South African National Essential Medicine List Review Process
Adult Hospital Level
Component: Neurology and Palliative Care

MEDICINE REVIEW

1. EXECUTIVE SUMMARY

Date: 18 April 2019
Medicine (INN): Opioid analgesia
Medicine (ATC): N02AA/B/C
ICD10 Code: M79.2
Patient population: Adults presenting with neuropathic pain where *second line treatment has failed*
Prevalence of condition: The prevalence of neuropathic pain in developed countries ranges between 7-8% (11-15). Although there are no published estimates of neuropathic pain in South Africa, it is postulated that the prevalence might be even higher, mainly contributed by the incidence of peripheral neuropathies in HIV.
Summary of results: McNicol et al published an updated review in 2013 for the use of opioid analgesia in neuropathic pain *(see detailed information below)*.
Short-term studies (opioid use for less than 24hours) provided equivocal evidence whilst intermediate-term studies (>24hours use) demonstrated significant efficacy of opioids over placebo; these results are likely to be subject to significant bias because of small sample size, short duration, low event rates, heterogeneity and potentially inadequate handling of dropouts. The overall point estimate of risk difference was 0.25 (95% confidence interval (CI) 0.13 to 0.37, P < 0.0001), translating to a number needed to treat for an additional beneficial outcome (NNTB) of 4.0 (95% CI 2.7 to 7.7). For a 50% reduction in pain the overall point estimate of risk difference between opioids (47%) and placebo (30%) was 0.17 (95% CI 0.02 to 0.33, P = 0.03), translating to an NNTB of 5.9 (3.0 to 50.0).
Constipation was the most common adverse event (34% opioid versus 9% placebo:
number needed to treat for an additional harmful outcome (NNTH) 4.0; 95% CI 3.0 to 5.6), followed by drowsiness (29% opioid versus 14% placebo: NNTH 7.1; 95% CI 4.0 to 33.3), nausea (27% opioid versus 9% placebo: NNTH 6.3; 95% CI 4.0 to 12.5), dizziness (22% opioid versus 8% placebo: NNTH 7.1; 95% CI 5.6 to 10.0), and vomiting (12% opioid versus 4% placebo: NNTH 12.5; 95% CI 6.7 to 100.0).
Level of Care: Secondary level of care
Prescriber level: Medical officers, doctors
Current standard of care: Amitriptyline and/or carbamazepine
PTC Affiliation: PTC East London Hospital Complex
Motivator/reviewer's name: Dr Anastasia Rossouw, Dr Alicia Sheriff

2. Name of author (s)/ motivator (s):

- Dr Anastasia Rossouw
- Dr Alicia Sherriff

3. Author affiliation and conflict of interest details:

Dr Anastasia Rossouw:

- *Affiliation:* Neurology Department, East London Hospital Complex; Adult Hospital Level Committee member
- *Conflict of interests declared:* Honorarium received for workshop training and conference sponsorship received from Boehringer Ingelheim; Honorarium received for workshop training from Sanofi Aventis; Consultant for South African Heart and Stroke Foundation.

Dr Alicia Sherriff:

- *Affiliation:* Oncology Department, University of Free State; Adult Hospital Level Committee member.
- *Conflict of interests declared:* No conflicts of interest declared.

4. Introduction/ Background

The 2011 International Association of the Study of Pain define neuropathic pain as "pain caused by a lesion or disease of the somatosensory system" (Jensen 2011).(1).

In general, the treatment of neuropathic pain is complex and relief is rarely achieved or sustained with any one medication (2). A multidisciplinary approach is now advocated, with pharmacological interventions being combined with physical interventions, cognitive interventions, or both (4).

Opioids are the most effective broad-spectrum analgesics available and are considered the cornerstone of therapy for moderate-to-severe acute pain or pain of similar intensity due to life-threatening illnesses. The use of opioids for neuropathic pain however remains controversial as studies have been small, have yielded equivocal results, and have not established the long term profile of benefits and risks for people with neuropathic pain (3).
Opioids include *opiates,* an older term that refers to such medicines derived from *opium*, including morphine and tramadol itself. Other opioids are *semi-synthetic and synthetic medicines* such as hydrocodone, oxycodone and fentanyl; *antagonist medicines* such as naloxone and endogenous peptides such as the endorphins.

