A META-ANALYSIS OF GABAPENTIN AND MULTIMODAL ANALGESICS

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Abstract

Multimodal analgesia has been proposed as a useful strategy to reduce postoperative pain while decreasing opioid consumption and thus opioid adverse events. Gabapentin is one such agent although previous results have been heterogeneous. This thesis aimed to review randomised controlled trials of gabapentin for reducing pain, opioid adverse effects and the haemodynamic response to intubation while attempted to predict clinical effectiveness from these trials using meta-regression. Extending this principle, we evaluated other multimodal analgesic agents to identify whether heterogeneity could be explained by various clinical and methodological covariates.

Our gabapentin review included 133 randomised controlled trials and demonstrated its efficacy in reducing pain scores, opioid consumption and opioid adverse events such as nausea, vomiting and pruritus. However, gabapentin increased the risk of sedation. Gabapentin was effective at reducing the haemodynamic response to intubation in 29 randomised controlled trials although trials failed to report on clinically relevant outcomes. Gabapentin exhibited no pre-emptive analgesic effect in 4 randomised controlled trials.

There was evidence of considerable statistical heterogeneity on meta-analysis of gabapentin for pain scores and 24-hour morphine consumption. Meta-regression analysis showed however that baseline risk predicted the majority of the heterogeneity between studies. Extending this approach to other multimodal analgesics from 344 randomised controlled trials; we demonstrated this was true for analgesic agents in general. In addition to baseline risk, methodological limitations, especially inadequate allocation concealment, explained some of the residual heterogeneity.

There was evidence of funnel plot asymmetry for most analgesic agents, suggesting publication bias. However, this may be a product of trials with higher baseline risk having larger standard errors, rather than true publication bias. Indeed, when we simulated meta-analyses with no publication bias, with both effect size and standard deviations dependent on baseline risk, funnel plot

asymmetry was still evident ($p<0.001$). Therefore, conventional funnel plots may be an unsuitable method of detecting publication bias where baseline risk predicts between-study heterogeneity. We present an alternative method using meta-regression residuals that corrects funnel plot asymmetry in the presence of no publication bias.

Finally, due to concerns that methodological limitations exaggerated effect estimates, we used trial sequential analysis to determine whether sufficient low risk of bias evidence exists to reject type I and type II errors in the analyses of analgesic adjuncts. We demonstrated there is currently insufficient evidence from low risk of bias trials to be confident of the efficacy of the majority of analgesic adjuncts.

Publications and presentations arising from this thesis

Publications

Doleman B, Heinink TP, Read DJ, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia* 2015; 70: 1186-1204 (*Article*).

Doleman B, Sherwin M, Lund JN, Williams JP. Gabapentin for the hemodynamic response to intubation: systematic review and meta-analysis. *Canadian Journal of Anesthesia* 2016; 63: 1042-1058 (*Article*).

Doleman B, Lund JN, Williams JP. Misuse of 'trend' to describe 'almost significant' differences in anaesthesia research. *British Journal of Anaesthesia* 2016; 116(6); 891-892 (*Letter*)

Doleman B, Lund JN, Williams JP. Preemptive versus postincision gabapentin for postoperative pain: systematic review and meta-analysis. *Global Anesthesia and Perioperative Medicine* 2016; doi: 10.15761/GAPM.1000150 (*Article*)

Doleman B, Williams JP. Patient controlled analgesia: effective and cost-effective management of acute pain within the Emergency Department? *Anaesthesia* 2017 [in press] (*Editorial*)

Presentations

Doleman B, Faleiro R, Williams JP. Preoperative gabapentin for postoperative pain in orthopaedic surgery: systematic review, meta-analysis and meta-regression. *Anaesthesia* 2015; 70(S2): 28 (*Poster Presentation*).

Prizes

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Abbreviations

AMED: Allied and Complementary Medicine Database

ASA: American Society of Anesthesiologists

bpm: beats per minute

CABG: coronary artery bypass graft

CENTRAL: Cochrane Central Register of Controlled Trials

CI: confidence intervals

CINAHL: The Cumulative Index to Nursing and Allied Health

COX: cyclooxygenase

DBP: diastolic blood pressure

ECG: electrocardiogram

ENT: ear nose and throat

GABA: gamma-aminobutyric acid

GRADE: The Grades of Recommendation, Assessment, Development and Evaluation Working Group

HR: heart rate

IS: information size

ISRCTN: International Standard Register Clinical/Social Study Number

kg: kilogram

MAP: mean arterial blood pressure

MD: mean difference

MeSH: medical subject heading

mg: milligrams

NSAIDS: non-steroidal anti-inflammatory drugs

OIH: opioid-induced hyperalgesia

OR: odds ratio

PCA: patient controlled analgesia

POISE: PeriOperative ISchemic Evaluation

PONV: postoperative nausea and vomiting

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses

PROSPERO: The International Prospective Register of Systematic Reviews

RCT: randomised controlled trial

RR: risk ratio

RRR: relative risk reduction

SBP: systolic blood pressure

SD: standard deviation

SE: standard error

SMD: standardised mean differences

TSA: trial sequential analysis

TURP: transurethral resection of prostate

US: United States of America

VAS: visual analogue scale

VIF: variance inflation factor

WHO: World Health Organisation

Overview

This thesis presents an overview of the peri-operative use of gabapentin and other multimodal analgesic adjuncts. Gabapentin has emerged as a versatile agent for reducing various negative consequences associated with anaesthesia and surgery. A wealth of clinical trials have been published over the last decade that demonstrate the benefit of gabapentin. The thesis begins with chapter one, which presents a narrative review of the many negative consequences of surgery and anaesthesia, justifying the study of these outcomes within this thesis. The second part of the chapter discusses gabapentin, providing a narrative review of its pharmacology and adverse effects. Reference will be made to both animal and human studies conducted on gabapentin to help elucidate its biological mechanisms in relation to pain management and reductions in the stress responses to endotracheal intubation. Following this, current meta-analyses in the area of gabapentin for postoperative pain will be discussed and their limitations highlighted. This chapter will conclude with a discussion of various meta-analytic techniques that aim to investigate heterogeneity between study results, identify potential publication bias and reduce type I and type II errors in analysis.

Chapter two presents the first systematic review and meta-analysis conducted on gabapentin, which focuses on the core outcomes of acute and chronic postoperative pain while addressing the limitations of those published previously. Moreover, this chapter will present the novel use of a meta-regression model to help predict the efficacy of gabapentin under different clinical conditions. Chapter three will build on the first meta-analysis by evaluating the use of gabapentin for other important peri-operative outcomes such as postoperative opioid side effects and gabapentin adverse effects. This chapter will also extend the use of the meta-regression model to evaluate whether gabapentin adverse effects are dose-dependent.

Chapter four examines whether gabapentin exhibits any pre-emptive analgesic effect by including trials that directly compared pre-operative with post-incision administration. Chapter five examines whether gabapentin has an

effect for attenuating the haemodynamic response to endotracheal intubation and whether this in turn can reduce postoperative myocardial events and mortality in high-risk patients.

Chapter six extends the meta-regression techniques used in chapter two to other analgesic adjuncts. It examines the prevalence of statistical heterogeneity and if present, uses meta-regression analysis to investigate clinical and methodological covariates as sources of heterogeneity. Furthermore, Bayesian analysis of baseline risk will be used to reduce the bias present in traditional, naive analysis. Ultimately, this chapter will argue the more appropriate use of meta-regression to present results from meta-analyses of analgesic adjuncts while also outlining other important implications for clinical practice, primary and secondary research studies.

Chapter seven examines publication bias in analgesic adjuncts and argues that for the outcome of morphine consumption, funnel plots may be an unsuitable method for highlighting potential publication bias due to correlation between baseline risk and standard errors. Furthermore, we present a novel method to overcome this correlation and demonstrate it using simulated meta-analyses with no publication bias present. Chapter eight will utilise trial sequential analysis, which is a method analogous to sample size calculations for primary research studies to help reduce type I and type II errors in meta-analyses. We use this analysis to examine whether sufficient low risk of bias evidence exists for analgesic adjuncts. The thesis concludes with chapter nine, which will summarise and discuss the results of the preceding chapters.

Chapter 1

Background and methodology

Background literature

1.1 Postoperative pain

Postoperative pain is a common consequence of surgery with an incidence of around 80%. In one US survey of 250 patients, 39% of patients with postoperative pain experienced severe or extreme pain (Apfelbaum *et al.* 2003). In another European survey of 1490 patients, 41% reported moderate or severe pain after surgery (Sommer *et al.* 2008). Pain is cited as one of the main concerns of patients undergoing surgical procedures (59%) (Apfelbaum *et al.* 2003). In patients who do receive analgesia in the postoperative period, 23% of patients suffer adverse effects such as drowsiness, nausea and constipation, usually as a result of opioid medication (Apfelbaum *et al.* 2003). Indeed, 72% of patients would choose non-opioid analgesia owing to concerns over adverse effects and potential addiction. Despite this, 88% of patients remain satisfied with their analgesia postoperatively and the incidence of moderate to severe pain has decreased over the last few decades (Dolin *et al.* 2002).

The use of opioids following surgery is prevalent. In one large European survey of medical practitioners involving 1558 respondents (Benhamou *et al.* 2008), over half of patients undergoing major surgery were treated with intravenous opioids within the first 24-hours postoperatively (52-57%). Patient controlled analgesia (PCA) with opioids was used in approximately half of patients undergoing abdominal, orthopaedic and gynaecological surgeries. As the results of these surveys suggest, postoperative pain is currently often inadequately controlled in the postoperative population. Intravenous opioids continue to be used in a large proportion of patients, despite patient concerns over side effects and addiction. In order to improve postoperative pain management, a variety of solutions have been proposed (White and Kehlet 2010). Amongst these solutions is the use of multimodal analgesia using non-opioid based medication, which has now become the gold standard. A move towards multimodal analgesia is reflected by >75% of respondents reporting its use following both minor and major surgery (Benhamou *et al.* 2008). Multimodal analgesia relies upon the use of various analgesics from a variety of drug classes which aims to target multiple mechanisms of pain and therefore

provide synergistic analgesic activity, reducing opioid use and associated adverse effects (Assouline *et al.* 2016; Doleman *et al.* 2015a).

The consequences of postoperative pain are not limited to negative psychological effects for the patient. Detrimental physiological sequelae can result from postoperative pain, which may lead to negative postoperative outcomes. Postoperative pain is associated with increases in postoperative delirium (Vaurio *et al.* 2006), pulmonary complications (Desai 1999) and increases in the stress response to surgery (Desborough 2000). Furthermore, postoperative pain can negatively affect the patient experience. Pain can interfere with general activities such as walking and sleeping while also negatively affecting mood (Strassels, Chen and Carr 2002). One large survey of 10,000 patients in Australia found moderate or severe postoperative pain was associated with patient dissatisfaction (odds ratio (OR) 3.94; 95% confidence interval (CI) 3.16 to 4.91) (Myles *et al.* 2000). However, evidence is currently lacking with regards to any form of analgesia reducing postoperative mortality or morbidity (Liu and Wu 2007). A previous large randomised controlled trial (RCT) has concluded no benefit in terms of mortality and major morbidity (beyond respiratory failure) with the use of epidural anaesthesia (Rigg *et al.* 2002). Conversely, previous meta-analyses have found the use of epidural analgesia may reduce mortality (Landoni *et al.* 2015; Rodgers *et al.* 2000) and myocardial infarction (Beattie, Badner and Choi 2001).

The effects of postoperative pain are not limited to the immediate postoperative period. Indeed, acute postoperative pain is associated with the development of chronic pain in 10-50% of patients, with incidence dependent on the type of surgery (Kehlet, Jensen and Woolf 2006). Of those patients experiencing chronic pain, it will be severe in around 10% of patients, with a relationship between increased acute postoperative pain levels and subsequent risk of chronic pain. This chronic pain may mimic neuropathic pain and therefore, damage to nerves during surgery is thought to mediate this process. Similar to preventative measures for acute postoperative pain, less invasive surgical

techniques and multimodal pre-emptive or preventive analgesia are all thought to have a role in reducing the incidence of chronic postoperative pain.

As discussed previously, postoperative pain is prevalent and potentially undermanaged. However, pain varies greatly between individuals and therefore many previous studies have examined whether particular patient characteristics can predict postoperative pain. This may help better target multimodal therapies and also explain varying results from previous trials with these therapies. A systematic review was conducted to identify independent predictors of postoperative pain (Ip *et al.* 2009). These factors included the presence of pre-operative pain, higher levels of pre-operative anxiety and the type of surgery performed. In addition, younger patients were found to experience higher levels of pain and have higher postoperative analgesic requirements. Both existing pain and reduced pain tolerance were found to increase postoperative pain. Open abdominal surgery, orthopaedic surgery and thoracic surgery were the types of surgery most likely to lead to increased postoperative pain. Longer duration of surgery was also cited as a further predictive factor. There were conflicting results when focussing on the influence of gender on postoperative pain.

These predictors have previously been incorporated into a pre-operative risk score to identify patients at high-risk of severe postoperative pain (Kalkman *et al.* 2003). Multivariate logistic regression was used to identify independent predictors of severe postoperative pain (defined as numeric rating score of >8/10 within the first hour postoperatively, which had an incidence of 26%). The factors identified were patients of a younger age, female gender, increased severity of pre-operative pain, larger incision size and type of surgery. With abdominal procedures causing the most pain, followed by orthopaedic, laparoscopy then ophthalmological procedures. Clearly, identification of patients at risk of severe postoperative pain could help inform postoperative analgesic strategies and target intensive therapies at those at the highest risk.

In summary, severe pain is prevalent in the postoperative period and continues to be under-managed. Such pain has negative physiological and psychological consequences for the patient. Current opioid-based analgesics are associated with patient concerns and therefore multimodal analgesia represents a viable adjunct to postoperative pain management.

1.2 Pre-operative anxiety and complications of opioid analgesia

1.2.1 Pre-operative anxiety

In addition to pain arising as a consequence of surgical injury, surgery itself in conjunction with anaesthetic agents and opioid analgesia are associated with complications for the patient. Prior to surgery, patients may suffer from anxiety. In one study of around 700 patients, the mean score for pre-operative anxiety was 30/100mm on a visual analogue scale (VAS). Predictors for anxiety included younger patients, female sex and a previous negative experience of surgery (Kindler *et al.* 2000). In addition to the distressing psychological nature of this anxiety, such anxiety is associated with postoperative pain (Ip *et al.* 2009) and lower patient satisfaction (Kindler *et al*. 2000).

1.2.2 Opioid adverse events

As previously discussed, opioid use is widespread in postoperative pain management. However, the use of opioids is associated with patient concerns over side effects and addiction (Apfelbaum *et al.* 2003). Opioid adverse events have been associated with increases in postoperative hospital costs and length of stay in two observational studies (Oderda *et al.* 2003; Oderda *et al.* 2007).

1.2.3 Postoperative nausea and vomiting

Postoperative nausea and vomiting (PONV) is common following surgery, with an incidence of around 25% for nausea and 20% for vomiting (Cohen *et al.* 1994). Risk factors include female sex, previous history of motion sickness or PONV, non-smokers and the use of peri-operative opioids (Koivuranta *et al.*

1997; Roberts *et al.* 2005). If all four factors were present, this resulted in an incidence of 79% for PONV (Apfel *et al.* 1999). Additional factors may also be involved, including age, obesity, anxiety and the type of surgical procedure (Watcha and White 1992). Postoperative nausea and vomiting has many negative effects including hospital readmission, increased recovery time, increased healthcare costs and patient dissatisfaction (Gan *et al.* 2003). Indeed, patients have cited postoperative vomiting as the most undesirable outcome of anaesthesia, ranking this above postoperative pain and sedation (Macario *et al.* 1999). Despite this, expert guidelines do not advocate the routine use of prophylactic anti-emetics for all patients (Gan *et al*. 2003). Therefore, treatment may be best targeted to those at highest risk.

1.2.4 Postoperative delirium

Postoperative opioid use can cause more direct adverse events during the postoperative period. A particular problem in the elderly population is postoperative delirium, which has an incidence of 46% in patients aged over 65 years (Vaurio *et al.* 2006). In addition to postoperative pain, the use of postoperative oral opioids reduced the odds of postoperative delirium when compared with intravenous PCA opioids (OR 0.40; 95% CI 0.20 to 0.70). However, one review found that only pethidine was consistently associated with postoperative delirium (Fong, Sands and Leung 2006). Postoperative delirium can lead to negative outcomes including increased morbidity, delayed functional recovery and increases in hospital length of stay (Parikh and Chung 1995).

1.2.5 Urinary retention

Urinary retention is common following surgery and anaesthesia, with an incidence ranging between 5 and 70% (Baldini *et al.* 2009). The use of systemic opioids have a direct and dose-dependent effect on the incidence of postoperative urinary retention. Furthermore, route of opioid administration is a further risk factor, with intravenous PCA opioids increasing the risk above intramuscular opioids. Moreover, the use of opioid-sparing analgesics is

associated with reductions in the incidence of postoperative urinary retention. This has important clinical implications, as urinary retention is associated with other postoperative complications such as increased parasympathetic activity (bradycardia, hypotension and vomiting), urinary tract infection and chronic bladder dysfunction (Baldini *et al*. 2009).

1.2.6 Respiratory depression

Postoperative respiratory depression has an incidence of 1.2% in opioid-treated patients (Shapiro *et al.* 2005). Although less common than other adverse events, respiratory depression represents an important challenge in opioid-treated patients as it may lead to fatal outcomes (Dahan, Aarts and Smith 2010). Reasons cited for respiratory depression following the use of opioid PCA devices includes drug interactions, dose escalation and inappropriate patient use (Looi-Lyons *et al.* 1996). Therefore, any peri-operative agent that can reduce postoperative opioid requirements may help reduce the incidence of this potentially fatal consequence of opioid treatment.

1.2.7 Pruritus

Postoperative pruritus is another common consequence of opioid treatment, mediated via histamine release from mast cells (Waxler *et al.* 2005). Following opioid administration, incidence is variable (Kam and Tan 1996) with a possible dose-dependent effect. Such symptoms are unpleasant for patients and reduction of pruritus postoperatively may improve patient satisfaction (Waxler *et al*. 2005). Pruritus can cause significant distress to the patient and the management of established pruritus is challenging (Kam and Tan 1996). Therefore, any routine analgesic agent that can reduce the incidence of pruritus represents a useful option to the anaesthetist in clinical practice.

1.2.8 Constipation

Opioid-induced constipation is a consequence of direct effects on opioid receptors in the gastro-intestinal tract. It can result in significant discomfort for

the patient and cause discontinuation of opioid treatment postoperatively, which in turn can negatively affect pain management (Pappagalio 2001). Moreover, other complications may result such as faecal impaction, pseudo-obstruction, decreased drug absorption, increased length of stay, increased healthcare costs and increases in pain over that of the surgical injury (Pappagalio 2001). During opioid dose escalation, constipation symptoms may increase (Klepstad *et al.* 2000); suggesting reducing the doses of postoperative opioids may reduce the incidence of constipation and improve patient discomfort. Although treatment for opioid-induced constipation is available such as non-pharmacological methods (mobilisation and adequate fluid intake) and laxatives, these agents may not effectively target the mechanisms of opioid-induced constipation, producing therapy that is sub-optimal (Pappagalio 2001). Alternatives such as the opioid antagonist methylnaltrexone are available (Bates, Foss and Murphy 2004), however costs may limit its use in clinical practice. Therefore, other potential treatments for opioid-induced constipation that limit opioid dosages would be welcomed.

1.2.9 Opioid-induced hyperalgesia

The use of peri-operative opioids have other associated sequelae, which is not limited to adverse events. Paradoxically, higher doses of intra-operative opioids have been associated with an increase in pain and hyperalgesia during the postoperative period. This phenomenon is termed opioid-induced hyperalgesia (OIH). A systematic review of clinical trials found evidence of increased postoperative opioid consumption in patients who received higher doses of intra-operative opioids (Angst and Clarke 2006). In the same review, human volunteer studies have provided direct evidence of OIH in pre-existing hyperalgesia and cold pressor pain tests. A more recent meta-analysis of clinical RCTs has shown higher doses of intra-operative opioids increased postoperative pain at one hour on a 100mm VAS (mean difference (MD) 9.4mm; 95% CI 4.4mm to 14.5mm) and increased 24-hour morphine consumption (standardised mean difference (SMD) 0.70; 95% CI 0.37 to 1.02) (Fletcher and Martinez 2014). These results suggest opioid use may in fact exacerbate postoperative pain through mechanisms of hyperalgesia.

1.2.10 Immune function

Opioid use may also be associated with immune dysfunction. In healthy volunteers, administration of morphine at therapeutic levels can suppress natural killer cell cytotoxicity (Yeager *et al.* 1995). These findings have been replicated in clinical studies that enrolled postoperative participants, with higher doses of fentanyl causing prolonged suppression of natural killer cell cytotoxicity (Beilin *et al.* 1996). Mechanisms for such immune suppression are yet to be fully elucidated; although a direct effect on immune cells via classic opioid receptors seems unlikely (Williams *et al.* 2007). Other mechanisms may be implicated, such as neuro-endocrine systems and non-classical opioid receptors (Al-Hashimi *et al.* 2013). Further studies are required to evaluate whether such immune suppression translates into increases in postoperative infections. Moreover, whether the use of multimodal analgesic agents can reduce the incidence of postoperative infections through reductions in opioid requirements.

1.2.11 Addiction

Addiction is a common concern for patients who are treated with postoperative opioids (Apfelbaum *et al*. 2003). Although continuation of opioid medication following surgery should correlate with continuing pain, one cohort study contradicted this expectation (Carroll *et al.* 2012). Using a sample of 134 postoperative patients, 6% were still using opioids at 150 days (the number of these patients in pain was not reported). This study calculated that using these figures, postoperative opioid use would contribute 1.1 million new users of opioids in the United States (US) each year. Using a multivariate Cox regression model, pre-operative opioid use, self-perceived risk of addiction and depressive symptoms better predicted the continued use of opioids when compared with postoperative pain intensity and duration. However, data is limited as to whether this prolonged use translated into longer-term addictive opioid use. Future studies may wish to follow participants for a longer duration to identify if this continued opioid use increases the number requiring treatment for opioid addiction. Despite this, this study does implicate

psychological factors as the most important determinants of prolonged opioid use when compared to pain-related factors. This further highlights the need to reduce peri-operative opioid use and the effects this could have on longer-term outcomes.

1.2.12 Summary

In summary, the negative consequences of both surgery and anaesthesia are diverse. Pain and vomiting are those feared most by patients and represent ideal targets to improve the patient experience. However, the continued widespread use of opioids may further exacerbate postoperative pain and vomiting, as well as having many other negative consequences. Therefore, alternative strategies are required for postoperative pain management that aim to limit the use of opioid medication and help improve patient outcomes.

1.3 Pre-emptive analgesia

The process of surgical injury can cause secondary changes in the central nervous system, which may lead to postoperative hyperalgesia and reductions in pain thresholds, so called central sensitisation. It has been postulated that by providing adequate analgesia before surgical incision, such central sensitisation could be reduced, a concept called pre-emptive analgesia (Woolf and Chong 1993). This led to development of clinical trials comparing treatments administered before surgical incision versus the same treatment given after surgical incision. The first review of pre-emptive analgesia (Moiniche, Kehlet and Dahl 2002) showed no benefit with NSAIDS, opioids, ketamine or local anaesthetic wound infiltration. There was evidence from some trials for pre-emptive epidural analgesia. A second review of pre-emptive analgesia (Ong *et al.* 2005) found a possible benefit for pre-emptive NSAIDS, epidural analgesia and local anaesthetic wound infiltration. However, due to the novel use of gabapentin over recent years, neither review examined a potential pre-emptive benefit for gabapentin.

The concept of pre-emptive analgesia is now outdated and the subject has now shifted focus to preventive analgesia, which aims to continue pre-emptive interventions longer into the postoperative period in order to target sensitisation as it develops throughout this period or initiate interventions sooner to treat pre-operative processes (Katz, Clarke and Seltzer 2011). This includes nociceptive input from pre-existing pain, surgical incision and postoperative inflammation from the injury site. A preventive effect is then demonstrated if the effect lasts beyond the therapeutic activity of the drug (Katz, Clarke and Seltzer 2011). For this reason, reductions in chronic pain remain a major priority for preventive analgesia as it is thought that by reducing peri-operative nociceptive input, chronic pain incidence can be reduced.

In terms of animal models evaluating the preventive effects of gabapentinoids, one study using a rat postoperative pain model concluded that administration of pregabalin (which binds to the same site as gabapentin) resulted in a longer duration of anti-hyperalgesia compared with post-incision administration (Field *et al.* 1997b). Another study found administration of gabapentin before formalin injection reduced pain responses compared to administration after injection (Yoon and Yaksh 1999). However, a study in human volunteers found gabapentin both prevented development of and treated established sensitisation (Dirks *et al.* 2002). Despite these animal and human volunteer studies, clinical data is lacking on whether gabapentin is beneficial as a pre-emptive analgesic in clinical practice.

1.4 Stress response to tracheal intubation

Tracheal intubation is the gold standard of securing the airway before general anaesthesia. However, this procedure is associated with negative sequelae including a pronounced stress response. This stress response causes haemodynamic changes such as increases in heart rate, blood pressure and circulating catecholamines (Derbyshire *et al.* 1987; Shribman, Smith and Achola 1987). Such changes may lead to myocardial ischaemia (Thompson *et al.* 1998) and increases in cardiac complications in high-risk patients, such as

those with pre-existing cardiovascular disease (Kovac 1996). Ultimately, such episodes of myocardial ischaemia may lead to myocardial infarction in a small number of patients (Slogoff and Keats 1985). One study followed untreated hypertensive patients and concluded myocardial ischaemia had a peri-operative incidence of 28% on analysing ECG recordings (Stone *et al.* 1998). All episodes were precipitated by stimulation such as intubation and emergence from anaesthesia. Another study (Roy, Edelist and Gilbert 1979) found rate-pressure products of greater than 11,000 were associated with myocardial ischaemia in 10 out of 11 patients who suffered myocardial ischaemia peri-operatively.

Stimulation from extubation can also cause rises in heart rate and blood pressure. One study (Edwards *et al.* 1994) included 35% of patients with ischaemic heart disease and 27% with cardiac risk factors. This study showed both intubation and extubation were associated with increases in rate-pressure products ($p<0.01$). During the study, 12 patients out of 60 developed cardiac ischaemia at some point during the peri-operative period. At extubation, increases in rate-pressure products were significantly higher in patients who suffered myocardial ischaemia. In another study (Fusciardi *et al.* 1986), a small control group of six patients with angina were enrolled in a randomised controlled trial. Four patients developed myocardial ischaemia during laryngoscopy and intubation. This group also had significant increases in mean blood pressure, heart rate and mean pulmonary wedge pressure. Although these studies are dated and enrolled a small number of participants, they demonstrate the potential for haemodynamic changes to affect myocardial perfusion, especially in high-risk patients.

Although conducted in a more invasive procedure, one study followed a cohort of patients with cardiovascular co-morbidity undergoing microlaryngoscopy and rigid bronchoscopy. Eleven percent of patients in the control group suffered myocardial ischaemic episodes on ECG monitoring and 88% had features of arrhythmias during the procedure, which were accompanied by increases in haemodynamic variables (Matot *et al.* 2000). These features were reduced in an intervention group administered clonidine, an alpha 2-agonist

with known efficacy in reducing the haemodynamic responses to intubation. Although these procedures are more invasive than direct laryngoscopy and endotracheal intubation, they help illustrate that in high-risk patients, changes in haemodynamic variables may have consequences for myocardial perfusion during the peri-operative period. Indeed, a previous meta-analysis has shown clonidine can reduce episodes of myocardial ischaemia in both cardiac and non-cardiac surgery (Nishina *et al.* 2002).

Many agents have been used to attenuate the haemodynamic response to intubation. However, while agents such as beta-blockers, clonidine and opioids are effective, they may be associated with bradycardia and hypotension (Blaudszun *et al.* 2012; Thompson *et al.* 1999). Therefore, alternative agents may be required that do not induce such adverse effects. Moreover, alternative agents that induce other therapeutic benefits may be advantageous. It is hoped such agents can reduce episodes of myocardial ischaemia, myocardial infarction and in turn reduce peri-operative mortality in high-risk patients.

1.5 Gabapentin

Gabapentin (1-(aminomethyl)cyclohexane acetic acid) is a structural analogue of gamma-aminobutyric acid (GABA) with a molecular weight of 171. It exists as a zwitterion (a neutral molecule with both positive and negative charges that are not adjacent) with pK_{a1} of 3.7 and pK_{a2} of 10.7. It is water-soluble with properties similar to that of an amino acid. It was originally developed as an anti-convulsant medication (Rose and Kam 2002). However, in recent years it has found favour in the treatment of a variety of pain conditions, including chronic neuropathic pain.

Gabapentin has shown early promise in clinical trials addressing many aspects of anaesthetic practice such as reductions in postoperative opioid consumption, pre-operative anxiolysis, PONV, attenuation of the haemodynamic response to intubation, reductions in chronic pain after surgery and reductions in postoperative delirium (Kong and Irwin 2007). Such multimodal effects from a single agent would be attractive to practising anaesthetists. However, in recent

years, numerous studies have been published on gabapentin in the peri-operative period and it has now become necessary to summarise and scrutinise the current evidence to guide clinical practice recommendations and future research focus.

Pharmacodynamics and pharmacokinetics of gabapentin

1.6 Pharmacodynamics

1.6.1 α2δ subunit of calcium channels

The most likely therapeutic target of gabapentin (Kong and Irwin 2007) involves binding to the α2δ subunit of voltage-dependent pre-synaptic calcium channels (Fink *et al.* 2002). The history of this discovery started when a specific gabapentin-binding site was discovered within the central nervous system (Suman-Chauhan *et al.* 1993). This later proved to be the aforementioned calcium channels. Both gabapentin and pregabalin (although not the R isomer of pregabalin) bind to the α2δ subunit. Indeed, the R isomer of pregabalin exhibits no anti-hyperalgesic effect. Therefore, this finding implicated these α2δ subunits as the mechanism of gabapentin activity in pain management (Jun and Yaksh 1998). Furthermore, over-expression of these channels in transgenic mice enhanced mechanical and thermal stimulation and increased pain-related behaviours (Li *et al.* 2006). This provides further corroborative evidence for the role of these channels in the pain process.

The consequence of binding to the α2δ subunit of calcium channels includes effects on pre-synaptic neurons and reductions in excitatory neurotransmitters such as glutamate, aspartate (Feng, Cui and Willis 2003) and potassium-stimulated noradrenaline release (Maneuf, Luo and Lee 2006). Other potential substances involved in pre-synaptic calcium channel inhibition include calcitonin gene related peptide (CGRP) and substance P (Fehrenbacher, Taylor and Vasko 2003; Kukkar *et al.* 2013).

1.6.2 GABA receptors

Although gabapentin is a structural analogue of GABA and was originally developed to exert increased GABA activity for treating epilepsy, it does not exert any direct effect on GABA receptors (Bloms-Funke and Loscher 1996) and is not converted metabolically into GABA. Although some research has indicated selective activation of heterodimeric $GABA_B$ receptors (Bertrand *et al.* 2001), elevated levels of GABA and increased synthesis of GABA from glutamate, it is unlikely this is the mechanism of action of gabapentin in the treatment of pain (Maneuf, Luo and Lee 2006). Indeed, administration of GABA antagonists failed to reverse the anti-allodynic effects of gabapentin (Cheng *et al.* 2006; Hwang and Yaksh 1997), which would argue against this as a mechanism. However, it remains possible that effects on GABA may mediate some of the other therapeutic effects of gabapentin, such as reductions in anxiety and increases in sedation.

1.6.3 NMDA receptors

Other potential sites of action for gabapentin (in addition to calcium channels) include indirect inhibition of NMDA receptors, as previous research has shown reversal of gabapentin effects using NMDA agonists (Partridge *et al.* 1998). However, gabapentin has been shown to have no direct binding sites on NMDA receptors and antagonism of the NMDA receptor did not reverse the anti-allodynic effects of gabapentin (Cheng and Chiou 2006). Therefore, this mechanism appears unlikely to be involved in the pain relieving effects of gabapentin (Mao and Chen 2000).

1.6.4 Opioid receptors

It is clear from the research conducted thus far that gabapentin does not have any effect on opioid receptors (Field *et al.* 1997). In a rat model, there was no cross-tolerance with opioids and the anti-hyperalgesic activity of gabapentin was not reversed using the opioid antagonist naloxone. Therefore, it is safe to assume this is unlikely to be the mechanism of action of gabapentin in reducing postoperative pain.

1.6.5 Other mechanisms

Gabapentin may affect other chemical targets such as sodium channels, protein kinase C, transient receptor potential ion channels and increases in spinal noradrenaline (Hayashida *et al.* 2008a). Spinal noradrenaline release may have particular relevance in a postoperative pain model (Hayashida *et al.* 2008b). Other studied targets include AMPA receptors, K_{ATP} channels and hyperpolarisation-activated cation current channels, although evidence is thus far conflicting (Cheng and Chiou 2006). One mechanism proposed was action via amino acid transporters on cell surfaces. However, this mechanism is also unlikely, as a previous study has shown injection of antagonists of the L-amino acid transporter did not reverse the analgesic effects of gabapentin (Cheng, Pan and Eisenach 2000).

In terms of gabapentin effects on haemodynamic parameters, an experiment in rats has shown that neither intra-thecal nor intra-peritoneal administration of gabapentin affects baseline blood pressure or heart rate (Yoon and Choi 2003). However, intra-cerebroventricular administration resulted in a rise in haemodynamic variables. Although no depressive effect was observed in rats, an *in vitro* study revealed a possible effect of gabapentin on catecholamine secretion (Todd *et al.* 2012). Using cultured bovine adrenal chromaffin cells, gabapentin inhibited catecholamine secretion by inhibiting release of secretory vesicles. Such work suggests a possible role for gabapentin in reducing stress responses to invasive procedures such as endotracheal intubation and surgery.

In conclusion, although a number of targets have been proposed, the exact mechanism of gabapentin is yet to be fully elucidated, although it appears that the α2δ subunits of calcium channels are the most likely mechanism in pain management. Other mechanisms may have relevance to other postoperative outcomes such as the role of GABA in anxiety reduction and reduced catecholamines in attenuating the stress response to endotracheal intubation.

1.6.6 Adverse events

Gabapentin is typically well tolerated, although it is associated with a number of adverse events. In a large study of over 2000 outpatients who were taking daily gabapentin, around 10% discontinued treatment due to adverse events, most commonly due to sedation (2%) and dizziness (2%) (McLean *et al.* 1999). However, 80% of patients rated the safety and tolerability as good or excellent. The most common side effects included sedation (15%), dizziness (11%), asthenia (6%) and headache (5%). Other less common side effects included nausea (3%), ataxia (3%), weight gain (3%) and amblyopia (2%). There were higher incidences of sedation (23%) and dizziness (24%) in a randomised controlled trial in patients with diabetic neuropathy (Backonja *et al.* 1998). With regards to postoperative pain management, a meta-analysis of randomised controlled trials revealed that gabapentin increased the risk of postoperative sedation (OR 3.86; 95% CI 2.50 to 5.94). There was however no significant increase in dizziness (OR 1.34; 95% CI 0.86 to 2.10) (Ho, Gan and Habib 2006).

1.7 Pharmacokinetics

Absorption of gabapentin is reliant on a saturable L-amino acid system within the intestine (Stewart *et al.* 1993). Therefore, increasing dosages of gabapentin result in a reduction in oral bioavailability as this transport system becomes saturated. A dose of 300mg has a bioavailability of around 65% although when increased to 1200mg, the bioavailability falls to around 35%. Peak levels following oral administration (Tmax) are achieved within 2-3 hours. In terms of distribution, gabapentin is well distributed within the human body at 0.6-0.8L/kg and is not bound to plasma proteins (McLean 1994). Following a single 600mg dose, concentrations in cerebrospinal fluid are around 9-14% of plasma levels (Ben-Menachem *et al.* 1992).

Gabapentin does not undergo hepatic metabolism, is not structurally altered by the body and does not cause induction or inhibition of hepatic cytochrome enzymes. Antacids reduce bioavailability by around 20% (Busch *et al.* 1992) and cimetidine decreases clearance of gabapentin when these are used

concurrently (Rose and Kam 2002). Gabapentin is renally excreted; exhibiting first order kinetics and plasma clearance is proportional to creatinine clearance (Blum *et al.* 1994). This is thought to be the cause of age-related reductions in drug clearance (Boyd *et al.* 1999). Gabapentin has a half-life of around 6-8 hours at steady state (Beydoun, Uthman and Sackellares 1995).

1.8 Gabapentin for postoperative pain

1.8.1 Animal models

Animal studies have proven gabapentin as an effective agent in reducing features of allodynia and hyperalgesia. Interestingly, in rat models of both neuropathic and acute nociceptive pain, gabapentin showed efficacy in treating allodynic pain with little effect on acute nociceptive pain (Hunter *et al.* 1997). This suggests that gabapentin is more effective is abnormal pain states and has little effect on acute pain transmission. Other studies have also demonstrated the utility of gabapentin in abnormal pain states. A further study in rats demonstrated gabapentin reversed heat-induced thermal injury in rats (Jun and Yaksh 1998). However, it again had no effect on response latency in normal hind paws, again suggesting effects only in abnormal pain states.

Further studies corroborate these findings of efficacy in abnormal pain states. Field *et al.* (1997b) used a plantaris incision to simulate postoperative pain. The administration of subcutaneous gabapentin one hour before the incision resulted in a reduction in allodynia and hyperalgesia. The highest dose reduced these for 49 and 24 hours respectively. Morphine reduced hyperalgesia although had no effect on tactile allodynia. Yoon and Yaksh (1999) studying a rat model found intra-thecal gabapentin reduced pain behaviour and cardiovascular responses to injury induced by formalin injection, without affecting resting cardiovascular responses or acute nociception.

Further evidence of the effect of gabapentin in abnormal pain states comes from another *in vitro* study on rats (Fehrenbacher, Taylor and Vasko 2003). This study found that gabapentin attenuated release of spinal sensory

neuropeptides in rats pre-treated with Freund's adjuvant but only in the presence of inflamed tissues and not in normal tissues. These results suggest, like in other animal models, that gabapentin effects are limited to abnormal pain states.

1.8.2 Human models

Results from animal models have been translated into human models of pain. In a human volunteer study (Dirks *et al.* 2002), a capsaicin sensitisation model was used to test the effect of gabapentin on acute nociception and neuronal sensitisation in order to mimic postoperative pain. Gabapentin was shown to reduce the incidence of and reduce established secondary hyperalgesia. However, in agreement with animal models, gabapentin did not affect acute nociceptive transmission in normal skin. Another study performed in healthy volunteers again showed that gabapentin reduced mechanical pain thresholds and secondary hyperalgesia and had no effect in normal skin (Werner *et al.* 2001). Another study used intra-dermal capsaicin to induce central sensitisation and found gabapentin administered over 15 days reduced the area of allodynia when compared with placebo (Gottrup *et al.* 2004). These models provide evidence for the theoretical potential of gabapentin to reduce postoperative and neuropathic pain in abnormal tissues only.

Other interesting observations have been noted from human volunteer studies. In one study of 12 healthy male volunteers, gabapentin was shown to have both a pharmacodynamic and pharmacokinetic interaction with morphine (Eckhardt *et al.* 2000). The co-administration of gabapentin and morphine was found to act synergistically to increase analgesic effects when compared to either drug alone. Furthermore, the pharmacokinetics of gabapentin were altered when co-administrated with morphine with absorption increased and renal clearance decreased ($p<0.05$). This suggests when both drugs are used together, they may offer improved efficacy in the treatment of pain than either agent alone, which has important implications for postoperative pain management, bearing in mind the prevalent use of opioids for postoperative pain management (Benhamou *et al.* 2008).

1.8.3 Central sensitisation and postoperative pain

Following injury induced by surgical incision, two processes take place that can exacerbate postoperative pain, beyond that induced by the injury itself. Peripheral sensitisation involves reductions in the threshold of afferent nerve fibres and central sensitisation, which increases the excitability of spinal neurons (Woolf and Chong 1993). This causes hyperalgesia of the affected tissues and increases in pain. Many chemical mediators are involved in peripheral sensitisation and are released following tissue damage (surgery). The result of this sensitisation is to cause both allodynia (normal sensations producing pain) and hyperalgesia (exaggerated pain response to noxious stimuli). Peripheral sensitisation allows low intensity stimulus to produce pain via Aδ and C nociceptors and central sensitisation allows normal sensory inputs from Aβ fibres to produce pain via the spinal cord.

Mechanisms have been postulated for the maintenance of central sensitisation, which mainly include NMDA receptors, as administration of NMDA antagonists reduced central facilitation induced by mustard oil (Woolf and Thompson 1991). Through understanding the mechanisms involved in the development and maintenance of postoperative pain, the search started for agents that could directly affect central sensitisation as a way of treating postoperative pain. NMDA-antagonists have proven efficacy in treating central sensitisation (Woolf 2011). However, gabapentin has emerged as an alternative agent. These mechanisms have been proven conceptually in the animal and human studies mentioned previously. This then led to clinical trials assessing the efficacy of gabapentin for postoperative pain.

1.9 Methodological limitations of meta-analyses of gabapentin for postoperative pain

1.9.1 Summary of published meta-analyses and findings

There have been numerous RCTs conducted on the use of gabapentin for postoperative pain, which have been summarised in various meta-analyses (Table 1.1). Hurley *et al.* (2006) published one of three meta-analyses published in 2006, which included 12 RCTs with 896 participants. Gabapentin reduced pain scores, opioid consumption, reduced anxiety and increased sedation. There was significant statistical and clinical heterogeneity in results, which was not investigated. There was some attempt to investigate for publication bias by calculating the failsafe N, which showed 119 studies would be required to observe a null result from their findings.

Seib and Paul (2006) also published a meta-analysis in the same year. This review included eight RCTs and found similar results to Hurley *et al.* (2006). It however found no difference in adverse effects. Although again statistical heterogeneity was considerable, there was little investigation of this heterogeneity and no assessment of publication bias, although the review included less studies than the minimum recommended for such analyses. The studies included in the review were most likely underpowered for detecting differences in adverse events for both gabapentin and opioid-induced adverse events.

Ho *et al.* published the final meta-analysis published in 2006. This review included a larger number of RCTs; 16 studies with 1151 participants. This review found lower pain scores, opioid consumption and increases in gabapentin-induced sedation. However, this was the first meta-analysis to show reductions in vomiting and pruritus. Although some attempt was made to analyse data in subgroups based on dose, these were not directly compared on subgroup analysis. Furthermore, publication bias was not assessed.

The following year, Peng, Wijeysundera and Li (2007) published a meta-analysis. It found similar results to those published previously, although contrary to those already published; it did find a significant increase in dizziness in the gabapentin group. This review included 18 RCTs, which again showed considerable clinical and statistical heterogeneity, which was not explored. Although assessment of publication bias involved visual inspection of funnel plots, no formal statistical test for publication bias was performed.

Tiippana *et al.* (2007) published a meta-analysis in the same year, which also included pregabalin. This review included 21 RCTs involving gabapentin. Results were similar to previous reviews. Meta-regression was undertaken using gabapentin dose as a covariate, which had no significant effect on 24-hour opioid consumption. Publication bias was not assessed. Although some attempt was made to analyse pain scores based on type of surgery, there were no formal subgroup analyses of 24-hour morphine consumption.

The most recent meta-analysis of gabapentin was published by Mathiesen *et al.* (2007) and included 23 RCTs with 1529 participants. This review attempted to analyse patients in specific surgical subgroups based on type of procedure. However, there were no formal subgroup comparisons between surgical subgroups. Furthermore, there was no other investigation of heterogeneity or assessment of publication bias. Results again were broadly in agreement with those published previously.

In conclusion, although each of the published meta-analyses has strengths, no single review satisfies the gold standard of current systematic review methodology. These inherent limitations and the publication of new studies since these previous reviews mandates an updated evaluation of the evidence. The following sections will discuss the limitations of the previous meta-analyses on gabapentin.

Author	Year	N (studies)	N (participants)	Heterogeneity investigation (covariate)	Publication bias	Risk of bias
Hurley	2006	12	896	No	Failsafe N	Cochrane
Seib	2006	8	663	NR	No	Jadad scale
Ho	2006	16	1151	Subgroup analysis (dose)	No	Oxford scale
Peng	2007	18	1181	Sensitivity analysis (methodology and pain severity)	Funnel plots	Yes (author created)
Tiippana	2007	21	1614	Meta-regression (dose)	No	Oxford scale
Mathiesen	2007	23	1529	Subgroup analysis (surgery)	No	Oxford scale

Table 1.1: Summary of previously published meta-analyses on gabapentin. NR=not reported

1.9.2 Outdated evidence

The main limitation of current meta-analyses on gabapentin relate to the amount of time lapsed since the last published review. The last three reviews were published in 2007. However, the Cochrane Collaboration suggests undertaking systematic reviews every two years (Higgins 2008). Although more recent procedure-specific meta-analyses have been published (Alayed *et al.* 2014; Yu *et al.* 2013), none have been recently published evaluating gabapentin in all forms of surgery. Over 100 RCTs on gabapentin have since been published, which mandates an updated review to help guide clinical practice and future clinical trials.

1.9.3 Internal validity

An important component of the systematic review process involves evaluating the internal validity of the included studies, since poorly conducted RCTs can bias the conclusions of a review. Indeed, one review of 122 meta-analyses (Juni *et al.* 2003) found that inadequate or unclear allocation concealment was associated with an average 21% (95% CI 11% to 30%; $p<0.001$) exaggerated effect compared to those with adequate allocation concealment. In addition, although not statistically significant, inadequate or unclear double blinding was associated with an average 12% (95% CI -4% to 25%; $p=0.13$) beneficial effect compared to those with adequate double blinding. These results suggest that the inclusion of trials at higher risk of bias can exaggerate the effects of interventions, which has important implications for using such reviews to inform clinical practice.

Of the current meta-analyses, five used aggregated scoring systems for quality assessment. These scoring systems have inherent limitations (Higgins *et al.* 2011), including assigning score weightings to different measures of internal validity that are not supported by empirical evidence. For example, the Jadad score used in some of the meta-analyses gives equal weighting to adequate randomisation and double blinding, which may not reflect empirical findings on their relative importance (Juni *et al.* 2003). Some validity scores also

confuse aspects of trial reporting (such as the presentation of data) with measures of internal validity (Juni *et al.* 2001). Furthermore, many scoring systems attribute a lack of reporting the same score as those whose methods are reported, although inadequate. For example, one trial may report randomisation according to date of birth (high risk of bias) and another trial may not report how randomisation was performed (unclear risk of bias), scoring systems may give these trials equal scores, which is inappropriate. Despite an association between poorly reported trials and methodological quality, this method causes misclassification of those trials that are poorly reported but well conducted. For these reasons, the use of component items such as the Cochrane risk of bias tool is preferable to composite scoring tools (Higgins *et al.* 2011). One review used the Cochrane risk of bias tool (Hurley *et al.* 2006), although did not report details of the risk of bias given to each study. In the wider anaesthesia literature, a recent meta-epidemiological study has shown that in a sample of 174 systematic reviews, the Jadad scale was still the most popular method used to assess internal validity (33%) when compared to the Cochrane risk of bias tool (20%) (Detweiler *et al.* 2016).

Although component item assessment is generally accepted as the method of choice for measuring the internal validity of trial findings, how to incorporate methodological quality into systematic review results is a subject of continued debate (Juni *et al.* 2001). Approaches include excluding trials of low methodological quality. However this method is subjective and may introduce bias into the systematic review process. For example, authors may exclude studies that contradict their expectations of the results. Effect estimates can also be weighted by study quality, although this method lacks any statistical or empirical evidence for its use (Juni *et al*. 2001). Thus, the recommended approach is to perform sensitivity analysis to evaluate whether study quality affects the conclusion of any given meta-analysis. Only one meta-analysis on gabapentin conducted such a sensitivity analysis (Peng, Wijeysundera and Li 2007).

1.9.4 Publication bias

In addition to issues of bias from the included trials, systematic reviews may be subject to other forms of bias. Publication bias relates to the preferential publication of positive trials by journals or preferential reporting of positive outcomes within a study ($p<0.05$). This results in bias in effect estimates in favour of the treatment under review. One cohort study of 218 studies (Stern and Simes 1997) showed that trials with positive results, defined as a $p<0.05$, were more likely to be published (hazard ratio (HR) 2.32; 95% CI 1.47 to 3.66) and published quicker (median time to publication 4.8 versus 8 years) than studies with negative outcomes. Another study found similar results (Easterbrook *et al.* 1991), with positive studies more likely to be published (adjusted OR 2.32; 95% CI 1.25 to 4.28) than those with negative results. A more recent systematic review (Dwan *et al.* 2008) and Cochrane review (Hopewell *et al.* 2009) were in agreement with the results above and also identified evidence of selective outcome reporting bias, the notion that statistically significant results within studies are more likely to be reported in manuscripts when compared to non-significant results.

Publication bias is thought to affect around 25%-40% of published meta-analyses (Egger *et al.* 1997a; Sterne, Gavaghan and Egger 2000). In the anaesthesia literature, a recent review has shown that when evaluating reviews from 2007-2015 in five anaesthesia journals there was a prevalence of publication bias of 50-80% (Hedin *et al.* 2016). Methods exist to help identify and correct for publication bias. Both funnel plots, which are graphical plots of effect estimates plotted against their standard error and regression methods, can be used to identify potential publication bias (or more appropriately, imprecise study effects). Using these methods, publication bias has been identified as being responsible for discrepancies in conclusions from meta-analyses that were later contradicted by large RCTs (Egger *et al.* 1997a). Other methods such as rank correlation tests are available. The regression method has more power to detect differences when compared to rank correlation tests, although regression tests have problems of false positives in particular situations; such

as treatments with large effects, trials of similar sample sizes or trials with a low numbers of events (Sterne, Gavaghan and Egger 2000).

Egger's regression test is a test for funnel plot asymmetry and tests that the Y intercept from a regression line equals zero. It regresses the standard normal deviate (effect size divided by standard error) with the precision (reciprocal of standard error) as the predictor variable (Illustration 1.1). In the presence of funnel plot symmetry, then the intercept should equal zero (the regression line should intercept the Y axis at 0). We can observe from the below plot that this is not the case, indicating funnel plot asymmetry. This is because smaller studies (with less precision) tend to have more extreme results compared to the effect estimate and therefore a predominance of 'positive' studies (with publication bias) will 'shift' the intercept away from 0 (as seen in Illustration 1.1).

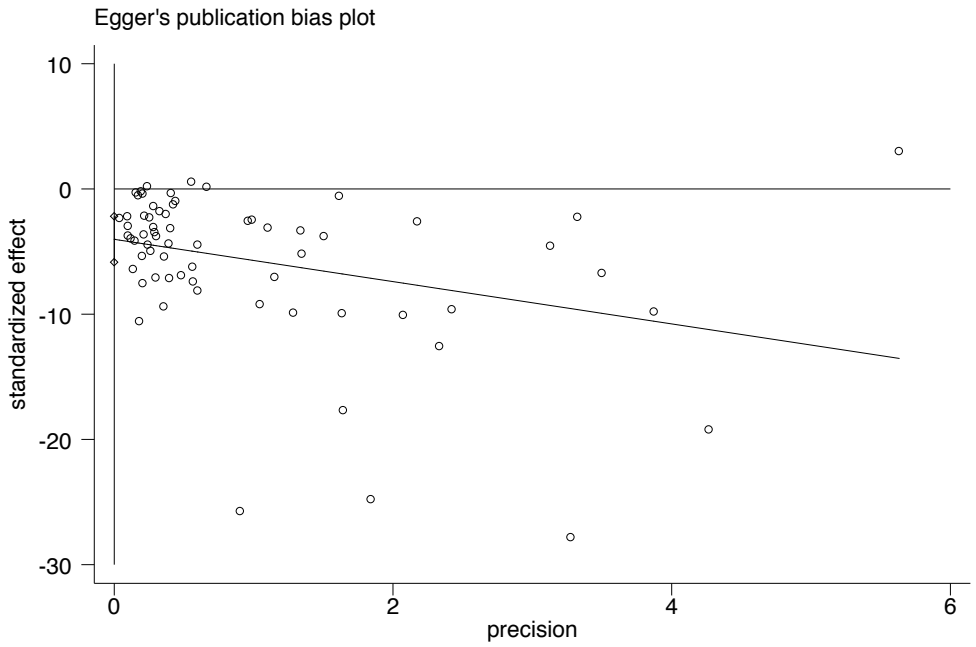


Illustration 1.1: Egger's linear regression test. Y-axis is standard normal deviate (effect size divided by the standard error) and the X-axis is the study precision (1 / standard error). The intercept is significantly different from zero ($p<0.05$).

Attempts have been made to devise statistical tests to correct for publication bias. Trim and fill analysis is one such method (Duval and Tweedie 2000). This method involves trimming extreme cases from the funnel plot, re-estimating the effect estimate and then producing an adjusted effect estimate in the presence of a symmetrical plot (Illustration 1.2). However, this analysis can underestimate the true effect in the presence of large between-study heterogeneity where no publication bias is present. In addition, this method relies on the assumption that an asymmetric funnel plot is entirely due to publication bias (Peters *et al.* 2007). Other causes of an asymmetric funnel plot exist such as internal validity issues in smaller trials and possible fraud.

Orwin's failsafe N is another analysis used to determine the likely influence of publication bias (Orwin 1983). This test calculates the number of additional negative studies needed to change the effect estimate to a pre-determined, clinically insignificant level. Although neither calculation is recommended for Cochrane reviews, such analysis can serve as sensitivity analyses to assess the extent of publication bias in any given review.

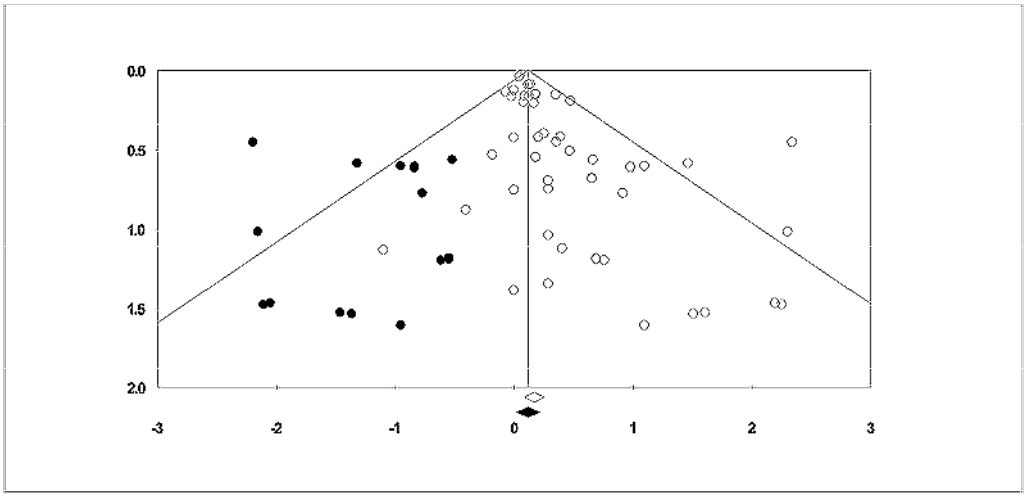


Illustration 1.2: Funnel plot with log risk ratio on the X-axis and the standard error (on a reverse scale) on Y-axis. Original studies (white circles) and effect estimate (white diamond) show the original studies in the meta-analysis, which show clear asymmetry. The new effect estimate (black diamond) and plotted

studies (black circles) show the new symmetrical plot following trim and fill analysis.

As alluded to previously, it should be noted that publication bias is not the only cause of funnel plot asymmetry. Other causes include poor methodological design, fraud and differences in the way the intervention was delivered in smaller studies (Sterne *et al.* 2011). Therefore, extensions to traditional funnel plots have been developed such as the use of contour enhanced funnel plots (Illustration 1.3). These plots add regions of statistical significance for each individual study. Studies falling within these regions are statistically significant at the level selected (in our example $p<0.05$ and $p<0.01$). We can see from the illustration overleaf that in plot A, studies are located in shaded areas of statistical significance, making publication bias more likely, as the studies in the analysis are statistically significant (the mechanism behind publication bias). In contrast, plot B shows studies in regions of non-statistical significance, suggested other causes for funnel plot asymmetry should be considered (Sterne *et al.* 2011). Authors have previously been found to be poor at visually identifying funnel plot asymmetry (Terrin, Schmid and Lau 2005) so adding contour lines for statistical significance may aid interpretation (Sterne *et al.* 2011).

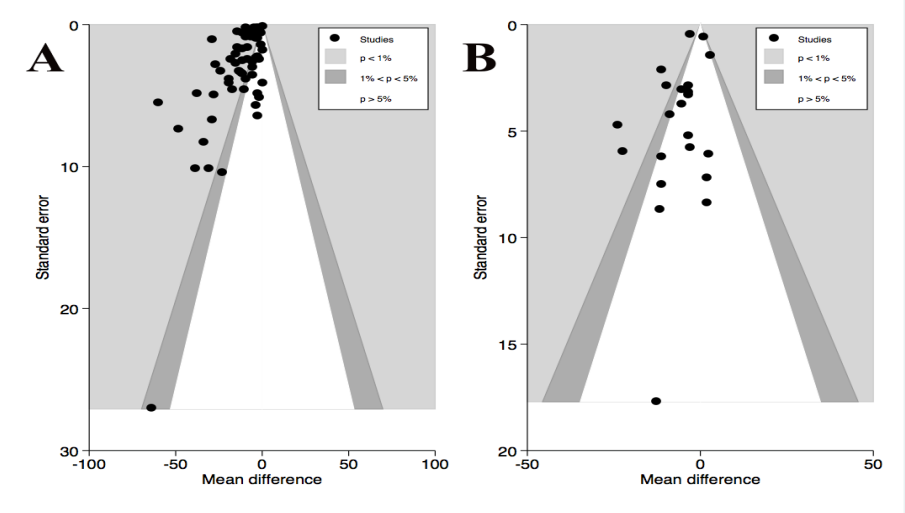


Illustration 1.3: Contour enhanced funnel plots. Plot A shows the majority of studies in regions of statistical significance (grey $p<0.01$ and dark grey $p<0.05$) suggesting publication bias as a cause. Plot B shows more studies in the region of statistical non-significance ($p>0.05$) suggested another cause for asymmetry.

Only one meta-analysis of gabapentin use in the perioperative period attempted to identify publication bias (Hurley *et al.* 2006) using the failsafe N. Another used qualitative assessment of funnel plots, although did not use quantitative methods such as Egger's linear regression test (Peng, Wijeysundera and Li 2007). Indeed, as already mentioned, previous research has shown that visual inspection of funnel plots can lead to false conclusions of whether asymmetry is present (Terrin, Schmid and Lau 2005). Lack of investigation of publication bias is also true for meta-analyses of acute postoperative pain in general, with only 8% assessing for the possibility of publication bias (Espitalier *et al.* 2013). As described previously, such publication bias has the potential to bias effect estimates in favour of gabapentin. In order to attempt to reduce publication bias, an extensive search for unpublished studies is required via clinical trial databases, conference proceedings and grey literature databases (Thornton and Lee 2000). None of the previously published meta-analyses have sought unpublished studies.

1.9.5 Clinical and statistical heterogeneity

Another issue with meta-analyses relates to the concept of heterogeneity. Clinical heterogeneity can arise due to differences in study inclusion criteria, dose of the intervention used, length of follow up and disease severity that may cause issues with the pooling of results (Thompson 1994). Statistical heterogeneity arises when effect estimates from individual trials differ, which may be due to clinical heterogeneity or methodological differences between individual trials. If all studies were conducted on the same population of participants, we would expect overlap of confidence intervals, as the only differences between studies would be due to sampling error. However, statistical heterogeneity exists when studies differ by more than would be expected from sampling error. Cochran's Q can quantify this which is the weighted sum of squares between individual study results and the overall meta-analysis results and is chi-squared distributed with k (number of included studies) minus one degrees of freedom. Unfortunately, this test has low power in the presence of a small number of studies. An alternative measure that uses Cochran's Q in it's calculation is the I^2 statistic, which quantifies the percentage of variation between the studies that is due to between-study variance compared to sampling variance (Higgins and Thompson 2002). The I^2 statistic is calculated as follows:

$$I^2 = \frac{(Q - df)}{Q} \times 100\%$$

Q = Cochran's Q
df = degrees of freedom (numbers of studies in analysis - 1)

Should heterogeneity be identified, there are methodological issues that can address this. The first is to avoid pooling results of trials that are too clinically heterogeneous and instead provide a narrative review of results (a decision based on clinical judgement rather than observing a high I^2 value). However, this method may be a lost opportunity to evaluate why results from trials differ, which may be useful for generating further hypotheses. If data are to be pooled,

then appropriate methods should be used. This involves the use of a random-effects model, which does not address heterogeneity, although this model incorporates a measure of heterogeneity into its calculation and consequently, the precision of estimates are reduced in the presence of between-study heterogeneity to reflect uncertainties in the data (DerSimonian and Laird 1983).

1.9.6 Investigation of heterogeneity

Probably the most clinically important analysis to conduct in the presence of clinical and statistical heterogeneity is a thorough investigation of its causes. Such analyses can be used to generate hypotheses for future clinical trials or give an indication of where an intervention may be more effective. Both subgroup analysis and meta-regression can be used for this purpose. These analyses use study-level covariates; such as the dose of an intervention, to assess the impact on effect estimates. Meta-regression has advantages over subgroup analysis as it allows analyses of multiple covariates, which reduces problems of confounding. Also, meta-regression focuses on differences between subgroups rather than the effects in each subgroup and makes allowances for the residual heterogeneity not explained by the sub-grouping (Thompson and Higgins 2002). However, it must be remembered that any conclusions are observational in nature and prone to confounding. Furthermore, using study-level covariates that are averaged for the trial (such as mean pain score or morphine consumption) may not reflect the effects in the individual trial participants, which results in aggregation bias (Thompson and Higgins 2002).

Heterogeneity is a particular problem in meta-analyses of acute postoperative pain trials. Such clinical heterogeneity can arise due to differences in drug doses, type of anaesthesia and surgery or how painful the procedure is. Espitalier *et al.* (2013) explored this by examining 61 published meta-analyses focusing on treatment of postoperative pain. Although all meta-analyses evaluated statistical heterogeneity, only 6% explored this using meta-regression. Subgroup analysis was performed in 90% of meta-analyses, with

around 50% using type of surgery and 70% using the intervention dose. This review concluded that clinical heterogeneity induced by pain level is under-considered, as only 63% of meta-analyses that pooled trials with a wide range of pain levels discussed this as a source of clinical heterogeneity. Furthermore, within the heterogeneous group of meta-analyses that included surgeries with varying levels of pain, only 38% pooled results using a random-effects model. In terms of the gabapentin meta-analyses, only one study conducted meta-regression using gabapentin dose as a covariate (Tiippana *et al.* 2007). One review used sensitivity analyses of trials with higher pain levels to determine if this had an influence on effect estimates (Peng, Wijeysundera and Li 2007). However, pain severity (>30mm on 100mm VAS) did not affect results.

As discussed previously, type of surgery is often cited as a cause of clinical and statistical heterogeneity in meta-analyses of gabapentin and analgesics for postoperative pain in general. However, none of the previous meta-analyses have thoroughly explored this through appropriate methods using meta-regression. Type of surgery is often considered as contributing to the efficacy of analgesic agents. Indeed, when different surgeries are combined together to measure analgesic efficacy; they may produce varying estimates if re-analysed for different types of surgery. For example, paracetamol has been found to be less effective in orthopaedic compared to dental surgeries (Gray *et al.* 2005). This paper also cites other examples of where analgesic agents are more effective in certain procedures when compared to others. However, it remains unclear whether the properties of the surgery itself, pain intensity, character of pain or type of anaesthesia are responsible for these differences.

1.9.7 Baseline risk

Baseline risk is a potentially important effect modifier. For example, in postoperative pain trials, the effect of an analgesic in question may be more effective in more painful surgeries (Averbuch *et al.* 2003). Identifying such effect modifiers has important implications for more targeted use of analgesic adjuncts. Ideally, determining which patients would benefit most from treatment would be derived from individual patient data. However, this

information is impossible to obtain from patients who only undergo one surgery and where analgesia is initiated before the measurement of the outcome of interest (24-hour opioid consumption). The traditional method of obtaining this data is to use the mean control group morphine consumption as a measure of baseline risk (Doleman *et al.* 2015a). However, this analysis may suffer from various forms of bias, which are highlighted below.

Sources of bias in this analysis are varied. Firstly, the use of control group morphine consumption as the covariate presents a problem, as this value is included in both the covariate value and the effect estimate. This dependence causes issues with regression to the mean (regression dilution bias). This can cause an association between baseline risk and effect estimate when in fact no relationship exists. Secondly, the analysis needs to account for the fact that the covariate for baseline risk is measured with error and are estimated from the data rather than 'true' values (Sharp and Thompson 2000). Because of these issues with naïve analyses, alternative analysis methods are recommended that implement Bayesian analysis using Gibbs sampling (Sharp and Thompson 2000). Interestingly, this analysis has been previously shown to improve model fit when examining the relationship between baseline risk and reductions in morphine consumption with paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS) (Achana *et al.* 2013).

1.9.8 Clinical versus statistical significance

A common criticism of both primary and secondary research is an over-reliance on statistical, rather than clinical significance. Previous meta-analyses of gabapentin have failed to express the benefits of gabapentin in terms of clinical, rather than statistical significance. To help illustrate the difference between these concepts, consider the following hypothetical example. We wish to know the efficacy of two different analgesic agents (x and y) for treating postoperative pain. We undertake two RCTs with both agents and pre-determine a clinically significant reduction in pain as 15mm (on a 100mm VAS) (Gallagher, Leibman and Bijur 2001). The first RCT with agent x enrols a large number of participants and demonstrates a mean difference of -5mm

(95% CI -3mm to -7mm; p<0.001). The second study with agent y recruits much fewer participants and demonstrates a mean difference of -12mm (95% CI 0.1mm to -24.1mm; p=0.06). Although the p value of the first study is very low, the results indicate that we can be confident this agent does not produce a clinically significant effect and should therefore not be used. The second study, although not statistically significant, does not exclude a clinically significant effect and requires more studies to be conducted in order to increase power and narrow the confidence interval. If we had relied solely on statistical significance, widely different and erroneous conclusions would be made.

Previous research has shown that patients regard minimally clinically significant average acute pain score reductions to be around 1.3 on a ten-point scale (Gallagher, Leibman and Bijur 2001). Another study, using data from three other chronic pain studies, cited reductions of 1 point on a 10-point scale as minimally important and 2 points as much improved (Dworkin *et al.* 2008). In terms of dichotomous data, the number needed to treat is the most appropriate metric to convey benefits as it is easily understood by clinicians while being easy for patients to interpret (Cook and Sackett 1995).

1.9.9 Quality of evidence

Although the previously discussed limitations with the current meta-analyses on gabapentin are not exclusive to this agent, they all negatively affect the confidence we can have in their conclusions. These issues can affect the quality the evidence derived from systematic reviews, which led to development of the GRADE criteria (Guyatt *et al.* 2008). The level of evidence from RCTs is regarded as high quality although can be downgraded to moderate, low or very low quality owing to the following concerns, which form the GRADE criteria (Higgins 2008):

- 'Limitations in the design and implementation of available studies suggesting high likelihood of bias'= this factor concerns the conduct of studies included in the review. This may relate to measures of internal validity such as allocation concealment or blinding. Although there are

no objective criteria on which to assign a particular group of included studies as at risk of bias and is therefore a subjective assessment on the part of the review author.

- 'Indirectness of evidence'= this measure relates to the population, intervention or outcomes measured and whether they are relevant to the population on which the evidence is to be used. This would be an issue with the external validity of the findings of a review. For example, as the evidence for gabapentin efficacy for attenuating the haemodynamic response to intubation is derived from mainly normotensive participants, this evidence may not be applicable to hypertensive patients.
- 'Unexplained heterogeneity or inconsistency of results'= this relates to the previously discussed clinical and statistical heterogeneity in results. For example, if authors fail to explain why results may vary from population to population through investigation of heterogeneity, evidence is downgraded.
- 'Imprecision of results'= as precision is derived from the confidence intervals, if a review includes too few participants and/or standard deviations are very large, this will result in imprecision and reduced confidence we can place in the conclusions.
- 'High probability of publication bias'= methods for detecting possible publication bias have been discussed previously. Should there be evidence of possible publication bias (imprecise study effects), then evidence is downgraded.

However, more rarely, observational studies can be upgraded for the following reasons (Higgins 2008):

- Well-performed observational studies can be upgraded if they show a large magnitude of effects (such as RR>2 or RR<0.5).
- Biases may exist that underestimate an intervention effect. For example, when estimating negative side effects of gabapentin, potential publication bias may overestimate the incidence of this adverse effect,

as studies that have shown no statistically significant difference between groups may not report the result.

- In observational studies, a dose-response effect may result in upgrading.

1.9.10 Type I and type II errors in meta-analysis

Meta-analyses in general, and especially those initiated when few trials have been published (as with previous meta-analyses on gabapentin), may produce erroneous findings due to both type I and type II errors. When few studies have been conducted, type I errors are more likely and may produce false positive conclusions. Alternatively, meta-analyses need to include an appropriate number of participants that can adequately answer the research question, which is called the information size (IS) (Borm and Donders 2009; Pogue and Yusuf 1998; Thorlund *et al.* 2009). Many of the previous reviews published on gabapentin have included a small number of studies and therefore may be prone to type I and II errors. Furthermore, the multiple significance tests of these reviews may inflate type I errors, analogous to multiple comparisons within primary research studies. Indeed, a recent review of the anaesthesia literature that included a random sample of 50 meta-analyses concluded that only 12% had a power of >80% and only 32% preserved the type I error rate at <5% (Imberger *et al.* 2015).

In primary RCTs, sample size calculations can be conducted to calculate the required number of patients required to answer the clinical question. As meta-analyses are prone to heterogeneity (Espitalier *et al.* 2013) this must be taken into account in these calculations. To deal with these issues, a method called trial sequential analysis (TSA) can be performed. Trial sequential analysis may yield more reliable results than traditional meta-analytic methods (Thorlund *et al.* 2009). To control type I error rates, monitoring boundaries can be employed that require a larger degree of statistical significance when fewer studies are included in a review (Illustration 1.4, A) when compared to traditional boundaries (Z score of 1.96; Illustration 1.4, B). Another advantage of this analysis is the calculation of the IS so the reviewer can be confident a

definitive sample size has been reached from all the included studies (Illustration 1.4, C).

In addition, TSA can be used to plot boundaries of futility. For example, when a meta-analysis result crosses this boundary, then further trials are unlikely to achieve the desired, pre-stated clinically significant effect. This can be calculated before the required IS is reached. This is essential so that resources are not wasted on future RCTs of futile interventions (Illustration 1.4, D). The Z curve is plotted as each additional trial is added (Illustration 1.4, E) and if this crosses any of these areas, conclusions can be made regarding adjusted statistical significance (A), adequate IS (C) or whether the conduct of further trials may be futile (D).

In conclusion, current meta-analyses on gabapentin are limited by the inclusion of a small number of studies and the publication of multiple meta-analyses may inflate the type I error rate. These reviews are also now largely outdated, due to the large number of studies published on gabapentin over the last decade. In terms of methodology, previous meta-analyses have failed to explore potential publication bias, use current recommended methods to assess internal validity, are limited in the outcomes assessed, have not searched for unpublished studies and failed to fully explore heterogeneity between studies. These flaws mandate an updated review on gabapentin that address the above limitations.

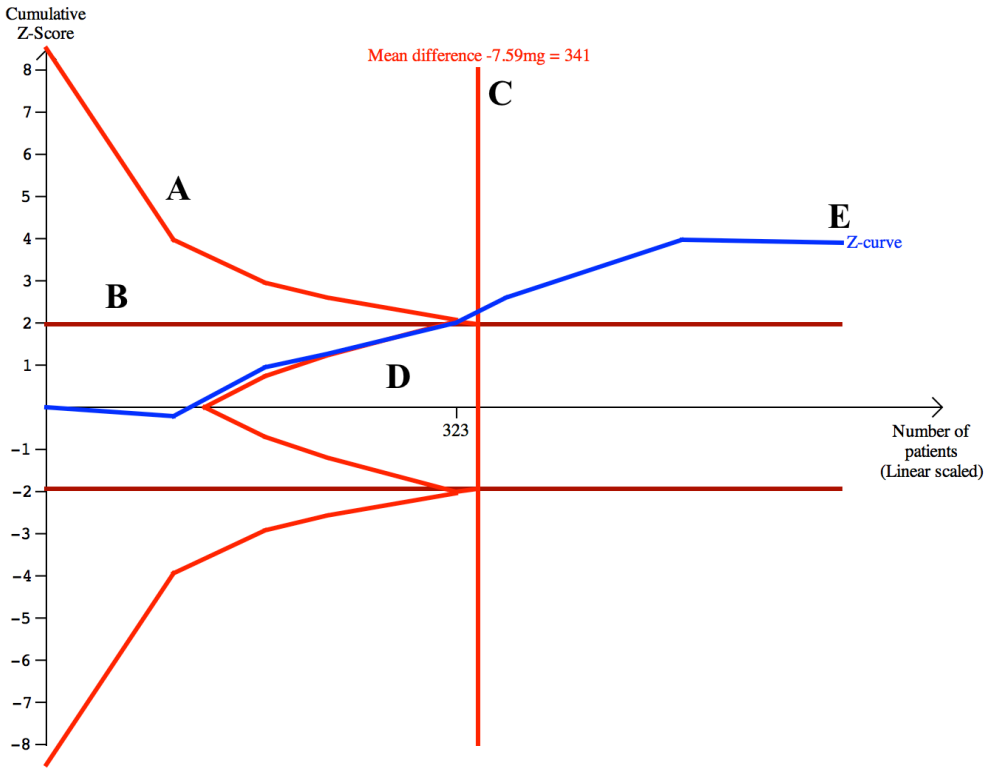


Illustration 1.4: Trial sequential analysis (TSA) plot. **A** on the plot indicates the monitoring boundaries for adjusted statistical significance for benefit with a larger Z score required to reach significance early in the review process. **B** indicates the traditional boundary for statistical significance ($p<0.05$), which is equivalent to a Z score of 1.96. **C** indicates the required information size (IS) for a conclusive review (341 participants). **D** indicates the area of futility where the addition of further trials will unlikely change the conclusions of the review. **E** shows the Z curve with each point indicating the addition of another trial.

1.10 Choice of methodology for thesis

Many types of methodologies are available in order to assess the effectiveness of an intervention. The optimum methodology for primary research studies would be the RCT (Higgins 2008). However, over the last decade there have been multiple (often small) RCTs published investigating gabapentin for a diverse range of outcomes. When focussing on acute postoperative pain, these trials often report variable results with regards to reductions in morphine consumption, ranging from 20-62% reductions (Tiippana *et al.* 2008). In addition, for other postoperative outcomes and adverse events, a small number of participants are studied, which are often limits the power of the analysis. Furthermore, other outcomes such as the haemodynamic response to intubation have had multiple primary studies published, which have not be analysed together in any previous meta-analysis. For the reasons stated above, systematic review methodology is a more appropriate methodology than undertaking a primary research study of gabapentin. This fact is also true for multimodal analgesic agents in general, with a vast number of published studies with heterogeneous results, which as yet has not been fully explored.

1.11 Aims of this thesis

1) To investigate whether gabapentin is an effective agent in reducing acute postoperative pain.
2) To investigate whether the efficacy of gabapentin is dependent on clinical factors such as baseline risk, dose of gabapentin and the type of anaesthesia/surgery.
3) To investigate whether gabapentin is effective at reducing many opioid adverse effects.
4) To evaluate if gabapentin causes any peri-operative adverse effects
5) To investigate whether gabapentin is an effective pre-emptive analgesic agent.
6) To investigate whether gabapentin is an effective agent in reducing the haemodynamic response to intubation.
7) To investigate whether heterogeneity can be explained in other multimodal analgesic agents.
8) To identify the prevalence of publication bias (imprecise study effects) in meta-analyses of other analgesic adjuncts and test whether this is caused by heterogeneity rather than true publication bias.
9) To investigate whether sufficient low risk of bias evidence exists for multimodal analgesics to reject type I and II errors.

Chapter 2

Gabapentin for acute and chronic postoperative pain: systematic review and meta-analysis

2.1 Introduction

Postoperative pain is common and continues to be undermanaged in clinical practice (Apfelbaum *et al.* 2003; Sommer *et al.* 2008). This can negatively affect the patient experience and have detrimental physiological consequences. Furthermore, acute postoperative pain can lead to chronic pain in up to 50% of patients (Kehlet, Jensen and Woolf 2006). Gabapentin has emerged as a potential therapy for treating postoperative pain and reduce the need for opioids during the postoperative period.

As discussed in chapter one, previous meta-analyses of gabapentin are no longer contemporary. Furthermore, they lack investigation for sources of heterogeneity, do not fully assess the presence or impact of publication bias and do not present adequate information on the internal validity of the included studies. Moreover, meta-analyses that include a low number of studies are prone to both type I and type II errors (Imberger *et al.* 2015). Therefore, this chapter aims to improve on those published previously by evaluating the effects of gabapentin on acute and chronic postoperative pain while utilising trial sequential methods to reduce potential errors that earlier reviews may have been prone to. Ultimately, this chapter will aim to fully investigate sources of heterogeneity and present a meta-regression model, which can be used in clinical practice or when planning future research studies in order to identify in which clinical situations gabapentin may more effective.

2.2 Methods

2.2.1 Reporting standards and prospective registration

Reporting standards are an important consideration when producing systematic reviews of RCTs. If reviews are not adequately reported, readers are unable to fully understand how a review was conducted or appreciate the strengths and weaknesses of the review (Moher *et al.* 2009). To help improve the standards of reporting, the PRISMA statement was produced which is now a requirement in many journals as a condition of publication. Therefore, this review was conducted in accordance with the PRISMA statement checklist.

Another consideration for producing an unbiased review is prospective registration of the review on a public database. Such registration improves accountability, transparency and prevents duplication of reviews addressing the same clinical questions (Moher *et al.* 2009). Moreover, the protocol allows outcomes to be pre-specified and help reduce type I errors that may result from multiple *post hoc* subgroup analyses. This review was registered on the PROSPERO website, which is a publically accessible database for systematic reviews, using the registration number CRD42014015521. Changes from the original protocol included changes to the investigation of heterogeneity using meta-regression only and the addition of the covariate control group morphine consumption or pain score (baseline risk).

2.2.2 Search strategy

The literature search was conducted on 8th December 2014. Databases searched included MEDLINE (1946-2014), EMBASE (1974-2014), CINAHL (1981-2014), AMED (1985-2014) and CENTRAL. These databases provide extensive coverage of RCTs and are recommended by the Cochrane Handbook (Higgins 2008). The MEDLINE search included the free text search terms ‘gabapentin’, ‘neurontin’, ‘surgery’ and the medical subject heading (MeSH) ‘SURGICAL PROCEDURES, OPERATIVE’ which was exploded. We chose these search terms in order to maximise the sensitivity of the search.

In order to try to reduce the impact of publication bias, we searched unpublished clinical trial databases (Thornton and Lee 2000). These included Clinicaltrials.gov and the ISRCTN registry. If studies were identified which had not been published, authors were contacted by email. To further maximise the sensitivity of the search, references of retrieved articles were hand-searched. Google Scholar was utilised to identify additional articles that had cited those retrieved. Google Scholar may be useful in obtaining more obscure citations, which may increase the breath of the articles retrieved (Falagas *et al.* 2008).

2.2.3 Inclusion criteria and outcomes

We followed a PICO (participants, interventions, comparator and outcomes) format in order to formulate the clinical question used for including studies in the review. The types of studies included were parallel group RCTs, as these are widely regarded as the optimum study design to assess the effectiveness of an intervention (Higgins 2008). Participants included patients undergoing any type of surgery with any type of anaesthesia. Both elective and emergency surgeries were included. Studies that evaluated paediatric populations only were excluded (for example, excluded patients >15 years old). The intervention was gabapentin at any dose administered either pre-operatively or postoperatively, with or without additional postoperative doses. We did not include studies that used single dose gabapentin for established postoperative pain. Comparator treatments included no treatment, placebo tablets or an active placebo with no recognised analgesic activity.

The primary outcome was 24-hour morphine consumption. This was chosen as the primary outcome as pain scores may be prone to confounding from variable morphine consumption between the groups. For example, two groups may have similar pain scores although the active drug group may have used less morphine, which would still indicate analgesic activity of the drug. However, the reverse may also be true, although as patients generally use PCA devices in the included studies, the participant can use as much opioid as they require in order to remain comfortable. Moreover, as stated in chapter one, morphine may

be responsible for many adverse effects during the postoperative period and therefore reducing consumption may also reduce these adverse effects.

If other opioids were used in the included studies, these were converted to morphine equivalents using the following conversion factors: pethidine/meperidine (7.5-10:1), ketobemidone (1:1), tramadol (25:1), fentanyl (1:100) and hydromorphone (1:5). Other secondary outcomes included postoperative pain assessed at rest at ≤1, 2, 6, 12 and 24-hours postoperatively. All scores were converted to a ten-point scale. We also assessed chronic pain at 1-2, 3, 6 and 12 months as a continuous outcome. Furthermore, due to different methods of reporting chronic pain, we included chronic pain as a dichotomous outcome, including studies at the earliest time-point in which they recorded the presence or absence of chronic pain. We regarded a mean reduction in pain score of 1.5 on a ten-point scale (Dworkin *et al.* 2008; Gallagher, Leibman and Bijur 2001) and a 10mg reduction in 24-hour morphine consumption as clinically significant. We could not find any studies regarding the clinical significance of morphine consumption so we chose one standard dose of morphine for this purpose. For chronic pain reported as a dichotomous outcome, we regarded a relative risk reduction (RRR) of 20% as clinically significant. Inclusion of studies was assessed independently by two authors and agreement reached by consensus.

2.2.4 Data extraction

Two study authors independently extracted data onto an electronic database. We collected data on the following as reported in the study: study name, year of publication, mean age of participants, sex of participants (% female), sample size, gabapentin dose and regimen, comparison, country in which the study was conducted, type of anaesthesia used and type of surgery. There was no language restriction for inclusion in the review. If studies were published in a non-English language, we used Google Translate to translate them. This helps maximise the breadth of the search and limits bias, as authors are more likely to publish statistically significant results in English language journals

compared with other language journals (English language bias) (Egger *et al.* 1997b).

Where data were not reported, authors were contacted to provide additional data. If we received no response, graphs were used to estimate data. If standard deviations were not reported, these were estimated from other, similar studies in the analysis (Higgins 2008). We chose this method due to the potential for negative results to not be fully reported (including standard deviations) increasing the potential for selective outcome reporting bias. In order to minimise any impact of these estimates, we subsequently removed these estimated standard deviations on sensitivity analysis.

2.2.5 Risk of bias in included studies

We assessed the internal validity of the included studies using the Cochrane tool for assessing risk of bias (Higgins *et al.* 2011). As discussed previously, this tool is preferable to composite scoring systems that were previously used in many of the previous reviews on gabapentin. This tool assigns one of three outcomes to each domain of internal validity. The tool includes randomisation, allocation concealment, blinding of participants and study personnel, blinding of outcome assessors, selective outcome reporting and other factors which may cause bias (such as imbalances in baseline characteristics). Each domain scores either low, high or unclear risk of bias dependent on the methods reported.

2.2.6 Statistical analysis

Continuous outcomes are presented as mean differences (MD) and aggregated using the inverse variance method. The MD was chosen as readers can easily interpret it as it retains results in the original format in which they were reported. For example, presenting a MD in milligrams of morphine allows readers to evaluate the clinical efficacy of gabapentin while also allowing direct comparison with other multimodal analgesic agents from previous reviews. Due to the different scales used to report chronic pain as a continuous outcome, these results are reported as standardised mean differences (SMD).

Dichotomous data are presented as risk ratios (RR) and numbers needed to treat (NNT) if results were statistically significant. These are both preferable to odds ratios as clinicians find them easier to interpret (Carlisle 2007; Cook and Sackett 1995).

