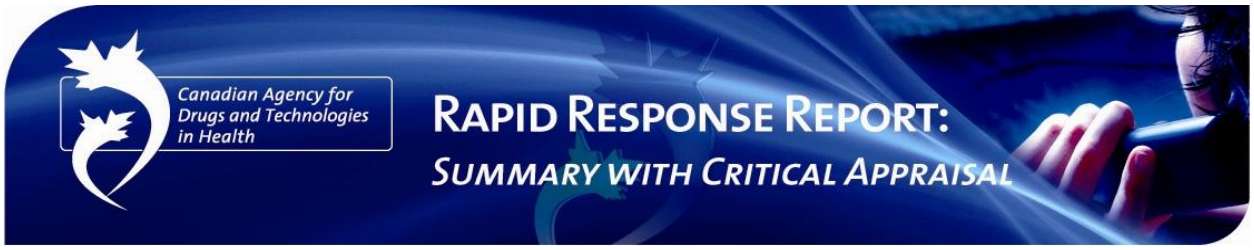

TITLE: Pregabalin for Acute Pain: A Review of the Clinical Effectiveness

DATE: 24 January 2017

CONTEXT AND POLICY ISSUES

Acute pain is defined as a normal physiologic response to a chemical, thermal or mechanical stimulus.[1] In contrast, chronic pain is defined as an abnormal physiologic response that persists once an initial noxious stimulus has resolved. Conventionally, acute pain is defined as pain that is short in duration, usually less than one month. Failure to adequately manage acute pain may result in neuronal remodeling that can lead to the development of chronic pain.[1] Therefore, effective management of acute pain is essential both in the short term care of patients and in long term prevention of chronic pain.

The American Academy of Family Physicians guidelines for managing acute pain recommends identifying the cause of pain followed by a stepwise approach to pharmacologic therapy with analgesia based on the severity of the pain.[2] These guidelines were adapted from the World Health Organization pain management ladder, which focuses primarily on cancer pain.[3] Acetaminophen or non-steroidal anti-inflammatories (NSAID) are recommended as first line pharmacologic analgesia for mild to moderate pain. Both acetaminophen and NSAIDs, however, are associated with potential toxicity.[2] Acetaminophen can cause hepatotoxicity and NSAIDs are associated with gastrointestinal toxicity and platelet dysfunction. Both acetaminophen and NSAIDs can cause renal toxicity.[2] The mainstay of treatment for severe acute pain is opioid analgesic agents of varying potency, such as morphine, hydromorphone or oxycodone. Concerns around the use of opioids are growing, specifically with respect to abuse and diversion potential.[2] Opioids are also associated with adverse effects including nausea, vomiting, constipation, and potential respiratory depression in cases of rapid dose escalation or overdose.[2] Adjuvant analgesic agents, such as tricyclic antidepressants or antiepileptic agents, can also be added for additional pain relief.[2]

Post-operative pain is one specific subset of acute pain. In 2012, the American Society of Anesthesiologists (ASA) published guidelines for the management of acute post-operative pain.[4] The ASA recommended a multi-modal approach to post-operative pain management including regularly scheduled acetaminophen or NSAIDs with consideration of the addition of pregabalin or gabapentin and regional blockade with local anesthetic.[4] While opioids are used

as part of a multimodal analgesic approach, they can be associated with the development of opioid-induced hyperalgesia in the post-operative setting.[5]

Pregabalin is an anti-seizure medication with structural similarity to gabapentin.[6] One of the effects of pregabalin in the central nervous system and peripheral nervous system is to bind to a subunit of the pre-synaptic voltage gated calcium channels, resulting in modulation of the release of excitatory neurotransmitters.[6,7] The entire mechanism of action of pregabalin remains to be fully elucidated. Pregabalin can be initiated at 75mg daily and titrated based on a patient's pain response to a maximum of 600mg daily.[6] This drug therapy is almost entirely renally excreted, and its should be adjusted based on a patient's renal function.[6] The most commonly reported adverse effects of pregabalin are dizziness and somnolence, which are both dose related.[6,7] The effectiveness of pregabalin is well established in the management of several chronic neuropathic pain syndromes, such as diabetic neuropathy, fibromyalgia and post-herpetic neuralgia.[6] A recent systematic review found that compared to placebo, pregabalin decreased post-operative pain.[8]

Current pharmacotherapeutic options for the management of acute pain, specifically opioids, can be associated with potential harms.[1,2] New therapeutic options are necessary to optimize the management of acute pain secondary to various causes. The objective of this report is to review the evidence for clinical effectiveness of pregabalin compared to placebo in the management of acute non-operative pain, and pregabalin in combination with opioids compared to opioids alone in the management of acute and post-operative pain.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of pregabalin for acute pain?