5. Purpose/Objective i.e. PICO question:

-P: Adult patients with neuropathic pain from any origin
-I: Opioids analgesia (various) via various routes of administration
-C: Amitriptyline and/of carbamazepine
-O: Primary outcome: Pain reduction of ≥ 50%
Secondary outcome: side effect profile of medication

***PICO question*:** In adult patients with neuropathic pain, are opioid analgesia (various) administered via many routes, comparable to standard of care (amitriptyline and/or carbamazepine) in terms of efficacy (reduction of at least 50% in pain reduction) and safety?

6. Search strategy

1. **Methods:**

A: Search I:

a. **Data sources:** Cochrane Library
b. **Search terms:** Opioid analgesia AND placebo AND treatment of neuropathic pain

4 Systematic reviews (SRs) –1 included (*Derry et al, 2016)*

B: Search II:

a. **Data sources:** PUBMED
b. **Search strategy A:** ((("analgesics, opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields]) AND ("analgesia"[MeSH Terms] OR "analgesia"[All Fields])) AND ("placebos"[MeSH Terms] OR "placebos"[All Fields] OR "placebo"[All Fields])) AND ("neuralgia"[MeSH Terms] OR "neuralgia"[All Fields] OR ("neuropathic"[All Fields] AND "pain"[All Fields]) OR "neuropathic pain"[All Fields])

55 studies retrieved; 5 SR (*McNicol et al,* 2013 &2017*), (Cooper et al* 2017*), (Duemhe et al* 2016*), (Gaskell et al,* 2016*)* and 1 RCT (*Simpson et al,* 2016*)* retrieved; 49 excluded

6.2 Evidence synthesis

Author, date	Type of study	Population	n	Comparators	Primary outcome	Effect sizes	Quality of evidence (GRADE)
McNicol et al 2013 Updated from 2006 review	SR of 31 RCTs, studying 10 various opioids with use over varying duration, some trials with short term use of less than 24hours whilst those trials of intermediate duration lasted a few days up to 12 weeks	Adults patients with central or peripheral neuropathic pain of varying aetiology	1237	Placebo, or where opioid agonists were compared to each other in varying doses, or compared to another class of medication used for neuropathic pain (e.g. antidepressants) Included studies in which medicines were administered by any of the following routes: oral, rectal, transdermal, intravenous, intramuscular, or subcutaneous.	*Primary outcome:* Efficacy of opioid agonists in producing a 33- 50% reduction in pain from baseline using participant reported measures of pain namely a visual analogue scale (VAS) ranging from 0 -100 or number rating scale (NRS) *Secondary outcome:* Incidence and severity of adverse effects caused by opioid agonists in people with neuropathic pain	17 short-term studies (392 participants) vs 14 intermediate- term studies (845 participants) *Primary outcome:* *Short term studies:* mean difference of -16 (on a 0 - 100 visual analogue scale (VAS)) (95% CI -23 to -9; P < 0.00001). *Intermediate term studies:* 208/367 (57%) receiving an opioid versus 122/360 (34%) of those receiving placebo, reported at least **33% pain relief** [risk difference was 0.25 (95% CI 0.13 to 0.37, P < 0.0001), translating to an NNTB of 4.0 (95% CI 2.7 to 7.7); also significant heterogeneity (P = 0.02, I^2 = 63%)] Participants achieving **50% pain relief**, showed a risk difference of 0.17 (95% CI 0.02 to 0.33, P = 0.03), translating to an NNTB of 5.9 (3.0 to 50.0). *Secondary outcome:* More participants withdrew from opioid treatment due to adverse events (13%) than from placebo (4%) (NNTH 12.5; 95% CI 8.3 to 25.0) Constipation most common adverse events 34% opioid versus 9% placebo: NNTH 4.0; 95% CI 3.0 to 5.6), followed by drowsiness (29% opioid versus 14% placebo: NNTH 7.1; 95% CI 4.0 to 33.3), nausea (27% opioid versus 9% placebo: NNTH 6.3; 95% CI 4.0 to 12.5), dizziness (22% opioid versus 8% placebo: NNTH 7.1; 95% CI 5.6 to 10.0), and vomiting (12% opioid versus 4% placebo: NNTH 12.5; 95% CI 6.7 to 100.0). **See below Figure 2-4**	**Low** most studies were small, most were short, and none used methods known to be unbiased Research questions were well defined – patient population included adults only; primary outcome is an outcome to which the participant makes a contribution. The selection of the primary outcome measures was based on the observation that pain relief tends to be bimodal. The authors allocated a pain score where studies did not report numbers of participants with at least33% or 50% improvement but rather a narrative of symptom improvement Search strategy was comprehensive and selection bias minimised; all language studies included in the analyses. Only reference lists of the reviews were scanned; no grey literature or abstracts or unpublished reports were included. Study flow diagram also included Review methodology, including quality assessment of included RCTs, was performed using two independent reviewers with disagreements resolved through discussion. "Risk of bias" table included: - only half of the studies described methods of randomisation adequately - a 1/3 described allocation concealment sufficiently - 5/17 short term studies and 10/14 intermediate term studies reported on blinding - reporting bias were not assessed