All effect estimates are presented with an estimate of precision using 95% confidence intervals (CI). Confidence intervals are an important measure as they move away from considering whether results are statistically significant, and instead focus on the uncertainty that surrounds an estimate. In clinical practice, it is more important to identify whether an intervention is clinically effective rather than reaching an arbitrary level of statistical significance (Gardner and Altman 1986). Therefore, this thesis will highlight effect estimates that may not reach the traditional level of statistical significance (equivalent to a 95% CI traversing the null portion of the effect estimate), as having a possible effect if suggested by both the estimate and the degree of CI overlap. As calculations of p values are determined by sample size, large studies may show small statistically but not clinically important differences, which may be misinterpreted by the reader as clinically important when p values are taken at face value (Gardner and Altman 1986). Although we accept that sample size also determines precision, CIs can be interpreted as stated above rather than p values being either statistically or not statistically significant.

Due to the expected clinical heterogeneity between studies, the random-effects model was used. As previously discussed, the random-effects model incorporates the degree of statistical heterogeneity into its calculation, resulting in less precise estimates in the presence of large between-study heterogeneity. In addition, the random-effects model assumes that there is no one underlying effect to be estimated, rather studies are selected representing a normal distribution of different underlying effects. Heterogeneity was assessed using the I^2 statistic and the p value derived from the chi-squared statistic. Statistical heterogeneity was considered with I^2 values of >50% or $p<0.10$ (Higgins and Thompson 2002). We conducted all analyses using Comprehensive Meta-analysis Version 3, STATA Version 14 and Review Manager Version 5.3.

2.2.7 Publication bias

We assessed for possible publication bias (imprecise study effects) qualitatively from funnel plots and quantitatively using Egger's linear regression test due to the increased power of this test compared to alternative tests (Higgins and Green 2008). We regarded $p<0.1$ (one-tailed) as evidence of imprecise study effects and thus possible publication bias (Egger *et al.* 1997a). If possible publication bias was found, we conducted sensitivity analysis using trim and fill analysis (Duval and Tweedie 2000) and Orwin's failsafe N (Orwin 1983). For failsafe N analysis, we used the most negative study in the analysis and regarded a null effect as a MD of zero or RR of one. For trim and fill analysis, we used a random-effects model. Although these methods have there limitations, especially in the presence of large between-study heterogeneity (Higgins and Green 2008), we felt it important to quantify the influence of possible publication bias, as this can vary depending on the number of studies at the base of the funnel plot.

2.2.8 Meta-regression

We undertook meta-regression analysis to investigate for possible sources of heterogeneity from clinical parameters, which included the covariates gabapentin dose, type of surgery, type of anaesthesia and control group morphine consumption or pain score (baseline risk). We used control group morphine consumption as an estimate of the degree of pain a participant would have experienced had they not received gabapentin. Using this surrogate measure allows exploration of whether gabapentin is more effective if participants experience more pain postoperatively. This may be product of both how painful the procedure is and the degree of concurrent analgesia used. Previous studies have shown that the efficacy of analgesic agents may be determined by the pain experienced by the participant and therefore this may be an important factor responsible for the heterogeneous results obtained from studies with gabapentin thus far (Averbuch and Katzper 2003; Bjune *et al.* 1996).

Meta-regression was performed using a method of moments, random-effects model. This method does not rely on the underlying assumption that the distribution of studies conforms to a normal distribution. In order to facilitate differences in the dose covariate, studies that reported multiple treatment groups based on dose were treated as separate studies for analysis and numbers in the control group re-distributed so that they were not analysed twice (Higgins and Green 2008). For categorical covariates, we created dummy variables for each comparison. We used hierarchical entry and used the model that explained the largest amount of heterogeneity between the studies. We report the R^2 analogue with a corresponding p value for the model. We used predicted and studentised residual plots to assess for heteroscedasticity and linearity. Studentised residuals were also used to assess outliers. Outliers have the potential to bias the regression model and may be identified from studentised residual values that exceed two or three. Heteroscedasticity refers to the residuals within the regression model. If present, this means that the variability of the residual changes as the independent variable increases. Visual inspection of the studentised residual versus predicted plots, if heteroscedasticity is present, will show a cone-shaped pattern rather than a random scatter of plots. Residuals were also tested for a normal distribution using histograms. Violations to normality include skew (positive and negative), leptokurtosis (higher peak as data points clustered around the mean) and platykurtosis (data points dispersed away from the mean resulting in a flatter peak).

We used Cook's distance to assess the model for influential cases and the variance inflation factor (VIF) to assess for collinearity. Influential cases can also bias the outcomes of a regression analysis. Influential cases may include outliers, although an outlier would only be influential if it significantly changed the regression slope if deleted. Cook's distance assesses the impact of deleting a value from the regression model to check its influence on the model. Values that exceed one have been cited as a cause for concern (Cook and Weisburg 1982). The VIF is used to assess if any independent predictors within a model are highly correlated. Such high correlations can bias a model, as the influence of each of these independent variables cannot be separated. Values of

more than ten (Besley, Kuh and Welsch 1980) or values that average more than one have been suggested as a cause for concern.

From the multivariate model, we constructed a formula in order to predict the likely reduction in morphine consumption from gabapentin under different clinical scenarios. Using the model that explained the largest proportion of heterogeneity, the following formula was used:

$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3$

Y=reduction in morphine consumption with gabapentin

β_0=intercept

β_i=coefficient of independent variables

X_i=value of independent variable

The aim of this formula is to help clinicians in clinical practice estimate the likely effects of gabapentin in their particular patient. In addition, the model could help guide future clinical trials, utilising gabapentin under conditions where it is expected to have the largest clinical effects.

2.2.9 Sensitivity analysis

Sensitivity analysis involved removing studies where standard deviations were estimated. One study removed sensitivity analysis was conducted to assess for any influential studies in the analysis. Finally, studies that received high risk of bias for any domain on the Cochrane risk of bias tool were excluded. Sensitivity analysis is important to identify whether changing decisions regarding study inclusion change the conclusions of the review. For example, if excluding studies that were at high risk of bias caused the positive conclusions of the review to change, this may suggest that such positive conclusions are a product of the underlying bias rather than a true effect.

2.2.10 Trial sequential analysis

As discussed previously, TSA can provide control of the false discovery rate (type I errors) and provide an IS to indicate whether definitive participant numbers have been enrolled in the studies published thus far (reduce type II errors). Furthermore, boundaries of futility can indicate when further trials are unlikely to change the findings of a meta-analysis. We performed a TSA for all outcomes where possible. We estimated control group incidences from both published literature and incidences from the studies included in each analysis. References for these are provided where used. For continuous outcomes, we used both clinically important differences (from subjective clinical experience) and those derived from the effect estimates obtained.

We used estimates of variance and heterogeneity corrections from the studies included in the meta-analysis. Heterogeneity corrections are calculated from statistical heterogeneity from the meta-analysis (D^2). These corrections incorporate the uncertainty from the included studies to increase a required IS in the presence of large between-study heterogeneity. For dichotomous outcomes, we regarded RRR of 20% as clinically significant if incidence was above 10% and for low incidence events (≤10%) we used a 50% RRR as clinically significant. We conducted sensitivity analyses around these estimates by changing various assumptions regarding heterogeneity corrections, measures of variance or changing the assumptions of the effect estimates. We constructed alpha spending monitoring boundaries using the O'Brien-Fleming method with a significance level of $p<0.05$. We used the DerSimonian and Laird method for calculating random-effects estimates. We also constructing futility boundaries using a $1-\beta=0.80$. For handling zero events, we used a constant value of 0.5. We conducted all analyses using TSA software from the Copenhagen Trial Unit (Version 0.9.5.5 beta).

2.2.11 Quality of evidence

As discussed previously, although meta-analyses can increase precision and power of results, they can be prone to problems that affect the quality of the evidence. The GRADE criteria can be used, which can assess the quality of the evidence provided. Evidence is downgraded owing to concerns over unexplained heterogeneity, imprecise effect estimates, high likelihood of publication bias, the risk of bias in the included studies and any indirectness of evidence (Section 1.9.9). We present the quality of the evidence for each outcome when two or more studies are included. With regards to risk of bias, high quality evidence could only be derived from studies scoring low risk for randomisation, allocation concealment, blinding of participants and outcome assessors and low attrition bias, with no high risk elements.

2.3 Results

2.3.1 Characteristics of included studies

Overall, 133 studies were included in the final review (Figure 2.1). The characteristics of the included studies are included in Table 2.1. All studies were parallel group RCTs. There was clinical heterogeneity in the participants studied, type of surgery, dose of gabapentin, administration regimen and type of anaesthesia. The risk of bias assessment for the included studies is presented in Figure 2.2.

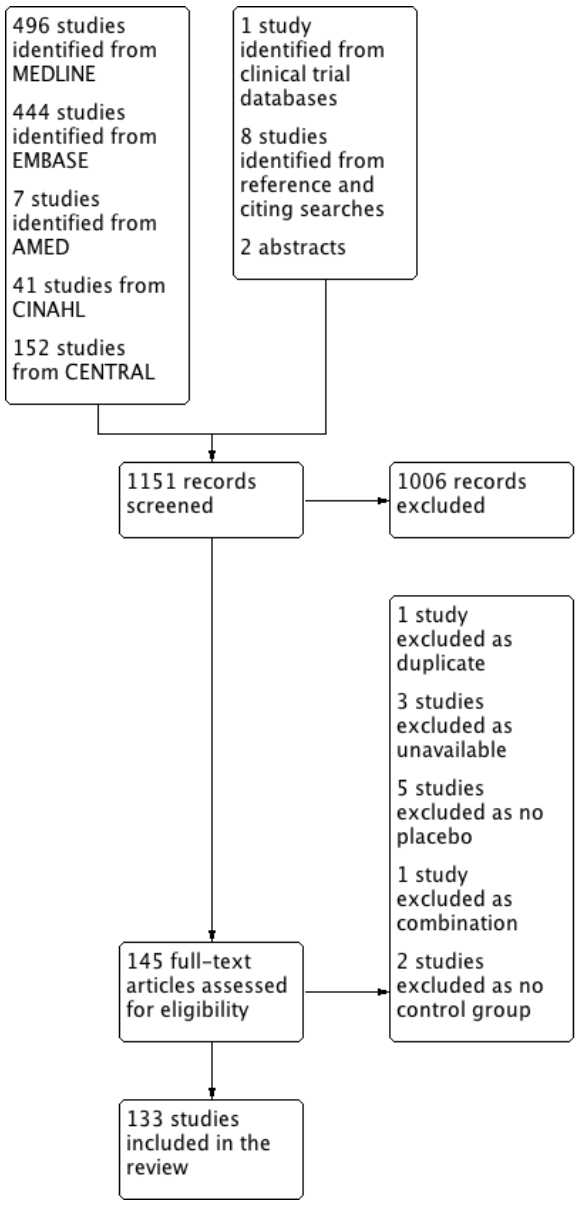
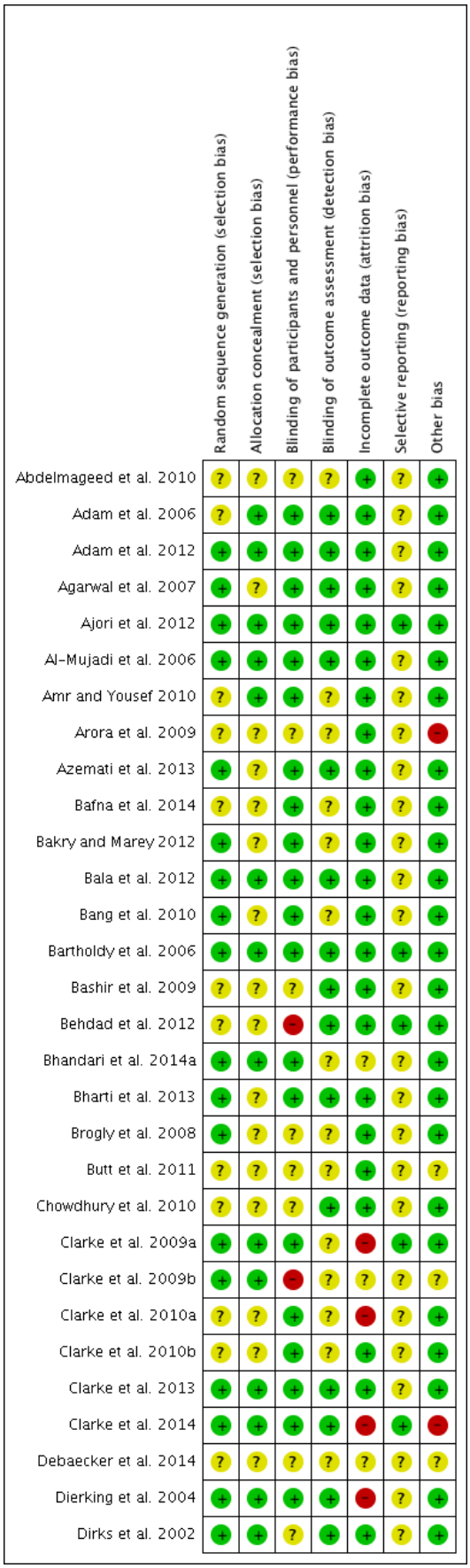
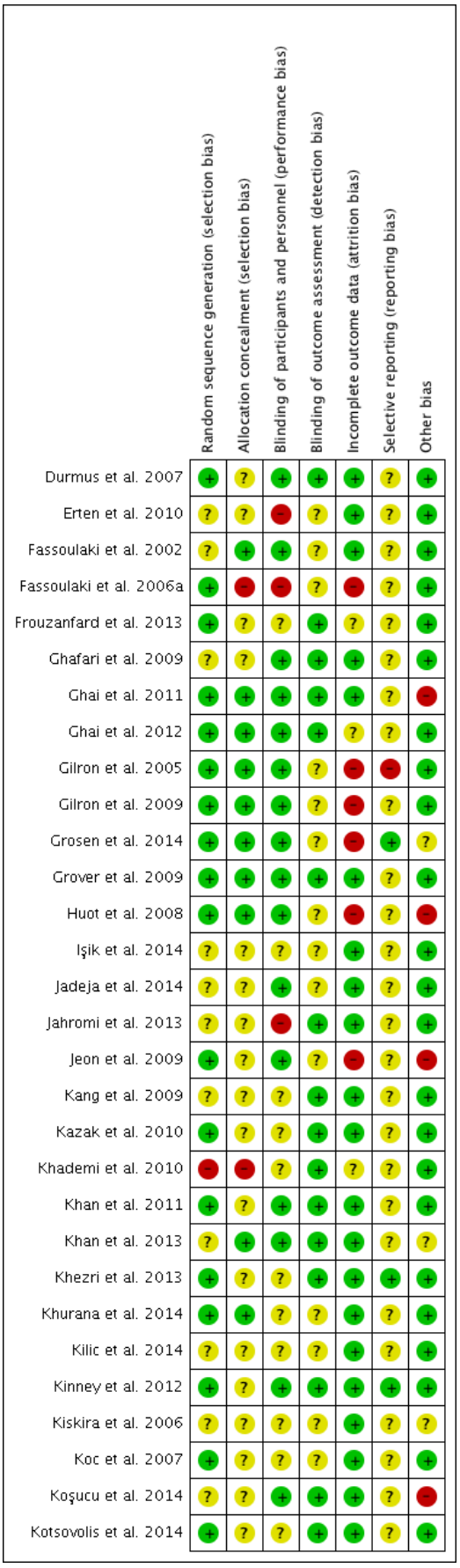
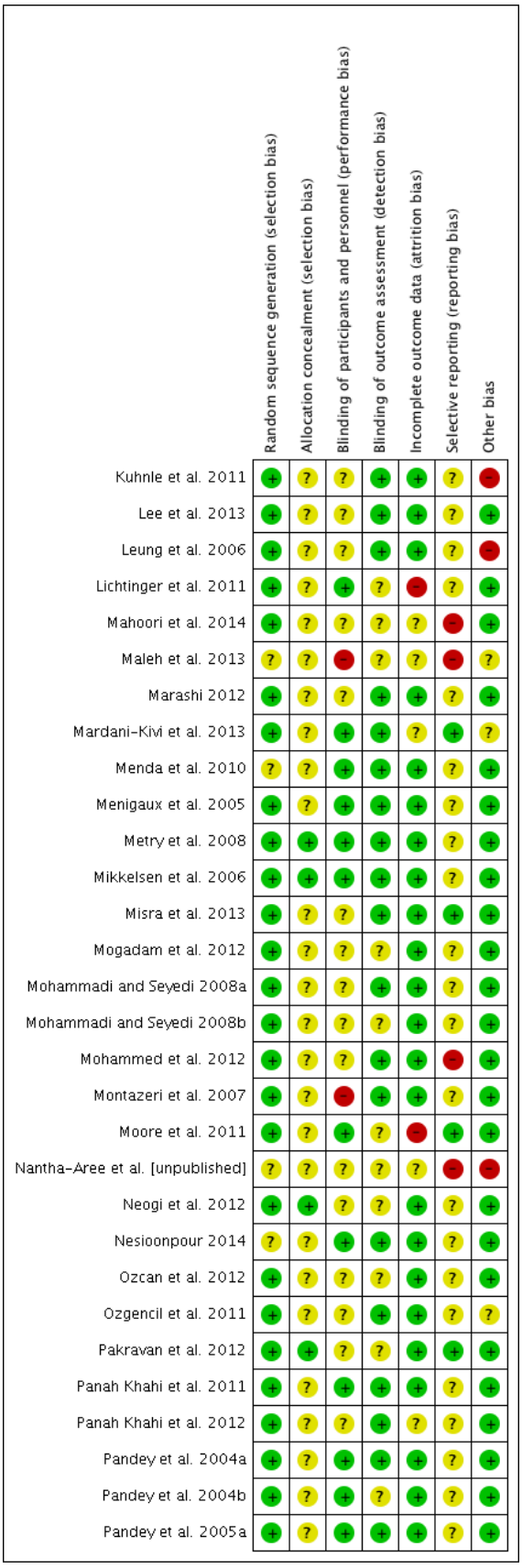
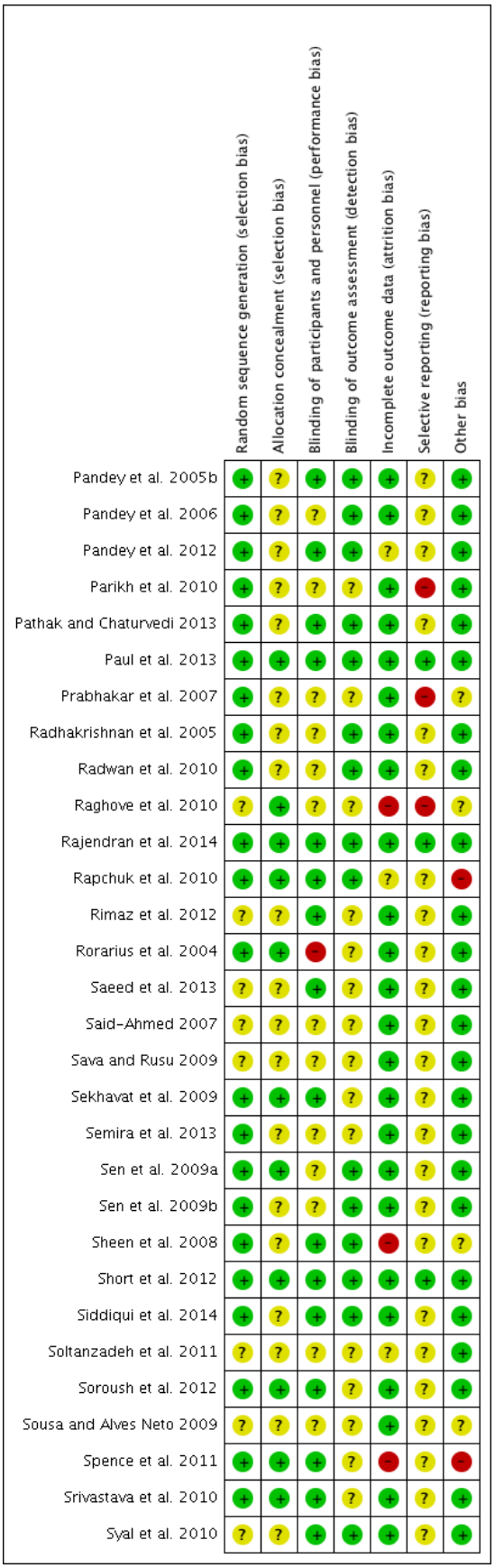


Figure 2.1: PRISMA flowchart of the included studies.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Abdelmageed et al. 2010
Adam et al. 2006
Adam et al. 2012
Agarwal et al. 2007
Ajori et al. 2012
Al-Mujadi et al. 2006
Amr and Yousef 2010
Arora et al. 2009
Azemati et al. 2013
Bafna et al. 2014
Bakry and Marey 2012
Bala et al. 2012
Bang et al. 2010
Bartholdy et al. 2006
Bashir et al. 2009
Behdad et al. 2012
Bhandari et al. 2014a
Bharti et al. 2013
Brogly et al. 2008
Butt et al. 2011
Chowdhury et al. 2010
Clarke et al. 2009a
Clarke et al. 2009b
Clarke et al. 2010a
Clarke et al. 2010b
Clarke et al. 2013
Clarke et al. 2014
Debaecker et al. 2014
Dierking et al. 2004
Dirks et al. 2002


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Durmus et al. 2007
Erten et al. 2010
Fassoulaki et al. 2002
Fassoulaki et al. 2006a
Frouzanfard et al. 2013
Ghafari et al. 2009
Ghai et al. 2011
Ghai et al. 2012
Gilron et al. 2005
Gilron et al. 2009
Grosen et al. 2014
Grover et al. 2009
Huot et al. 2008
Işik et al. 2014
Jadeja et al. 2014
Jahromi et al. 2013
Jeon et al. 2009
Kang et al. 2009
Kazak et al. 2010
Khademi et al. 2010
Khan et al. 2011
Khan et al. 2013
Khezri et al. 2013
Khurana et al. 2014
Kilic et al. 2014
Kinney et al. 2012
Kiskira et al. 2006
Koc et al. 2007
Koşucu et al. 2014
Kotsovolis et al. 2014


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Kuhnle et al. 2011
Lee et al. 2013
Leung et al. 2006
Lichtinger et al. 2011
Mahoori et al. 2014
Maleh et al. 2013
Marashi 2012
Mardani-Kivi et al. 2013
Menda et al. 2010
Menigaux et al. 2005
Metry et al. 2008
Mikkelsen et al. 2006
Misra et al. 2013
Mogadam et al. 2012
Mohammadi and Seyedi 2008a
Mohammadi and Seyedi 2008b
Mohammed et al. 2012
Montazeri et al. 2007
Moore et al. 2011
Nantha-Aree et al. [unpublished]
Neogi et al. 2012
Nesioonpour 2014
Ozcan et al. 2012
Ozgencil et al. 2011
Pakravan et al. 2012
Panah Khahi et al. 2011
Panah Khahi et al. 2012
Pandey et al. 2004a
Pandey et al. 2004b
Pandey et al. 2005a


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Pandey et al. 2005b
Pandey et al. 2006
Pandey et al. 2012
Parikh et al. 2010
Pathak and Chaturvedi 2013
Paul et al. 2013
Prabhakar et al. 2007
Radhakrishnan et al. 2005
Radwan et al. 2010
Raghove et al. 2010
Rajendran et al. 2014
Rapchuk et al. 2010
Rimaz et al. 2012
Rorarius et al. 2004
Saeed et al. 2013
Said-Ahmed 2007
Sava and Rusu 2009
Sekhavat et al. 2009
Semira et al. 2013
Sen et al. 2009a
Sen et al. 2009b
Sheen et al. 2008
Short et al. 2012
Siddiqui et al. 2014
Soltanzadeh et al. 2011
Soroush et al. 2012
Sousa and Alves Neto 2009
Spence et al. 2011
Srivastava et al. 2010
Syal et al. 2010

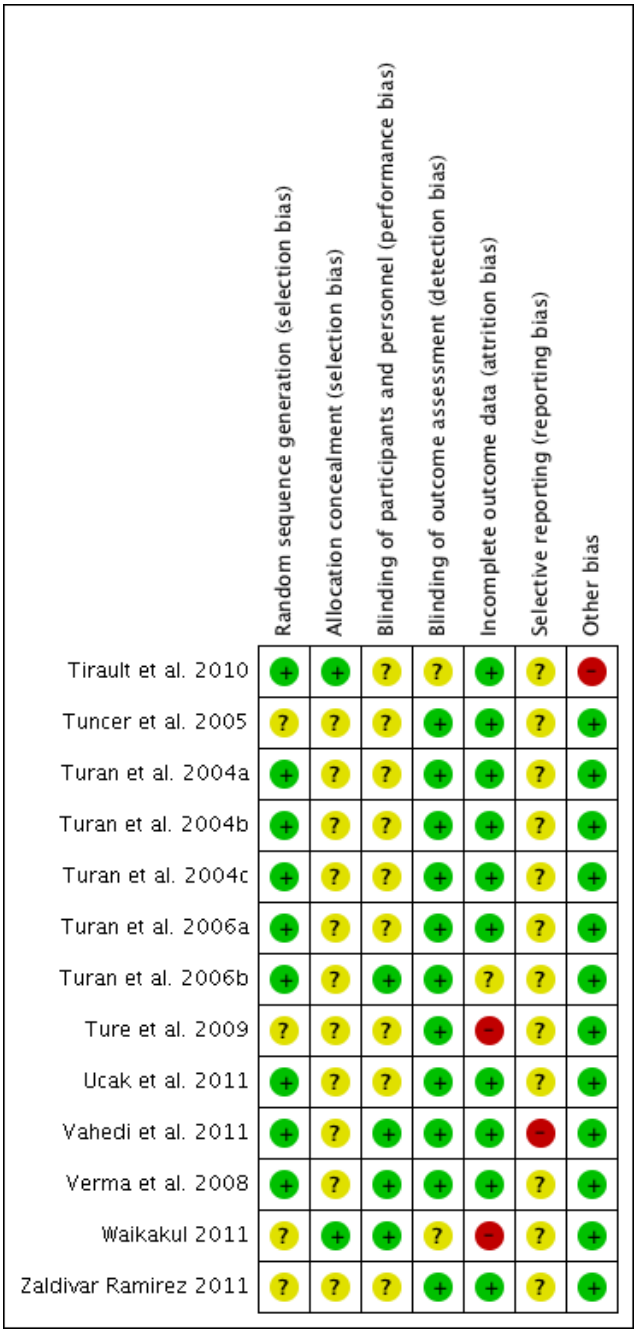


Figure 2.2: Risk of bias assessments for the included studies. Red indicates high risk, yellow unclear risk and green low risk. Any study scoring high risk for any element on quality assessment was later excluded on sensitivity analysis.

Study	Mean age	Sex	N	Intervention	Comparison	Country	Type of anaesthesia	Type of surgery
JOINT ARTHROSCOPY								
Adam *et al.* 2006	45	32%	53	800mg 2hrs before surgery	Placebo	France	General anaesthesia with intra-scalene brachial plexus block	Arthroscopic shoulder surgery
Bang *et al.* 2010	57.9	63%	46	300mg 2hrs before surgery	Placebo	South Korea	General anaesthesia	Arthroscopic rotator cuff repair
Mardani-Kivi *et al.* 2013	31	12%	114	600mg 2hrs before surgery	Placebo	Iran	General anaesthesia	Arthroscopic anterior cruciate ligament repair
Menigaux *et al.* 2005	31	32%	40	1200mg 1-2hrs before surgery	Placebo	France	General anaesthesia	Arthroscopic anterior cruciate ligament repair
Montazeri *et al.* 2007	34.6	23%	70	300mg 2hrs prior to surgery	Placebo	Iran	General anaesthesia	Knee arthroscopy
Spence *et al.* 2011	31.6	16%	57	300mg within 1hr surgery, 300mg night after surgery then 300mg BD for 48hrs	Placebo	USA	General anaesthesia with intra-scalene brachial plexus block	Shoulder arthroscopy
JOINT ARTHROPLASTY								

Clarke *et al.* 2009a	60.2	39%	114	600mg 2hrs before operation or 2hrs after	Placebo	Canada	Spinal anaesthesia	Total hip arthroplasty
Clarke *et al.* 2009b	62.4	61%	36	600mg 2hrs before operation and 4 groups different postoperative doses	Placebo	Canada	Spinal anaesthesia	Total knee arthroplasty
Clarke *et al.* 2010a	NR	28%	82	600mg 2hrs before operation or 2hrs after	Placebo	Canada	Spinal anaesthesia	Total hip arthroplasty
Clarke *et al.* 2010b	43.5	NR	70	600mg 2hrs before operation	Placebo	Canada	Spinal anaesthesia	Total hip arthroplasty
Clarke *et al.* 2014	62.8	50%	179	600mg 2hrs before surgery and 200mg TDS for 4 days	Placebo	Canada	Spinal anaesthesia with sciatic and femoral nerve block	Total knee arthroplasty
Nantha-Aree *et al.* 2011 [unpublished]	60.7	43%	102	600mg preoperatively and 200mg postoperatively then 200mg TDS for 2	Placebo	Canada	Spinal anaesthesia	Total hip arthroplasty

				days				
Paul *et al.* 2013	62.8	63%	101	600mg preoperatively and 600mg per day first 2 days after operation	Placebo	Canada	Spinal anaesthesia	Total knee arthroplasty
HYSTERECTOMY								
Ajori *et al.* 2012	48.7	100%	138	600mg 1hr before induction	Placebo	Iran	General anaesthesia	Abdominal hysterectomy
Behdad *et al.* 2012	47	100%	61	100mg night before and 300mg 2hrs before surgery	Multivitamin	Iran	General anaesthesia	Abdominal hysterectomy
Dierking *et al.* 2004	46.9	100%	71	1200mg 1hr before surgery and 600mg TDS for one day	Placebo	Denmark	General anaesthesia	Abdominal hysterectomy with/without salpingo-oophorectomy
Durmus *et al.* 2007	48	100%	50	1200mg 1hr before induction	Placebo	Turkey	General anaesthesia	Abdominal hysterectomy
Fassoulaki *et al.* 2006a	42	100%	53	400mg QDS day before surgery and 5 days postoperatively	Placebo	Greece	General anaesthesia	Abdominal hysterectomy

Frouzanfard *et al.* 2013	44.2	100%	50	1200mg 2hrs before operation	Placebo	Iran	General anaesthesia	Abdominal hysterectomy
Ghafari *et al.* 2009	44.6	100%	66	300mg night before and 1hr before surgery	Placebo	Iran	General anaesthesia	Abdominal hysterectomy with salpingo-oophorectomy
Ghai *et al.* 2011 and 2012	44.5	100%	60	900mg 1-2hrs before operation	Placebo	India	General anaesthesia	Abdominal hysterectomy
Gilron *et al.* 2005	44.5	100%	103	600mg 1hr before induction then TDS for 2 days after surgery and rofecoxib	Placebo and rofecoxib	Canada	General anaesthesia	Abdominal hysterectomy
Khan *et al.* 2013	44	100%	69	1200mg 2hrs before operation	Placebo	Pakistan	General anaesthesia	Abdominal hysterectomy
Rorarius *et al.* 2004	46	100%	75	1200mg 2.5hrs before induction	Oxazepam	Finland	General anaesthesia	Vaginal hysterectomy
Sekhavat *et al.* 2009	42.7	100%	98	600mg 1hr before surgery and 100mg TDS for one day	Placebo	Iran	General anaesthesia	Abdominal hysterectomy
Sen *et al.* 2009a	46.5	100%	40	1200mg 1hr before	Placebo	Turkey	General anaesthesia	Abdominal hysterectomy

				surgery				with salpingo-oophorectomy
Turan *et al.* 2004b	51.4	100%	50	1200mg 1hr before surgery	Placebo	Turkey	General anaesthesia	Abdominal hysterectomy with salpingo-oophorectomy
Turan *et al.* 2006a	50.8	100%	100	1200mg 1hr before surgery and OD for 2 days and rofecoxib	Placebo and rofecoxib	Turkey	General anaesthesia	Abdominal hysterectomy with salpingo-oophorectomy
Verma *et al.* 2008	50.8	100%	50	300mg 2hr before surgery	Placebo	India	Spinal and epidural anaesthesia	Abdominal hysterectomy
CARDIOTHORACIC SURGERY								
Grosen *et al.* 2014	64.5	50%	67	1200mg 2hrs before surgery then 300mg BD for one day, 300mg TDS for one day and 300mg QDS for 3 further days	Placebo	Denmark	General anaesthesia and epidural	Thoracotomy for lung malignancy
Huot *et al.* 2008	60	45%	51	1200mg 2hrs before surgery	Placebo	Canada	General anaesthesia and epidural	Thoracotomy

Kinney *et al.* 2012	64.3	48%	120	600mg 2hrs before surgery	Diphenhydra -mine	USA	General anaesthesia and epidural	Thoracotomy
Koşucu *et al.* 2014	54.8	52%	60	1200mg 1hr before surgery	Placebo	Turkey	General anaesthesia	Thoracotomy for segmentectomy
Menda *et al.* 2010	51	0%	60	600mg 2hrs before surgery	Placebo	Turkey	General anaesthesia	CABG
Rapchuk *et al.* 2010	60.2	11%	54	1200mg 2hrs before surgery and 600mg BD for 2 days	Placebo	Canada	General anaesthesia	Cardiac surgery with median sternotomy
Soltanzadeh *et al.* 2011	56.8	0%	60	800mg 2hrs before surgery and 400mg 2hrs after extubation	Placebo	Iran	General anaesthesia	CABG
Ucak *et al.* 2011	61.1	40%	40	1200mg 1hr before surgery and following 2 days	Placebo	Turkey	General anaesthesia	CABG
CHOLECYSTECTOMY								
Bashir *et al.* 2009	NR	75%	100	600mg 2hrs before surgery	Vitamin B	India	General anaesthesia	Laparoscopic cholecystectomy
Bhandari *et al.* 2014a	42.7	65%	40	600mg 2hrs before	Placebo	India	General anaesthesia	Laparoscopic

				surgery and 12hrs after first dose				cholecystectomy
Gilron *et al.* 2009	NR	76%	60	1200mg 1hr before surgery and 400mg the night of surgery then TDS for 2 days and meloxicam 15mg for 3 days	Meloxicam 15mg for 3 days	Canada	General anaesthesia	Laparoscopic cholecystectomy
Khademi *et al.* 2010	51.7	92%	87	600mg 2hrs before surgery	Placebo	Iran	General anaesthesia	Open cholecystectomy
Kotsovolis *et al.* 2014	50.8	73%	48	600mg 4hrs before and 24hrs after surgery	Placebo	Greece	General anaesthesia	Laparoscopic cholecystectomy
Maleh *et al.* 2013	40.3	100%	80	600mg 1hr before surgery	Placebo	Iran	General anaesthesia	Laparoscopic cholecystectomy
Neogi *et al.* 2012	40.4	63%	60	900mg 2hrs before induction	Vitamin B	India	General anaesthesia	Laparoscopic cholecystectomy
Pandey *et al.* 2004b	42.6	65%	306	300mg 2hrs before surgery	Placebo	India	General anaesthesia	Laparoscopic cholecystectomy

Pandey *et al.* 2006	42.3	83%	250	600mg 2hrs before surgery	Placebo	India	General anaesthesia	Laparoscopic cholecystectomy
Pandey *et al.* 2012	43.4	51%	70	600mg 2hrs before surgery	Placebo	India	General anaesthesia	Laparoscopic cholecystectomy
Pathak and Chaturvedi 2013	39.5	86%	80	1200mg 2hrs before surgery	Placebo	Nepal	General anaesthesia	Open cholecystectomy
Saeed *et al.* 2013	40.1	83%	100	600mg 2hrs before surgery	Vitamin B	Iraq	General anaesthesia	Laparoscopic cholecystectomy
Semira *et al.* 2013	40.9	72%	60	600mg 2hrs before surgery	Placebo	India	General anaesthesia	Laparoscopic cholecystectomy
Soroush *et al.* 2012	47.2	83%	92	600mg 2hrs before surgery and 6hrs after	Placebo	Iran	General anaesthesia	Laparoscopic cholecystectomy
Sousa and Alves Neto 2009	NR	NR	40	1200mg 2hrs before induction	Placebo	Brazil	General anaesthesia	Cholecystectomy
Srivastava *et al.* 2010	43.8	68%	120	600mg 2hrs before surgery	Placebo	India	General anaesthesia	Minilap open cholecystectomy
Syal *et al.* 2010	39.7	76%	120	1200mg 2hrs before induction and paracetamol	Placebo and paracetamol	India	General anaesthesia	Open cholecystectomy

BREAST SURGERY								
Amr and Yousef 2010	43.5	100%	100	300mg a day the night before surgery for 10 days	Placebo	Egypt	General anaesthesia	Partial or radical mastectomy with axillary dissection
Azemati *et al.* 2013	47.2	100%	100	600mg 30mins before induction	Placebo	Iran	General anaesthesia	Modified radical mastectomy or quadrantectomy with axillary node dissection
Bharti *et al.* 2013	46.5	100%	40	600mg 2hrs before surgery	Placebo	India	General anaesthesia	Total mastectomy with axillary node clearance
Butt *et al.* 2011	NR	100%	100	1200mg 1hr before surgery	Placebo	India	General anaesthesia	Mastectomy
Dirks *et al.* 2002	60	100%	65	1200mg 1hr before surgery	Placebo	Denmark	General anaesthesia	Radical mastectomy with axillary dissection
Fassoulaki *et al.* 2002	43.6	100%	46	400mg TDS the evening before surgery for 10 days	Placebo	Greece	General anaesthesia	Modified radical mastectomy or lumpectomy with axillary node dissection
Grover *et al.* 2009	45.8	100%	46	600mg 1hr before	Vitamin B	India	General anaesthesia	Total mastectomy with

				surgery				axillary node dissection
Metry *et al.* 2008	57.8	100%	101	1200mg 2 hours before or 1200mg postoperatively	Placebo	Egypt	General anaesthesia	Mastectomy
ENT/DENTAL								
Abdelmageed *et al.* 2010	30.6	42%	60	1200mg 2hrs before induction	Placebo	Saudi Arabia	General anaesthesia	Tonsillectomy
Al-Mujadi *et al.* 2006	47	74%	72	1200mg 2hrs before surgery	Placebo	Kuwait/India	General anaesthesia	Thyroidectomy
Brogly *et al.* 2008	49	86%	43	1200mg 2hrs before surgery	Placebo	France	General anaesthesia	Total or partial thyroidectomy
Debaecker *et al.* 2014	NR	NR	83	1200mg 2hrs before surgery	Placebo	France	General anaesthesia	Thyroid surgery
Işik *et al.* 2014	34.3	73%	60	600mg 30mins before endodontic treatment	Placebo	Turkey	Local anaesthesia	Endodontic treatments
Jahromi *et al.* 2013	31.8	35%	60	300mg 1hr before surgery	Placebo	Iran	General anaesthesia	Open reduction and internal fixation maxillofacial trauma
Jeon *et al.* 2009	26.1	53%	58	600mg night before	Placebo	South Korea	General anaesthesia	Tonsillectomy

				and 1hr before surgery				
Kazak *et al.* 2010	34	42%	60	600mg 1hr before surgery	Placebo	Turkey	Local anaesthesia and sedation	Nasal septal or nasal sinus surgery
Kilic *et al.* 2014	37	48%	60	1200mg 1hr before surgery	Placebo	Turkey	General anaesthesia	Functional endoscopic sinus surgery
Lee *et al.* 2013	48.7	76%	71	600mg 1hr before induction	Placebo	Korea	General anaesthesia	Total or partial thyroidectomy
Marashi 2012	38.3	82%	44	900mg 2hrs before surgery	Placebo	Iran	General anaesthesia	Total thyroidectomy
Mikkelsen *et al.* 2006	NR	69%	49	1200mg 1hr before induction and 600mg BD then 600mg TDS for 5 days	Placebo	Denmark	General anaesthesia	Tonsillectomy
Mogadam *et al.* 2012	14.5	38%	60	20mg/kg 1hr before surgery	Placebo	Iran	General anaesthesia	Tonsillectomy
Mohammed *et al.* 2012	32.1	NR	80	1200mg 1hr before surgery	Placebo	Egypt	General anaesthesia	Functional endoscopic sinus surgery
Nesioonpour 2014	28.6	45%	62	800mg 1hr before	Placebo	Iran	General anaesthesia	Repair of deviated nasal

				surgery				septum
Turan *et al.* 2004c	28.5	NR	50	1200mg 1hr before surgery	Placebo	Turkey	Local anaesthesia and sedation	Nasal septal or nasal sinus surgery
SPINAL SURGERY								
Erten *et al.* 2010	44.1	46%	59	900mg or 1200mg 1hr preoperatively	Vitamin C	Turkey	General anaesthesia	Elective laminectomy
Khan *et al.* 2011	41.8	35%	175	600mg, 900mg or 1200mg 2hrs pre or immediately post-incision via NG tube	Placebo	Iran	General anaesthesia	Single level lumbar laminectomy
Khurana *et al.* 2014	48	27%	60	300mg 1hr preoperatively and TDS	Placebo	India	General anaesthesia	Lumbar discectomy
Kiskira *et al.* 2006	NR	NR	40	1200mg 1hr before surgery	Placebo	Greece	NR	Lumbar discectomy
Leung *et al.* 2006	59.6	48%	21	900mg 1-2hrs preoperatively	Placebo	USA	General anaesthesia	Spinal surgery
Ozgencil *et al.* 2011	49.6	53%	60	600mg 2hrs before operation and 10 and	Placebo	Turkey	General anaesthesia	Elective decompressive lumbar laminectomy and

				22hrs after operation				discectomy
Pandey *et al.* 2004a	38.8	32%	56	300mg 2hrs before surgery	Placebo	India	General anaesthesia	Single-level disc surgery
Pandey *et al.* 2005a	41.2	33%	100	Four groups receiving doses of gabapentin 2hrs before surgery (300-1200mg)	Placebo	India	General anaesthesia	Single-level disc surgery
Radhakrishnan *et al.* 2005	40.6	33%	60	400mg (one dose night before surgery and one dose 2hrs prior to induction)	Placebo	India	General anaesthesia	Elective lumbar laminectomy and discectomy
Turan *et al.* 2004a	46.5	44%	50	1200mg 1hr before operation	Placebo	Turkey	General anaesthesia	Lumbar discectomy or spinal fusion
Vahedi *et al.* 2011	44.4	42%	76	300mg 2hrs before operation	Placebo	Iran	General anaesthesia	Single level lumbar laminectomy and discectomy
CAESAREAN SECTION								
Moore *et al.* 2011	34	100%	44	600mg 1hr before surgery	Placebo	Canada	Spinal anaesthesia	Caesarean section

Short *et al.* 2012	35.1	100%	126	300mg or 600mg 1hr before surgery	Placebo	Canada	Spinal anaesthesia	Caesarean section
GENERAL SURGERY								
Jadeja *et al.* 2014	38.4	64%	50	1200mg 2hrs before surgery	Placebo	India	General anaesthesia	Upper abdominal surgery
Mahoori *et al.* 2014	47.2	0%	50	400mg 2hrs before surgery	Placebo	Iran	Spinal anaesthesia	Inguinal herniorrhaphy
Mohammadi and Seyedi 2008	40	NR	80	300mg 1hr before surgery	Placebo	Iran	General anaesthesia	Abdominal surgery (general and gynaecological)
Parikh *et al.* 2010	39.6	60%	60	600mg 1hr before surgery	Placebo	India	General anaesthesia	Abdominal surgery
Radwan *et al.* 2010	38.1	54%	50	600mg 1hr before surgery	Placebo	Egypt	General anaesthesia	Abdominal surgery
Sava and Rusu 2009	62.5	40%	50	800mg 2 hrs before surgery	Placebo	Romania	General anaesthesia	Colorectal surgery
Sen *et al.* 2009b	24	0%	60	1200mg 1hr before surgery	Placebo	Turkey	Spinal anaesthesia	Inguinal herniorrhaphy
Siddiqui *et al.* 2014	37.6	NR	72	600mg 1hr before	Placebo	Canada	General anaesthesia	Laparotomy for IBD

				surgery				
Zaldivar Ramirez 2011	48.1	47%	34	300mg 1hr before surgery and 300mg BD after surgery	Placebo	Mexico	General anaesthesia	Laparoscopic Nissen fundoplication
GYNAECOLOGICAL SURGERY								
Bafna *et al.* 2014	42	100%	60	600mg 1hr before surgery	Placebo	India	Spinal anaesthesia	Gynaecological surgery (total abdominal hysterectomy and laparotomy for ovarian cyst)
Bartholdy *et al.* 2006	37	100%	80	1200mg 30mins before surgery	Placebo	Denmark	General anaesthesia	Laparoscopic sterilisation
Chowdhury *et al.* 2010	40.5	100%	200	300mg 2hrs before surgery	Placebo	India	General anaesthesia	Internal ligation, pelvic floor repair, Bartholian cyst marsupialisation and Gartner's duct cyst excision
Kang *et al.* 2009	45.3	100%	100	300mg, 600mg or 1200mg 2hrs before	Placebo	Korea	General anaesthesia	Laparotomy for gynaecological surgery

				surgery				
Mohammadi and Seyedi 2008b	31.6	100%	70	300mg 1hr before surgery	Placebo	Iran	General anaesthesia	Laparoscopic surgery for assisted reproductive technologies
Said-Ahmed 2007	37	100%	80	300mg, 600mg or 1200mg 2hrs before surgery	Placebo	Egypt	General anaesthesia	Myomectomy
PLASTIC SURGERY								
Rimaz *et al.* 2012	49.4	70%	50	1200mg 2hrs before surgery	Placebo	Iran	General anaesthesia	Debridement of burn wounds
Turan *et al.* 2006b	52	NR	40	1200mg 1hr before surgery and OD for 2 days	Placebo	Turkey	General and epidural anaesthesia	Scar revision and/or skin graft
ORTHOPAEDIC SURGERY								
Panah Khahi *et al.* 2011	32.5	17%	64	300mg 2hrs before surgery	Placebo	Iran	Spinal anaesthesia	Internal fixation of tibia
Panah Khahi *et al.* 2012	32.5	27%	64	300mg immediately after surgery	Placebo	Iran	Spinal anaesthesia	Internal fixation of tibia
Raghove *et al.* 2010	30.6	0%	90	200mg or 600mg 1hr	Placebo	India	Spinal anaesthesia	Lower limb orthopaedic

				before operation				
Sheen *et al.* 2008	27.5	4%	80	1200mg 2hrs before operation	Placebo	Taiwan	Spinal anaesthesia	Cruciate ligament reconstruction, open reduction, removal of implant and arthroscopy
Tuncer *et al.* 2005	37.3	NR	45	800mg or 1200mg 1hr before operation	Placebo	Turkey	General anaesthesia	Major orthopaedic surgery
Waikakul 2011	49.6	46%	99	400mg 1-2hrs before operation and 300mg 12hrs and 24hrs after operation and celecoxib	Placebo and celecoxib	Thailand	General anaesthesia	Major orthopaedic surgery
OPTHALMOLOGY								
Bakry and Marey 2012	62.3	28%	60	1200mg 2 hours before anaesthesia	Placebo	Egypt	Peribulbar nerve block	Cataract surgery
Khezri *et al.* 2013	74.2	41%	80	600mg 1.5hrs before surgery	Placebo	Iran	Retrobulbar nerve block	Cataract surgery
Kuhnle *et al.* 2011	31.8	11%	82	300mg TDS for 7 days started 2 days	Placebo	USA	NR	Photorefractive keratectomy

				before surgery				
Lichtinger *et al.* 2011	26.7	62%	40	300mg night before surgery, BD on day of surgery and TDS 3 days postoperatively	Placebo	Mexico	Local anaesthesia	Photorefractive keratectomy
Pakravan *et al.* 2012	26.6	55%	100	300mg TDS for 3 days starting 2 hours after surgery	Placebo	Iran	Local anaesthesia	Photorefractive keratectomy
NEUROSURGERY								
Misra *et al.* 2013	44	45%	73	600mg 2hrs before induction	Vitamin B complex	India	General anaesthesia	Craniotomy for supratentorial tumour
Özcan *et al.* 2012	52.8	40%	40	600mg 1hr before surgery	Placebo	Turkey	General anaesthesia	Craniotomy for supratentorial tumour
Ture *et al.* 2009	47	52%	75	1200mg for 7 days before surgery	Phenytoin	Turkey	General anaesthesia	Craniotomy for supratentorial tumour
MIXED								
Adam *et al.* 2012	37.5	39%	64	1200mg 2-3hrs before surgery	Placebo	France	General and regional anaesthesia	Orthopaedic or open inguinal hernia repair
Arora *et al.* 2009	41	37%	60	1200mg 1hr before	Multivitamin	India	Spinal anaesthesia	Infra-umbilical surgery

				anaesthesia				
Clarke *et al.* 2013	41.7	100%	44	1200mg 2 hrs before surgery	Placebo	Canada	NR	General, gynaecological, plastics and ENT surgery
Prabhakar *et al.* 2007	29.2	5%	20	800mg 2hrs before surgery	Placebo	India	General anaesthesia	Surgery for brachial plexus injury
Rajendran *et al.* 2014	42.2	35%	60	900mg 1hr before surgery	Placebo	India	Spinal anaesthesia	General, urological, vascular and plastic surgery
Tirault *et al.* 2010	45	64%	135	1200mg 2hrs before surgery	Placebo	France	General anaesthesia	Orthopaedic, ENT, spinal, general, gynaecological and endoscopic procedures
UROLOGY								
Agarwal *et al.* 2007	39	18%	108	600mg 1hr before surgery	Placebo	India	General anaesthesia	Percutaneous nephrolithotomy
Bala *et al.* 2012	53.3	21%	100	600mg or 1200mg 1hr before surgery	Placebo	India	Spinal anaesthesia	Transurethral resection of bladder tumour
Koç, Memis and Sut 2007	38.5	0%	80	800mg 1hr before surgery and	Placebo and dexamethaso	Turkey	General anaesthesia	Varicocele surgery

				dexamethasone	-ne			
Pandey *et al.* 2005b	43.6	68%	60	600mg 2hrs before or 600mg post-incision	Placebo	India	General anaesthesia	Open donor nephrectomy

Table 2.1: Characteristics of the included studies. NR=not reported; OD=once daily, BD=twice daily; TDS=three times daily; QDS=four times daily; CABG=coronary artery bypass graft; ENT=ear, nose and throat; IBD=inflammatory bowel disease. Sex is reported as the % female. Ghai 2011 and 2012 are duplicates of the same study.

2.3.2 24 hour morphine consumption

Overall, 66 studies with 5257 participants were included in the analysis. Gabapentin resulted in lower consumption of morphine in the first 24 hours after surgery (MD -8.44mg; 95% CI -9.62mg to -7.26mg; Figure 2.3). There was evidence of considerable statistical heterogeneity (I^2=98%; p<0.001). The quality of evidence was regarded as low according to GRADE (downgraded due risk of bias and potential publication bias).

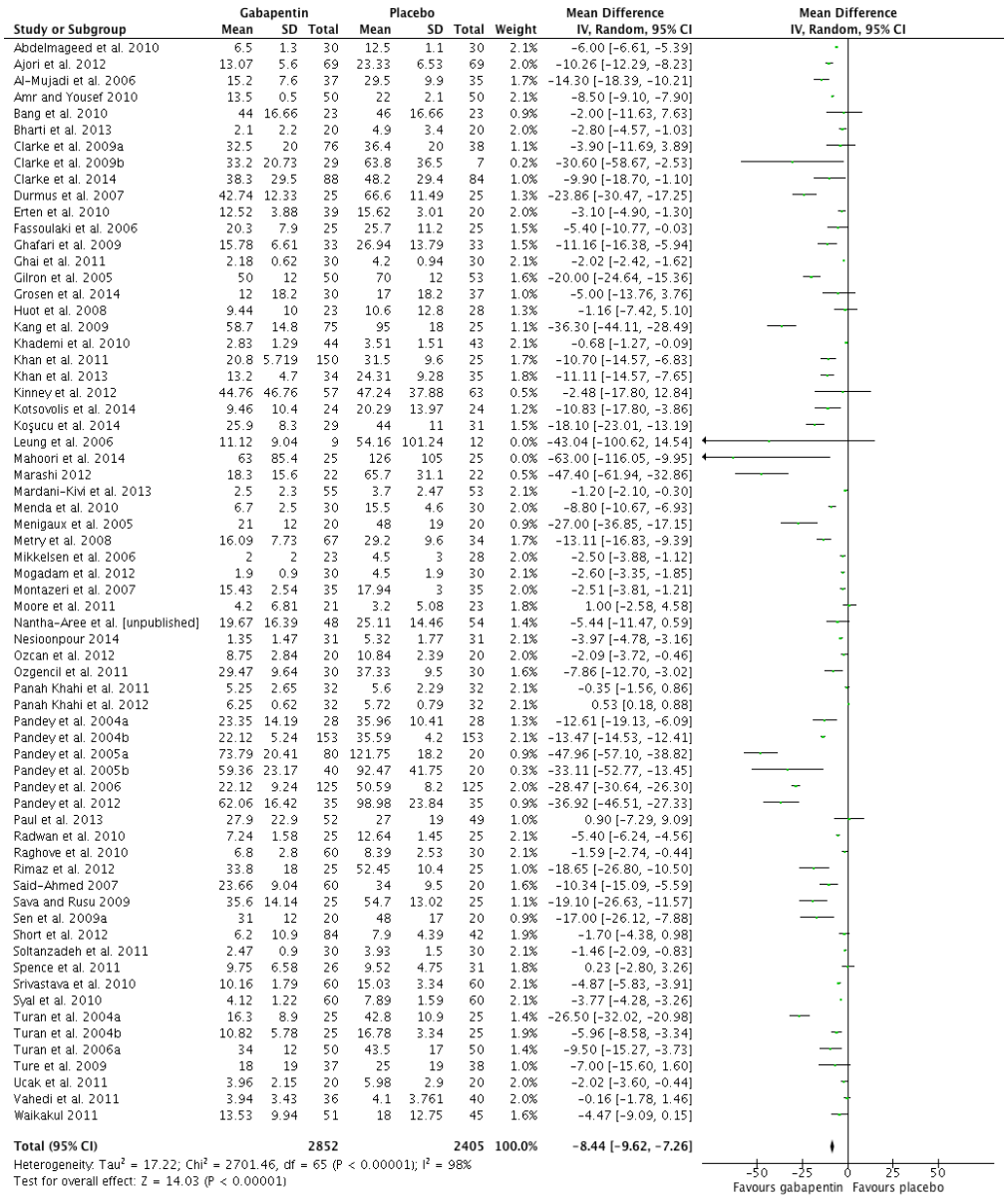


Figure 2.3: Forest plot of gabapentin effect on 24-hour morphine consumption (mg).

In addition, there was evidence of imprecise study effects with an asymmetric funnel plot (Figure 2.4) and a statistically significant Egger's regression test ($p<0.001$). Trim and fill analysis found only three missing studies to the right of the mean, which did not significantly change the effect estimates (MD -7.97mg; 95% CI -9.16mg to -6.78mg) and Orwin's failsafe N calculated an additional 211 negative studies would be required to observe a negative result.

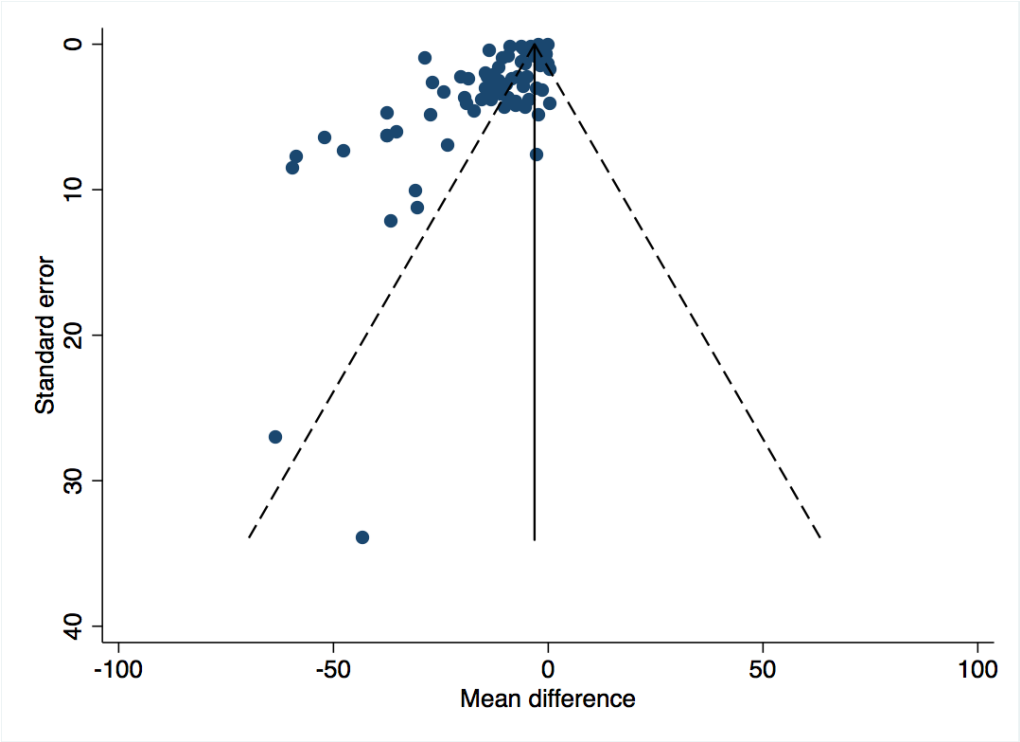


Figure 2.4 Funnel plot of gabapentin effects on 24-hour morphine consumption. X-axis shows the mean difference and the Y-axis shows the standard error.

Meta-regression analysis revealed that the heterogeneity between the studies was largely predicted by the 24-hour morphine consumption in the control group (R^2=81%; $p<0.001$) (Figure 2.5). The addition of type of anaesthesia and gabapentin dose significantly improved this (R^2=90%; $p<0.001$). The addition of type of surgery did not improve the model. Using the meta-regression equation, the following reductions in morphine consumption would be expected in the following clinical examples:

Firstly, for a patient undergoing a procedure with an expected morphine consumption of 30mg, using a gabapentin dose of 1200mg and undergoing general anaesthesia, the expected reduction in morphine consumption would be:

3.73 + (-0.378 x 30) + (-0.0023 x 1200) + (-1.917 x 1) = 12.29mg

Conversely, a patient undergoing a procedure with an expected morphine consumption of 10mg, using a gabapentin dose of 600mg and undergoing spinal anaesthesia, the expected reduction in morphine consumption would be:

3.73 + (-0.378 x 10) + (-0.0023 x 600) + (-1.917 x 0) = 1.43mg

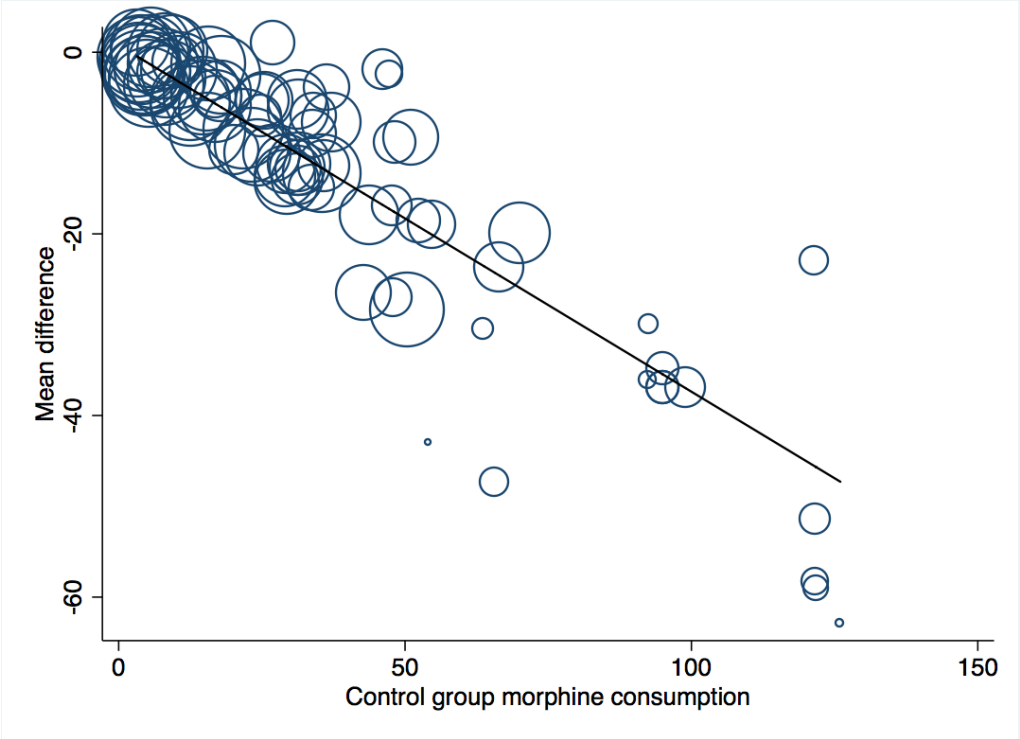


Figure 2.5 Meta-regression plot. X-axis shows the control group morphine consumption in mg and the Y-axis the mean difference in morphine consumption with gabapentin in mg.

In terms of regression diagnostics, predicted versus studentised residual plots revealed no violations of the assumptions of linearity and homoscedasticity. Histograms showed residuals to be approximately normally distributed. Although 13 studies had studentised residuals of more than two, Cook's distance revealed there were no influential cases in the model. The final model had no VIF values above 10. However, the model that included type of surgery showed evidence of multicollinearity with spinal anaesthesia and orthopaedic surgery (VIF 14.4 and 11.8 respectively).

On sensitivity analysis, removal of studies that estimated standard deviations did not significantly affect the results. In addition, removal of each study from the analysis did not identify any influential studies. Finally, removing studies that were at high risk of bias did not change the results.

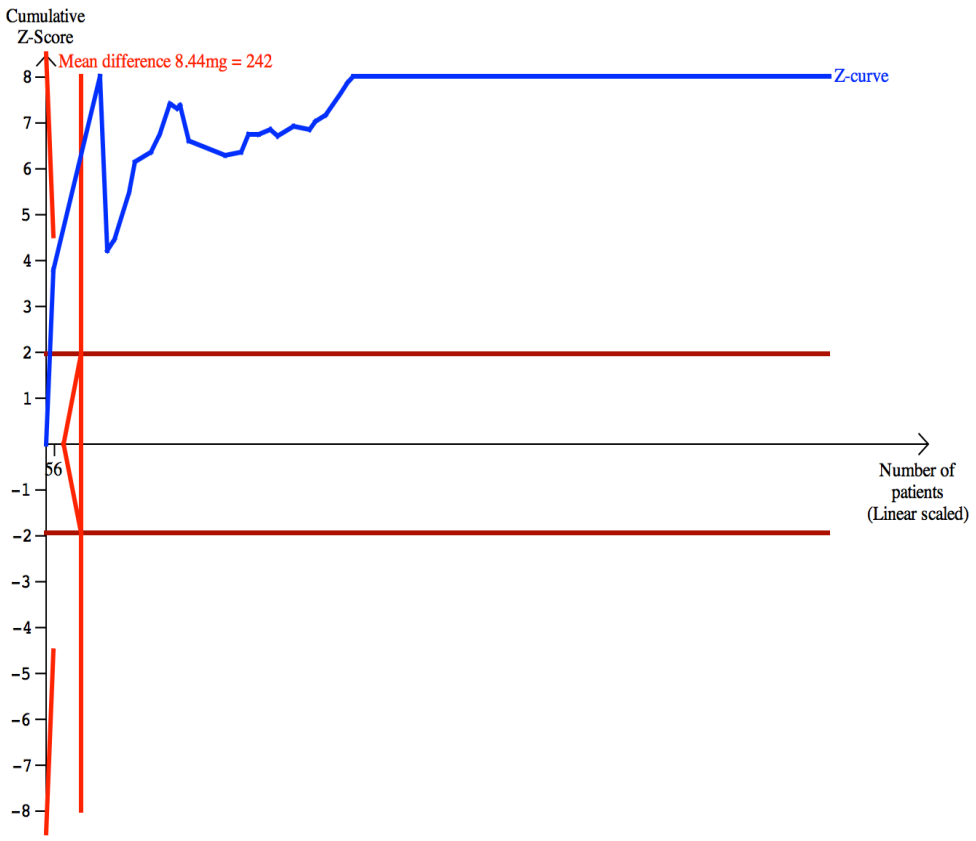


Figure 2.6: Trial sequential analysis of 24-hour morphine consumption (mg). Performed assuming a mean difference of 8.44mg, variance of 7.8, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 98. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis could not be performed for a 10mg reduction, as there was not enough information for analysis. Using an empirical -8.44mg morphine reduction, gabapentin crossed the O'Brien-Fleming boundary for benefit (adjusted CI -9.62mg to -7.26mg) (Figure 2.6). In addition, gabapentin reached the required IS for a definitive answer (242 participants). On sensitivity analysis, increasing the variance to 14 did not affect the results obtained with an IS of 424 participants. We did not perform any further sensitivity analysis with heterogeneity corrections due to high value already used in the analysis.

2.3.3 Pain scores one hour

Overall, 43 studies with 2874 participants were included in the analysis. Gabapentin resulted in a clinically significant reduction in pain scores at one hour on a ten-point scale (MD -1.69; 95% CI -2.01 to -1.35; Figure 2.7). There was evidence of considerable statistical heterogeneity (I^2=93%; p<0.001). The quality of evidence was regarded as moderate according to GRADE (downgraded due to risk of bias).

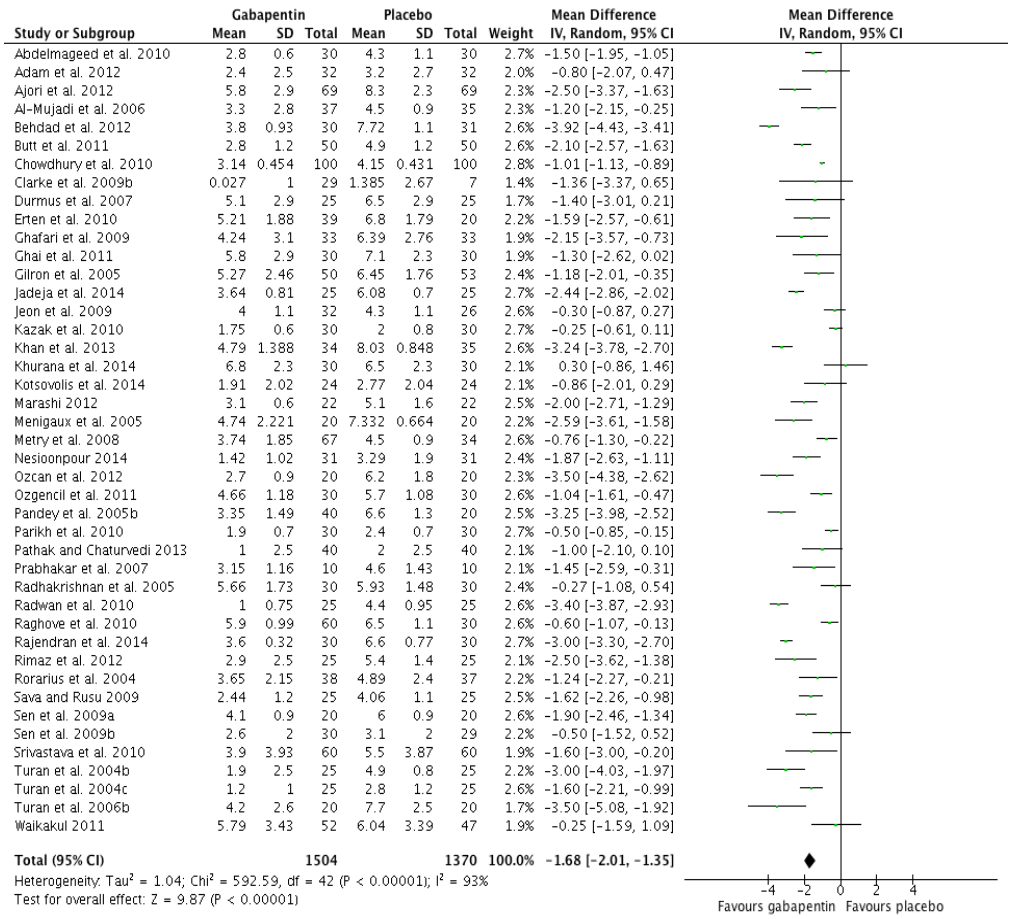


Figure 2.7 Forest plot of pain scores at one hour postoperatively.

Although there was little asymmetry on visual inspection of the funnel plot (Figure 2.8), Egger's regression test suggested statistically significant evidence of imprecise study effects (p=0.06). However, trim and fill analysis showed the two missing studies were to the left of the plot resulting in a larger adjusted effect estimate (MD -1.75; 95% CI -2.08 to -1.42). Orwin's failsafe N estimated 211 studies were needed to observe a negative effect.

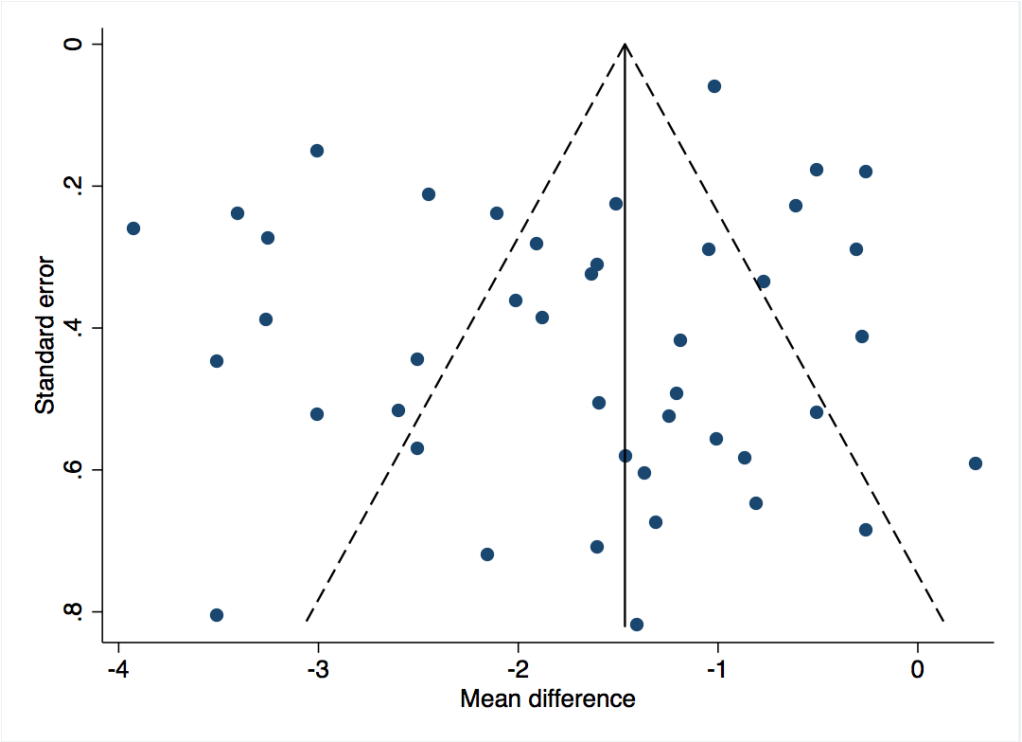


Figure 2.8 Funnel plot of gabapentin effects on pain scores at one hour. X-axis shows the mean difference and the Y-axis shows the standard error.

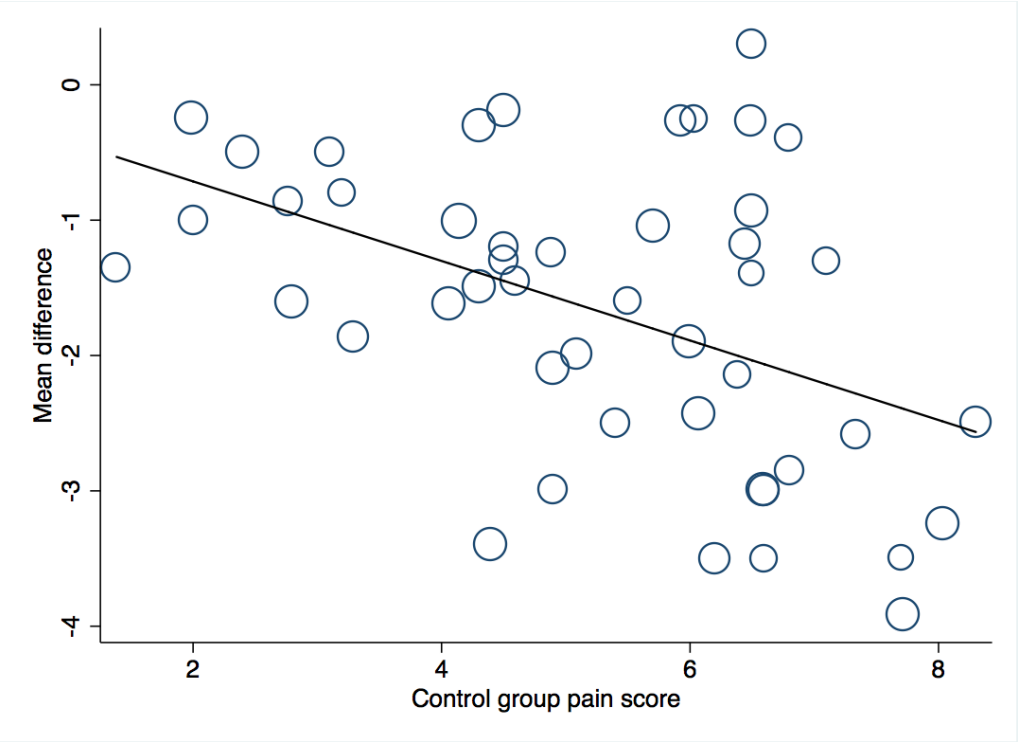


Figure 2.9 Meta-regression plot. X-axis shows the control group pain score and the Y-axis the mean difference in pain score with gabapentin.

On meta-regression analysis, control group pain score explained a large proportion of the heterogeneity between the studies (R^2=43%; p<0.001) (Figure 2.9). The addition of type of surgery improved the proportion of the heterogeneity explained by the model (R^2=57%; p<0.001). Diagnostics showed only three studies had a studentised residual of more than two and no study had a Cook's distance of more than one. Residuals were normally distributed on histograms. Predicted versus studentised residual plots demonstrated homoscedasticity and linearity. There were no covariates with a VIF of more than ten.

On sensitivity analysis, removing studies at high risk of bias and those where standard deviations were estimated did not significantly affect the results. One study removed sensitivity analysis did not reveal any influential studies in the analysis.

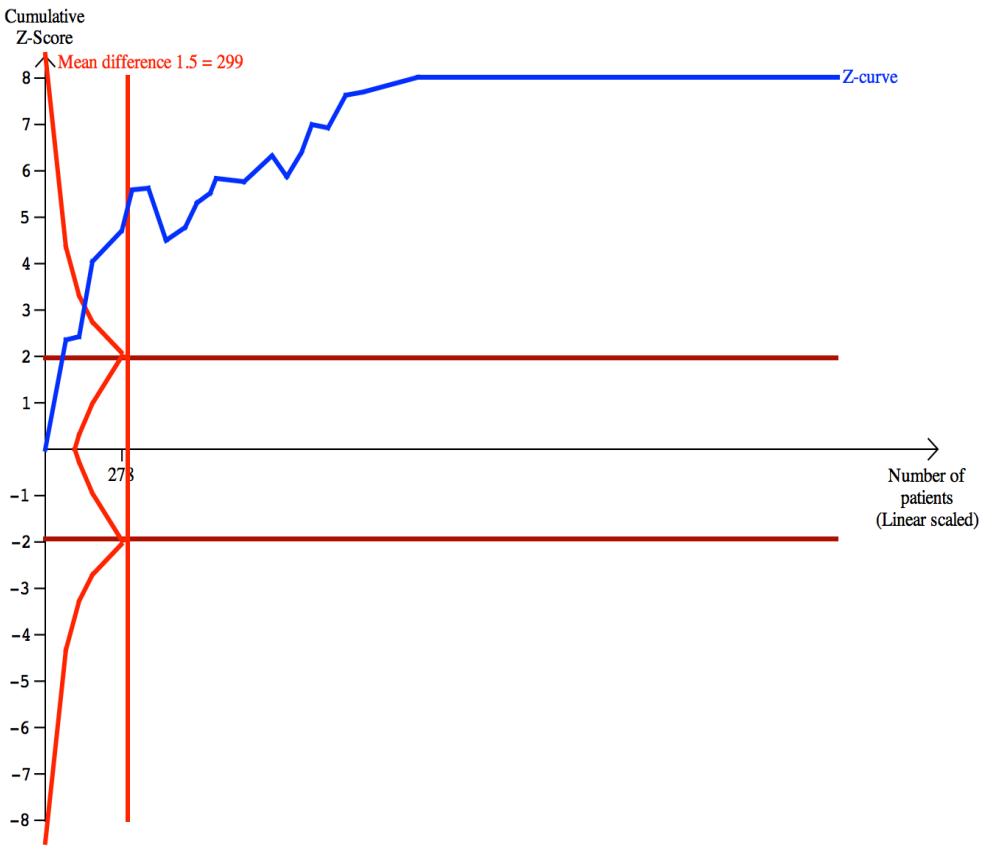


Figure 2.10: Trial sequential analysis of pain score at one hour. Performed assuming a mean difference of 1.5 in pain score, variance of 1.11, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 95. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for statistical significance (Figure 2.10). The results reached the required IS for a definitive answer (299 participants). On sensitivity analysis, similar results were obtained using a mean difference of 1.68 (IS 243 participants) or increasing the variance to 2.5 (IS 654 participants). We did not perform any further sensitivity analysis with heterogeneity corrections due to high value already used in the analysis.

2.3.4 Pain scores two hours

Overall, 40 studies with 2666 participants were included in the final analysis. Gabapentin resulted in a reduction in pain scores at two hours (MD -1.21; 95% CI -1.55 to -0.88; Figure 2.11). However, this reduction was not clinically significant. There was evidence of considerable statistical heterogeneity (I^2=91%; p<0.001). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias in the included studies).

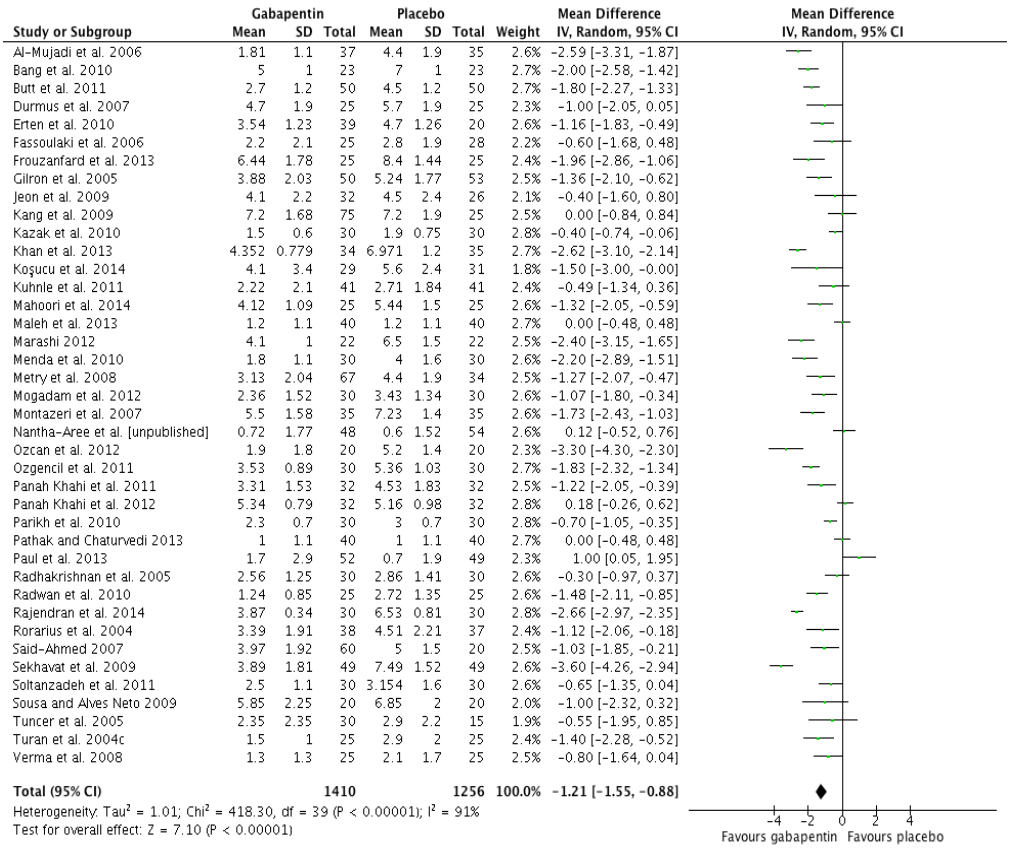


Figure 2.11 Forest plot of pain scores at two hours postoperatively.

There was no evidence of an asymmetric funnel plot on visual inspection (Figure 2.12). Egger's regression test showed no statistical evidence of imprecise study effects (p=0.41). Therefore, trim and fill analysis and failsafe N analyses were not conducted.

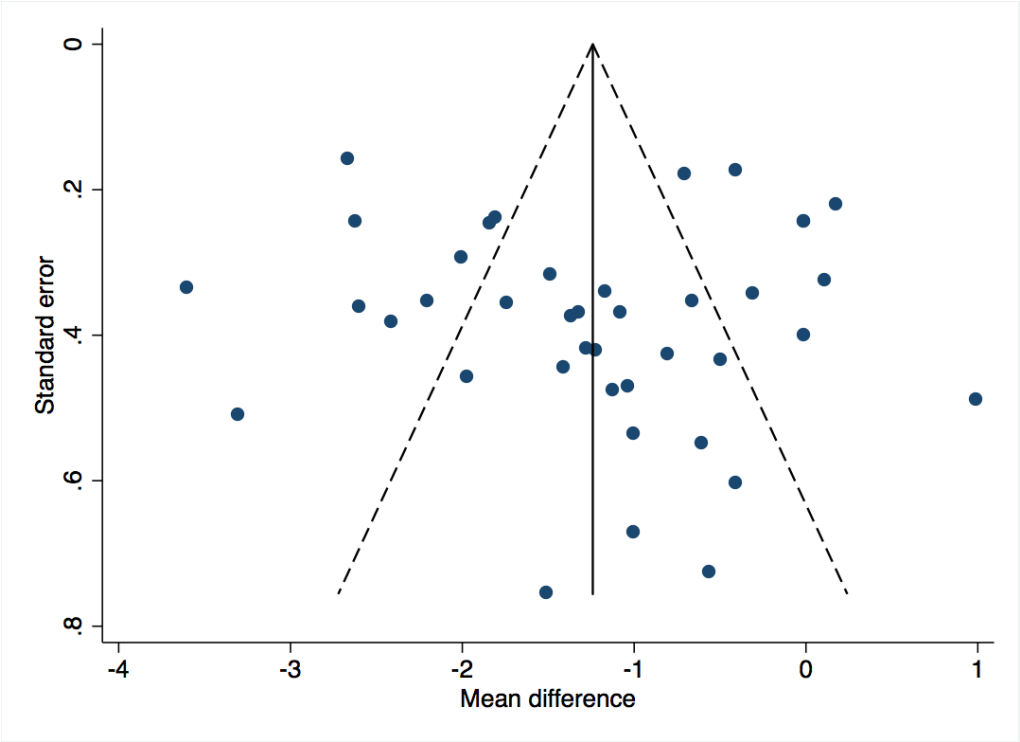


Figure 2.12 Funnel plot of gabapentin effects on pain scores at two hours. X-axis shows the mean difference and the Y-axis shows the standard error.

