as an analgesic for the treatment of adult patients with migraine or chronic pain?
2. What are the evidence-based guidelines regarding the use of magnesium as an analgesic in adult patients with migraine or chronic pain?

Key Findings

Definitive conclusions on the effectiveness of intravenous magnesium for the treatment of migraine and oral magnesium for migraine prophylaxis, compared with placebo, were not possible. For migraine treatment with magnesium compared with placebo, benefit with respect to pain intensity and need for rescue medication was reported in one systematic review but no benefit was reported in one systematic review. One systematic review on migraine treatment showed that in a subgroup of patients experiencing migraine with aura, there was a benefit with respect to headache relief and headache severity with magnesium compared with placebo. For migraine prophylaxis, one RCT showed that magnesium was more effective than placebo in reducing the number of migraine attacks but there were no statistically significant between group differences with respect to reduction in the number of days with migraine or migraine severity. Evidence for migraine treatment was from three systematic reviews with overlapping studies, and for migraine prophylaxis from one RCT.

For complex regional pain syndrome, one RCT found that intravenous magnesium did not result in any benefit over placebo, and one RCT found benefit of intramuscular magnesium, compared with placebo, for pain by some measures but not for others.

For refractory chronic low back pain, one RCT showed that intravenous magnesium followed by oral magnesium, was statistically significantly beneficial for pain management compared to placebo.

Magnesium was not recommended for the acute treatment of migraine, in one guideline. Magnesium was recommended for migraine prophylaxis, in two guidelines.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and March 2, 2017

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult (18 years or older) patients with migraine or chronic pain (i.e., disorders with associated pain lasting >3 months [e.g., chronic complex regional pain syndrome, chronic low back pain, fibromyalgia, neuropathy, pain of vascular origin such as peripheral arterial occlusive disease]) at any body site
Intervention	Magnesium (any route of administration [e.g., oral, intravenous, intraarticular, transdermal]) as a standalone or adjuvant therapy
Comparator	Q1: Placebo; opioids Q2: No comparator required
Outcomes	Q1: Clinical effectiveness (e.g., pain scores, frequency of episodic pain, reduction resolution of pain, time to satisfactory analgesia, use of primary pain treatment [e.g,. reduction in opioid dose or frequency of use], level of impairment, quality of life, mental health scores); Safety (e.g., mortality, hypotension, gastrointestinal symptoms [e.g., nausea, vomiting], cardiovascular side effects, muscle weakness, hypermagnesemia) Q2: Evidence-based guideline recommendations regarding the use of magnesium for chronic pain
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), non-randomized studies, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. Systematic reviews including studies already included in selected systematic reviews and not providing additional information were excluded. Studies on pain related to surgical procedures, leg cramps, menstrual cramps, and cancer pain were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR,[8] randomized studies were critically appraised using the Downs and Black checklist,[9] and guidelines were assessed with the AGREE II instrument.[10] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 573 citations were identified in the literature search. Following screening of titles and abstracts, 556 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, seven publications were excluded for various reasons, while 10 publications met the inclusion criteria and were included in this report. These 10 publications comprised three systematic reviews,[4,11,12] four RCTs,[7,13-15] and three guidelines.[1,16,17] Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Systematic reviews and clinical studies

Summary of the characteristics of the included systematic reviews and clinical studies are presented below and details are available in Appendix 2, Tables 2 and 3.

Study Design

Migraine

Three relevant systematic reviews,[4,11,12] and one RCT on migraine were identified. One systematic review[11] included six relevant RCTs published between 2001 and 2005, one systematic review[12] included four relevant RCTs published between 2001 and 2005, and one systematic review[4] included two relevant RCT published in 2002 and 2005.

The included RCT[15] was a single-blinded study.

Complex regional pain syndrome (CPRS)

Two double-blind RCTs[7,13] on CPRS were identified

Chronic low back pain

One double-blind RCT[14] on chronic low back pain was identified.

Country of Origin

Migraine

One systematic review[12] was published in 2012 from Canada for the Agency of Health and Quality research (AHRQ), USA; one systematic review[4] was published in 2015 from the USA; and one systematic review[11] was published in 2014 from the UK. None of the relevant RCTs included in these systematic reviews were conducted in Canada.

The RCT[15] was published in 2012 from Iran.

CPRS

The two RCTs on CPRS were published from The Netherlands in 2013.

Chronic low back pain

The one RCT on chronic low back pain was published in 2013 from Egypt.

Patient Population

Migraine

The systematic reviews[4,11,12] include adults with acute migraine. The number of patients was 268 in one systematic review,[12] 289 in one systematic review,[11] and was not reported in one systematic review.[4]

The RCT[15] included 133 patients who suffer from migraine of mean age ranging between 32 years and 37 years, and with disease duration ranging between 10 years and 12 years in the four treatment groups. The percentage of females was 80%.

CPRS

One RCT[7] was on 56 patients with chronic CRPS type 1 (CRPS-1), with a mean age of 47 years and 93% female and one RCT[13] was on 22 patients with CRPS-1 and suffering from

tonic or intermittent dystonia, of median age 40 years and median disease duration of 11.5 years, and 95% female .

Chronic low back pain

The RCT[14] was on 80 patients with chronic low back pain with a neuropathic component, of mean age 51 and 58 years and percentage females 38% and 30% in the two treatment groups.

Interventions and Comparators

Migraine

The systematic reviews[4,11,12] compared magnesium with placebo, for treatment of migraine. Two systematic reviews[4,12] mentioned that magnesium was used as magnesium sulfate and was administered intravenously. Details were not available in one systematic review.[11]

In the RCT[15] on migraine prophylaxis, there were four treatment arms: magnesium + L-carnitine vs magnesium alone vs L-carnitine alone vs control. Magnesium was used as magnesium oxide. Details of the control were not provided.

CPRS

In both RCTs,[7,13] in the magnesium group magnesium sulfate was used and in the placebo group saline. In one RCT,[7] the agents were administered intravenously and in one RCT,[13] the agents were administered intramuscularly.

Chronic low back pain

In the included RCT[14] the magnesium group received magnesium sulfate intravenously and later followed by oral magnesium sulfate; and the placebo group received saline intravenously and later followed by oral sugar filled capsules.

Outcomes

Migraine

Outcomes reported in the systematic reviews included pain reduction,[4,11,12,15] pain intensity,[4,12] headache recurrence,[12] need for rescue medication,[11,12] and side effects.[11,12] In the RCT,[15] reduction in the number of migraine attacks, reduction in days with migraine, reduction in migraine severity, and reduction in migraine index were reported.[15] The migraine index was determined by multiplying the number of migraine days per month by the migraine severity.

CPRS

Of the two included RCTs,[7,13] one RCT[13] focused on dystonia in CRPS but also reported on pain and hence is included in this report. Outcomes reported included pain rating,[7,13] impairment level,[7] functional rating,[13] and adverse effects.[7,13]

Chronic low back pain

The included RCT,[14] reported on pain rating, lumbar spine movement, and adverse effects.

Guidelines

The characteristics of the guidelines are presented below and details are available in Appendix 2, Tables 4 and 5.

Of the three included evidence-based guidelines,[1,16,17] two guidelines from the Canadian Headache Society were published in 2012[1] and 2015[16] and one guideline from the American Headache Society[17] was published in 2012. One guideline[16] was on acute treatment of migraine and two guidelines[1,17] were on prophylaxis of migraine. Two guidelines[1,16] described the levels of evidence and strength of recommendations and one guideline[17] did not.

Summary of Critical Appraisal

Systematic reviews and clinical studies

Critical appraisal of the systematic reviews and clinical studies are summarized below and details are presented in Appendix 3, Tables 6 and 7.