2. What is the comparative effectiveness of concurrent pregabalin and opioid use versus opioids alone for the management of acute or post-operative pain?

KEY FINDINGS

One randomized controlled trial (RCT) demonstrated that compared to opioids alone, a single pre-operative dose of pregabalin in combination with post-operative opioids significantly reduced post-operative opioid consumption, pain scores and use of breakthrough analgesia at 48 hours. A second RCT demonstrated that compared to placebo, pregabalin significantly reduced various symptom components of the neuropathic pain scale and procedural pain over four weeks in patients with severe burn injury. A third randomized controlled cross-over trial failed to demonstrate a significant reduction in pain scores when a single dose of pregabalin was compared to placebo in patients with acute pain secondary to herpes zoster. There was no significant increase in adverse effects associated with pregabalin in any of the studies.

Overall, pregabalin may be a viable option for post-operative pain management as part of a multimodal approach. The evidence for pregabalin use in acute pain is weak and limited to pain secondary to acute burns. No evidence was found for the use of pregabalin in combination with opioids compared to opioids alone in acute non-surgical pain.

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, and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and December 16, 2016.

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	Q1. Patients with acute pain Q2. Patients with acute or post-operative pain
Intervention	Q1. Pregabalin Q2. Pregabalin and opioids in combination
Comparator	Q1. Opioids or placebo/standard of care Q2. Opioids alone
Outcomes	Clinical effectiveness (e.g. pain management, quality of life), safety and harms, reduction in opioid use (dose or duration), opioid sparing
Study Designs	Health Technology Assessment, Systematic Reviews, Meta-Analyses Randomized Controlled Trials (RCT)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, were duplicate publications, included as one of the studies in a systematic review or were published prior to 2011.

Critical Appraisal of Individual Studies

The included RCTs were critically appraised using the Cochrane Risk of Bias tool.[9] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 404 citations were identified in the literature search. Following screening of titles and abstracts, 359 citations were excluded and 45 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 44 publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Characteristics of the included studies are summarized below. Additional details can be found in Appendix 2.

Study Design

Two RCTs[10,11] and one cross-over RCT[12] with samples sizes ranging from 8 to 90 patients were included in this report.

Country of Origin

The RCTs were conducted in South Korea[10] and Australia.[11] The cross-over RCT was conducted in the USA.[12]

Patient Population

One RCT[10] included patients undergoing arthroscopic shoulder surgery. Participants underwent two different types of arthroscopic surgery; 25% had a Bankart repair while 75% had a rotator cuff repair. A second RCT[11] included patients with acute pain after a severe burn injury of any depth covering at least 5% of their total body surface area (TBSA). Skin grafts were performed in 75% of the patients. The cross-over RCT[12] included patients with acute pain secondary to herpes zoster.

Interventions and Comparators

One RCT[10] compared a single 150mg dose of pregabalin to control given one hour prior pre-operatively. All patients also received intravenous patient controlled analgesia (PCA) that consisted of fentanyl 20 mcg/kg in 100mL of 0.9% normal saline at a background rate of 1mL/hr with 1mL bolus as required with a 15-minute lock-out period. Rescue analgesia was provided with 30mg of intravenous ketorolac if pain was at least 5 on the numeric rating scale (NRS). A second RCT[11] compared 28 days of a titratable dose of pregabalin to placebo. The mean dose in the pregabalin group was 520mg per day, and the mean dose in the placebo group was 574mg over the final 3 weeks of the trial. The cross-over RCT[12] compared a single 150mg dose of pregabalin to placebo. After a minimum of 48 hours, the participants crossed over to the other treatment group and received an additional single dose of either pregabalin or placebo.

Outcomes

All three studies reported pain management and adverse events as outcomes.[10-12] Two studies[10,11] also reported on opioid use.