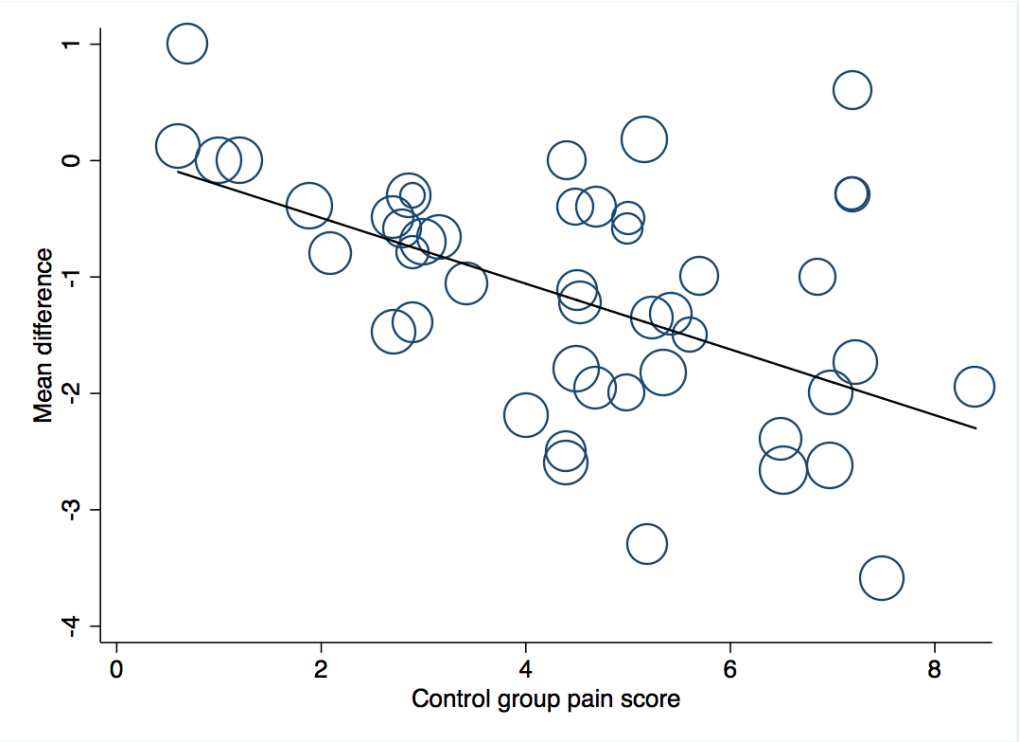


Figure 2.13 Meta-regression plot. X-axis shows the control group pain score and the Y-axis the mean difference in pain score with gabapentin.

On meta-regression analysis, the majority of the heterogeneity between studies was explained by the mean pain score in the control group (R^2=54%; p<0.001) (Figure 2.13). This was improved by the addition of the covariate gabapentin dose (R^2=59%; p<0.001). Regression diagnostics revealed four studies had a studentised residual of more than two, although no study had a Cook's distance of more than one. Histograms showed residuals were approximately normally distributed. Predicted versus studentised residual plots did not violate the assumptions of homoscedasticity or linearity. No covariate had a VIF value of more than ten.

Sensitivity analysis showed no change in the results if studies where standard deviations were estimated were removed or removing studies at high risk of bias. One study removed sensitivity analysis revealed no influential studies in the analysis.

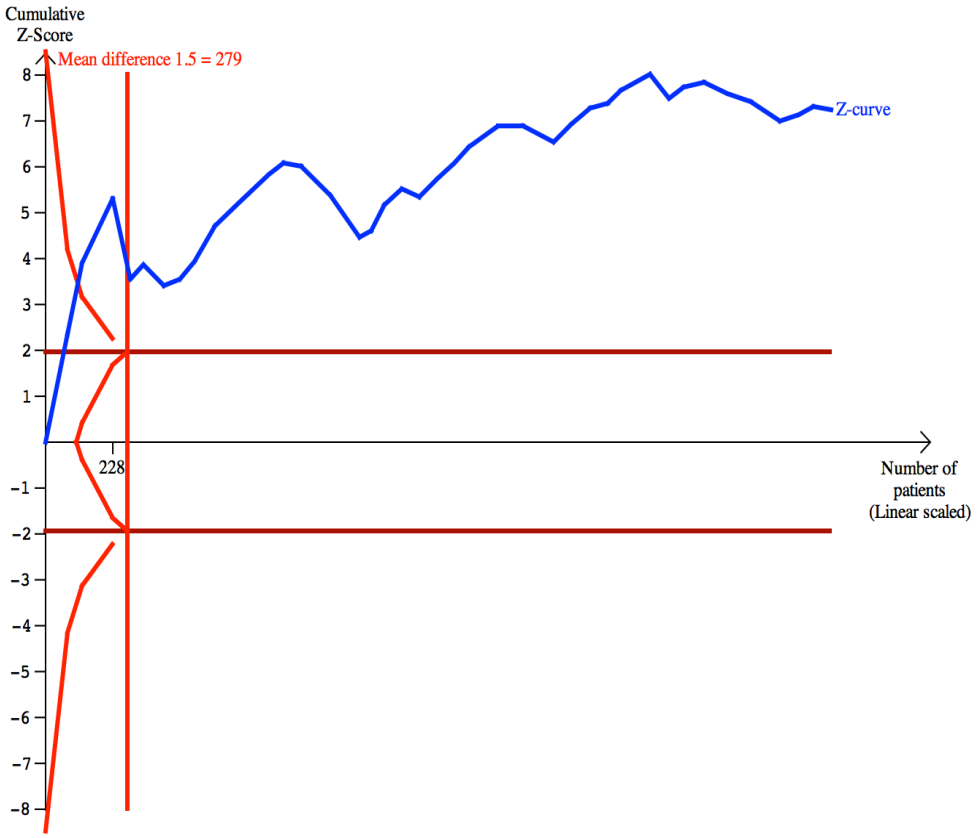


Figure 2.14: Trial sequential analysis of pain scores at two hours postoperatively. Performed assuming a mean difference of 1.5 in pain score, variance of 1.68, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 91. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis showed gabapentin crossed the O'Brien-Fleming boundary for benefit (adjusted CI -1.62 to -0.86) (Figure 2.14). The effect of gabapentin on pain scores at two hours passed the IS required for a definitive answer (279 participants). On sensitivity analysis, assuming a variance of 3 increased the required IS, which was still reached with gabapentin (488 participants). Assuming a mean difference of 1.21 did not change the results (IS 407 participants). We did not perform any further sensitivity analysis with heterogeneity corrections due to high value already used in the analysis.

2.3.5 Pain scores six hours

Overall, there were 40 studies with 2914 participants included in the analysis. Gabapentin reduced pain scores at six hours (MD -1.28; 95% CI -1.57 to -0.98; Figure 2.15). However, this reduction was not clinically significant. There was evidence of considerable statistical heterogeneity (I^2=93%; p<0.001). The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and possible publication bias).

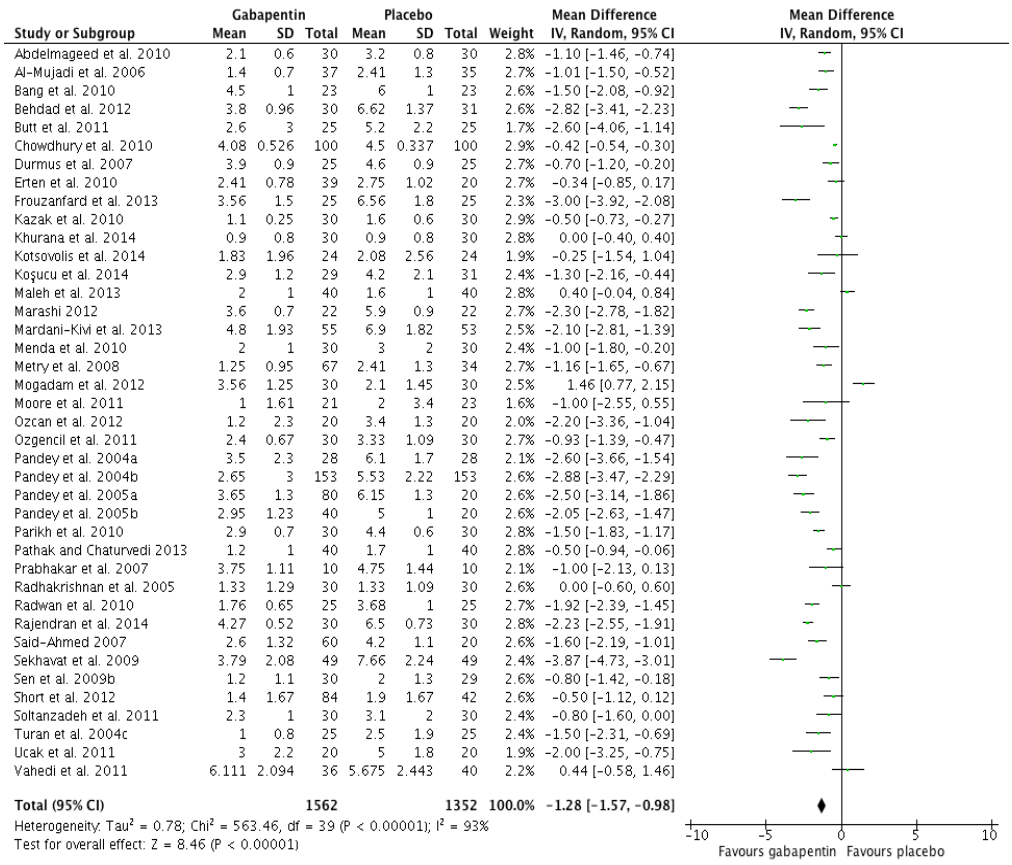


Figure 2.15 Forest plot of pain scores at six hours postoperatively.

Funnel plots revealed no gross asymmetry on visual inspection (Figure 2.16). However, Egger's regression test was statistically significant (p=0.004). Trim and fill analysis showed no missing studies either side of the plot and failsafe N showed 25 negative studies would be required to observe a negative effect of the intervention.

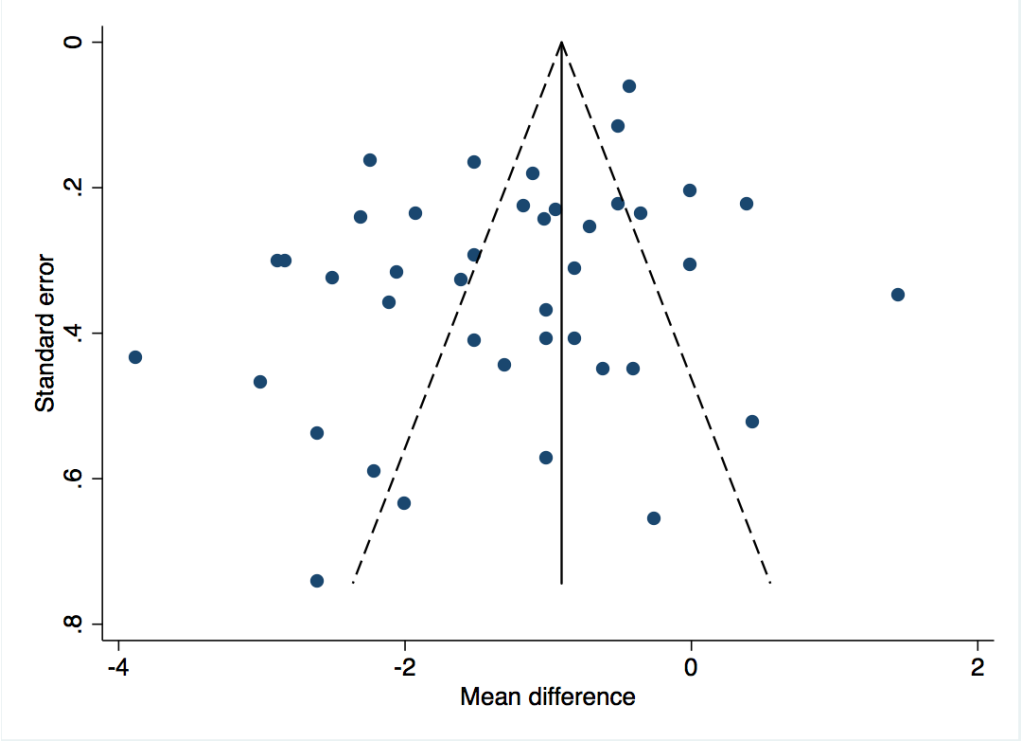


Figure 2.16 Funnel plot of gabapentin effects on pain scores at six hours. X-axis shows the mean difference and the Y-axis shows the standard error.

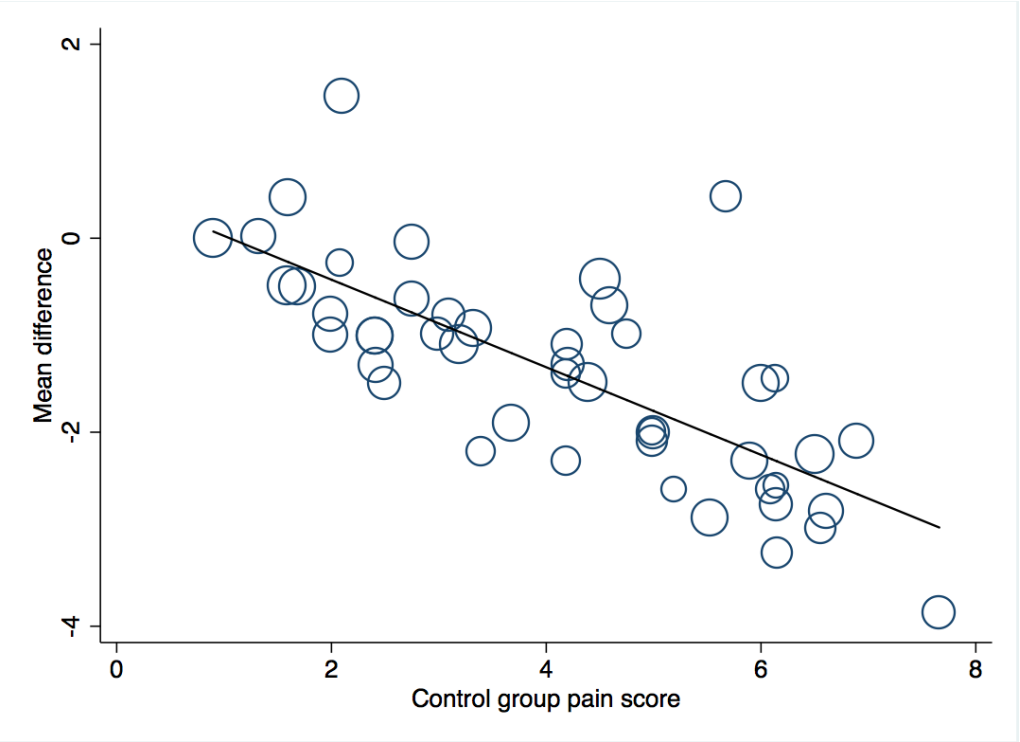


Figure 2.17 Meta-regression plot. X-axis shows the control group pain score and the Y-axis the mean difference in pain score with gabapentin.

On meta-regression analysis, mean pain score in the control group explained a large proportion of the between-study heterogeneity (R^2=37%; p<0.001) (Figure 2.17). The addition of the covariates gabapentin dose and type of surgery improved the model (R^2=65%; p<0.001). Diagnostics revealed three studies had studentised residuals of more than two although no study had a Cook's distance of more than one. Histograms of residuals showed some positive skew. Residual plots showed no violation of the assumption of linearity and homoscedasticity. No covariate had a VIF of more than ten.

Sensitivity analysis showed results did not change when studies where standard deviations were estimated were removed or removing studies that were at high risk of bias. One study removed sensitivity analysis showed there were no influential studies in the analysis.

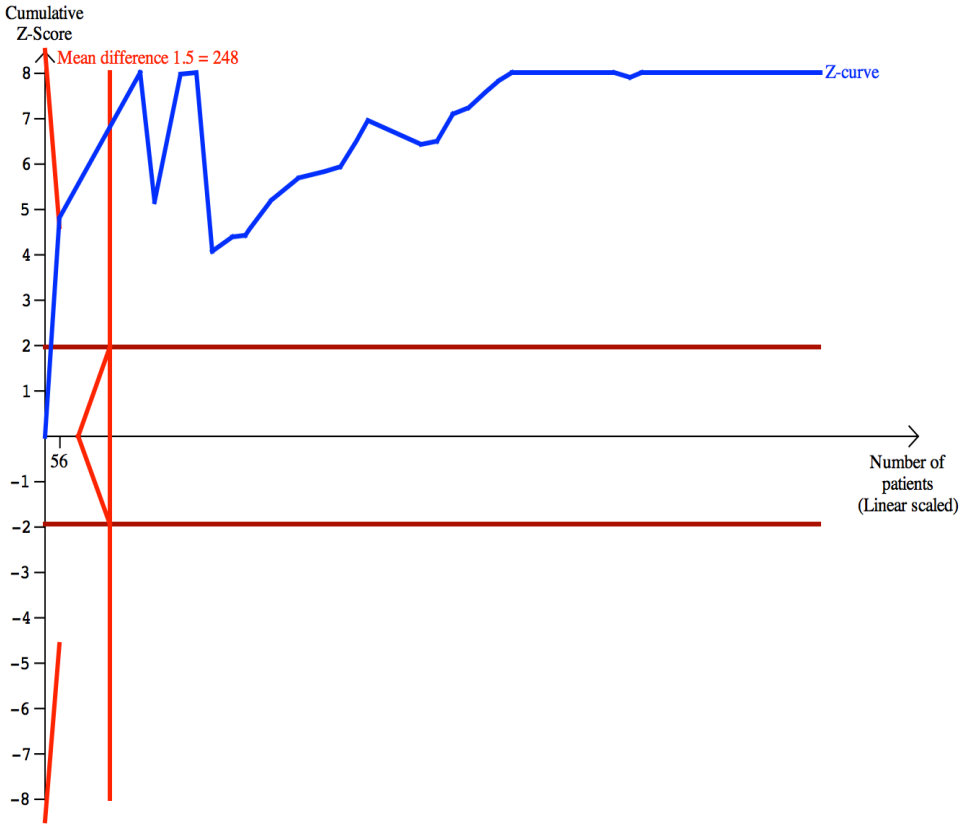


Figure 2.18: Trial sequential analysis of pain score at six hours postoperatively. Performed assuming a mean difference of 1.5 in pain score, variance of 0.94, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 94. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 2.18). The results reached the required IS for a definitive answer (248 participants). On sensitivity analysis, increasing the variance to 2 increased the IS, which gabapentin reached (496 participants). Assuming a mean difference of -1.28 increased the required IS (336 participants). Neither analysis changed the results obtained. We did not perform any further sensitivity analysis with heterogeneity corrections due to high value already used in the analysis.

2.3.6 Pain scores 12 hours

Overall, 60 studies with 4266 participants were included in the analysis. Gabapentin reduced pain scores at 12 hours (MD -1.12; 95% CI -1.33 to -0.91; Figure 2.19). However, this reduction was not clinically significant. There was evidence of considerable statistical heterogeneity (I^2=86%; p<0.001). The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and possible publication bias).

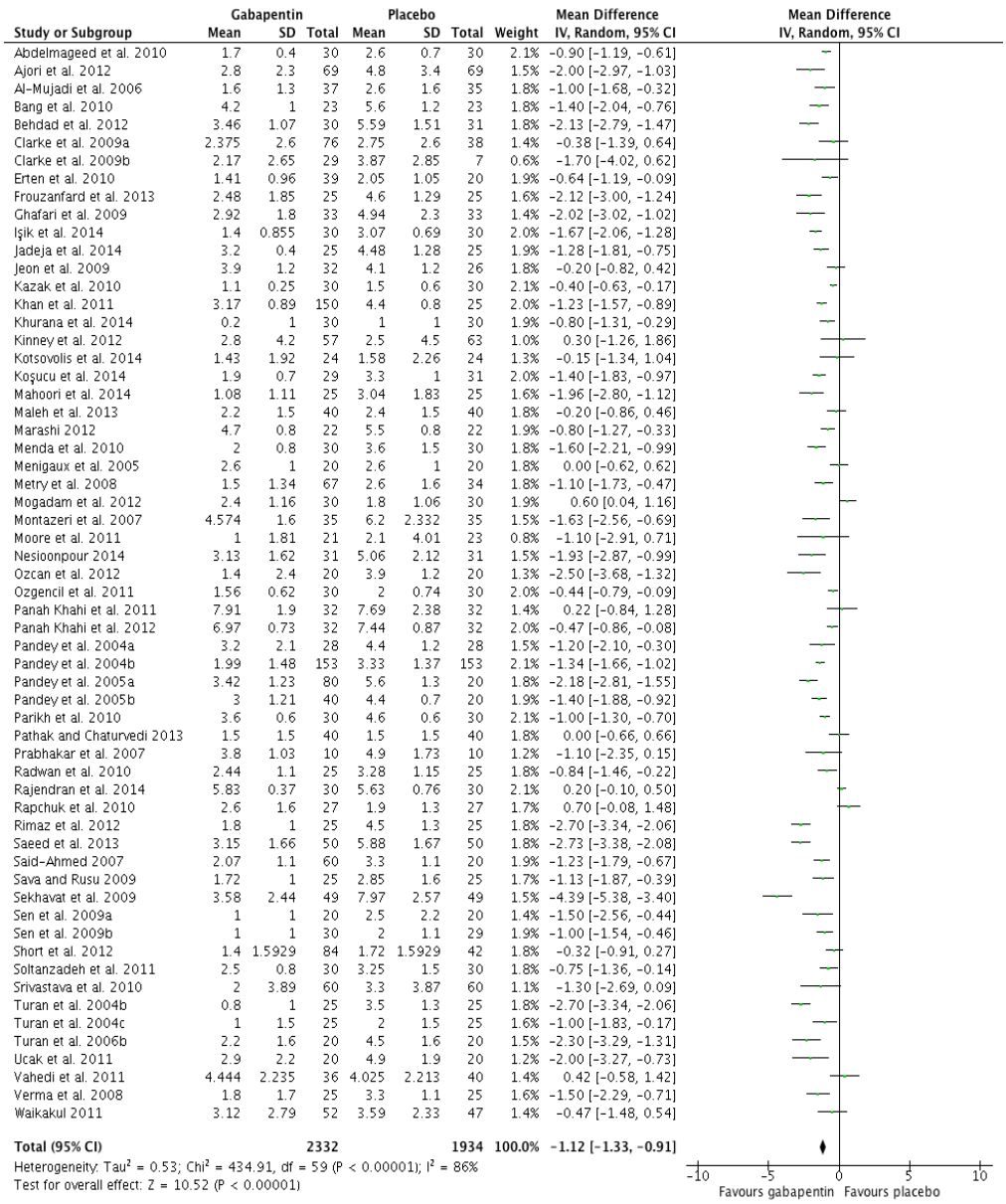


Figure 2.19 Forest plot of pain scores at 12 hours postoperatively.

Funnel plots showed no obvious asymmetry (Figure 2.20). However, Egger's linear regression test showed statistically significant imprecise study effects (p=0.01). Trim and fill analysis showed 13 studies were missing from the right of the mean, which reduced the effect estimates (MD -0.87; 95% CI -1.07 to -0.66). Failsafe N stated 83 negative studies would be required to observe a negative effect with gabapentin.

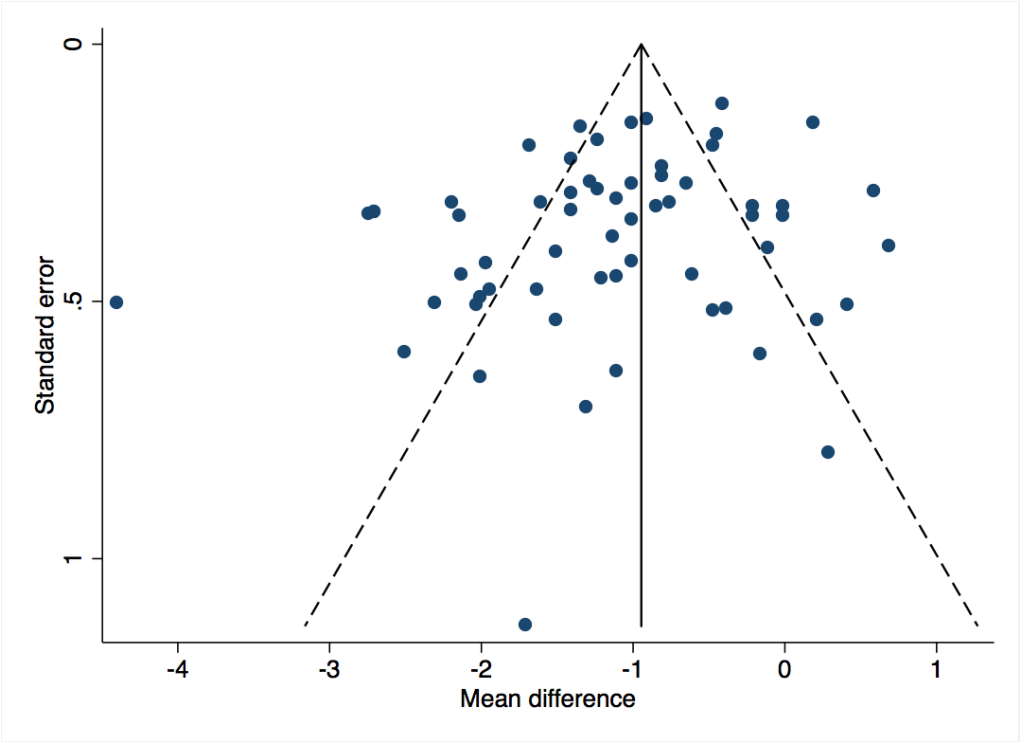


Figure 2.20 Funnel plot of gabapentin effects on pain scores at 12 hours. X-axis shows the mean difference and the Y-axis shows the standard error.

On meta-regression analysis, the majority of the between-study heterogeneity was explained by type of surgery and mean control group pain score (R^2=61%; p<0.001). Only one value had a studentised residual of more than two and no study had a Cook's distance of more than one. Histograms showed residuals were normally distributed. Studentised residual versus predicted plots did not violate the assumptions of homoscedasticity or linearity. Sensitivity analysis showed no change in results if studies where standard deviations were estimated were removed or excluding studies at high risk of bias. One study removed sensitivity analysis showed no studies to be influential in the analysis.

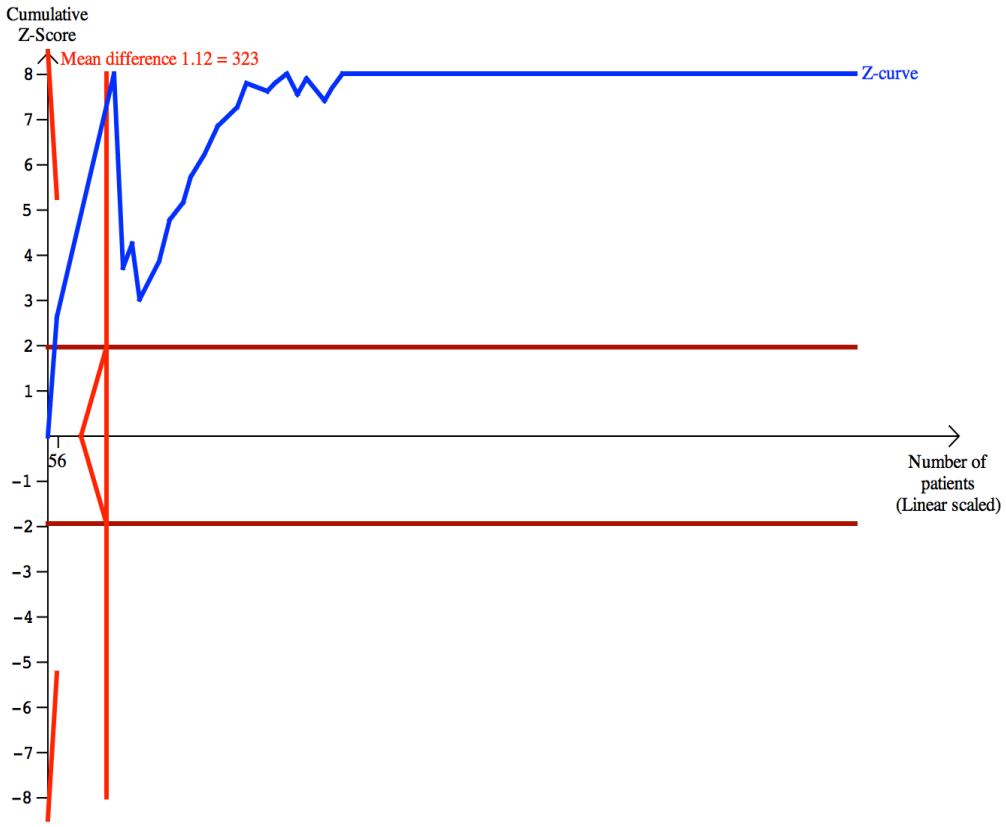


Figure 2.21: Trial sequential analysis of pain scores at 12 hours postoperatively. Performed assuming a mean difference of 1.12 in pain score, variance of 1.46, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 89. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis for a MD of 1.5 showed that inner boundaries for benefit and futility boundaries could not be constructed. Therefore, analysis was conducted for an empirical MD of 1.12 (Figure 2.21). Gabapentin crossed the O'Brien-Fleming boundary for benefit. In addition, the IS for a definitive answer was reached (323 participants). On sensitivity analysis, increasing the variance to 3 increased the IS, which gabapentin still reached (664 participants). We did not perform any further sensitivity analysis with heterogeneity corrections due to high value already used in the analysis.

2.3.7 Pain scores 24 hours

Overall, 73 studies with 5195 participants were included in the analysis. Gabapentin reduced pain scores at 24 hours (MD -0.71; 95% CI -0.87 to -0.56; Figure 2.22). However, this reduction was not clinically significant. There was evidence of considerable statistical heterogeneity (I^2=85%; p<0.001). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

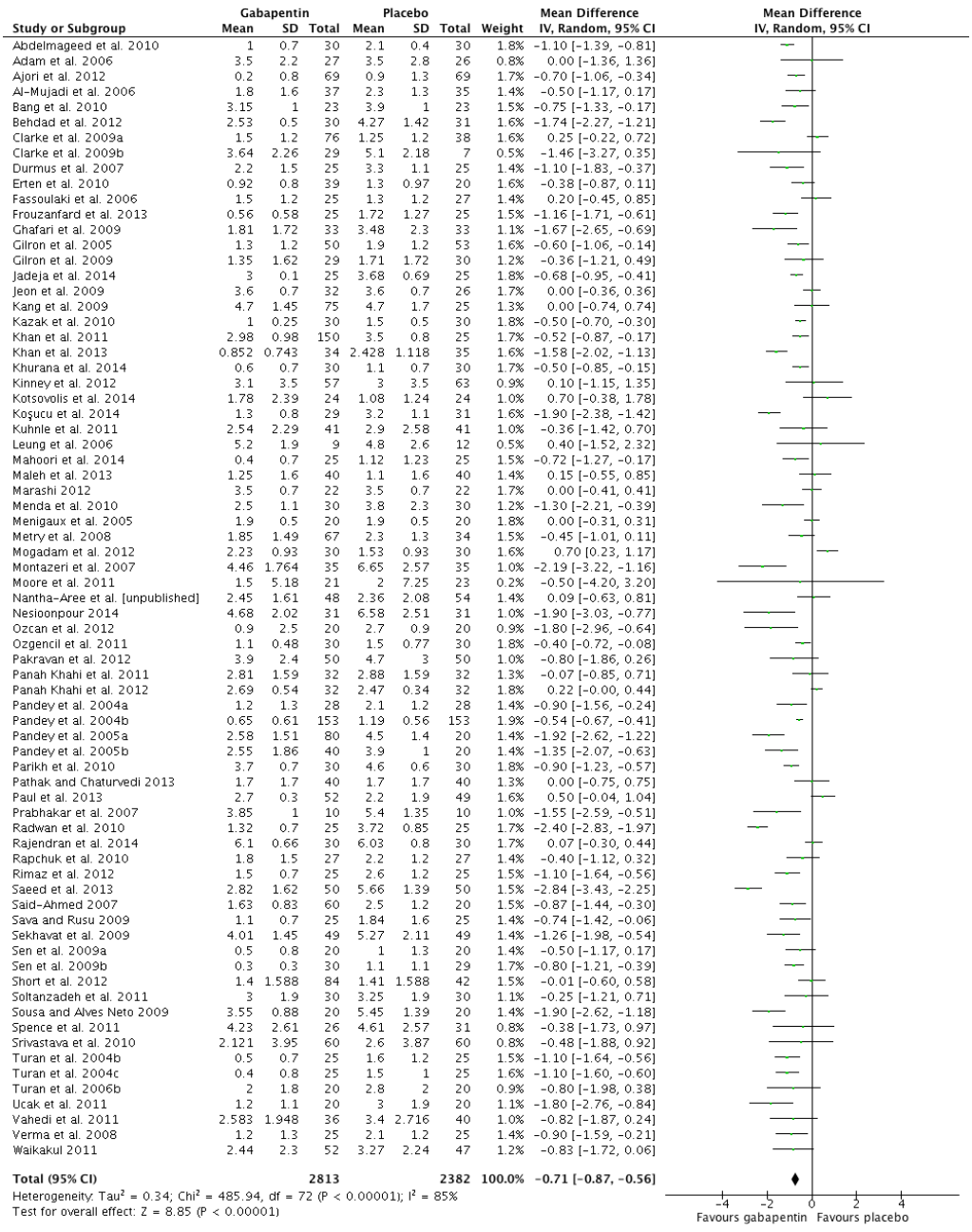


Figure 2.22 Forest plot of pain scores at 24 hours postoperatively.

There was no obvious asymmetry on visual inspection of the funnel plot (Figure 2.23). However, Egger's linear regression test showed evidence of statistically significant imprecise study effects (p=0.05). Trim and fill analysis showed four studies were missing from the left of the mean, suggesting bias against the effect of gabapentin (adjusted MD -0.77; 95% CI -0.93 to -0.61). Failsafe N showed 62 studies would be required to observe a negative effect with gabapentin.

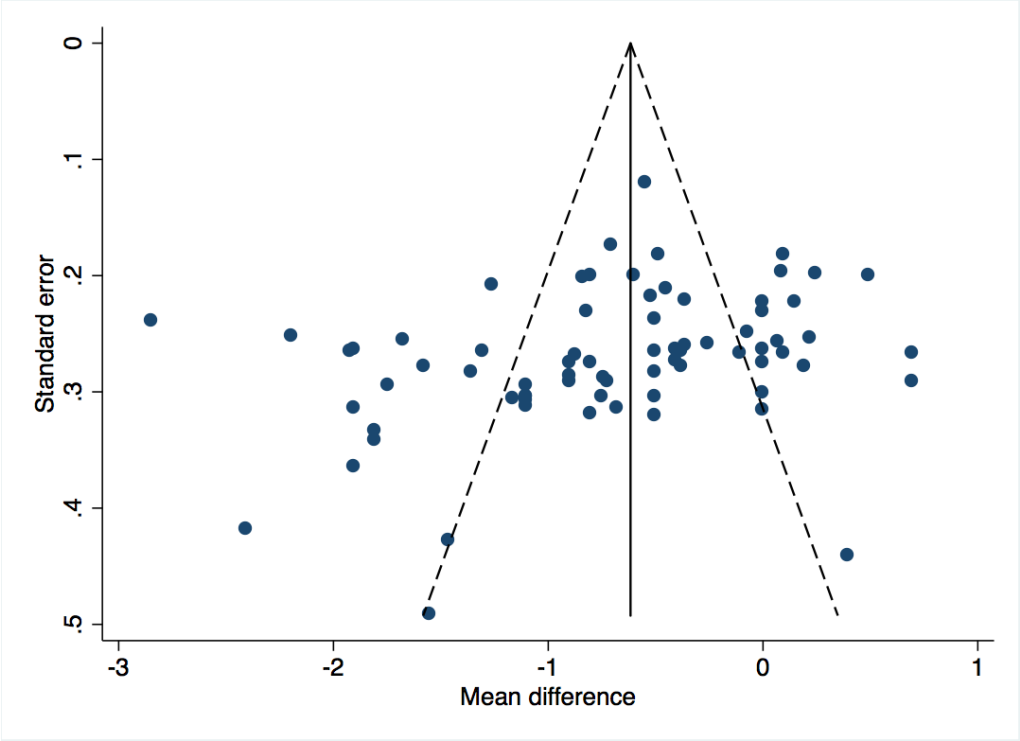


Figure 2.23 Funnel plot of gabapentin effects on pain scores at 24 hours. X-axis shows the mean difference and the Y-axis shows the standard error.

On meta-regression analysis, a smaller proportion of the between study heterogeneity was explained by mean control group pain score and type of surgery (R^2=23%; p<0.001). Only four studies had studentised residuals of more than two and no study had a Cook's distance of more than one. Histograms of residuals showed they were approximately normally distributed. Residual plots did not violate the assumptions of linearity or homoscedasticity. No VIF value for any of the covariates exceeded ten.

On sensitivity analysis, removing studies where standard deviations were estimated or studies at high risk of bias did not change results. One study removed analysis showed there were no influential studies in the meta-analysis.

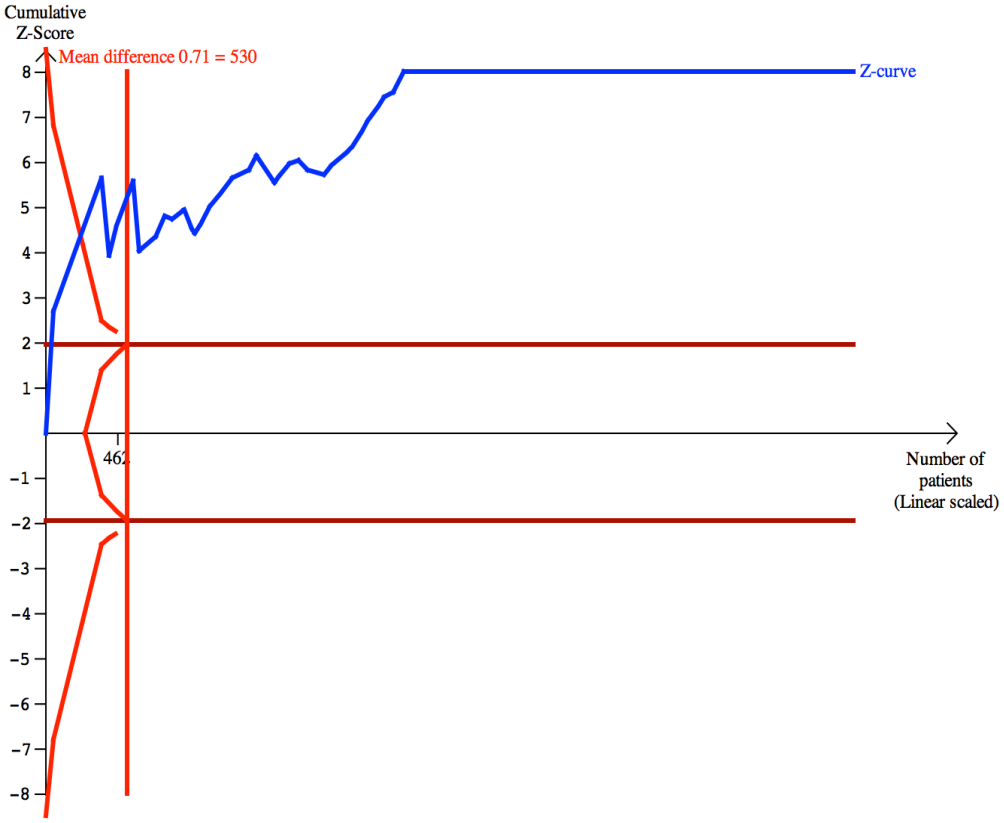


Figure 2.24: Trial sequential analysis of pain scores at 24 hours postoperatively. Performed assuming a mean difference of 0.71, variance of 1, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 88. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis could not be performed for a mean difference of 1.5. Using a mean difference of 0.71, gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 2.24) and reached the required IS for a definitive answer (530 participants). On sensitivity analysis, assuming an increased variance of 2 increased the IS, which gabapentin reached (1036 participants). We did not perform any further sensitivity analysis with heterogeneity corrections due to high value already used in the analysis.

2.3.8 Chronic pain (dichotomous)

Overall, nine studies with 539 participants were included in the analysis. Gabapentin did not affect the incidence of chronic pain, although a clinically significant effect could not be excluded (RR 0.85; 95% CI 0.68 to 1.06; Figure 2.25). There was a significant reduction in one study, which reported chronic pain at two months (Kosucu *et al.* 2014). There was no evidence of statistical heterogeneity (I^2=0%; p=0.49). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

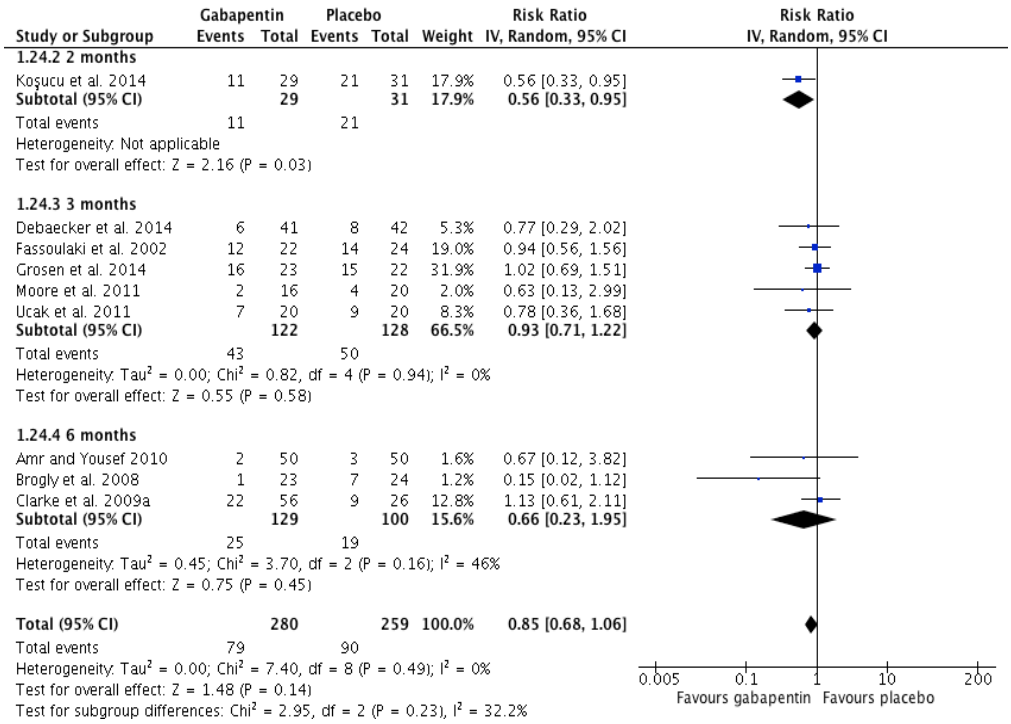


Figure 2.25 Forest plot of the incidence of chronic pain at various follow up times.

Due to the low number of studies, tests for publication bias were not undertaken. Due to the lack of statistical heterogeneity and low number of studies, meta-regression was not undertaken. On sensitivity analysis, one study-removed analysis did not reveal any influential studies. Excluding studies at high risk of bias did not change results.

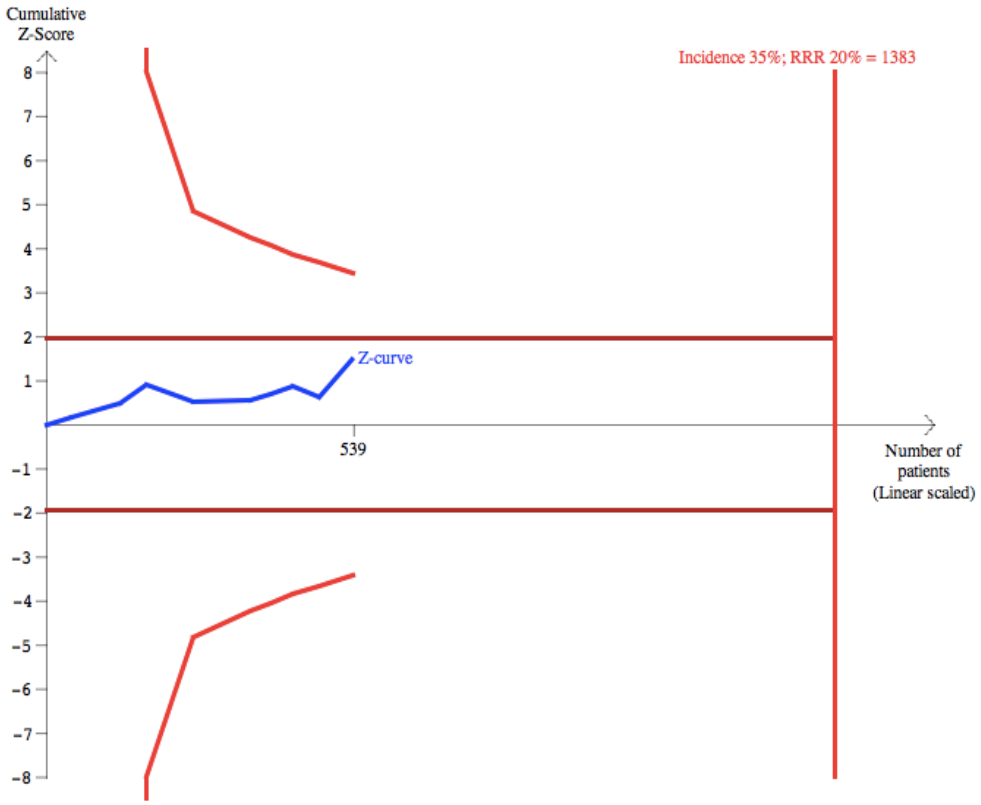


Figure 2.26: Trial sequential analysis of chronic post-surgical pain (dichotomous). Performed assuming an incidence of 35% in the control group (Kehlet, Jensen and Woolf 2006), RRR of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis showed that the effects of gabapentin on chronic pain did not cross any boundary for benefit (Figure 2.26) and did not reach the required IS for a definitive answer (1383 participants). There was too few data to construct boundaries for futility. On sensitivity analysis, assuming an incidence as low as 10% (Kehlet, Jensen and Woolf 2006), increased the required IS (6429 participants). Assuming a RRR of 50%, gabapentin crossed the boundary of futility and then reached the required IS of no benefit. Assuming a heterogeneity correction of 25 required a larger IS (1844 participants).

2.3.9 Chronic pain one to two months

Overall, six studies with 405 participants were included in the analysis. Gabapentin did not reduce pain scores at one to two months (SMD -0.72; 95% CI -1.57 to 0.14; Figure 2.27), although a clinically significant effect could not be excluded. There was evidence of considerable statistical heterogeneity (I^2=93%; p<0.001). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

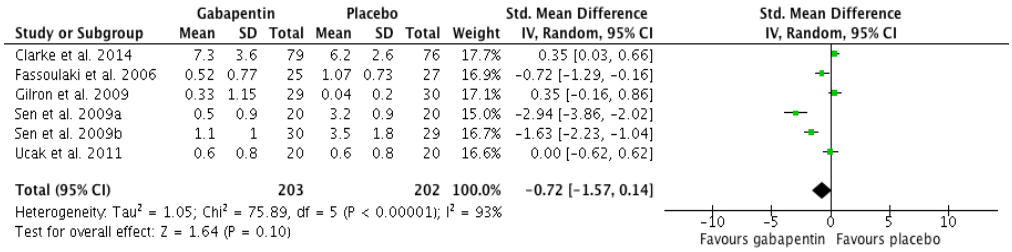


Figure 2.27: Forest plot of chronic pain scores at one to two months.

Tests for publication bias were not performed due to the low numbers of included studies. On meta-regression analysis, between-study heterogeneity was not explained by gabapentin dose or type of anaesthesia. After deleting the one study that used an alternative pain score (Clarke *et al.* 2014), baseline pain score predicted the majority of the heterogeneity between studies (R^2=84%; p<0.001). No study had a studentised residual of more than two. However, one study (Sen *et al.* 2009b) had a Cook's distance of 2.8 and was therefore deemed to be highly influential on the model. Residual plots were not performed due to the low number of studies.

Sensitivity analysis removing high risk of bias studies did not change results. One study-removed analysis did not change results. Due to the use of standardised mean differences to report the effect estimate, trial sequential analysis was not performed.

2.3.10 Chronic pain three months

Overall, eight studies with 528 participants were included in the analysis. Gabapentin reduced chronic pain scores at three months (SMD -0.37; 95% CI -0.75 to 0; Figure 2.28). There was evidence of considerable statistical heterogeneity (I^2=76%; p<0.001). The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

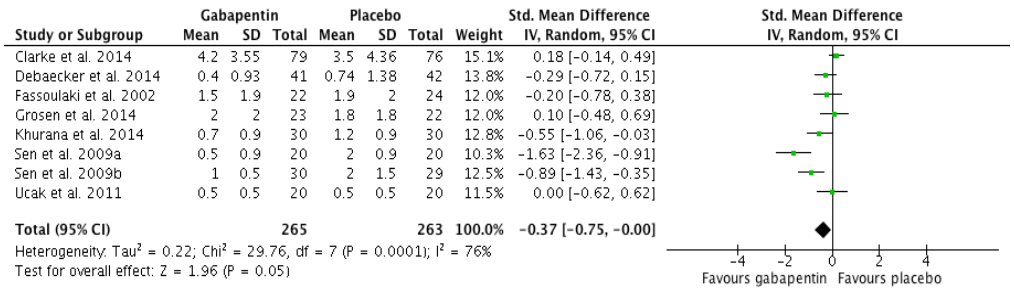


Figure 2.28: Forest plot of chronic pain scores at three months

Due to the low number of studies, tests for publication bias were not undertaken. On meta-regression analysis, after deleting the study that used a different pain scale (Clarke *et al.* 2014), no covariates were significant predictors of between-study heterogeneity. On sensitivity analysis, removing the study where standard deviations were estimated resulted in confidence intervals that overlapped the null effect. Removing studies at high risk of bias improved effect estimates in favour of gabapentin (SMD -0.56; 95% CI -0.97 to -0.16). One study-removed analysis showed two studies to be influential (Sen *et al.* 2009a and 2009b). Due to the use of standardised mean difference to report the effect estimate, trial sequential analysis was not performed.

2.3.11 Chronic pain six and 12 months

Overall, three studies with 131 participants were included in the analysis of chronic pain at six months. No studies reported chronic pain scores at 12 months. Gabapentin did not reduce chronic pain scores at 6 months (SMD -0.55; 95% CI -1.21 to 0.11; Figure 2.29). There was evidence of substantial statistical heterogeneity (I^2=70%; p=0.04). The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

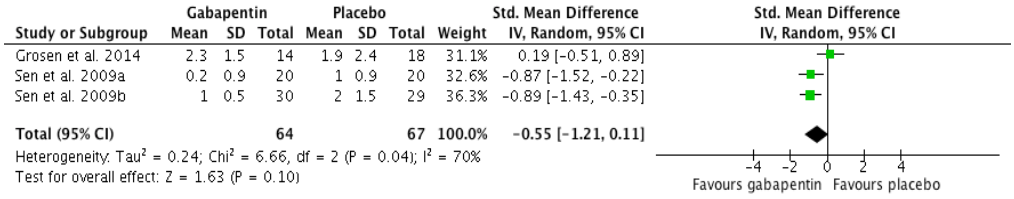


Figure 2.29: Forest plot of chronic pain scores at six months.

Due to the small number of studies, exploration of publication bias and investigation of heterogeneity were not undertaken. Sensitivity analysis showed removing the one study at high risk of bias (Grosen *et al.* 2014), resulted in a significant reduction in pain scores (SMD -0.88; 95% CI -1.30 to -0.47). Due to the use of standardised mean difference to report the effect estimate, trial sequential analysis was not performed.

2.4 Discussion

2.4.1 Summary of results

We found that gabapentin reduced opioid consumption and pain scores during the first 24 hours after surgery. However, the results from clinical trials thus far have been highly heterogeneous with morphine reductions ranging from 0-63mg in the first 24 hours postoperatively. The efficacy of gabapentin was found to be largely dependent on the degree of pain and the amount of opioid consumed without gabapentin (baseline risk). When, on average, participants experienced more pain or had higher opioid consumption for the procedure under study, the absolute effects of gabapentin were improved. General anaesthesia and increases in dose also improved the efficacy of gabapentin. There was some evidence that type of surgery contributed to heterogeneity between studies, although this was less convincing than for other covariates. However, with regards to pain scores, only early postoperative pain scores (one hour) were clinically significant. For acute postoperative pain and morphine consumption, trial sequential analysis showed that gabapentin demonstrated benefit adjusted for multiple comparisons (false discovery rate) while also reaching the required IS for a definitive answer.

There was little evidence for the effects of gabapentin on chronic pain. We found limited evidence of reduced chronic pain at three months when measured on a continuous scale and only one study found reductions in the incidence of chronic pain at two months. However, there was no evidence of any reductions at any other time point. Trial sequential analysis showed that the results obtained for the incidence of chronic pain (dichotomous) did not show any benefit, although this analysis did not reach the required IS. Therefore, further research is likely required for these outcomes.

Imprecise study effects were evident for many outcomes, raising the possibility of publication bias. However, on sensitivity analysis, adjusted effect estimates assuming a symmetric funnel plot did not change results to a large degree, suggesting any potential missing studies would not substantially alter our

conclusions. In addition to potential publication bias, uncertainty over risk of bias for many studies (unclear risk on Cochrane risk of bias tool) reduced the quality of evidence for many outcomes.

2.4.2 Links with previous research

Our meta-regression analysis demonstrated the main determinant of gabapentin efficacy related to the degree of pain experienced by the participant and not the type of surgery the participant underwent. For example, imagine two patients undergoing abdominal hysterectomy and two undergoing spinal surgery, with one patient undergoing one form of surgery experiencing severe postoperative pain and requiring large doses of morphine in the postoperative period and the other patient having lower pain scores and morphine requirements. The expected effect of gabapentin on opioid consumption would be determined by the patient's pain and not by the type of surgery they had undergone. Indeed, despite greater reductions in opioid consumption in certain procedures, type of surgery was not in itself independently associated with heterogeneity between studies in relation to 24-hour morphine consumption. However, caution is advised with this example above owing to concerns over aggregation bias.

This finding is consistent with previous research studies, which have shown larger absolute reductions in pain with higher postoperative pain scores (Averbuch and Katzper 2003; Bjune *et al.* 1996). The first study (Averbuch and Katzper 2003) included previous studies that had used ibuprofen in a dental extraction model and included 527 participants. These participants were divided into those with moderate (2/3) and severe pain (3/3). Pain scores were then taken after administration of 400mg ibuprofen. After two hours, the group with severe pain had greater absolute reductions in pain scores, which converged with the moderate group after two hours. Similar findings were found in the other study, which used paracetamol and codeine following Caesarean section (Bjune *et al.* 1996). Study medication was only effective in participants who had severe baseline pain scores (>6/10) compared to those with moderate pain (4-6/10). These primary studies help strengthen the biological basis on which we base our meta-regression model.

Previous groups have advocated the use of procedure-specific evidence as a way of limiting heterogeneity between postoperative pain trials, largely based on the observed differences in analgesic efficacy between different procedures (Espitalier *et al.* 2013; Gray *et al.* 2005). Our results suggest this difference may largely be due to different levels of pain/opioid consumption within surgical subtypes rather than the type of surgery itself. Indeed, even within surgical subgroups statistical heterogeneity was still considerable (data not shown), most of which was accounted for by the mean control group morphine consumption. As procedure specific meta-analyses emerge, heterogeneity still remains an issue (Alayed *et al.* 2014).

Such differences in morphine consumption within certain surgical subtypes may be due to different procedures within a trial (Waikakul 2011), for instance open versus laparoscopic surgery, different procedures within surgical subgroups (ENT for example), variation in concurrent analgesic drugs and techniques, genetic variations in participants and variations in the prescribing practices of attending doctors and the administration practices of nursing staff. The lack of an association between type of surgery and 24-hour morphine consumption is in agreement with a recent meta-analysis of pregabalin (Mishriky, Waldron and Habib 2014). Similar to our review, this review performed meta-regression analysis on 24-hour morphine consumption and found the proportion of between-study heterogeneity was explained by pregabalin dose (R^2=14%) and type of anaesthesia (R^2=3%). However, type of surgery was not a significant predictor of pregabalin effect.

The dose of gabapentin altered the analgesic effect less than the amount of pain. The effect of gabapentin dose was inconsistent for all outcomes, with dose only explaining a small proportion of the heterogeneity between studies (Mishriky, Waldron and Habib 2014). Some RCTs have suggested that the maximum effective analgesic dose of gabapentin is 600 mg or 900 mg (Khan *et al.* 2011; Pandey *et al.* 2005a). One dose ranging study suggested larger doses (Van Elstraete *et al.* 2008). This study used an up-and-down sequential allocation technique in 67 participants. They concluded that the median effective dose of gabapentin was 21.7mg/kg (95% CI 19.9mg/kg to

23.5mg/kg). This would translate into approximately 1500mg for a 70kg patient. Based on these studies and our meta-regression analysis, future studies should aim to use doses of between 600-1200mg. However, it is as yet unknown whether these increased dosages will translate into an increase in gabapentin adverse effects. This will be the subject of the meta-regression analysis in the next chapter.

The statistically significant imprecise study effects indicate possible publication bias in favour of the analgesic effect of gabapentin (Hopewell *et al.* 2009), although some analyses contradicted this expectation. The conclusions of meta-analyses uninformed by analyses of possible publication bias may overstate the effects of gabapentin. Publication bias is one reason why the results of meta-analyses and subsequent large RCTs disagree (Egger *et al.* 1997a). However, other causes of an asymmetrical funnel plot include larger effects or methodological differences in smaller studies, sampling variation and possible fraud. Furthermore, some of our results for imprecise study effects showed missing studies to the left of the mean (for one and 24 hour pain scores), which would suggest bias against gabapentin.

With regards to chronic pain, there was limited evidence of reductions at three months and one study, which showed a significant reduction at two months (Kosucu *et al.* 2014). There was no evidence of reductions at any other time points or any reductions in the overall incidence. However, TSA indicates further research is required before definitive conclusions can be made, although further analysis revealed that gabapentin is unlikely to be able to achieve RRR in chronic pain of 50%, as this crossed the boundary for futility. Our results contradict those in a previous review of gabapentin, which found gabapentin reduced the incidence of chronic pain (OR 0.52; 95% CI 0.27 to 0.98) (Clarke *et al.* 2012). However, our results included a more contemporary sample of studies and did not include one study that showed a large positive result as it measured chronic pain at one month, which is outside of contemporary definitions of chronic post-surgical pain (Fassoulaki *et al.* 2006a).

2.4.3 Limitations

There are several limitations with this review. Firstly, the use of meta-regression, the analysis from which we derived our conclusions, should be regarded as observational in nature and is therefore prone to bias and confounding. Examples of bias include aggregation bias, where pain scores and morphine consumption averaged for a group may not represent differences at the participant level. This means the data we used as a surrogate for pain experienced by the participant may not be applicable. Despite this, there is no other method that can be used to estimate how much pain individual participants would have had if they had not been given gabapentin using reported measures from the included studies. Indeed, even with access to individual participant data, there is no way of obtaining baseline scores for outcomes which are measured after an intervention is administered.

Examples of confounding were evident when type of surgery and type of anaesthesia were analysed together as we found evidence of multi-collinearity with VIF values exceeding ten. This makes it difficult to separate the effects of these covariates. Within this model, we found that gabapentin was less effective after spinal anaesthesia, but the cause might be the type of surgery (orthopaedic, caesarean section and joint arthroplasty) with which spinal anaesthesia was used more often. In addition, our regression model may have been biased as the covariate used in the analysis is also used in the calculation of the effect estimate (Thompson and Higgins 2002).

Secondly, methodological weaknesses in the some of the included studies may have been responsible for statistical heterogeneity between the studies. As we only included clinical covariates in the model, we cannot exclude the possibility that such methodological deficiencies may have been responsible for heterogeneity. For example, smaller studies at higher risk of bias may be a marker for poor study conduct, which may have included less intensive analgesic protocols resulting in higher levels of postoperative pain. Such studies could have lower mean differences in morphine consumption due to bias in the conduct of the study rather than the higher control group morphine

consumption *per se.* Therefore, the association between mean control group morphine consumption would be confounded by high risk of bias in the study conduct. This possible confounding will be the subject of chapter six.

Thirdly, we found evidence of statistically significant imprecise study effects, which may indicate possible publication bias. As discussed previously, such bias is the reason why large RCTs and meta-analyses may disagree (Egger *et al.* 1997a). Therefore, results from our analysis should be interpreted with caution. Finally, the risk of bias was unclear for many domains of internal validity in the included trials, particularly for allocation concealment, which may distort effect estimates in favour of gabapentin (Schulz and Grimes 2002a). Indeed, both of these limitations reduce the strength of the evidence derived from our meta-analyses according to GRADE criteria (Guyatt *et al.* 2008). Although we were able to explain a large proportion of the between-study heterogeneity found in previous reviews, the limitations above limit the validity of the data on which our regression models are based and therefore should be interpreted with further caution.

The design of future clinical trials should attempt to use our regression model to ensure the targeted use of gabapentin in clinical situations in which it will derive the most benefit, such as using higher doses in more painful procedures performed under general anaesthesia. However, such increases in doses are unknown in relation to increases in adverse events. With regards to clinical practice, although the evidence has limitations, if anaesthetists are to use gabapentin to reduce postoperative pain, use of our regression model could help more effectively target its use. Information on expected postoperative morphine consumption could be derived from small audit data and inform gabapentin use in more beneficial clinical contexts (although the limitations of our analyses should be considered).

2.4.4 Conclusion

In conclusion, gabapentin was an effective acute analgesic agent, with the absolute effect being proportionate to the mean opioid requirement or pain score in the control group, gabapentin dose and type of anaesthesia. However, the quality of the evidence was of moderate to low quality owing to concerns over risk of bias and possible publication bias. Further research should focus on chronic pain and aim to use gabapentin in situations expected to derive the most benefit.

Chapter 3

Gabapentin adverse events and other postoperative effects

3.1 Introduction

In addition to pain, surgery and anaesthesia have many adverse effects. Some of these such as PONV are common (Cohen *et al.* 1994) and lead to other consequences such as increased costs, length of stay and patient dissatisfaction (Gan *et al.* 2003). Indeed, patients rank PONV above pain as the most feared outcome of surgery and anaesthesia (Macario *et al.* 1999). Other adverse events such as pruritus and urinary retention similarly can increase length of stay and reduces patient satisfaction, and therefore any agent capable of reducing these may help improve the patient experience. This chapter will therefore use the studies identified from the second chapter to extract data on the effects of gabapentin on various postoperative outcomes. Furthermore, we will present in this chapter use of meta-regression to investigate whether increases in gabapentin dose, as suggested in the conclusions of the second chapter, result in an increase in adverse events or whether larger doses help further reduce opioid side effects. We also aim to investigate whether reductions in opioid adverse events were dependent on the degree of morphine reduction achieved in the study.

3.2 Methods

The methods used for the data collection in this chapter are identical to those used in chapter two (Section 2.2). We did not consider data from observational studies, which may be a more appropriate methodology to assess adverse events. Changes for this chapter of the thesis include limiting meta-regression analysis to gabapentin dose in order to identify any dose-response reductions in opioid adverse events or increases in gabapentin side effects. Furthermore, for opioid side effects where more than twenty studies were included, we used opioid reduction as a covariate to test if reductions in opioid adverse events were dependent on the degree of opioid reduction in the individual study. For pre-operative anxiety, baseline anxiety (mean anxiety level in the placebo group) was used as a covariate (baseline risk). We regarded clinically significant reductions in events as a RRR of 20%.

3.3 Results

3.3.1 Characteristics of included studies

The characteristics of the included studies are listed in Table 2.1. We included only studies that reported the outcomes described. There was clinical heterogeneity in the time point at which outcomes were measured.

3.3.2 Nausea

Overall, 58 studies with 4062 participants were included in the analysis. Gabapentin resulted in clinically significant reductions in the risk of postoperative nausea (RR 0.78; 95% CI 0.69 to 0.87; Figure 3.1). There was evidence of moderate statistical heterogeneity (I^2=27%; p=0.03). The NNT to prevent one episode of nausea was 11 (95% CI 8.1 to 15). The quality of evidence was very low according to GRADE (downgraded owing to concerns over risk of bias, unexplained heterogeneity and possible publication bias).

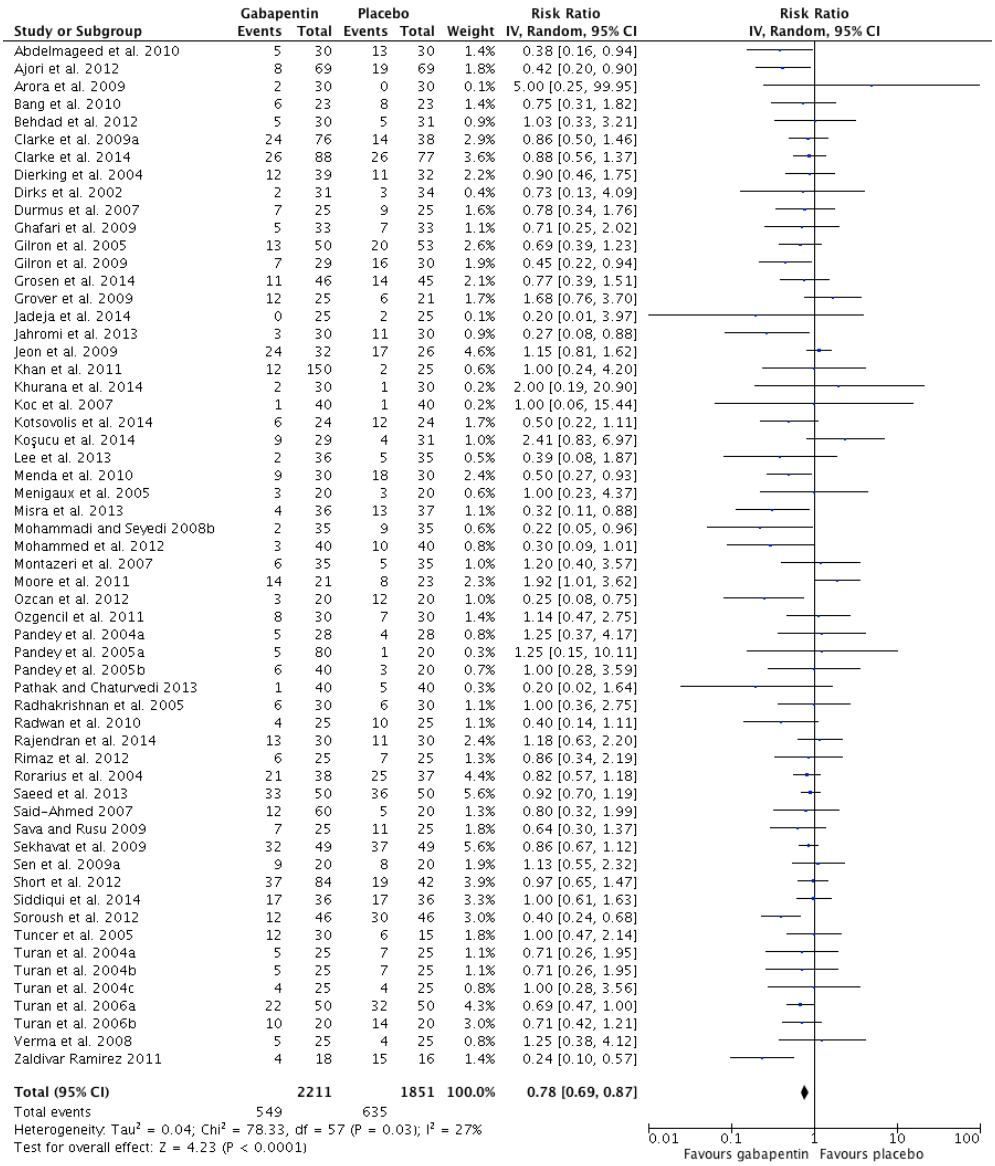


Figure 3.1: Forest plot for the risk of postoperative nausea.

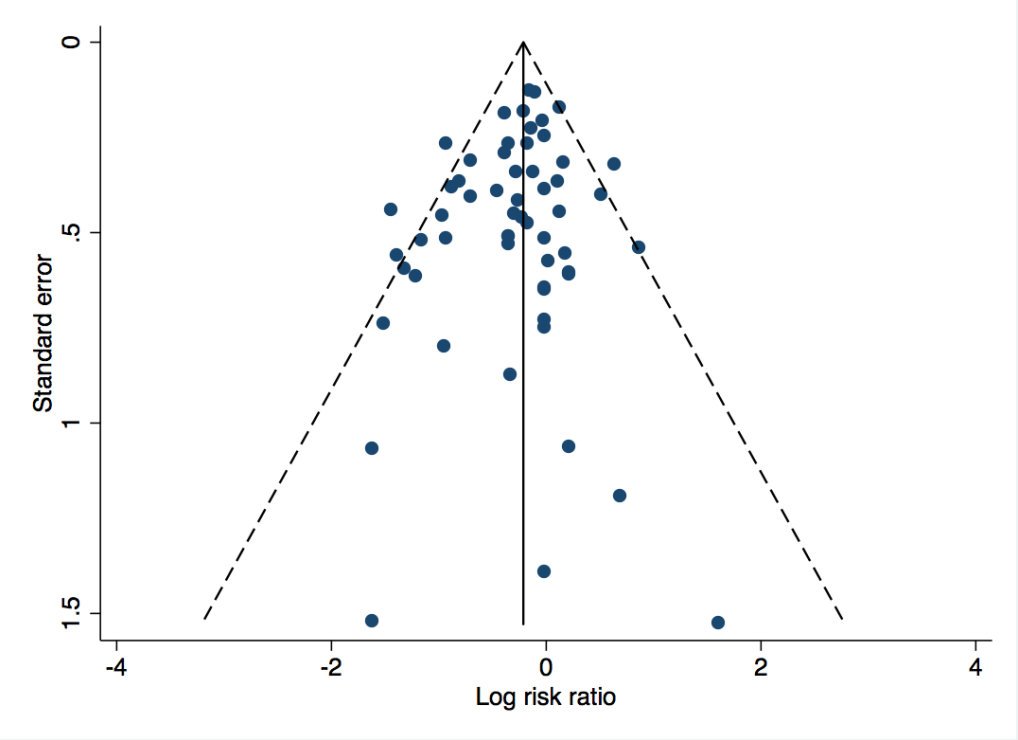


Figure 3.2: Funnel plot of gabapentin effects on postoperative nausea. X-axis shows the log risk ratio and the Y-axis shows the standard error of the log risk ratio.

Visual inspection of the funnel plot demonstrated little asymmetry (Figure 3.2). Egger's linear regression test was statistically significant indicating possible publication bias (p=0.05). Trim and fill analysis revealed no studies were missing from either side of the mean. Failsafe N showed eight negative studies would be required to observe a negative effect with gabapentin. On meta-regression analysis, neither dose (R^2=0%; p=0.82) nor degree of morphine reduction (R^2=0%; p=0.90) accounted for any of the between-study heterogeneity. On sensitivity analysis, excluding high risk of bias studies gave similar results. One study-removed analysis identified no influential studies.

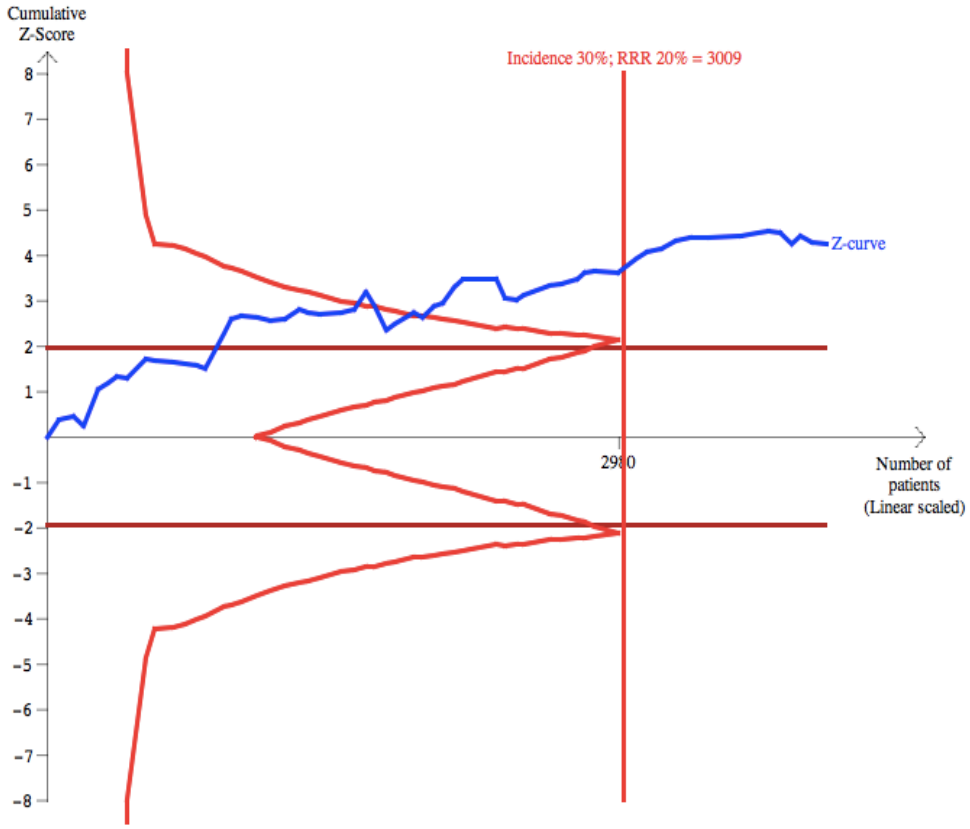


Figure 3.3: Trial sequential analysis of postoperative nausea. Performed assuming an incidence of 30% in the control group, RRR of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 43. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis showed that the analysis for nausea reached the required IS (3009 participants) for a definitive answer (Figure 3.3). The cumulative Z score also passed the O'Brien-Fleming monitoring boundaries (adjusted CI 0.69 to 0.87) and avoided the area of futility. Assuming an incidence as low as 10%, gabapentin crossed the boundary for benefit although did not meet the required IS of 11256 participants. Gabapentin did not pass the boundary for a 50% RRR. Assuming a heterogeneity correction of 75, the results did not reach the required IS.

3.3.3 Vomiting

Overall, there were 57 studies with 3880 participants included in the analysis. Gabapentin resulted in a clinically significant reduction in the risk of postoperative vomiting (RR 0.67; 95% CI 0.59 to 0.76; Figure 3.4). There was no evidence of statistical heterogeneity (I^2=3%; p=0.42). The NNT to prevent one episode of vomiting was 10 (95% 7.5 to 12.1). The quality of the evidence was low according to GRADE (downgraded owing to concerns over risk of bias and possible publication bias).

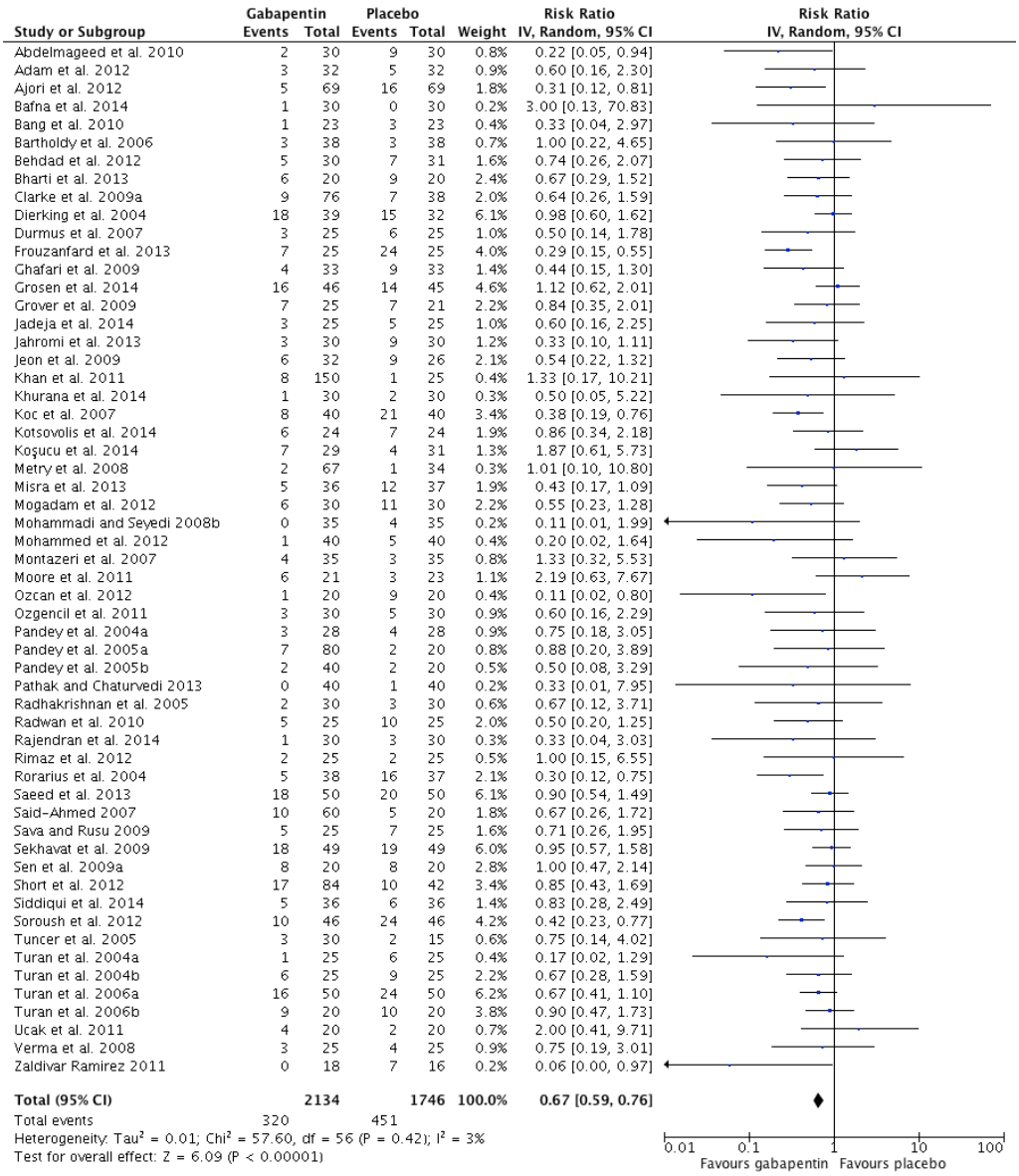


Figure 3.4: Forest plot for the risk of postoperative vomiting.

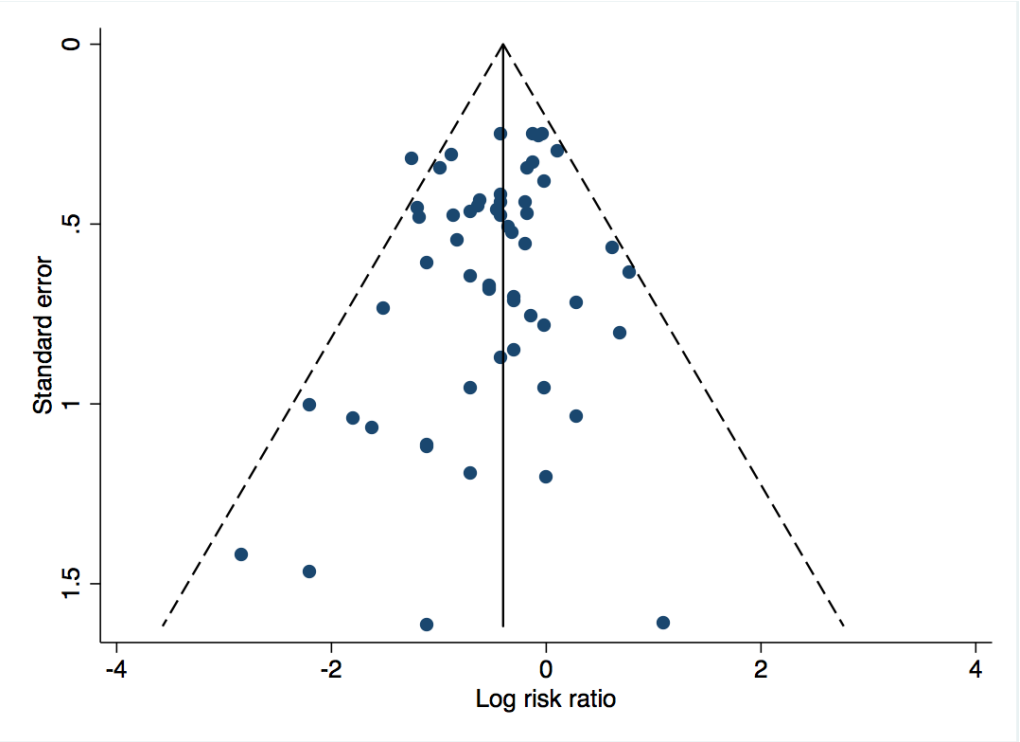


Figure 3.5: Funnel plot of gabapentin effects on postoperative vomiting. X-axis shows the log risk ratio and the Y-axis shows the standard error of the log risk ratio.

Visual inspection of funnel plots revealed some asymmetry (Figure 3.5). Indeed, this reflected in a statistically significant Egger's linear regression test (p=0.05). Trim and fill analysis indicated five studies were missing from the right of the plot although the addition of these studies did not affect results (RR 0.68; 95% CI 0.59 to 0.78). Failsafe N showed 21 negative studies would be required to observe a negative effect with gabapentin. On meta-regression analysis, neither dose (R^2=0%; p=0.32) nor morphine reduction (R^2=0%; p=0.81) explained the heterogeneity between studies. On sensitivity analysis, excluding high risk of bias trials did not affect results. One study-removed analysis revealed no influential studies.

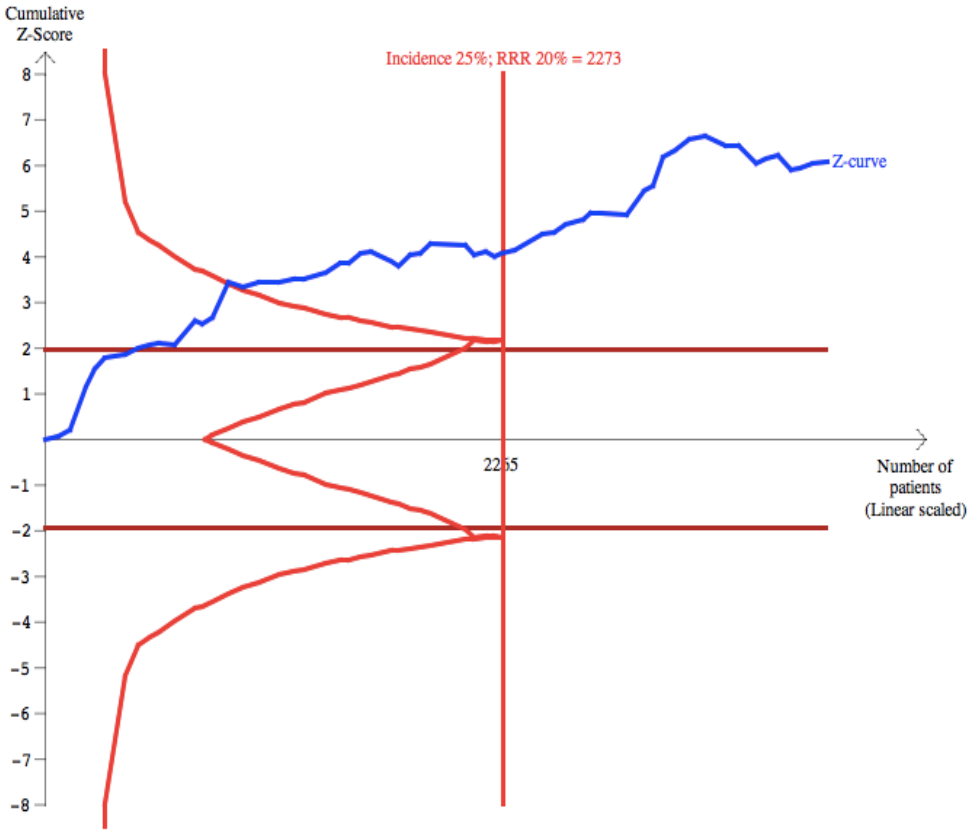


Figure 3.6: Trial sequential analysis of postoperative vomiting. Performed assuming an incidence of 25% in the control group (Cohen *et al.* 1994), RRR of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 3.6. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis showed that the included trials passed both the O'Brien-Fleming monitoring boundaries (adjusted CI 0.58 to 0.77; p<0.001) and passed the required IS for a definitive answer (2273 participants) while avoiding the boundaries of futility (Figure 3.6). However, the results did not cross the boundary for benefit when assuming a 50% RRR. Assuming an incidence of vomiting as low as 10%, gabapentin passed the monitoring boundary but did not reach the required IS. Assuming a heterogeneity correction of 25, this did not change the results.