Migraine

The three included systematic reviews[4,11,12] were well conducted. In all the systematic reviews, the objectives, and inclusion and exclusion criteria were stated; multiple databases were searched; article selection was described; article selection and data extraction were done in duplicate; a list of included articles was provided; and characteristics of the included studies were presented. Quality assessment was conducted in all the systematic reviews and the studies were found to be of variable quality. In two systematic reviews,[11,12] meta-analyses were conducted. For one systematic review,[11] the meta-analyses included a comparator not relevant for this review, hence the pooled results were not relevant; only the results of the individual relevant studies are presented in this report. One systematic review,[12] conducted meta-analyses using appropriate methods. It was mentioned in two systematic reviews[11,12] that the authors had no conflicts of interest and in one systematic review [4] conflicts of interest were declared and some of the authors were associated with industry but it was unclear if there was any conflicts of interest.

In the included RCT,[15] the objective and inclusion and exclusion criteria were stated; and patient characteristics, interventions, and outcomes were described. Details of the control intervention were not provided. Details of the assessment scales were not always provided. It was a single blind, randomized study; the randomization method was not presented. There were 6% and 11% withdrawals in the magnesium and magnesium plus carnitine groups respectively and the impact of this on findings was unclear. It was unclear if sample size determinations were conducted. Conflicts of interest were not mentioned.

CRPS

In the two RCTs,[7,13] the objective and inclusion and exclusion criteria were stated, and patient characteristics, interventions and outcomes were described. Details of the assessment scales were not always provided. Randomization methods appeared to be appropriate in one RCT[13] and were not described in one RCT.[7] Both RCTs were double-blinded. In one RCT[7] a sample size calculation was done but the required number of participants was not met and in one RCT[13] it was unclear if sample size calculations had been undertaken. Withdrawals were similar in both groups in both the groups. The authors mentioned that there were no conflicts of interest.

Chronic low back pain

In the included RCT[14] on chronic low back pain, the objective and inclusion and exclusion criteria were stated; and the patient characteristics, intervention and outcomes were described. Randomization was described and appeared to be appropriate. It was a double-blind study. The necessary sample size was calculated and met. The authors mentioned that there were no conflicts of interest. It was unclear if there were any withdrawals.

Guidelines

Critical appraisal of the guidelines is summarized below and details are presented in Appendix 3, Table 8.

In all three included evidence-based guidelines[1,16,17] the purpose was stated, the guideline development group comprised of individuals with relevant expertise, a systematic review was undertaken to identify evidence, and recommendations were graded. Patient views and preferences, resource implications, and implementation barriers appear to have been considered in one guideline[1] but was unclear if these were considered in the other two guidelines.[16,17] Conflicts of interest were declared in all the guidelines. In one guideline[17] it was explicitly stated that significant efforts were made to minimize potential for conflicts to influence the recommendations and in two guidelines[1,16] it was unclear as no statement to this effect was presented.

Summary of Findings

What is the clinical effectiveness of magnesium as an analgesic for the treatment of adult patients with chronic pain?

Findings from the systematic reviews and RCTs are summarized below and details are available in Appendix 4, Table 9.

For treatment with magnesium, several magnesium compounds have been used, such as magnesium sulfate, magnesium oxide and magnesium gluconate. Patients groups treated with any magnesium compound are referred to as the magnesium (Mg) group.

Migraine

The three systematic reviews[4,11,12] were on treatment of migraine, using magnesium or placebo administered intravenously. One systematic review[11] reported risk differences. It showed that there was no statistically significant difference with magnesium compared to placebo with respect to pain relief or need for rescue medication. However, there was a statistically significant difference between the two treatments with respect to side effects; favoring placebo. One systematic review,[12] reported relative risks for majority of the outcomes and mean difference for pain intensity. It showed that there was a statistically significant difference with magnesium compared to placebo with respect to pain intensity, headache response at 60 minutes, and use of rescue medication; favoring magnesium. However, there were no statistically significant differences between the groups with respect to pain reduction and headache recurrence. The authors considered the strength of evidence to be moderate for pain intensity; and low or insufficient for most other outcomes, based on the strength of the various evidence domains (risk of bias, consistency, directness and precision). Side effects (skin flushing) were reported for magnesium. One systematic review,[4] showed that in a subgroup of patients experiencing migraine with aura, there was a statistically significant difference with magnesium compared with placebo with respect to

headache relief and headache intensity, favoring magnesium. In this systematic review, no statistically significant benefit with magnesium compared with placebo was found for patients having migraine without aura.

The included RCT by Tarighat et al.[15] on migraine prophylaxis showed that oral supplementation with magnesium, L-carnitine, or concurrent magnesium and L-carnitine were statistically significantly more effective than placebo with respect to number of migraine attacks. However results did not reach statistical significance with respect to reduction in days with migraine, reduction in migraine severity, and reduction in migraine index. Authors cautioned that larger trials are needed to confirm these preliminary findings.

CPRS

The two included RCTs on patients with CPRS-1 compared magnesium with placebo using intravenous administration in the RCT by Fischer et al.[7] and intramuscular administration in the RCT by van der Plas et al.[13] One RCT[7] found that intravenous magnesium did not result in any significant benefit over placebo, as assessed using pain scores with the numerical rating scale (NRS), the McGill pain questionnaire scores, and the impairment level sum score. Common side effects with magnesium were flushing and dizziness. In both groups pain near the insertion site of the intravenous cannula was reported. In one RCT[13] the results were conflicting; statistically significant benefits of magnesium over placebo were found for assessments with pain scores with the NRS, and the number of words chosen of the McGill Pain Questionnaire (McGill NWC) but there was no statistically significant between group difference in the pain rating index of the McGill Pain Questionnaire (McGill PRI) scores and in the functional rating scores with Radbound Skills Questionnaire [RASQ]. Adverse events were numerically higher in the magnesium group compared with the placebo group.

Chronic low back pain

The RCT by Yousef and Al-deeb[14] demonstrated that in patients with refractory chronic low back pain who were treated with intravenous magnesium followed by oral magnesium had reduction in pain during a six month period, based on the NRS. Higher scores indicated greater pain intensity. The NRS scores at pre-treatment were similar for both the magnesium and placebo groups (NRS scores, mean ± standard deviation [SD]: 7.4 ± 2.4 for Mg and 7.5 ± 2.2 for placebo; $P = 0.62$). At two weeks of treatment, statistically significant reductions in pain were observed in both the Mg and placebo groups (for within group difference compared to the respective pre-treatment scores, $P = 0.02$ for Mg, $P = 0.04$ for placebo). In the placebo group the pain reduction was not sustained during the six months of follow up. In the magnesium group, the reduction in pain intensity was sustained during the six months of follow up. At six months, the pain intensity was statistically significantly less in the Mg group compared to the placebo group (NRS score, mean ± SD: 4.7 ± 1.8 for Mg, and 7.2 ± 2.5 for placebo; $P = 0.03$).

Overall, adverse effects with magnesium were minimal. Mild diarrhea was reported in four patients but this did not necessitate discontinuation of the treatment.

What are the evidence-based guidelines regarding the use of magnesium as an analgesic in adult patients with chronic pain?

Recommendations from the guidelines are summarized below and details are presented in Appendix 4, Table 10.

Of the three included guidelines, one guideline[16] was on acute treatment of migraine and two guidelines[1,17] were on migraine prophylaxis. The guideline[16] on migraine treatment did not recommended the use of magnesium for acute treatment of migraine (weak recommendation, moderate quality evidence). The two guidelines on migraine prophylaxis recommended the use of magnesium for migraine prophylaxis (mentioned as strong recommendation, low quality evidence in one guideline[1] and level B [i.e. probably effective and should be considered]) in the other guideline.