Summary of Critical Appraisal

Strengths and limitations of the included studies are provided in Appendix 3.

Overall, two of the RCTs were of good quality[10,11] and one was of poor quality[12] based on the results of the Cochrane Risk of Bias Tool.

The sample sizes ranged from 8 to 90 participants across all trials. Two studies were single centred[10,11] and one did not report how many centres participated in the study.[12] Randomization was completed using a computerized random number table in two studies.[10,11] Jensen-Dahm et al. reported that randomization was computer generated but no further details with respect to the method of randomization were provided. Allocation concealment was achieved with sealed envelopes in one study[10] and not described in two studies[11,12]. All three studies used identical appearing placebo capsules to ensure blinding. Study participants, researchers and burn unit personnel were all blinded in the study by Gray et al..[11] Jensen-Dahm et al.[12] described their study as "double-blind".[12] Ahn et al. did not describe who was blinded.[10] Ahn et al.[10] were the only included study that reported blinding of outcome assessors. All patients randomized in both the study published by Ahn et al.[10] and Jensen-Dahm[12] et al. were included in the final analysis, and there were no withdrawals from either study. Withdrawals were 25% over 28 days, but even across treatment groups in the study by Gray et al., and participants were analyzed according to the intention to treat principle.[11] Outcome reporting was complete in all of the studies.[10-12] Ahn et al.[10] used one pre-operative dose of pregabalin and assessed short term outcomes at 48 hours only. Patients over the age of 65 years were excluded from participation in the study by Ahn[10] which limits extrapolation of the data to an older population. Generalizability of the findings of the studies by Gray[11] and Jensen-Dahm[12] may be limited as many patients initially recruited to participate in the study were ineligible. In the study Gray et al.[11] the main reason for study ineligibility was burn less than 5% TBSA. In the study by Jensen-Dahm[12] the main reason patients were ineligible for the study was the presence of post-herpetic neuralgia. Jensen-Dahm[12] were unable to reach their target population of 34 and had 8 patients participate in their study, which resulted in the study being underpowered. There was a preponderance of male patients in the study by Gray et al.[11] making generalizability to female patients difficult.

Summary of Findings

The overall findings are summarized below and details are available in Appendix 4.

1. <u>What is the clinical effectiveness of pregabalin for acute pain?</u>

Pain Management

In patients with acute pain secondary to severe burn injury, one RCT[11] found that a titrated dose of pregabalin significantly decreased the mean "sharp" and "hot" pain scores on the self-administered NPS over 4 weeks. Other components of the NPS also showed a significant reduction over 4 weeks in the pregabalin group including the mean score for "itch",

"unpleasantness of the pain" and "surface pain". There was no significant difference in the remaining components of the NPS score between pregabalin and placebo. There was a significant improvement in procedural pain over 4 weeks with pregabalin compared to placebo. Pain was present in 11 patients (26%) of the pregabalin group compared to 12 patients (29%) in the placebo group at 6 months.

In patients with acute pain secondary to herpes zoster, one RCT[12] found that there was no difference in pain reduction with a single dose of pregabalin compared to placebo. When pain was measured on a Visual Analogue Scale every 30 minutes from the time the dose was given to 6 hours after the dose, the time point where pregabalin demonstrated a significant reduction in pain compared to placebo was at 1.5 hours. At no other time point did pregabalin demonstrate a significant reduction in pain compared to placebo. Maximal pain reduction was not significantly different between the two groups. Change in the area and severity of allodynia was not significantly different between pregabalin and placebo.

Opioid Use

In patients with acute pain secondary to severe burn injury, one RCT[11] found no significant difference in the mean daily opioid requirement at either the end of week 1 or week 2 between pregabalin and placebo groups.

Adverse Events

No significant difference in adverse events was found between pregabalin and placebo groups in the RCT of patients with acute pain secondary to severe burn injury[11] or the RCT[12] of patients with acute pain secondary to herpes zoster. A total of 4 patients from the RCT in patients with severe burns[11] withdrew secondary to adverse effects; 3 of these patients were in the placebo group.