							Random effects model was used to combine data due to marked heterogeneity of the various studies. Heterogeneity assessed appropriately and conflicts of interests were not declared. Funding of study not stated.
McNicol et al 2017	SR of 3 RCTs, cross-over studies ranging from 3- 8 weeks comparing **methadone t**o placebo	Adults patients with central or peripheral neuropathic pain of varying aetiology	105 (55 received Methadone)	Placebo or another active treatment in chronic neuropathic pain (one study included morphine and another tricyclic antidepressants).	*Primary outcome:* Pain reduction of between 30-50%	At least 2 studies reported moderate (30%) reduction in [11/29) with 0/19 reported 50% reduction in pain in one study	**Very low** Two review authors independently considered trials for inclusion in the review, assessed risk of bias, and extracted data. There were insufficient data to perform pooled analyses. Overall quality assessment of the evidence for each outcome was performed using GRADE Several risk of biases, particularly incomplete reporting, selective outcome reporting, and small sample sizes; also studies heterogeneous of varying duration
Cooper et al 2017	SR of 5 RCTs, cross-over studies ranging from 4-7 weeks comparing **morphine t**o placebo	Adults patients with central or peripheral neuropathic pain of varying aetiology	236	Placebo	Primary outcome: Efficacy of pain reduction by 30-50% Secondary outcome: Adverse event rate/profile and patient withdrawals	Only 152 (64%) participants completed all treatment periods Moderate improvement was experienced by 63% (87/138) of participants with morphine and 36% (45/125) with placebo Risk difference (RD) was 0.27 (95% confidence interval (CI) 0.16 to 0.38, fixed-effects analysis) NNT 3.7 (2.6 to 6.5). Adverse events infrequently reported with 2 deaths occurring across the 5 studies	Very low Low risk of bias, but there were concerns over small study size and the imputation method used for participants who withdrew from the studies, both of which could lead to overestimation of treatment benefits and underestimation of harm. Two review authors independently extracted data and assessed trial quality and potential bias. Measures of treatment effect: fixed-effect model
Duehmke et al 2016	SR of 6 RCTs **Tramadol hydrochloride** started at 100mg and increased to 400mg over one to two weeks	Adults patients with central or peripheral neuropathic pain of varying aetiology	436	Placebo	Primary outcome: Efficacy of pain reduction by 30-50% Secondary outcome: Adverse event rate/profile	At least 50% pain intensity reduction was reported in three studies (265 participants, 110 events), RR 2.2 (95% CI 1.02 to 4.6). NNT 4.4 (95% CI 2.9 to 8.8) Reported AEs was higher with tramadol (58%) than placebo (34%) (4 studies, 266 participants, 123 events; RR 1.6 [95% CI 1.2 to 2.1; NNH 4.2 (95% CI 2.8 to 8.3)].	Very Low Small study design of limited duration Measurement of treatment effect conducted on pooled data set due to low event rate Marked heterogeneity between the studies Each study had at least one high risk of potential bias