Limitations

There was considerable overlap in the studies included in the included systematic reviews. Hence findings are not exclusive.

Comparison of the findings across studies was difficult, as the dose and routes of administration of the study agents varied. Also various outcome measures were used.

Studies on magnesium treatment, were available only for migraine, CRPS and chronic low back pain and not for the other chronic pain conditions. Guidelines for the use of magnesium for treatment of chronic pain besides migraine were not identified.

Studies comparing magnesium with opioids were not identified.

None of the studies were conducted in Canada, hence may not be generalizable for the Canadian setting.

Conclusions and Implications for Decision or Policy Making

A total of 10 relevant publications, comprising three systematic reviews,[4,11,12] four RCTs,[7,13-15] and three guidelines.[1,16,17] were identified. Three systematic reviews,[4,11,12] were on migraine treatment, one RCT[15] was on migraine prophylaxis, two RCTs[7,13] were on CRPS-1, and one RCT[14] was on low back pain.

Definitive conclusions on the effectiveness of magnesium (as magnesium sulfate, administered intravenously) compared to placebo for treatment of migraine were not possible. One systematic review[11] reported no statistically significant benefit with magnesium compared to placebo and one systematic review reported statistically significant benefit with magnesium with respect to pain intensity assessed using a visual analogue scale but no statistically significant between group differences with respect to pain reduction and headache recurrence. One systematic review[4] reported a statistically significant benefit with magnesium compared with placebo in a subgroup of migraine patients: patients having migraine with aura. No statistically significant benefit with magnesium compared with placebo was found for patients having migraine without aura. For migraine prophylaxis, one RCT[15] reported a statistically significant benefit with oral magnesium compared to placebo with respect to number of migraine attacks, but no statistically significant between group differences with respect to reductions in migraine days, migraine severity, or migraine index.

For CRPS-1, one RCT[7] found that intravenous magnesium did not result in any statistically significant benefit over placebo and one RCT[13] found statistically significant benefit of intramuscular magnesium compared with placebo for some outcomes but not for other outcomes.

For refractory chronic low back pain, one RCT[14] showed that intravenous magnesium followed by oral magnesium was statistically significantly beneficial for pain management compared to placebo.

In one guideline[16], magnesium was not recommended for the acute treatment of migraine (weak recommendation, moderate quality evidence). In two guidelines,[1,17] magnesium was recommended for migraine prophylaxis (strong recommendation, low quality evidence in one guideline[1] and level B [i.e. probably effective and should be considered]) in the other guideline.[17]

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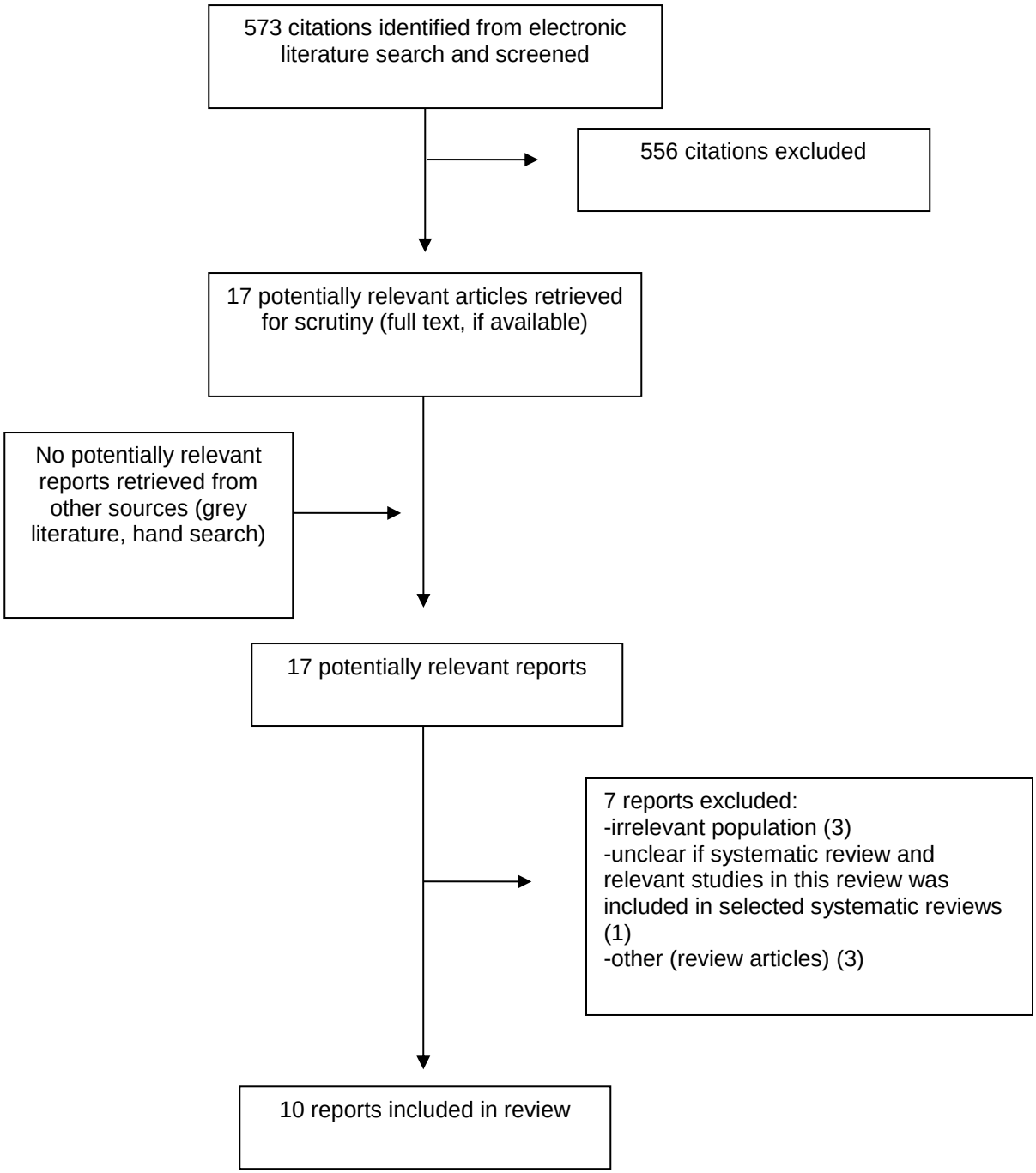
Abbreviations

AAN	American Academy of Neurology
AHRQ	Agency for Healthcare Research and Quality
ANOVA	Analysis of variance
ASH	American Society of Headache
car	carnitine
CI	confidence interval
CRPS	complex regional pain syndrome
CRPS-1	complex regional pain syndrome type 1
g	gram
gr	group
IQR	interquartile range
IV	intravenous
LANSS	Leeds Assessment of Neuropathic Signs and Symptoms
McGill NWC	number of words chosen of McGill Pain Questionnaire
McGill PRI	pain rating index of McGill Pain Questionnaire
MD	mean difference
Mg	magnesium
$MgSO_4$	magnesium sulphate
NR	not reported
NRS	numerical rating scale
NWC	number of words chosen
plb	placebo
PRI	pain rating index
RASQ	Radbound Skills Questionnaire
RD	risk difference
RR	risk ratio
SD	standard deviation
SR	systematic review
Tx	treatment
VAS	visual analog scale
vs	versus