2. <u>What is the comparative effectiveness of concurrent pregabalin and opioid use versus opioids alone for the management of acute or post-operative pain?</u>

Pain Management

One RCT[10] found that a single pre-operative dose of pregabalin significantly reduced pain intensity scores compared to control at 6, 24, and 48 hours. There were no significant differences in pain scores between groups while patients were still in the Post-Anesthesia Care Unit (PACU). The use of breakthrough analgesia was significantly lower in the pregabalin group at both 24 and 48 hours. There was no significant decrease in the amount of breakthrough analgesia between the pregabalin and control groups in the PACU or at 6 hours follow-up.

Opioid Use

One RCT [10] found that a single pre-operative dose of pregabalin significantly reduced the cumulative consumption of fentanyl 48 hours post-operatively (1,126.0mcg versus 1,641.4mcg), mean difference (95% confidence interval) = 515.4mcg (359.0 to 671.8).

Adverse Events

One RCT[10] found that adverse events including the incidence of post-operative nausea was not significantly different between pregabalin and control.

No evidence was found for the use of pregabalin in combination with opioids compared to opioids alone in acute non-operative pain.

Limitations

Three RCTs evaluated the role of pregabalin compared to placebo in acute pain[11,12] and in combination with opioids compared to opioids alone in post-operative pain.[10] Two of the RCTs had a low risk of bias[10,11] and one had a high risk of bias.[12] All three of the RCTs were limited by sample sizes ranging from 8 to 90 participants.[11,12] One study[12] was unable to reach their target sample size of 34 patients secondary to slow enrolment, resulting in the study being underpowered to detect a difference between the two treatment groups. In addition to being underpowered, the study by Jansen-Dahm et al.[12] did not report many of the details of the study conduct including the number of centers that participated, method of randomization and allocation concealment. The study by Ahn[10] used a single pre-operative 150mg dose of pregabalin in combination with post-operative opioid PCA. It is unknown whether other doses of pregabalin would be effective or if repeated dosing of pregabalin would improve post-operative pain control compared to opioids alone. Patients were followed for 48 hours post-operatively, so it is unknown whether pregabalin is effective in longer term post-operative pain control or in the prevention of chronic post-operative pain. Patients who completed an NPS score on a daily basis only were included in the analysis in the study of pregabalin in acute burn pain.[11] This approach may have introduced bias into the outcome reporting and study findings. Gray et al.[11] also had a 25% withdrawal rate over the short 28-day trial, primarily because of participants being discharged from the Burns Unit and discontinuing the study medication. One patient in the pregabalin group discontinued the drug secondary to intolerable adverse effects, and the research team withdrew two patients secondary to rising liver enzymes. The withdrawals and reason for withdrawal were reported and balanced between the two groups. Overall, the generalizability of the study findings is limited to patients younger than 65 years of age without significant underlying medical or psychiatric illness, including substance abuse.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Three RCTs that evaluated the clinical effectiveness of pregabalin for acute or post-operative pain were identified.[10-12] Compared to opioids alone, a single pre-operative dose of pregabalin in combination with post-operative opioids demonstrated a significant reduction in post-operative opioid consumption at 48 hours.[10] Pain scores and use of breakthrough analgesia were also significantly reduced at various post-operative time points outside of the PACU. These findings are consistent with previous systematic reviews that focused on the comparison of pregabalin to placebo in the post-operative period.[8,13-18]

In patients with acute pain secondary to severe burn injury, pregabalin significantly reduced various symptom components of the NPS scale and procedural pain over 4 weeks compared to placebo.[11] The generalizability of this trial is limited by the sample size, single center design, and the risk of reporting bias as only patients who completed the NPS on a daily basis were included in the analysis.

In patients with acute pain secondary to acute herpes zoster, one cross-over RCT failed to demonstrate a difference in pain scores after a single 150mg dose of pregabalin. This trial was underpowered due to slow recruitment and both the interpretation and generalizability of the findings are very limited as a result.[12]

Overall, pregabalin in combination with opioids, compared to opioids alone, in post-operative pain management reduces opioid requirements and pain scores. Pregabalin may be a viable option for post-operative pain management as part of a multimodal approach. The evidence for pregabalin use in acute pain is weak and limited to pain secondary to acute burns. No significant increase in adverse events was found to be associated with pregabalin use in any of the included studies.[10-12] No evidence was found for the use of pregabalin in combination with opioids compared to opioids alone in acute non-surgical pain.