							Two review authors independently extracted data and assessed trial quality and potential bias
Gaskell et al 2016	SR of 5 included RCTs, two using cross-over design and 3 used parallel group design, **Oxycodone modified release**	Adults patients, 637 with painful diabetic neuropathy and 50 with post herpetic neuralgia	638	Placebo	Primary outcome: Efficacy of pain reduction by 30-50% Secondary outcome: Withdrawals due to adverse event rate/profile	No data available for 50% reduction in pain relief Three studies reported moderate pain relief (30% reduction in pain) 44% vs 27%, RR 1.7 (95% CI 1.3 to 2.1) NNT 5.7 (95% CI 4.0 to 9.9) More AE reported in oxycodone vs placebo (86% vs 63%) group, RR 2.4 (95% CI 1.5 to 4.0) NNH= 4.3	Very low Measurement of treatment effect presented as mean pain scores
Derry et al 2016	One study with initial open-label titration phase, followed by randomisation **Fentanyl (transdermal patch**)	Adult patients, with postherpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain.	258 (titration phase), 163 randomisation	Placebo	Primary outcome: Efficacy of pain reduction by 30-50% Secondary outcome: Withdrawals due to adverse event rate/profile	49/ 84 vs 32/79 participants reported moderate pain relief in both groups. RR and NNT not calculated 14/84 vs 4/79 withdrew due to adverse events	Very low
Simpson et al 2016	Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Trial Transdermal **Buprenorphine**	Adults patients with painful diabetic peripheral neuropathy ,	186	Placebo	Primary outcome: Efficacy of pain reduction by 30-50% Secondary outcome: Withdrawals due to adverse event rate/profile	IIT analysis: 51.7% of patients on Buprenorphine reported a 30 % reduction in pain vs placebo, 41.3%, (OR 1.56, 95% CI 0.82, 2.97; p = 0.175) Per protocol population, 86.3% vs 55.6%, OR 6.88 95% CI 2.20, 21.47; p< 0.001) 37/93 buprenorphine and 24/93 in the placebo group withdrew due to adverse events Nausea, vomiting and constipation were the common adverse events that lead to withdrawal	Measurement of outcomes based on mixed analysis, both ITT and per protocol Patients were randomly allocated by a web based application to active or placebo treatment in equal proportions; no further response on risk of bias management, allocation concealment etc Small numbers Both patient and assessor blinded to therapy

***** Outcomes: Primary [Participant-reported pain relief of 30 to 50% or greater and Patient Global Impression of Change scale (PGIC) much or very much improved], Secondary (Any pain-related outcome indicating some improvement AND withdrawals due to lack of efficacy, adverse events & for any cause AND participants experiencing any adverse event AND participants experiencing any serious adverse event)

Analysis 1.1. Comparison 1 Short-term Efficacy Studies: opioid vs placebo, Outcome 1 Pain intensity post-opioid/placebo.