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Author, Year, Country	Type and Number of Primary Studies Included, Aim	Population Characteristics	Comparison	Outcome
Choi,[11] 2014, UK	The SR included 6 RCTs of which 5 RCTs (published between 2001 and 2005) were relevant for this report and are included here (the comparison in the remaining RCT was not relevant for our report). The RCTs were conducted in the emergency departments or acute headache clinic settings Aim: To examine the efficacy and tolerability of intravenous magnesium for the treatment of acute migraine in adults	Adults with acute migraine attack N = 289	Magnesium vs placebo Mg: magnesium 1 g to 2 g, Plb: saline Both administered intravenously	Pain relief, need for rescue medication. Side effects or adverse events
Marmura[4] / American Headache Society 2015, USA	The SR assessed various pharmacological therapies and the 2 RCTs (published in 2002, 2005) on magnesium are included in this report. Aim: To assess pharmacological therapies for acute migraine	Adults treated for acute migraine. N = NR	Magnesium vs placebo Magnesium sulfate (1g or 2g) administered intravenously	Headache relief, headache freedom, headache intensity
Sumamo Schellenberg,[12] 2012, Canada (for AHRQ, USA)	The SR assessed various pharmacological therapies and the 4 RCTs (published between 2001 and 2005) on magnesium are included in this report. The RCTs were conducted at headache clinics (2) and at gemergency departments (2) Aim: To assess pharmacological therapies for acute migraine	Adults with moderate to severe acute migraine N = 268	Magnesium vs placebo Magnesium sulfate (1g or 2g) Both magnesium and placebo were administered intravenously	Pain intensity (using VAS), pain reduction, head ache recurrence, head ache response, use of rescue medication

AHRQ = Agency for Healthcare Research and Quality; RCT = randomized controlled trial; SR = systematic review

Table 3: Characteristics of Included Clinical Studies

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome, Follow up
Fischer,[7] 2013, The Netherlands	RCT, double-blind, study with an additional extension study where the plb group received Mg treatment after the double-blind phase. (patient, researcher and physician were blinded)	Patients with chronic CRPS-1 (according to the International Association for the study of pain. Patients were recruited between June 2006 and December 2011. Disease duration (mean [IQR])	$MgSO_4$ vs placebo (saline). Mg gr: $MgSO_4$ (70 mg/kg), Plb gr: Saline (0.9%) Both administered via intravenous infusion of 25 mL/h for 4 hours a day for 5 consecutive day, using indistinguishable syringes.	Pain score, impairment level, Side effects Follow up: 12 weeks.

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome, Follow up
	Randomization was in blocks of four so that half of the patients received and the others placebo (plb) Aim: To investigate the effects of intravenously administered magnesium in patients with complex regional pain syndrome type 1 (CRPS-1)	(months): 16.0 (6.0 to 41.8). CRPS score at baseline (mean [SD]): 12.2±2.3. N = 56 (29 in Mg gr, 27 in plb gr) Age (mean [SD]) (years): 46.7±11.5 Female (%): 93	Concomitant use ofanalgesics were allowed according to the Dutch multidisciplinary treatment guideline. All patients received standard physical therapy	
Tarighat,[15] 2012, Iran	RCT, single-blind. Setting: Outpatient clinic belonging to Tabriz University of Medical Sciences, Iran Aim: To investigate oral magnesium oxide, L-carnitine and concurrent magnesium-L-carnitine supplementation on migraine prophylaxis	Patients with migraine N = 139 recruited but 6 withdrew and data were reported for133 (33 in Mg gr, 35 in Car gr, 20 in Mg+Car gr, and 35 in control) Age (mean) (years): 32 to 37 in the 4 grs Female (%): 80 Disease duration (years): 10 to 12 in the 4 grs	4 groups (grs): Mg vs Car vs (Mg+Car) vs control. Mg: magnesium oxide (500 mg/day), Car: L-carnitine (500 mg/ day) Control: details not provided. Oral administration. Supplementation was for 12 weeks. Conventional treatments and migraine elimination diet were continued during the study period	Reductions in number of migraine attacks, migraine days, migraine severity, and migraine index. Follow up: after 12 weeks of supplementation
van der Plas,[13] 2013, The Netherlands	RCT, double-blind, cross-over study. (patients, assessor and treating physicians were blinded for the sequence of treatments). Wash out period was one week and considered to be appropriate based on pharmacokinetic data Setting: Movement disorders outpatient clinic of the Leiden University Medical Center. Aim: To investigate the effects of intramuscular magnesium sulfate in patients with CRPS-related dystonia.	Patients with CRPS1 and suffering from tonic or intermittent dystonia, resulting in slight disability. CRPS 1 according to the International Association for the study of pain. Study period: October 2009 to May 2012 N = 30 (16 assigned to Mg then plb and 14 assigned to plb then Mg). However only 22 completed the study. Information on the 22 patients, who completed the study are presented here. Age (median [IRQ]) (years): 40 (29 to 52) Female (%): 95%	$MgSO_4$ vs placebo (saline). Mg gr: 100mg/ mL, Plb gr: 0.9% sodium chloride (saline) Both agents administered intramuscularly. Each patient received 2 intramuscular treatments each week for 3 weeks. There was a washout period of one week before crossover. Treatment was initiated at 5 mL twice daily and was increased in week 2 and 3 to twice daily volumes of 7.5 and 10 mL. To alleviate injection site pain 2.5g lidocaine-prilocaine 5% cream was applied 120	Dystonia rating, pain rating, functional rating Adverse effects. Treatment duration: 3 weeks

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome, Follow up
		CRPS duration (median [IQR]) (years): 11.5 (6.0 to 16.0) Pain level: NRS score (median [IQR]): 7 (6 to 8)	minutes before the injection.	
Yousef,[14] 2013, Egypt	RCT, double-blinded (patients and assessors blinded) Aim: To investigate the therapeutic role of sequential intravenous and oral magnesium for the treatment of patients with chronic low back pain with a neuropathic component	Patients with chronic low back pain with a neuropathic component (LANSS pain scale score ≥ 12), with or without leg pain for more than 6 months and had inadequate pain relief with conventional therapies N = 80 (40 in Mg gr and 40 in plb gr) Age (years) (mean): 51.1 in Mg, 57.8 in plb. Female (%): 37.5% in Mg 30% in plb. LANSS pain scale (mean): 18 in Mg, 16 in plb. Patients who received prior oral opioids (tramadol): 55% in Mg, 62% in plb. Patients who received prior oral opioids (morphine): 25% in Mg, 22.5% in plb. No statistically significant differences in the characteristics reported, between the two groups.	$MgSO_4$ vs placebo (plb) Mg gr: $MgSO_4$ 1g in 250 ml saline given intravenously for 4 hours every day for 2 weeks. After 2 weeks, oral Mg (capsules containing 400 mg magnesium oxide and 100 mg magnesium gluconate) were taken twice daily for 4 weeks. Plb gr: 250 ml saline followed by placebo sugar filled capsules. Dosage schedule was same as for the Mg gr. All patients received orally 300 mg gabapentin 3 times daily, 25 mg amitriptyline hydrochloride at bedtime, and 200 mg celecoxib twice daily. All patients received inferential current therapy	Pain (using NRS), lumbar spine motion. Side effects Follow up: 6 months

car = carnitine; CRPS = complex regional pain syndrome; CRPS-1 = CRPS type 1; IQR = interquartile range; Mg = magnesium; LANSS = Leeds Assessment of Neuropathic Signs and Symptoms; $MgSO_4$ = magnesium sulfate; NRS = numeric rating scale; RCT = randomized controlled trial; SD = standard deviation

Table 4: Characteristics of Included Guidelines

First Author/ Group, Year, Country	Objective	Guideline Development Group (GDG), Target Users	Methodology
Holland[17] AAN and AHS, 2012, USA	To provide recommendations for the preventive treatment of migraine	The authors were from relevant areas (clinical, research methodology) Target users not specified	A systematic review was conducted to identify evidence. Studies were assigned classes, details not presente. Recommendation levels were provided, details not presented
Orr[16] / Canadian Headache Society, 2015, Canada	To evaluate the evidence from RCTs on the effectiveness and tolerability of pharmacologic and nutraceutical interventions for the acute treatment of migraine pain in adults presenting at the emergency department or similar setting and provide recommendations	The authors were from relevant areas (clinical, research methodology) Target users not specified	A systematic review was conducted to identify evidence. Quality assessment of the individual studies was conducted using the Cochrane risk of bias tool Levels of evidence and grading of recommendations were provided. The GRADE methodology was used.
Pringsheim[1]/ Canadian Headache Society, 2012, Canada	To provide guidance on the appropriate prophylactic medication for migraine.	The GDG comprised of individuals with relevant expertise (neurologist, family physician, nurses, and pharmacist) Primary target users were practitioners caring for patients with migraine, including family physicians and specialists, and other health care professionals involved in the care of patients with migraine. Secondary target users were individuals with migraine and their families	A systematic review was conducted to identify evidence. Individual studies were graded on methodological quality using criteria developed by the US Preventive Services Task Force. Levels of evidence and grading of recommendations were provided. The GRADE methodology was used.