There is an ongoing trial evaluating the role of pregabalin in the prevention of acute pain syndrome associated with the use of the chemotherapy agent paclitaxel.[19] When available, the results of this trial will add to the body of evidence for the use of pregabalin in patients with acute pain.

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REFERENCES

1. Carr DB, Goudas LC. Acute pain. Lancet. 1999 Jun 12;353(9169):2051-8.

2. Blondell RD, Azadfard M, Wisniewski AM. Pharmacologic therapy for acute pain. Am Fam Physician [Internet]. 2013 Jun 1 [cited 2017 Jan 10];87(11):766-72. Available from: http://www.aafp.org/afp/2013/0601/p766.html

3. WHO's cancer pain ladder for adults [Internet]. Geneva (CH): World Health Organization; 2017. [cited 2017 Jan 10]. Available from: http://www.who.int/cancer/palliative/painladder/en/

4. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012 Feb;116(2):248-73.

5. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet. 2011 Jun 25;377(9784):2215-25.

6. Toth C. Drug safety evaluation of pregabalin. Expert Opin Drug Saf. 2012 May;11(3):487-502.

7. Baidya DK, Agarwal A, Khanna P, Arora MK. Pregabalin in acute and chronic pain. J Anaesthesiol Clin Pharmacol [Internet]. 2011 Jul [cited 2016 Dec 22];27(3):307-14. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3161452

8. Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent postoperative pain: A systematic review and meta-analysis. Br J Anaesth [Internet]. 2015 Jan [cited 2016 Dec 22];114(1):10-31. Available from: http://bja.oxfordjournals.org/content/114/1/10.full.pdf+html

9. Higgins JPT, Green S, editors. Cochrane handbook for systematic reviews of interventions [Internet]. Version 5.1.0. London (England): The Cochrane Collaboration; 2011 Mar. Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of bias. [cited 2017 Jan 10]. Available from: http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm

10. Ahn S, Byun SH, Park K, Ha JL, Kwon B, Kim JC. Analgesic efficacy of preemptive pregabalin administration in arthroscopic shoulder surgery: A randomized controlled trial. Can J Anaesth. 2016 Mar;63(3):283-9.

11. Gray P, Kirby J, Smith MT, Cabot PJ, Williams B, Doecke J, et al. Pregabalin in severe burn injury pain: A double-blind, randomised placebo-controlled trial. Pain. 2011 Jun;152(6):1279-88.

12. Jensen-Dahm C, Rowbotham MC, Reda H, Petersen KL. Effect of a single dose of pregabalin on herpes zoster pain. Trials [Internet]. 2011 [cited 2016 Dec 22];12:55. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3059274

13. Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: A meta-analysis. Br J Anaesth. 2011 Apr;106(4):454-62.

14. Mao Y, Wu L, Ding W. The efficacy of preoperative administration of gabapentin/pregabalin in improving pain after total hip arthroplasty: A meta-analysis. BMC Musculoskelet Disord [Internet]. 2016 [cited 2016 Dec 22];17(1):373. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5004259

15. Dong J, Li W, Wang Y. The effect of pregabalin on acute postoperative pain in patients undergoing total knee arthroplasty: A meta-analysis. Int J Surg [Internet]. 2016 Oct [cited 2016 Dec 22];34:148-60. Available from: http://fulltext.study/preview/pdf/4285263.pdf

16. Pesonen A, Suojaranta-Ylinen R, Hammaren E, Kontinen VK, Raivio P, Tarkkila P, et al. Pregabalin has an opioid-sparing effect in elderly patients after cardiac surgery: A randomized placebo-controlled trial. Br J Anaesth [Internet]. 2011 Jun [cited 2016 Dec 22];106(6):873-81. Available from: http://bja.oxfordjournals.org/content/106/6/873.full.pdf+html

17. Engelman E, Cateloy F. Efficacy and safety of perioperative pregabalin for post-operative pain: A meta-analysis of randomized-controlled trials. Acta Anaesthesiol Scand. 2011 Sep;55(8):927-43.