3.3.4 Pruritus

Overall, 29 studies with 2248 participants were included in the meta-analysis. Gabapentin resulted in clinically significant reductions in the incidence of postoperative pruritus (RR 0.64; 95% CI 0.51 to 0.80; Figure 3.7). There was evidence of moderate statistical heterogeneity (I^2=51%; p=0.001). The NNT to prevent one episode of pruritus was 12 (95% CI 8.2 to 19.4). The quality of evidence was very low according to GRADE (downgraded owing to concerns over risk of bias, unexplained heterogeneity and possible publication bias).

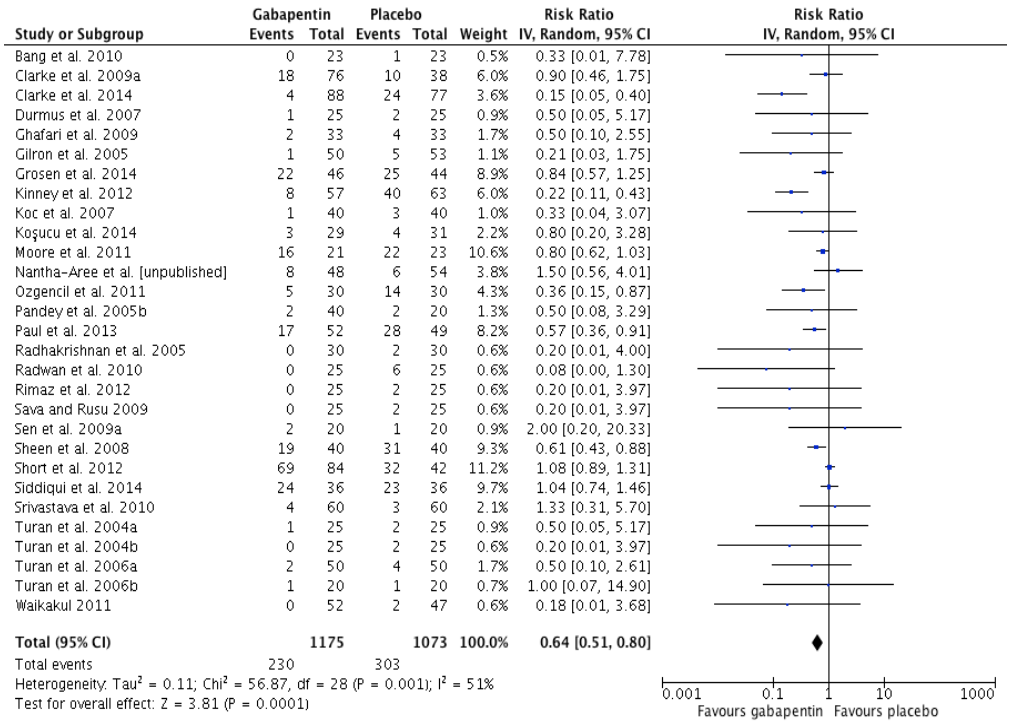


Figure 3.7: Forest plot for the risk of postoperative pruritus.

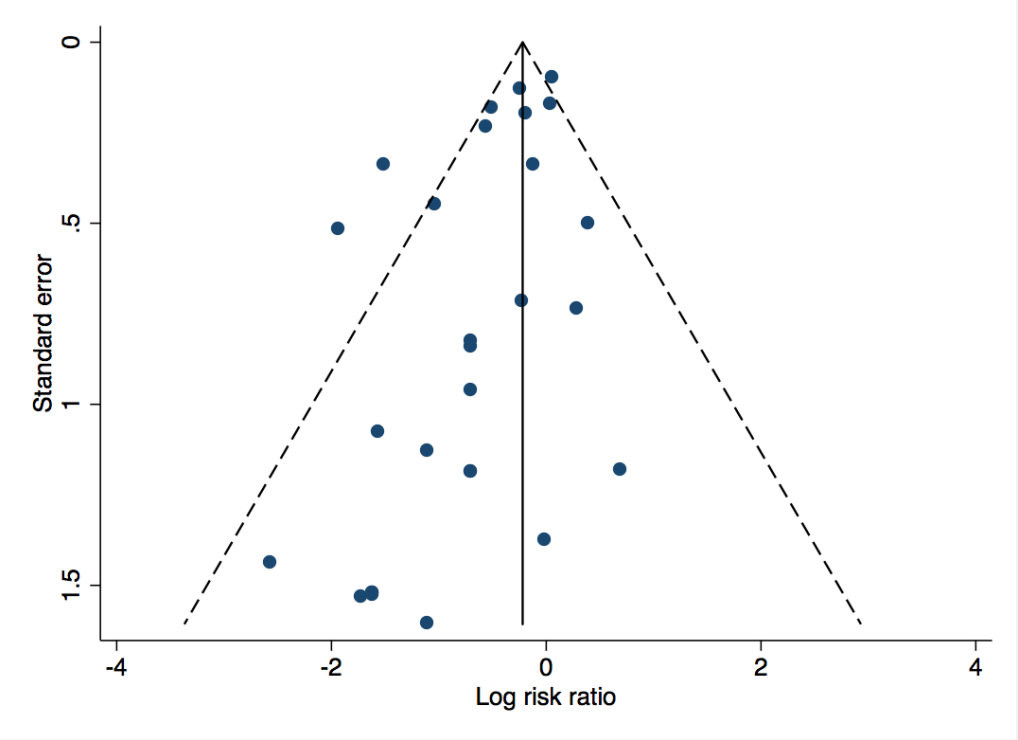


Figure 3.8: Funnel plot of gabapentin effects on postoperative pruritus. X-axis shows the log risk ratio and the Y-axis shows the standard error of the log risk ratio.

The funnel plot showed some evidence of asymmetry and the result from Egger's linear regression test was statistically significant (Figure 3.8; p=0.002). Trim and fill analysis showed 11 studies were missing from the right of the plot. Including these missing studies reduced the efficacy of gabapentin on postoperative pruritus, although the result remained clinically significant (RR 0.80; 95% CI 0.63 to 1.03). Failsafe N stated 10 negative studies would be required to observe a negative effect with gabapentin. On meta-regression analysis, neither dose (R^2=0%; p=0.75) nor morphine reduction (R^2=4%; p=0.28) explained between-study heterogeneity. On sensitivity analysis, removing studies at high risk of bias did not affect results. One study-removed analysis revealed no influential studies.

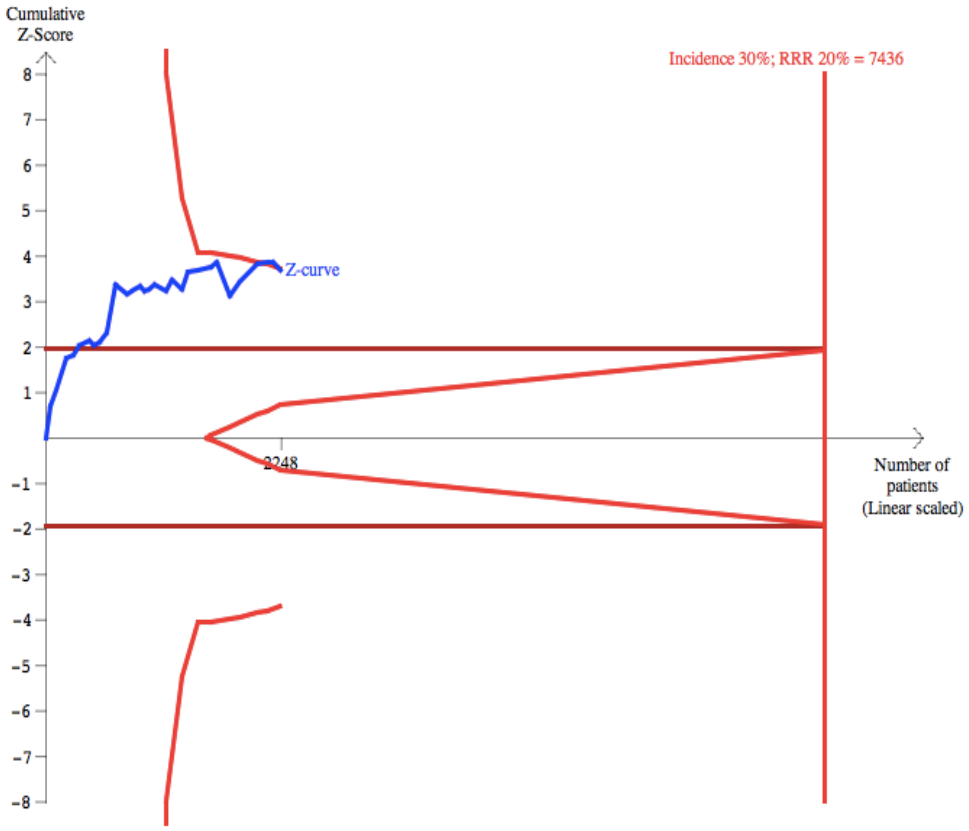


Figure 3.9: Trial sequential analysis of postoperative pruritus. Performed assuming an incidence of 30% in the control group, RRR of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 77. Blue line indicates cumulative Z score with values more than zero indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming monitoring boundary (adjusted 95% CI 0.42 to 0.88) and did not cross the boundary for futility (Figure 3.9). However, gabapentin failed to reach the required IS for a definitive answer (7436 participants). Assuming an incidence of 10%, gabapentin did not reach either the boundary for benefit or the required IS. Gabapentin did not reach the boundary for benefit assuming a RRR of 50%.

3.3.5 Pre-operative anxiety

For pre-operative anxiety, eight studies with 527 participants were included in the analysis. As different scales were used, this outcome was analysed using SMD. Gabapentin reduced pre-operative anxiety (SMD -0.84; 95% CI -1.2 to -0.48; Figure 3.10). There was evidence of substantial statistical heterogeneity (I^2=74%; p<0.001). The quality of evidence was moderate (downgraded owing to concerns over risk of bias).

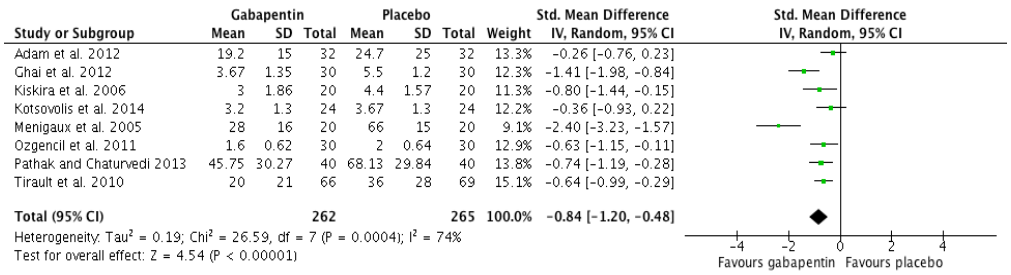


Figure 3.10: Forest plot of gabapentin effects on pre-operative anxiety. Reported as SMD due to the different scales used in the studies.

Tests for publication bias were not conducted due to the low number of included studies. On meta-regression analysis, baseline anxiety score in the control group predicted a large proportion of the between-study heterogeneity (R^2=35%; p=0.02) (Figure 3.11). Dose was not a significant predictor of pre-operative anxiety (R^2=0%; p=0.52). In terms of diagnostics, histograms showed residuals within the model were normally distributed. One studentised residual was more than two (Menigaux *et al.* 2005). Due to the small number of studies, homoscedasticity and linearity were not assessed. No data point had a Cook's distance of more than one. We were unable to perform trial sequential analysis, as SMD was used for the effect estimate. On sensitivity analysis, excluding the one high risk of bias trial (Tirault *et al.* 2010) did not affect results. One study-removed analysis did not identify any influential studies.

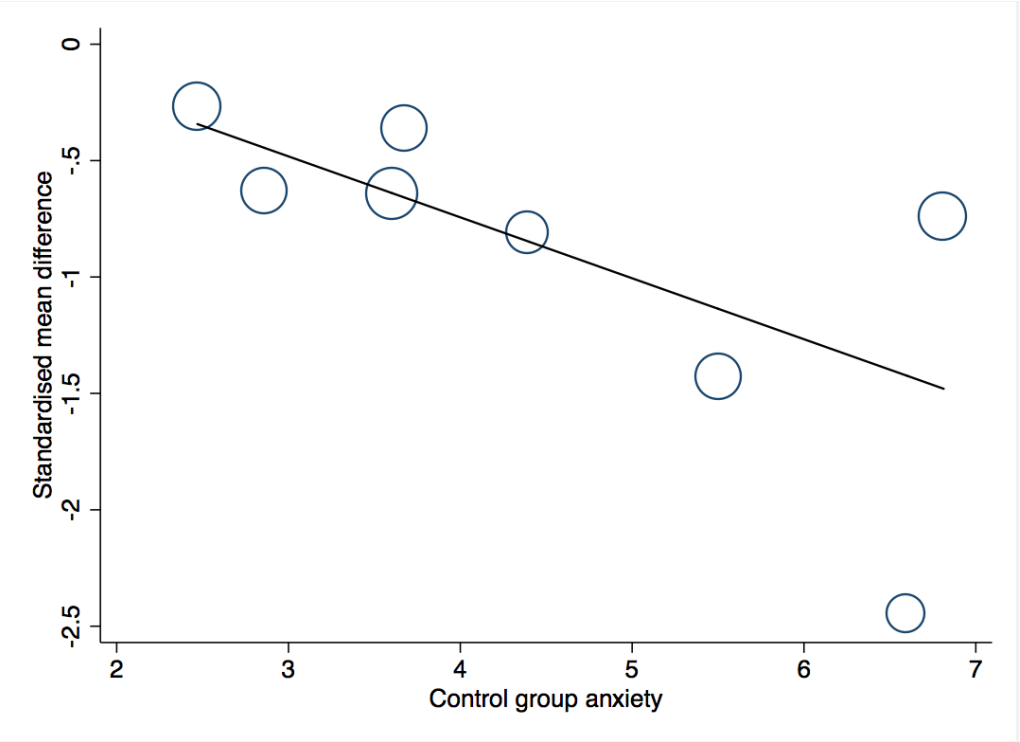


Figure 3.11: Meta-regression plot. X-axis shows the mean control group anxiety score and the Y-axis the standardised mean difference in anxiety with gabapentin.

3.3.6 Sedation

Overall, 52 studies with 4112 participants were included in the analysis. Gabapentin increased the risk of postoperative sedation (RR 1.18; 95% CI 1.09 to 1.28; Figure 3.12). There was evidence of some statistical heterogeneity (I^2=28%; p=0.03). The NNH for one episode of sedation was 13 (95% CI 9 to 18.2). The quality of evidence was very low according to GRADE (downgraded owing to concerns over risk of bias, possible publication bias and unexplained heterogeneity).

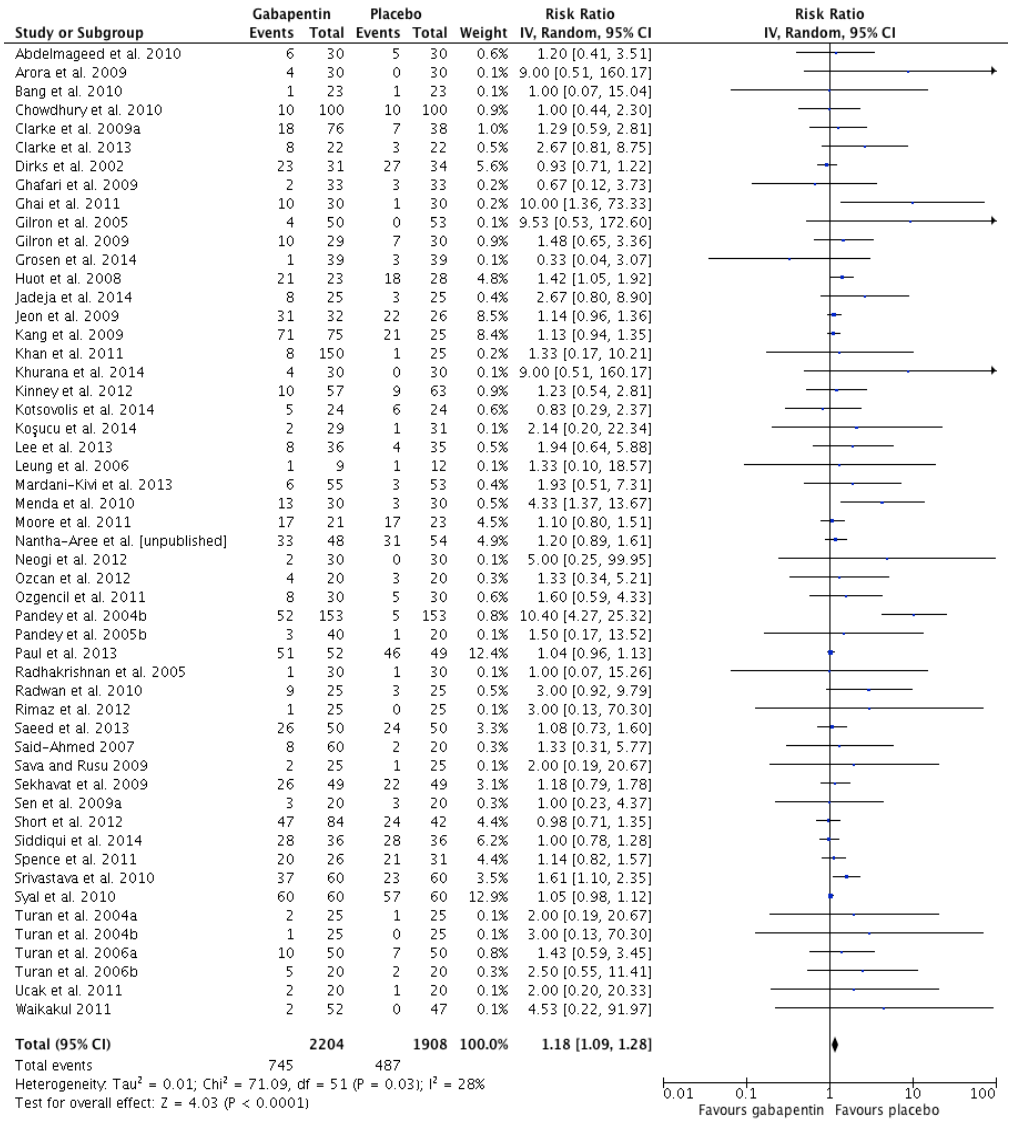


Figure 3.12: Forest plot of gabapentin effects on the incidence of postoperative sedation.

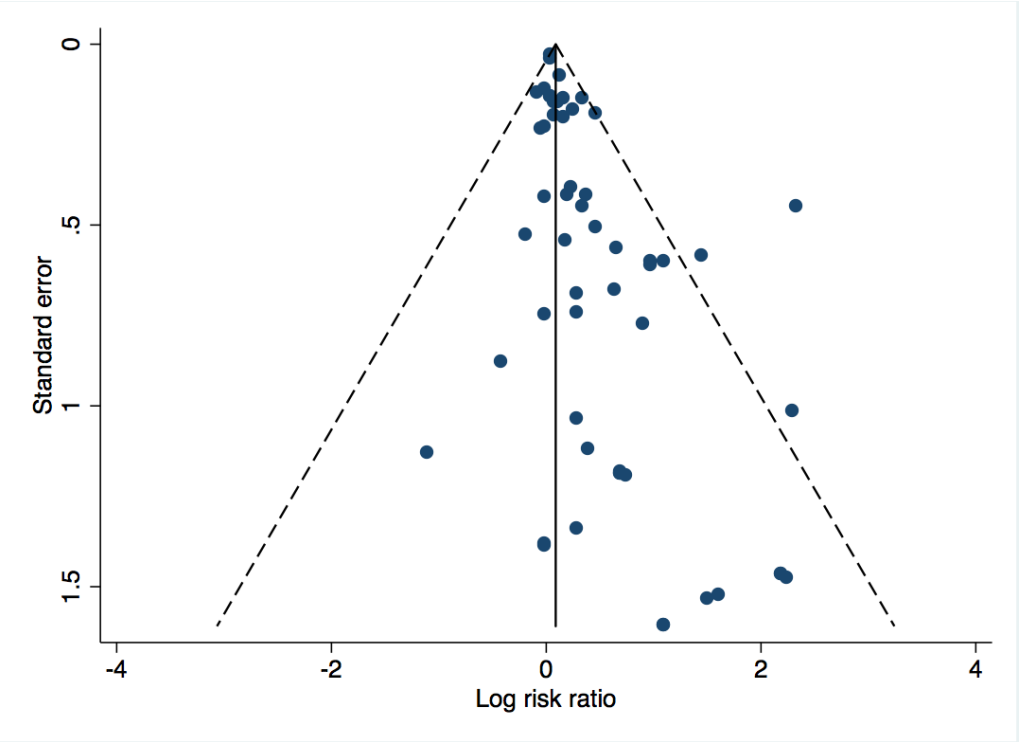


Figure 3.13: Funnel plot of gabapentin effects on postoperative sedation. X-axis shows the log risk ratio (with data points to the right indicating an increase in sedation) and the Y-axis shows the standard error of log risk ratio.

Visual inspection of the funnel plot showed asymmetry, with more studies on the right of the plot (Figure 3.13). Egger's linear regression test was statistically significant ($p<0.001$). Trim and fill analysis showed there were 19 studies missing from the left of the plot, which adjusted the risk closer to the null effect (RR 1.12; 95% CI 1.01 to 1.25). Failsafe N indicated five negative studies would be required to observe no effect with gabapentin on sedation. On meta-regression analysis, dose did not predict the incidence of postoperative sedation (R^2=0%; p=0.94). On sensitivity analysis, removing studies at high risk of bias did not affect results. One study-removed analysis revealed no influential studies.

Figure 3.14: Trial sequential analysis of postoperative sedation. Performed assuming an incidence of 25% in the control group, relative risk increase of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 74. Blue line indicates cumulative Z score with values less than 0 indicating harm with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming monitoring boundary for harm and avoided the area for futility (adjusted 95% CI 1.04 to 1.32) (Figure 3.14). However, gabapentin did not reach the required IS for a definitive answer (9704 participants). Gabapentin did not cross any boundary for harm assuming an incidence as low as 10%. Furthermore, gabapentin did not pass the boundary for a relative increase in sedation of 50%. We did not perform sensitivity analysis around the heterogeneity correction due to the high number already included in the analysis.

3.3.7 Confusion

Overall, three studies with 184 participants were included in the analysis. Confidence intervals suggested a possible reduction in the incidence of postoperative confusion with gabapentin, however this was not statistically significant (RR 0.50; 95% CI 0.19 to 1.34; Figure 3.15). There was no evidence of statistical heterogeneity (I^2=0%; p=0.52). There were too few studies in the analysis to assess publication bias or perform meta-regression analysis. The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and imprecision of effect estimates). On sensitivity analysis, only one study remained when excluding high risk of bias trials (Siddiqui *et al.* 2014), which also resulted in no reduction in postoperative confusion. One study-removed analysis revealed no influential studies in the analysis.

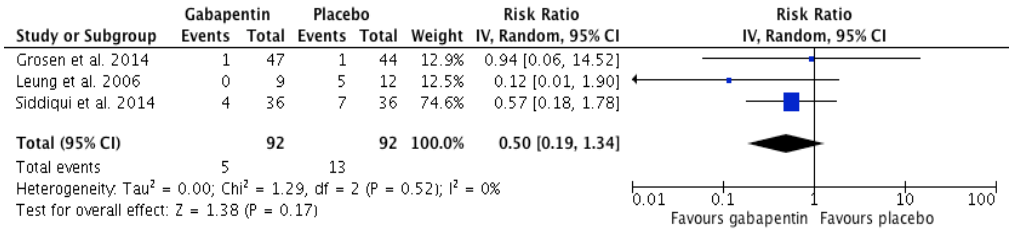


Figure 3.15: Forest plot of gabapentin effects on the incidence of postoperative sedation.

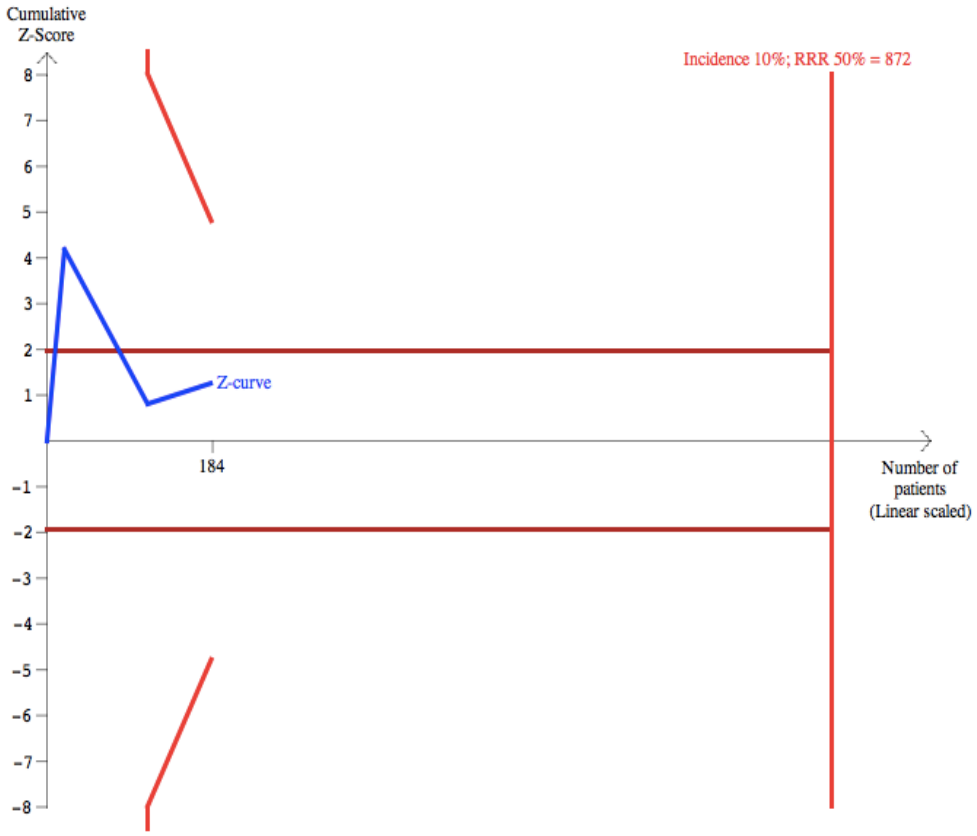


Figure 3.16: Trial sequential analysis of postoperative confusion. Performed assuming an incidence of 10% in the control group, RRR of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin failed to reach the boundary for benefit and did not reach the required IS (872 participants) (Figure 3.16). Following publication of the first study with a small number of participants (21) (Leung *et al.* 2006), meta-analyses would have falsely concluded that gabapentin was effective. However, subsequent publications have concluded that overall results demonstrate no clear benefit.

3.3.8 Constipation

Overall, 10 studies with 565 participants were included in the analysis. There was no significant reduction in the incidence of postoperative constipation with gabapentin (RR 0.80; 95% CI 0.44 to 1.44; Figure 3.17). There was no evidence of statistical heterogeneity (I^2=0%; p=0.81). The quality of the evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

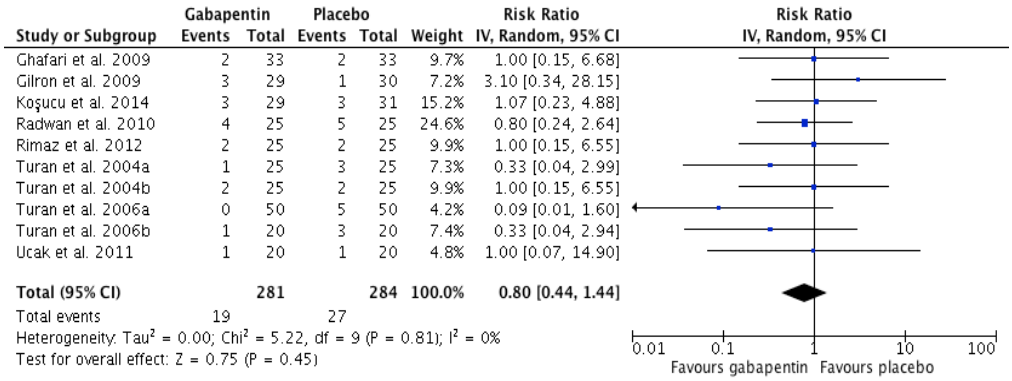


Figure 3.17: Forest plot of gabapentin on the incidence of postoperative constipation.

There was no evidence of publication bias on either visual inspection of the funnel plot (Figure 3.18) or on Egger's linear regression test (p=0.18). On meta-regression, dose did not predict the incidence of constipation (R^2=0%; p=0.84). On sensitivity analysis, removing studies at high risk of bias did not affect results. One study-removed analysis showed no influential studies in the analysis.

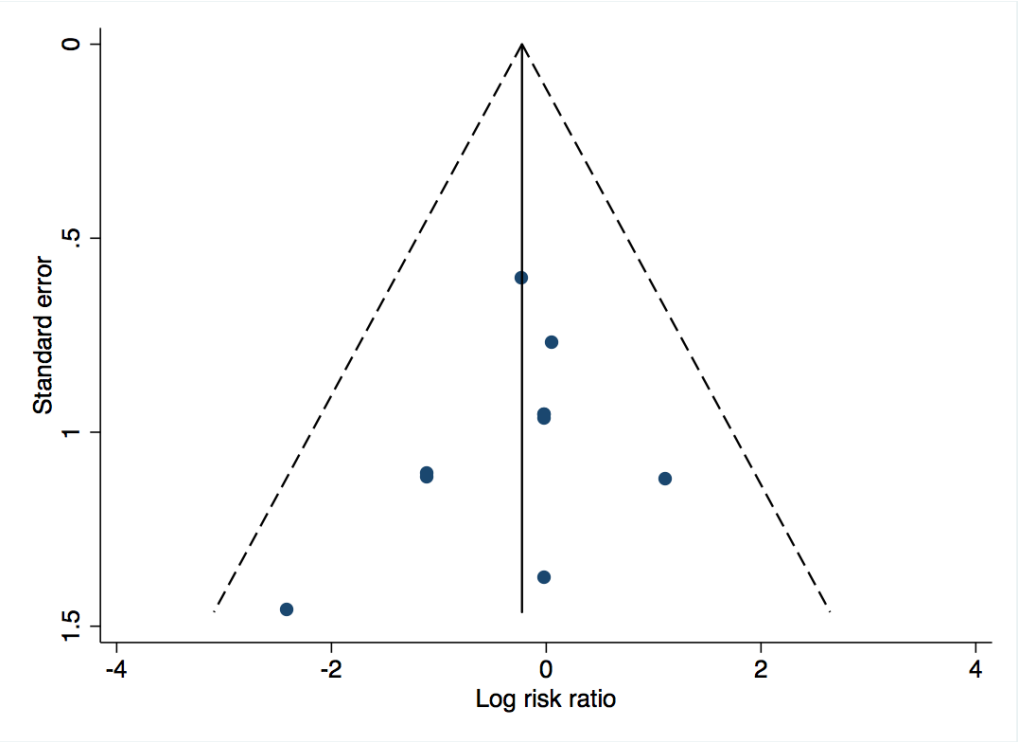


Figure 3.18: Funnel plot of gabapentin effects on postoperative constipation. X-axis shows the log risk ratio and the Y-axis shows the standard error of log risk ratio.

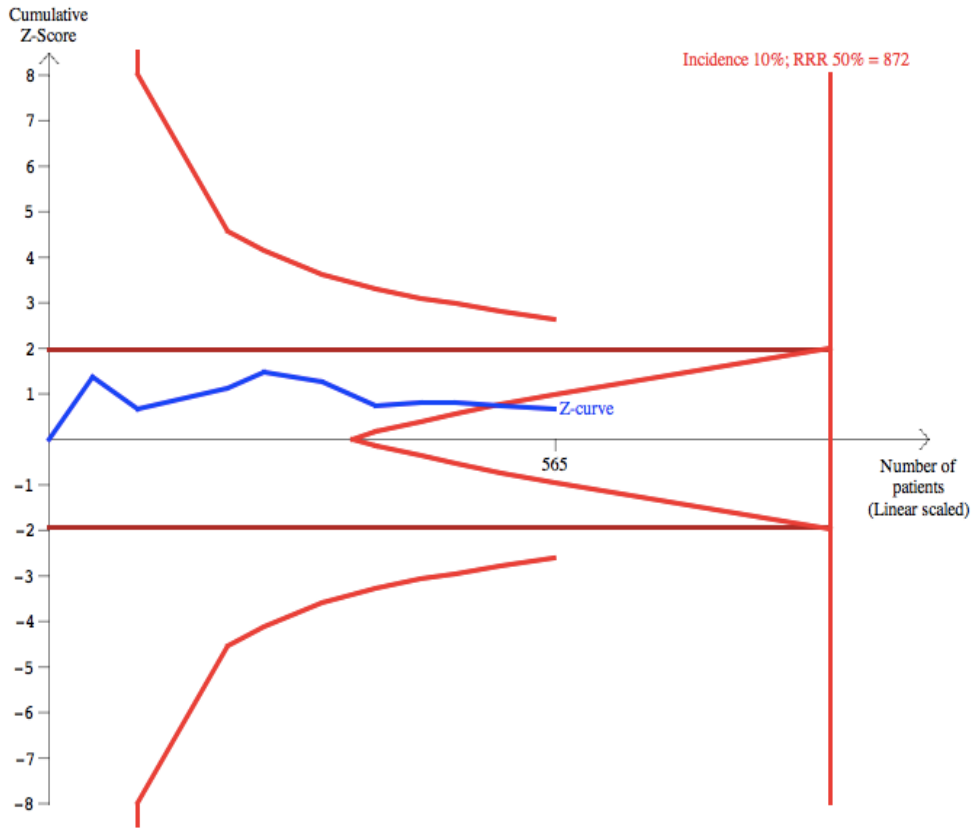


Figure 3.19: Trial sequential analysis of postoperative constipation. Performed assuming an incidence of 10% in the control group, RRR of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin did not pass any boundary for benefit assuming an incidence of 10% and a RRR of 20%. However, assuming an incidence of 10% and a RRR of 50%, gabapentin crossed the boundary for futility (Figure 3.19). None of the analyses reached the required IS for a definitive answer.

3.3.9 Dizziness

Overall, 51 studies with 3746 participants were included in the analysis. Gabapentin did not increase the risk of postoperative dizziness (RR 1.04; 95% CI 0.94 to 1.15; Figure 3.20). There was no evidence of statistical heterogeneity (I^2=0%; p=0.91). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

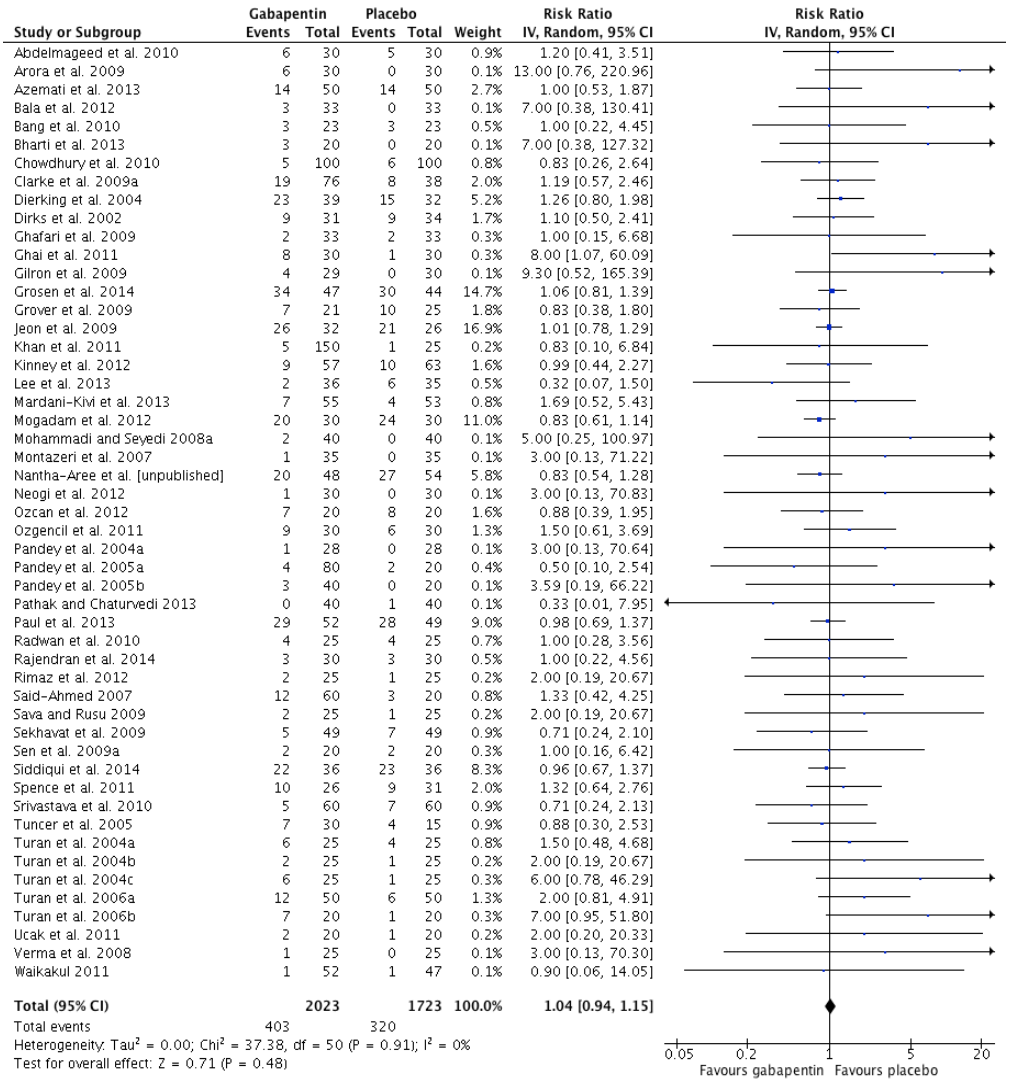


Figure 3.20: Forest plot of gabapentin on the incidence of postoperative dizziness.

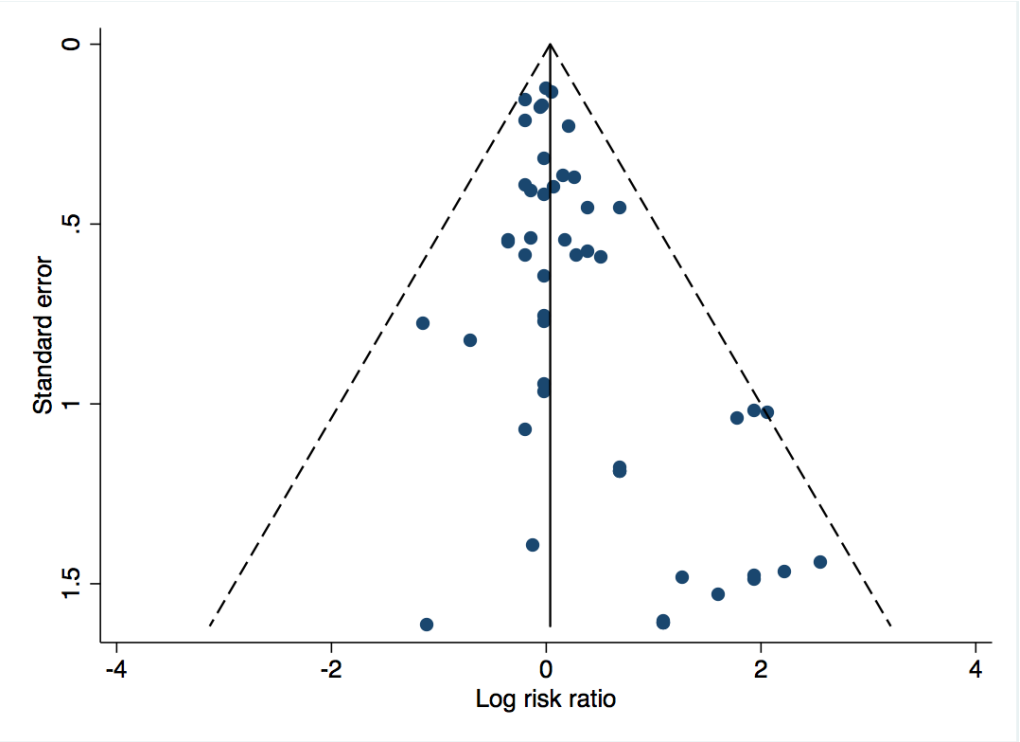


Figure 3.21: Funnel plot of gabapentin on the incidence of postoperative dizziness. X-axis shows the log risk ratio and the Y-axis shows the standard error of log risk ratio.

There was evidence of funnel plot asymmetry (Figure 3.21) and Egger's linear regression test was statistically significant ($p<0.001$). Trim and fill analysis showed 11 missing studies were to the left of the mean, which demonstrated a bias against gabapentin for this outcome (adjusted RR 1.00; 95% CI 0.91 to 1.11). Failsafe N was not conducted, as the original results were not statistically significant. On meta-regression analysis, gabapentin dose did not predict the incidence of postoperative dizziness (R^2=0%; p=0.16). On sensitivity analysis, removing studies at high risk of bias did not affect results. One study-removed analysis showed there were no influential studies.

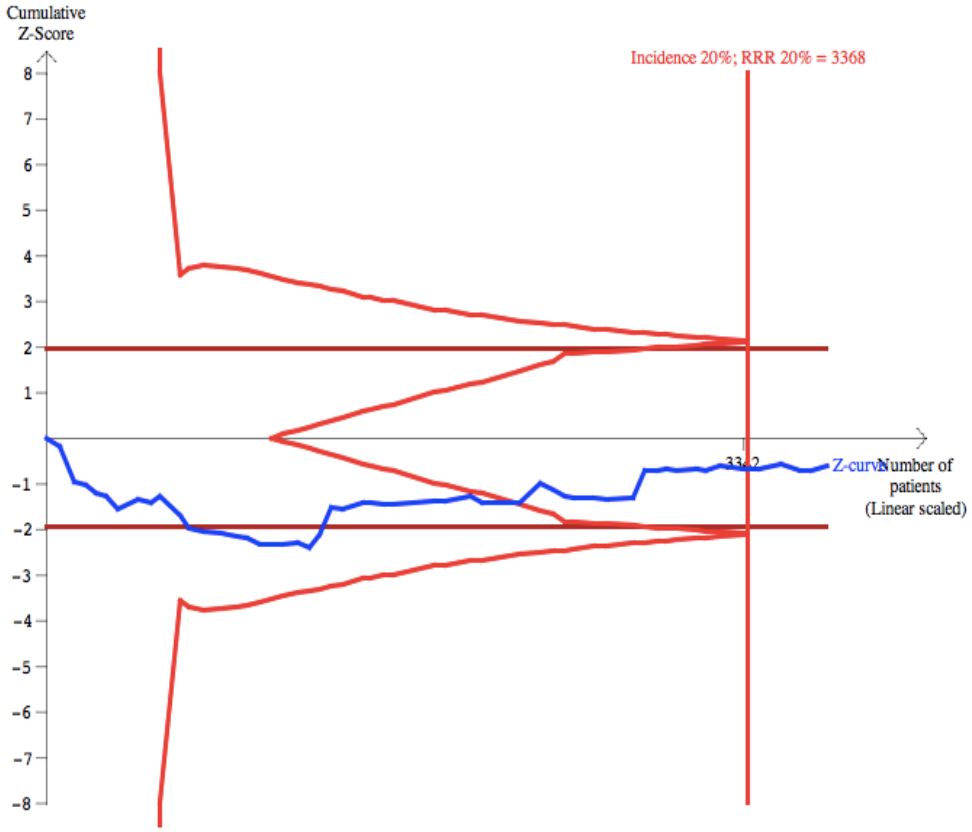


Figure 3.22: Trial sequential analysis of postoperative dizziness. Performed assuming an incidence of 20% in the control group, relative risk increase of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values less than 0 indicating harm with gabapentin.

Trial sequential analysis showed that gabapentin reached the required IS for a definitive answer (3368 participants) (Figure 3.22). Gabapentin entered the area of futility and subsequently did not reach the monitoring boundary for harm. Following the publication of one study (Gilron *et al.* 2009), the effects of gabapentin crossed the conventional boundary for harm (unadjusted $p<0.05$). However, this effect subsequently returned to no harm. On sensitivity analysis, assuming a heterogeneity correction of 25, gabapentin did not reach the required IS. Gabapentin did not cross the boundary for a 50% increase in dizziness. Assuming an incidence as low as 10%, gabapentin crossed the boundary of futility without reaching the required IS.

3.3.10 Headache

Overall, 24 studies with 1710 participants were included in the analysis. There was no difference in the incidence of headache between the groups (RR 1.05; 95% CI 0.82 to 1.33; Figure 3.23). There was no evidence of statistical heterogeneity (I^2=8%; p=0.35). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

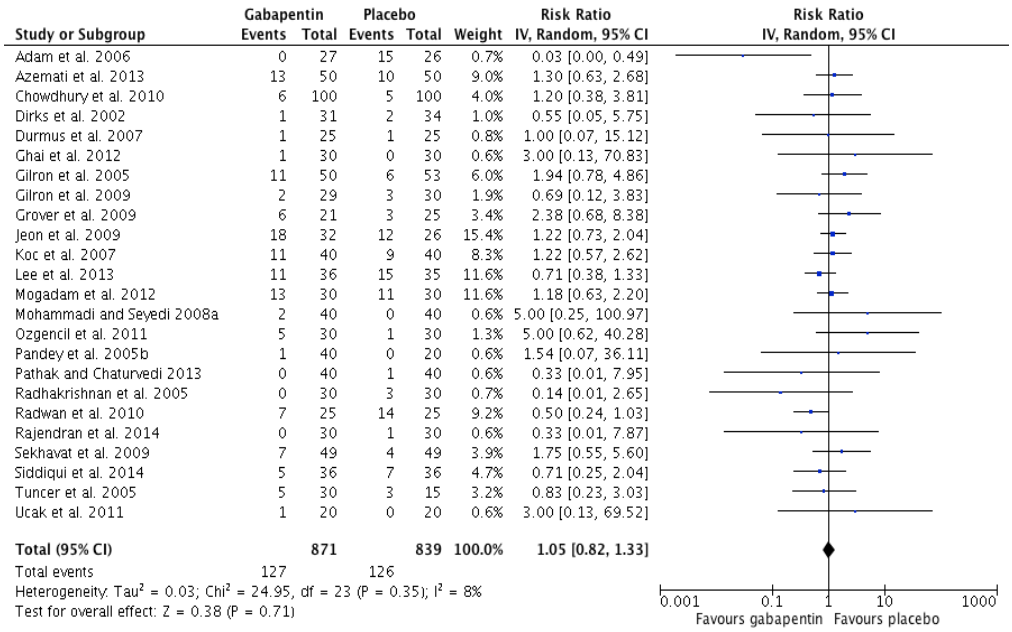


Figure 3.23: Forest plot of gabapentin effects on the incidence of postoperative headache.

There was no evidence of an asymmetric funnel plot (Figure 3.24) and Egger's linear regression test was not statistically significant (p=0.38). On meta-regression analysis, dose did not predict the incidence of postoperative headache (R^2=0%; p=0.84). On sensitivity analysis, removing studies at high risk of bias did not affect the results. One study-removed analysis showed there were no influential studies in the analysis.

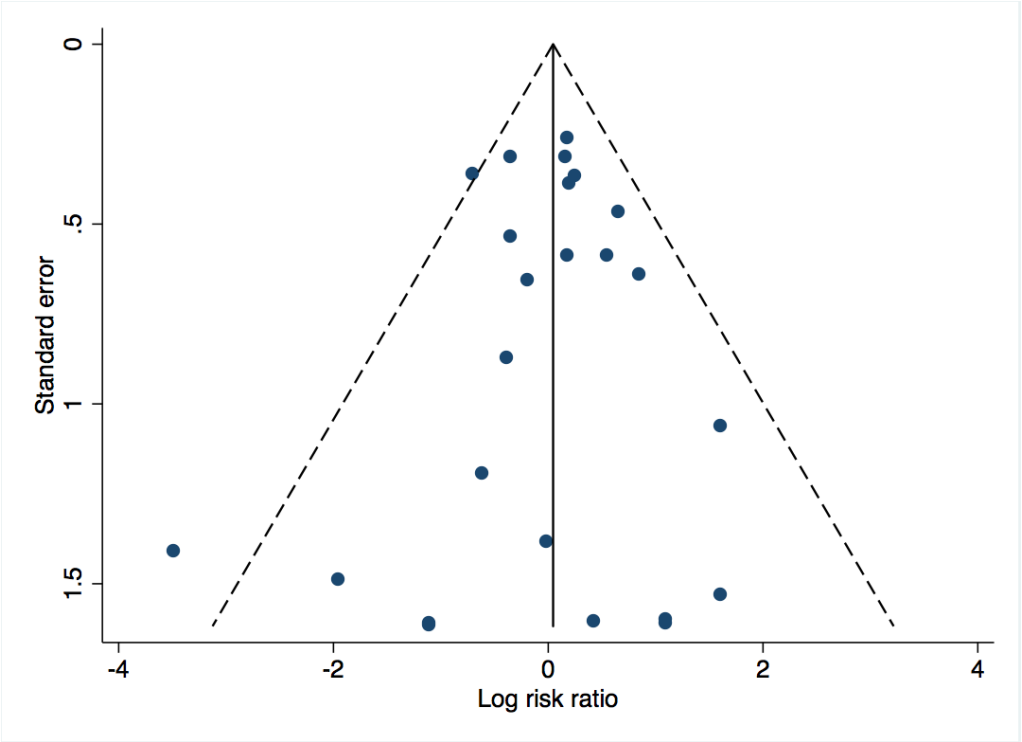


Figure 3.24: Funnel plot of gabapentin effects on postoperative headache. X-axis shows the log risk ratio and the Y-axis shows the standard error of log risk ratio.

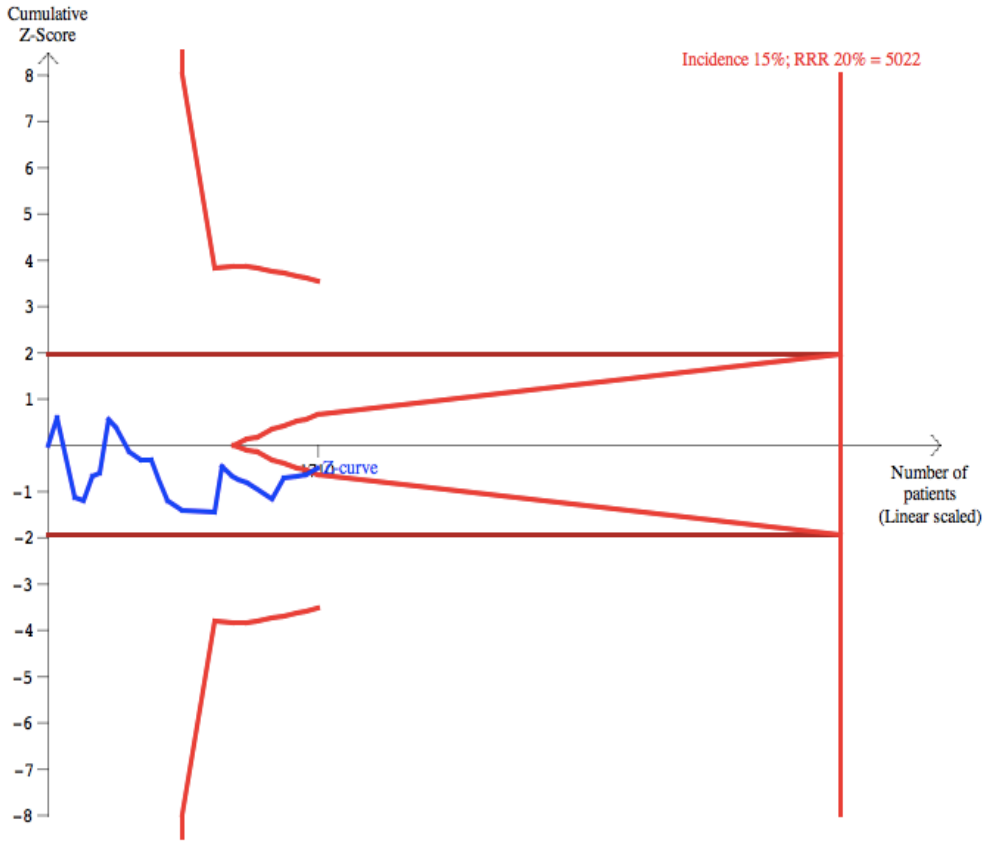


Figure 3.25: Trial sequential analysis of postoperative headache. Performed assuming an incidence of 15% in the control group, relative risk increase of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 4. Blue line indicates cumulative Z score with values less than 0 indicating harm with gabapentin.

Trial sequential analysis shows that gabapentin crossed the boundary of futility for harm (Figure 3.25). Gabapentin did not reach the required IS for a definitive answer (5022 participants). On sensitivity analysis, assuming an incidence of 10% and a relative risk increase of 20%, no futility boundaries could be constructed, although the results did not pass any boundary for harm. For an incidence of 15% and relative risk increase of 50%, gabapentin did not reach the boundary for harm. Assuming a heterogeneity correction of 25 increased the required IS (5432 participants).

3.3.11 Patient satisfaction

Overall, eight studies with 454 participants were included in the analysis. Gabapentin resulted in an increase in patient satisfaction (SMD 0.59; 95% CI 0.18 to 1.00; Figure 3.26). Results are reported as SMD due to different scales used. There was evidence of considerable statistical heterogeneity (I^2=77%; p<0.001). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias). Due to the low number of studies, tests for publication bias were not undertaken.

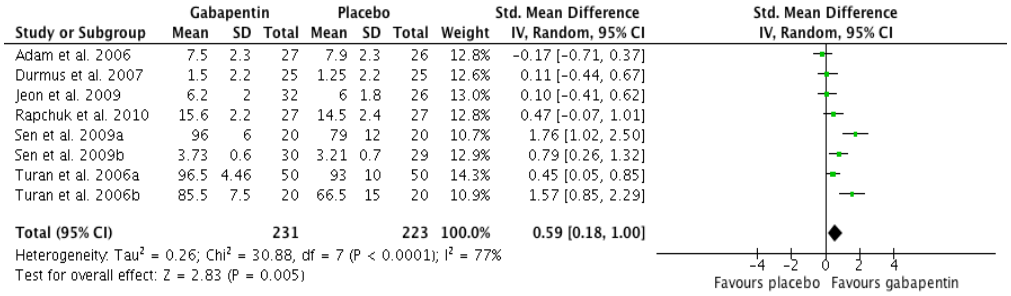


Figure 3.26: Forest plot of gabapentin effects on patient satisfaction.

On meta-regression analysis, there was some evidence that increases in dose predicted increases in patient satisfaction (R^2=19%; p=0.07) (Figure 3.27). On diagnostics, there were no studentised residuals with a value of more than two and no study had a Cook's distance of more than one. Histograms showed residuals to be normally distributed. Homoscedasticity and linearity were difficult to assess due to the low number of data points. Due to the use of SMD for this outcome, TSA could not be performed. Sensitivity analysis showed that removing studies at high risk of bias or those where standard deviations were estimated did not affect results. One study-removed analysis showed there were no influential studies in the analysis.

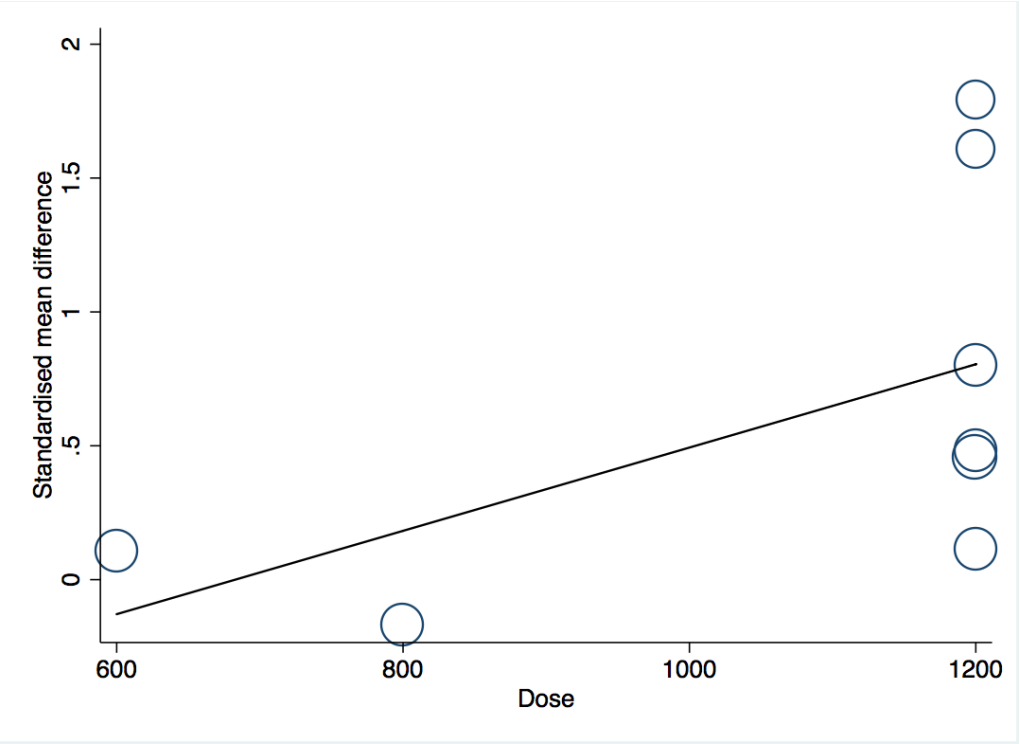


Figure 3.27: Meta-regression plot. X-axis shows gabapentin dose (mg) and the Y-axis the standardised mean difference in patient satisfaction scores.

3.3.12 Respiratory depression

Overall, there were seven studies with 801 participants included in the analysis. There was no difference in the incidence of postoperative respiratory depression with gabapentin (RR 1.08; 95% CI 0.51 to 2.29; Figure 3.28). There was no evidence of statistical heterogeneity (I^2=0%; p=0.71). The quality of the evidence was moderate according to GRADE (downgraded owing to concerns with risk of bias).

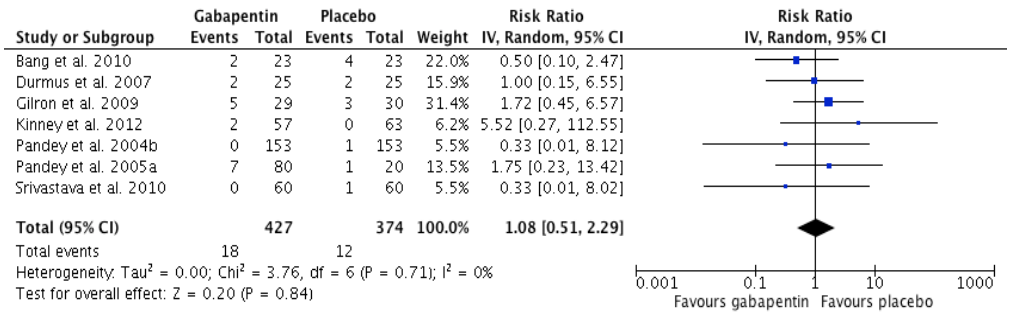


Figure 3.28: Forest plot of gabapentin effect on respiratory depression.

Due to the low number of studies, tests for publication bias were not conducted. On meta-regression analysis, dose did not predict the effect of gabapentin on respiratory depression (R^2=0%; p=0.28). On sensitivity analysis, excluding studies at high risk of bias did not affect results. One study-removed analysis showed there were no influential studies.

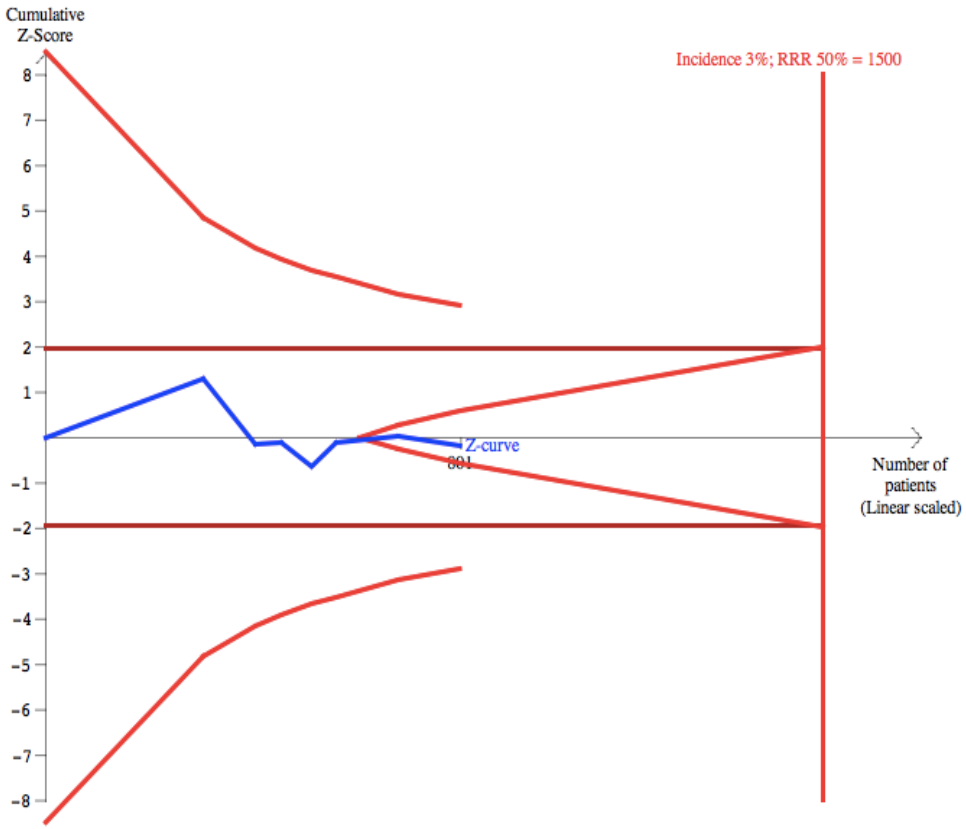


Figure 3.29: Trial sequential analysis of postoperative respiratory depression. Performed assuming an incidence of 3% in the control group, relative risk increase of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values less than 0 indicating harm with gabapentin.

Trial sequential analysis showed that the effects of gabapentin on respiratory depression crossed the boundary for futility (Figure 3.29). However, this effect did not reach the required IS (1500 participants). There was too few information to perform sensitivity analysis using a relative risk difference of 20% or an incidence as low as 1% with a 50% relative risk difference. Assuming a heterogeneity correction of 25, this increased the required IS (4092 participants).

3.3.13 Urinary retention

Overall, 14 studies with 888 participants were included in the analysis. Gabapentin did not reduce the incidence of postoperative urinary retention, although confidence intervals suggested a possible effect (RR 0.64; 95% CI 0.40 to 1.04; Figure 3.30). There was no evidence of statistical heterogeneity (I^2=0%; p=0.60). The quality of the evidence was low according to GRADE (downgraded owing to concerns over risk of bias and imprecision in results).

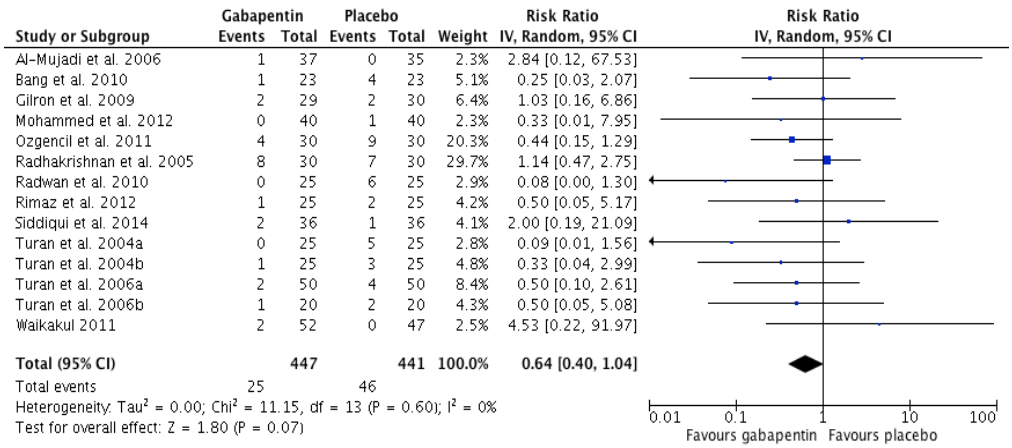


Figure 3.30: Forest plot of the effects of gabapentin on the incidence of urinary retention.

Visual inspection of the funnel plot revealed no asymmetry (Figure 3.31) and Egger's linear regression test was not significant (p=0.21). On meta-regression analysis, dose did not predict the incidence of postoperative urinary retention (R^2=0%; p=0.37). On sensitivity analysis, removing studies at high risk of bias resulted in a reduction in the incidence of urinary retention (RR 0.60; 95% CI 0.36 to 1.00). One study-removed analysis showed there were two influential studies in the analysis (Radhakrishnan *et al.* 2005; Waikakul 2011), which when removed resulted in reductions in urinary retention.

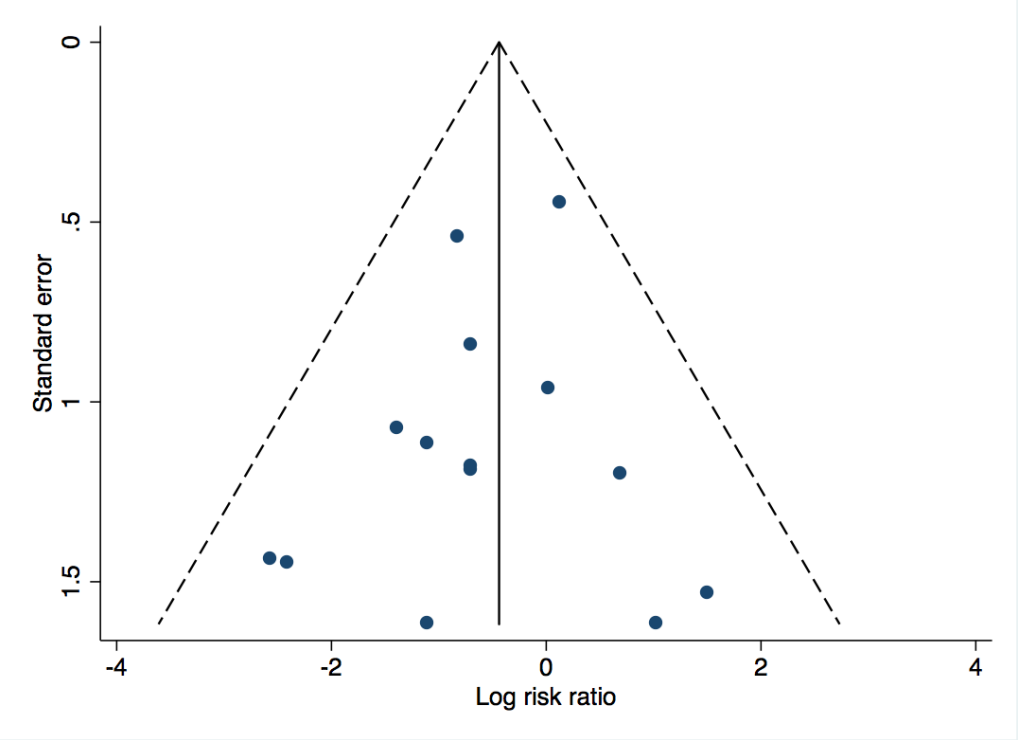


Figure 3.31: Funnel plot of gabapentin effects on the incidence of postoperative urinary retention. X-axis shows the log risk ratio and the Y-axis shows the standard error of log risk ratio.

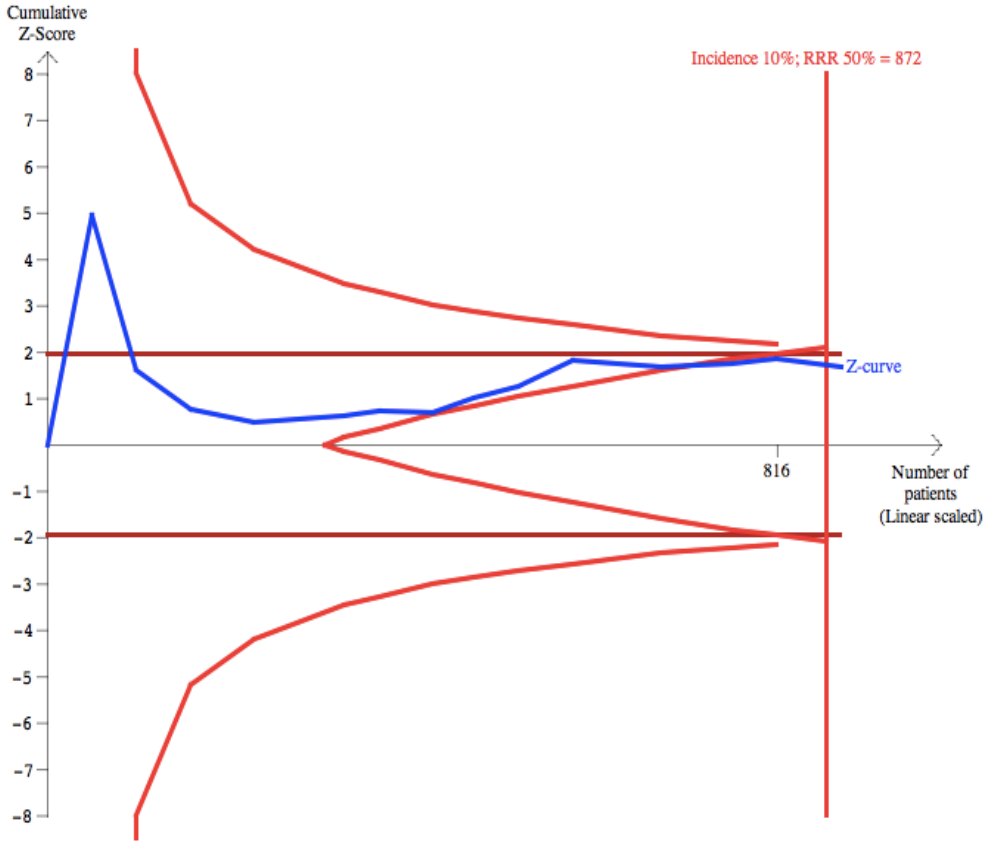


Figure 3.32: Trial sequential analysis of postoperative urinary retention. Performed assuming an incidence of 10% in the control group, RRR of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed gabapentin demonstrated benefit using conventional boundaries following the publication of one trial (Turan *et al.* 2004a). However, publication of subsequent trials reduced this effect (Figure 3.32). Gabapentin results reached the required IS for a 50% RRR (872 participants) and did not cross the boundary for benefit. On sensitivity analysis, assuming a 20% RRR, the effects of gabapentin did not reach the required IS (6429 participants) or cross any boundary for benefit or futility. Assuming a heterogeneity correction of 25 or an incidence as low as 5%, gabapentin did not reach the required IS or area of futility.

3.3.14 Visual disturbance

Overall, four studies with 348 participants were included in the analysis. Gabapentin did not increase the incidence of postoperative visual disturbance (RR 1.36; 95% CI 0.77 to 2.40; Figure 3.33). There was no evidence of statistical heterogeneity (I^2=0%; p=0.89). Due to the low number of studies, tests for publication bias or investigation of heterogeneity were not undertaken. The quality of the evidence was low according to GRADE (downgraded owing to concerns over risk of bias and imprecision of results). On sensitivity analysis, removing studies at high risk of bias did not affect results. One study-removed analysis showed there were no influential studies.

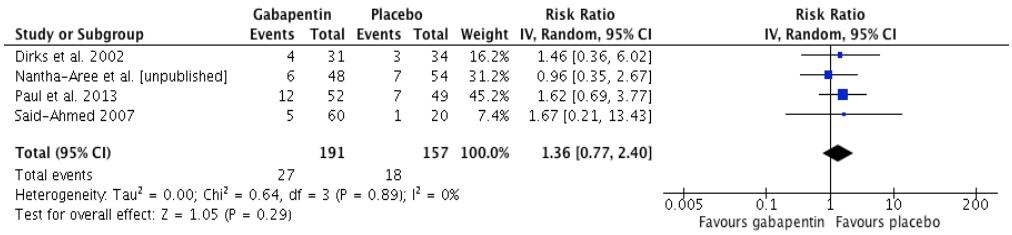


Figure 3.33: Forest plot of the effects of gabapentin on the incidence of visual disturbance.

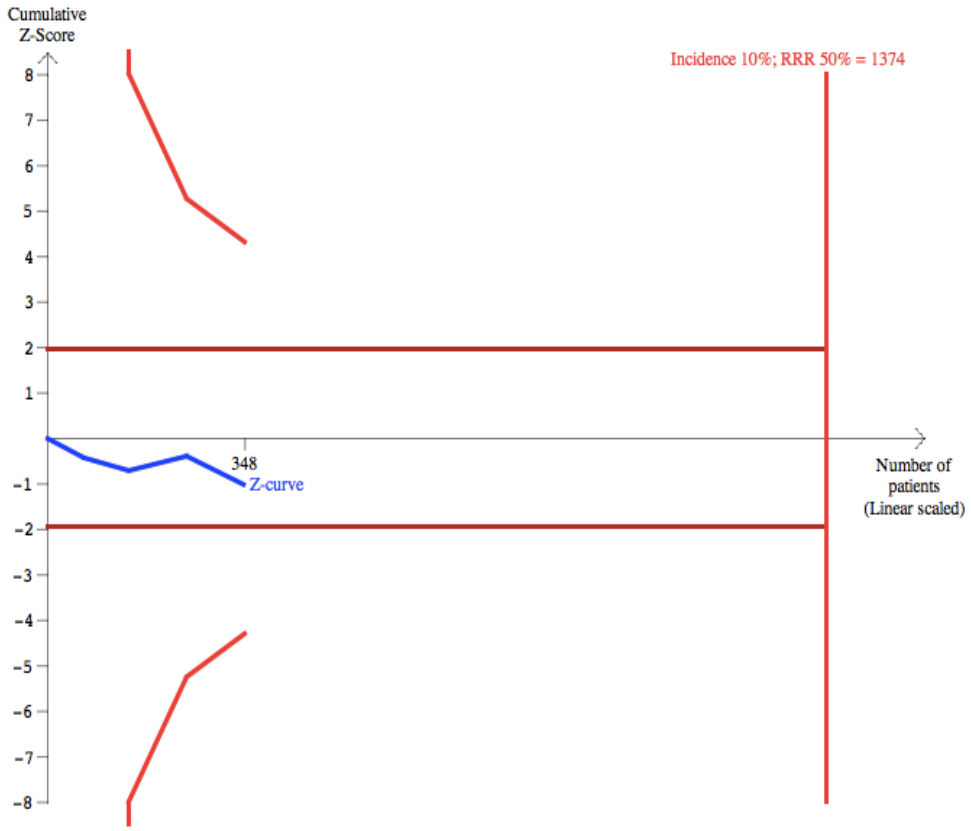


Figure 3.34: Trial sequential analysis of postoperative visual disturbance. Performed assuming an incidence of 10% in the control group, relative risk increase of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values less than 0 indicating harm with gabapentin.

Trial sequential analysis showed gabapentin did not cross any boundary for harm assuming a 50% increase in visual disturbance (Figure 3.34). Gabapentin did not reach the required IS for a definitive answer (1374 participants). On sensitivity analysis, assuming a relative risk increase of 20%, a heterogeneity correction of 25 or an incidence as low as 5% did not change the results.

3.3.15 Ataxia

Only one study reported the incidence of postoperative ataxia (Adam *et al.* 2006). There was no difference between the groups (RR 1.08; 95% CI 0.74 to 1.56). As only one study was identified, no analyses for publication bias, investigation of heterogeneity or TSA were performed.

3.3.16 Fatigue

Overall, eight studies with 527 participants were included in the analysis. There was no difference in the incidence of postoperative fatigue between the groups (RR 0.88; 95% CI 0.65 to 1.19; Figure 3.35). There was evidence of moderate statistical heterogeneity (I^2=46%; p=0.08). The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

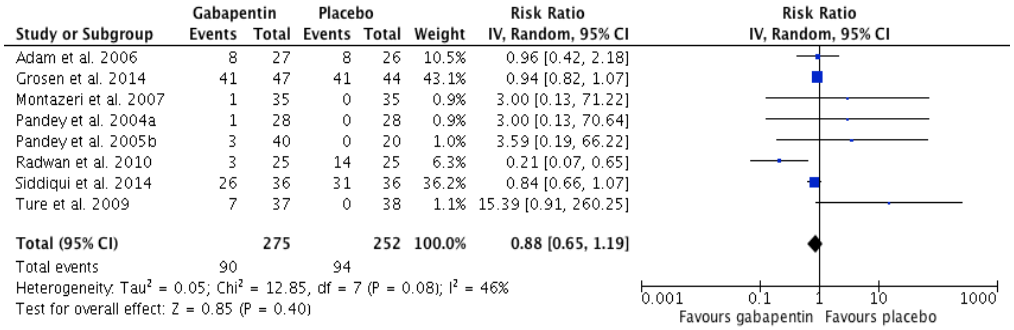


Figure 3.35: Forest plot of the effects of gabapentin on the incidence of postoperative fatigue.

Due to the low number of studies, tests for publication bias were not undertaken. On meta-regression analysis, gabapentin dose did not predict the incidence of postoperative fatigue (R^2=0%; p=0.61). On sensitivity analysis, removing studies at high risk of bias did not affect results. One study-removed analysis showed there were no influential studies.

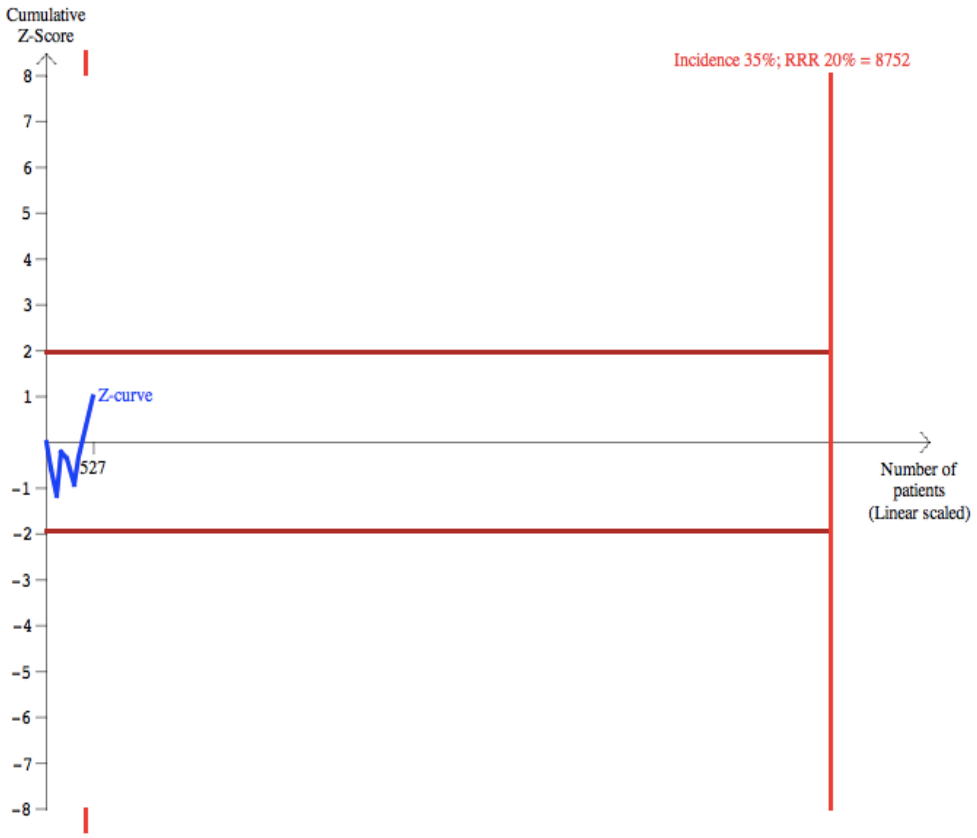


Figure 3.36: Trial sequential analysis of postoperative fatigue. Performed assuming an incidence of 35% in the control group, RRR of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 84. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed the results for gabapentin on the incidence of fatigue did not cross any boundary for benefit or harm (Figure 3.36). Gabapentin did not reach the required IS for a definitive answer (8752 participants). On sensitivity analysis, similar results were obtained assuming a RRR of 50% and an incidence as low as 10%. Sensitivity analysis around estimates of heterogeneity corrections were not performed due to the high value already used in the analysis.

3.3.17 Catheter-related bladder discomfort

Overall, two studies with 208 participants were included in the analysis. Although there was no statistically significant reduction with gabapentin, the confidence intervals suggested a possible decrease in the incidence of catheter-related bladder discomfort (RR 0.22; 95% CI 0.02 to 1.96; Figure 3.37). Furthermore, individually, each study showed a significant reduction. There was evidence of considerable statistical heterogeneity (I^2=93%; p<0.001). Due to the low number of studies, analyses for publication bias or investigation of heterogeneity were not conducted. The quality of the evidence was very low according to GRADE (downgraded owing to concerns over risk of bias, unexplained heterogeneity and imprecision of results). No studies were removed on sensitivity analysis of high risk of bias studies. Removal of each study resulted in significant reductions on both analyses.

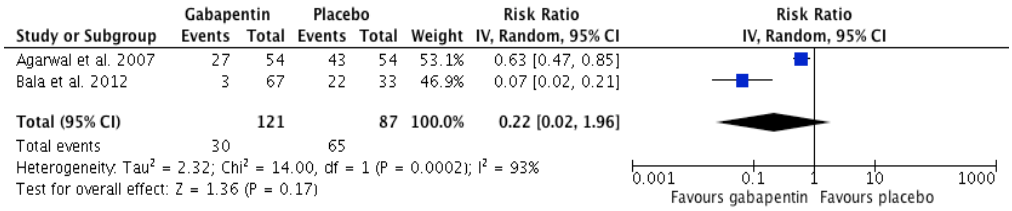


Figure 3.37: Forest plot of the effects of gabapentin on the incidence of catheter-related bladder discomfort.

Figure 3.38: Trial sequential analysis of the effects of gabapentin on postoperative catheter-related bladder discomfort. Performed assuming an incidence of 75% in the control group, RRR of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 98. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential could not be performed for a RRR of 20% due to too little information. When analysing using a RRR of 50% (Figure 3.38), the effects of gabapentin crossed the conventional boundary for significance following the publication of the first trial (Agarwal *et al.* 2007), which subsequently returned to the area of no effect on the publication of the second trial. The analysis for gabapentin did not reach the required IS (3147 participants). On sensitivity analysis, similar results were obtained assuming an incidence as low as 50%.