AAN = American Academy of Neurology; AHS = American Society of Headache; GRADE = Grading of Recommendations Assessment, Development, and Evaluation;

Table 5: Grade of Recommendations and Level of Evidence

<table>
<tr><th>First Author/ Group, Year,</th><th>Grade of Recommendation</th><th>Level of Evidence</th></tr>
<tr><td>Holland[17] AAN and AHS, 2012, USA</td><td>Details not presented</td><td>Details not presented</td></tr>
<tr><td>Orr[16] / Canadian Headache Society, 2015, Canada</td><td>“
<table>
<tr><th>Recommendation grade</th><th>Benefit vs. risks</th><th>Clinical implications</th></tr>
<tr><td>Strong: high-quality evidence</td><td>The benefits clearly outweigh the risks and burdens for the majority of patients.</td><td>Can apply to most patients in most circumstances.</td></tr>
<tr><td>Strong: moderate quality evidence</td><td>The benefits clearly outweigh the risks and burdens for the majority of patients.</td><td>Can apply to most patients, but the recommendations could change with further research.</td></tr>
<tr><td>Strong: low-quality evidence</td><td>The benefits clearly outweigh the risks and burdens for the majority of patients.</td><td>Can apply to most patients, but the recommendations are likely to change with further research.</td></tr>
<tr><td>Weak: high-quality evidence</td><td>The benefits are more closely balanced with the risks and burdens for the majority of patients.</td><td>The use of this intervention will depend on patient circumstances.</td></tr>
<tr><td>Weak: moderate-quality evidence</td><td>The benefits are more closely balanced with the risks and</td><td>The use of this intervention will depend on patient circumstances, but there is less certainty about</td></tr>
</table></td><td>
<table>
<tr><th>Level</th><th>Explanation</th></tr>
<tr><td>“High</td><td>We are confident that the estimate of the effect of the intervention, as reported in the evidence, lies close to the true effect and further research is unlikely to change our confidence in the estimate.</td></tr>
<tr><td>Moderate</td><td>We are moderately confident that the estimate of the effect of the intervention, as reported in the evidence, lies close to the true effect but further research is likely to change our confidence in the estimate.</td></tr>
<tr><td>Low</td><td>We have limited confidence that the estimate of the effect of the intervention, as reported in the evidence, lies close to the true effect and further research is very likely to change our confidence in the estimate.” Page 273</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author/ Group, Year,</th><th>Grade of Recommendation</th><th>Level of Evidence</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>burdens for the majority of patients.</td><td>when it should be used.</td></tr>
<tr><td>Weak: low-quality evidence</td><td>The benefits are more closely balanced with the risks and burdens for the majority of patients.</td><td>There is considerable uncertainty about when this intervention should be used.</td></tr>
<tr><td></td><td></td><td></td></tr>
</table>
“ Page 273
</td><td></td></tr>
<tr><td>Pringsheim[1]/ Canadian Headache Society, 2012, Canada</td><td>
<table>
<tr><td>Recommendation Grade</td><td>Benefits vs Risks</td><td>Clinical Implications</td></tr>
<tr><td>Strong – high quality evidence</td><td>Benefits clearly outweigh risks and burdens for most patients</td><td>Can apply to most patients in most circumstances</td></tr>
<tr><td>Strong – moderate quality evidence</td><td>Benefits clearly outweigh risks and burdens for most patients</td><td>Can apply to most patients, but there is a chance the recommendation may change with more research</td></tr>
<tr><td>Strong – Low quality evidence</td><td>Benefits clearly outweigh risks and burdens for most patients</td><td>Can apply to most patients, but there is a good chance the recommendation could change with more research</td></tr>
<tr><td>Weak – high quality evidence</td><td>Benefits are more closely balanced with risks and burdens for many patients</td><td>Whether a medication is used will depend upon patient circumstances</td></tr>
<tr><td>Weak – Moderate</td><td>Benefits are more closely</td><td>Whether a medication is</td></tr>
</table>
</td><td>
<table>
<tr><th>Level</th><th>Explanation</th></tr>
<tr><td>High</td><td>“We are confident that the true effect lies close to the estimate given by the evidence available.” Page 10</td></tr>
<tr><td>Moderate</td><td>“We are moderately confident in the effect estimate, but there is a possibility it is substantially different.” Page 10</td></tr>
<tr><td>Low</td><td>“Our confidence in the effect estimate is limited. The true effect may be substantially different.” Page 10</td></tr>
<tr><td>Very Low</td><td>“We have little confidence in the effect estimate.” Page 10</td></tr>
</table>
</td></tr>
</table>

First Author/ Group, Year,	Grade of Recommendation	Level of Evidence
	quality evidence / balanced with risks and burdens for many patients / used will depend upon patient circumstances, but there is less certainly about when it should be used Weak – low quality evidence / Benefits are more closely balanced with risks and burdens / There is considerable uncertainty about when to use this medication Page 10	

AAN = American Academy of Neurology; AHS = American Society of Headache; GRADE = Grading of Recommendations Assessment, Development, and Evaluation

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[8]

Strengths	Limitations
Choi,[11] 2014, UK	
• The objective was clearly stated. • The inclusion criteria were stated. • Multiple databases (Medline, Embase, and CINAHL) were searched. Also, trial registries and databases, conference proceedings and reference lists of retrieved articles were searched. • Study selection was described • List of included studies was provided • Article selection was done in duplicate • Data extraction was done in duplicate • Quality assessment was done using the Jadad score (score range 0 to 5, higher score indicating better quality). Of the five included RCTs the Jadad score was 5 for 3 RCTs, 2 for 1 RCT and 0 for 1 RCT. • Characteristics of the individual studies were provided. However, details of the interventions were sparse. • Meta-analyses were conducted • The authors stated that there was no conflict of interest.	• Exclusion criteria were not explicitly stated • Flow chart of study selection was not presented • List of excluded studies was not provided • Publication bias does not appear to have been explored •
Marmura,[4] 2015, USA	
• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases (Medline, Embase) up to December 2013 were searched. • Study selection was described • List of included studies was provided • Article selection was done in duplicate • Data extraction was done in duplicate • Level of evidence was presented and assigned Level B. Level B: probably effective treatment (supported by 1 Class 1 or 2 Class II studies). Both the included RCTs were Class II studies. • Characteristics of the individual studies were provided. • The authors declared their conflicts of interest. Some authors have received honoraria or funding from industry. Unclear if this could be an issue for this report.	• Flow chart of study selection was not presented • List of excluded studies was not provided • Meta-analysis was not conducted however results of individual studies were presented • Publication bias does not appear to have been explored
Sumamo Schellenberg,[12] 2012, Canada (for AHRQ, USA)	
• The objective was clearly stated. • The inclusion and exclusion criteria were stated. • Multiple databases (Medline, Embase, PASCAL, Biosis Previews, Cochrane Central Register of Controlled Trials, Cochrane database of systematic reviews and other databases) were searched from inception to January, 2012.. • Study selection was described and flow chart was	• Authors mentioned that formal assessment of publication bias was not possible because of the small number of studies

Strengths	Limitations
presented • Lists of included and excluded studies were provided • Article selection was done in duplicate • Data extraction was done in duplicate • Risk of bias was assessed using the Cochrane risk of bias tool. The overall risk of bias was low for 2 RCTs and unclear for 2 RCTs. Strength of evidence was presented • Meta-analysis was conducted • Characteristics of the individual studies were provided. • The authors stated that there was no conflict of interest. .	