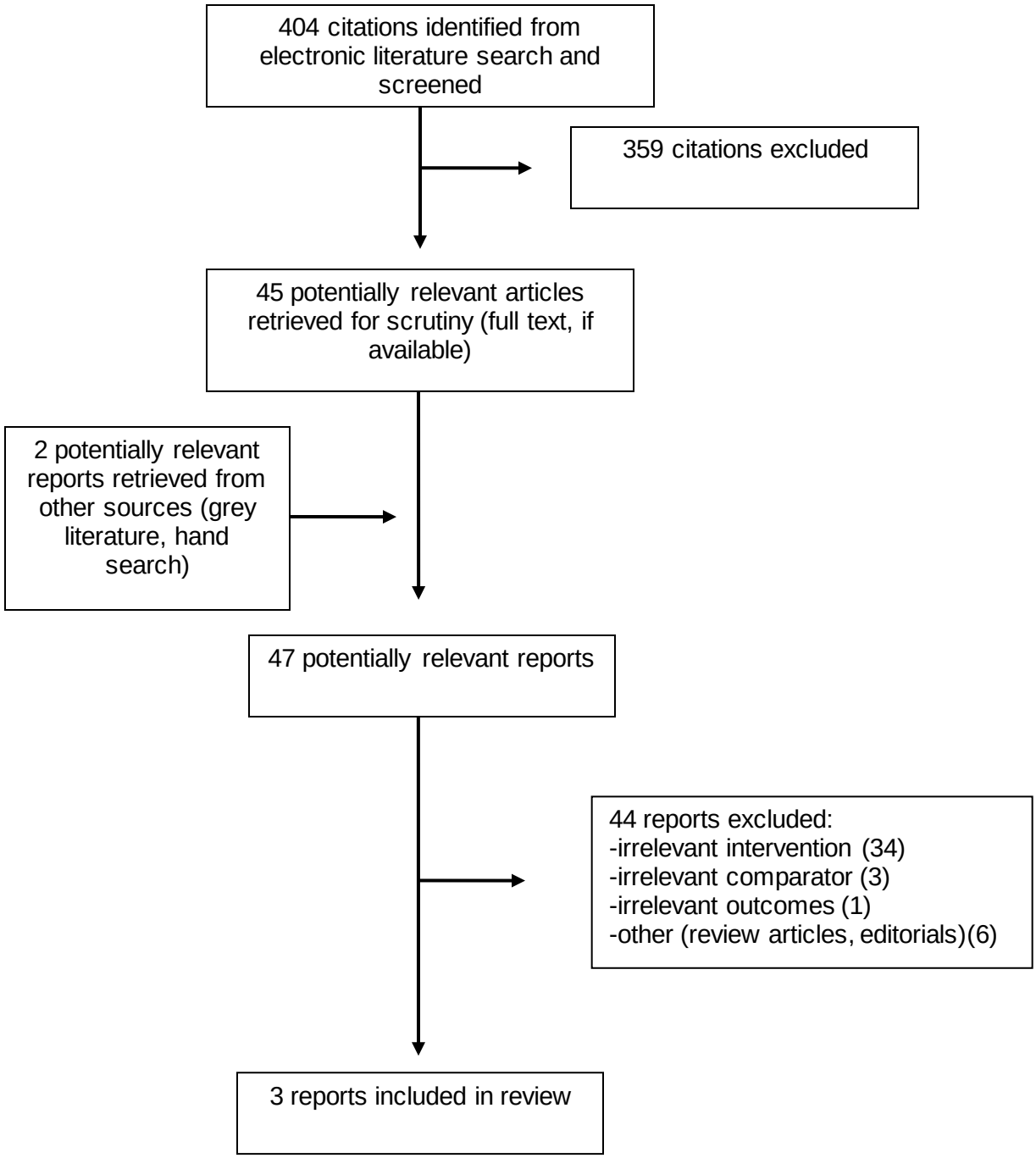
18. Yoshimura N, Iida H, Takenaka M, Tanabe K, Yamaguchi S, Kitoh K, et al. Effect of postoperative administration of pregabalin for post-thoracotomy pain: A randomized study. J Cardiothorac Vasc Anesth. 2015 Dec;29(6):1567-72.

19. Academic and Community Cancer Research United. Pregabalin in preventing acute pain syndrome in patients receiving paclitaxel. 2012 Mar 9 [cited 2016 Dec 22; updated 2016 Jul 20]. In: ClinicalTrials.gov [Internet]. Bethesda (MD): U.S. National Library of Medicine; 2000 - . Available from: https://clinicaltrials.gov/ct2/show/NCT01637077 Identifier: NCT01637077.