3.3.18 Anti-emetic requirement

Overall, there were 22 studies with 1863 participants included in the analysis. Gabapentin reduced the number of participants requiring anti-emetics (RR 0.64; 95% CI 0.53 to 0.76; Figure 3.39). There was evidence of moderate statistical heterogeneity (I^2=36%; p=0.05). The NNT to prevent one patient requiring an anti-emetic was 7 (95% CI 4.9 to 8.4). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

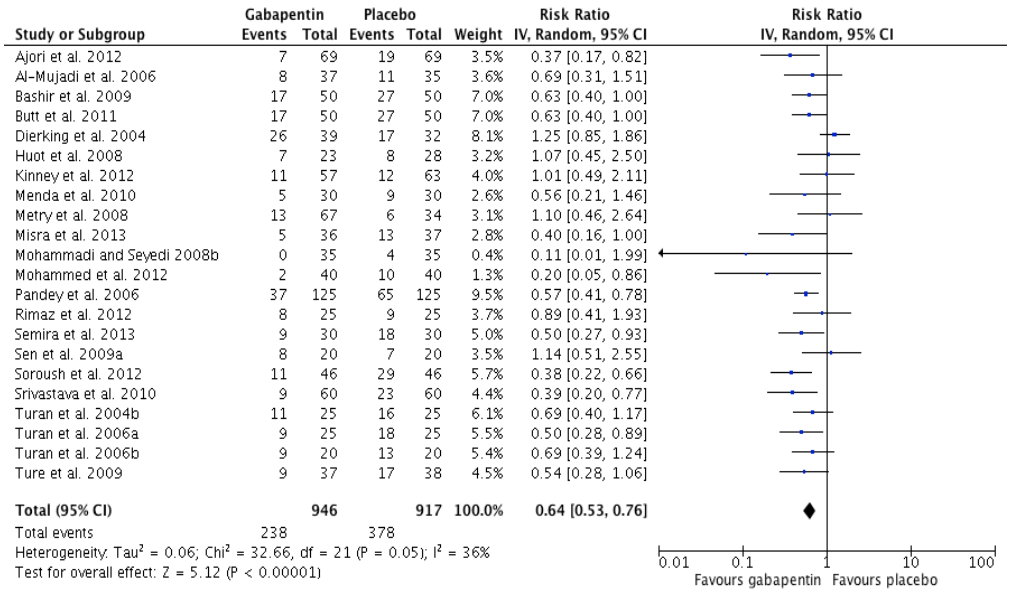


Figure 3.39: Forest plot of the effect of gabapentin on the incidence of patients requiring anti-emetics.

There was evidence of funnel plot asymmetry (Figure 3.40). However, Egger's linear regression test was not significant (p=0.15). Therefore, further analyses for publication bias were not performed.

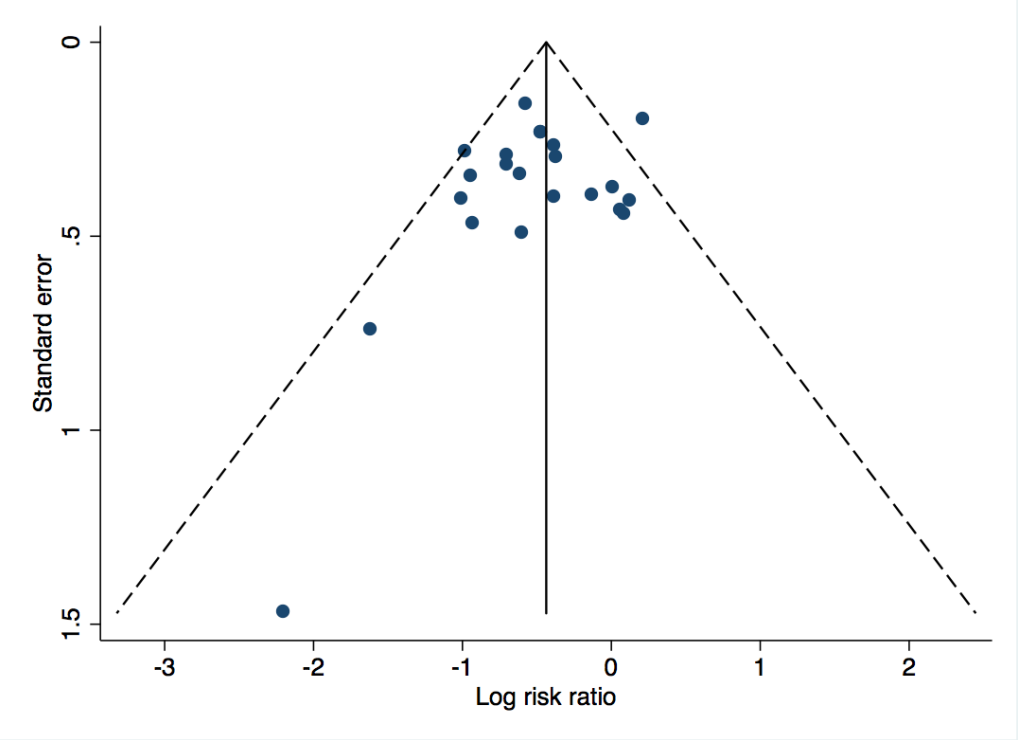


Figure 3.40: Funnel plot of gabapentin effects on the incidence of patients requiring anti-emetics. X-axis shows the log risk ratio and the Y-axis shows the standard error of log risk ratio.

Paradoxically, on meta-regression analysis, increasing gabapentin doses predicted more patients requiring anti-emetic treatment (R^2=66%; p=0.008) (Figure 3.41). On regression diagnostics, only one study had a studentised residual of more than two and no study had a Cook's distance of more than one. Residuals were normally distributed on histograms and plots for homoscedasticity and linearity showed no violations of these assumptions. On sensitivity analysis, removing studies at high risk of bias did not affect the results. One study-removed analysis showed there were no influential studies.

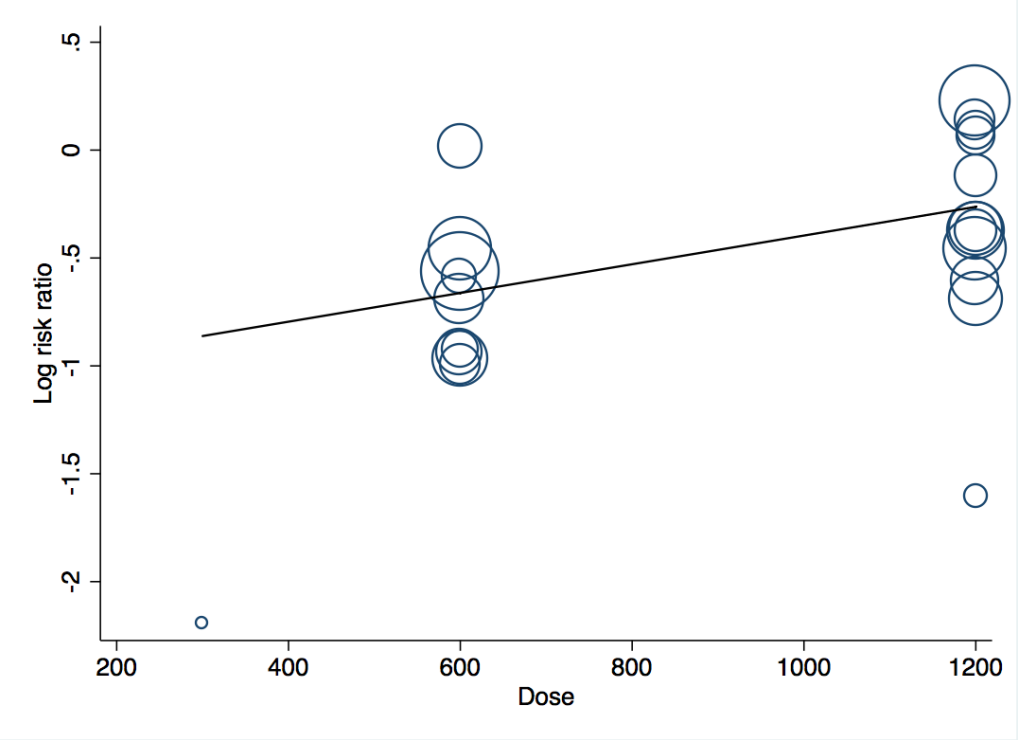


Figure 3.41: Meta-regression plot. X-axis shows gabapentin dose (mg) and the Y-axis the log risk ratio of patients requiring anti-emetic treatment.

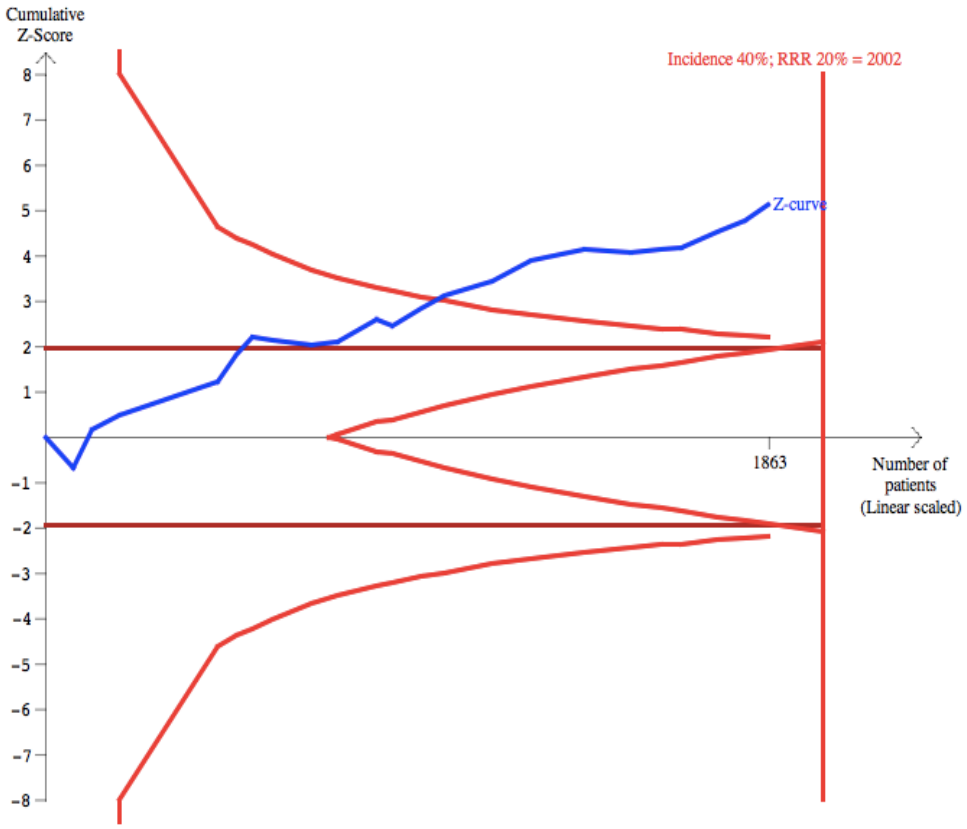


Figure 3.42: Trial sequential analysis of postoperative patients requiring anti-emetics. Performed assuming an incidence of 40% in the control group, RRR of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 44. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the monitoring boundary for benefit (adjusted CI 0.52 to 0.76) (Figure 3.42). However, gabapentin did not reach the required IS for a definitive answer (2002 participants). On sensitivity analysis, similar results were found assuming an incidence as low as 20%. Gabapentin did not cross the boundary for benefit assuming a 50% RRR.

3.3.19 Emergence agitation

One study reported emergence agitation (Azemati *et al.* 2013). It found a reduction with gabapentin (RR 0.33; 95% CI 0.13 to 0.85).

3.3.20 Postoperative shivering

Overall, three studies with 174 participants were included in the analysis. Gabapentin reduced the incidence of postoperative shivering (RR 0.38; 95% CI 0.17 to 0.86; Figure 3.43). The NNT to prevent one episode of postoperative shivering was 8 (95% CI 4.1 to 29.4). There was no evidence of statistical heterogeneity (I^2=0%; p=0.70). Due to the low number of studies no investigations for publication bias or heterogeneity were undertaken. The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias). On sensitivity analysis, removing studies at high risk of bias resulted in the confidence interval crossing the line of null effect. One study-removed analysis showed that two studies (Ozgencil *et al.* 2011; Rapchuk *et al.* 2010) were influential and their removal caused the confidence interval to cross the line of no effect.

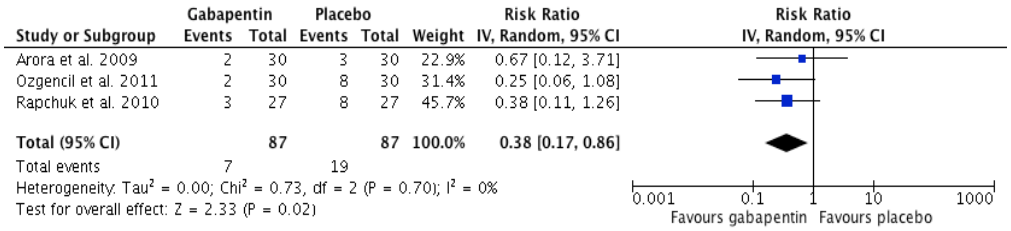


Figure 3.43: Forest plot of the effects of gabapentin on the incidence of postoperative shivering.

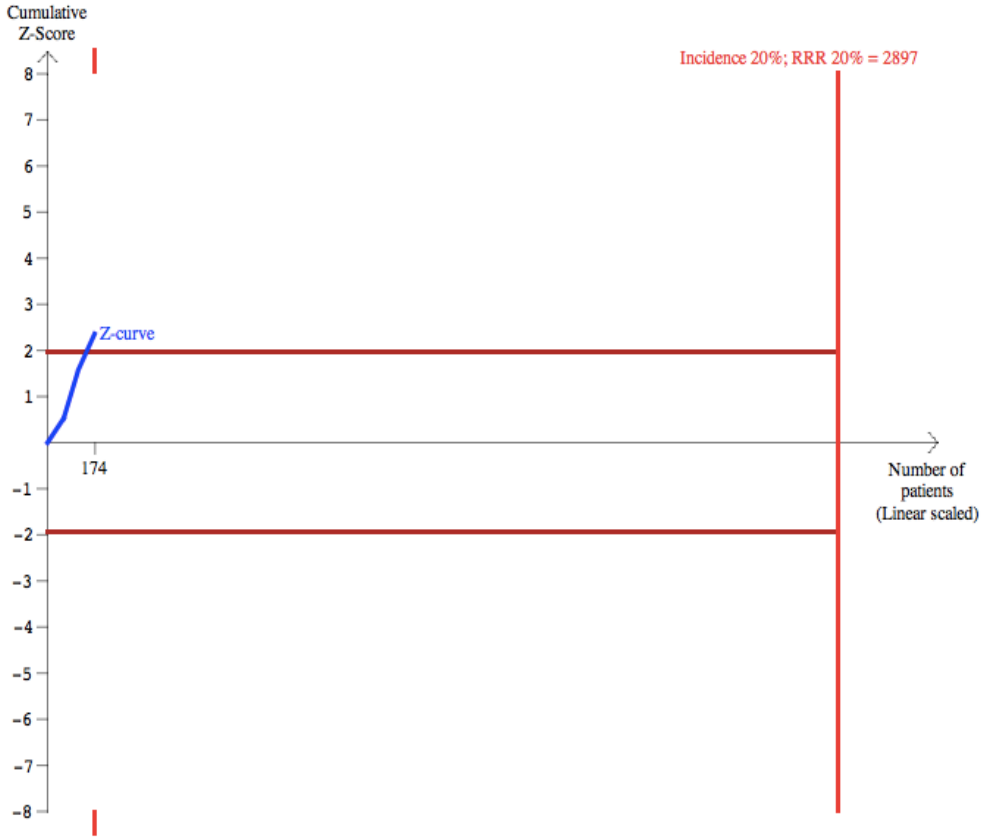


Figure 3.44: Trial sequential analysis of postoperative shivering. Performed assuming an incidence of 20% in the control group, RRR of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that although gabapentin crossed the conventional boundary for statistical significance (Figure 3.44), it did not cross the adjusted O'Brien-Fleming boundary. Furthermore, the results for gabapentin did not reach the required IS for a definitive answer (2897 participants). On sensitivity analysis, similar results were obtained assuming an incidence of 10%, a heterogeneity correction of 25 and a RRR of 50%.

3.3.21 Vertigo

Overall, three studies with 566 participants reported the incidence of postoperative vertigo. There was no difference between the groups (RR 0.69; 95% CI 0.13 to 3.74; Figure 3.45). There was evidence of substantial statistical heterogeneity (I^2=62%; p=0.07). Due to the low number of included studies, analyses for publication bias or heterogeneity were not undertaken. The quality of evidence was very low according to GRADE (downgraded owing to concerns over risk of bias, unexplained heterogeneity and imprecision of results). On sensitivity analysis, no studies were at high risk of bias. One study-removed analysis showed no influential studies.

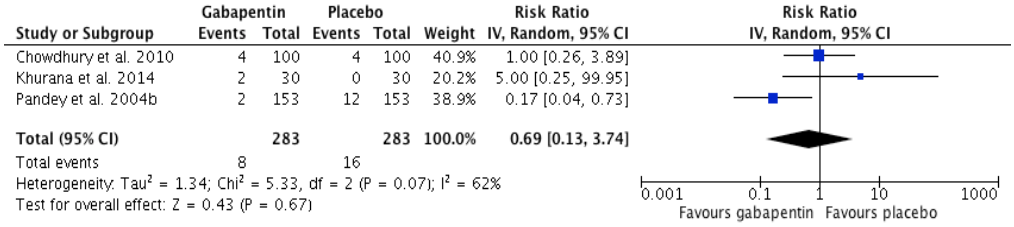


Figure 3.45: Forest plot of the effects of gabapentin on the incidence of postoperative vertigo.

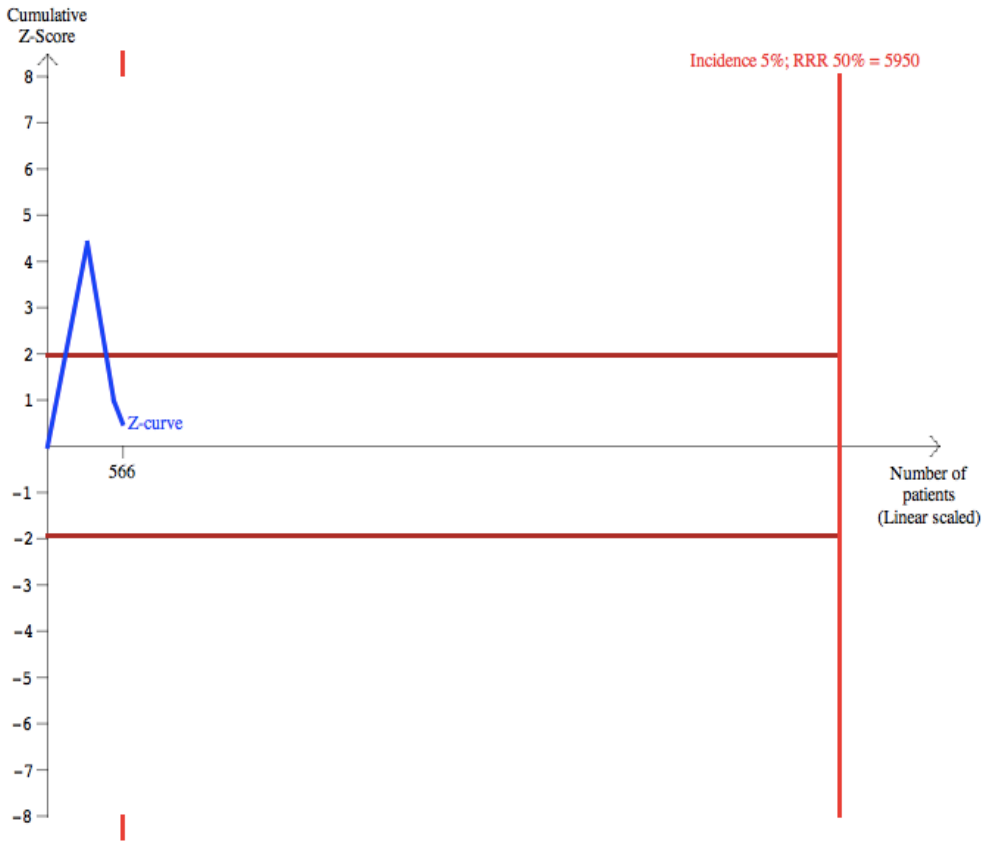


Figure 3.46: Trial sequential analysis of postoperative vertigo. Performed assuming an incidence of 5% in the control group, RRR of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 70. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that after the publication of the first trial (Pandey *et al.* 2004b), gabapentin crossed the conventional boundary for benefit ($p<0.05$). However, subsequent trials resulted in no benefit with gabapentin (Figure 3.46). Gabapentin did not reach the required IS for a definitive answer (5950 participants). On sensitivity analysis, similar results were obtained assuming a 20% RRR or an incidence as low as 1%. Sensitivity analysis around heterogeneity corrections was not performed due to the high value already in the analysis.

3.3.22 Time to mobilise (hours)

Overall, four studies with 174 participants were included in the analysis. Gabapentin reduced the time to first mobilisation (MD -5.02 hours; 95% CI -10.02 hours to -0.02 hours; Figure 3.47). There was evidence of considerable statistical heterogeneity (I^2=95%; p<0.001). Due to the low number of studies, further analyses for publication bias or heterogeneity were not undertaken. The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity). On sensitivity analysis, there were no high risk of bias trials. One study-removed analysis showed that removing three studies resulted in the confidence interval crossing the line of null effect (Frouzanfard *et al.* 2013; Sen *et al.* 2009a; Turan *et al.* 2006a). However, removing one study (Zaldivar Ramirez 2011) resulted in more precise confidence intervals (MD -2.38 hours; 95% CI -3.56 hours to -1.21 hours).

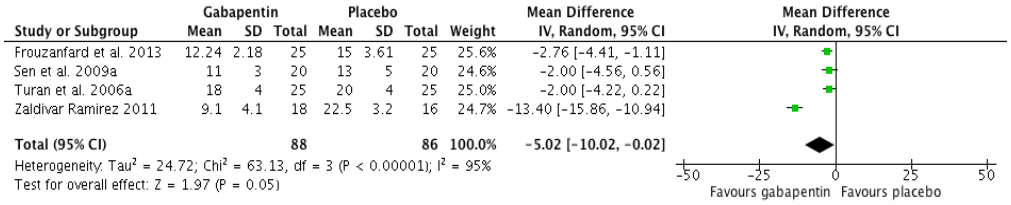


Figure 3.47: Forest plot of the effects of gabapentin on the time to mobilise (hours).

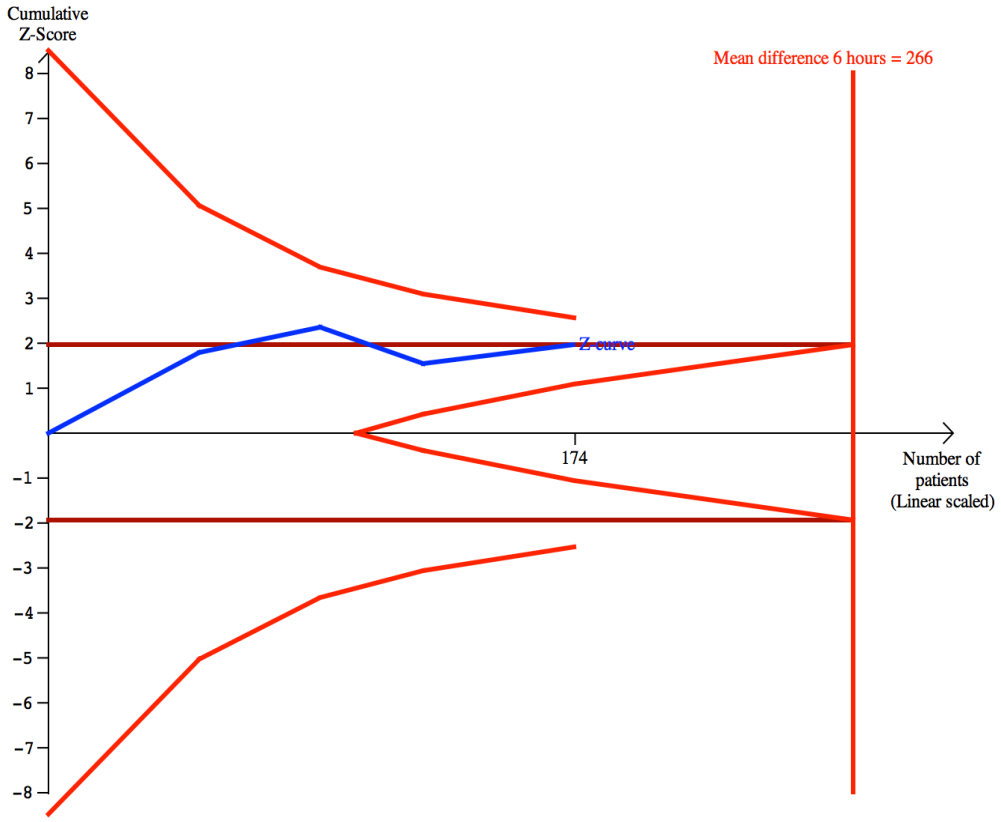


Figure 3.48: Trial sequential analysis of time to mobilise (hours). Performed assuming a clinically significant reduction of 6 hours, variance of 12.8, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 95. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin resulted in a significant decrease in time to mobilise using conventional boundaries (Figure 3.48). However, gabapentin did not cross the O'Brien-Fleming boundary or reach the required IS (266 participants). On sensitivity analysis, using the reported mean difference did not change results (IS 355 participants). Doubling the variance (to 25 hours) resulted in an increased IS requirement (488 participants).

3.3.23 Dry mouth

Overall, nine studies with 561 participants were included in the analysis. There was no difference between the groups in the incidence of dry mouth (RR 1.00; 95% CI 0.95 to 1.06; Figure 3.49). There was no evidence of statistical heterogeneity (I^2=0%; p=0.58). The quality of the evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

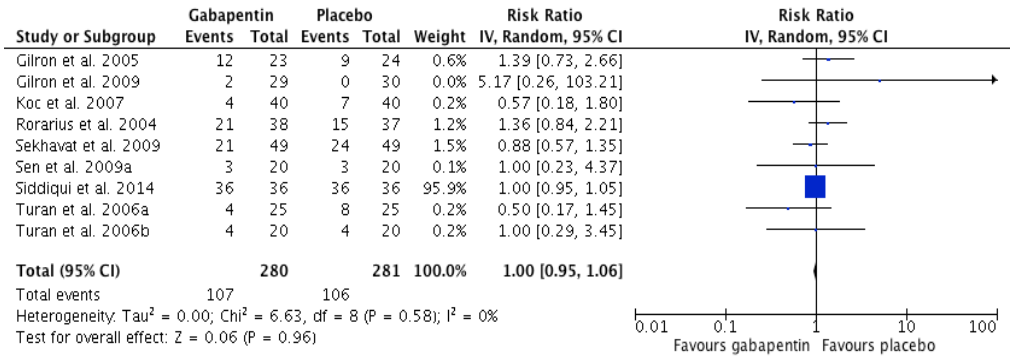


Figure 3.49: Forest plot of the effects of gabapentin on the incidence of postoperative dry mouth.

Due to the low number of studies, tests for publication bias were not conducted. On meta-regression analysis, dose did not predict the incidence of dry mouth (R^2=0%; p=0.66). On sensitivity analysis, removing studies at high risk of bias did not affect results. One study-removed analysis revealed no influential studies.

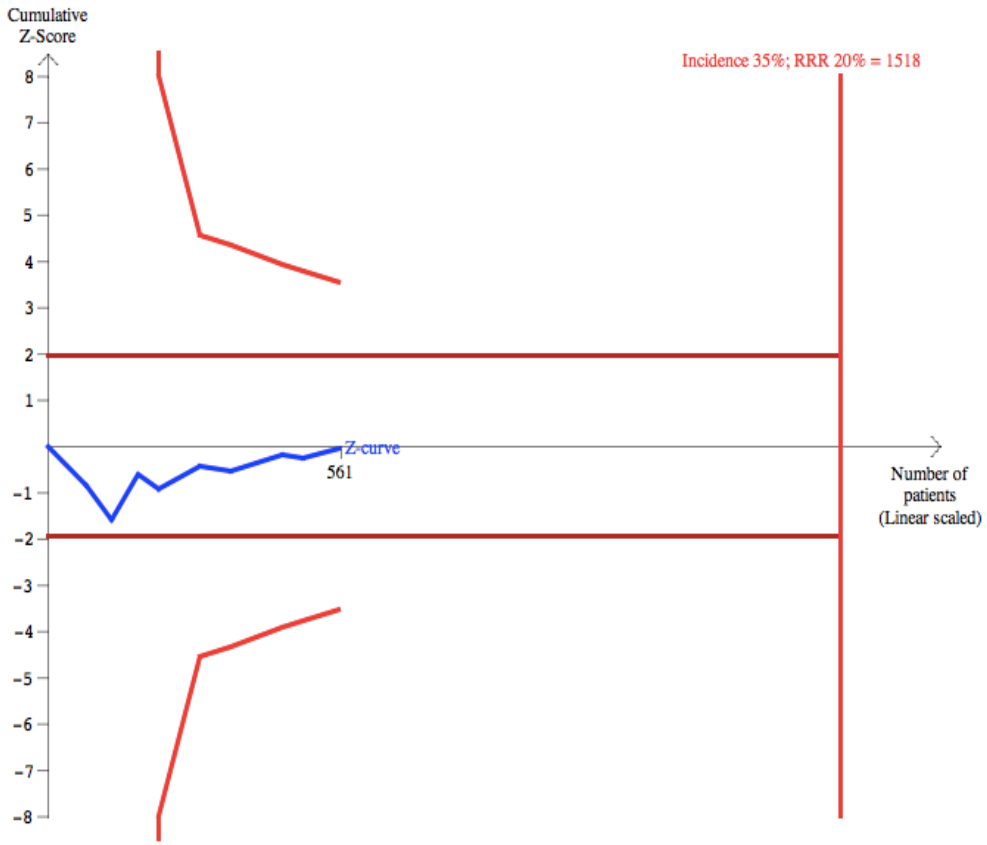


Figure 3.50: Trial sequential analysis of postoperative dry mouth. Performed assuming an incidence of 35%, a relative risk increase of 20%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values less than 0 indicating harm with gabapentin.

Trial sequential analysis found that the effects of gabapentin on postoperative dry mouth did not cross any boundary for harm or reach the required IS (1518 participants) (Figure 3.50). On sensitivity analysis, assuming a relative risk increase of 50%, gabapentin crossed the boundary for futility then reached the required IS. Similar results from the main results were obtained for an incidence as low as 10%. Assuming a heterogeneity correction of 25, the IS increased to 2024 participants.

3.3.24 Re-admission

One study reported the number of patients re-admitted (Grosen *et al.* 2014). Although fewer patients in the gabapentin group were readmitted, this difference was not statistically significant. However, the confidence intervals suggested a possible decrease with gabapentin (RR 0.09; 95% CI 0.01 to 1.60).

3.3.25 Postoperative arrhythmia

Overall, three studies with 198 participants were included in the analysis. All were conducted in patients undergoing cardiac surgery. Although gabapentin reduced the incidence of postoperative arrhythmia, this was not statistically significant (RR 0.55; 95% CI 0.28 to 1.08; Figure 3.51). There was no evidence of statistical heterogeneity (I^2=0%; p=0.98). Due to the low number of studies, analyses for publication bias or heterogeneity were not undertaken. The quality of evidence was low according to GRADE (downgrading owing to concerns over risk of bias and imprecision of results). On sensitivity analysis, removing studies at high risk of bias left only one study (Ucak *et al.* 2011), which gave similar results. One study-removed analysis identified no influential studies.

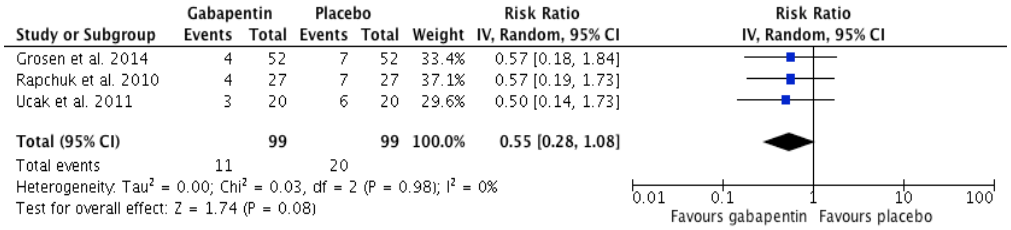


Figure 3.51: Forest plot of the effects of gabapentin on the incidence of postoperative arrhythmia.

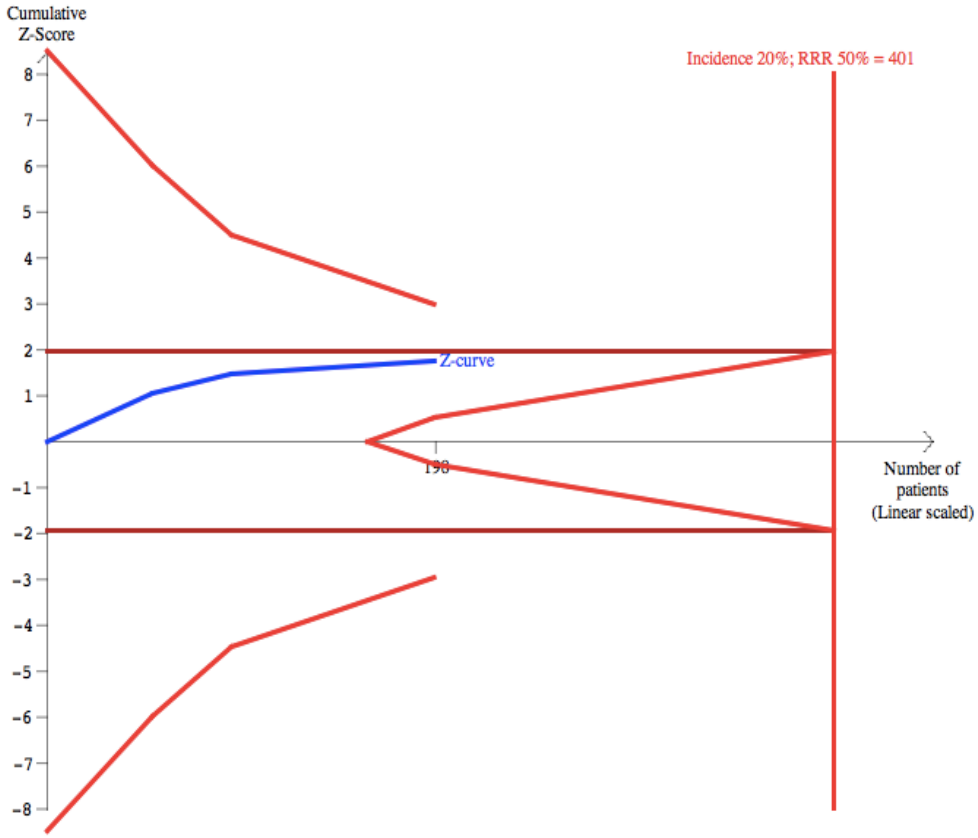


Figure 3.52: Trial sequential analysis of postoperative arrhythmia. Performed assuming an incidence of 20%, a RRR of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin did not cross any of the boundaries for benefit for a RRR of 20%. In addition, gabapentin did not reach the required IS (2897 participants). However, for a 50% RRR (Figure 3.52) as suggested by the data, gabapentin avoided the boundary of futility although did not reach the required IS (401 participants) or conventional boundary for benefit. On sensitivity analysis, assuming an incidence of 10% required an IS of 6429 participants and assuming a heterogeneity correction of 25, 3862 participants would be required for a definitive answer.

3.3.26 Hallucinations

Overall, two studies with 131 participants were included in the analysis. There was no difference in the incidence of hallucinations between the two groups (RR 1.15; 95% 0.07 to 19.91; Figure 3.53). There was evidence of substantial statistical heterogeneity (I^2=72%; p=0.06). Analyses of heterogeneity and publication bias were not undertaken due to the low number of included studies. There was too few information to perform TSA. The quality of evidence was very low according to GRADE (downgraded owing to concerns over risk of bias, unexplained heterogeneity and imprecision of results). On sensitivity analysis, removing high risk of bias studies left only one study (Turan *et al.* 2006b), which gave similar results. One study-removed analysis showed no influential studies.

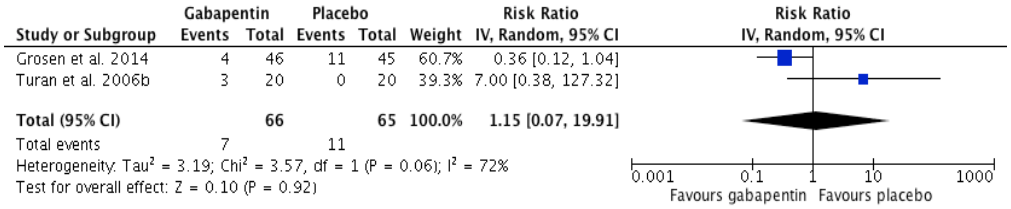


Figure 3.53: Forest plot of the effects of gabapentin on the incidence of hallucinations.

3.3.27 Postoperative sore throat

One study reported the incidence of postoperative sore throat (Lee *et al.* 2013). This study showed the incidence of postoperative sore throat was reduced with the administration of gabapentin (RR 0.66; 95% 0.44 to 0.99). The NNT to prevent one episode of sore throat was 5 (95% CI 2.2 to 48.3). However, this study was at high risk of bias.

3.3.28 Lack of concentration

Overall, four studies with 502 participants were included in the analysis. There was no difference between the groups in the incidence of lack of concentration (RR 1.31; 95% CI 0.79 to 2.17; Figure 3.54). There was no evidence of statistical heterogeneity (I^2=0%; p=0.85). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias). None of the included studies were at high risk of bias. One study-removed analysis showed no influential studies were included in the analysis.

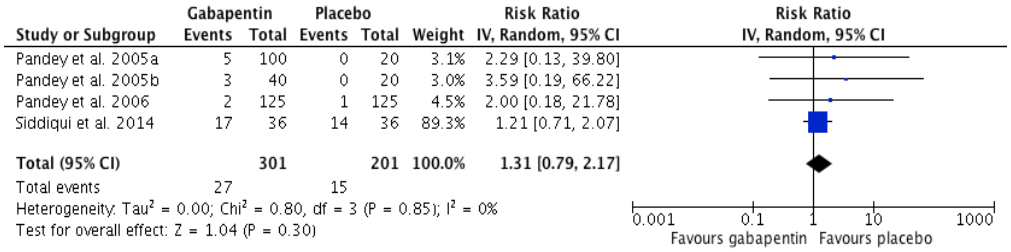


Figure 3.54: Forest plot of gabapentin effect on the incidence of lack of concentration.

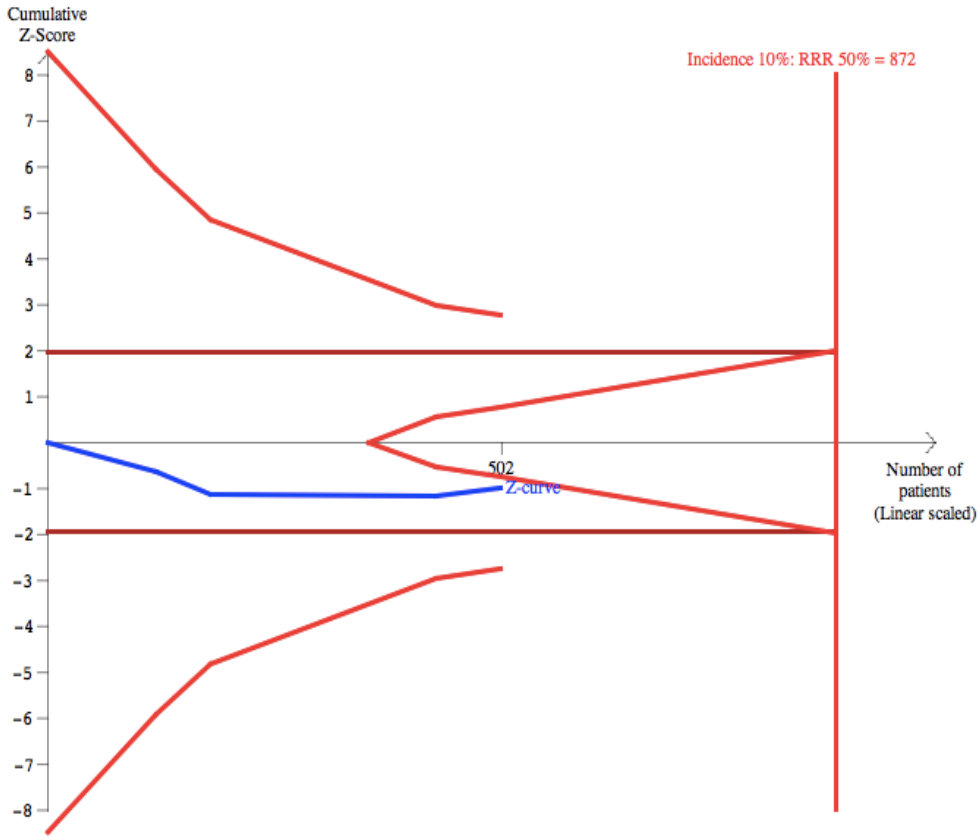


Figure 3.55: Trial sequential analysis of postoperative lack of concentration. Performed assuming an incidence of 10%, a relative risk increase of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values less than 0 indicating harm with gabapentin.

Trial sequential analysis showed that the effects of gabapentin on lack of concentration did not cross the boundary for harm or reach the required IS (872 participants). However, the results were close to the boundary for futility (Figure 3.55). On sensitivity analysis, similar results were found assuming a relative risk increase of 20%, although the IS increased (6429 participants). Assuming a heterogeneity correction of 25 increased the IS to 1162 participants.

3.3.29 Fasciculations

Only one study reported the incidence of postoperative fasciculations (Pandey *et al.* 2012). There was no significant reduction with gabapentin, although the confidence intervals suggested an effect (RR 0.67; 95% CI 0.41 to 1.09). As only one study was included, no further analyses were conducted.

3.3.30 Euphoria

Overall, three studies with 430 participants were included in the analysis. Although the incidence of euphoria was not statistically significantly different with gabapentin, the confidence intervals suggested an increase (RR 2.48; 95% CI 0.44 to 14.03; Figure 3.56). There was no evidence of statistical heterogeneity (I^2=0%; p=0.90). As only three studies were included, tests for publication bias or investigation of heterogeneity were not performed. There was too few information from the included studies to perform TSA. The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and imprecision of results). On sensitivity analysis, there were no studies at high risk of bias. One study-removed analysis showed there were no influential studies.

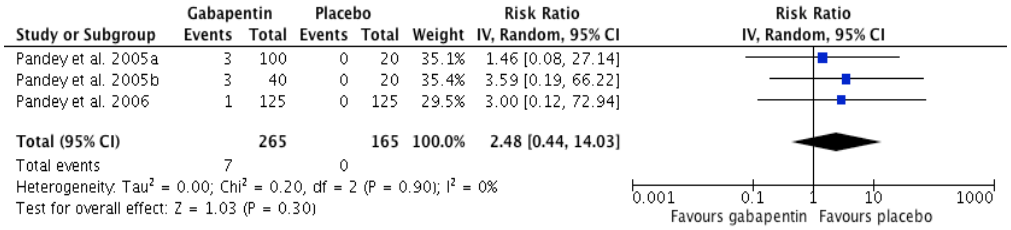


Figure 3.56: Forest plot of gabapentin effect on the incidence of euphoria.

3.3.31 Myalgia

Overall, two studies with 145 participants reported the incidence of postoperative myalgia. Although the reduction with gabapentin was not statistically significant, the confidence intervals suggested an effect (RR 0.45; 95% CI 0.17 to 1.22; Figure 3.57). There was no evidence of statistical heterogeneity (I^2=0%; p=0.53). As only two studies were included, tests for publication bias or investigation of heterogeneity were not performed. There was too few information from the included studies to perform TSA. The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and imprecision of results). On sensitivity analysis, removing high risk of bias studies and one study-removed analysis did not affect results.

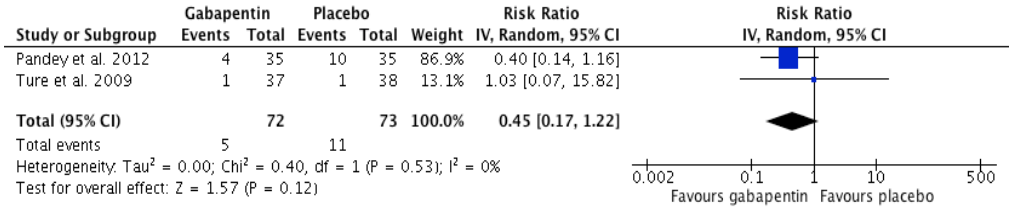


Figure 3.57: Forest plot of the effects of gabapentin on the incidence of myalgia.

3.3.32 Time to first flatus (hours)

Overall, three studies with 130 participants were included in the analysis. Although the difference was not statistically significant, the confidence intervals suggested a decrease in time to first flatus with gabapentin (MD -6.85 hours; 95% CI -14.27 hours to 0.57 hours; Figure 3.58). There was evidence of considerable statistical heterogeneity (I^2=86%; p<0.001). As only three studies were included, tests for publication bias or investigation of heterogeneity were not performed. The quality of the evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity). On sensitivity analysis, no trials were at high risk of bias. One study-removed analysis did not identify any influential studies.

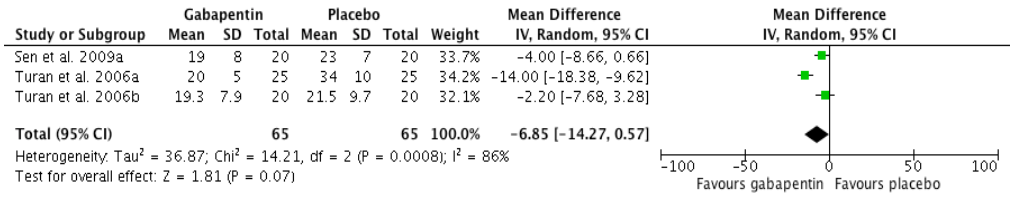


Figure 3.58: Forest plot of the effects of gabapentin on time to first flatus (hours).

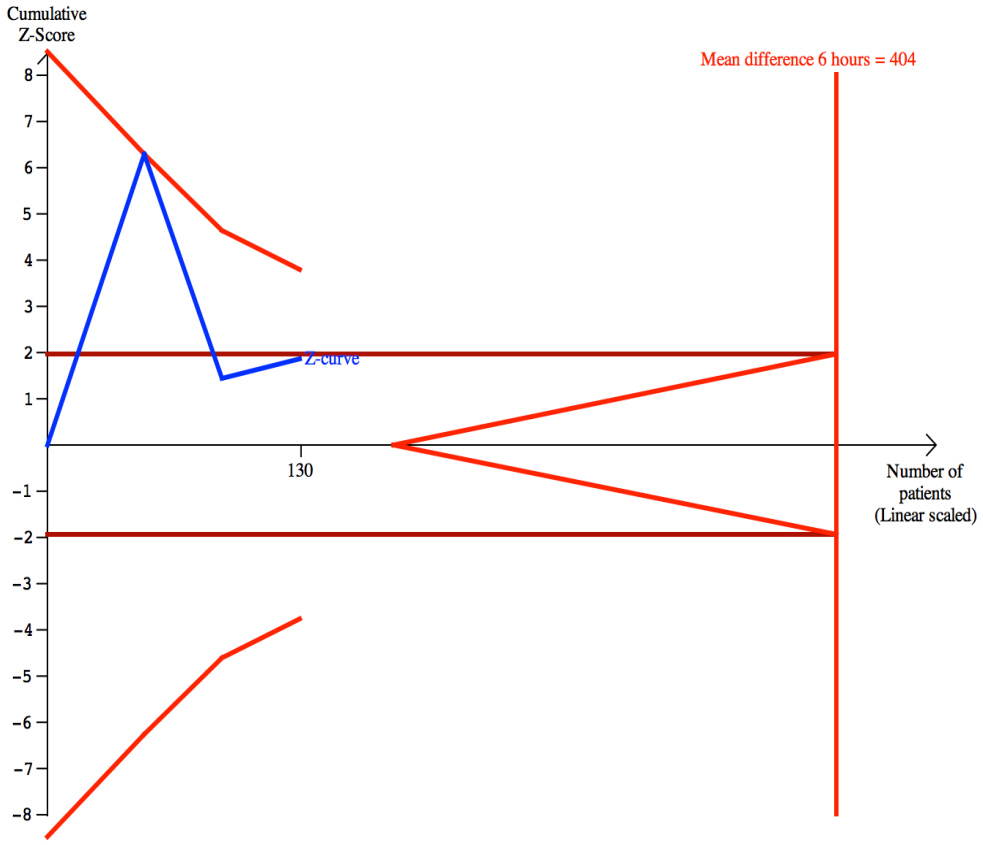


Figure 3.59: Trial sequential analysis of time to first flatus (hours). Performed assuming a MD of 6 hours, a variance of 64, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 86. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the conventional boundary for statistical significance, although this reversed on publication of subsequent studies (Figure 3.59). Gabapentin did not cross the O'Brien-Fleming boundary for benefit or reach the required IS for a definitive answer (404 participants). On sensitivity analysis, assuming a mean difference of 12 hours did not affect the results. Assuming a doubling of the variance increased the IS required (794 participants). Sensitivity analysis around heterogeneity corrections was not undertaken as the value in the analysis was already high.

3.3.33 Time to return of bowel function (hours)

Overall, four studies with 202 participants were included in the analysis. Although the confidence intervals suggested gabapentin reduced the time to return of bowel function, this difference was not statistically significant (MD -2.87 hours; 95% CI -6.45 hours to 0.71 hours; Figure 3.60). There was evidence of substantial statistical heterogeneity (I^2=74%; p=0.01). The quality of evidence was low according to GRADE (downgrading owing to concerns over risk of bias and unexplained heterogeneity). On sensitivity analysis, there were no studies at high risk of bias. One study-removed analysis identified no influential studies.

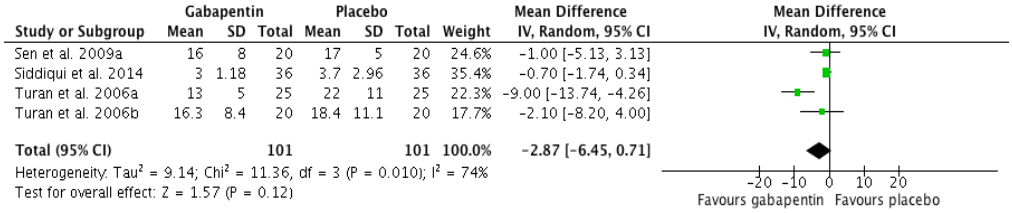


Figure 3.60: Forest plot of the effects of gabapentin on time to return of bowel function (hours).

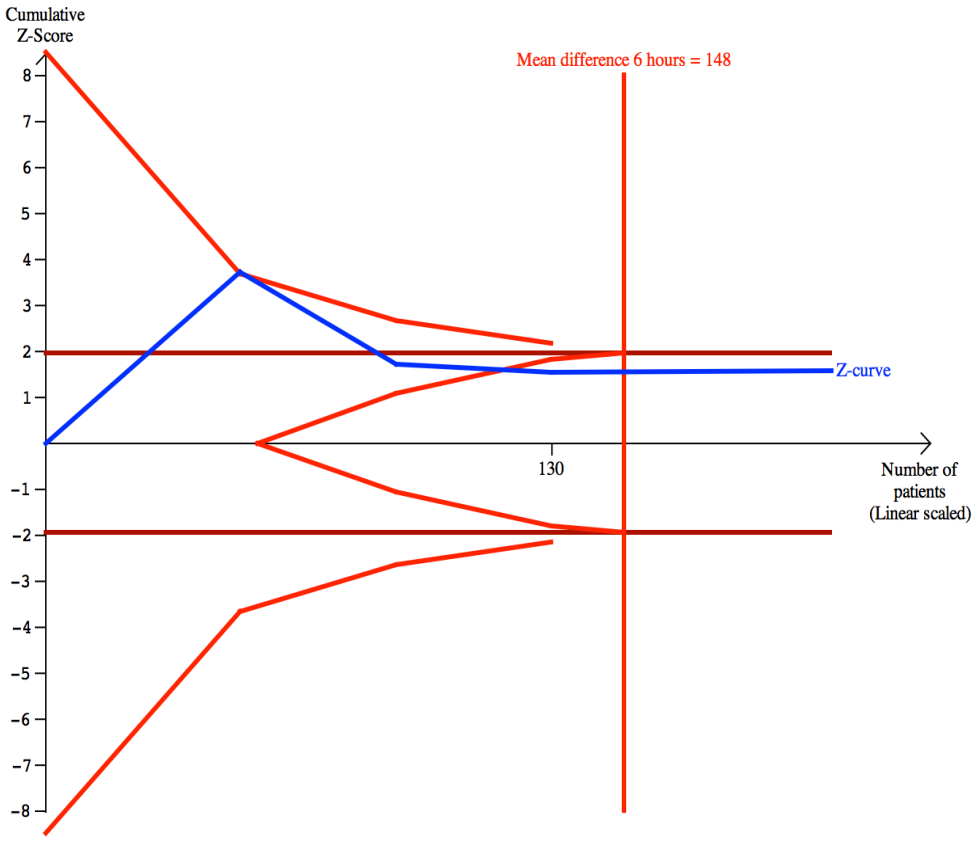


Figure 3.61: Trial sequential analysis of time to return of bowel function (hours). Performed assuming a MD of 6 hours, a variance of 12.5, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 93. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis of gabapentin on time to return of bowel function showed that gabapentin initially crossed the boundary for conventional statistical significance ($p<0.05$) although after the publication of the second trial this benefit was lost (Figure 3.61). Gabapentin crossed the boundary for futility and then reached the required IS (148 participants). On sensitivity analysis, assuming an empirical MD of 2.87 hours, this increased the required IS (648 participants). Assuming a variance as high as 25 also increased the IS (297 participants). Sensitivity analysis around heterogeneity corrections was not undertaken as the value in the analysis was high.

3.3.34 Dysphagia

One study reported the incidence of postoperative dysphagia following Nissen fundoplication (Zaldivar Ramirez 2011). Gabapentin reduced the incidence of postoperative dysphagia (RR 0.24; 95% CI 0.08 to 0.72). The NNT to prevent one episode of dysphagia was 2 (95% CI 1.2 to 4.2).

3.3.35 Hospital length of stay (days)

Overall, nine studies with 526 participants were included in the analysis. There was no reduction in the length of hospital stay with gabapentin (MD -0.30 days; 95% CI -0.76 days to 0.15 days; Figure 3.62). There was evidence of considerable statistical heterogeneity (I^2=97%; p<0.001). The quality of the evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity). On sensitivity analysis, there were no studies at high risk of bias. One study-removed analysis identified no influential studies.

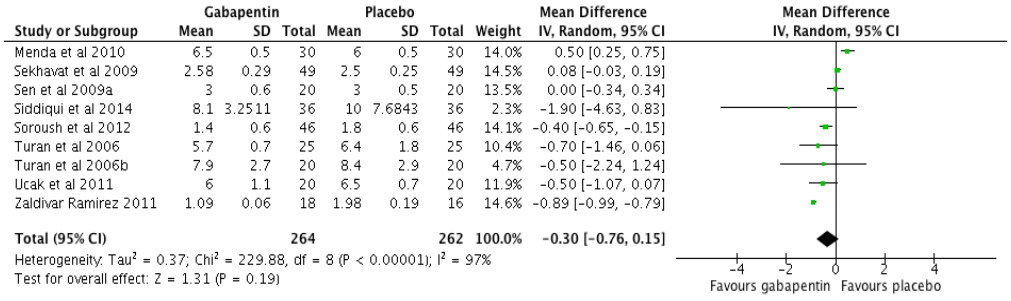


Figure 3.62: Forest plot of gabapentin effect on length of stay (days).

Due to the low number of studies, tests for publication bias were not undertaken. On meta-regression analysis, dose did not predict reductions in length of stay on statistical testing, although the R^2 analogue was above zero (R^2=21%; p=0.92). Trial sequential analysis could not be performed due to a lack of information.

3.4 Discussion

3.4.1 Summary of results

In summary, there was consistent evidence from multiple RCTs that gabapentin reduced nausea, vomiting, anti-emetic requirement, pruritus, pre-operative anxiety and increased patient satisfaction (possibly via reducing opioid usage). However, the quality of the evidence derived from these outcomes was very low to moderate due to concerns over possible publication bias and risk of bias in the original studies. There was some evidence that higher gabapentin doses increased patient satisfaction and paradoxically, increased the number of patients requiring anti-emetics. In terms of pre-operative anxiety, higher baseline risk predicted larger reductions in pre-operative anxiety. Other outcomes where results suggest gabapentin is unlikely to have an effect include constipation and respiratory depression, where TSA showed either no effect where the required IS was reached or the results passed the boundary for futility.

In terms of gabapentin adverse events, there was evidence that gabapentin increased the risk of postoperative sedation, although this effect may be overestimated by imprecise study effects (possible publication bias). Indeed, following correction for publication bias, results for sedation were close to the line of no effect. We found no evidence of increases in dizziness or headache with gabapentin. On meta-regression analysis, there was no evidence that increases in dose caused increases in adverse events. However, this analysis may be limited by lower levels of underlying statistical heterogeneity.

Other outcomes that require further studies, where results have suggested a possible benefit with gabapentin include postoperative confusion, bladder-related discomfort, urinary retention, postoperative arrhythmia (in cardiac surgery patients) and time to first flatus or bowel function. Gabapentin may also increase the risk of lack of concentration, euphoria and visual disturbance. However, further studies are required to confirm these findings. Gabapentin was also found to decrease the time to mobilisation, although caution should be

advised as this finding failed to reach the monitoring boundary for benefit or reach the required IS and we suggest future studies are required to confirm these findings.

3.4.2 Links with previous research

We found evidence that peri-operative use of gabapentin reduced nausea, vomiting and reduced the number of patients requiring anti-emetics. Previous meta-analyses of gabapentin have demonstrated gabapentin is effective at reducing PONV, the most recent of which was undertaken in patients undergoing abdominal surgeries (Achuthan *et al.* 2015). With regards to a non-postoperative population of patients, an open-label study has found benefit when gabapentin was used in patients with chemotherapy-induced nausea (Gattuso, Roscoe and Griggs 2003). Possible mechanisms for this reduction in PONV include decreases in tachykinin neurotransmission and effects on the area postrema (Achuthan *et al.* 2015).

Intuitively, as gabapentin is known to reduce opioid consumption and opioids are commonly associated with PONV, this may be a mechanism that could lead to reductions in PONV observed in our meta-analysis. However, on our meta-regression analysis, reductions in opioid consumption did not predict the effect of gabapentin in reducing PONV. Therefore, other direct mechanisms may be involved, particularly bearing in mind its efficacy on chemotherapy-induced emesis. The reductions in PONV with gabapentin compare well with traditional anti-emetics such as metoclopramide, ondansetron and cyclizine (RR 0.60-0.80) (Carlisle and Stevenson 2006). Therefore, gabapentin may be a suitable alternative to these agents in routine anaesthetic practice although impracticalities with oral dosing may limit its use. Indeed, since the publication of this chapter (Doleman 2015b), one RCT has compared gabapentin to the 5HT3 antagonist granisetron in reducing PONV. It found that both agents produced similar reductions in the incidence and severity of PONV in patients undergoing middle ear surgery (Heidari *et al.* 2015). Future similar studies may allow comparisons with other anti-emetics and given the multitude of other benefits from gabapentin (postoperative pain and opioid reduction), if

equivalent benefit can be demonstrated this may lead to more routine use of gabapentin as a pre-operative anti-emetic.

With regards to pruritus, similar to our results with PONV, morphine reductions did not predict the efficacy of gabapentin for treating pruritus; again suggesting other mechanisms may be involved. Previous studies have demonstrated the efficacy of gabapentin for treating a number of conditions that cause itching such as uraemia (Gunal *et al.* 2004) and burns (Goutos *et al.* 2010). The mechanism of which is uncertain. As pruritus causes patient distress and is challenging to manage, gabapentin prophylaxis may represent a useful option to prevent this condition in clinical practice, particularly due to its other beneficial effects.

Gabapentin was also found to reduce pre-operative anxiety, with mean control group anxiety score predicting larger reductions in anxiety scores (baseline risk) as demonstrated on our meta-regression analysis. Gabapentin has been shown to increase GABA levels within the central nervous system (Maneuf, Luo and Lee 2006) and decrease excitatory neurotransmitters, which may exert an anxiolytic effect prior to surgery. In other areas of clinical practice, gabapentin may have efficacy in anxiety-related conditions such as panic disorder (Pande *et al.* 2000), social phobia (Pande *et al.* 1999) and anxiety from public speaking in healthy volunteers (Quevedo *et al.* 2003). Moreover, as anxiety is a risk factor for postoperative pain (Ip *et al.* 2009), reductions in anxiety may contribute to the effect of gabapentin on pain scores and opioid consumption. Such reductions in anxiety may also help contribute to improved patient experience observed in this chapter. Again, if gabapentin is to be considered as a standard agent in the treatment of pre-operative anxiety, further studies are required comparing gabapentin to the gold standard of benzodiazepines. Indeed, one study within our review (Rorarius *et al.* 2004) compared gabapentin with oxazepam 15mg and found gabapentin was inferior at reducing pre-operative anxiety (median VAS 10 versus 20; p=0.02).

We also found limited evidence that gabapentin reduced the time to mobilisation (MD -5.02 hours; 95% CI -10.02 hours to -0.02 hours), although

this finding did not result in a significant reduction in hospital length of stay. However, caution is advised with this result as it was dependent on results from one unpublished study (Zaldivar Ramirez 2011) and did not reach any boundary for benefit on TSA. Moreover, our results may not be clinically significant. Although this result may be intuitive owing to the effects of gabapentin on reducing pain scores and adverse events such as PONV and pruritus, other effects such as increases in sedation may impair postoperative mobility. Gabapentin is often used in enhanced recovery protocols, which encourage early mobilisation, and future studies may focus on its use in this context.

There was some evidence gabapentin reduced the incidence of postoperative shivering and sore throat. Although again, caution is advised due to possibility of type I errors in these analyses. Postoperative sore throat is a common complication related to endotracheal intubation with an incidence of around 14-50% (McHardy and Chung 1999). As such symptoms can contribute to patient discomfort postoperatively, the reduction of this may help improve patient experience. Postoperative shivering is another common occurrence and may cause associated problems such as patient discomfort, increased oxygen consumption, increases in vascular resistance and increased intracranial pressure (Kranke *et al.* 2002). Therefore, future trials should aim to study these outcomes in order reduce the possibility of type I errors in our results.

Gabapentin was found to increase the risk of postoperative sedation with a NNH of 13. However, our analysis of publication bias suggests the effect may be overestimated by the presence of imprecise study effects (possible publication bias) and adjusted analysis for this shows a relative risk increase of 13% (18% unadjusted). Gabapentin is known to cause sedation in an outpatient population (McLean *et al.* 1999), however in the context of differential postoperative opioid use between active and placebo groups, this relationship becomes more complex, as opioids are also known to cause sedation. Anecdotally, gabapentin use is associated with patient sedation, which may limit its appeal to practising anaesthetists. Our results suggest this increase in risk is small and as many other beneficial effects have been found, such a trade

off may be acceptable to patients undergoing surgery. However, over-sedation may be a risk factor for serious adverse effects such as respiratory depression. A recent healthy volunteer study has found that a combination of pregabalin and remifentanil may increase respiratory depression as measured by increasing end-tidal CO2 (Myhre, Diep and Stubhaug 2016). However, we found no evidence of increasing postoperative respiratory depression with gabapentin from the RCTs published thus far. This again may due to the differential opioid consumption during the postoperative period.

In order to resolve the issues surrounding the positive and negative effects of gabapentin, patient satisfaction can be used to estimate whether the use of gabapentin improves the patient experience. However, only eight studies reported this outcome and although the use of gabapentin was associated with a moderately clinically significant increase in patient satisfaction, there was evidence of possible publication bias. This result suggests the patient may, on average, be willing to accept a degree of sedation if gabapentin has other beneficial effects. Indeed, in a previous study (Macario *et al.* 1999) of 101 patients found events such as vomiting (first), pain (third), shivering and sore throat were all more feared than sedation (last of ten) when patients were asked to rank what were the most undesirable outcomes of anaesthesia. As gabapentin reduces vomiting and pain, these effects may be responsible for the higher satisfaction scores in the gabapentin group. Furthermore, the results of this study suggest that fears of over-sedating patients from anaesthetists may be unfounded and potentially should not discourage the peri-operative use of gabapentin, particularly in clinical situations where patients may derive maximum benefit (high postoperative opioid consumption).

The results from our meta-regression analysis in chapter two demonstrated that some of the pain relieving effects of gabapentin might be dose-dependent. However, such increases in dose may be offset by theoretical increases in adverse events. Within the limitations of meta-regression analysis, we found no evidence that increases in dose increase the adverse effects of gabapentin. Moreover, such increases in dose were also found to improve patient satisfaction as well as previous improvements in postoperative pain and opioid

consumption. These analyses suggest future studies should use higher doses to improve the beneficial effects of gabapentin without any clear increase in adverse events. However, large dose-ranging studies would allow for more accurate assessment of the gabapentin dose-response relationship, which should aim to measure pain scores and opioid consumption concurrently with adverse/opioid adverse events on a continuous scale in order to retain power.

3.4.3 Limitations

There are several limitations with this review. Firstly, the number of studies included in some outcomes was small. Trial sequential analysis showed many of these failed to reach the required IS and therefore type II errors cannot be excluded. Some of these outcomes, such as sedation, did cross the monitoring boundary meaning we can conclude a likely effect. However, many outcomes did not cross any boundary for benefit/harm, futility or reach the required IS. These outcomes require further study, especially those where a possible effect may be present including postoperative arrhythmia in cardiac patients, postoperative confusion and emergence agitation. Our TSA has provided the likely number of participants required and for the dichotomous outcomes we studied, definitive answers may require thousands of participants in order to retain adequate power. Studies of this size are currently not present in the anaesthesia postoperative pain literature. Nevertheless, observational studies may be a more appropriate methodology to assess adverse events and may also have provided adequate numbers compared with the small sample size RCTs included in this chapter.

Secondly, there was evidence of imprecise study effects for many outcomes, which raises the possibility of publication bias. This may overestimate benefits where gabapentin reduced incidence, while also possibly overestimating negative effects such as sedation. Indeed, we found evidence of publication bias against adverse effects such as sedation and dizziness. Although it has to be remembered that other causes of imprecise study effects exist, such as methodological limitations and possible clinical differences in smaller studies

such as higher doses. The only way to truly overcome concerns over possible publication bias is to conduct large RCTs.

Thirdly, many studies were at high or unclear risk of bias for many domains, especially for allocation concealment, which may also overestimate the benefits observed with gabapentin (Schulz and Grimes 2002a). Issues with risk of bias, possible publication bias and unexplained heterogeneity reduce the quality of the evidence and therefore limit the confidence we can have in the conclusions of this review. Although, meta-analyses have advantages over smaller primary research studies such as increasing power and precision, this may be offset by the issues of possible publication bias. Again, this requires further conduct of RCTs which are conducted using low risk of bias methods. Finally, meta-regression has many limitations, which were discussed in the limitations section of chapter two (Section 2.4.3).

3.4.4 Conclusions

Gabapentin reduced the incidence of many postoperative outcomes such as PONV, pruritus and pre-operative anxiety. However, gabapentin increased the risk of sedation. Despite this, as sedation is regarded by patients as the least undesirable outcome from anaesthesia and other outcomes such as vomiting and pain are rated as more undesirable, patients may be willing to accept a degree of sedation if offset by these benefits. Indeed, the use of gabapentin was associated with an increase in patient satisfaction suggesting its benefit for patients undergoing surgery.

Chapter 4

Pre-emptive and preventive effects of gabapentin on acute postoperative pain

4.1 Introduction

Pre-emptive analgesia involves administration of analgesia prior to surgical incision. This has been proposed as an additional strategy to help improve postoperative pain (Dahl and Kehlet 1993) and reduce opioid consumption during the postoperative period. Preventive analgesia emerged from pre-emptive analgesia and extends the definition of pre-emptive analgesia by continuing analgesia further into the postoperative period to further reduce peri-operative sensitisation (Dahl and Kehlet 2011). Such timing of administration has the potential to reduce intra-operative nociception and central sensitisation (Woolf and Chong 1993) that results from surgical incision, leading to improved postoperative pain control. Previous meta-analyses have demonstrated conflicting results on the clinical efficacy of pre-emptive analgesia (Møiniche, Kehlet and Dahl 2002; Ong *et al.* 2005). However, the results of these reviews are nearly a decade old and new evidence is emerging on the potential of other analgesic agents that are able to induce a pre-emptive analgesic effect in clinical trials. As yet, it is unknown whether gabapentin is capable of such pre-emptive or preventive analgesic activity. Therefore, the aim of this chapter was to evaluate the effects of pre-emptive or preventive gabapentin compared to post-incision gabapentin for postoperative pain management.

4.2 Methods

The methods used for the data collection in this chapter are identical to those used in chapter two (Section 2.2). We included data from RCTs that evaluated pre-emptive gabapentin administration (defined as administered before surgical incision) or preventive gabapentin (defined as administered before surgical incision and continued postoperatively) versus post-incision gabapentin (defined as administered after surgical incision). The outcomes were 24-hour morphine consumption and pain scores at rest at one, two, six, 12 and 24 hours after surgery. For inclusion, each study needed to give identical dosages in order to be comparable. We aimed to conduct meta-regression and tests for publication bias. However, the low number of identified studies precluded these analyses. We conducted TSA for each pain outcome as described in chapter two. The quality of the evidence was assessed according to GRADE and rated as high, moderate, low or very low quality.

4.3 Results

4.3.1 Characteristics of the included studies

The characteristics of the included studies are listed in Table 4.1. Overall, only four RCTs compared pre-emptive gabapentin with post-incision gabapentin (Figure 4.1) (Clarke *et al.* 2009a; Khan *et al.* 2011; Metry *et al.* 2008; Pandey *et al.* 2005b). No studies evaluated preventive gabapentin. Dosages ranged from 600-1200mg and all trials were performed in a different type of surgery. One study used spinal anaesthesia while the others used general anaesthesia. Risk of bias for each study is presented in Figure 4.2.

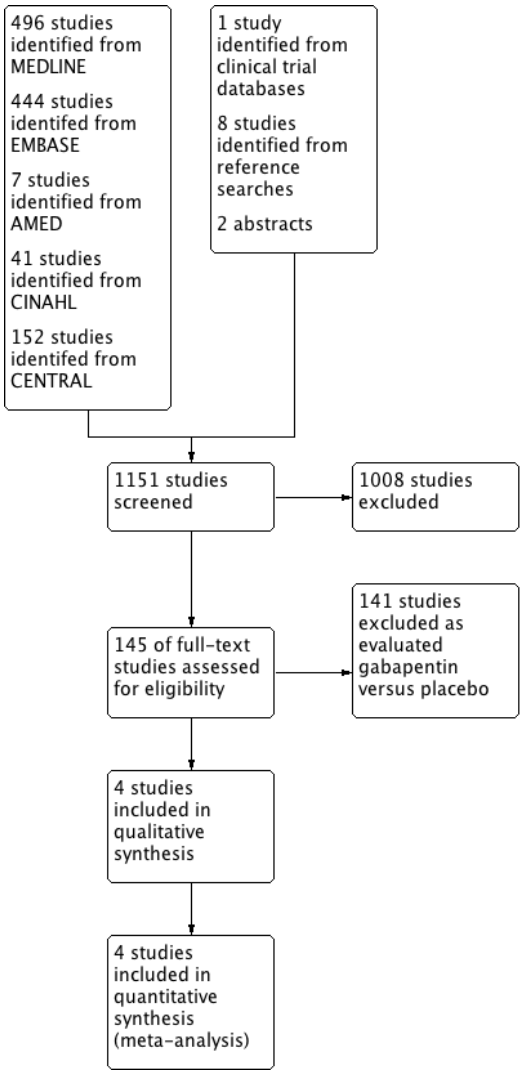


Figure 4.1: PRISMA flowchart for the included studies.

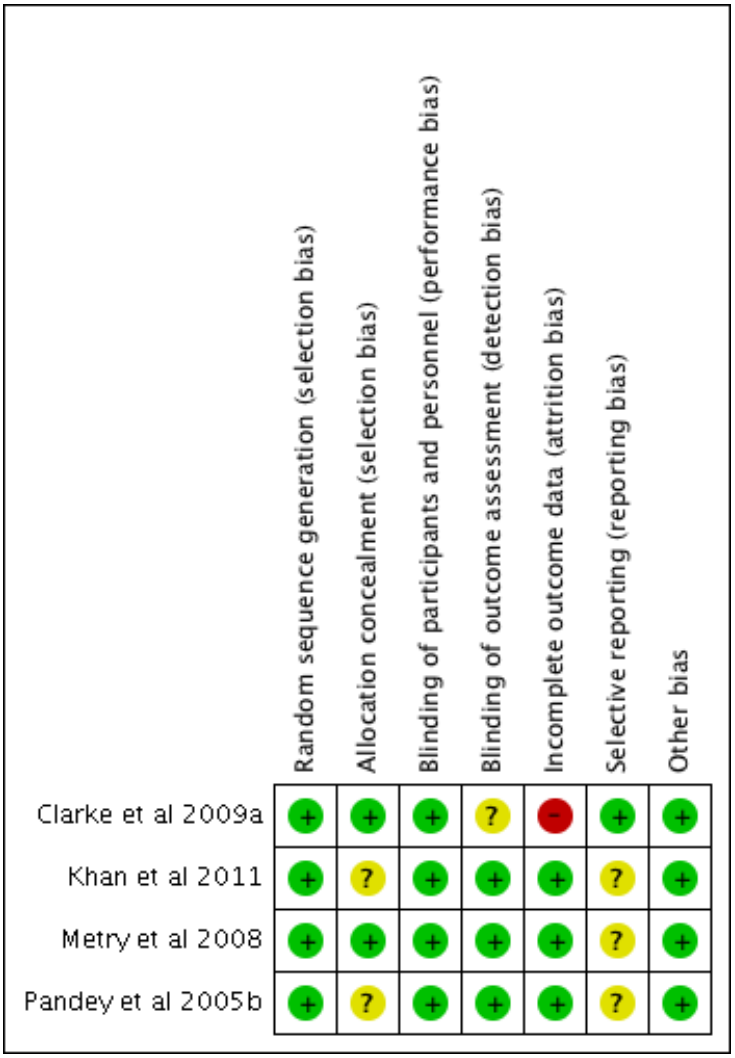


Figure 4.2: Risk of bias for the included studies. Green indicates low risk, yellow indicates unclear risk and red indicates high risk.

Study	Mean age	Sex	N	Intervention and comparison	Country	Type of anaesthesia	Type of surgery
Clarke *et al.* 2009a	60.2	39%	114	600mg 2hrs before operation or 2hrs after	Canada	Spinal anaesthesia	Total hip arthroplasty
Khan *et al.* 2011	41.8	35%	175	600mg, 900mg or 1200mg 2hrs pre or immediately post-incision via NG tube	Iran	General anaesthesia	Single level lumbar laminectomy
Metry *et al.* 2008	57.8	100%	101	1200mg 2 hours before or 1200mg 2hrs postoperatively	Egypt	General anaesthesia	Mastectomy
Pandey *et al.* 2005b	43.6	68%	60	600mg 2hrs before or 600mg post-incision	India	General anaesthesia	Open donor nephrectomy

Table 4.1: Characteristics of the included studies. mg=milligrams; hrs=hours; NG=naso-gastric.

4.3.2 24-hour morphine consumption

Overall, four studies with 333 participants were included in the analysis. Pre-emptive gabapentin did not reduce morphine consumption during the first 24-hours postoperatively (MD -0.11mg; 95% CI -1.59mg to 1.36mg; Figure 4.3). There was no evidence of statistical heterogeneity (I^2=0%; p=0.73). Due to the low number of included studies, analyses for publication bias or investigation of heterogeneity were not undertaken. There was not enough information to perform TSA. The quality of the evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

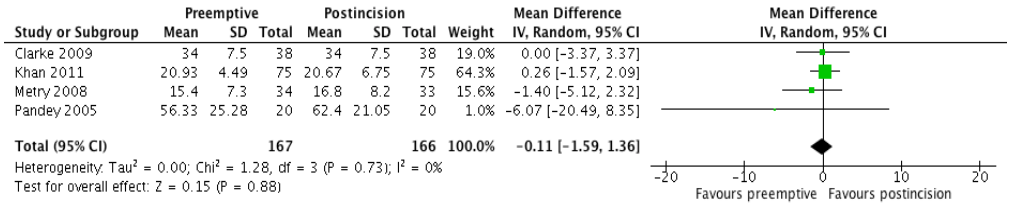


Figure 4.3: Forest plot of pre-emptive gabapentin effects on 24-hour morphine consumption.

4.3.3 Pain scores one hour

Only one study reported pain scores at one hour (Pandey *et al.* 2005b). The study by Metry *et al.* (2008) was not included as the post-incision dose was administered two hours after surgery. Pre-emptive gabapentin did not reduce pain scores at one hour (MD -0.50; 95% CI -1.42 to 0.42).

4.3.4 Pain scores two hours

No study reported pain scores at two hours.

4.3.5 Pain scores six hours

Overall, two studies with 107 participants reported pain scores at six hours. There was no significant reduction in pain scores with pre-emptive gabapentin (MD 0.20; 95% CI -0.20 to 0.59; Figure 4.4). There was no evidence of statistical heterogeneity (I^2=0%; p=0.38). There was not enough information to perform TSA. The quality of the evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

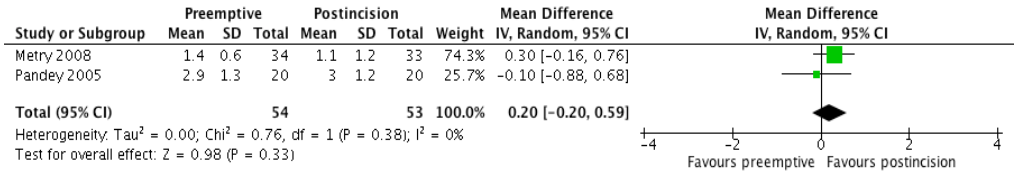


Figure 4.4: Forest plot of pre-emptive gabapentin effects on pain scores at six hours.

4.3.6 Pain scores 12 hours

Overall, four studies with 333 participants were included in the analysis. Pre-emptive gabapentin did not reduce pain scores at 12 hours (MD -0.02; 95% -0.37 to 0.33; Figure 4.5). There was evidence of moderate statistical heterogeneity (I^2=64%; p=0.04). Due to small number of included studies, analyses for publication bias or investigation of heterogeneity were not undertaken. The quality of the evidence was low according to GRADE (downgraded owing to concerns over unexplained heterogeneity and risk of bias).

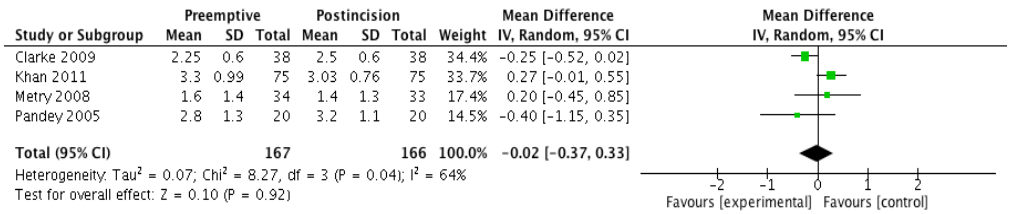


Figure 4.5: Forest plot of pre-emptive gabapentin effects on pain scores at 12 hours.

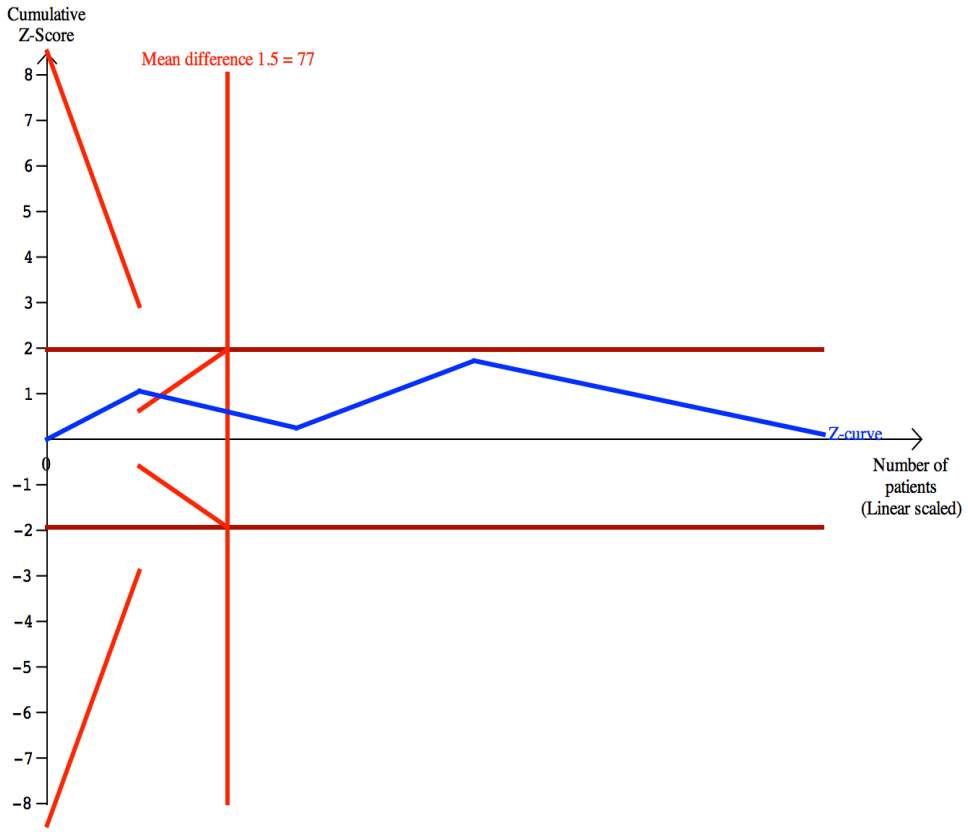


Figure 4.6: Trial sequential analysis of pain score at 12 hours. Performed assuming a mean difference of 1.5, a variance of 0.7, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 73. Blue line indicates cumulative Z score with values more than 0 indicating benefit with pre-emptive gabapentin.

Trial sequential analysis showed that gabapentin did not cross the boundary for benefit (Figure 4.6). However, gabapentin did reach the required IS for a definitive answer (77 participants) and crossed the boundary for futility. On sensitivity analysis, assuming a variance of 3 increased the required IS (155 participants).

4.3.7 Pain scores 24 hours

Overall, four studies with 333 participants were included in the analysis. Pre-emptive gabapentin did not reduce pain scores at 24 hours (MD 0.00; 95% -0.15 to 0.15; Figure 4.7). There was no evidence of statistical heterogeneity (I^2=0%; p=0.99). Due to the low number of included studies, analyses of publication bias or investigation of heterogeneity were not undertaken. There was not enough information to perform TSA. The quality of the evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

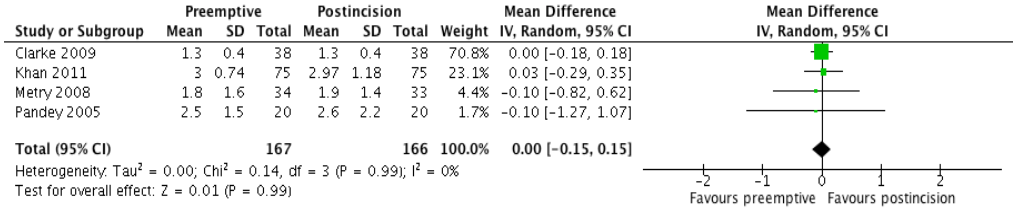


Figure 4.7: Forest plot of pre-emptive gabapentin effects on pain scores at 24 hours.

4.4 Discussion

4.4.1 Summary of results

This chapter found that pre-emptive gabapentin did not offer superior analgesic efficacy when compared with post-incision gabapentin. There was neither a reduction in pain scores during the first day postoperatively or any reduction in 24-hour morphine consumption. There were too few studies to assess publication bias or investigate heterogeneity. Furthermore, type II errors cannot be excluded due to there being too few information to conduct TSA for many outcomes. The quality of the presented evidence is regarded as moderate to low according to GRADE. There were no studies that assessed preventive gabapentin and therefore no conclusions can be made on the efficacy of this analgesic strategy.