Table 7: Strengths and Limitations of Randomized Controlled Trials using Downs and Black checklist[9]

Strengths	Limitations
Fischer,[7] 2013, The Netherlands	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment scales were not always provided • Randomization was performed in blocks of four • Double-blinded study (patient, researcher, and physician were blinded) • Sample size calculation was conducted. It indicated that 33 patients per group was required to detect a significant change, however the numbers in the two groups were slightly less: 29 and 27 in the $MgSO_4$ and placebo groups respectively • Withdrawals were reported and were due to protocol violation (withdrawals: 14% for MgSO4 and 15% for placebo) • ITT and per-protocol analyses were conducted • *P*-values were reported • The authors mentioned that there was no conflict of interest	• Details of randomization were lacking • Sample size was less than that calculated to detect a significant change
Tarighat,[15] 2012, Iran	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the control intervention was lacking • Withdrawals were described. Withdrawals were 11% and 6% in the Mg and (Mg+Car) groups, respectively • *P*-values were reported	• Randomization was not described • Single blinded study. Blinding details not presented • Details of the control intervention was lacking • Unclear if sample size calculations were done • ITT analyses do not appear to have been undertaken. Those who withdrew were not considered in the analyses • Conflicts of interest of the authors were not mentioned. Financial support was received from the Drug Applied Research Center and the Research vice-Chancellor of Tabriz University of Medical Sciences.

Strengths	Limitations
van der Plas,[13] 2013, The Netherlands	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the assessment scales were not always provided • Randomization was in blocks of four using a computer generated list • Double-blinded study (patient, assessor, and treating physician were blinded) • Withdrawals were reported and were 7.7% in Mg group and 8% in the placebo group • *P*-values were reported • Three of the four authors were reported to have no conflicts of interest and one author received an unconditional research grant from industry but reported to have no financial interest on the subject matter or any competing material.	• Unclear if sample size determinations were conducted • ITT analysis was not was not done for efficacy data. Data from those who completed the study were analyzed. However for safety, all available adverse events data were reported.
Yousef,[14] 2013, Egypt	
• The objective was clearly stated • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomized was performed using a sealed envelope technique. Randomization envelopes, drug containers and their coded labels were prepared at the hospital pharmacy by persons not involved in the study. • Double-blinded study (patients and assessors were blinded) • *P*-values were reported • Sample size calculation was conducted and met • The authors mentioned that there was no conflict of interest	• Unclear if there were any withdrawals. • Unclear if ITT analysis was performed

ITT = intention-to-treat

Table 8: Strengths and Limitations of Guidelines using AGREE II[10]

Strengths	Limitations
Holland[17] AAN and AHS, 2012, USA	
• The scope and purpose were clearly stated. • The authors had relevant expertise (clinical and research methodology) • A systematic review was conducted using multiple databases. • The evidence was categorized as various classes but further details were not presented • Recommendations were assigned levels but further details were not presented • The document was externally reviewed • Conflicts of interest of the authors were declared. Some authors had association with industry. However, it was stated that significant efforts were made to minimize potential for conflicts to influence the recommendations.	• Unclear if patient views and preferences were considered • Unclear if resource implications and organizational barriers were considered • Unclear if there was any policy for updating of the recommendations

Strengths	Limitations
Orr[16] / Canadian Headache Society, 2015, Canada	
• The scope and purpose were clearly stated. • The authors had relevant expertise (clinical and research methodology) • Methodology used for identifying evidence was rigorous. A systematic review using multiple databases was undertaken • The scientific evidence was synthesized using the GRADE approach • Recommendations were graded. • The document was externally reviewed • Conflicts of interest of the authors were declared. Some authors had association with industry. However, it was not explicitly stated if there was any issue or not.	• Unclear if patient views and preferences were considered • Unclear if resource implications and organizational barriers were considered • Unclear if there was any policy for updating of the recommendations
Pringsheim[1] / Canadian Headache Society, 2012, Canada	
• The scope and purpose were clearly stated. • The guideline development group (GDG) comprised of individuals with relevant expertise (neurologist, family physician, nurses, and pharmacist) • Methodology used for identifying evidence was rigorous. A systematic review using multiple databases was undertaken • Patient views and preferences were considered • Resource implications and organizational barriers were considered • The scientific evidence was synthesized using the GRADE approach • Recommendations were graded. • The guideline was externally reviewed • The recommendations will be reviewed and updated at least every two years • Conflicts of interest of the authors were declared. Some authors had association with industry. However, it was not explicitly stated if there was any issue or not.	• Appears to have no major limitations

AAN = American Academy of Neurology; AHS = American Society of Headache; GRADE = Grading of Recommendations Assessment, Development, and Evaluation

Appendix 4: Main Study Findings and Author's Conclusions

Table 9: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Systematic Reviews</td></tr>
<tr><td colspan="2">Choi,[11] 2014, UK</td></tr>
<tr><td>
Risk difference (RD) for pain relief after 30 mins for magnesium versus placebo in adults with acute migraine
<table>
<tr><th>Study</th><th>RD (95% CI)</th></tr>
<tr><td>Bigal et al., 2002</td><td>0.00 (-0.23 to 0.09)</td></tr>
<tr><td>Cete et al., 2005</td><td>0.21 (-0.02 to 0.41)</td></tr>
<tr><td>Corbo et al., 2001</td><td>-0.24 (-0.47 to -0.03)</td></tr>
<tr><td>Frank et al., 2004</td><td>-0.05 (-0.30 to 0.21)</td></tr>
</table>
Risk difference for need for rescue medication for magnesium versus placebo in adults with acute migraine
<table>
<tr><th>Study</th><th>RD (95% CI)</th></tr>
<tr><td>Bigal et al., 2002</td><td>-0.07 (-0.31 to 0.18)</td></tr>
<tr><td>Cete et al., 2005</td><td>-0.21 (-0.41 to 0.02)</td></tr>
<tr><td>Corbo et al., 2001</td><td>0.11 (-0.17 to 0.37)</td></tr>
<tr><td>Frank et al., 2004</td><td>-0.05 (-0.29 to 0.19)</td></tr>
</table>
Risk difference of side effects for magnesium versus placebo in adults with acute migraine
<table>
<tr><th>Study</th><th>RD (95% CI)</th></tr>
<tr><td>Cete et al., 2005</td><td>0.08 (-0.01 to 0.22)</td></tr>
<tr><td>Corbo et al., 2001</td><td>0.41 (0.11 to 0.64)</td></tr>
<tr><td>Demirkaya et al., 2001</td><td>0.77 (0.56 to 0.89)</td></tr>
<tr><td>Frank et al., 2004</td><td>0.33 (0.03 to 0.58)</td></tr>
</table>
</td><td>"The meta-analyses have failed to demonstrate a beneficial effect of intravenous magnesium in terms of reduction in pain relief in acute migraine in adults, showed no benefit in terms of the need for rescue medication and in fact have shown that patients treated with magnesium were significantly more likely to report side-effects/adverse events." Page 2</td></tr>
<tr><td colspan="2">Marmura,[4] 2015, USA</td></tr>
<tr><td>
Comparison of treatments with magnesium vs placebo in adults with acute migraine
<table>
<tr><th>Study</th><th>Outcome</th><th>Finding</th></tr>
<tr><td>Bigal et al., 2002.</td><td>Headache relief at 60 min</td><td>For migraine with aura: 50% vs 13%, P <0.05
For migraine without aura: 33% vs 17%, P = NS</td></tr>
<tr><td></td><td>Headache freedom</td><td>For migraine with aura: 37% vs 7%, P <0.05
For migraine without aura: 23% vs 10%, P = NS</td></tr>
<tr><td>Cete et al., 2005.</td><td>Headache intensity (using VAS) at 30 min</td><td>For migraine: 3.7 mm vs 4.8 mm, difference: NS. For the subgroup having migraine with aura, the difference was significant (P = 0.04)</td></tr>
</table>
</td><td>" (Level B) […] MgSO4 IV (migraine with aura) 1-2 g" Page 13