ABBREVIATIONS

ASA	American Society of Anesthesiologists
NPS	Neuropathic Pain Scale
NRS	Numeric Rating Scale
NSAID	Non-steroidal anti-inflammatory
PACU	Post-Anesthesia Care Unit
PCA	Patient Controlled Analgesia
RCT	Randomized Controlled Trial
TBSA	Total Body Surface Area
USA	United States of America
VAS	Visual Analogue Scale

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Study Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Ahn[10], 2016, South Korea	RCT	n=60 Arthroscopic shoulder surgery Age (mean): 51-55 years 43% male Bankart repair: 25% Rotator cuff repair: 75%	Pregabalin 150mg 1 hour prior to induction Fentanyl 20 mcg/kg in 100mL NS run at 1mL/hr with 1mL bolus PRN (15-minute lockout)	Control 1 hour prior to induction Fentanyl 20 mcg/kg in 100mL NS run at 1mL/hr with 1mL bolus PRN (15-minute lockout)	Total post-operative fentanyl consumption at 48 hours Pain intensity Number of rescue analgesic drugs administered Nausea
Gray[11], 2011, Australia	RCT	n=90 Burn injury of any depth covering ≥5% TBSA Age (mean): 35 years Skin grafts 75% of patients	Pregabalin Titratable dose Mean (final 3 weeks): 520mg 91% male	Placebo Titratable dose Mean (final 3 weeks): 574mg 75% male	Neuropathic pain scale Opioids requirement Procedural pain score Adverse events
Jensen-Dahm[12], 2011, USA	RCT Crossover	n=8 Acute herpes zoster pain Age (median): Placebo-first: 77 years Pregabalin-first: 65 years % female: Placebo-first: 33% Pregabalin-first: 40% Days between outbreak and study entry: Placebo-first: 31 Pregabalin-first: 23	Pregabalin 150mg (single dose) n=5 pregabalin first	Placebo (single dose) n=3 placebo first	Pain (VAS) Allodynia Adverse events

RCT=Randomized Controlled Trail; TBSA=Total Body Surface Area; VAS=Visual Analog Scale

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Randomized Controlled Trials using Cochrane Risk of Bias Tool[9] }

Strengths	Limitations
Ahn[10], 2016, South Korea	
• Computerized randomization table was used to randomize participants to a treatment group • Allocation concealment was achieved through the use of sealed envelopes, although authors did not specify whether the envelopes were opaque • Blinding was achieved through the use of placebo capsules that were identical in appearance to the pregabalin capsules • There were no patients lost to follow-up and all patients were included in the final analysis • Outcome assessor was blind to treatment allocation	• Sample size (N=60), single center, exclusion of patients with chronic pain or use of analgesia within 48 hours pre-operatively • Only a single pre-operative dose of pregabalin was used • Outcomes were assessed only in the short term (48 hours), no long-term outcomes were assessed • No functional outcomes such as ability to mobilize or participate in rehab were analyzed • Elderly patients (> 65 years) were excluded
Gray[11], 2011, Australia	
• Randomization was a block design using a random number table and was stratified by TBSA of burn involvement • Study participants, researchers and burn unit staff were all blinded. Placebo and pregabalin capsules were identical (grey capsules) • Both short (28 day) and longer term (6 months) follow-up was considered • Withdrawals were similar between treatment groups • Outcomes were analyzed using an intention to treat principle • Complete outcome reporting	• Single center, sample size (N=90) • Method used to blind treatment allocation was unclear • Generalizability of study findings questionable as many patients were not eligible for study inclusion • Generalizability to female patients questionable as almost all study participants were male • Possible selective outcome reporting as only patients who completed the NPS on a daily basis were included • Dropout rate of 25% over a 4-week trial
Jensen-Dahm[12], 2011, USA	
• Study was reported to be “double-blind” however, it is unclear who was blinded • Blinding was achieved through the use of identical appearing placebo capsules • All participants completed the study and were included in the analysis • Outcome reporting was complete	• Randomization was computer generated and managed by the study pharmacist, no further details were provided as to the method used • Method of allocation concealment was not reported • Unclear why 48 washout period before cross over was selected • Generalizability of study findings questionable as many patients were not eligible for study inclusion • Investigators were unable to reach their target sample size of 34 participants • Sample size (N=8 patients)