4.4.2 Links with previous research

Previous reviews have been undertaken evaluating pre-emptive analgesia for postoperative pain control. Whilst the most recent review found a potential role for NSAIDS, epidural anaesthesia and local anaesthetic wound infiltration (Ong *et al.* 2005) and recent reviews have suggested a role for pre-emptive paracetamol (Doleman *et al.* 2015a), to the best of our knowledge, no previous review has evaluated the role of pre-emptive gabapentin. As the strategy of pre-emptive analgesia involves changing the timing of analgesic administration, it offers a simple and cost-effective solution to reducing acute postoperative pain (if effective).

The results of this clinical review contradict findings obtained from *in vitro* experiments with gabapentinoids. Using a rat postoperative pain model, pregabalin (a similar medication that binds to the same site as gabapentin) administered before incision resulted in a longer duration of anti-hyperalgesia compared to post-incision administration (Field *et al.* 1997b). In another study, administration of intra-thecal gabapentin was more effective when administered before injection of formalin in reducing phase two responses, when compared to administration after formalin injection (Yoon and Yaksh

1999). However, these observations have not been replicated in the clinical studies included in our review, the reasons for which remain unclear. However, in a human volunteer study (Dirks *et al*. 2002a), gabapentin was effective both at reducing the development of and treating existing secondary hyperalgesia. These results may help explain why gabapentin was equally effective when given pre-incision or post-incision.

With regards to the timing of gabapentin administration, although this review has found no benefit of pre-emptive administration in terms of reductions in postoperative pain, pre-emptive administration may offer other clinical and logistical advantages over post-incision administration. Pre-emptive gabapentin allows administration with the patient fully alert and capable of swallowing the tablet. Indeed, included studies that gave post-incision doses had to do so via a nasogastric tube (Khan *et al.* 2011) or two hours after surgery (Clarke *et al.* 2009a; Metry *et al.* 2008). Therefore, post-incision administration may create the need for additional clinical procedures (nasogastric tube) or miss clinically significant reductions in postoperative pain found in chapter two (if administered two hours after surgery). Furthermore, reductions in pre-operative anxiety with gabapentin would be lost with post-incision dosing. The next chapter will examine the effects of gabapentin on the haemodynamic response to intubation, which may highlight further advantages of pre-operative dosing or identify adverse haemodynamic effects, which may suggest post-incision dosing to be the safest time of administration.

4.4.3 Limitations

There are several limitations with this review. Firstly, included RCTs were clinically heterogeneous in terms of types of surgery, dose of gabapentin used and timing of gabapentin administration. With the low number of included studies, we were unable to explore such heterogeneity or undertake analyses for publication bias, which limits our findings. Secondly, as no studies evaluated preventive gabapentin administration, we could not make any conclusions on the efficacy of this strategy. Continuing gabapentin longer into the postoperative period may help further reduce peri-operative sensitisation

and offer superior analgesic activity when compared with pre-emptive administration.

Thirdly, current studies may be underpowered for many outcomes, as we were not able to undertake TSA for the majority of pain scores and 24-hour morphine consumption. Therefore, type II errors cannot be excluded in our analyses. However, we were able to undertake this analysis for pain scores at 12 hours, which suggested a small number of participants would be required for an appropriate IS. Because of this, future studies may be required to adequately resolve whether gabapentin exerts any pre-emptive effect.

Lastly, although only one study received high risk of bias for one element on risk of bias assessments, only one study was regarded as low risk of bias for most elements (Metry *et al.* 2008). Again, there was unclear risk of bias for allocation concealment, which has previously been shown to over-estimate effect estimates in RCTs of identical interventions (Schulz and Grimes 2002a). Therefore, our results should be interpreted with caution. Such deficiencies in study conduct meant the quality of evidence derived from our results was at best, moderate quality.

4.4.4 Conclusions

In conclusion, it appears from the limited data thus far that gabapentin exerts no pre-emptive effect for postoperative analgesia. However, future studies are still required due to low number of participants included in this review. Despite a lack of clinical efficacy on reducing postoperative pain, pre-emptive doses of gabapentin may have other clinical advantages and disadvantages, which may complicate the issue of when is the best time to administer peri-operative gabapentin.

Chapter 5

Gabapentin for attenuating the haemodynamic response to endotracheal intubation

5.1 Introduction

Endotracheal intubation is the gold standard for securing the airway prior to surgery. However, this procedure may cause activation of the sympathetic nervous system and release of catecholamines with the resulting haemodynamic response causing increasing heart rate and blood pressure. This response does not cause problems in most patients. However, in high-risk patient groups such as those with pre-existing cardiovascular disease, such responses may increase the risk of myocardial ischaemia, myocardial infarction and mortality (Kovac 1996; POISE Study Group 2008). As the number of elderly patients undergoing surgery increases, adverse cardiovascular responses to endotracheal intubation may therefore present an increasing problem during the peri-operative period. Many agents have been used to attenuate this response, however few studies report clinically relevant outcomes such as morbidity or mortality (Khan and Ullah 2013).

Increases in haemodynamic and sympathetic responses around the peri-operative period increase myocardial demand leading to adverse cardiac outcomes. Triggers for this include intubation, extubation, surgery and pain (Devereaux *et al.* 2005). This led to RCTs evaluating agents such as beta-blockers and clonidine in reducing peri-operative myocardial events. The POISE study (POISE Study Group 2008) found that metoprolol reduced myocardial infarction. However, there was an increase in overall mortality and stroke thought secondary to episodes of hypotension and bradycardia. Clonidine has also shown initial promise (Wallace *et al.* 2004), although the recent POISE 2 study showed no reduction in cardiac events or mortality and an increase in clinically significant hypotension and non-fatal cardiac arrest (Devereaux *et al.* 2014). Therefore, the search for alternative agents that do not produce such adverse effects is a clinically important issue for high-risk patients undergoing surgery.

Randomised controlled trials have been published over the last decade indicating gabapentin may be useful for attenuating the haemodynamic response to intubation (Kong and Irwin 2008). However, these studies have

included a small number of participants and have not been conducted in multiple clinical populations. Moreover, it is as yet unknown whether such reductions in haemodynamic variables can translate into reductions in clinically relevant postoperative outcomes.

Due to the disappointing results from the clinical trials of clonidine and beta-blockers in reducing peri-operative myocardial events (Sear, Higham and Foex 2015) this review aimed to evaluate whether gabapentin can attenuate the haemodynamic response to intubation and whether this can translate into reductions in myocardial ischaemia, myocardial infarction and ultimately reduce postoperative mortality.

5.2 Methods

5.2.1 Reporting standards and prospective registration

This review was undertaken in accordance with the PRISMA checklist (Moher *et al.* 2009). We prospectively registered the review on the PROSPERO website using the registration number CRD42015027012.

5.2.2 Search strategy

We searched the following databases: MEDLINE (1946-2015), EMBASE (1974-2015), CINAHL (1981-2015), AMED (1985-2015) and CENTRAL. We searched for studies using the keywords in the title and abstract 'gabapentin' 'neurontin' and 'intubation'. The MeSH term 'INTUBATION, INTRATRACHEAL' was exploded and combined with the above terms. We also searched for unpublished studies from Clinicaltrials.gov, the ISRCTN registry and the WHO international clinical trials registry. Furthermore, we searched reference lists of identified studies and used Google Scholar to identify studies that had cited those included. We contacted the authors if further information was required.

5.2.3 Inclusion criteria and outcomes

We included RCTs that compared gabapentin with placebo or no treatment in patients undergoing endotracheal intubation prior to surgery. We included adult patients only (>15 years old) undergoing any type of surgery. There were no restrictions on the basis of publication status or language. Where necessary, non-English language papers were translated using Google Translate. Two of the authors independently evaluated the identified studies against the inclusion criteria and agreement was reached by consensus.

The primary outcomes were mortality, myocardial ischaemia and myocardial infarction. We defined mortality as early (<48 hours) and late (30-days). If studies reported more than one time-point, the earliest was included in the analysis. Myocardial ischaemia was defined as ST segment depression from

continuous ECG recordings. Myocardial infarction was defined as two of the following three criteria: chest pain, ECG ischaemic changes and/or >25% rise in high-sensitivity troponin measurements. Secondary outcomes included heart rate (HR), mean arterial blood pressure (MBP), systolic blood pressure (SBP) and diastolic blood pressure (DBP) measured at one, five and 10 minutes after intubation. We also measured the following outcomes: arrhythmias, plasma catecholamine concentrations, hypotension (requiring treatment), bradycardia (requiring treatment) and tachycardia or hypertension (requiring treatment).

5.2.4 Data extraction

Two authors extracted the following information onto an electronic database: study name, year of publication, mean age of participants, percentage of female participants, sample size, intervention, comparator, country in which the study was conducted, concurrent peri-operative medication, induction agents used (with dose), maintenance agents, laryngoscope and endotracheal tube used, participant population, type of surgery and duration of intubation (seconds).

5.2.5 Risk of bias in included studies

Two study authors assessed risk of bias using the Cochrane tool for assessing risk of bias (Higgins *et al.* 2011) and agreement was reached by consensus. We assessed the following domains: randomisation, allocation concealment, blinding, attrition bias, selective outcome reporting and other sources of bias. These domains were assessed as low, unclear and high risk and presented in a risk of bias table.

5.2.6 Statistical analysis

We presented continuous outcomes using the difference in means (MD) and dichotomous outcomes using risk ratios (RR). The precision of outcomes was presented with 95% confidence intervals (95% CI). We regarded differences of 10% in dichotomous outcomes, 10mmHg in blood pressure and 5 beats per minute (bpm) in heart rate as clinically significant. Where data were not

presented, authors were contacted to provide further information. If no response was received, these results were estimated from published graphs. If standard deviations were not reported we estimated these from other studies in the meta-analysis (Higgins 2008). We used the GRADE criteria to assess the level of evidence for each outcome. Evidence was downgraded owing to any concerns regarding the indirectness of evidence, lack of precision in effect estimates, potential publication bias, unexplained heterogeneity and risk of bias in included trials. This was a qualitative downgrading from high quality to moderate, low or very low quality dependent on the concerns cited above. We made no statistical adjustment of results.

Data was aggregated using a random-effects model due to substantial clinical heterogeneity in gabapentin dose and the baseline haemodynamic variables of the participants. Statistical heterogeneity was presented using the I^2 statistic with a corresponding p value derived from the chi-squared statistic. We regarded I^2 of >50% or $p<0.1$ as evidence of statistical heterogeneity. When more than ten studies were included in the meta-analysis, we assessed imprecise study effects, including possible publication bias using Egger's linear regression test (Egger *et al.* 1997a). We regarded a one-tailed $p<0.1$ as evidence of imprecise study effects. All analyses were undertaken using Review Manager 5.3, STATA Version 14 and Comprehensive Meta-analysis V3.3.

5.2.7 Meta-regression

Investigation of heterogeneity was undertaken using a method of moments, random-effects meta-regression (Thompson and Higgins 2002). Covariates included dose of gabapentin and baseline haemodynamic variables of the participants. We calculated the baseline haemodynamic measurements by taking the mean measurement from the gabapentin and control groups recorded before induction of anaesthesia (where reported). We assessed residuals for normality, linearity and heteroscedasticity. We used Cook's distance to assess the model for influential cases and the VIF for evidence of multicollinearity.

We presented results as the R^2 analogue with a corresponding p value for the model (significance level $p<0.05$).

5.2.8 Sensitivity analysis

We conducted sensitivity analysis by including studies at low risk of bias (defined as low risk for randomisation, allocation concealment, blinding and attrition bias and no high risk domains), excluding studies where standard deviations were estimated and using one study-removed analysis.

5.2.9 Trial sequential analysis

We performed TSA for all outcomes. We estimated control group incidences from both published literature and events from the studies included in each analysis. For continuous outcomes, we used both clinically important differences (from subjective clinical experience) and empirical estimates for the main results.

We used estimates of variance from the studies included in the meta-analysis. For dichotomous outcomes we regarded RRR of 20% as clinically significant if incidence was above 10% and for low incidence events (≤10%) we used a 50% RRR. We conducted sensitivity analysis around these estimates by changing various assumptions regarding heterogeneity corrections, measures of variance or changing assumptions on the effect estimates. We calculated alpha spending monitoring boundaries using the O'Brien-Fleming method with a significance level of $p<0.05$. We used the DerSimonian and Laird method for calculating random-effects estimates. We also constructed futility boundaries with a $1-\beta=0.80$. For handling zero events, we used a constant value of 0.5. We applied a heterogeneity adjustment factor as the ratio between the fixed and random effects model. We conducted all analyses using TSA software from the Copenhagen Trial Unit (Version 0.9.5.5 beta).

5.3 Results

5.3.1 Characteristics of the included studies

We screened 95 studies identified from the searching of electronic databases and hand-searching of reference lists (Figure 5.1). Overall, 29 RCTs were included in the meta-analysis (Table 5.1). All the included studies enrolled ASA I or II patients with no pre-existing cardiac disease. Only one study included patients with hypertensive disease (Bala *et al.* 2015) and only one study used invasive blood pressure monitoring to record haemodynamic variables (Ali *et al.* 2009). There was clinical heterogeneity in the doses of gabapentin used, with doses ranging from 300-1200mg. Most studies administered gabapentin between 1 to 2 hours before surgery. In terms of risk of bias assessments, allocation concealment was rarely adequately reported. The risk of bias assessment for each included study is presented in Figure 5.2.

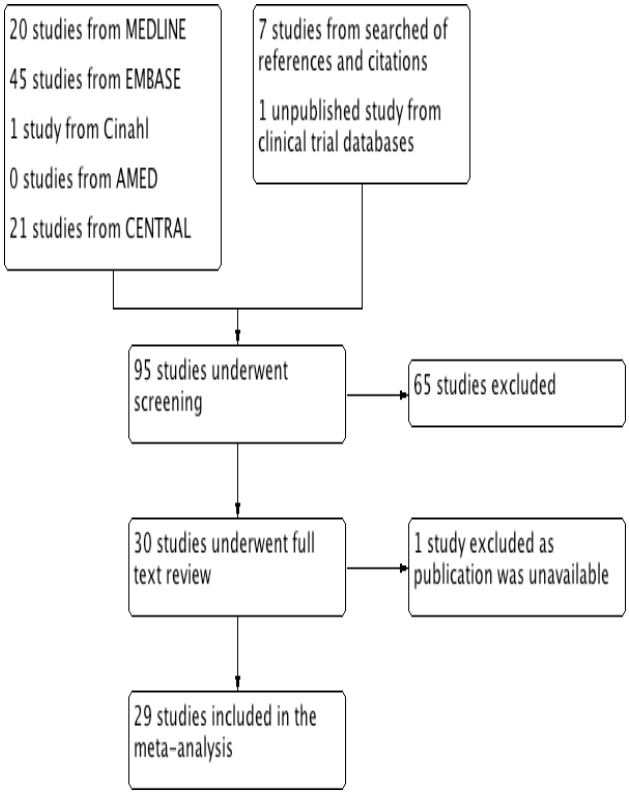


Figure 5.1: PRISMA flowchart for the included studies.

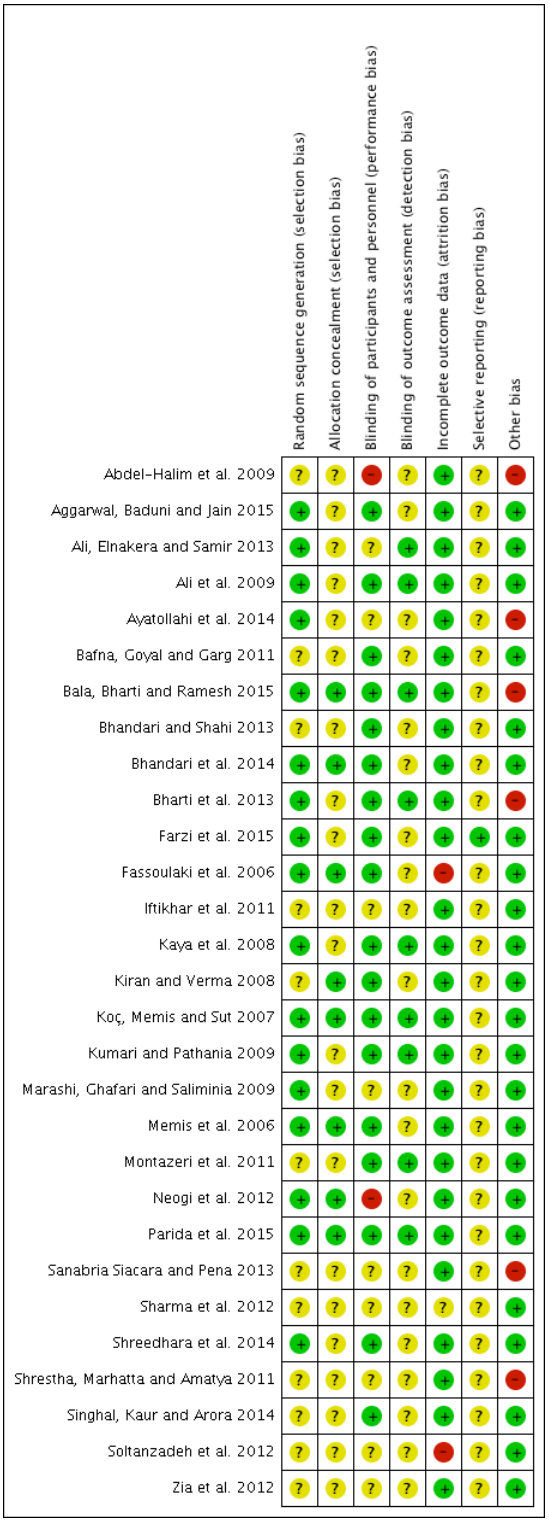


Figure 5.2: Risk of bias in the included studies. Green indicates low risk, yellow indicates unclear risk and red indicates high risk.

Study name	Mean age	Female (%)	N	Intervention	Comparator	Country	Type of surgery
Abdel-Halim *et al.* 2009	46.3	100%	80	800mg gabapentin one hour before surgery	1) No medication 2) 16mg dexamethasone	Egypt	Mastectomy
Aggarwal, Baduni and Jain 2015	36.6	83%	90	1) 300mg gabapentin night before and day of surgery 2) 300mg gabapentin night before and 600mg day of surgery	Placebo	India	Laparoscopic cholecystectomy
Ali *et al.* 2009	29.5	46%	50	1200mg gabapentin two hours before surgery	Placebo	Egypt	Elective surgery (hernioplasty, arthroscopy, cholecystectomy and vitrectomy)
Ali, Elnakera and Samir 2013	31.6	50%	60	1) 800mg gabapentin two hours before surgery 2) 1200mg gabapentin two hours before surgery	Placebo	Egypt	Elective cataract surgery
Ayatollahi *et al.* 2014	NR	NR	30	100mg gabapentin night before and 800mg 90 minutes before surgery	Placebo	Iran	Microlaryngeal surgery

Bafna, Goyal and Garg 2011	39.7	76%	90	1) 600mg gabapentin one hour before surgery 2) 1000mg gabapentin one hour before surgery	Placebo	India	Elective surgery
Bala, Bharti and Ramesh 2015	54.6	68%	100	1) 800mg gabapentin two hours before induction 2) 800mg night before and two hours before induction	Placebo	India	Elective surgery
Bhandari and Shahi 2013	42.6	NR	40	900mg gabapentin two hours before induction	Placebo	India	Elective surgery
Bhandari *et al.* 2014b	42.9	66%	40	600mg gabapentin two hours before surgery	Placebo	India	Laparoscopic cholecystectomy
Bharti *et al.* 2013	46.5	100%	40	600mg gabapentin two hours before surgery	Placebo	India	Mastectomy for breast cancer
Farzi *et al.* 2015	27.6	85%	103	900mg gabapentin two hours before surgery	Placebo	Iran	Septo-rhinoplasty
Fassoulaki *et al.* 2006b	42	100%	44	400mg gabapentin TDS day before surgery and 6am on the day of surgery	Placebo	Greece	Abdominal hysterectomy
Iftikhar *et al.* 2011	36.5	40%	60	800mg gabapentin one hour before surgery	Placebo	Pakistan	Elective surgery

Kaya *et al.* 2008	43.5	53%	60	800mg gabapentin two hours before surgery	Placebo	Turkey	Elective surgery
Kiran and Verma 2008	33.8	54%	100	800mg gabapentin night before and morning of surgery	Placebo	India	Elective surgery
Koç, Memis and Sut 2007	38.5	0%	80	800mg gabapentin one hour before surgery	1) Placebo 2) 8mg dexamethasone	Turkey	Varicocele surgery
Kumari and Pathania 2009	30.7	49%	78	900mg gabapentin two hours before induction	Placebo	India	Elective surgery
Marashi, Ghafari and Saliminia 2009	32.8	51%	75	900mg gabapentin two hours before surgery	1) Placebo 2) 0.2mg clonidine	Iran	Elective orthopaedic and general surgery
Memiş *et al.* 2006	44.6	42%	89	1) 400mg gabapentin one hour before surgery 2) 800mg gabapentin one hour before surgery	Placebo	Turkey	Elective surgery
Montazeri *et al.* 2011	38	45%	96	800mg gabapentin 90 minutes before surgery	1) Placebo 2) 0.3mg clonidine	Iran	Elective surgery
Neogi *et al.* 2012	40.4	63%	60	900mg gabapentin two hours before induction	Vitamin B	India	Laparoscopic cholecystectomy

Parida *et al.* 2015	37.9	58%	50	800mg gabapentin two hours before surgery	1) Placebo 2) Fentanyl	India	Elective non-cardiac surgery
Sanabria Siacara and Pena 2013	31.5	37%	30	600mg gabapentin one hour before surgery	Clonidine 2mcg/kg	Mexico	Elective surgery
Sharma *et al.* 2012	37.6	NR	120	800mg gabapentin one hour before induction	1) Placebo 2) 0.3mg clonidine 3) 400mg gabapentin and 0.15mg clonidine	Kashmir	Elective surgery
Shreedhara *et al.* 2014	40.4	48%	90	900mg gabapentin two hours before surgery	1) Placebo 2) 0.2mg clonidine	India	Elective surgery
Shrestha, Marhatta and Amatya 2009	33.8	NR	72	1200mg gabapentin two hours before induction	1) Placebo 2) Esmolol	Nepal	Elective surgery
Singhal, Kaur and Arora 2014	32.8	63%	100	900mg gabapentin 90 minutes before surgery	Clonidine 0.2mg	India	Elective surgery
Soltanzadeh *et al.* 2012	28.4	50%	90	900mg gabapentin two hours before surgery	Placebo	Iran	Elective surgery
Zia *et al.* 2012	36.7	40%	110	800mg gabapentin two hours before	Placebo	Pakistan	Elective surgery (2-3

				surgery			hours)

Table 5.1: Baseline characteristics of included studies. NR=not reported; mg=milligrams.

5.3.2 Mortality

None of the included studies reported mortality as an outcome.

5.3.3 Myocardial infarction

None of the included studies reported myocardial infarction as an outcome.

5.3.4 Myocardial ischaemia

Nine studies reported myocardial ischaemia (Aggarwal, Baduni and Jain 2015; Ali *et al.* 2009; Bafna, Goyal and Garg 2011; Bala, Bharti and Ramesh 2015; Kaya *et al.* 2008; Koc, Memis and Sut 2007; Memis *et al.* 2006; Montazeri *et al.* 2011; Parida *et al.* 2015). However, there were no events reported in any of the included studies.

5.3.5 MAP one minute

Overall, 18 studies with 1147 participants were included in the analysis. Gabapentin resulted in a clinically significant attenuation in the rise in MAP at one minute (MD -12.54mmHg; 95% CI -16.93 mmHg to -8.14 mmHg; Figure 5.3). There was evidence of considerable statistical heterogeneity (I^2=87%; p<0.001). The quality of the evidence according to GRADE was low (downgraded owing to concerns over unexplained heterogeneity and risk of bias).

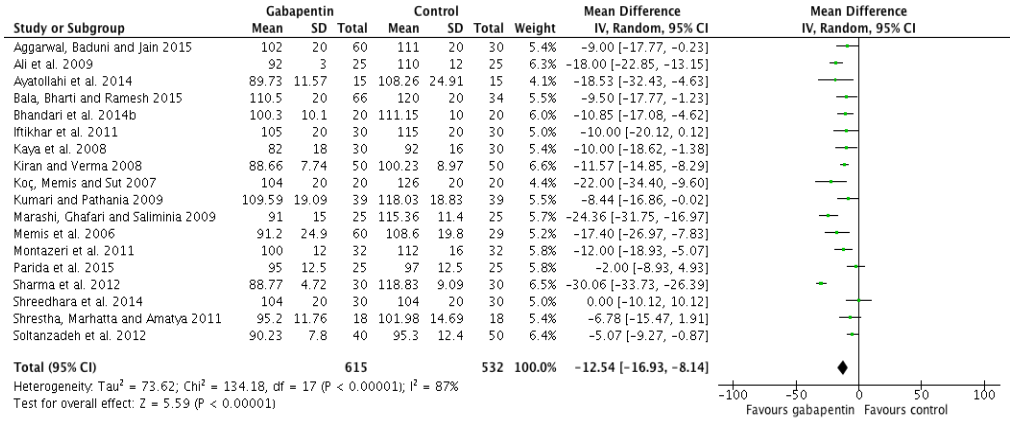


Figure 5.3: Forest plot of MAP at one minute.

There was no clear asymmetry when observing funnel plots (Figure 5.4). Indeed, Egger's linear regression test was not significant (p=0.14). Therefore, further tests of publication bias were not conducted. On meta-regression analysis, neither covariate (dose nor baseline MAP) predicted the efficacy of gabapentin.

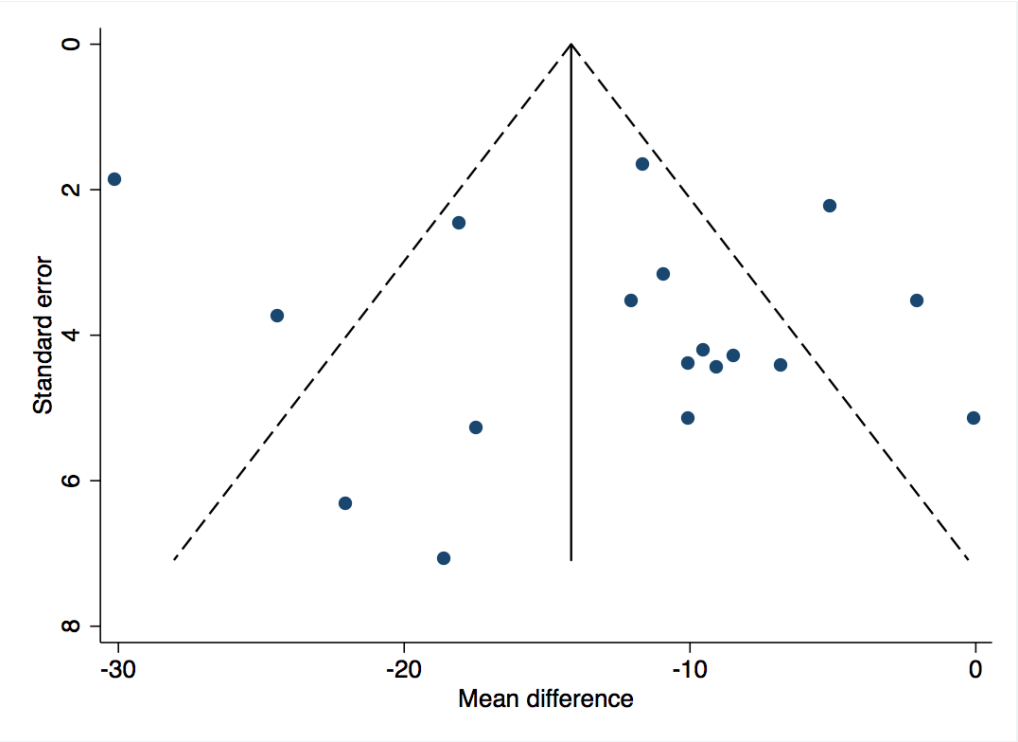


Figure 5.4: Funnel plot of MAP at one minute. X-axis shows the MD and the Y-axis shows the standard error of the MD.

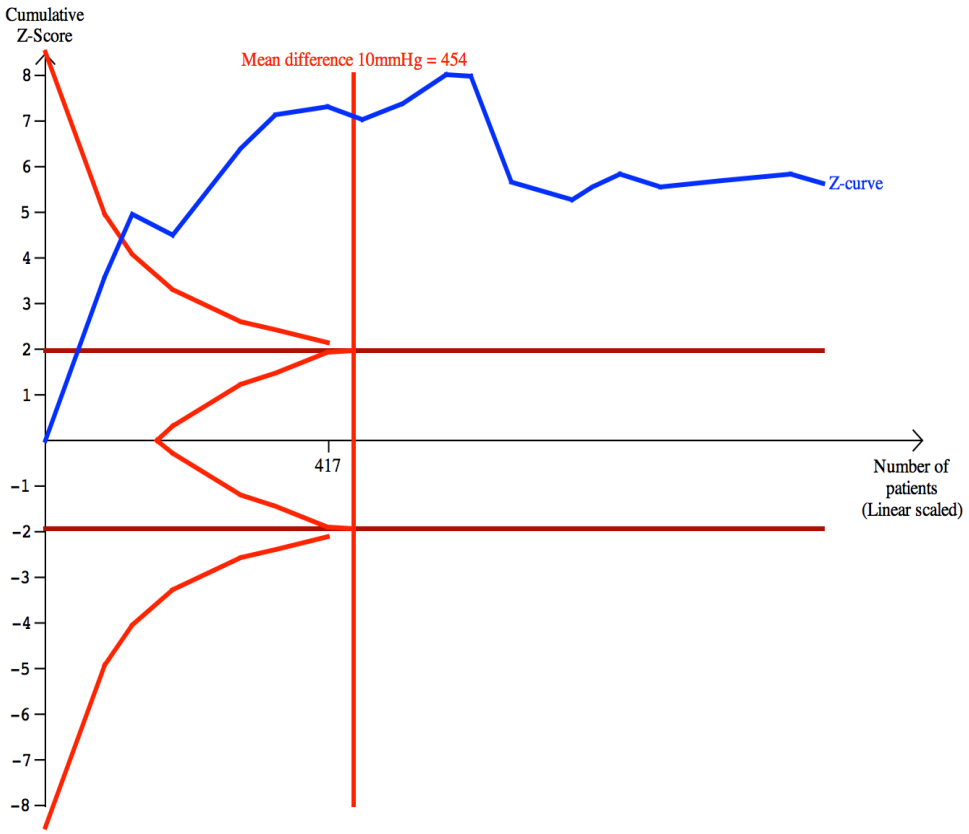


Figure 5.5: Trial sequential analysis of MAP at one minute. Performed assuming a mean difference of 10mmHg, a variance of 161, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 89. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.5). The results also reached the required IS for a definitive answer (454 participants). On sensitivity analysis, assuming a variance of 300 increased the required IS (847 participants). Assuming an empirical MD of 12.56mmHg still showed benefit with gabapentin while reducing the required IS (294 participants).

5.3.6 MAP five minutes

Overall, 21 studies with 1350 participants were included in the analysis. Gabapentin attenuated the rise in MAP at five minutes after intubation (MD -9.31mmHg; 95% CI -13.14 mmHg to -5.49 mmHg; Figure 5.6). There was evidence of considerable statistical heterogeneity (I^2=93%; p<0.001). The quality of evidence according to GRADE was low (downgraded owing to concerns over unexplained heterogeneity and risk of bias).

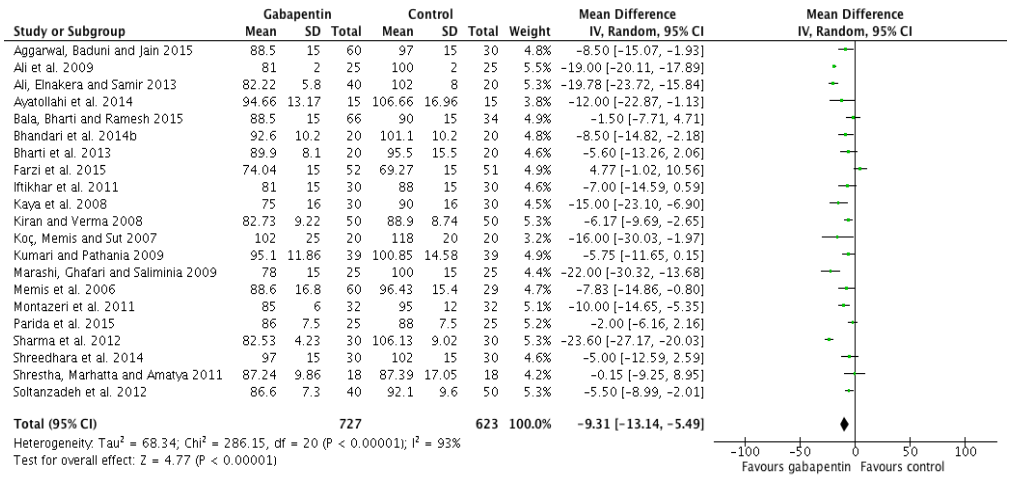


Figure 5.6: Forest plot of MAP at five minutes.

There was no obvious asymmetry on visual inspection of the funnel plot (Figure 5.7). However, Egger's linear regression test showed evidence of possible publication bias (p=0.001). Despite this, the missing studies were missing from the left of the mean suggesting a bias against gabapentin for this outcome. When performing trim and fill analysis, two missing studies were added resulting in a larger attenuation with gabapentin (MD -10.52mmHg; 95% CI -14.15mmHg to -6.89mmHg). When performing failsafe N, 1034 negative studies would be required to observe a null effect with gabapentin. On meta-regression analysis, neither dose (p=0.27) nor baseline MAP (p=0.48) predicting the efficacy of gabapentin.

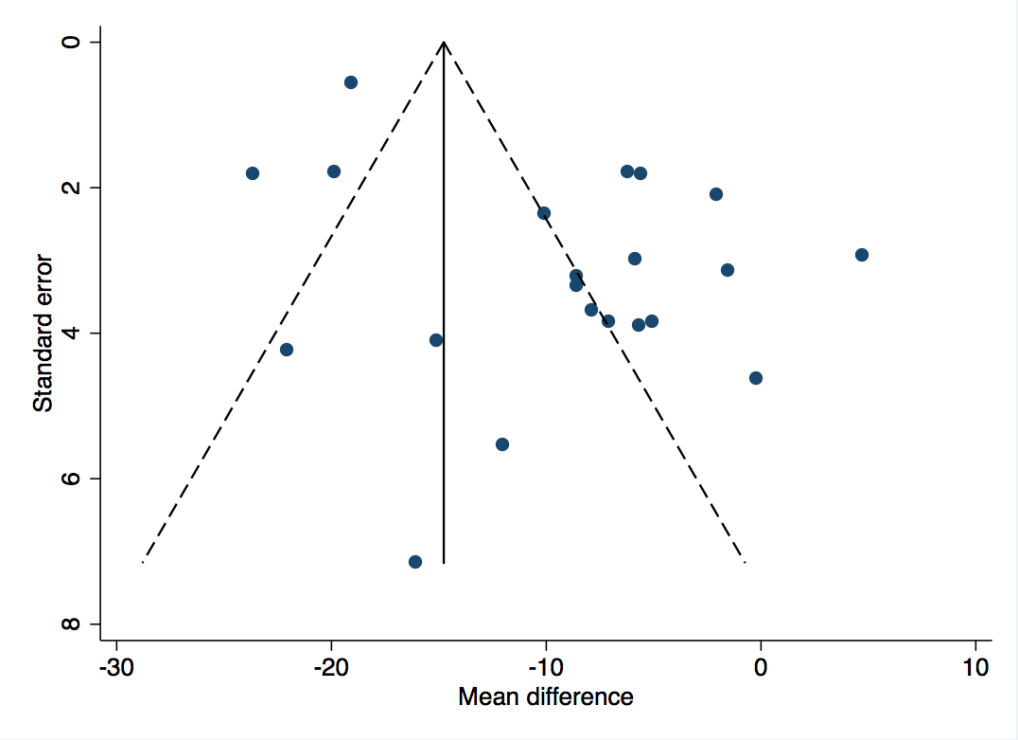


Figure 5.7: Funnel plot of MAP at five minutes. X-axis shows the MD and the Y-axis shows the standard error of the MD.

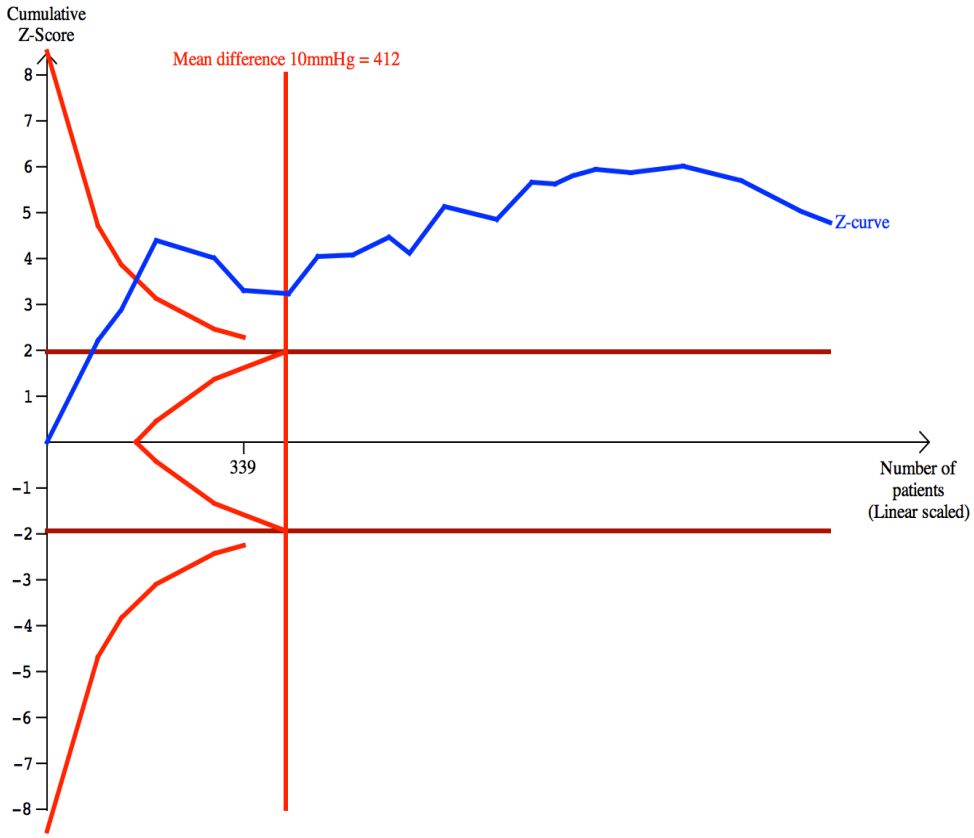


Figure 5.8: Trial sequential analysis of MAP at five minutes. Performed assuming a mean difference of 10mmHg, a variance of 59, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 95. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.8). In addition, the results for gabapentin reached the required IS for a definitive answer (412 participants). On sensitivity analysis, using the empirical MD did not change the results (IS 477 participants). Assuming a variance of 100 increased the required IS (694 participants).

5.3.7 MAP 10 minutes

Overall, 18 studies with 1244 participants were included in the analysis. Gabapentin attenuated the rise in MAP at 10 minutes (MD -8.14mmHg; 95% CI -11.05mmHg to -5.23mmHg; Figure 5.9). There was evidence of considerable statistical heterogeneity (I^2=82%; p<0.001). The quality of the evidence was low according to GRADE (downgraded owing to concerns over unexplained heterogeneity and risk of bias).

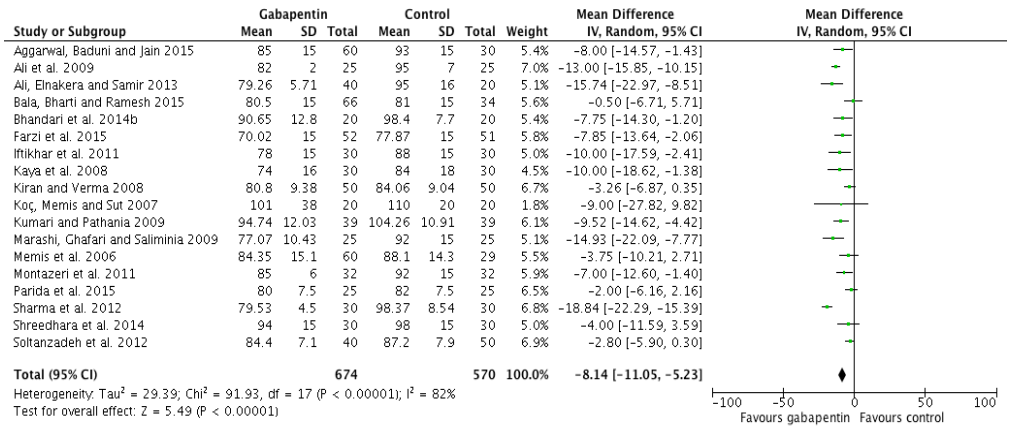


Figure 5.9: Forest plot of MAP at 10 minutes.

Visual inspection of funnel plots showed no obvious asymmetry (Figure 5.10). Indeed, Egger's linear regression test was not significant (p=0.36). Therefore, further analyses of publication bias were not conducted. On meta-regression analysis, neither gabapentin dose (p=0.14) nor baseline MAP (p=0.69) predicted the efficacy of gabapentin.

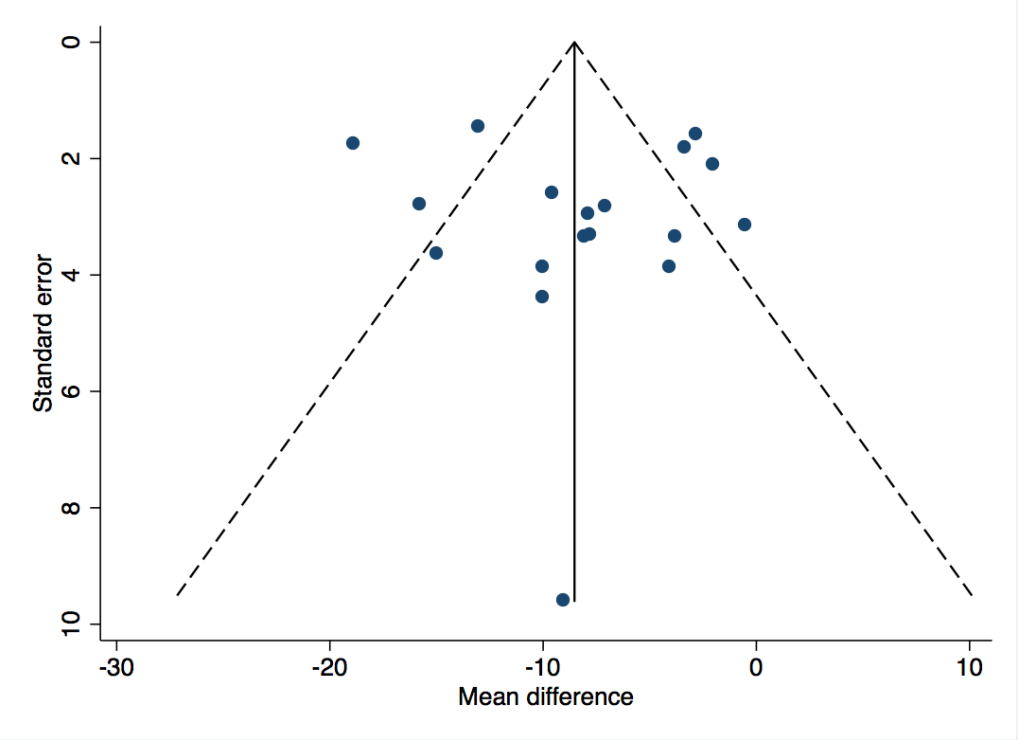


Figure 5.10: Funnel plot of MAP at 10 minutes. X-axis shows the MD and the Y-axis shows the standard error of the MD.

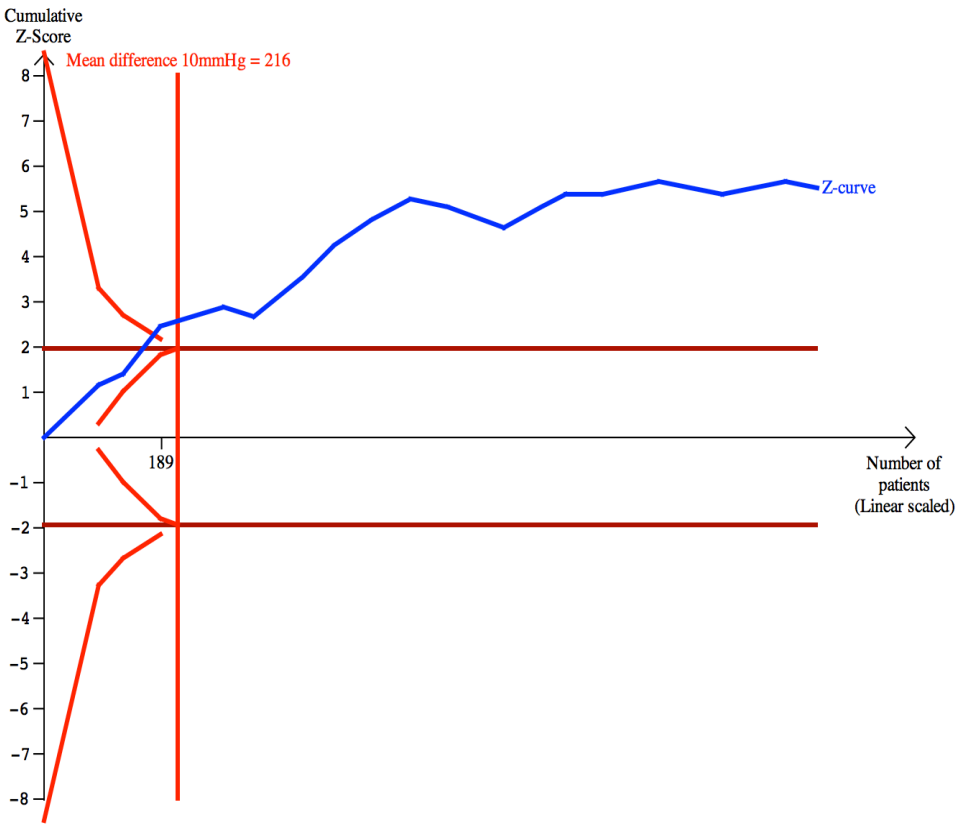


Figure 5.11: Trial sequential analysis of MAP at 10 minutes. Performed assuming a MD of 10mmHg, a variance of 111, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 84. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.11). Gabapentin also reached the required IS for a definitive answer (216 participants). On sensitivity analysis, using an empirical MD of -8.14mmHg gave similar results (327 participants). Assuming a variance of 200 resulted in a larger IS, which the results with gabapentin achieved (389 participants).

5.3.8 HR one minute

Overall, 23 studies with 1471 participants were included in the analysis. Gabapentin resulted in a clinically significant attenuation of the HR response to intubation when compared to control (MD -8.64bpm; 95% CI -11.53bpm to -5.75bpm; Figure 5.12). There was evidence of considerable statistical heterogeneity (I^2=76%; p<0.001). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

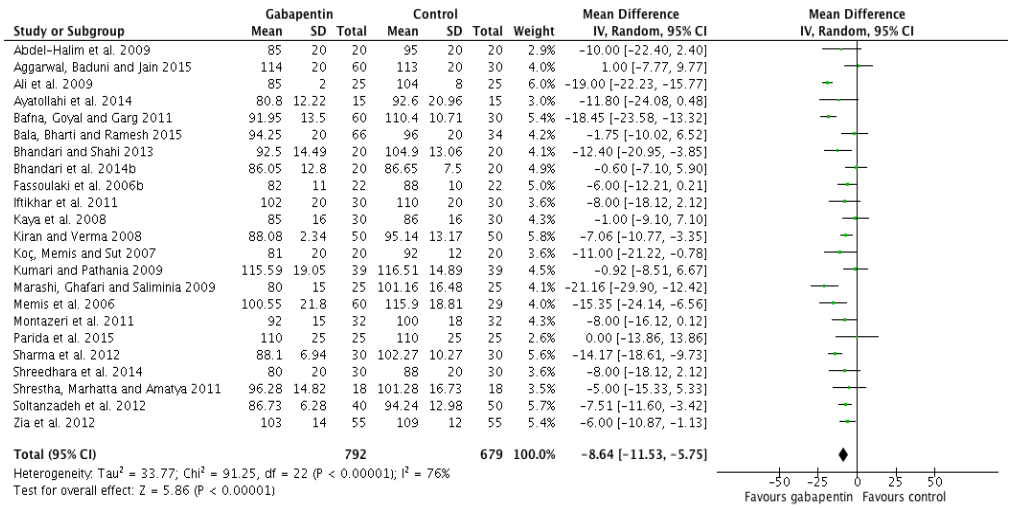


Figure 5.12: Forest plot of HR at one minute.

Visual inspection of funnel plots revealed no obvious asymmetry (Figure 5.13). However, Egger's linear regression test found evidence of statistically significant imprecise study effects (p=0.05). On trim and fill analysis, there were two missing studies to the left of the mean, suggesting a bias against gabapentin (adjusted MD -9.28bpm; 95% CI -12.1bpm to -6.46bpm). Failsafe N showed 232 studies would be required to observe a negative effect with gabapentin.

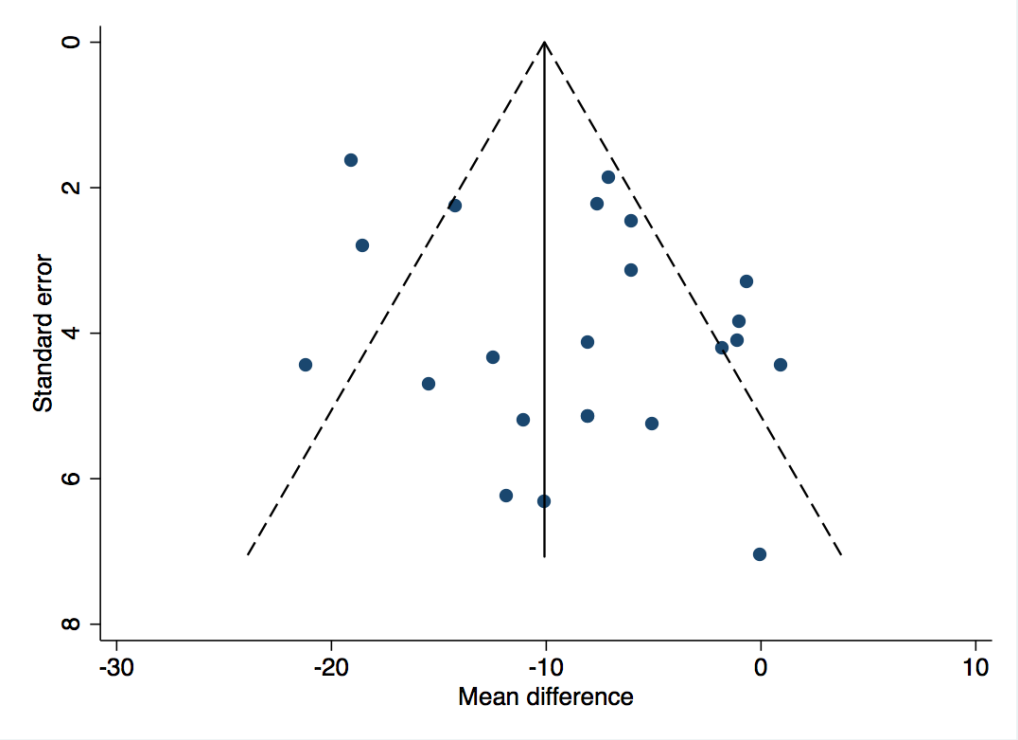


Figure 5.13: Funnel plot of HR at one minute. X-axis shows the MD and the Y-axis shows the standard error of the MD.

On meta-regression analysis, increasing gabapentin dose predicted greater attenuation of the HR response to intubation (R^2=35%; p=0.006) (Figure 5.14). Baseline HR was not a significant predictor of gabapentin response (p=0.45). Regression diagnostics showed one study has a studentised residual above two and one study had one above three. No study had a Cook's distance of more than one. Histograms of residuals showed they were approximately normally distributed although there was evidence of some negative skew. Predicted versus studentised residual plots showed possible evidence of heteroscedasticity.

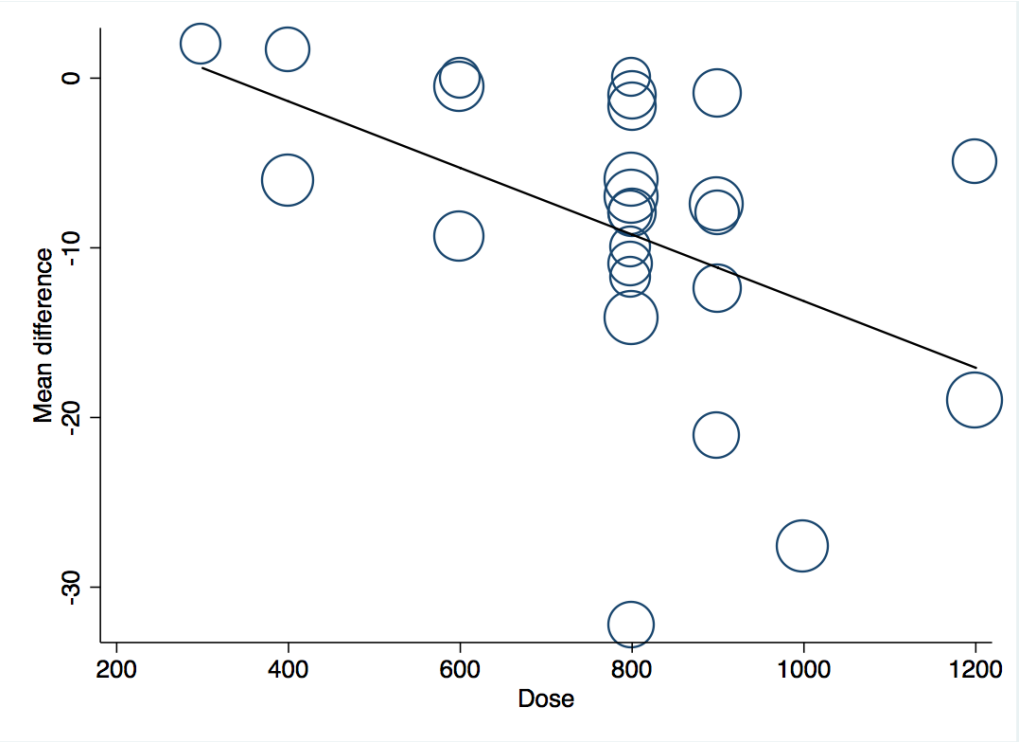


Figure 5.14: Meta-regression plot. X-axis shows gabapentin dose (mg) and the Y-axis the MD in HR at one minute.

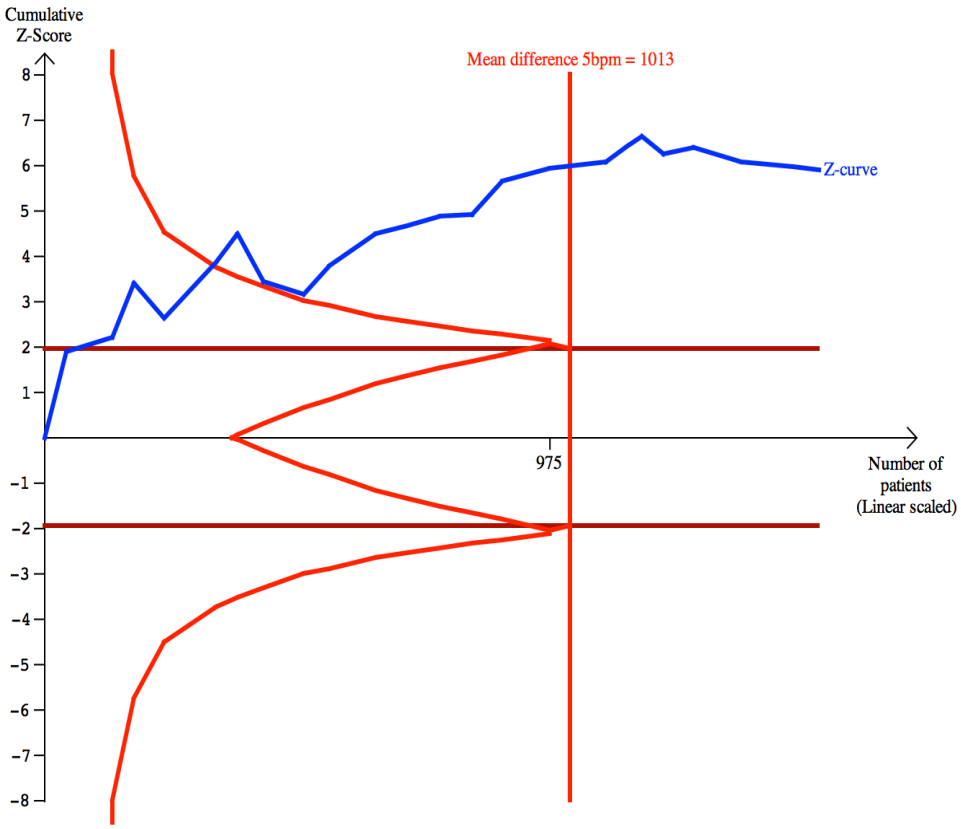


Figure 5.15: Trial sequential analysis of HR at one minute. Performed assuming a MD of 5bpm, a variance of 166, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 79. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien Fleming boundary for benefit (Figure 5.15). Gabapentin also reached the required IS for a definitive answer (1013 participants). On sensitivity analysis, assuming an empirical MD of -8.64bpm, gabapentin both crossed the boundary for benefit and reached the required IS (344 participants). Assuming a variance of 300 increased the required IS (1828 participants) which gabapentin did not reach.

5.3.9 HR five minutes

Overall, 25 studies with 1564 participants were included in the analysis. Gabapentin produced a clinically significant attenuation of the HR response to intubation (MD -6.20bpm; 95% CI -8.48bpm to -3.92bpm; Figure 5.16). There was evidence of considerable statistical heterogeneity (I^2=76%; p<0.001). The level of evidence according to GRADE was moderate (downgraded owing to concerns over risk of bias).

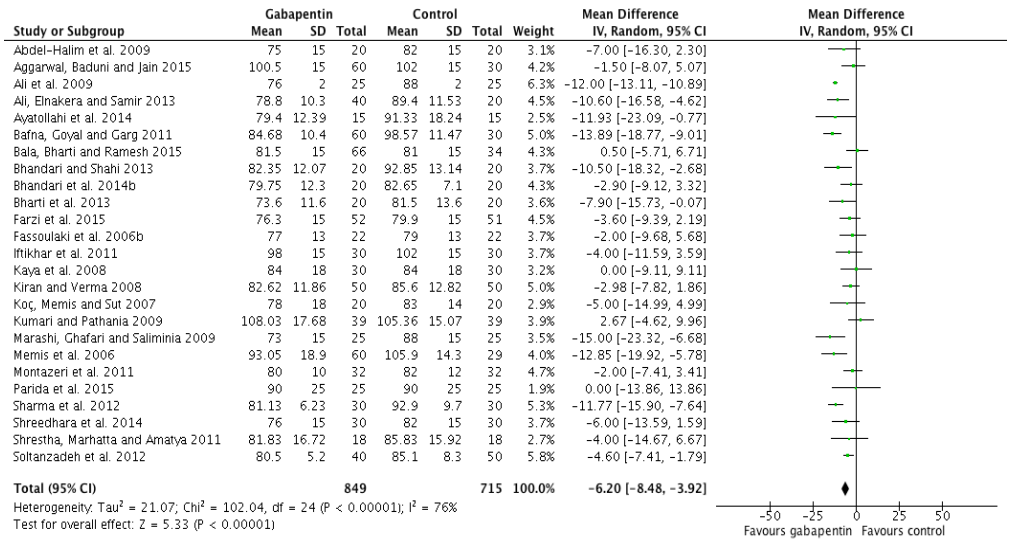


Figure 5.16: Forest plot of HR at five minutes.

On visual inspection of funnel plots, there was no obvious asymmetry (Figure 5.17). However, Egger's linear regression test showed evidence of imprecise study effects (p<0.001). Despite this, trim and fill analysis showed the missing studies were from the left of the mean, suggesting a bias against gabapentin (adjusted MD -6.88bpm; 95% CI -9.07bpm to -4.70bpm). Failsafe N showed 88 negative studies would be required to observe a negative effect with gabapentin.

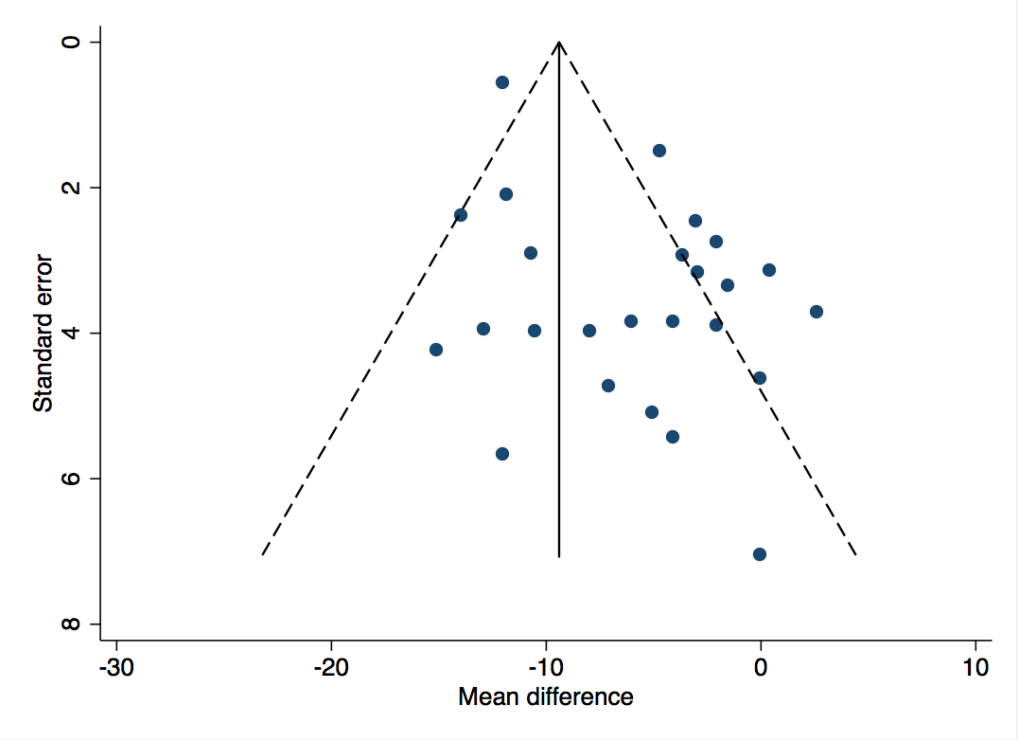


Figure 5.17: Funnel plot of HR at five minutes. X-axis shows the MD and the Y-axis shows the standard error of the MD.

On meta-regression analysis, increasing gabapentin dose predicted greater attenuation of the HR response to intubation (R^2=38%; p=0.02) (Figure 5.18). However, baseline HR was not a significant predictor (p=0.83). On regression diagnostics, only one study had a studentised residual of more than two and no study had a Cook's distance of more than one. Residuals were approximately normally distributed on histograms. Predicted versus residual plots revealed possible evidence of heteroscedasticity. As only one predictor was used in the final model, no tests for multicollinearity were performed.

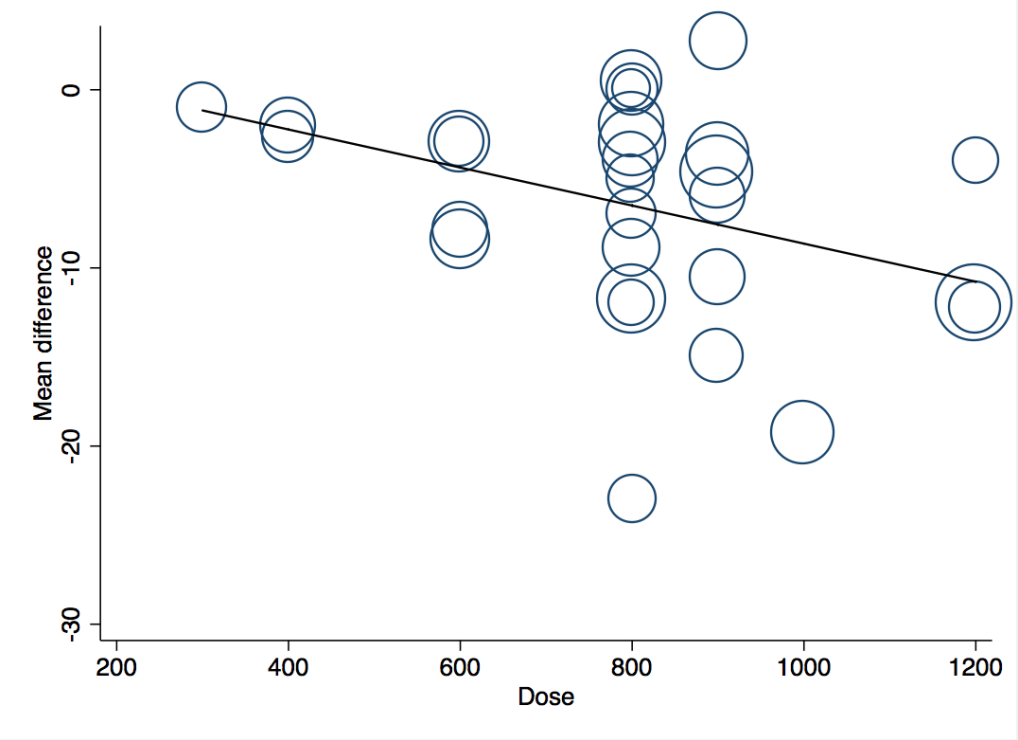


Figure 5.18: Meta-regression plot. X-axis shows gabapentin dose (mg) and the Y-axis the MD in HR at five minutes.

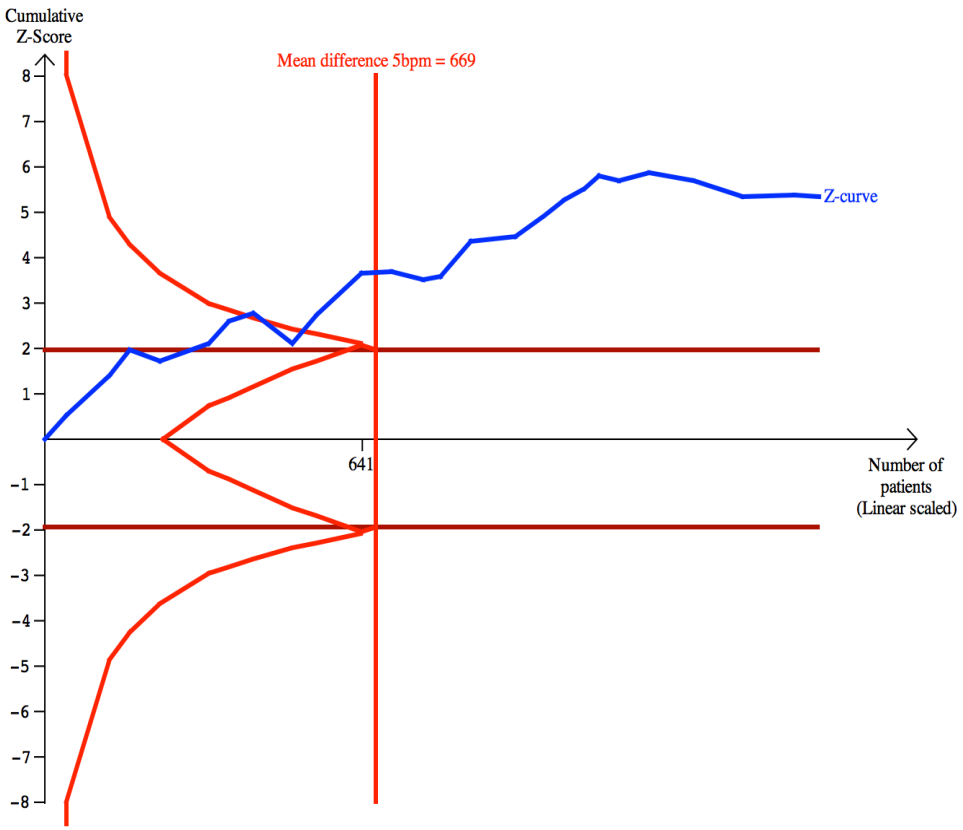


Figure 5.19: Trial sequential analysis of HR at five minutes. Performed assuming a MD of 5bpm, a variance of 70.5, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 87. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.19). In addition, gabapentin reached the required IS for a definitive answer (669 participants). On sensitivity analysis, assuming an empirical MD of 6.2bpm did not change results (IS 436 participants). Assuming a variance of 140 increased the required IS to 1324 participants, which the results for gabapentin still reached.

5.3.10 HR 10 minutes

Overall, 22 studies with 1458 participants were included in the analysis. Gabapentin produced a clinically significant attenuation of the HR response 10 minutes after intubation (MD -5.41bpm; 95% CI -7.26bpm to -3.55bpm; Figure 5.20). There was evidence of moderate statistical heterogeneity (I^2=46%; p=0.009). The quality of evidence was moderate according to GRADE (downgraded owing to concerns over risk of bias).

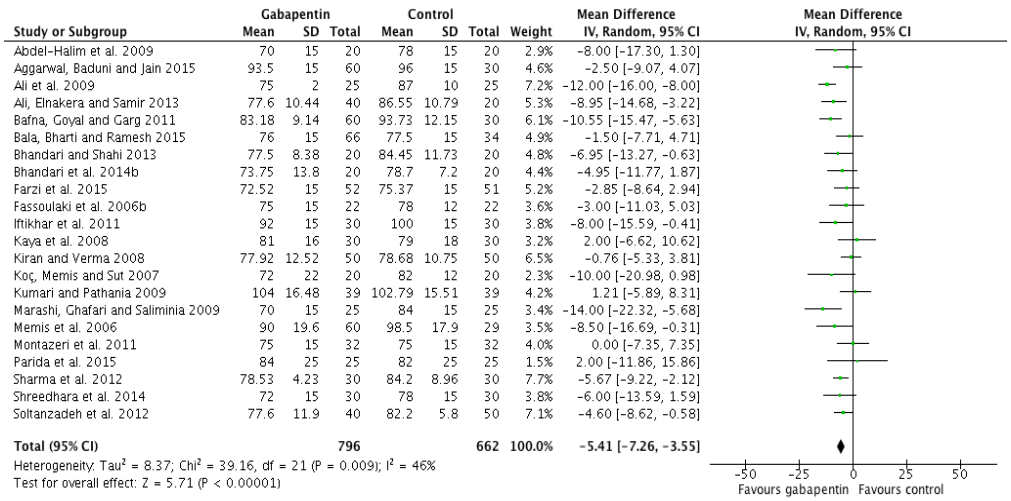


Figure 5.20: Forest plot of HR at 10 minutes.

There was no obvious asymmetry on visual inspection of funnel plots (Figure 5.21). Indeed, Egger's linear regression test was not statistically significant (p=0.19). On meta-regression analysis, baseline HR did not predict the efficacy of gabapentin (p=0.79). However, increasing gabapentin dose predicted greater attenuation of HR response to intubation (R^2=52%; p=0.004) (Figure 5.22). On regression diagnostics, no study had a studentised residual of more than two and no study had a Cook's distance of more than one. Histograms showed residuals were approximately normally distributed. Predicted versus studentised residual plots revealed some evidence of heteroscedasticity.

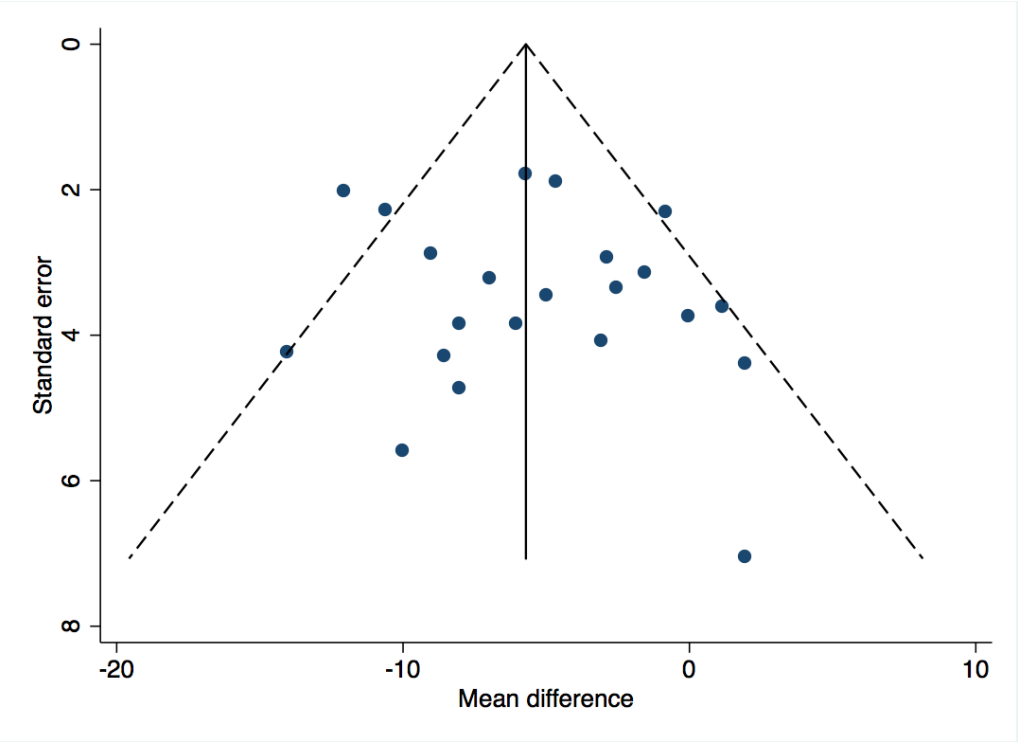


Figure 5.21: Funnel plot of HR at 10 minutes. X-axis shows the MD and the Y-axis shows the standard error of the MD.

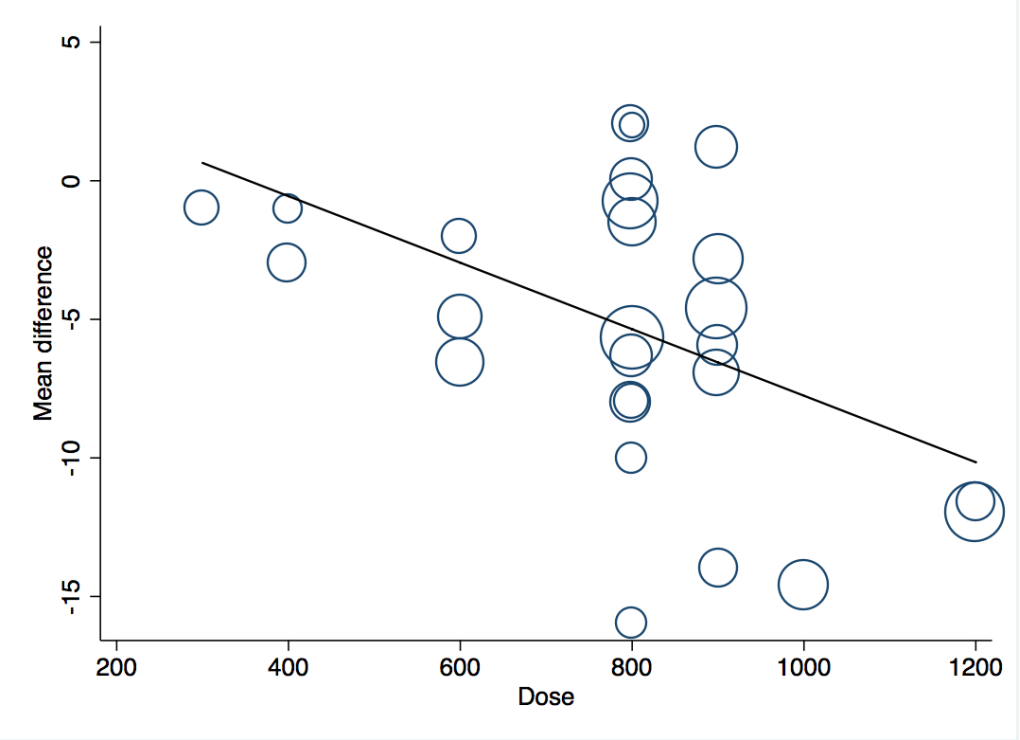


Figure 5.22: Meta-regression plot. X-axis shows gabapentin dose (mg) and the Y-axis the MD in HR at 10 minutes.

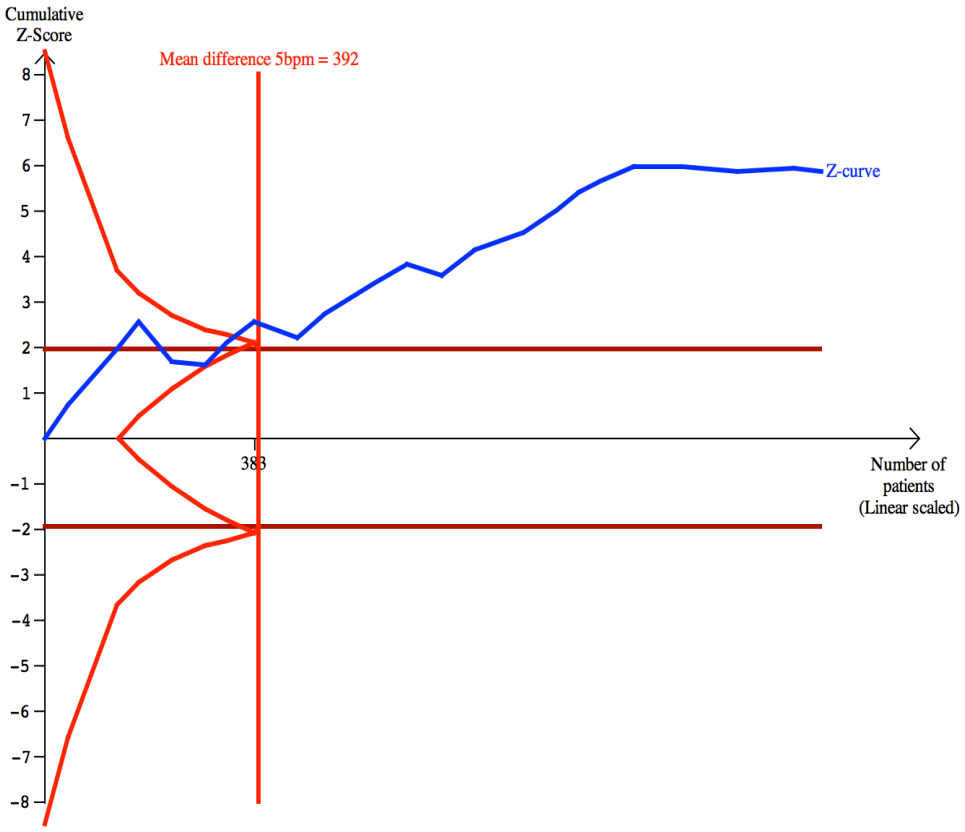


Figure 5.23: Trial sequential analysis of HR at 10 minutes. Performed assuming a MD of 5bpm, a variance of 157, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 49.5. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.23). In addition, gabapentin reached the required IS for a definitive answer (392 participants). On sensitivity analysis, assuming an empirical MD of 5.41bpm did not change results (IS 326 participants). Assuming a variance of 300 increased the required IS (746 participants), as did assuming a heterogeneity correction of 90 (1980 participants), which gabapentin did not reach.

5.3.11 SBP one minute

Overall, 15 studies with 928 participants were included in the analysis. Gabapentin produced a clinically significant attenuation of the SBP response to intubation after one minute (MD -15.68mmHg; 95% CI -21.98mmHg to -9.38mmHg; Figure 5.24). There was evidence of considerable statistical heterogeneity (I^2=90%; p<0.001). The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

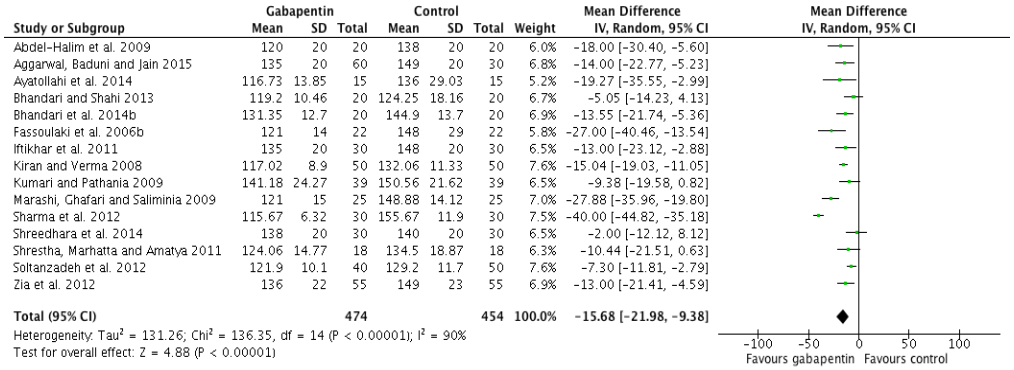


Figure 5.24: Forest plot of SBP at one minute.

Visual inspection of the funnel plot revealed no obvious asymmetry (Figure 5.25). Indeed, Egger's linear regression test was not statistically significant (p=0.27). Therefore, no sensitivity analyses for publication bias were undertaken. On meta-regression analysis, neither dose (p=0.59) nor baseline SBP (p=0.58) predicted the efficacy of gabapentin on SBP responses to intubation.

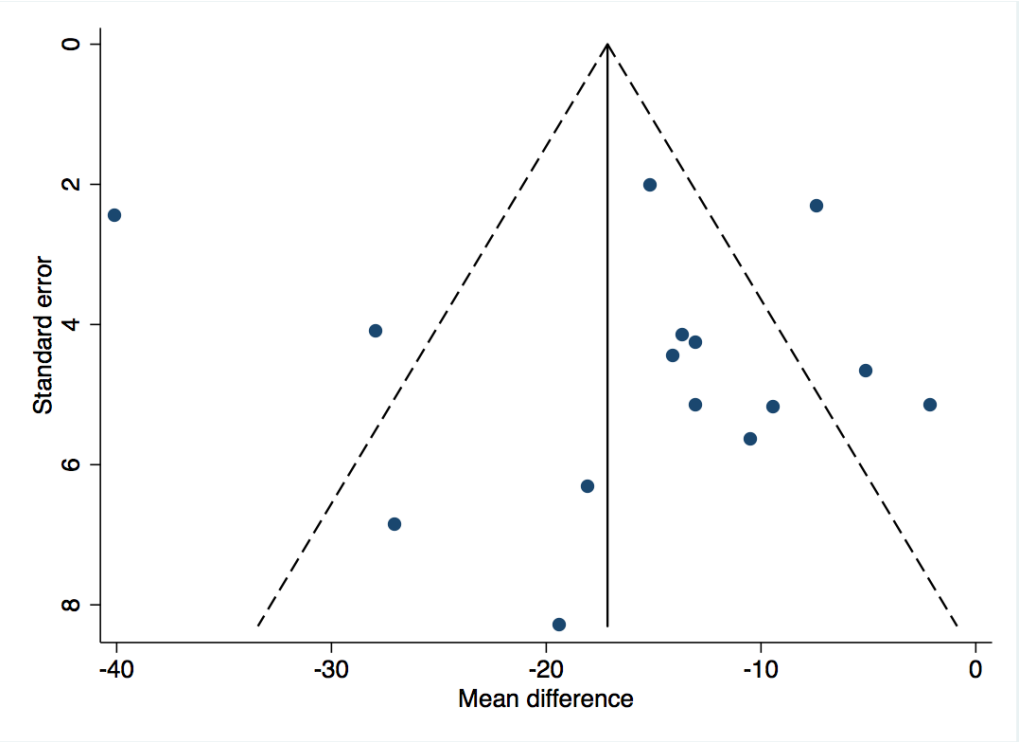


Figure 5.25: Funnel plot of SBP at one minute. X-axis shows the MD and the Y-axis shows the standard error of the MD.