Review: Opioids for neuropathic pain

Comparison: 1 Short-term Efficacy Studies: opioid vs placebo

Outcome: 1 Pain intensity post-opioid/placebo

Study or subgroup	Opioid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Peripheral Pain							
Kupers 1991 peripheral	8	28 (14)	8	40 (28)		9.6 %	-12.00 [-33.69, 9.69]
Rowbotham 1991	19	33 (33)	19	44 (29)		11.6 %	-11.00 [-30.75, 8.75]
Wu 2002 phantom limb	20	30 (22)	20	46 (22)		24.4 %	-16.00 [-29.64, -2.36]
Wu 2002 stump	22	33 (18)	22	50 (26)		26.0 %	-17.00 [-30.21, -3.79]
Subtotal (95% CI)	**69**		**69**			**71.7 %**	**-15.01 [-22.97, -7.06]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.34$, df = 3 (P = 0.95); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.70 (P = 0.00022)							
2 Central Pain							
Attal 2002	15	33 (23)	15	52 (19)		19.9 %	-19.00 [-34.10, -3.90]
Kupers 1991 central	6	43 (13)	6	58 (26)		8.4 %	-15.00 [-38.26, 8.26]
Subtotal (95% CI)	**21**		**21**			**28.3 %**	**-17.81 [-30.48, -5.15]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.08$, df = 1 (P = 0.78); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.76 (P = 0.0058)							
Total (95% CI)	**90**		**90**			**100.0 %**	**-15.81 [-22.54, -9.07]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.55$, df = 5 (P = 0.99); $I^2 = 0.0\%$							
Test for overall effect: Z = 4.60 (P < 0.00001)							
Test for subgroup differences: $Chi^2 = 0.13$, df = 1 (P = 0.71), $I^2 = 0.0\%$							

Figure 2. Short term efficacy for patients reporting pain relief from baseline for four studies (data available for meta-analysis)

Analysis 2.1. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 1 Number of participants with at least 33% pain relief.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 1 Number of participants with at least 33% pain relief

