**Appendix L: Primary and Secondary Outcomes for Drugs with <5 Studies**

**Acetaminophen**: Results were not pooled for the two studies that evaluated acetaminophen due to heterogeneity of duration of administration and surgical procedure. One study administered 4 doses of 1g of IV acetaminophen every 6 hours for 24 hours for cardiac surgery and concluded no reduction in intensity or incidence of pain 90 days after surgery.1 The second study administered 1g of IV acetaminophen every 6 hours for 3 days after hysterectomy and found that acetaminophen patients were over 2 times more likely to rate a lower pain score than saline patients 3 months post-surgery (95% CI: 1.33-3.59).2

**Amantadine**: Results were not pooled for the 2 studies that evaluated amantadine; 1 study provided prevalence of any pain at 3 and 6 months’ post breast cancer surgery concluded that amantadine does not prevent the development of postmastectomy pain syndrome;3 the other reported pain intensity using a 0-10 pain intensity scale after mandibular fracture surgery found amantadine did not reduce chronic pain 6 months post-surgery.4

**Dexmedetomidine**: 1 study evaluated dexmedetomidine and found the incidence of chronic post hysterectomy pain at 2, 6 and 12 months post-surgery was significantly lower in the intervention group compared to placebo (13.9%, 5.6%, 2.8% in the Dex group versus 30.3%, 24.2%, 18.2% in the placebo group, respectively (P < 0.05)).5

**Dextromethorphan**: 1 study that evaluated dextromethorphan reported median scores for pain detection thresholds using von Frey stimulation 3 months after abdominal hysterectomy concluded no prolonged effects on pain or wound hyperalgesia.6

**Duloxetine**: Results were not pooled for the 2 studies that evaluated duloxetine; 1 study reported mean “worst pain” scores 3 months after total knee arthroplasty, and pain prevalence data was obtained from the authors: worst pain at 3 months NRS>0: 34 (72.3%) duloxetine group and 35 (71.4) placebo group; NRS ≥4: 10 (21.3%) duloxetine group and 9 (18.4%) placebo group.7 The other study reporting mean pain measures using the Brief Pain Inventory (BPI) and SF-36 pain subscale 3 months after spine neurosurgery concluded that duloxetine seems to improve pain.8 Drop-outs due to treatment-related adverse effects were reported in 1 study for patients undergoing spine neurosurgery; 3 patients in the duloxetine arm and 2 in the placebo arm due to “perceived problems with the medication". No further details were provided.8

**Etanercept**: 1 study evaluated a single dose of etanercept and provided dichotomous results for any pain and moderate/severe pain at 3, 6 and 12 months after unilateral inguinal hernia repair and found no significant differences in the prevalence of pain at any of the time-points.9

**Fentanyl**: 1 study evaluated fentanyl as part of a five-arm study comparing standard regimens of preoperative, intraoperative and postoperative analgesia using PCA or epidural analgesia.10 The study concluded that optimized analgesia with an epidural opioid or PCA started 48 hours before surgery and continuing for 48 hours decreases phantom limb pain at 6 months.

**Magnesium**: 1 study evaluated magnesium as part of a 3-arm trial that also evaluated IV lidocaine. Chronic pain was measured with the Korean version of the McGill Pain Questionnaire (KSF-MPQ) and prevalence of any pain at 3 months was not significantly different between groups (8 (21.1%) in the magnesium group versus 14 (35.9%) in the placebo group (p>0.05)).11

**Memantine**: 1 study found that memantine significantly improved phantom limb pain 6 months post traumatic amputation however, concluded no long-term benefit given no significant reduction was observed at the 12 month follow up.12

**Mexiletine**: 2 studies that evaluated mexiletine provided prevalence of any pain 3 months after breast cancer surgery.13,14 Subgroup analyses based on duration of treatment longer than 24 hours resulted in a non-significant effect of mexiletine compared to placebo (2 trials; RR 0.96, 95% CI 0.68-1.35) (Figure 5). Drop-outs due to treatment-related adverse effects occurred in 2/46 (4.3%) patients who received mexiletine and 0/49 (0.0%) who received placebo. Adverse events included nausea and vomiting.

**Analysis 7.1. Mexiletine versus placebo comparisons, prevalence of any pain at 3 months (drug administration > 24 hours)**

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**Minocycline**: Results were not pooled for the 2 studies evaluating minocycline due to heterogeneity of outcome measurement. One study concluded that perioperative minocycline administration for 8 days does not improve persistent pain 3 months after lumbar discectomy.15 The second study reported that minocycline does not reduce time to pain resolution after carpal tunnel surgery.16 Drop-outs due to treatment-related adverse effects occurred in 4/110 (3.6%) patients who received minocycline and 3/106 (2.8%) who received placebo. Adverse events included headache, stomach ache, nausea, and dizziness.

**Nefopam**: Results were not pooled for the 4 studies that evaluated nefopam.17-20 One study reported continuous data using median Neuropathic Pain Symptom Inventory (NPSI) scores 3 months after spine surgery and concluded that nefopam significantly reduced the neuropathic

pain at 1 month post-surgery, however results were not significant 3 months post-surgery.19 Another study reported continuous data using median and interquartile ranges for the verbal numerical rating scale (VNRS 0-100) and concluded that nefopam effectively reduced chronic pain and discomfort 3 months after thyroidectomy without adverse effects.20 Two studies provided pain prevalence data, however results were not pooled due to heterogeneity of the timing of outcome measurement; 1 study reported a significant difference in the prevalence of any pain 3 months after breast surgery (15 (36.6%) in the nefopam group versus 25 (59.5%) in the placebo group (p=0.04)),18 while the other study reported no significant differences in the prevalence of any pain and moderate/severe pain 6 and 12 months after total knee arthroplasty.17

**Nitrous oxide**: Results were not pooled for the 2 studies that evaluated nitrous oxide due to heterogeneity of the timing of outcome measurement post-surgery; 1 study collected any pain 12 months after surgery and concluded no impact of nitrous oxide on CPSP, while the median time to follow-up in the other study was 4.5 years and reported a significant difference in pain specific to the wound site that had persisted since surgery (15/214 (7.0%) patients in the nitrous oxide group and 31/209 (14.8%) patients in the control group (OR = 0.43, 95% CI = 0.23–0.83, P = .01).21

**Valproic acid**: 1 study evaluated valproic acid provided pain prevalence results (≥3/10) 3 months after amputation or amputation revision surgery and found no significant difference: 36/55 in the valproic acid group versus 37/52 in the placebo group.22

**Venlafaxine**: 1 study evaluated venlafaxine and reported continuous outcomes using a 0-10 pain intensity scale and collected data on chronic pain descriptors (i.e. throbbing, aching, tender) and concluded that venlafaxine significantly reduced the incidence of chronic pain 6 months after breast cancer surgery.23

**Vitamin C**: 1 study evaluated Vitamin C and reported continuous outcomes using visual analogue scale (VAS), at 1, 3, 6 months, and 1 year and found no significant difference between groups 1 year after posterior lumbar interbody fusion.24

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