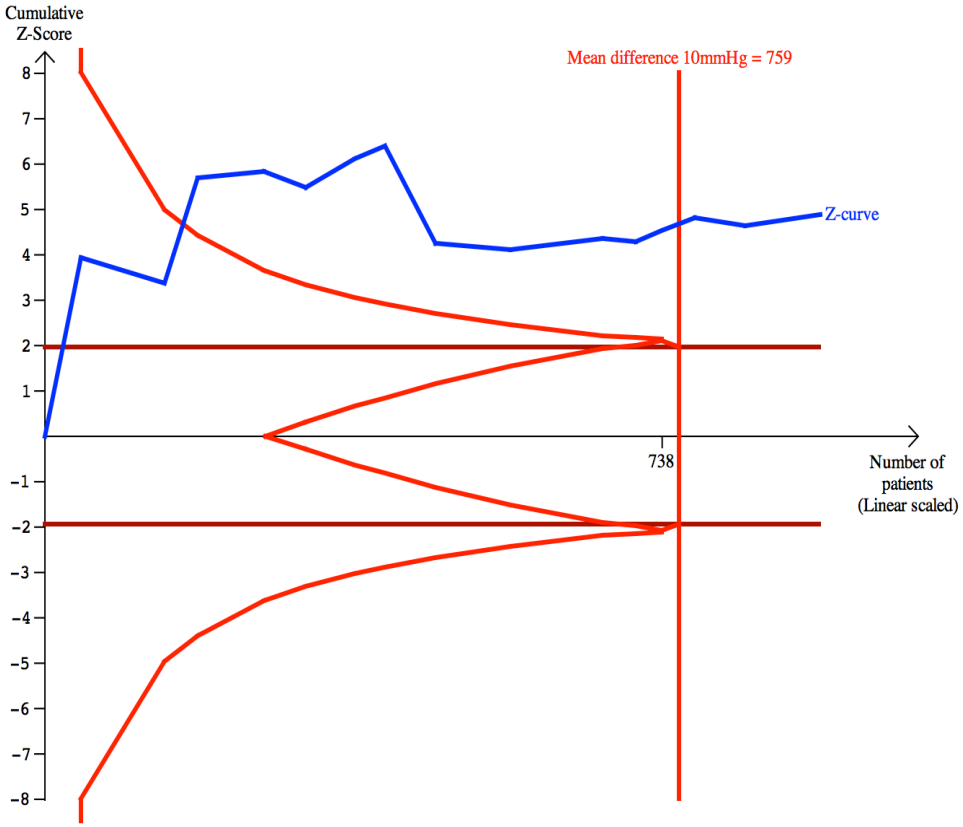


Figure 5.26: Trial sequential analysis of SBP at one minute. Performed assuming a MD of 10mmHg, a variance of 218, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 91. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.26). In addition, gabapentin reached the required IS for a definitive answer (759 participants). On sensitivity analysis, assuming an empirical MD of 15.68mmHg, gabapentin crossed the boundary for benefit and reached the required IS (308 participants). Assuming variance of 400 increased the required IS (1386 participants) which gabapentin did not reach.

5.3.12 SBP five minutes

Overall, 15 studies with 921 participants were included in the analysis. Gabapentin produced a clinically significant attenuation of the SBP response five minutes following intubation (MD -10.03mmHg; 95% CI -15.59mmHg to -4.47mmHg; Figure 5.27). There was evidence of considerable statistical heterogeneity (I^2=89%; p<0.001). The level of evidence was regarded as low quality according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

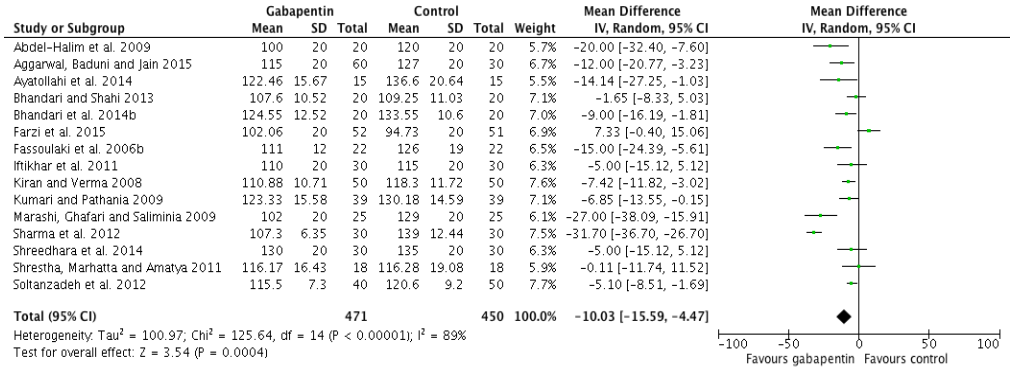


Figure 5.27: Forest plot of SBP at five minutes.

Visual inspection of funnel plots revealed no obvious asymmetry (Figure 5.28). Indeed, Egger's linear regression test was not statistically significant (p=0.43). Therefore, no sensitivity analyses for publication bias were undertaken. On meta-regression analysis, neither dose (p=0.30) nor baseline SBP (p=0.81) predicted the effects of gabapentin on SBP.

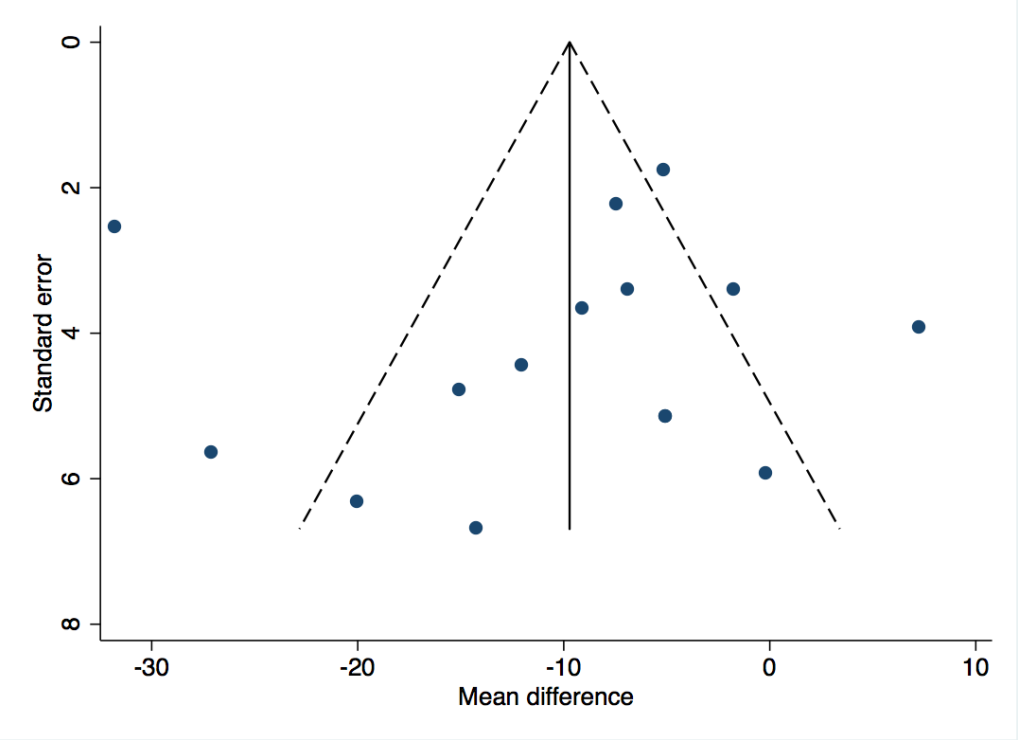


Figure 5.28: Funnel plot of SBP at five minutes. X-axis shows the MD and the Y-axis shows the standard error of the MD.

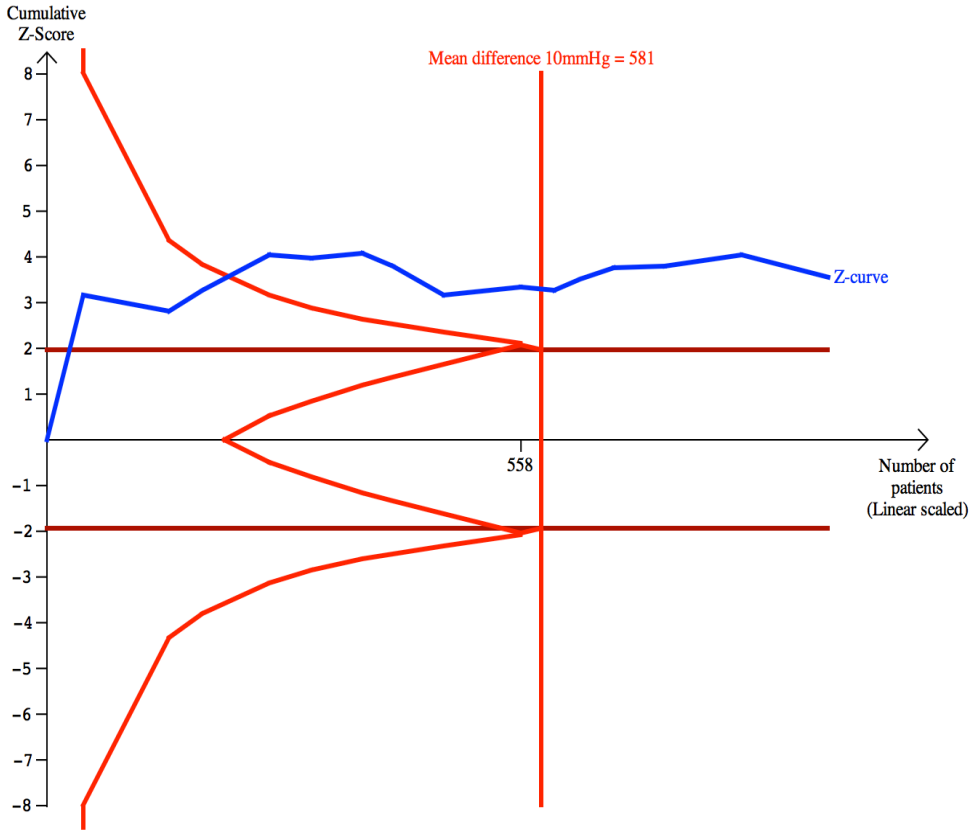


Figure 5.29: Trial sequential analysis of SBP at five minutes. Performed assuming a MD of 10mmHg, a variance of 181, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 90. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.29). In addition, gabapentin reached the required IS for a definitive answer (581 participants). On sensitivity analysis, assuming a variance of 300 increased the IS to 969 participants.

5.3.13 SBP 10 minutes

Overall, 13 studies with 855 participants were included in the analysis. Although gabapentin attenuated the SBP response 10 minutes following intubation (MD -8.78mmHg; 95% CI -15.63mmHg to -1.92mmHg; Figure 5.30), this was not clinically significant. However, the CI could not exclude a clinically significant result. There was evidence of considerable statistical heterogeneity (I^2=94%; p<0.001). The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

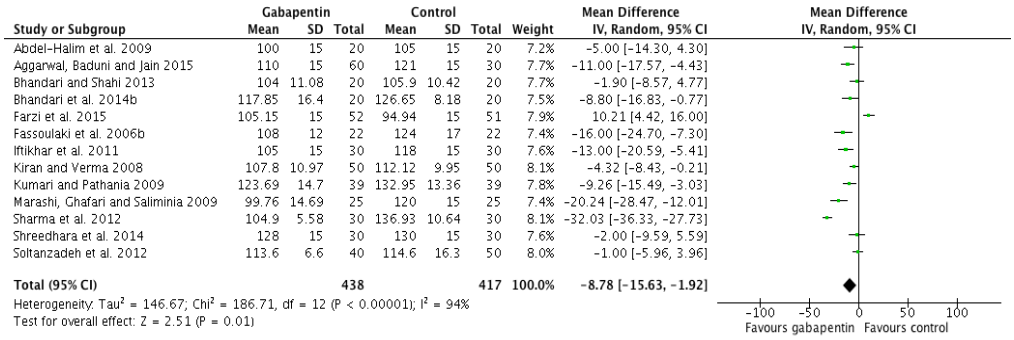


Figure 5.30: Forest plot of SBP at 10 minutes.

Visual inspection of funnel plots revealed no obvious asymmetry (Figure 5.31). Indeed, Egger's linear regression test was not statistically significant (p=0.30). Therefore, further analyses for publication bias were not undertaken. On meta-regression analysis, neither gabapentin dose (p=0.42) nor baseline SBP (p=0.92) predicted the efficacy of gabapentin.

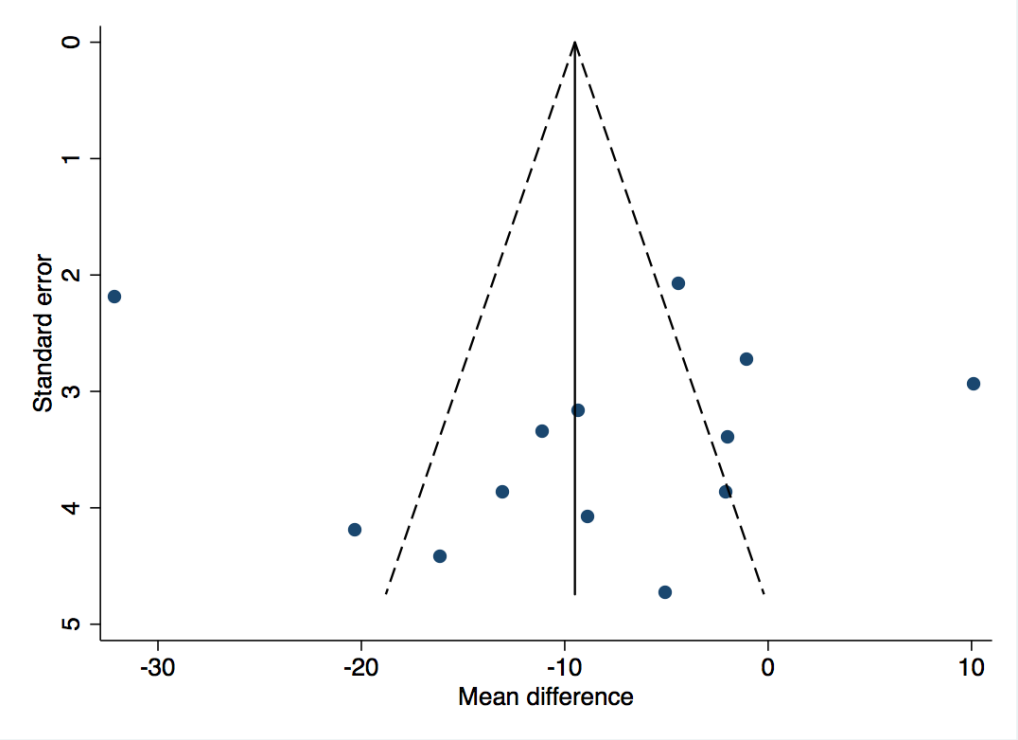


Figure 5.31: Funnel plot of SBP at 10 minutes. X-axis shows the MD and the Y-axis shows the standard error of the MD.

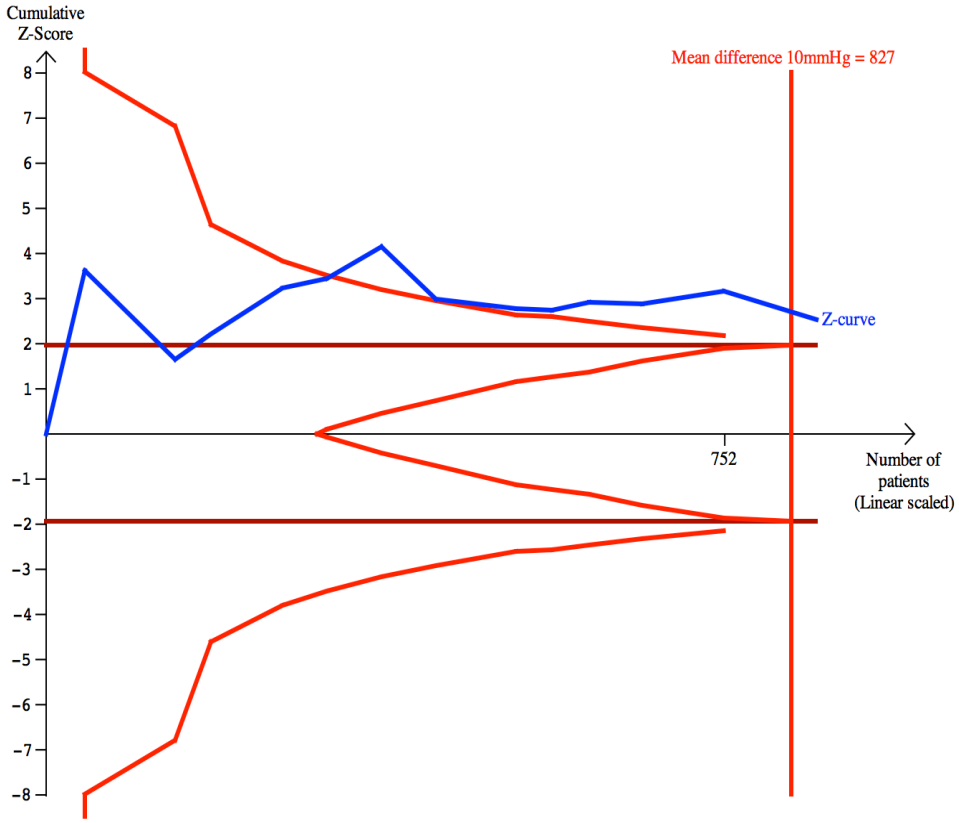


Figure 5.32: Trial sequential analysis of SBP at 10 minutes. Performed assuming a MD of 10mmHg, a variance of 161, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 94. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.32). In addition, gabapentin reached the required IS for a definitive answer (827 participants). On sensitivity analysis, similar results were obtained with an empirical MD of -8.78mmHg although gabapentin did not reach the required IS (1070 participants). Assuming a variance of 300 increased the required IS (1540 participants).

5.3.14 DBP one minute

Overall, 14 studies with 892 participants were included in the analysis. Gabapentin produced a clinically significant attenuation of the DBP response one minute after intubation (MD -11.26mmHg; 95% CI -15.46mmHg to -7.07mmHg; Figure 5.33). There was evidence of considerable statistical heterogeneity (I^2=84%; p<0.001). The level of evidence was regarded as low quality according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

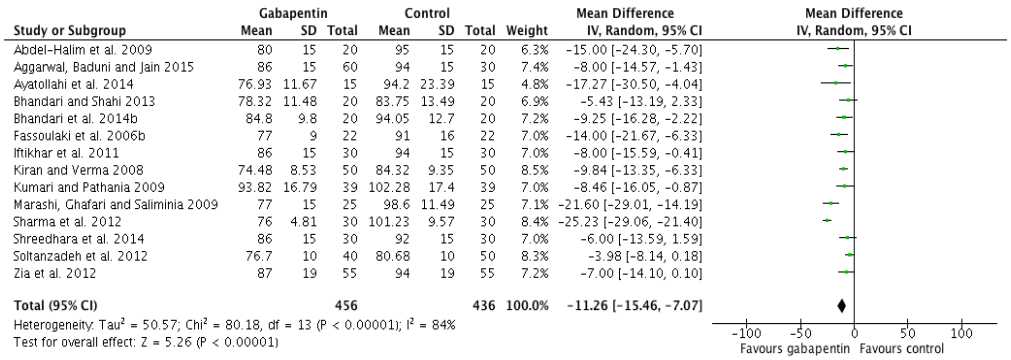


Figure 5.33: Forest plot of DBP at one minute.

Visual inspection of funnel plots revealed no obvious asymmetry (Figure 5.34). Indeed, Egger's linear regression test was not statistically significant (p=0.32). Therefore, no sensitivity analyses of publication bias were undertaken. On meta-regression analysis, neither gabapentin dose (p=0.97) nor baseline DBP (p=0.58) predicted the efficacy of gabapentin.

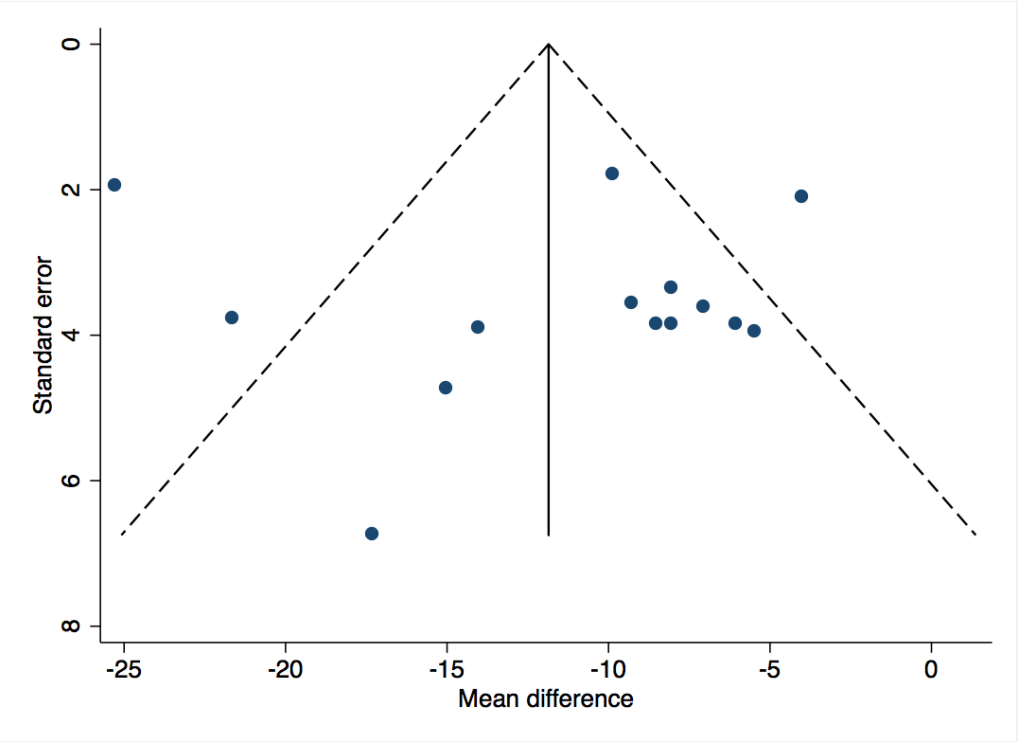


Figure 5.34: Funnel plot of DBP at one minute. X-axis shows the MD and the Y-axis shows the standard error of the MD.

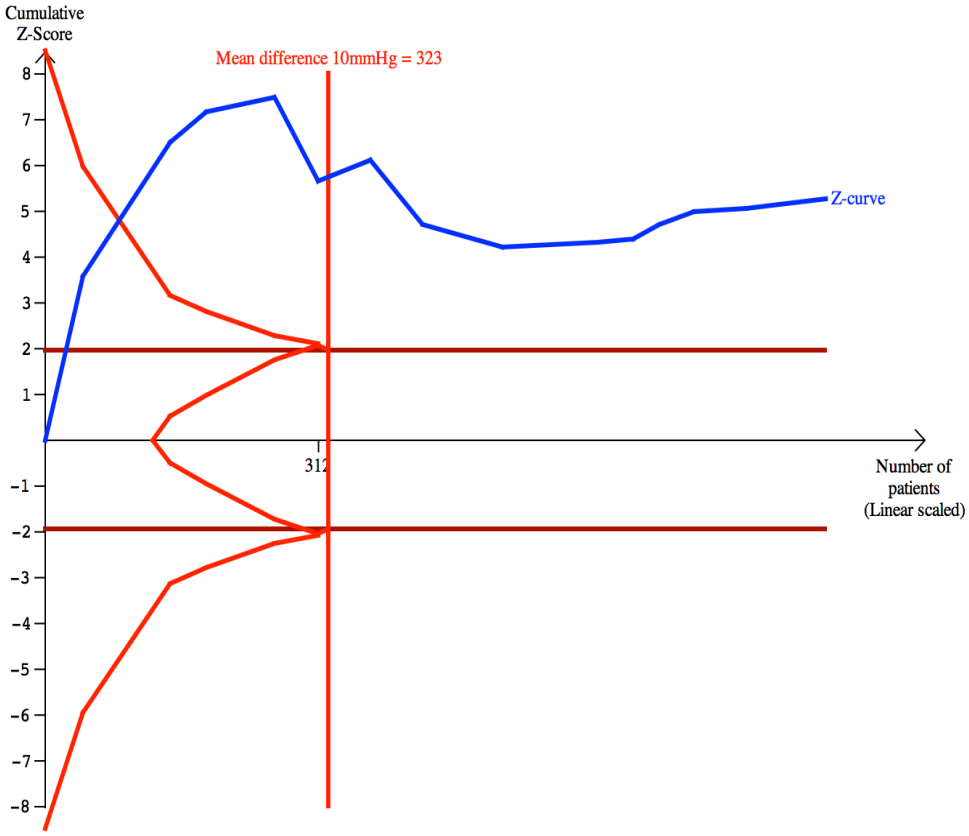


Figure 5.35: Trial sequential analysis of DBP at one minute. Performed assuming a MD of 10mmHg, a variance of 148, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 85. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.35). In addition, the results for gabapentin reached the required IS for a definitive answer (323 participants). On sensitivity analysis, assuming an empirical MD of -11.26mmHg did not change results (IS 254 participants). Assuming a variance of 300 increased the required IS (654 participants).

5.3.15 DBP five minutes

Overall, 14 studies with 885 participants were included in the analysis. Gabapentin attenuated the DBP response five minutes following intubation (MD -7.40mmHg; 95% CI -10.90mmHg to -3.89mmHg; Figure 5.36). However, this result was not clinically significant. There was evidence of considerable statistical heterogeneity (I^2=79%; p<0.001). The level of evidence was low quality according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

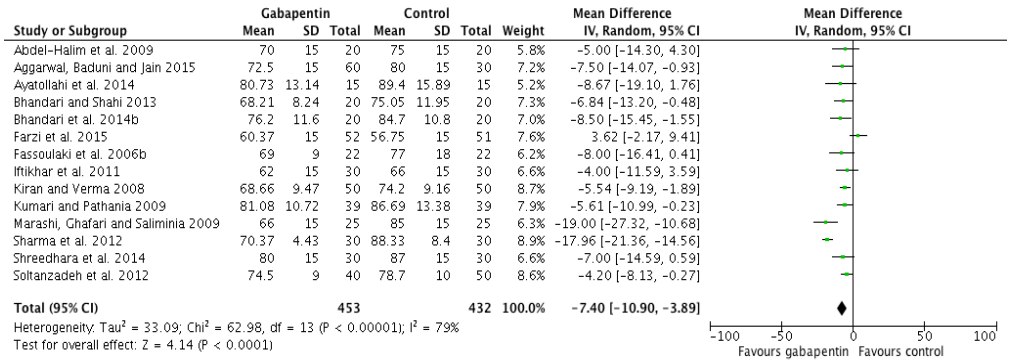


Figure 5.36: Forest plot of DBP at five minutes.

Visual inspection of funnel plots revealed no obvious asymmetry (Figure 5.37). Indeed, Egger's linear regression test was not statistically significant (p=0.24). Therefore, no sensitivity analyses for publication bias were undertaken. On meta-regression analysis, neither gabapentin dose (p=0.79) nor baseline DBP (p=0.98) predicted the efficacy of gabapentin.

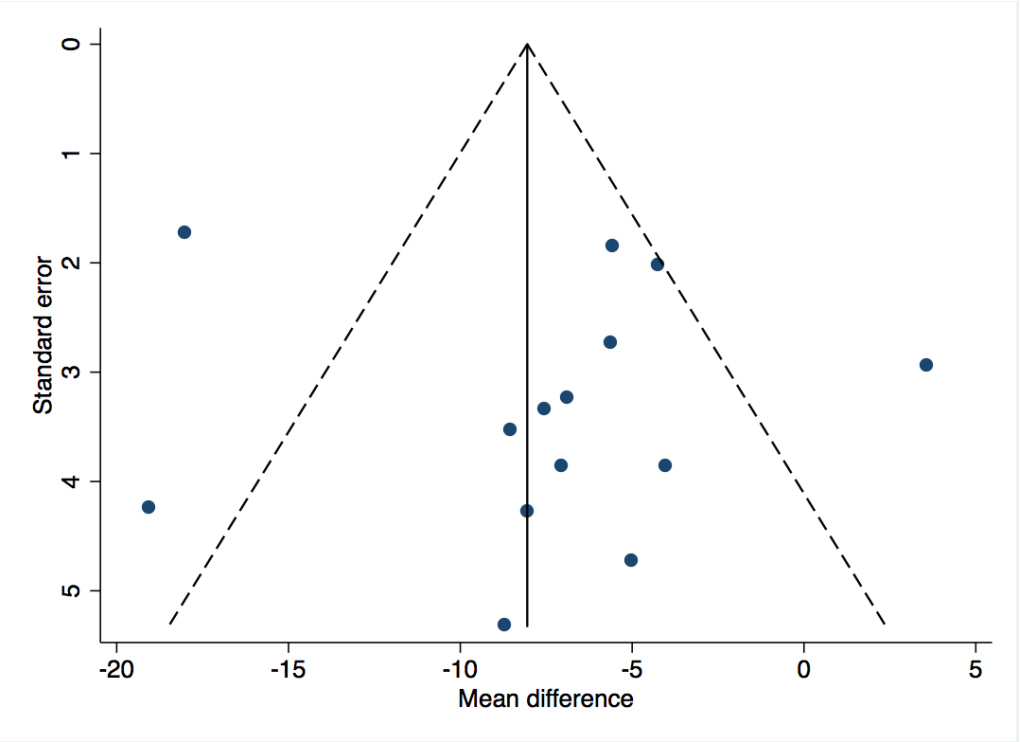


Figure 5.37: Funnel plot of DBP at five minutes. X-axis shows the MD and the Y-axis shows the standard error of the MD.

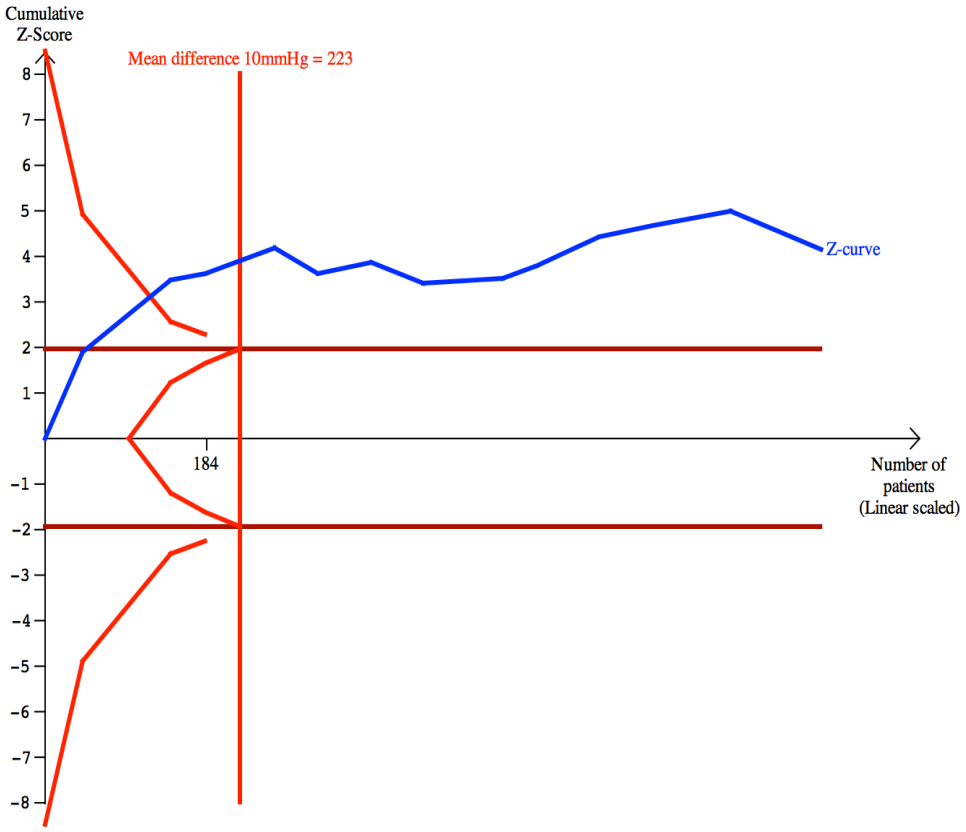


Figure 5.38: Trial sequential analysis of DBP at five minutes. Performed assuming a MD of 10mmHg, a variance of 130, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 82. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.38). In addition, gabapentin results reached the required IS for a definitive answer (223 participants). On sensitivity analysis, assuming an empirical MD of -7.4mmHg did not change results (IS 408 participants). Assuming a variance of 250 increased the IS (430 participants), which the results for gabapentin reached.

5.3.16 DBP 10 minutes

Overall, 13 studies with 855 participants were included in the analysis. Gabapentin attenuated the DBP response 10 minutes following intubation (MD -6.37mmHg; 95% CI -10.29mmHg to -2.45mmHg; Figure 5.39). However, this result was not clinically significant. There was evidence of considerable statistical heterogeneity (I^2=89%; p<0.001). The quality of evidence was low according to GRADE (downgraded owing to concerns over risk of bias and unexplained heterogeneity).

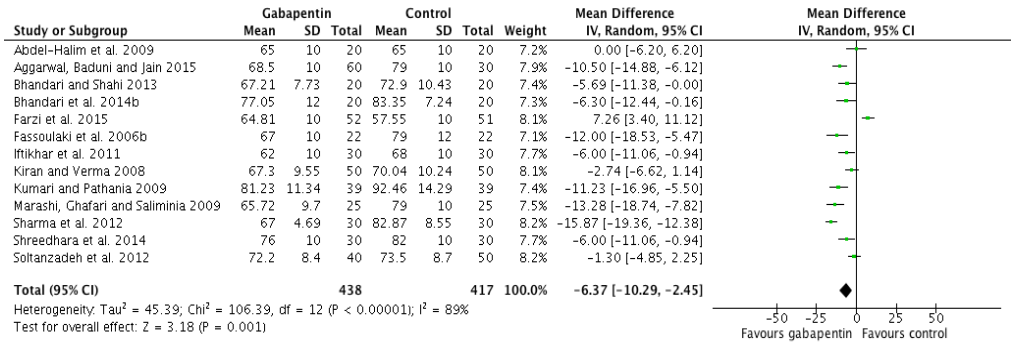


Figure 5.39: Forest plot of DBP at 10 minutes.

Visual inspection of funnel plots revealed no obvious asymmetry (Figure 5.40). Indeed, Egger's linear regression test was not statistically significant (p=0.30). Therefore, further sensitivity analyses for publication bias were not undertaken. On meta-regression analysis, neither gabapentin dose (p=0.24) nor baseline DBP (p=0.80) predicted the efficacy of gabapentin.

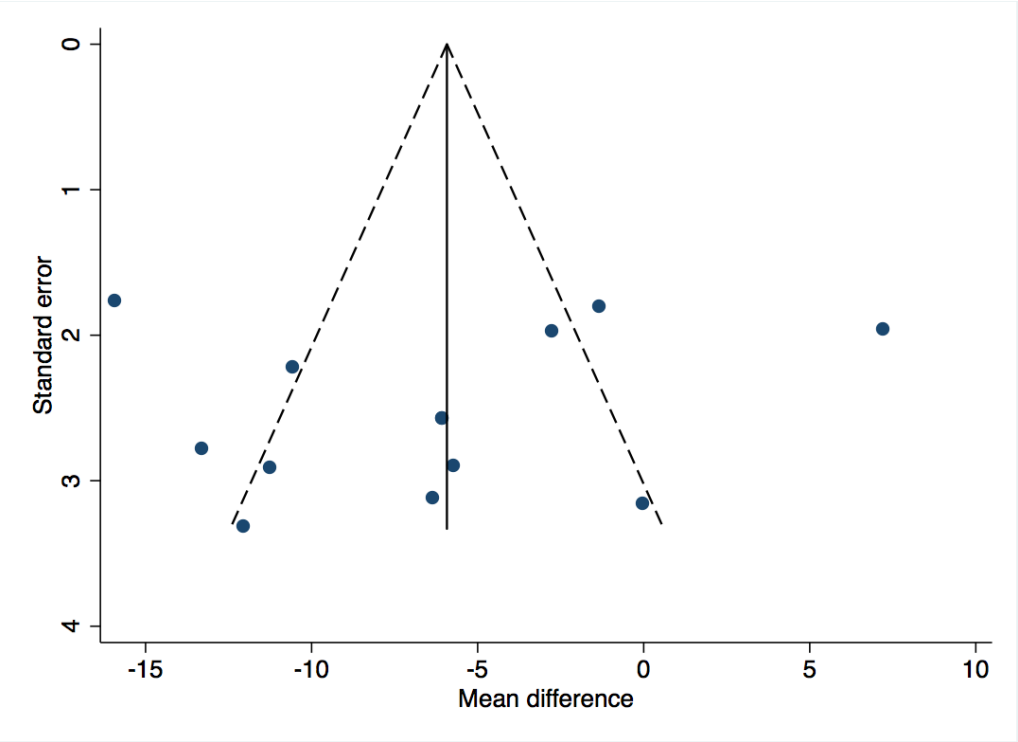


Figure 5.40: Funnel plot of DBP at 10 minutes. X-axis shows the MD and the Y-axis shows the standard error of the MD.

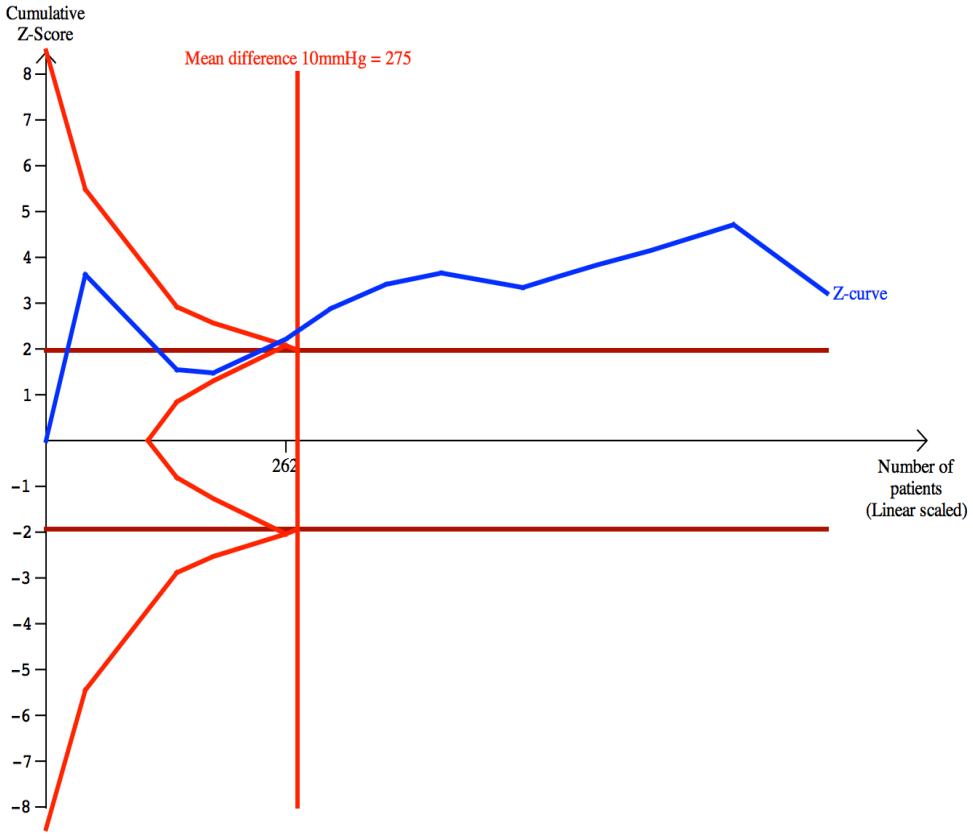


Figure 5.41: Trial sequential analysis of DBP at 10 minutes. Performed assuming a MD of 10mmHg, a variance of 93, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 89. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis showed that gabapentin crossed the O'Brien-Fleming boundary for benefit (Figure 5.41). In addition, gabapentin reached the required IS for a definitive answer (275 participants). On sensitivity analysis, using an empirical MD of -6.37mmHg increased the IS, which gabapentin reached (669 participants). Assuming a variance 180 also increased the IS (522 participants).

5.3.17 Catecholamines

Only one study reported serum catecholamine concentrations following intubation (Ali *et al.* 2009). Gabapentin resulted in a lower secretion of adrenaline one minute following intubation (MD -5 pg/ml; 95% -9.43 pg/ml to -0.57 pg/ml). However, at the same time point, the secretion of noradrenaline was higher with gabapentin compared to control (MD 65 pg/ml; 95% CI 46.51 pg/ml to 83.49 pg/ml).

5.3.18 Hypertension or tachycardia requiring treatment

Overall, five studies with 339 participants were included in the analysis. Gabapentin reduced the risk of patients requiring treatment for hypertension or tachycardia (RR 0.15; 95% CI 0.05 to 0.48; Figure 5.42). There was no evidence of statistical heterogeneity (I^2=0%; p=0.80). The level of evidence was moderate quality according to GRADE (downgraded owing to concerns over risk of bias). Due to the low number of studies, tests for publication bias were not undertaken. Definitions for this outcome were as follows; SBP >200mmHg or >30% increase from baseline for more than 60 seconds (Ali *et al.* 2009; Memis *et al.* 2006); HR >130bpm, SBP >200mmHg or >30% increase from baseline for more than 60 seconds (Bala, Bharti and Ramesh 2015); MAP or HR >20% of baseline (Bharti *et al.* 2013); MAP >110mmHg (Neogi *et al.* 2012).

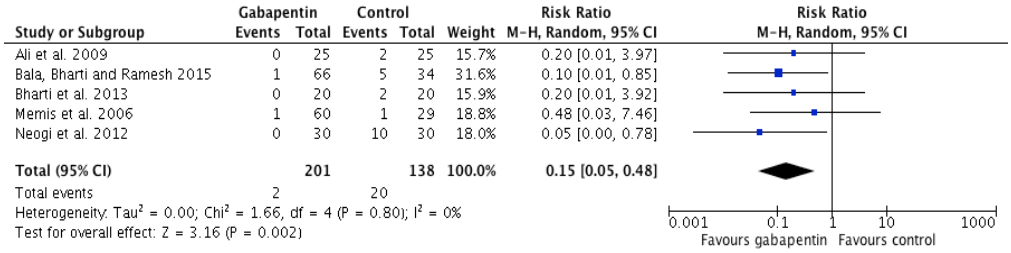


Figure 5.42: Forest plot of the risk of hypertension or tachycardia requiring treatment.

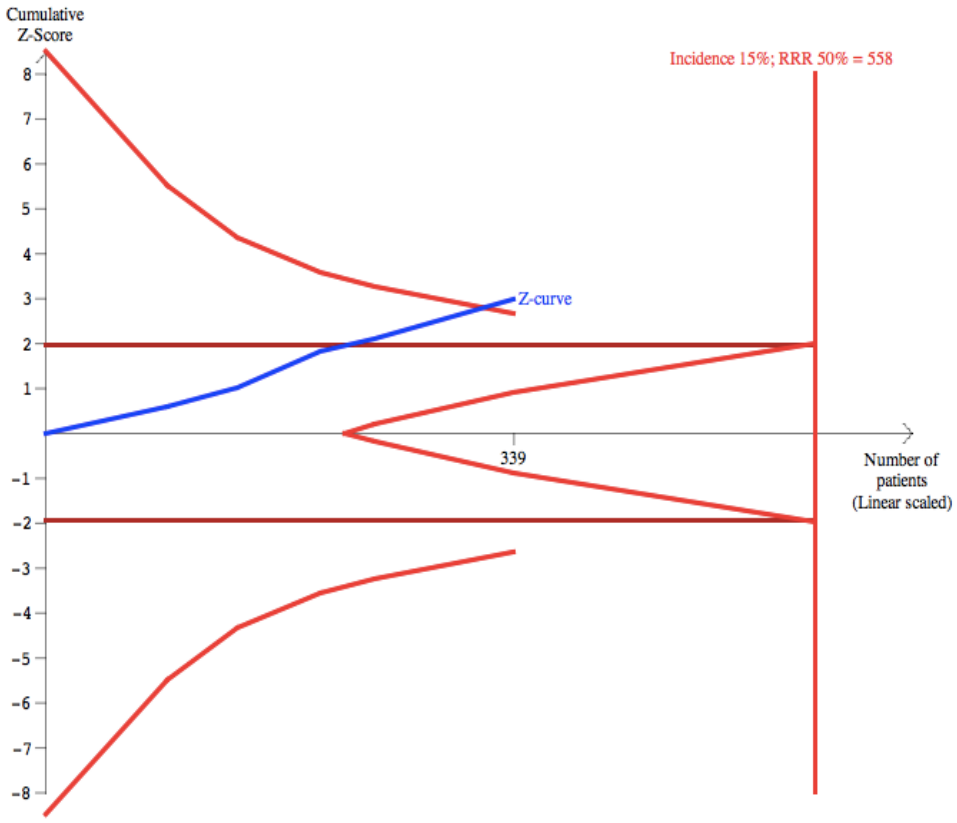


Figure 5.43: Trial sequential analysis of hypertension or tachycardia requiring treatment. Performed assuming an incidence of 15%, a RRR of 50%, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

Trial sequential analysis could not be performed for RRR of 20% due to too little information. Therefore, it was conducted assuming a RRR of 50% (Figure 5.43). Gabapentin crossed the O'Brien-Fleming boundary for benefit. However, it did not reach the required IS for a definitive answer (558 participants). On sensitivity analysis, assuming an incidence of 10% meant gabapentin did not cross the boundary for benefit and did not reach the required IS (872 participants). Assuming a heterogeneity correction of 25 increased the required IS (744 participants).

5.3.19 Hypotension requiring treatment

Only one study reported this outcome (Bala, Bharti and Ramesh 2015). There was an increase in the risk of hypotension with gabapentin (SBP <90mmHg or >30% from baseline lasting more than 60 seconds), although the CI overlapped the null result and would therefore be regarded as not statistically significant (RR 2.40; 95% CI 0.74 to 7.79).

5.3.20 Bradycardia requiring treatment

Only one study reported this outcome (Fassoulaki *et al.* 2006). There was no increase in the risk of bradycardia (HR<40bpm) with gabapentin although the CI suggested a possible increase in risk (RR 3.00; 95% CI 0.13 to 69.87).

5.3.21 Sensitivity analysis

Including only studies at low risk of bias left only two studies (Koc, Memis and Sut 2009; Parida *et al.* 2015), which resulted in no significant reductions for many outcomes. Excluding studies where standard deviations were estimated did not significantly affect results. One study-removed sensitivity analysis showed there were no influential studies in any of the analyses.

5.4 Discussion

5.4.1 Summary of results

This chapter found that no studies evaluated the use of gabapentin in high-risk patients undergoing surgery and consequently reported no incidences of any of the primary, clinically relevant outcomes. Despite this, gabapentin produced clinically significant attenuation in the rises in MAP, HR, SBP and DBP when compared to the control group (moderate to low quality evidence). In addition, gabapentin reduced the proportion of patients requiring treatment for hypertension or tachycardia. Following intubation, one study found gabapentin reduced circulating levels of adrenaline and increased noradrenaline. Adverse haemodynamic effects such as hypotension and bradycardia were rarely reported and data remains thus far limited, although confidence intervals suggest a possible increase. Increasing gabapentin dosages led to greater attenuation of HR responses on meta-regression analysis.

5.4.2 Links with previous research

The haemodynamic response to intubation involves a stress response, which causes increases in catecholamine levels and subsequent increases in HR and blood pressure (Kovac 1996). In high-risk patients, such increases can lead to myocardial ischaemia and therefore myocardial infarction (Kovac 1996; Roy, Edelist and Gilbert 1979; Sloghoff and Keats 1985). In such patients, myocardial infarction occurs in around 5% and stroke in 0.5% (POISE Study Group 2008). Many agents have been used to attenuate the haemodynamic response to intubation and thus aim to reduce myocardial ischaemia (Khan and Ullah 2013). Although agents such as clonidine (Wijeysundera, Naik and Beattie 2003) and beta-blockers have shown promise in reducing peri-operative cardiac events, the large randomised controlled POISE studies showed an increase in mortality and stroke with peri-operative beta-blocker therapy (POISE Study Group 2008) and increases in clinically important hypotension and non-fatal cardiac arrest with clonidine (Devereaux *et al.* 2014). Therefore, the search continues for effective agents that can reduce peri-operative

myocardial events in high-risk patients without increasing adverse events such as hypotension and bradycardia and therefore all-cause mortality.

Although peri-operative events such as intubation, extubation, surgery and pain can all contribute to increasing myocardial demand (Devereaux *et al.* 2005), our review only focused on the brief haemodynamic response following intubation and therefore caution is advised in extrapolating these results with any direct link with longer-term adverse cardiac events during the peri-operative period, such as those studied in POISE. Despite this, gabapentin is known to reduce postoperative pain, attenuate the hemodynamic response to intubation and reduce catecholamine and cortisol responses postoperatively (Karbic *et al.* 2014). Therefore it may have longer-term effects on reducing myocardial demand in the postoperative period, which should be the focus of future studies.

As observed in chapter two, gabapentin has proven efficacy as a peri-operative analgesic with reductions in pain scores and opioid consumption in various types of surgery. Other beneficial effects include reductions in pre-operative anxiety, vomiting, pruritus at the expense of increased sedation. Interestingly, these trials provide the only evidence of the possible haemodynamic effects of gabapentin in high-risk patients. In chapter two, when observing studies within these postoperative pain trials that included participants undergoing cardiothoracic surgery (which included high risk cardiac patients), the results suggested a reduction in postoperative arrhythmia with gabapentin (RR 0.55; 95% CI 0.28 to 1.08).

Our review suggests gabapentin may also be an effective agent in reducing the haemodynamic response to intubation. We found only one study that suggested this might be mediated by reductions in adrenaline when compared to control (Ali *et al.* 2009). Previous *in vitro* research has suggested that gabapentin may inhibit the release of catecholamines from adrenal chromaffin cells (Todd *et al.* 2012), which may confirm this as a possible mechanism of action. Furthermore, a recent RCT has demonstrated that pre-operative gabapentin can reduce postoperative catecholamine (both adrenaline and noradrenaline) and

cortisol concentrations in women undergoing hysterectomy (Karbic *et al.* 2014). However, the magnitude of difference between the groups in our review was around 8%, which may be regarded as clinically small. Another potential mechanism may relate to calcium channel inhibition. As calcium channel blockers can attenuate the haemodynamic response to intubation and share a target mechanism with gabapentin, this may produce similar effects in a clinical population (Cheng and Chiou 2006).

On meta-regression analysis, we found that gabapentin dose influenced the attenuation of HR responses, with higher doses producing lower heart rates when compared with the control group. Our previous meta-regression has shown a similar effect when evaluating morphine reductions during the postoperative period. However, baseline haemodynamic variables recorded before induction did not influence our results. This suggests that similar differences would be achieved regardless of the baseline blood pressure or HR of the participants. Despite this, it should be noted that most of the included studies included low risk, non-hypertensive patients and therefore the range of baseline values was limited. These meta-regression results, suggest future studies should aim to use higher doses in order to improve the absolute effects of gabapentin on HR responses. However, the oral route of gabapentin used in the included studies has implications for its use in high-risk patients, which may be prohibitive in emergency surgery. In addition, it is unclear whether titration of gabapentin dose would alter efficacy, an issue raised in the first POISE study. Moreover, it is unclear whether such increases in dose would affect the incidence of bradycardia and hypotension, which may have been responsible for the increased mortality in POISE. With regards to the pharmacokinetics of gabapentin, bioavailability is known to decrease with increasing dosages, therefore plasma concentrations may not reflect the dose administered (Stewart *et al.* 1993).

Gabapentin was found to reduce the risk of hypertension or tachycardia that required treatment. This result is intuitive given the observed effects of gabapentin on HR and blood pressure. However, data from the studies included in this chapter are limited with regards to episodes of bradycardia or

hypotension, with wide CIs suggesting a possible increase in risk. Indeed, one study in the review excluded three patients from the analysis due to hypotension (Soltanzadeh *et al.* 2012) and one study excluded a patient for an episode of bradycardia (Fassoulaki *et al.* 2006). The former was not included in the meta-analysis, as it did not report whether these patients required treatment. As intra-operative hypotension may be associated with stroke (Ng, Chan and Gelb 2011), myocardial injury, acute kidney injury (Walsh *et al.* 2013) and mortality (Bijker *et al.* 2009), future studies with gabapentin should aim to report these adverse outcomes. Although previous research in rats has shown no reductions in baseline haemodynamic variables with gabapentin administration (Yoon and Choi 2003), such effects are unknown in peri-operative clinical practice.

5.4.3 Limitations

There are several limitations with this chapter. Firstly, we were unable to provide any results for the primary outcomes owing to the inclusion of low risk patients resulting in zero incidences of these events or these outcomes not being evaluated in the included studies. Secondly, as previously discussed, there is limited evidence with regards to adverse events such as hypotension and bradycardia, which have the potential to cause fatal peri-operative events. The CI in our review suggested a possible increase and this warrants further study. Thirdly, many studies were at potential risk of bias, particularly for allocation concealment, which may bias the results of this review (Schulz and Grimes 2002a). Indeed, only two studies included in the review were deemed to be at low risk of bias for most domains, which limited the quality of the evidence. Although we found evidence of possible publication bias, this was at the expense of gabapentin, meaning effect estimates would more likely be underestimated should the assumption of a symmetric funnel plot hold.

In addition to these issues with internal validity, many of the studies included in the review were conducted in non-G7 countries and therefore it is unclear how applicable our results are to North American and Western European populations. Very few of the included studies provided details of the

equipment used to obtain non-invasive blood pressure measurements. As values from oscillometric methods are algorithmically derived, these may vary between devices, which may introduce heterogeneity into our results. Also, this lack of information meant evaluating whether such devices are valid, precise and accurate was problematic. As the majority of the included studies measured blood pressure at discrete time-points, important hypotensive or hypertensive episodes may have been missed, as such discrete measurements may not reflect the average values occurring between such measurements.

5.4.4 Conclusions

In conclusion, this review has found evidence that gabapentin reduces HR and blood pressure responses to intubation, which may be dose-dependent in relation to HR. However, data is limited with regards to adverse haemodynamic events and clinically relevant outcomes in high-risk patients. Therefore, future studies are required that recruit many more participants, are conducted with higher standards of internal validity while including high risk patients and measuring clinically-relevant outcomes such as myocardial ischaemia, infarction and mortality.

Chapter 6

Meta-regression analysis of other multimodal analgesic adjuncts

6.1 Introduction

Meta-analyses have emerged as a useful method to summarise research findings and increase the statistical power of primary research studies. However, one of the major limitations of this form of analysis is the aggregation of trials conducted in both different populations and in different clinical circumstances. This is termed clinical heterogeneity. Such clinical heterogeneity, along with other methodological disparities, may give rise to statistical heterogeneity (Higgins and Thompson 2002). For example, if all studies within a meta-analysis were assessing the same agent from the same population, we would expect confidence intervals to overlap, as the only differences between studies would be due to sampling variance from the population. However, when clinical heterogeneity or methodological disparities occur, this can cause confidence intervals to vary by more than would be expected by chance, which can be quantified using measures such as the I^2 statistic (Higgins and Thompson 2002).

Unexplained statistical heterogeneity can increase the uncertainty surrounding effect estimates derived from meta-analyses and reduce the quality of evidence used to inform healthcare decisions (Guyatt *et al.* 2008). In addition, in the presence of statistical heterogeneity, effect estimates may be inaccurate and lead to erroneous conclusions on the clinical significance of a particular agent. Therefore, investigating the causes for heterogeneity is essential using techniques such as meta-regression analysis (Thompson and Higgins 2002). Baseline risk is a particular covariate that can help predict between-study heterogeneity in meta-analyses. However, conventional meta-regression analysis may be limited by bias caused by measurement error in the covariate and regression to the mean (Sharp, Thompson and Altman 1996; Sharp and Thompson 2000). Therefore, alternative analyses such as Bayesian meta-regression are recommended (Achana *et al.* 2013).

Heterogeneity is a particular problem in meta-analyses of analgesics used to prevent postoperative pain (Espitalier *et al*. 2013). Indeed, a previous review has suggested that type of surgery should be explored in these reviews

(Espitalier *et al*. 2013). However, even within the same type of surgical procedure, pain levels can be heterogeneous. In addition, differing analgesic protocols can further confound the association between type of surgery and the efficacy of the analgesic under study. Previous primary research has shown that the pain level experienced by a participant determines analgesic efficacy, with higher pain levels resulting in higher absolute pain score reductions following analgesic administration (Averbuch and Katzper 2003; Bjune *et al.* 1996). We have previously demonstrated that using control group morphine consumption (baseline risk), we were able to predict a large degree of between-study heterogeneity for 24-hour morphine consumption (Doleman *et al*. 2015a; Doleman *et al.* 2015b).

This finding may have important clinical implications as meta-analyses are often used to inform clinical decision-making. However, any one finding from a meta-analysis of an analgesic adjunct may be confounded by the variable control group morphine consumption from the included trials. If control group morphine consumption is found to be a significant predictor of between-study heterogeneity, quoting regression parameter estimates from a fixed value of morphine consumption would allow more accurate comparisons between analgesics and help better inform clinical decision-making. In addition, explaining heterogeneity could improve the quality of systematic review evidence as per GRADE (Guyatt *et al*. 2008). With regards to clinical practice and RCT conduct, more targeted use of analgesic adjuncts in situations where expected postoperative morphine consumption is high would help improve their clinical significance and may help further reduce opioid adverse effects.

Therefore, the aims of this chapter were as follows: 1) to perform a meta-epidemiological study of methods for investigating heterogeneity in reviews and methodological conduct in RCTs of analgesic adjuncts 2) to identify the prevalence of considerable statistical heterogeneity 3) investigate heterogeneity using control group consumption and other clinical and methodological covariates 4) utilise these principles to construct a league table of analgesic adjuncts assuming a fixed consumption of postoperative morphine to more accurately report efficacy.

6.2 Methods

6.2.1 Search strategy, reporting standards and registration

We reported this chapter in accordance with the PRISMA checklist (Moher *et al.* 2009). We prospectively registered the review on the PROSPERO website using the registration number CRD42016039109. The aim of the study search was to identify previous reviews of postoperative analgesic agents and perform a meta-epidemiological study of these with analyses of both the reviews themselves and through secondary analysis of the individual RCTs. We searched all databases from inception to May 2016: MEDLINE, EMBASE, CINAHL, AMED and the *Cochrane Database of Systematic Reviews*. We used the following search terms 'postoperative AND pain', 'surgery', 'analgesi*', 'morphine AND consumption', 'opioid AND consumption' and we exploded the MeSH term 'ACUTE PAIN'. We combined these terms with the specific generic term for the analgesic agent. We then limited our search to reviews and meta-analyses.

6.2.2 Data extraction

We extracted data onto an electronic database. If results were not reported in the original meta-analysis, we extracted data from the original publications. In order to reduce selective reporting bias, if standard deviations were not reported, we estimated these from other studies in the analysis (Higgins and Green 2008). We did not attempt to calculate means and standard deviations from medians or inter-quartile ranges due to the high likelihood of non-normal data (Higgins and Green 2008). If results were not reported in the text, these were estimated from published graphs. We extracted the following data: study author, type of agent, postoperative opioid used and data used to calculate effect estimates.

6.2.3 Inclusion criteria and outcomes

We had no language restrictions for inclusion in our review and we translated non-English language papers (Egger *et al.* 1997b). We included reviews that

included the following analgesic agents versus placebo for postoperative pain: paracetamol, non-steroidal anti-inflammatory drugs (NSAIDS) and cyclooxygenase (COX) 2 inhibitors, tramadol, intravenous ketamine, alpha-2 agonists (clonidine and dexmedetomidine), gabapentin, pregabalin, nefopam, lidocaine, magnesium and dexamethasone. We aimed to identify reviews of prophylactic administration (defined as first dose given before the onset of pain or agents added to postoperative analgesic regimens, such as PCA). We did not include reviews evaluating single dose analgesics for established postoperative pain or reviews in dental surgery as these are unlikely to report 24-hour morphine consumption.

The outcome of interest was 24-hour opioid consumption. We chose opioid consumption as this serves as a surrogate measure for both how painful the procedure was and any concurrent analgesia used. In addition, as participants within these trials can use variable amounts of morphine to achieve a desired level of comfort, it may be more appropriate than pain score data, which may be confounded by variable morphine use between the groups. We only included primary studies where we could extract morphine consumption data. If studies reported dosage per kilogram (kg), we converted this to a 70kg weight. We also used data from the day of surgery or postoperative day one and analysed this as 24-hour data. If alternative opioids were reported, these were converted to morphine equivalents using the following conversion factors: oral to intravenous morphine (3:1) (Takahashi *et al.* 2003), pethidine/meperidine (10:1) (Stanley *et al.* 1996), ketobemidone (1:1) (Jylli *et al.* 2004), tramadol (20:1) (Marcou *et al.* 2005), fentanyl (1:100) (Galinski *et al.* 2005), remifentanil (1:100) (Glass, Gan and Howell 1999), piritramide (1:0.75) (Kay 1971), hydromorphone (1:3) (Dunbar *et al.* 1996), oral hydrocodone (2:1), intravenous oxycodone (1:1.5) (Lenz *et al.* 2009), oral oxycodone (2.5:1), papaveretum (1.5:1) (Loan, Dundee and Clark 1966), meptazinol (5:1) (Siegel *et al.* 1989), nalbuphine (1:1) (Yeh *et al.* 2008), propoxyphene (10:1) (Fraser and Isbell 1960), sublingual buprenorphine (1:25) (Maunuksela, Korpela and Olkkola 1988) and trimeperidine (2:1).

6.2.4 Risk of bias

We undertook assessment of RCTs from included reviews using the Cochrane risk of bias tool. For blinding to receive low risk, studies had to describe in enough detail study drugs and placebos that were identical or similar in appearance rather than simply describe the study as 'double-blind' (Schultz and Grimes 2002b). Outcome assessment also needed to be blinded to receive low risk. Attrition bias would receive high risk if patients were excluded from the analysis for reasons that may influence opioid consumption, such as those with uncontrolled pain or potential opioid adverse effects. Studies only received low risk for selective outcome reporting if outcomes were pre-stated in a published protocol or trial registration referenced in the included study. Other bias included baseline characteristic imbalances, which have been associated with influencing pain (for example gender and pre-operative pain) (Kalkman *et al.* 2003) or industry sponsorship (Lexchin *et al*. 2003).

6.2.5 Statistical analysis

To quantify the degree of statistical heterogeneity we used the I^2 statistic, with values exceeding 75% as evidence of considerable heterogeneity and those exceeding 50% as evidence of moderate statistical heterogeneity (Higgins and Thompson 2002). For the available data, we calculated the mean difference (MD) in morphine consumption (mg) with 95% confidence intervals (CI) using a random-effects model. In order to identify whether control group morphine consumption could explain the between-study heterogeneity we undertook meta-regression analysis (Thompson and Higgins 2002). This analysis is similar to conventional regression analysis, although it involves using study-level covariates, such as the dose of the analgesic used in the trial as the predictor variable and the effect estimate as the outcome variable, with each study weighted for the precision of the results (lower standard errors having more weight).

We performed meta-regression initially using control group morphine consumption as a covariate based on previous findings (Doleman *et al.* 2015a;

Doleman 2015b). We also used the following clinical covariates: dose or route of drug administration, type of surgery and type of anaesthesia. For type of surgery, where possible, we aimed to include procedure-specific evidence, if this was not possible we grouped procedures by specialty or anatomical location. In addition, we assessed whether measures of internal validity were responsible for statistical heterogeneity including: randomisation, allocation concealment, blinding and attrition bias. Except for attrition bias, these covariates were only included in models if they exaggerated effect estimates. Control group morphine consumption was initially added to the model, we then added other covariates to a multivariate model to adjust regression estimates for these confounding variables, if they significantly improved the model, in a stepwise approach ($p<0.1$).

Due to the problems with analysing baseline risk using conventional meta-regression, we also undertook Bayesian meta-regression (performed by a statistician) using Markov Chain Monte Carlo with Gibbs sampling (Achana *et al.* 2013). We used vague prior distributions and burnt in the MCMC chains for 10,000 iterations and then used a sample of 50,000 iterations on which to base inferences. We checked convergence visually by looking at history plots of the sampled values. We present the results of regression parameters using the median estimate with 95% credible intervals (CrIs).

For conventional meta-regression, we used a restricted maximum likelihood, random-effects model. We also used the Knapp-Hartung method to estimate p values for each covariate. We assessed linearity and heteroscedasticity from predicted versus residual plots and residuals were assessed for normality using histograms. We assessed outliers from studentised residual values and leverage using Cook's distance (with values greater than one regarded as a cause for concern). We present results as the proportion of variation explained by the model (R^2 analogue) with a corresponding p value. We undertook sensitivity analysis removing studies that had significant leverage on the model. We regarded p values for final models <0.005 as statistically significant following Sidak adjustment for multiple comparisons.

If we identified control group morphine consumption as a significant predictor of between-study heterogeneity, we produced a league table of analgesic adjuncts based on a fixed control group consumption of 50mg. We regarded a difference of >20mg as a large clinically significant difference, >10mg a moderate clinically significant difference and >5mg of small clinical significance. We were unaware of any literature regarding clinically significant reductions in morphine consumption. Therefore, we selected these values based on two (20mg) and one (10mg) standard dose of morphine. This analysis allows comparison of analgesic adjuncts when adjusted for the variable control group morphine consumption from the included RCTs in order to reduce confounding. Where dose or route of administration was found to be a significant predictor, we included results from the most effective clinical situation and specified this where appropriate. We present both Bayesian parameter estimates and adjusted conventional estimates with 95% CIs/CrIs. We conducted all analyses using Comprehensive Meta-analysis Version 3, STATA Version 14 and WinBUGS Version 1.4.

6.3 Results

6.3.1 Characteristics of reviews and randomised controlled trials

We included 344 RCTs with 28,130 participants (Table 6.1). We identified these studies from eight narrative reviews (Baidya *et al.* 2011; Chang *et al.* 2014; De Kock and Lavand'homme 2007; Girard, Chauvin and Verleye 2016; Koh, Nguyen and Jahr 2015; Nossaman *et al.* 2010; Radvansky *et al.* 2015; Scott and Perry 2000), 25 systematic reviews (Andersen *et al.* 2014; Armand *et al.* 1998; Ben-Abraham 2001; Carstensen and Moller 2010; Chan, Cheung and Chong 2010; Choyce and Peng 2002; Clivatti, Sakata and Issy 2009; Dube and Granry 2003; Hyllested *et al.* 2002; Jebaraj *et al.* 2013; Jibril *et al.* 2015; Jouguelet-Lacoste *et al.* 2015; Macario and Royal 2011; Mathews *et al.* 2012; Mazzeffi, Johnson and Paciullo 2015; McCarthy and Megalla 2010; McCartney, Sinha and Katz 2004; Remerand *et al.* 2011; Romsing *et al.* 2004; Romsing *et al.* 2005; Schmid, Sandler and Katz 1999; Suzuki 2009; Wang *et al.* 2015; Zakkar, Fraser and Hunt 2013; Zemmel 2006) and 72 meta-analyses (Abdallah, Abrishami and Brull 2013; Achuthan *et al.* 2015; Afman, Welge and Steward 2006; Alayed *et al.* 2014; Albrecht *et al.* 2013; Apfel *et al.* 2003; Bai *et al.* 2015; Bainbridge *et al.* 2006; Bell *et al.* 2006; Blaudszun *et al.* 2012; De Oliveira *et al.* 2011; De Oliveira, Agarwal and Benzon 2012; De Oliveira *et al.* 2013; De Oliveira, Castro-Alves and McCarthy 2015; Doleman *et al.* 2015a; Doleman *et al.* 2015b; Eipe *et al.* 2015; Elia and Tramer 2005; Elia, Lysakowski and Tramer 2005; Elia *et al.* 2008; Engelman and Marsala 2013; Evans, Lysakowski and Tramer 2008; Gobble *et al.* 2014; Gurusamy, Vaughan and Toon 2014; Heesen *et al.* 2015; Ho, Gan and Habib 2006; Hurley *et al.* 2006; Hwang *et al.* 2016; Jessen, Korvenius and Moller 2016; Khan *et al.* 2016; Kranke *et al.* 2004; Kranke *et al.* 2015; Lam *et al.* 2015; Laskowski *et al.* 2011; Lin and Pei 2012; Liu *et al.* 2012; Lysakowski *et al.* 2007; Marret *et al.* 2005; Marret *et al.* 2008; Mathiesen, Moiniche and Dahl 2007; McDaid *et al.* 2010; McNicol *et al.* 2003; Mishriky, Waldron and Habib 2015; Murphy *et al.* 2013; Ong *et al.* 2010; Peng, Wijeysundera and Li 2007; Peng *et al.* 2014; Remy, Marret and Bonnet 2005; Martinez, Guichard and Fletcher 2015; Romsing, Moiniche and Dahl 2002; Savoia, Loreto and Scibelli 2000;

Schnabel *et al.* 2013; Seib and Paul 2006; Stephens *et al.* 2015; Stevens, Woodman and Owen 2015; Stomatology and Yan 2015; Straube *et al.* 2005; Subramaniam, Subramaniam and Steinbrook 2004; Sun *et al.* 2012; Tiippana *et al.* 2007; Villasis-Keever, Rendon-Macias and Escamilla 2009; Ventham *et al.* 2015; Vigneault *et al.* 2011; Waldron *et al.* 2013; Wei, Zhao and Li 2013; Wu *et al.* 2014; Wu, Huang and Sun 2015; Yang *et al.* 2014; Yao, Shen and Zhong 2015; Yu *et al.* 2013; Zhang, Ho and Wang 2011; Zhong *et al.* 2015) (Figure 6.1).

There was evidence of considerable heterogeneity is 91% of analyses (95% CI 74% to 100%). Of the included reviews that conducted a meta-analysis, 78% (95% CI 68% to 88%) investigated heterogeneity. In 75% (95% CI 65% to 85%), investigation of heterogeneity was conducted using subgroup/sensitivity analysis and only 18% (95% CI 9% to 27%) conducted meta-regression. In 32% (95% CI 21% to 43%) of meta-analyses, investigation of heterogeneity was based on type of surgery, 35% (95% CI 24% to 46%) used dose and 11% (95% CI 4% to 18%) used type of anaesthesia. In 31% (95% CI 20% to 42%) of meta-analyses, heterogeneity was investigated using methodological covariates. On risk of bias assessment of the individual RCTs, adequate randomisation was described in 58% (95% CI 53% to 63%) of studies, adequate allocation concealment in 29% (95% CI 24% to 34%), adequate blinding in 50% (95% CI 45% to 55%) and lack of attrition bias in 71% (95% CI 66% to 76%) (Figure 6.2 to 6.11 and Figure 2.2).

Table 6.1: Meta-regression estimates for each analgesic adjunct. Asterisk denotes statistical significance (p<0.1). CI=confidence interval; CrIs=credible intervals; N/A=not applicable; R^2=proportion of between-study variance explained by model; I^2=measure of variability in results due to between-study differences compared to sampling variance.

Analgesic	**Studies (participants)**	**I^2**	**R^2 control morphine (p value)**	**Intercept**	**Beta coefficient and (95% CIs)**	**Intercept**	**Bayesian beta coefficient (median) and (95% CrIs)**
Paracetamol	25 (1812)	99%	**R^2=79%; p<0.001**	0.84	-0.39 (-0.49 to -0.29)	0.77	-0.38 (-0.48 to -0.28)
NSAIDS and COX-2 inhibitors	86 (6937)	92%	**R^2=81%; p<0.001**	2.42	-0.35 (-0.41 to -0.30)	2.56	-0.36 (-0.41 to -0.30)
Tramadol	11 (889)	90%	**R^2=48%; p=0.03**	2.93	-0.30 (-0.56 to -0.05)	2.96	-0.30 (-0.55 to -0.03)
Ketamine	62 (4309)	95%	**R^2=29%; p<0.001**	-1.05	-0.18 (-0.25 to -0.10)	-1.01	-0.18 (-0.24 to -0.10)
Alpha-2 agonists	33 (1930)	96%	**R^2=66%; p<0.001**	-0.52	-0.34 (-0.47 to -0.21)		

						-0.95	-0.32 (-0.44 to -0.19)
Gabapentin	67 (5082)	97%	**R^2=92%; p<0.001**	1.12	-0.39 (-0.44 to -0.34)	1.11	-0.39 (-0.43 to -0.35)
Pregabalin	34 (3201)	94%	**R^2=58%; p<0.001**	-2.62	-0.21 (-0.30 to -0.12)	-2.91	-0.20 (-0.28 to -0.11)
Nefopam	5 (394)	38%	N/A	N/A	N/A	N/A	N/A
Lidocaine	22 (1319)	80%	**R^2=62%; p<0.001**	-0.25	-0.20 (-0.31 to -0.09)	-0.29	-0.20 (-0.30 to -0.08)
Magnesium	22 (1194)	90%	**R^2=15%; p=0.02**	-1.74	-0.17 (-0.31 to -0.03)	-1.35	-0.19 (-0.34 to -0.04)
Dexamethasone	16 (2163)	88%	**R^2=100%; p<0.001**	0.69	-0.19 (-0.23 to -0.14)	0.86	-0.18 (-0.24 to -0.12)

Table 6.2: League table of analgesic adjuncts assuming a 50mg consumption of morphine in the control group based on Bayesian parameter estimates. Random-effects mean difference, adjusted frequentist and Bayesian meta-regression parameter estimates are presented. For adjusted models, covariates are listed in parentheses. mg=milligrams; N/A=not applicable.

Analgesic adjunct	**Mean difference on meta-analysis**	**Reduction in 24-hour morphine (adjusted)**	**Reductions in 24-hour morphine (Bayesian; median with 95% CrIs)**
Gabapentin	-8.6mg (-9.73mg to -7.46mg)	-20.07mg (dose; 1200mg)	-18.49mg (-19.90mg to -17.07mg)
Paracetamol	-8.18mg (-10.57mg to -6.73mg)	-17.96mg (administration; intravenous and allocation)	-18.39mg (-21.54mg to -15.02mg)
Alpha-2 agonists	-10.7mg (-12.38mg to -9.01mg)	-18.39mg (administration; intravenous and attrition)	-16.94mg (-20.09mg to -13.57mg)
NSAIDS and COX-2 inhibitors	-11.09mg (-12.73mg to -9.45mg)	-15.31mg (none)	-15.20mg (-16.54mg to -13.81mg)
Pregabalin	-8.18mg (-9.6mg to -6.76mg)	-11.36mg (allocation)	-12.75mg (-15.23mg to -10.11mg)

Tramadol	-8.48mg (-11.88mg to -4.89mg)	-12.17mg (none)	-11.99mg (-16.21mg to -7.28mg)
Magnesium	-6.77mg (-8.39mg to -5.15mg)	-3.91mg (allocation)	-10.60mg (-14.19mg to -7.10mg)
Lidocaine	-5.04mg (-7.42mg to -2.66mg)	-9.15mg (administration; intravenous and attrition)	-10.09mg (-13.49mg to -6.36mg)
Ketamine	-8.13mg (-10.23mg to -6.03mg)	-7.75mg (allocation and blinding)	-9.76mg (-12.15mg to -7.33mg)
Dexamethasone	-4.23mg (-5.79mg to -2.67mg)	-5.18mg (type of surgery and blinding)	-8.07mg (-9.79mg to -6.04mg)
Nefopam	-14.75mg (-19.34mg to -10.17mg)	N/A	N/A

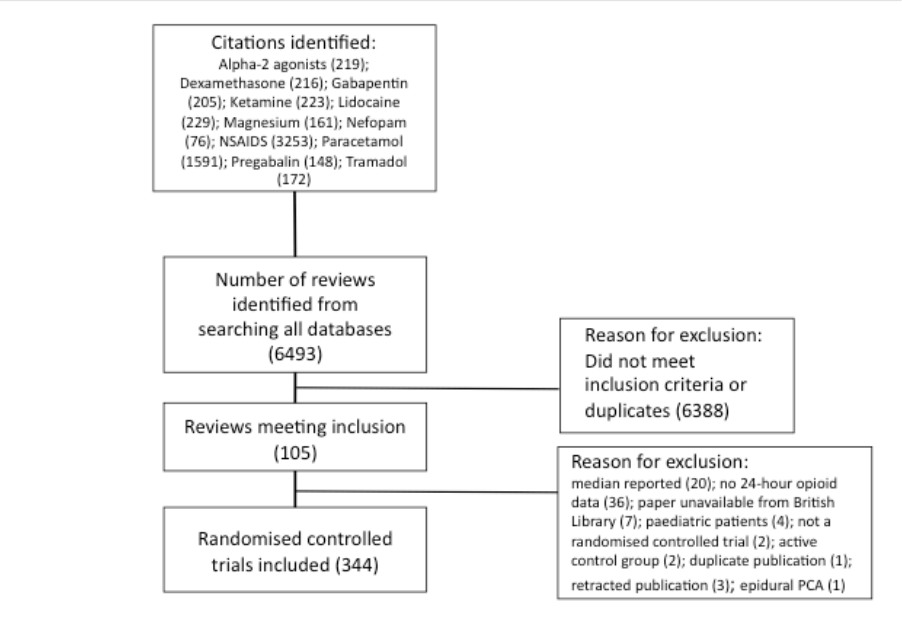


Figure 6.1: PRISMA flowchart for the included studies.

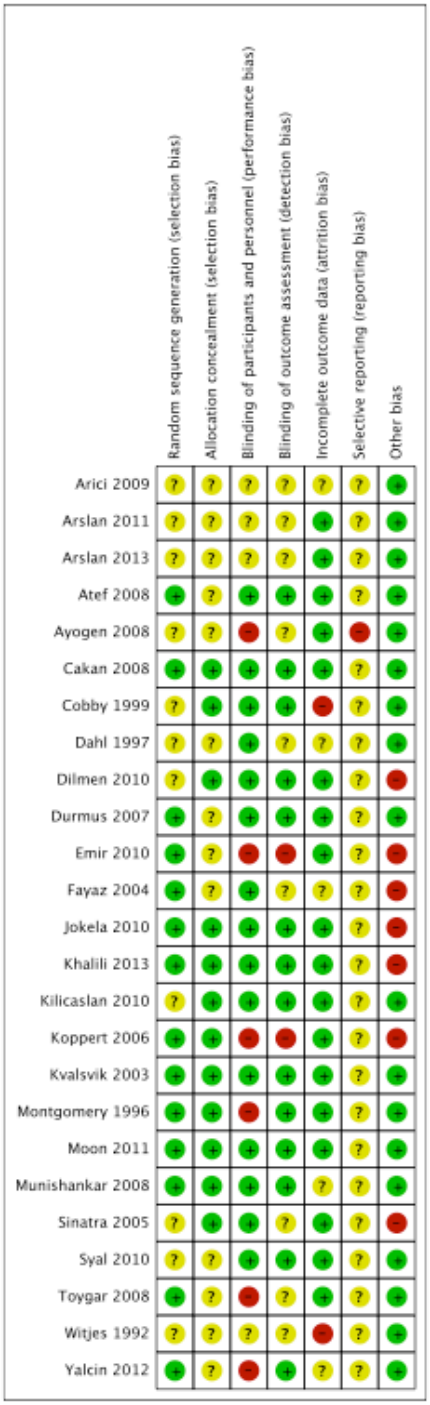
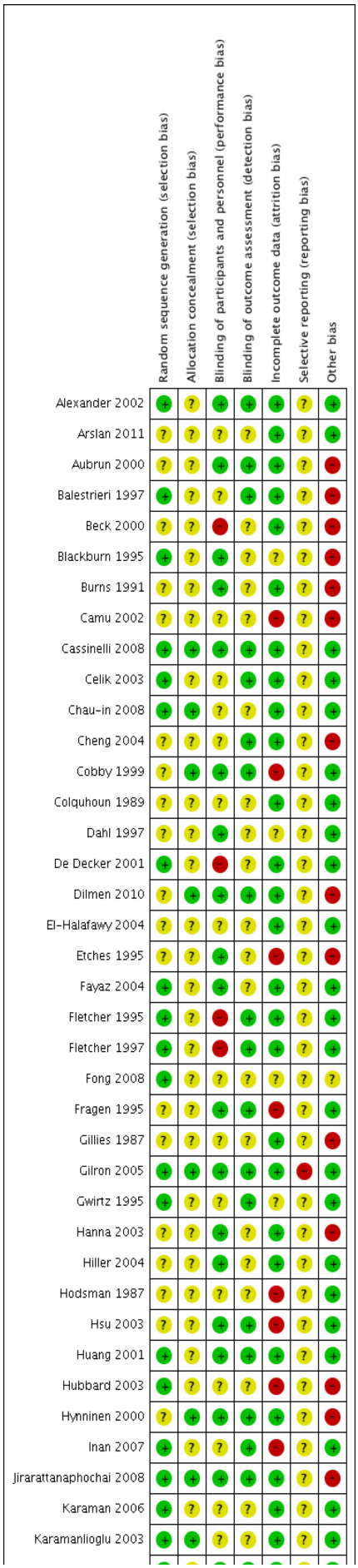


Figure 6.2: Risk of bias for paracetamol RCTs.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Alexander 2002
Arslan 2011
Aubrun 2000
Balestrieri 1997
Beck 2000
Blackburn 1995
Burns 1991
Camu 2002
Cassinelli 2008
Celik 2003
Chau-in 2008
Cheng 2004
Cobby 1999
Colquhoun 1989
Dahl 1997
De Decker 2001
Dilmen 2010
El-Halafawy 2004
Etches 1995
Fayaz 2004
Fletcher 1995
Fletcher 1997
Fong 2008
Fragen 1995
Gillies 1987
Gilron 2005
Gwirtz 1995
Hanna 2003
Hiller 2004
Hodsman 1987
Hsu 2003
Huang 2001
Hubbard 2003
Hynninen 2000
Inan 2007
Jirarattanaphochai 2008
Karaman 2006
Karamanlioglu 2003

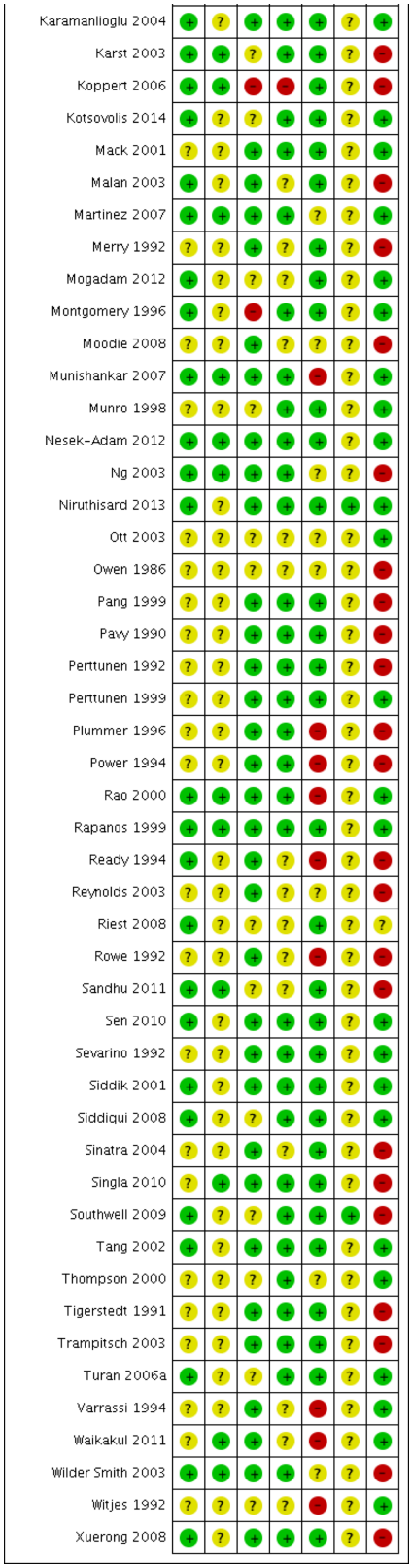


Figure 6.3: Risk of bias for NSAIDS and COX-2 inhibitors RCTs.