("Level B; Medications are probably effective for acute migraine treatment based on available evidence" Page 13)</td></tr>
</table>

Main Study Findings	Author's Conclusion

Sumamo Schellenberg,[12] 2012, Canada (for AHRQ, USA)

Comparison of treatments with $MgSO_4$ vs placebo in adults with acute migraine

Outcome	Included RCTs, No. of patients (N)	Finding	Strength of evidence
Pain intensity (VAS [mm])	3 (Bigal et al., Cete et al., Frank et al.), N = 238	MD (95% CI): -9.73 (-16.75 to -2.72),	Moderate
Pain reduction	2 (Demirkaya et al., Frank et al.), N = 72	RR (95% CI): 2.75 (0.20 to 37.76)	Insufficient
Headache recurrence	2 (Bigal et al., Cete et al.), N = 196	RR (95% CI): 0.68 (0.29 to 1.63)	Low
Headache response at 60 min	1 (Bigal et al.), N = 120	RR (95% CI): 2.78 (1.42 to 5.44)	Insufficient
Use of rescue medication	1 (Bigal et al.), N = NR	RR (95% CI): 0.65 (0.53 to 0.82)	NR

Adverse effects: The authors mentioned that high rates of skin flushing (10%) and local reactions (43%) were reported for MgSO4 It was unclear from which studies these results were obtained.

"$MgSO_4$ was more effective than placebo for pain relief (moderate strength of evidence) and headache recurrence (low strength of evidence)." Page 113

Randomized Controlled Trials (RCTs)

Fischer,[7] 2013, The Netherlands

Comparison of pain management (using NRS scores)with magnesium vs placebo for CRPS-1 patients

Time point[a]	Pain score using NRS, mean (SD); Number of patients (N)		
	$MgSO_4$	Placebo	All[b]
T0	6.1 (1.8), N = 29	6.3 (1.6), N = 27	6.2 (1.7), N = 56
T1	5.2 (2.4), N = 29	5.4 (2.3), N = 26	5.3 (2.3), N = 55
T2	5.3 (2.8), N = 27	5.5 (2.4), N = 26	5.4 (2.6), N = 53
T3	5.2 (3.1), N = 27	5.3 (2.5), N = 27	5.3 (2.8), N = 54
T4	5.1 (3.0), N = 27	5.4 (2.3), N = 25	5.2 (2.7), N = 52

[a]Time point: T0 = one week before the intravenous treatment (baseline) ; T1 = during the administration of trial medication; and T2, T3, and T4 are respectively 3, 6, and 12 weeks following start of intervention
[b]All indicates the $MgSO_4$ and placebo groups during the double-blind trial phase and the off label phase when the placebo group received $MgSO_4$

Comparison of Impairment level sum score (ISS) for treatment with magnesium vs placebo for CRPS-1 patients

Time point[a]	ISS, median (IQR); Number of patients (N)		
	$MgSO_4$	Placebo	All[b]
T0	30 (25.25–33), N = 28	30 (25–37), N = 27	30 (25–33), N = 55
T1	24.5[c] (19–30.75), N = 25	26[d] (22–31.5), N = 25	25[c] (21–31), N = 53
T2	28 (18–34), N = 25	27 (24–34.5), N = 25	27[d] (22.75–34), N = 50
T3	29.5 (23–33.75), N = 25	29[d] (18.5–34), N = 25	29[d] (22–33.5), N = 49
T4	28 (22–32.5), N =25	29[d] (19.5–35.5), N = 25	28[d] (20–34.25), N = 50

[a]Time point: T0 = one week before the intravenous treatment (baseline) ; T1 = during the administration of trial medication; and T2, T3, and T4 are respectively 3, 6, and 12 weeks following start of intervention

"Intravenous administration of magnesium as used in our study has no additional benefit over placebo in treatment of CRPS-1 in chronic CRPS-1. Studies involving selected groups of CRPS-1 patients with shorter disease duration, a florid inflammatory profile, or severe signs and symptoms of sensitization are required in order to assess magnesium for its additional value to available treatment methods for CRPS-1." Page 1396-97

Main Study Findings	Author's Conclusion

[b]All indicates the $MgSO_4$ and placebo groups during the double-blind trial phase and the off label phase when the placebo group received $MgSO_4$
[c]Significant and relevant improvement (ISS change > 5) compared with baseline ($P < 0.05$)
[d]Significant difference from baseline ($P < 0.05$)

Comparison of McGill pain questionnaire scores for treatment with magnesium vs placebo for CRPS-1 patients

Time point[a]	Measure	Score, median (IQR); Number of patients (N)	
		$MgSO_4$	Placebo
T0	NWC	12 (9–16), N = 28	12 (11–16), N = 27
T1		9[b,c] (6.25–12.75) , N = 28	11.5 (9.75–17.50), N =26
T2		10.5[b] (6.75–13.25), N = 26	13 (8.75–17.25) , N = 26
T3		10[b] (5.5–14), N = 25	12[b] (7.50–15), N = 26
T4		11 (6.25–15.25), N =25	13 (8.5–16.5), N = 25
T0	PRI	22.5 (16.25–30.25), N = 28	25 (19–29) , N = 27
T1		16.5[b] (9.25–21), N = 28	21.5[b] (12.75–28.25), N =26
T2		20[b] (9.5–26), N = 26	21.5[b] (11.75–27), N =26
T3		17[b] (10–28), N = 25	19[b] (12–26.75), N =26
T4		18.5 (10.5–32, N =25	22 (13.5–29), N =27

[a]Time point: T0 = one week before the intravenous treatment (baseline); T1 = during the administration of trial medication; and T2, T3, and T4 are respectively 3, 6, and 12 weeks following start of intervention
[b]Significant improvement compared with T0 ($P < 0.05$)
[c]Significant difference compared with placebo

Adverse effects:
Common side effects with $MgSO_4$ were flushing and dizziness during and shortly after the 4-hour infusion. In both the $MgSO_4$ and placebo groups, pain near the insertion site of the intravenous cannula was reported

Tarighat,[15] 2012, Iran

Comparison of changes in migraine indicators after supplementation with magnesium (Mg), carnitine (Car), Mg+Car or control for migraine prophylaxis

Outcome	Reduction in outcome (PreTx – PostTx)				P value (from one way ANOVA)
	Mg	Car	Mg+Car	Control	
Reduction in no. of migraine attacks	4.44±0.77	3.04±0.64	3.45±0.55	0.12±1.38	0.008
Reduction in days with migraine	4.59±0.91	4.63±0.98	6.61±1.62	2.54±1.91	0.217
Reduction in migraine severity	1.00±0.94	0.87±0.11	0.71±0.12	0.87±0.05	0.305
Reduction in migraine index	14.39±3.08	13.35±2.80	19.81±4.81	8.28±5.71	0.321