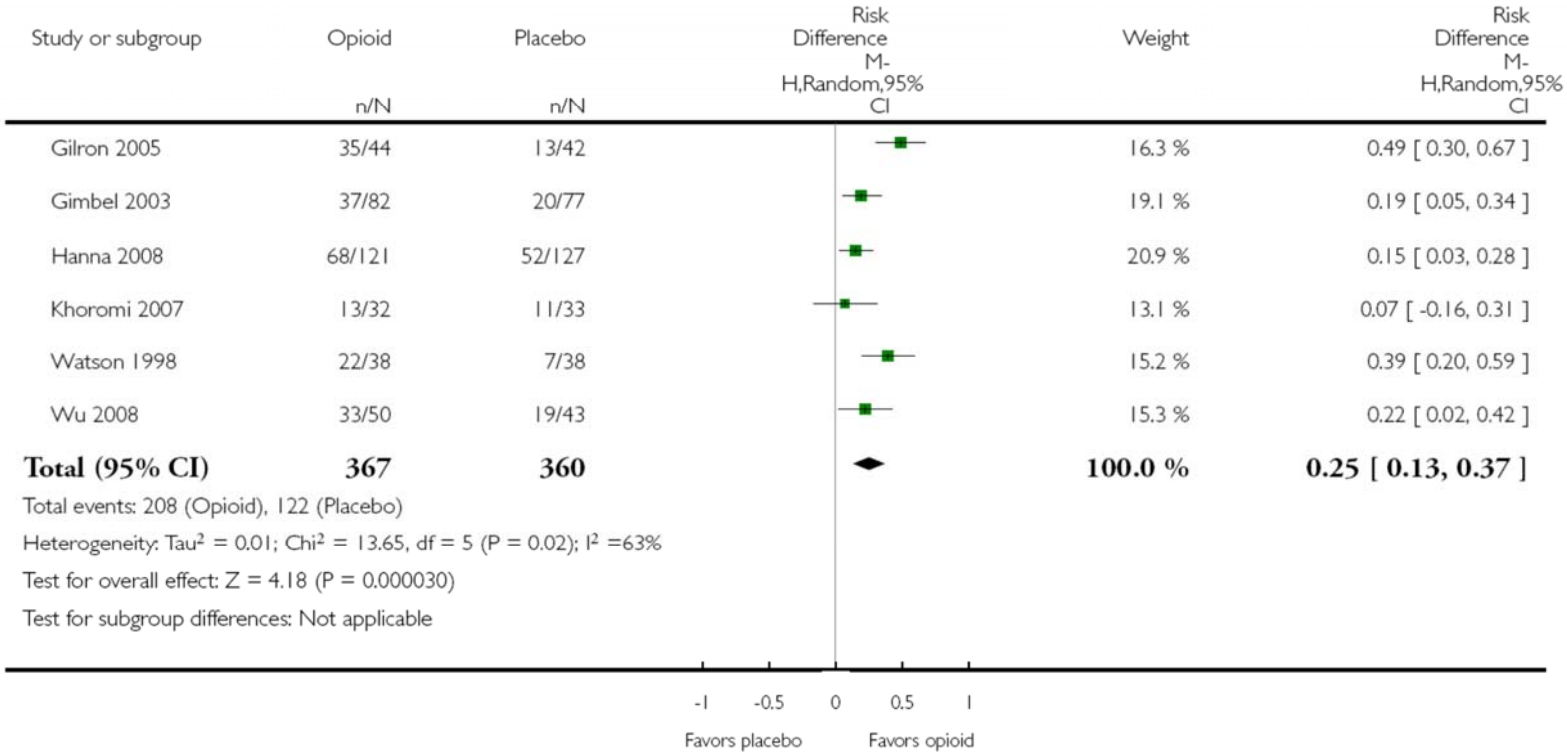

Figure 3: Intermediate term efficacy for patients reporting a 33% reduction in pain intensity from baseline (3)

Analysis 2.2. Comparison 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 2 Number of participants with at least 50% pain relief.

Review: Opioids for neuropathic pain

Comparison: 2 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 2 Number of participants with at least 50% pain relief