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Studies

Ahn[10], 2016

Main Study Findings

Fentanyl consumption (mcg), mean (SD)

Time	Control (n=30)	Pregabalin (n=30)	MD (95%CI)	P-value
0-48hrs	1641.4 (320.3)	1126.0 (283.6)	515.4 (359.0,671.8)	<0.001
PACU	97.9 (44.6)	77.1 (42.7)	20.8 (-1.7 ,43.4)	0.070
0-6hrs	298.3 (126.4)	132.7 (112.3)	165.5 (103.2,227.8)	<0.001
6-24hrs	506.8 (262.8)	406.7 (206.5)	100.2 (-22.8, 223.1)	0.108
24-48hrs	746.7 (258.6)	509.5 (163.3)	237.2 (93.6, 380.9)	0.002

Pain scores, mean (SD)

Time	Control (n=30)	Pregabalin (n=30)	MD (95%CI)	P-value
PACU	8.1 (1.0)	7.8 (0.9)	0.2 (-0.2 ,0.8)	0.270
6hrs	7.5 (1.5)	4.7 (2.7)	2.9 (1.8, 4.0)	<0.001
24hrs	6.1 (1.5)	3.3 (2.2)	2.9 (1.9, 3.8)	<0.001
48hrs	4.5 (1.5)	3.0 (1.7)	1.5 (0.6,2.3)	0.001

Bonferroni correction was applied, P<0.0125 is considered significant

Incidence of pain rescue, n (%)

Time	Control (n=30)	Pregabalin (n=30)	P-value
PACU	28 (93)	24 (80)	0.250
6hrs	12 (40)	8 (26)	0.410
24hrs	12 (40)	4 (13)	0.020
48hrs	12 (40)	3 (10)	0.010

Bonferroni correction was applied, P<0.0125 is considered significant

Nausea:

Control: 11 (36%) vs. Pregabalin: 7 (23%), P=0.260

Author's Conclusions

- Administration of a single dose of pregabalin prior to arthroscopic shoulder resulted in a significant opioid sparing effect and improved pain scores 48 hours after surgery without an increase in adverse effects

Gray[11], 2011

Main Study Findings

Neuropathic Pain Scale (NPS) over 4-weeks

NPS2 "sharp pain" P=0.04
NPS3 "hot pain" P=0.01
NPS7 "itch" P=0.01
NPS8 "unpleasantness of the pain" P=0.02
NPS9b "surface pain" P=0.03

Opioid Requirement (daily morphine parenteral

Author's Conclusions

- Pregabalin significantly reduces several symptoms of acute neuropathic pain (hot pain, sharp pain, unpleasantness of the pain, surface pain, and itch) in patients with severe burn injury

Table A3: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
equivalents) **Time point** / **Pregabalin** / **Placebo** end of week 1 / 36mg/day / 43mg/day end of week 2 / 28mg/day / 35mg/day P>0.05 at both time points **Procedural pain:** End of 4 weeks pregabalin vs. placebo P=0.02 **Side effects:** Pregabalin vs. placebo P>0.05	
Jensen-Dahm[12], 2011	
Outcome mean (95%CI) / **Pregabalin (n=8)** / **Placebo (n=8)** **Overall pain % reduction** / 33 (13.2,52.9) / 14.0 (-5.8,33.8) **Overall pain VAS reduction** / 14.7 (5.1,24.3) / 8.5 (-1.1,18.1) **Allodynia severity, overall % reduction** / 25.2 (0.9,49.5) / 30.7 (7.5,53.9) **Allodynia area, overall % reduction** / -1.4 (-59.6, 56.8) / -12.4 (-70.8, 45.9) **Total side-effect score** / 1.7 (0.2, 3.9) / 1.1 (0, 4.1) **Pain Reduction,** % (95%CI): Pregabalin vs. placebo: -19% (-42.5%, 4.5%); P=0.096 **Maximal Pain Reduction,** % (95%CI): Pregabalin vs. placebo: -22.9% (-52%, 6%); P=0.100	• A single dose of pregabalin demonstrated a trend for reducing acute zoster pain

CI=confidence interval; PACU=post-anesthesia care unit; SD=standard deviation; VAS=Visual Analog Scale