"Oral supplementation with magnesium oxide and L-carnitine and concurrent supplementation of Mg–L-carnitine besides routine treatments could be effective in migraine prophylaxis; however, larger trials are needed to confirm these preliminary findings." Page 42

Main Study Findings	Author's Conclusion

van der Plas,[13] 2013, The Netherlands

Comparison of pain reduction with magnesium vs placebo for CRPS patients

Outcome	Time point	Pain score, mean ± SD; (N = 22)		*P* value
		Mg	Placebo	
NRS (scale range 0 to 10)	Baseline	7.3 ± 1.6	7.2 ± 1.5	
	3 weeks	6.7 ± 2.1	7.3 ± 1.6	0.01[a]
McGill NWC (scale range: 0 to 20)	Baseline	13.4 ± 3.5	13.2 ± 3.1	
	3 weeks	12.0 ± 3.3	13.0 ± 3.1	0.05[b]
McGill PRI (scale range: 0 to 63)	Baseline	27.4 ± 10.4	26.5 ± 9.1	
	3 weeks	23.3 ± 11.5	26.2 ± 10.4	0.11[a]

[a]Paired samples t-test of non- transformed data
[b]Paired samples t-test of transformed data

Comparison of function with magnesium vs placebo for CRPS patients

Outcome	Time point	Score, mean ± SD; (N = 20)		*P* value
		Mg	Placebo	
Functional rating using RASQ (scale range 1 to 5)	Baseline	3.6 ± 0.9	3.6 ± 0.9	
	3 weeks	3.5 ± 1.1	3.6 ± 1.0	0.57[a]

[a]Paired samples t-test of non- transformed data

Adverse events (≥ 3 in Mg or placebo groups)

Adverse events	Mg, (N = 27)	Placebo, (N = 15)
Injection pain	19	9
Subcutaneous hematoma	7	-
Mild allergy	3	2
Headache	1	3
Other types	8	8
All	38	22

"In conclusion, this explanatory study revealed no evidence of a muscle relaxant effect of MG in CRPS-related dystonia. Although several limitations may impede the interpretation of our data, we feel there is insufficient support for new studies evaluating the efficacy of other routes of MG administration in CRPS-related dystonia." Page 1346

Yousef,[14] 2013, Egypt

Comparison of pain management (using NRS scores)with magnesium vs placebo for chronic low back pain

Time point	Pain score using NRS, mean (SD)		*P* value		
	Mg	Placebo	Between groups	Within Mg group	Within placebo group
Pre-tx	7.5 (2.2)	7.4 (2.4)	0.62		
2 weeks	3.4 (1.15)	3.6 (1.4)	0.28	0.022	0.036
6 weeks	3.9 (1.4)	6.6 (1.7)	0.003	0.029	0.26
3 months	4.4 (1.6)	6.8 (2.2)	0.045	0.016	0.51
6 months	4.7 (1.8)	7.2 (2.45)	0.027	0.034	0.25

Patients in both groups experienced statistically significant improvements in their lumbar spine ranges of movement at the 2-week time point. However, only for the Mg group the improvement was sustained during the 6-month period.

"We believe that the use of magnesium presents a viable treatment option for patients with refractory chronic back pain who have failed to respond to conventional treatment. Further studies are needed to identify the optimum period of treatment, optimum dose, and potential benefit of combining magnesium use with other NMDA antagonists when managing patients with different forms of neuropathy." Page 265

Main Study Findings	Author's Conclusion
Adverse effects: Overall, adverse effects with magnesium were minimal. Mild diarrhea was reported in four patients but this did not necessitate discontinuation of the treatment.	

CI = confidence interval; CRPS = complex regional pain syndrome; CPRS-1 = complex regional pain syndrome type 1; McGill NWC = number of words chosen of McGill Pain Questionnaire; McGill PRI = pain rating index of McGill Pain Questionnaire ; MD = mean difference; NR = not reported; NRS = numerical rating scale; NWC = number of words chosen ; PRI = pain rating index; RASQ = Radbound Skills Questionnaire; RCT = randomized controlled trial; RD = risk difference; RR = risk ratio; SD (standard deviation; Tx = treatment; VAS = visual analog scale;

Table 10: Summary of Findings of Included Evidence-based Guidelines

Main Study Findings	Recommendations
Holland[17] /AAN and AHS	
This document is an update to the original guideline of 2000. According to the original guideline magnesium was indicated as probably effective for migraine prevention. This was based on two positive Class II studies and one negative Class III study. Since then an additional Class II study comparing a combination of magnesium, riboflavin and MIG-99 with placebo was identified. In this study there was improvement in both groups compared to baseline but there was no between group difference. The study however was not powered to detect between group differences. Since magnesium was used in combination, the impact of magnesium alone was unclear.	Magnesium is probably effective and should be considered for migraine prevention (Recommendation: Level B)
Orr[16] / Canadian Headache Society, 2015, Canada	
Findings from four studies were presented. Three studies (Bigal et al., 2002; Corbo et al., 2001, and Cete et al.,) were published as full-text articles and one study (Abrishami et al., 2010) was available as an abstract. One small study (Abrishami et al.) of poor quality indicated intravenous $MgS0_4$ was superior to placebo. One fair quality trial (Bigal et al.) indicated that intravenous $MgS0_4$ was superior to placebo for several secondary efficacy outcomes. One poor quality trial (Cete et al.) indicated that there was no difference in efficacy between intravenous $MgSO_4$ and placebo, and that flushing was the side effect in the $MgSO_4$ group. One good quality trial (Corbo et al.) indicated that intravenous MgSO4 was inferior to placebo with respect to several efficacy outcomes and had higher incidences of side effects, majority being flushing	"Weak recommendation, moderate-quality evidence. We recommend against the use of MgSO4 for the acute treatment of migraine." Page 279
Pringsheim[1] / Canadian Headache Society, 2012, Canada	
Findings from three studies on patients with migraine were presented, of which two RCTs (Piekert et al., and Pfaffenrath et al.) were for fair quality and one RCT (Köseoglu et al.) was of poor quality. The Piekert study compared magnesium (600 mg elemental	"Strong recommendation, low quality evidence: We recommend that clinicians offer magnesium to eligible patients for migraine prophylaxis. There is some evidence for benefit and side effects are minimal. Due to the contrary evidence presented in these trials, we recommend that 24 mmol (600 mg) of elemental

Main Study Findings	Recommendations
magnesium as trimagnesium dicitrate) with placebo, taken daily for 12 weeks for migraine prophylaxis. Patients on magnesium had a significantly greater reduction in frequency of migraine attacks compared to placebo, in the final month of treatment. Within the first four weeks of treatment 8 (19%) patients in magnesium group developed soft stools or diarrhea, and of these 2 had to discontinue treatment. No other complications were reported. The Pfaffenrath study compared magnesium (243 mg elemental magnesium as magnesium-L-aspartate-hydrochloride trihydrate) with placebo, taken twice daily for 12 weeks. There was no significant difference in reduction of duration or intensity of migraine at the end of treatment compared to baseline, in both groups. In the magnesium group, patients had soft stool or diarrhea. The Köseoglu study was on patients with migraine without aura and compared magnesium (600 mg elemental magnesium as magnesium citrate) with placebo taken daily over 3 months. Patients on magnesium had a significantly greater reduction in frequency of migraine attacks compared to placebo, when post/pre-treatment ratios of attack frequency were compared (*P* = 0.005)	magnesium daily as magnesium citrate be used for migraine prophylaxis, since a positive result was only obtained with this compound." Page 23

AAN = American Academy of Neurology; AHS = American Society of Headache