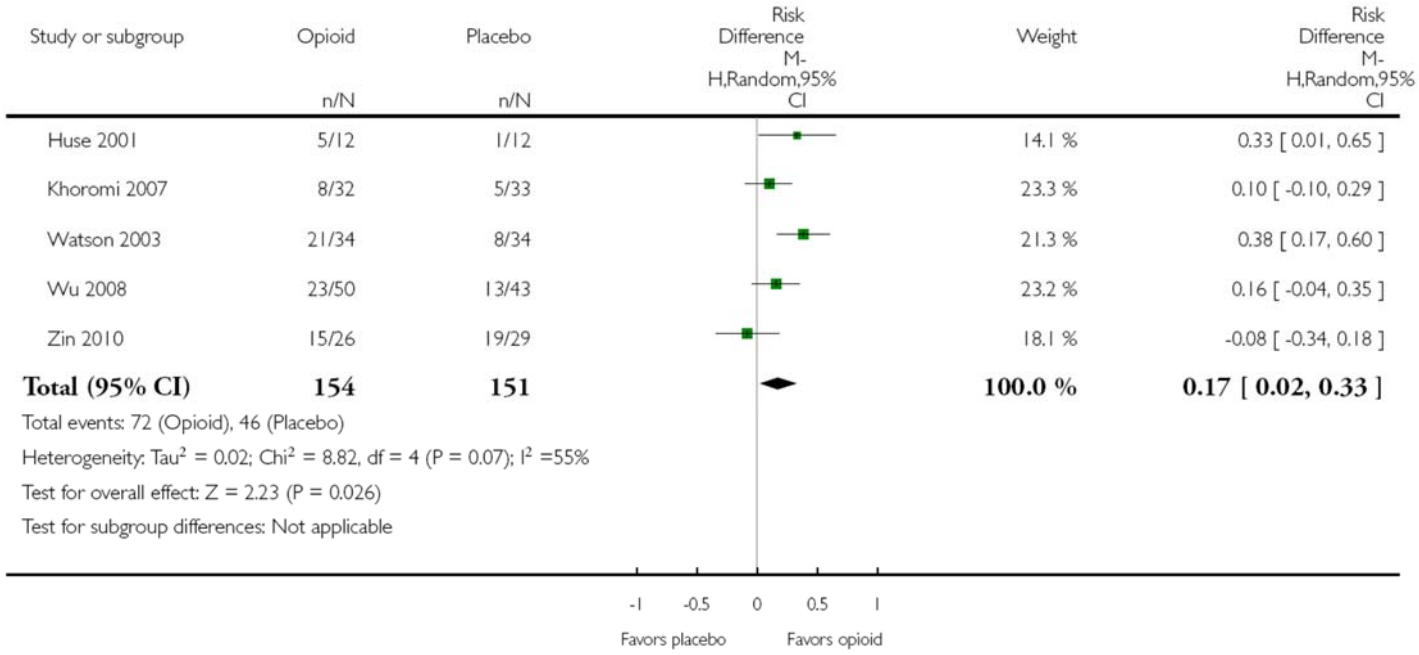

Figure 4. Intermediate term efficacy for patients reporting a 50% reduction in pain intensity from baseline (3)

Amstar checklist*

1. Was an 'a priori' design provided?	not all studies **
2. Was there duplicate study selection and data extraction?	yes
3. Was a comprehensive literature search performed?	yes
4. Was the status of publication (i.e. grey literature) used as an inclusion criteria?	yes
5. Was a list of studies (included and excluded) provided?	yes
6. Were the characteristics of the included studies provided?	yes
7. Was the scientific quality of the included studies assessed and documented?	yes
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	yes
9. Were the methods used to combine the findings of studies appropriate?	yes - random effect model
10. Was the likelihood of publication bias assessed?	no
11. Was the conflict of interests included?	yes

*AMSTAR Checklist performed on all Cochrane Reviews (16-20)

** "a priori" study design was not possible in some studies, as despite an outcome of "50% reduction in pain" some interventions did not achieve this and the measured effect was reduced to a "30% reduction in pain"

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [ ] Not confident [x] Uncertain [ ]	Quality of evidence: very low
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [ ] Harms outweigh benefits [x] Benefits = harms or Uncertain [ ]	
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [x]	Cost of medicines: **Medicine** / **ZAR** Morphine 10mg slow release tab, 60 — 625.11* Morphine 30mg slow release tab, 60 — 974.39* Morphine 60mg slow release tab, 60 — 1494.01* Morphine 100mg slow release tab, 60 — 2153.43* Morphine 10mg/ml inj, 1ml — 3.57** Morphine 15mg/ml inj, 1ml — 3.67** Methadone 2mg/ml, syrup, 60ml — 159.65* Fentanyl 25mcg/h, patches, 5 — 584.40* Fentanyl 50mcg/h, patches,5 — 916.34* Oxycodone 5mg caps, 30 — 290.68* Oxycodone 10mg caps, 30 — 441.59* Oxycodone 20mg caps, 30 — 530.39* Tramadol oral, 50mg caps, 100 — 34.64* *SEP database, accessed 30 June 2019 (cheapest generic, where available) ** Contract circular RT289-2019 (weighted average prices) **Additional resources:** n/a
EQUITY	**Would there be an impact on health inequity?** Yes [x] No [ ] Uncertain [ ]	

FEASIBILITY	Is the implementation of this recommendation feasible?	
	Yes [ ] No [x] Uncertain [ ]	

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	[X]	[ ]	[ ]	[ ]	[ ]

Recommendation: Based on the appraisal of the evidence presented in this technical review, the Adult Hospital Level Committee does not recommend the use of opioid analgesia for the treatment of long-term neuropathic pain.
Rationale: Limited evidence of clinical efficacy (defined as 50% pain reduction) (7).
Level of Evidence: II Systematic review of low quality RCTs

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	[ ]	[ ]

VEN status: n/a

Vital	Essential	Necessary
[ ]	[ ]	[ ]

NEMLC MEETING OF 11 JULY 2019:
NEMLC accepted the proposed recommendation not to the use of opioid analgesia for the treatment of long-term neuropathic pain.

Monitoring and evaluation considerations:

Research priorities: Larger RCTs are needed to confirm the efficacy of opioid analgesia in the treatment of neuropathic pain.

References:

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