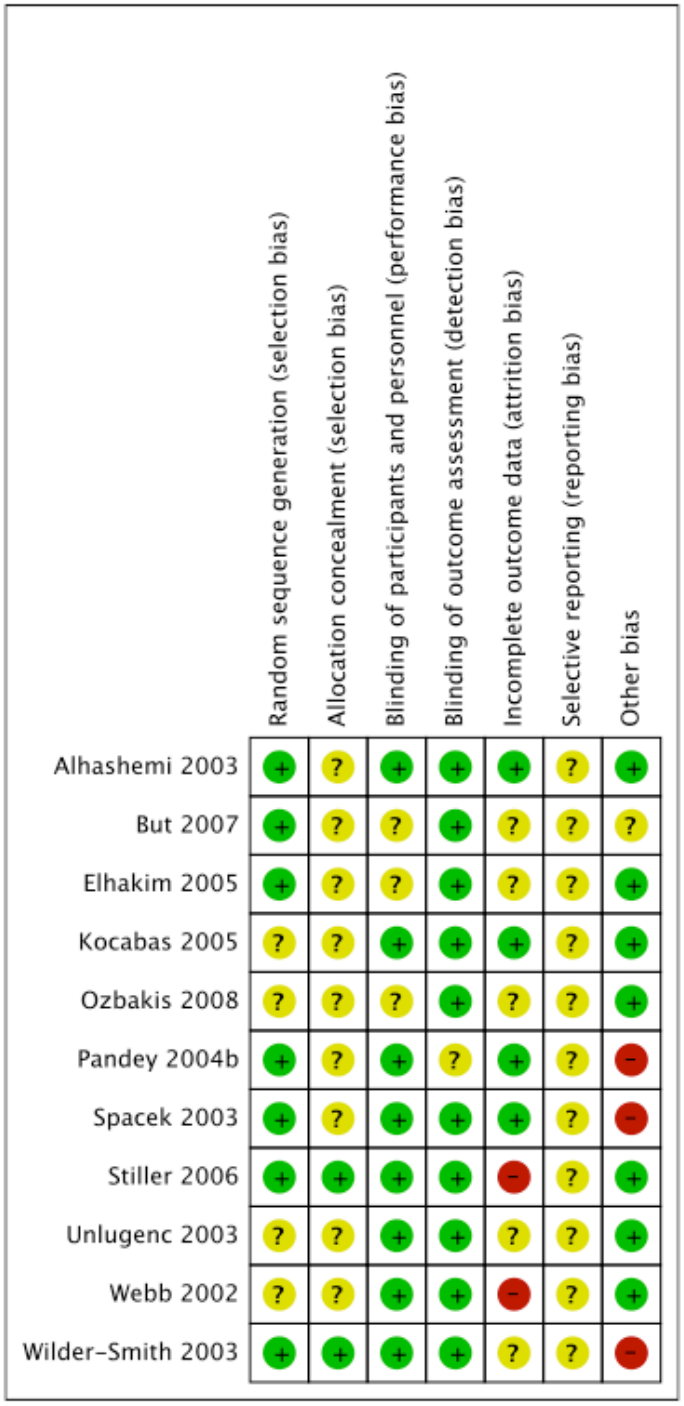
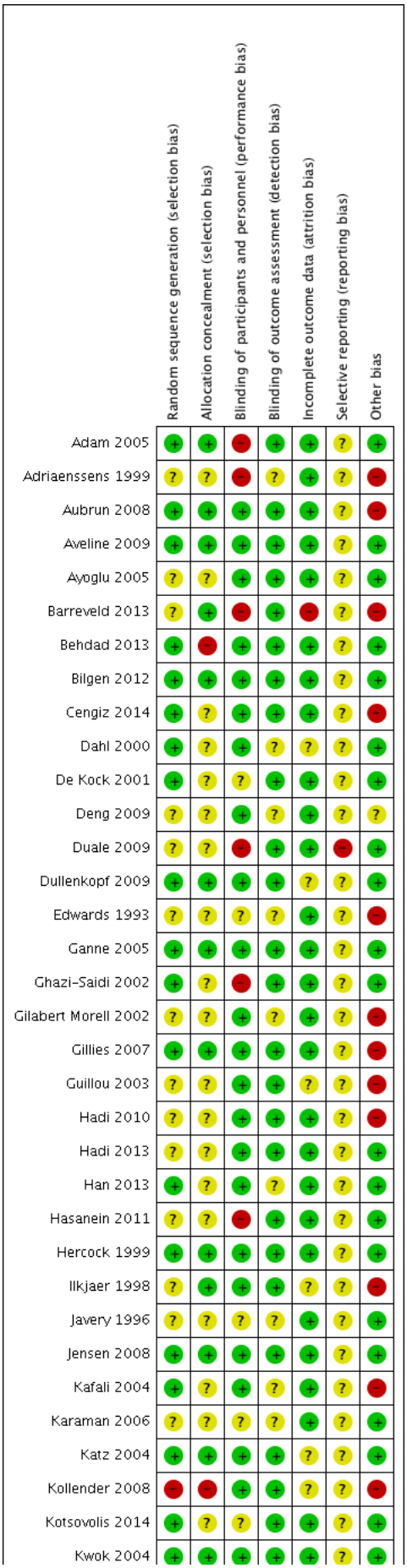


Figure 6.4: Risk of bias for tramadol RCTs.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Adam 2005
Adriaenssens 1999
Aubrun 2008
Aveline 2009
Ayoglu 2005
Barreveld 2013
Behdad 2013
Bilgen 2012
Cengiz 2014
Dahl 2000
De Kock 2001
Deng 2009
Duale 2009
Dullenkopf 2009
Edwards 1993
Ganne 2005
Ghazi-Saidi 2002
Gilabert Morell 2002
Gillies 2007
Guillou 2003
Hadi 2010
Hadi 2013
Han 2013
Hasanein 2011
Hercock 1999
Ilkjaer 1998
Javery 1996
Jensen 2008
Kafali 2004
Karaman 2006
Katz 2004
Kollender 2008
Kotsovolis 2014
Kwok 2004

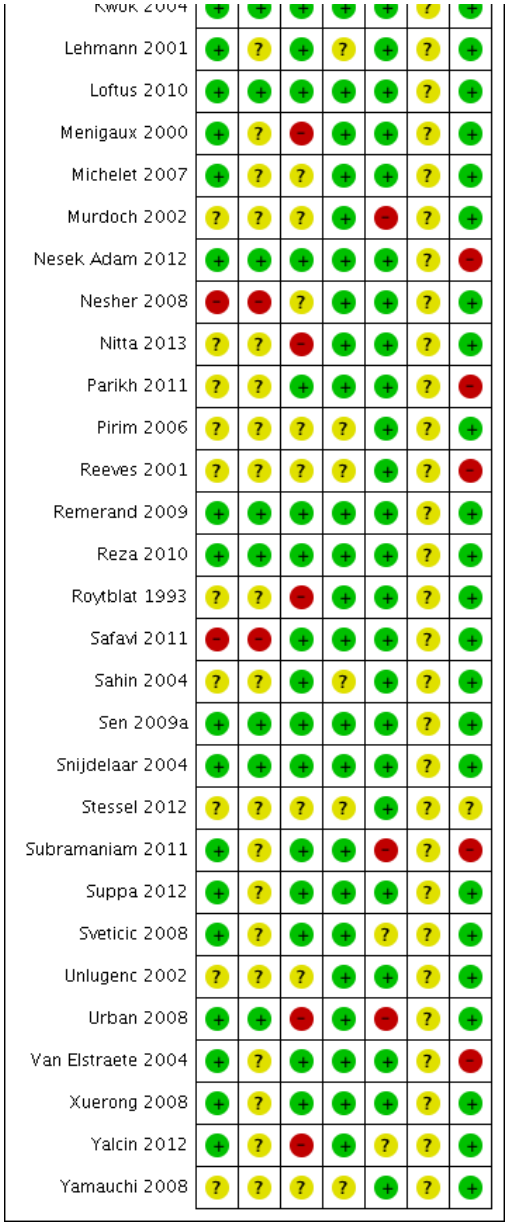


Figure 6.5: Risk of bias for ketamine RCTs.

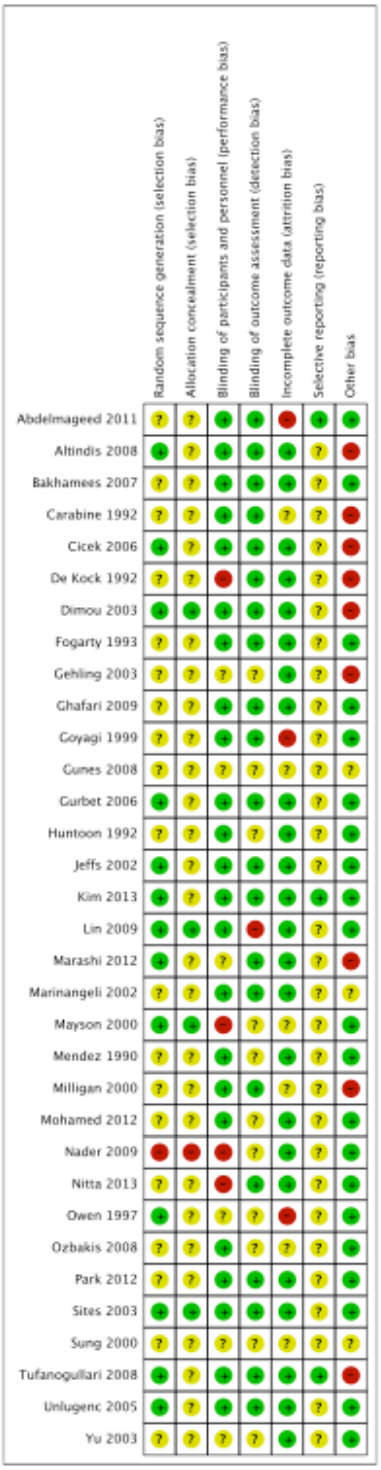


Figure 6.6: Risk of bias for alpha-2 agonists RCTs.

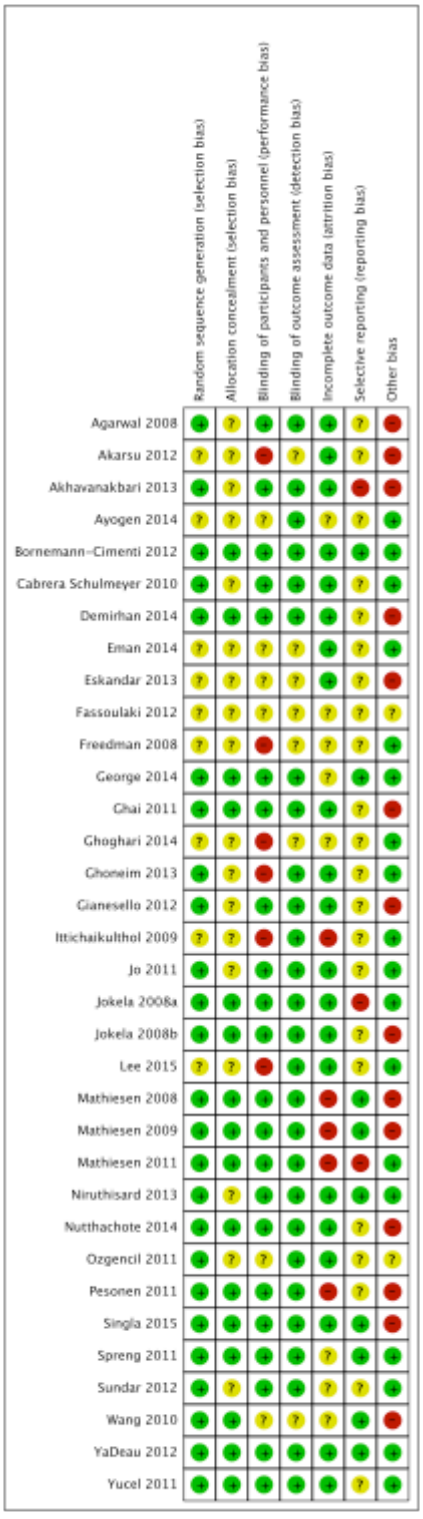


Figure 6.7: Risk of bias for pregabalin RCTs.

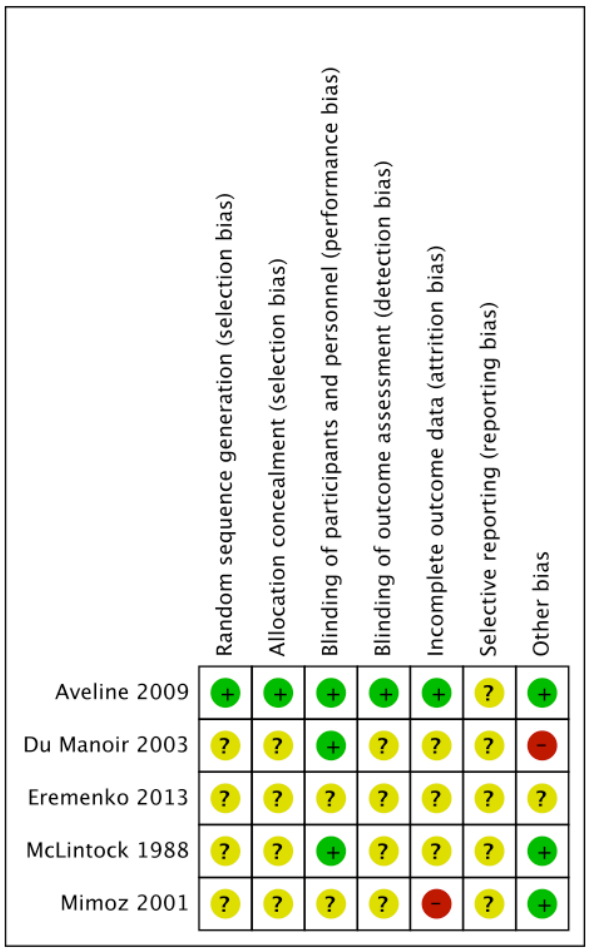


Figure 6.8: Risk of bias for nefopam RCTs.

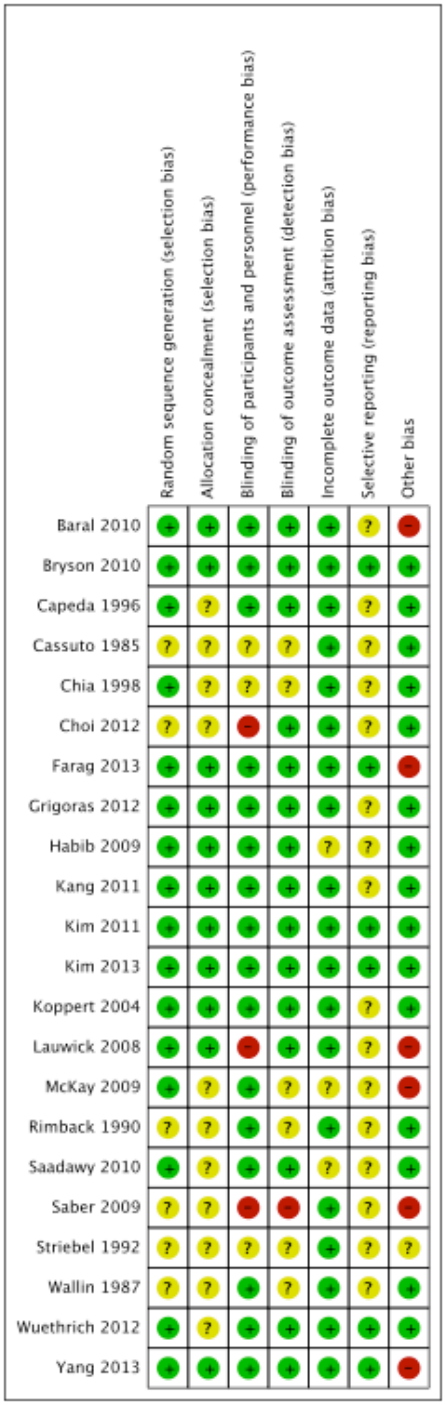


Figure 6.9: Risk of bias for lidocaine RCTs.

Figure 6.10: Risk of bias for magnesium RCTs.

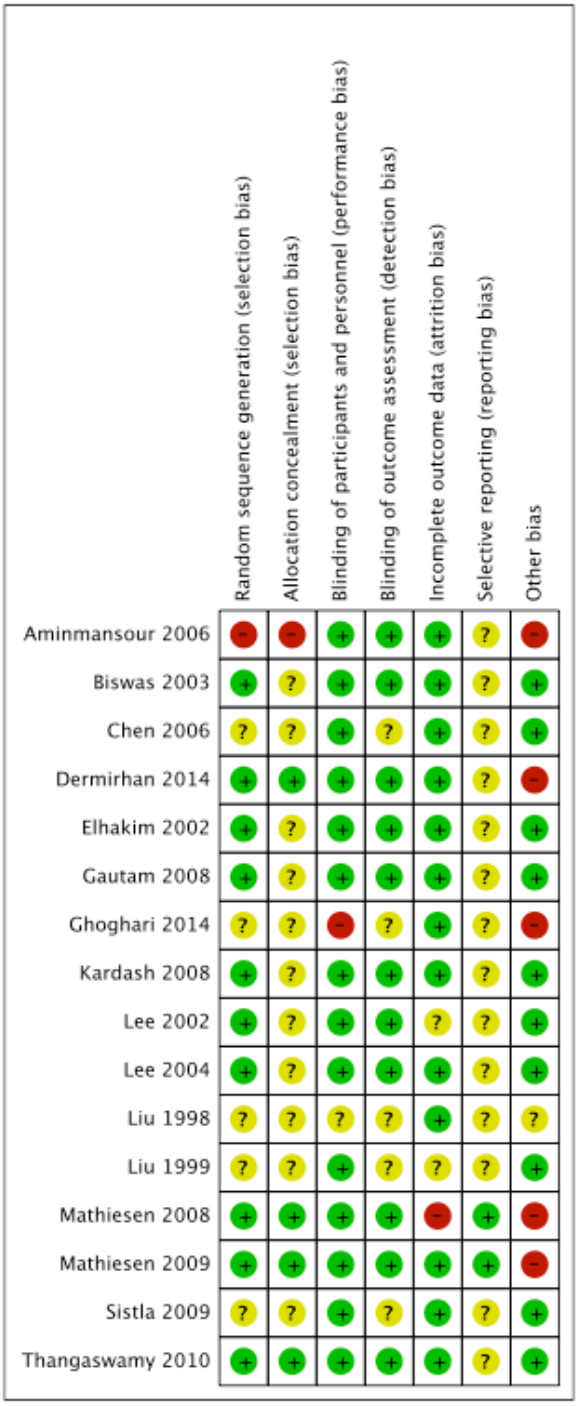


Figure 6.11: Risk of bias for dexamethasone RCTs.

6.3.2 Paracetamol

The paracetamol analysis included 25 RCTs with 1812 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=99%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=79%; p<0.001) (Figure 6.12). Bayesian meta-regression estimates were similar. The model was improved by the addition of route of administration (intravenous the most effective) and allocation concealment (low versus unclear risk) (R^2=94%; p<0.001). The model was not improved by the addition of type of surgery (CABG, ENT, cholecystectomy, C-section, orthopaedic, hysterectomy and spinal surgery) (p=0.22), type of anaesthesia (p=0.95), randomisation (p=0.80), blinding (p=0.21) or attrition bias (p=0.97). When assuming a fixed consumption of morphine (50mg), intravenous paracetamol was the second most effective analgesic with a moderate clinically significant reduction in morphine consumption (-18.39mg; 95% CrIs -21.54mg to -15.02mg) (Table 6.2). When testing regression assumptions, there were no violations for this analysis.

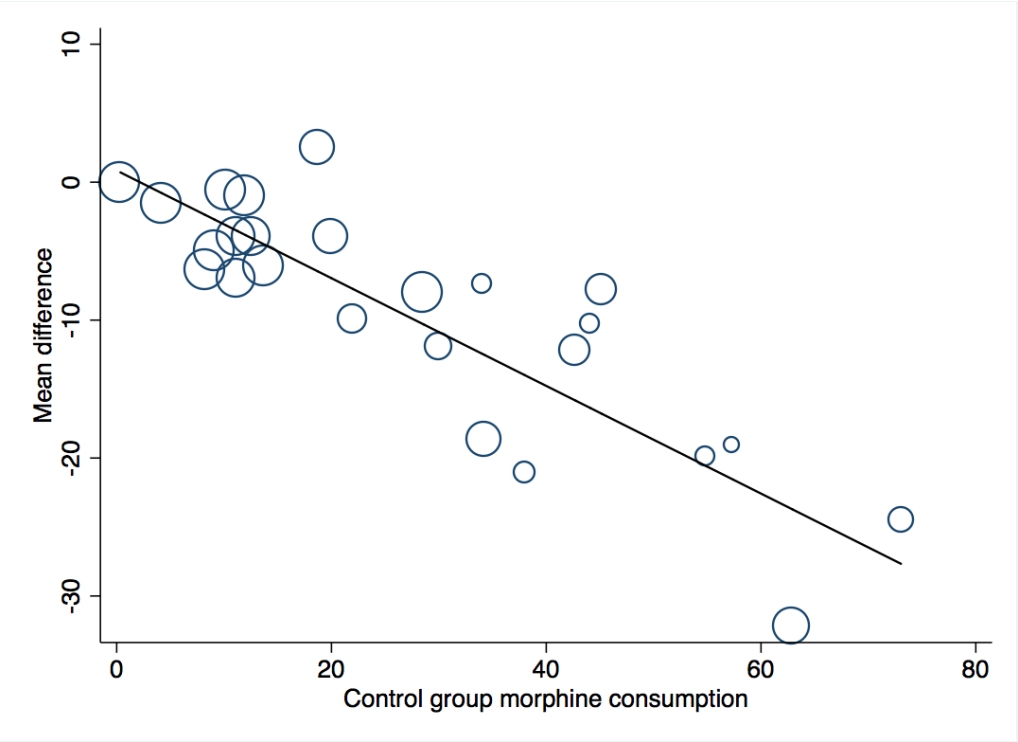


Figure 6.12: Meta-regression plot for paracetamol. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.3 NSAIDS and COX-2 inhibitors

The NSAIDS and COX-2 inhibitors analysis included 86 RCTs with 6937 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=92%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=81%; p<0.001) (Figure 6.13). Bayesian meta-regression estimates were similar. The addition of other clinical or methodological covariates failed to improve the model. These included type of surgery (abdominal, mixed arthroplasty, C-section, CABG, cholecystectomy, hip arthroplasty, hysterectomy, knee arthroplasty, mixed surgeries, orthopaedic, spinal surgery, thoracotomy, thyroid and tonsillectomy) (p=0.31), type of anaesthesia (p=0.18), COX-2 versus NSAID (p=0.83), type of administration (p=0.89), randomisation (p=0.47), allocation concealment (p=0.31), blinding (p=0.17) and attrition bias (p=0.84). When assuming a fixed consumption of morphine (50mg), NSAIDS and COX-2 inhibitors were the fourth most effective analgesic with a moderate clinically significant effect (-15.20mg; 95% CrIs -16.54mg to -13.81mg) (Table 6.2). There were no violations to any of the assumptions for this model.

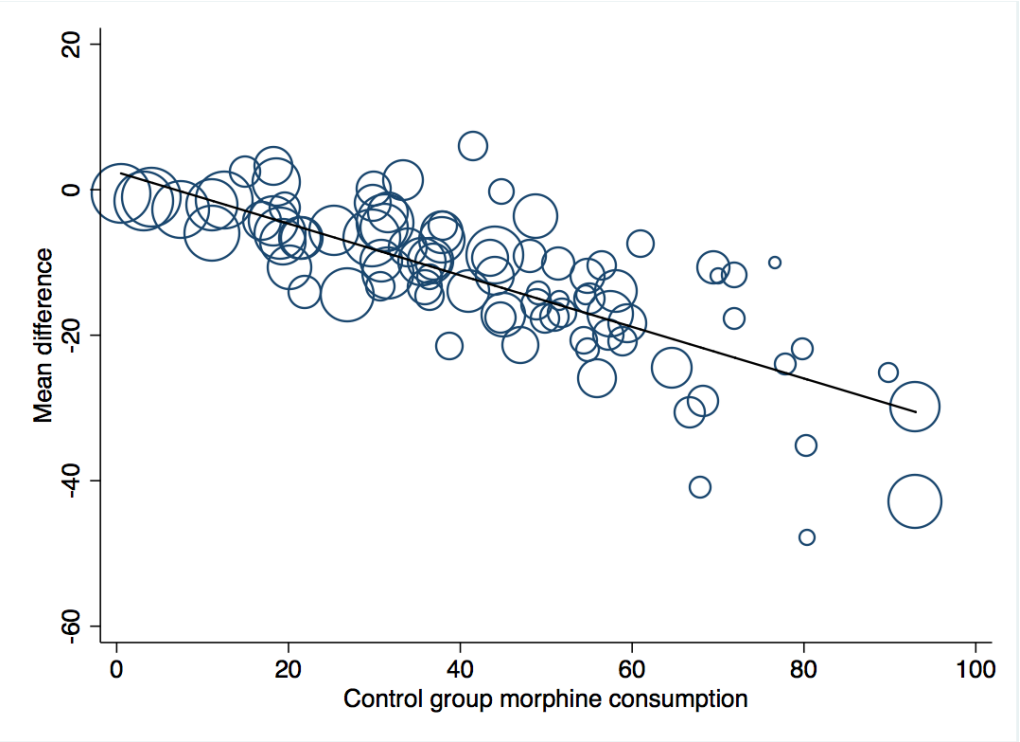


Figure 6.13: Meta-regression plot for NSAIDS and COX-2 inhibitors. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.4 Ketamine

The intravenous ketamine analysis included 62 RCTs with 4309 participants (Table 6.1). There was evidence of considerable statistical heterogeneity in this analysis (I^2=95%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=29%; p<0.001) (Figure 6.14). Bayesian meta-regression parameter estimates were similar. The addition of blinding (low, unclear and high risk) and allocation concealment (low, unclear and high risk) significantly improved the model (R^2=56%; p<0.001). However, the model was not improved by the addition of type of surgery (abdominal, arthroplasty, arthroscopy, C-section, cholecystectomy, ENT, gynaecology, hysterectomy, mixed surgeries, orthopaedic, spinal surgery and thoracotomy) (p=0.45), type of anaesthesia (p=0.44), dose (p=0.86) or attrition bias (p=0.45). Although the addition of randomisation improved the model in isolation, it was not an independent predictor on multivariate analysis. When assuming a fixed consumption of postoperative morphine (50mg), ketamine was the ninth most effective analgesic with a small clinically significant effect (-9.76mg; 95% CrIs -12.15mg to -7.33mg) (Table 6.2). There were no violations to the assumptions for this model.

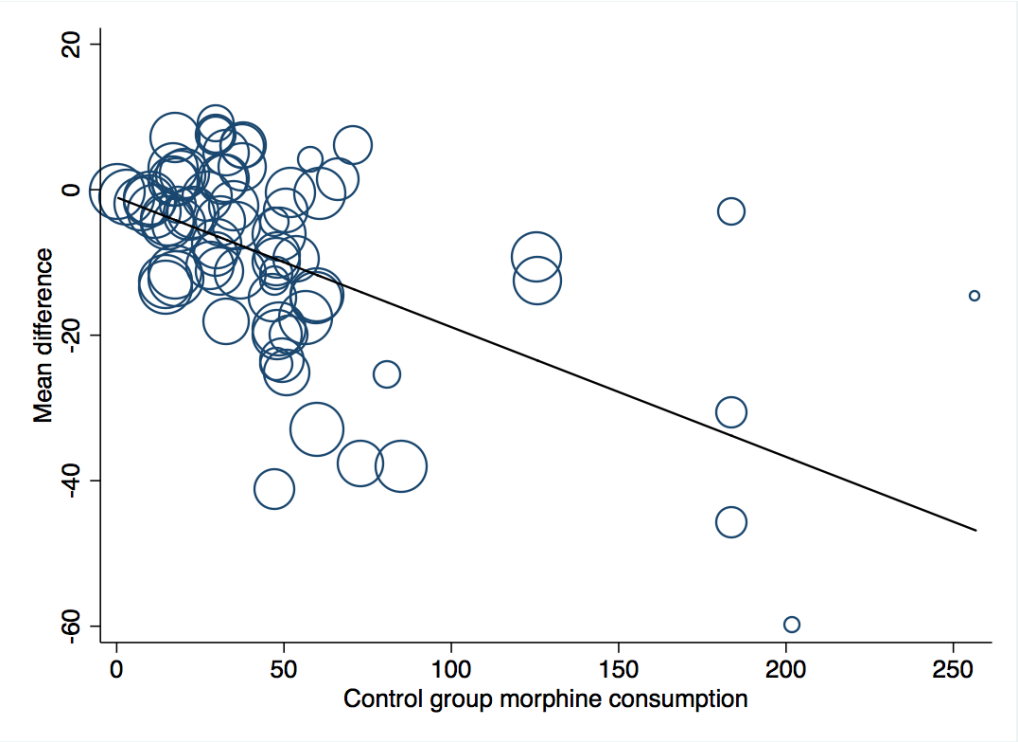


Figure 6.14: Meta-regression plot for ketamine. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.5 Alpha-2 agonists (clonidine and dexmedetomidine)

The alpha-2 agonists analysis included 33 RCTs with 1930 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=96%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=66%; p<0.001) (Figure 6.15). Bayesian meta-regression estimates were similar. The addition of route of administration (intravenous and spinal/epidural the most effective) and attrition bias (low, unclear and high risk) significantly improved the model (R^2=75%; p<0.001). However, the model was not improved by the addition of type of surgery (abdominal, arthroplasty, C-section, CABG, ENT, gynaecology, hysterectomy, spinal surgery and cholecystectomy) (p=0.87), type of anaesthesia (p=0.53), clonidine versus dexmedetomidine (p=0.12), randomisation (p=0.87), allocation concealment (p=0.87) and blinding (p=0.60). When assuming a fixed consumption of postoperative morphine (50mg), alpha-2 agonists were the third most effective analgesics (-16.94mg; 95% CrIs -20.09mg to -13.57mg) (Table 6.2). On testing assumptions, there was some evidence of heteroscedasticity for this analysis.

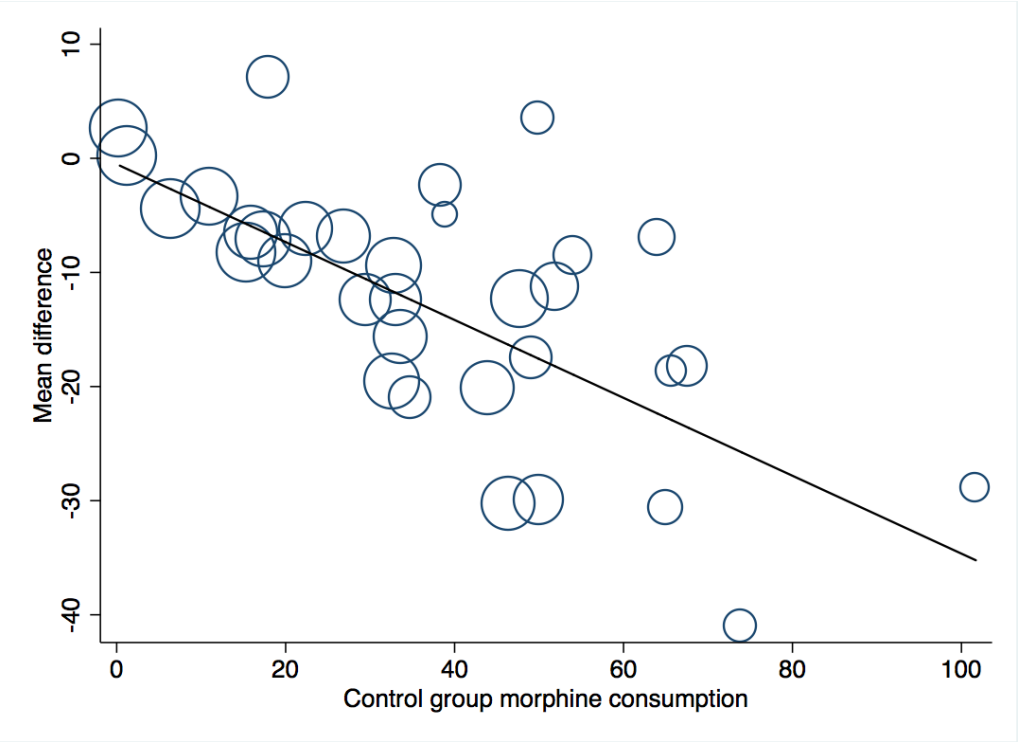


Figure 6.15: Meta-regression plot for alpha-2 agonists. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.6 Gabapentin

The gabapentin analysis included 67 RCTs with 5082 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=97%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=92%; p<0.001) (Figure 6.16). Bayesian meta-regression estimates were similar. The addition of peri-operative dose significantly improved the model (R^2=93%; p<0.001). The model was not improved by the addition of type of surgery (abdominal, hysterectomy, breast, CABG, cholecystectomy, C-section, arthroplasty, arthroscopy, nasal, neurosurgery, orthopaedic, plastic surgery, spinal surgery, thoracotomy, thyroid and tonsillectomy) (p=0.36), randomisation (p=0.99), allocation concealment (p=0.84), blinding (p=0.15) or attrition bias (p=0.12). Although type of anaesthesia improved the model (p=0.08) it was not an independent predictor in the final model. When assuming a fixed consumption of postoperative morphine (50mg), gabapentin was the most effective analgesic with a moderate clinically significant effect (-18.49mg; 95% CrIs -19.90mg to -17.07mg) (Table 6.2). However, assuming a dose of 1200mg, this effect became a large clinically significant difference. On testing assumptions, residuals were leptokurtic and there was evidence of some heteroscedasticity.

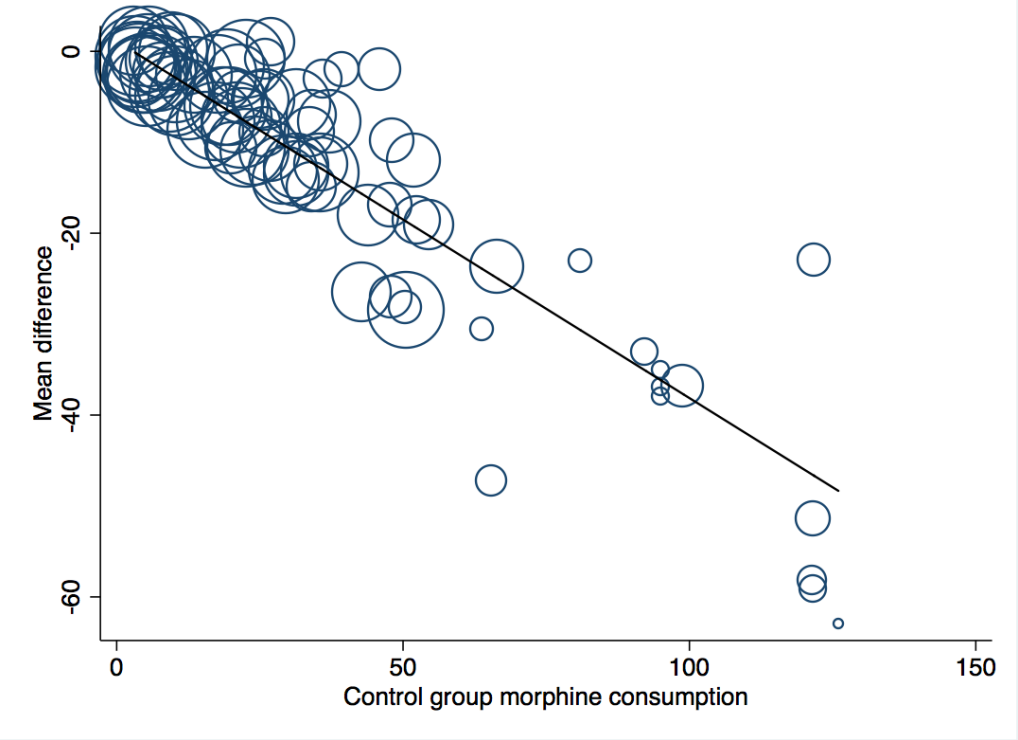


Figure 6.16: Meta-regression plot for gabapentin. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.7 Pregabalin

The pregabalin analysis included 34 RCTs with 3201 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=94%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=58%; p<0.001) (Figure 6.17). Bayesian meta-regression estimates were similar. The addition of allocation concealment (low versus unclear risk) significantly improved the model (R^2=78%; p<0.001). The model was not improved by the addition of type of surgery (abdominal, arthroscopy, breast, cardiac surgery, cholecystectomy, ENT, hysterectomy, laparoscopic abdominal, mixed surgeries, orthopaedic, spinal surgery and arthroplasty) (p=0.89), type of anaesthesia (p=0.58), peri-operative dose (p=0.84), randomisation (p=0.11) or attrition bias (p=0.70). Although blinding improved the model (p=0.01) it was not an independent predictor in the final model. When assuming a fixed consumption of postoperative morphine (50mg), pregabalin was the fifth most effective analgesic with a moderate clinically significant reduction in morphine consumption (-12.75mg; 95% CrIs -15.23mg to -10.11mg) (Table 6.2). On testing of assumptions, residuals were leptokurtic and there was evidence of heteroscedasticity.

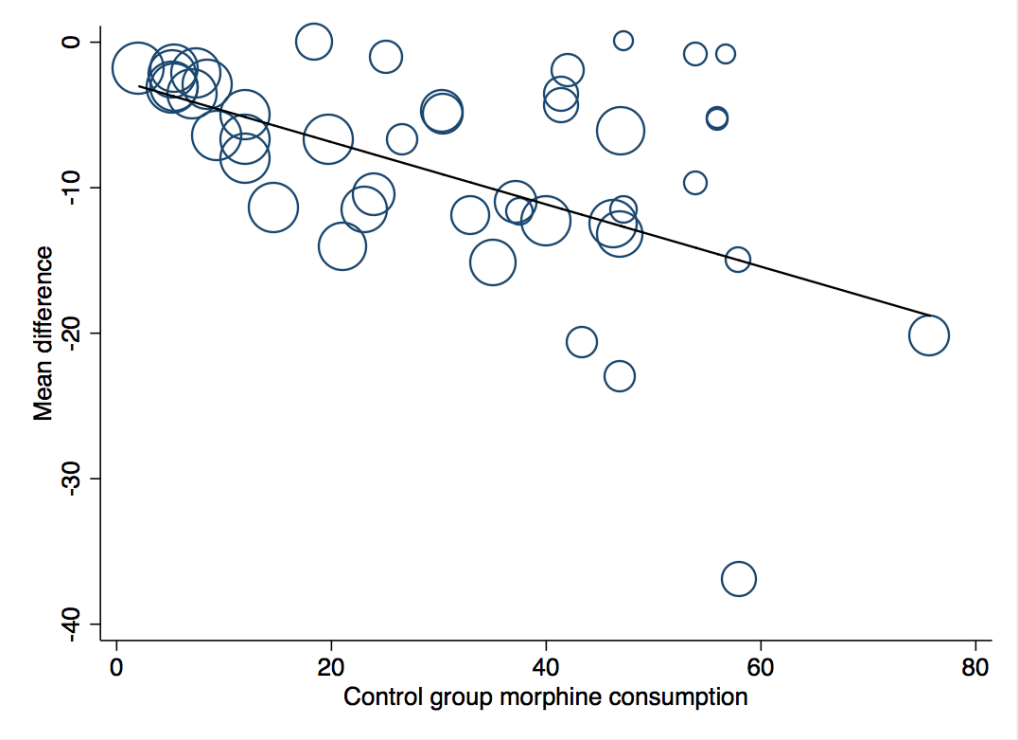


Figure 6.17: Meta-regression plot for pregabalin. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.8 Nefopam

There were too few studies to investigate heterogeneity for nefopam.

6.3.9 Lidocaine

In the lidocaine analysis there were 22 RCTs with 1319 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=80%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=62%; p<0.001) (Figure 6.18). Bayesian meta-regression estimates were similar. The addition of route of administration (intravenous the most effective) and attrition bias (low versus unclear risk) significantly improved the model (R^2=87%; p<0.001). The model was not improved by the addition of type of surgery (abdominal, breast, cholecystectomy, ENT and spinal surgery) (p=0.33), dose (p=0.99), allocation concealment (p=0.58) or blinding (p=0.18). Although randomisation was a significant predictor, it was not included as it did not exaggerate the effect estimate (p=0.06). Assuming a fixed consumption of postoperative morphine (50mg), intravenous lidocaine was the eighth most effective analgesic with a moderate clinically significant reduction in morphine (-10.09mg; 95% CrIs -13.49mg to -6.36mg) (Table 6.2). There were no violations when testing model assumptions.

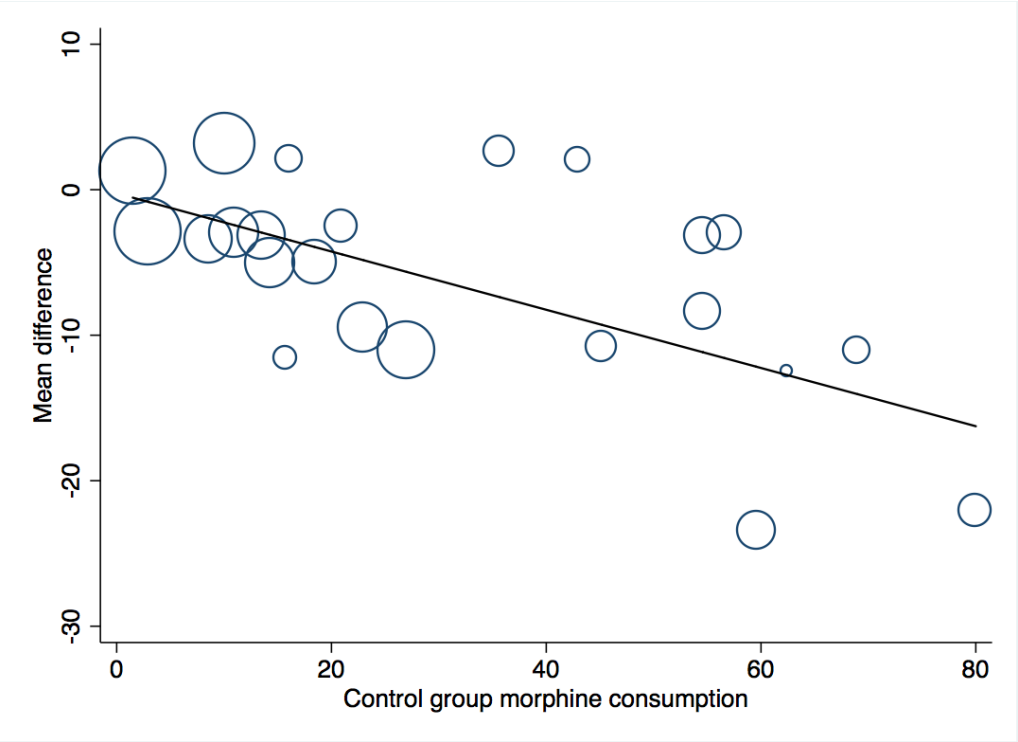


Figure 6.18: Meta-regression plot for lidocaine. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.10 Dexamethasone

In the dexamethasone analysis there were 16 RCTs with 2163 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=88%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=100%; p<0.001) (Figure 6.19). Bayesian meta-regression estimates were similar. The addition of type of surgery (abdominal, cholecystectomy, ENT, hysterectomy, mixed surgeries, orthopaedic and spinal surgery) and blinding (low, unclear and high risk) significantly improved the model (R^2=100%; p<0.001). The model was not improved by the addition of type of anaesthesia (p=0.63), dose (p=0.12), allocation concealment (p=0.18) or attrition bias (p=0.67). Although the addition of randomisation improved the model (p=0.1) when added to control group morphine consumption, it was not an independent predictor in the final model. Assuming a fixed consumption of postoperative morphine (50mg), dexamethasone was the least effective analgesic with a small clinically significant reduction (-8.07mg; 95% CrIs -9.79mg to -6.04mg) (Table 6.2). On testing assumptions, there was evidence of multicollinearity between unclear and high risk of bias for blinding and spinal, ENT and cholecystectomy surgeries. In addition, one study was highly influential in this analysis (Cook's distance of 20), although removing this study had no effect on results.

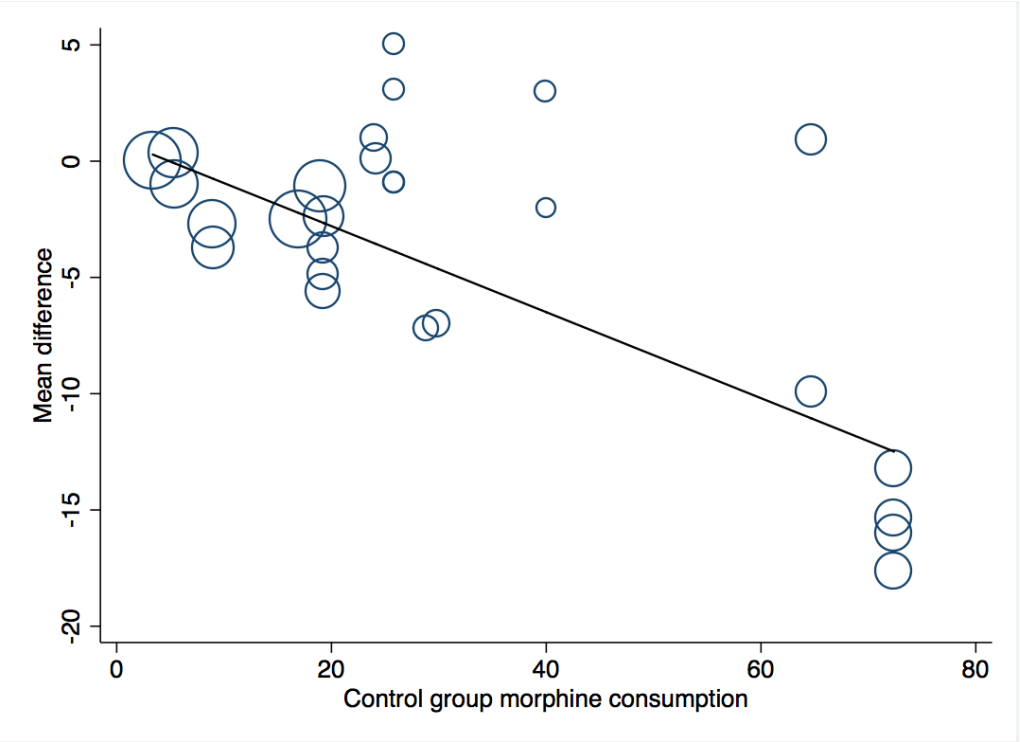


Figure 6.19: Meta-regression plot for dexamethasone. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.11 Magnesium

The magnesium analysis included 22 RCTs with 1194 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=90%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=15%; p=0.02) (Figure 6.20). Bayesian meta-regression estimates were similar. The addition of allocation concealment (low versus unclear risk) significantly improved the model (R^2=32%; p=0.006). The model was not improved by the addition of type of surgery (abdominal, cardiac surgery, cholecystectomy, hysterectomy, mixed surgeries, orthopaedic and spinal surgery) (p=0.69), type of anaesthesia (p=0.33), blinding (p=0.87) and attrition bias (p=0.97). Although dose (p=0.02) and randomisation (p=0.06) improved the model, they were not included, as they did not exaggerate the effect estimate. Assuming a fixed consumption of postoperative morphine (50mg), magnesium was the seventh most effective analgesic with a moderate clinically significant reduction in morphine consumption (-10.60mg; 95% CrIs -14.19mg to -7.10mg) (Table 6.2). There were no violations when testing regression model assumptions.

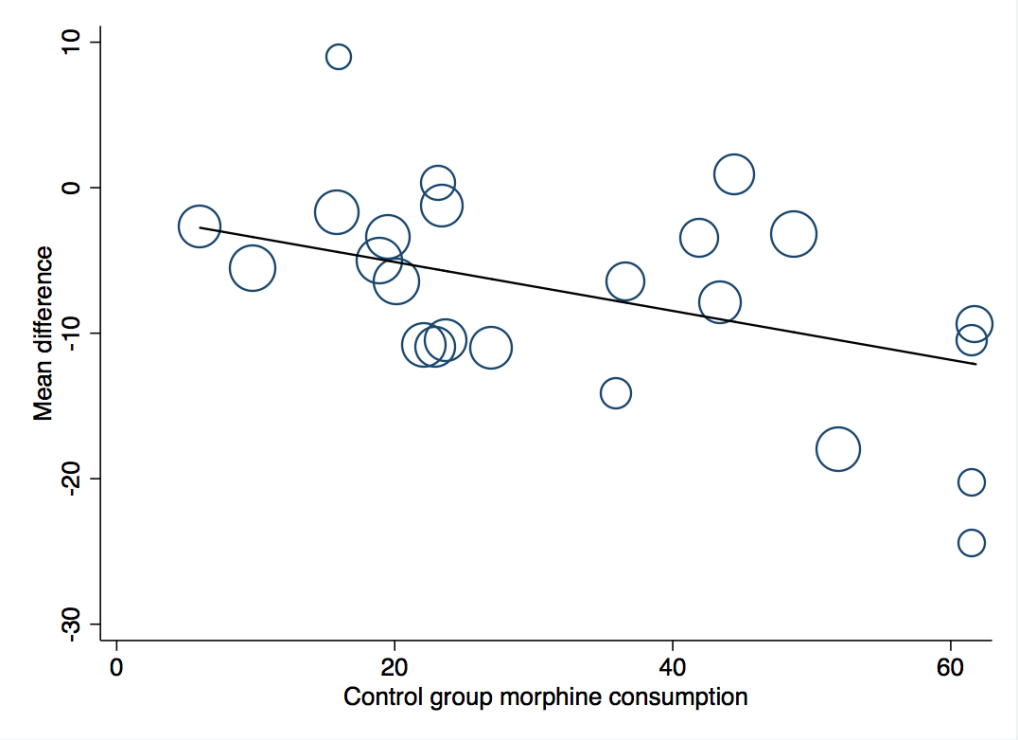


Figure 6.20: Meta-regression plot for magnesium. X-axis is control group morphine consumption (mg) and Y-axis is MD for 24-hour morphine reductions (mg).

6.3.12 Tramadol

The tramadol analysis included 11 RCTs with 889 participants (Table 6.1). There was evidence of considerable statistical heterogeneity (I^2=90%). Control group morphine consumption was a significant predictor of between-study heterogeneity (R^2=48%; p=0.03). Bayesian meta-regression estimates were similar. No other covariates improved the final model. These included type of surgery (abdominal, C-section, CABG, knee arthroplasty and TURP) (p=0.99), type of anaesthesia (p=0.47), route of administration (p=0.59), dose (p=0.25), randomisation (p=0.80), allocation concealment (p=0.22), blinding (p=0.87) and attrition bias (p=0.63). When assuming a fixed consumption of postoperative morphine (50mg), tramadol was the sixth most effective analgesic with a moderate clinically significant reduction in morphine consumption (-11.99mg; 95% CrIs -16.21mg to -7.28mg) (Table 6.2). There were no violations when testing regression model assumptions.

6.4 Discussion

6.4.1 Summary of results

In this chapter we report a novel, empirically derived, consistent and large predictor of between-study heterogeneity in meta-analyses of analgesic adjuncts. Control group morphine consumption (baseline risk) was a consistent predictor of between-study heterogeneity for all included meta-analyses. In addition, we found evidence that some methodological limitations explained some of the residual heterogeneity. Type of surgery or anaesthesia did not appear to be an independent predictor. Moreover, we have presented a method for more accurately reporting the efficacy of analgesics, which mitigates the variable morphine consumption from the included trials within systematic reviews. Furthermore, these models are able to adjust estimates for clinical and methodological confounding variables from the included studies.

6.4.2 Links with previous research

Recent meta-analyses have attempted to explore heterogeneity using clinical covariates such as dose and type of surgery (Mishriky, Waldron and Habib 2015). However, these often report a low proportion of variation explained when compared to our results using control group morphine consumption (baseline risk). We derived this covariate from previous empirical studies suggesting larger reductions in pain scores following analgesic treatment with higher baseline pain scores. One study examined around 500 participants following dental extraction and found those with severe pain (3/3) had greater reductions in pain scores following treatment with ibuprofen compared to those with moderate pain (2/3) (Averbuch and Katzper 2003). Another study found paracetamol and codeine treatment following Caesarean section was only effective in those participants with severe pain (>6/10) (Bjune *et al.* 1996). Although it should be noted other factors in addition to the degree of pain may also influence postoperative opioid consumption such as access to PCA devices, concurrent analgesic protocols, patient characteristics (Ip *et al.* 2009) and the prescribing practices of attending medical professionals (which may be region dependent).

A previous study of postoperative pain reviews has found widespread statistical heterogeneity and suggested that this should be explored based on type of surgery or pain scores (Espitalier *et al*. 2013). This review recommended future meta-analyses should include only trials from the same surgical procedures or those with close acute postoperative pain levels and explore this using subgroup analysis. We would argue that postoperative analgesic consumption is a more appropriate covariate than type of surgery and meta-regression a more useful analysis than subgroup analysis as it allows reporting of the proportion of heterogeneity explained by the model (R^2) as well as the ability to adjust for other confounding variables. In our previous meta-analysis with gabapentin, morphine consumption varied even within procedure-specific subgroups and type of surgery was a small determinant of heterogeneity between studies in relation to morphine consumption and pain scores (Doleman *et al.* 2015b). Our results suggest that expected postoperative morphine consumption (as a surrogate for pain, participant characteristics and concurrent analgesia) is a large determinant of heterogeneity between studies.

Our results demonstrate that with control group morphine consumption held constant, type of surgery was not a significant predictor of between-study heterogeneity for nearly all analyses. Previous groups have argued that procedure-specific evidence is necessary when evaluating evidence derived from trials of analgesic agents (Kehlet *et al.* 2007). Our results suggest that the efficacy of analgesic agents is determined more by the degree of morphine consumption during the postoperative period rather than the type of surgery. Indeed, procedure-specific meta-analyses still suffer from considerable statistical heterogeneity (Yu *et al.* 2013). Therefore, we could find little empirical basis for conducting such procedure-specific reviews for analgesic adjuncts. Although we acknowledge that other interventions such as regional anaesthesia may have more relevance to procedure-specific evidence.

When reporting the results from analgesics using a fixed consumption of postoperative morphine, we found the most effective analgesics were gabapentin, paracetamol, alpha-2 agonists, NSAIDS and COX-2 inhibitors, pregabalin, tramadol, magnesium and lidocaine, all with moderate clinically

significant effects. Ketamine and dexamethasone had small clinically significant effects. However, efficacy is not the only consideration when considering use of these agents. Adverse effects should also be considered. Agents such as paracetamol, where the incidence of adverse events is low may be preferable to agents that induce peri-operative adverse effects such as sedation with gabapentin. Moreover, our findings may still be influenced by publication bias (as with other meta-analyses) so should be interpreted with caution.

6.4.3 Implications for clinical practice

In terms of the implications of our work for clinical practice, as meta-analyses are often used to inform clinical practice, reviews should present opioid reductions using a fixed consumption of morphine to more accurately reflect efficacy, as quoting the mean difference will be heavily influenced by the mean control morphine consumption in the included trials. In addition, indiscriminate use of analgesic adjuncts around the peri-operative period should be avoided, instead, clinicians can use information from small audits of mean opioid consumption and the regression parameters in our analysis to estimate the likely reduction in mean morphine consumption for samples of patients in that particular clinical situation. As all agents are associated with adverse effects, this more targeted use of analgesic adjuncts may help improve clinical significance and avoid inappropriate use of multiple agents where expected opioid reductions are small. Moreover, greater absolute reductions in morphine consumption may reduce the incidence of opioid adverse events, which a previous study has shown may be opioid dose-dependent (Zhao *et al.* 2004).

6.4.4 Implications for primary research studies

In terms of RCT design, when studying analgesic agents for postoperative pain, trials should be conducted in surgeries where expected postoperative morphine consumption is anticipated to be high. For example, for intravenous paracetamol where the expected mean postoperative morphine consumption is either 70mg or 20mg in the first 24-hours postoperatively, the anticipated

reduction in morphine would be 26mg and 6mg respectively. Relying solely on the mean difference (8mg) may underestimate clinical significance in the context where postoperative morphine consumption is high.

In terms of trial conduct, as with previous studies, we have found evidence that methodological limitations, in particular allocation concealment were associated with larger reductions in morphine for many adjuncts (Schultz and Grimes 2002a). Indeed, previous studies have shown similar results and found that inadequate or unclear allocation concealment can exaggerate effect estimates by around 40% (Schultz *et al.* 1995). Given that only 29% of the included trials reported adequate allocation concealment, this is a particular area of internal validity future studies should aim to address. Similarly, although less so, we found evidence that inadequate or unclear attrition bias and blinding exaggerated effect estimates. This also supports previous investigations, which have found exaggerated effect estimates in studies that were not blinded, although this was less severe than studies with inadequate or unclear allocation concealment (41% versus 17%; Schultz *et al.* 1995). Given only 50% of trials described adequate blinding of participants, researchers and outcome assessors, future trials should aim to conduct both adequate blinding procedures and full reporting of these in manuscripts.

6.4.5 Implications for secondary research

In terms of secondary research studies, future meta-analyses of postoperative analgesic agents should aim to explore heterogeneity using control group morphine consumption, in addition to other sources of clinical heterogeneity such as dose or route of administration. Such explanation of statistical heterogeneity would lead to higher quality evidence derived from these reviews as per GRADE (Guyatt *et al.* 2008). Estimates from these reviews should be reported using a fixed consumption of morphine to avoid confounding by the variable consumption in the included primary studies. As an extension to this, residual confounding can be further reduced by incorporating other clinical and methodological covariates into these regression models to adjust estimates for differences in study design. As systematic

reviews are inherently observational (despite deriving data from randomised studies) (Smith and Carlisle 2015), more advanced and appropriate statistical methods are required (regression) that allows more accurate prediction (rather than using mean differences), while having the additional advantage of controlling for known confounders. For these reasons, future reviews of postoperative analgesics should avoid univariate subgroup analyses (due to confounding) and move towards multivariate regression models, which include control group morphine consumption (as is common practice in observational primary research).

6.4.6 Limitations

There are several limitations with this review. Firstly, as alluded to in previous chapters, meta-regression analysis should be regarded as observational despite deriving data from randomised studies. Such analyses are prone to both residual confounding (from covariates we have not included in our models) and aggregation bias (as results are based on aggregated study estimates rather than from individual patients). For this reason, our implications for clinical practice focus on aggregated patient outcomes (from audits) rather than applying these to individual patients. Although it should also be noted that even with individual patient data, baseline risk cannot be determined for any individual patient as interventions are initiated before outcome measurement (24-hours).

Secondly, we cannot rule out type I errors in our analyses. Although conventional to set a lower level of significance to covariate adjustment in regression models ($p<0.1$), this may also increase false positive results. Indeed, for some covariates, the results suggested the addition of certain covariates (such as dose for magnesium or randomisation for lidocaine) underestimated effect estimates, which appear to have no biologically plausible explanation. Therefore, type I errors seem likely. Thirdly, although our models can adjust for confounding variables, our analyses are limited to published primary research studies and are therefore still susceptible to publication bias. There are currently no methods that allow incorporation of true publication bias into our, and other models. Indeed, even identification of imprecise study effects

secondary to true publication bias is problematic and therefore this limits our findings. This will be the subject of the next chapter.

Finally, more appropriate methods are available to compare the relative efficacy of analgesics, such as the use of network meta-analysis. However, as our search focussed on previously published reviews which generally included an intervention versus placebo, this made network meta-analysis unsuitable as this requires inclusion of trials where analgesic interventions were compared with each other. Therefore, future investigations may wish to conduct searches, which aim to include these studies and perform network meta-analysis adjusted for baseline risk.

6.4.7 Conclusions

In conclusion, we have identified widespread, considerable statistical heterogeneity in meta-analyses of analgesic adjuncts. Moreover, we have demonstrated for the first time, an empirically-derived, consistent covariate responsible for a large proportion of between-study heterogeneity in meta-analyses of analgesics for postoperative pain. Extending this principal, we have presented methods for more accurate presentation of the efficacy of analgesics that can adjust for other clinical and methodological covariates. Despite the limitations of our analysis, we recommend use of these principles in clinical practice, primary and secondary research studies.

Chapter 7

Publication bias in analgesics for postoperative pain

7.1 Introduction

Meta-analyses have gained popularity within the academic community. The synthesis of results from all available studies results in increased precision in effect estimates and investigation of heterogeneity can generate new hypotheses and help direct future research. However, as many meta-analyses include data from published studies only, this makes them susceptible to bias (Sutton *et al.* 2000). Publication bias results from the preferential publication of studies with statistically significant results, which are both more likely to be published and are published faster than trials with negative findings (Hopewell *et al.* 2009; Stern and Simes 1997). Furthermore, within study publications, outcomes with statistically significant effects are more likely to be reported than non-significant results (Dwan *et al.* 2008).

Ideally, a review will aim to mitigate the effects of publication bias by searching unpublished clinical trials databases (combined with wider editorial policies on mandatory registration of primary studies), grey literature sources and conference proceedings (Dickersin 1990; Thornton and Lee 2000). Following the analysis, methods exist to help authors identify the presence of possible publication bias (imprecise study effects) including observation for funnel plot asymmetry (Peters *et al.* 2008) and quantitative tests such as Egger's linear regression test (Egger *et al.* 1997a; Sterne, Gavaghan and Egger 2000). Indeed, use of this test has previously found that publication bias is the reason many meta-analyses conclusions and subsequent large RCTs disagree. In addition to identification of possible publication bias, tests exist that can adjust effect estimates if funnel plot asymmetry is found such as the trim and fill method (Duval and Tweedie 2000), although recommended only as a sensitivity analysis (Peters *et al.* 2007).

It is as yet unknown how many reviews of analgesic adjuncts employ both methods to prevent and analyse to help identify publication bias. Furthermore, little is known about the prevalence of publication bias from the studies included in these reviews. Moreover, as we have recently described widespread between-study heterogeneity secondary to baseline risk in these trials (Chapter

6), it is unknown what influence this between-study heterogeneity has on evaluation of funnel plot asymmetry. Therefore, the aim of this chapter was to: 1) perform a meta-epidemiological study to evaluate reviews for the use of methods to prevent and evaluate publication bias 2) perform a secondary analysis of RCTs included in these reviews for the presence of imprecise study effects (possible publication bias) 3) to evaluate the effects of baseline risk on funnel plot asymmetry and propose novel methods to overcome this issue.

7.2 Methods

7.2.1 Search strategy, registration and data extraction

We reported this review in accordance with the PRISMA checklist (Moher *et al.* 2009). We prospectively registered the review on the PROSPERO website using the registration number CRD42016043924. Our search strategy is described elsewhere (Section 6.2.1). We extracted data onto an electronic database. We initially searched for review articles in order to conduct a meta-epidemiological study and then performed a secondary analysis of RCTs from within these reviews. If results were not reported in the original meta-analysis, we extracted data from the original publications. In order to reduce selective reporting bias, if standard deviations were not reported, we estimated these from other studies in the analysis. This is due to statistically non-significant results being less likely to be fully reported than significant results. If multiple subgroups were reported within a study (such as different doses), we used data from the most significant subgroup, as we assumed one statistically significant subgroup would increase the chances of that study being published.

7.2.2 Inclusion criteria and outcomes

To reduce bias, we had no language or publication status restrictions for inclusion in our review. As described previously, we included reviews that included the following analgesic agents versus placebo for postoperative pain: paracetamol, NSAIDS and COX-2 inhibitors, tramadol, intravenous ketamine, alpha-2 agonists (clonidine and dexmedetomidine), gabapentin, pregabalin, lidocaine, magnesium and dexamethasone. We did not include nefopam as only five studies were previously identified, which precluded quantitative assessment of publication bias (Sterne *et al.* 2011). The outcome of interest was 24-hour morphine consumption as this outcome is commonly reported as a primary outcome. If studies reported dosage per kilogram, we converted this to a 70kg weight. We also used data from the day of surgery or postoperative day one and analysed this as 24-hour data. We converted alternative opioids to intravenous morphine-equivalents using the conversion factors reported previously (Section 6.2.3).

7.2.3 Statistical analysis

From the included reviews, we report the proportion of reviews searching unpublished clinical trials databases, grey literature databases and conference proceedings (Thornton and Lee 2000). In addition, if more than ten primary studies were included, we report the proportion of reviews assessing for possible publication bias through visual inspection for funnel plot asymmetry, quantitative evaluations such as Egger's linear regression test and/or the proportion of studies attempting methods to correct for potential publication bias using trim and fill analysis. We only included meta-analyses in these descriptive outcomes (Sterne *et al.* 2011). We also report the number of included RCTs that were registered on clinical trial databases, as reported in the study publication. As clinicaltrials.gov was established in the year 2000, we only included trials published in or after 2010 to allow for study completion and publication.

We then performed a secondary analysis of RCTs from within these reviews. We initially performed contour-enhanced funnel plots (Illustration 1.3), which add contours for statistical significance (we used $p<0.01$ and $p<0.05$ as contour regions) to help distinguish funnel plot asymmetry secondary to publication bias from other causes (such as methodological disparities in smaller studies) (Sutton *et al.* 2000). This is because publication of a particular study is dependent on the p value rather than just the direction of the result. Therefore, if funnel plot asymmetry is present and studies are located in regions of statistical significance, then this suggests publication bias is responsible rather than other causes. Secondly, we performed quantitative analysis for funnel plot asymmetry using Egger's linear regression test (Illustration 1.1) with a one-tailed $p<0.1$ regarded as evidence of imprecise study effects (Egger *et al*. 1997a; Higgins and Green 2008).

Thirdly, we constructed funnel plots, which we divided into subgroups based on the degree of control group morphine consumption (baseline risk). We defined these subgroups as follows: low consumption (<20mg), medium consumption (20-50mg) and high consumption (>50mg). This analysis aimed

to identify whether funnel plot asymmetry was secondary to underlying publication bias or whether between-study heterogeneity may be responsible. As funnel plots are frequently constructed from standard errors from individual studies and postoperative pain trials are approximately similar in sample size, larger control group morphine consumption is often accompanied by larger standard deviations. This relationship could lead to asymmetry in funnel plots due to a relationship between effect estimates and their associated standard errors. In order to test this formally, we performed a linear regression analysis with standard errors as the outcome variable and control group morphine consumption (baseline risk) as the predictor variable. Fourthly, we conducted sensitivity analysis using trim and fill analysis (Section 1.9.4 and Illustration 1.2) and report the percentage change in effect estimates assuming a symmetric funnel plot using a random-effects model.

Finally, we performed simulations to create eight hypothetical meta-analyses where no publication bias was present. These simulations attempted to recreate the conditions present in meta-analyses of analgesic adjuncts. Specifically, that both effect sizes and standard deviations were dependent on baseline risk (R code below).

```
study.gen.br <- function(b.risk, t.diff, sd, n.arm) {
response.c <- rnorm(n.arm, mean = b.risk, (sd+(0.5*b.risk)))
response.t <- rnorm(n.arm, mean = b.risk + t.diff -0.5*b.risk, (sd+(0.5*b.risk)))
m.c <- mean(response.c)
m.t <- mean(response.t)
sd.c <-sqrt(var(response.c))
sd.t <-sqrt(var(response.t))
n.c <- n.arm
n.t <- n.arm
values = data.frame(n.c, n.t, m.c, m.t, sd.c, sd.t)
return(values)
}
```

We then produced funnel plots for the simulated meta-analyses and performed Egger's linear regression test ($p<0.1$ as evidence of imprecise study effects). Following this, we present an alternative method of constructing funnel plots using residual values (Figure 7.12) from the meta-regression of baseline risk to identify whether this could resolve any funnel plot asymmetry. All analyses were conducted using STATA Version 14.2 and Comprehensive Meta-Analysis Version 3. Simulations were performed using R statistical package and performed by a statistician (Alex Sutton).

7.3 Results

7.3.1 Description of included studies and descriptive results

We included 344 RCTs with 25,348 participants in the final analysis. The references for the included reviews and the PRISMA flowchart have been reported previously (Section 6.3.1 and Figure 6.1). Of the included reviews that conducted a meta-analysis, 65% (95% CI 52% to 78%) evaluated included studies for imprecise study effects. In 53% of reviews (95% CI 39% to 67%), funnel plots were used and 43% (95% CI 29% to 57%) used quantitative methods such as Egger's linear regression test. Only 6% (95% CI 0% to 13%) attempted to correct for imprecise study effects using trim and fill analysis. In 16% (95% CI 7% to 25%) of meta-analyses, unpublished studies were sought from clinical trial databases, 9% (95% CI 2% to 16%) searched conference proceedings and 4% (95% CI 0% to 9%) searched grey literature databases. Since 2010, only 23% (95% CI 15% to 31%) of RCTs were registered on clinical trial databases.

7.3.2 Paracetamol

The paracetamol analysis included 25 RCTs. There was evidence of funnel plot asymmetry with a statistically significant Egger's linear regression test (p=0.02). Contour-enhanced funnel plots showed that the majority of studies were in the region of statistical significance, suggesting publication bias as a cause rather than other factors (Figure 7.1).

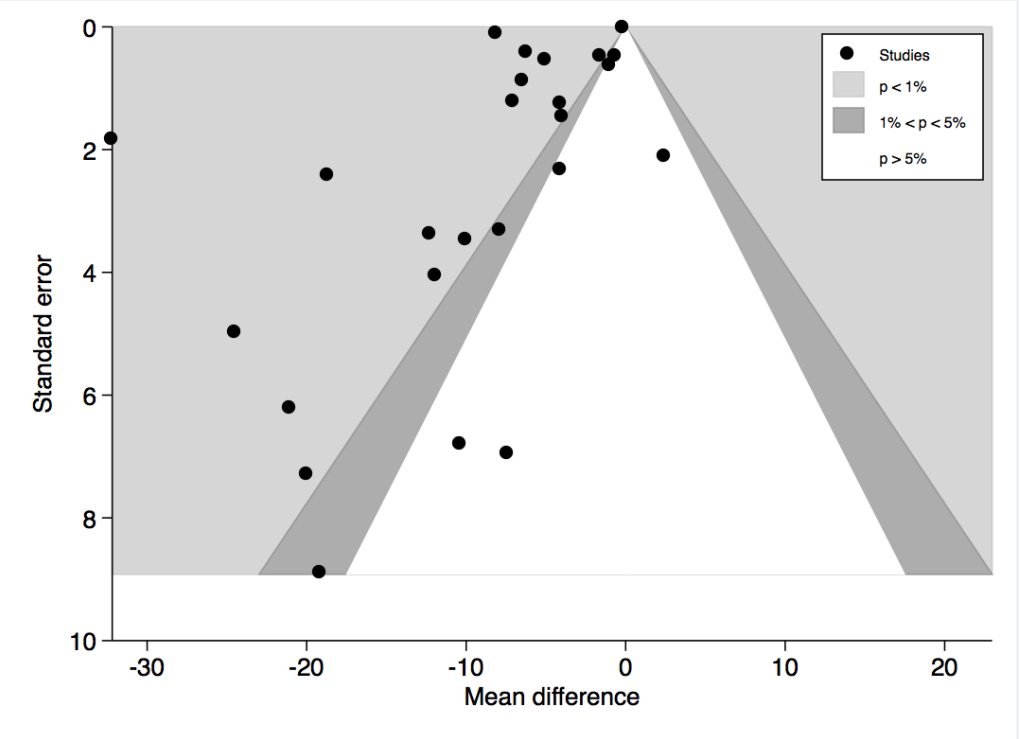


Figure 7.1: Contour-enhanced funnel plot for paracetamol. Areas represent: statistical non-significance (p>0.05; white) and areas of statistical significance (p<0.05; dark grey and p<0.01; light grey).

However, when re-examining funnel plots when studies were sub-grouped on the degree of control group morphine consumption, the plot showed a relationship between standard errors and baseline risk (Figure 7.2). On linear regression analysis, control group morphine consumption was a significant predictor of standard errors (R^2=52%; p<0.001). On testing assumptions, one study had a studentised residual of more than three although no study had a Cook's distance of more than one. Residuals were normally distributed and there was no evidence of heteroscedasticity. When performing trim and fill analysis, seven studies were trimmed which reduced effect estimates by 43%.

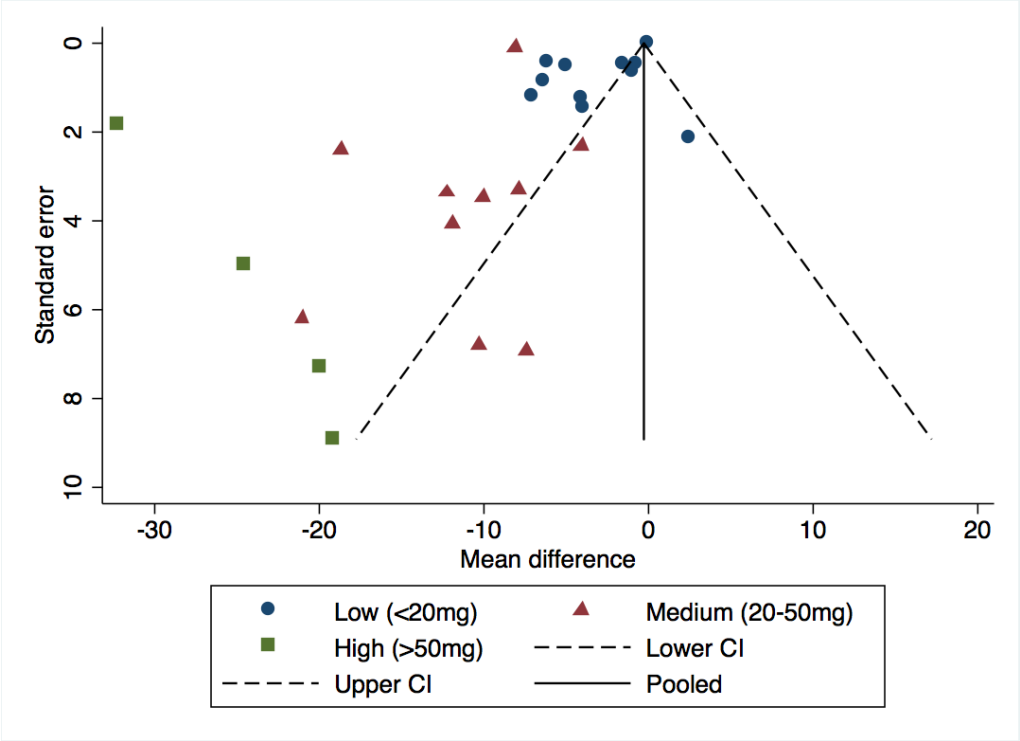


Figure 7.2: Funnel plot for paracetamol. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.3 NSAIDS and COX-2 inhibitors

The NSAIDS and COX-2 inhibitors analysis included 86 RCTs. There was evidence of funnel plot asymmetry with a statistically significant Egger's linear regression test ($p<0.001$). Contour-enhanced funnel plots showed most of the studies were in regions of statistical significance suggesting publication bias as a cause rather than other factors (Figure 7.3).

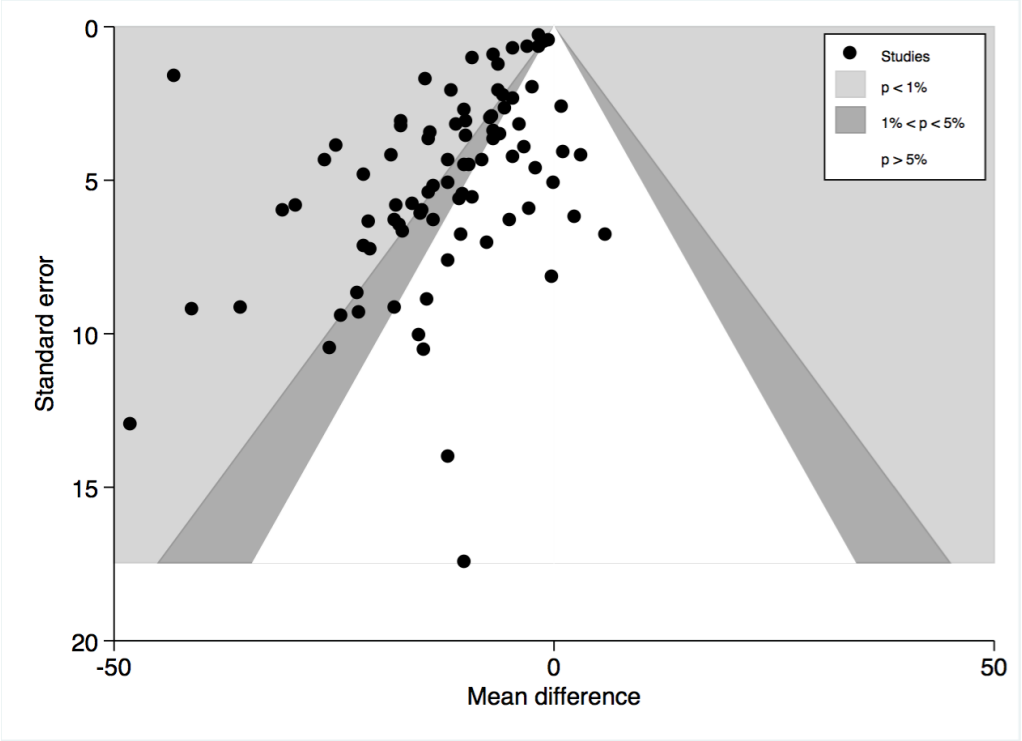


Figure 7.3: Contour-enhanced funnel plot for NSAIDS and COX-2 inhibitors. Areas represent: statistical non-significance ($p>0.05$; white) and areas of statistical significance ($p<0.05$; dark grey and $p<0.01$; light grey).

However, when re-examining funnel plots sub-grouped on the basis of control group morphine consumption, there appeared to be a relationship with studies with higher consumption having larger standard errors (Figure 7.4). When performing linear regression analysis, control group morphine consumption was a significant predictor of standard errors (R^2=45%; p<0.001). On testing regression assumptions, residuals were normally distributed and there was no evidence of heteroscedasticity. One study had a studentised residual of more than three although no study had a Cook's distance of more than one. When performing trim and fill analysis, 27 studies were trimmed which decreased effect estimates by 60%.

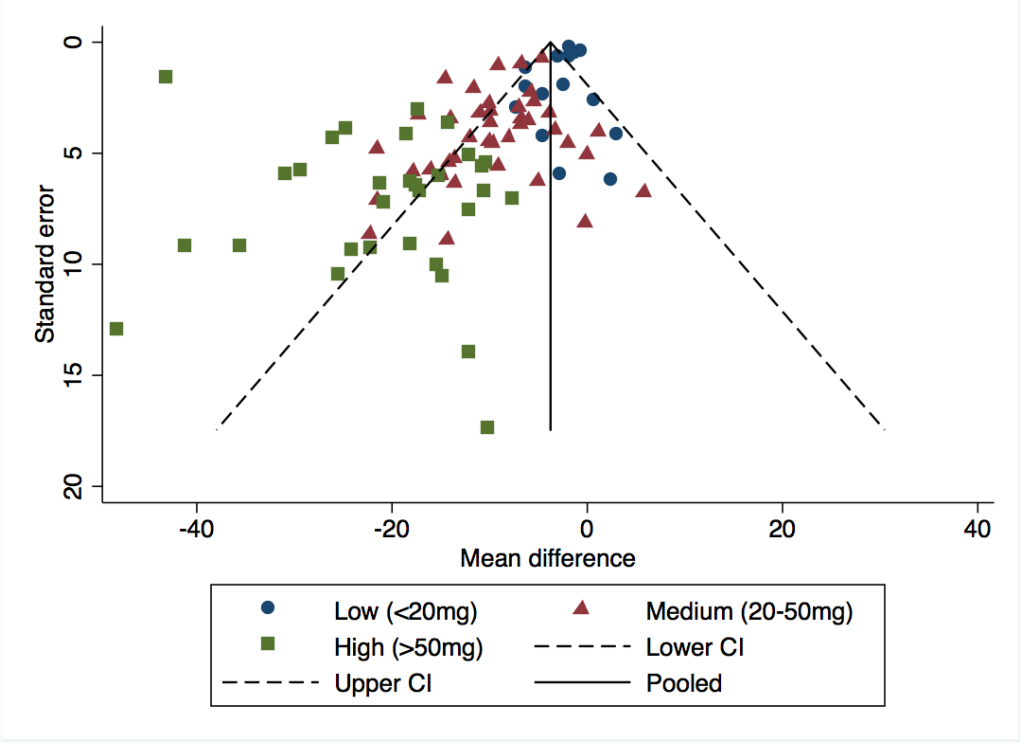


Figure 7.4: Funnel plot of NSAIDS and COX-2 inhibitors. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.4 Ketamine

The ketamine analysis included 62 RCTs. Although there was some funnel plot asymmetry, Egger's linear regression was not statistically significant (p=0.17) (Figure 7.5). It was difficult to see in which regions studies were located.

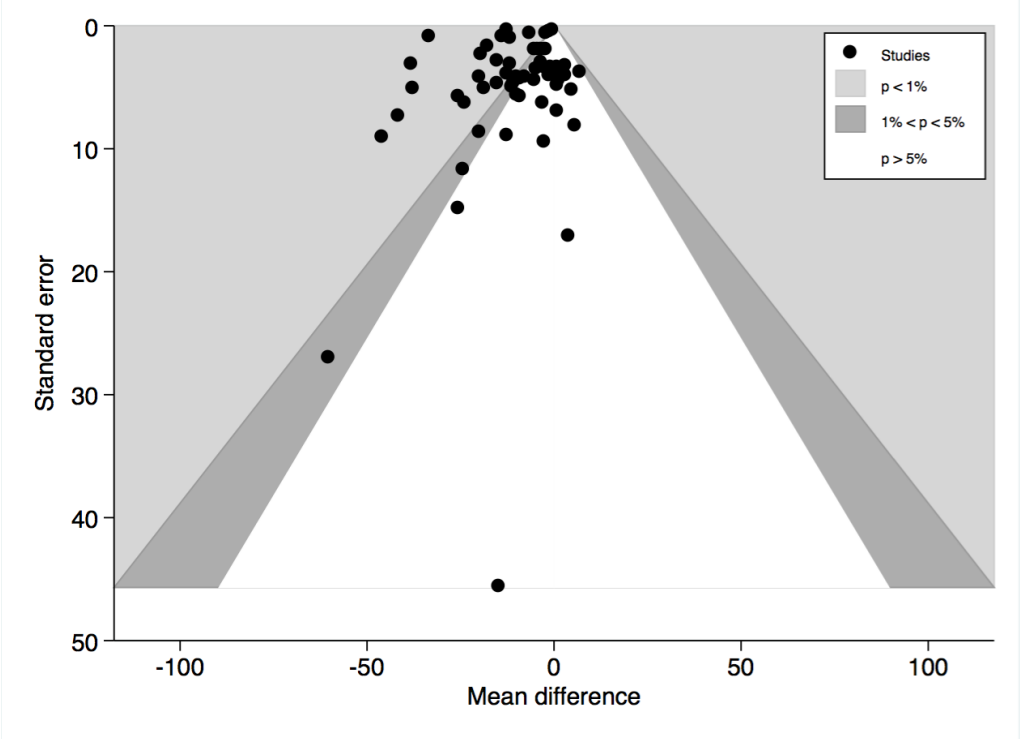


Figure 7.5: Contour-enhanced funnel plot for ketamine. Areas represent: statistical non-significance (p>0.05; white) and areas of statistical significance (p<0.05; dark grey and p<0.01; light grey).

When re-examining funnel plots with studies sub-grouped on the degree of control group morphine consumption, there appeared to be relationship between morphine consumption and study standard errors, although less so than with previous analyses (Figure 7.6). On linear regression analysis, control group morphine consumption predicted standard errors (R^2=63%; p<0.001). On testing assumptions, residuals were normally distributed, although there was some evidence of heteroscedasticity. Two studies had a studentised residual of more than three and one study had a Cook's distance of more than one. Deleting this data point reduced the variation explained (R^2=45%; p<0.001). When performing trim and fill analysis, three studies were trimmed but this increased effect estimates by 8%.

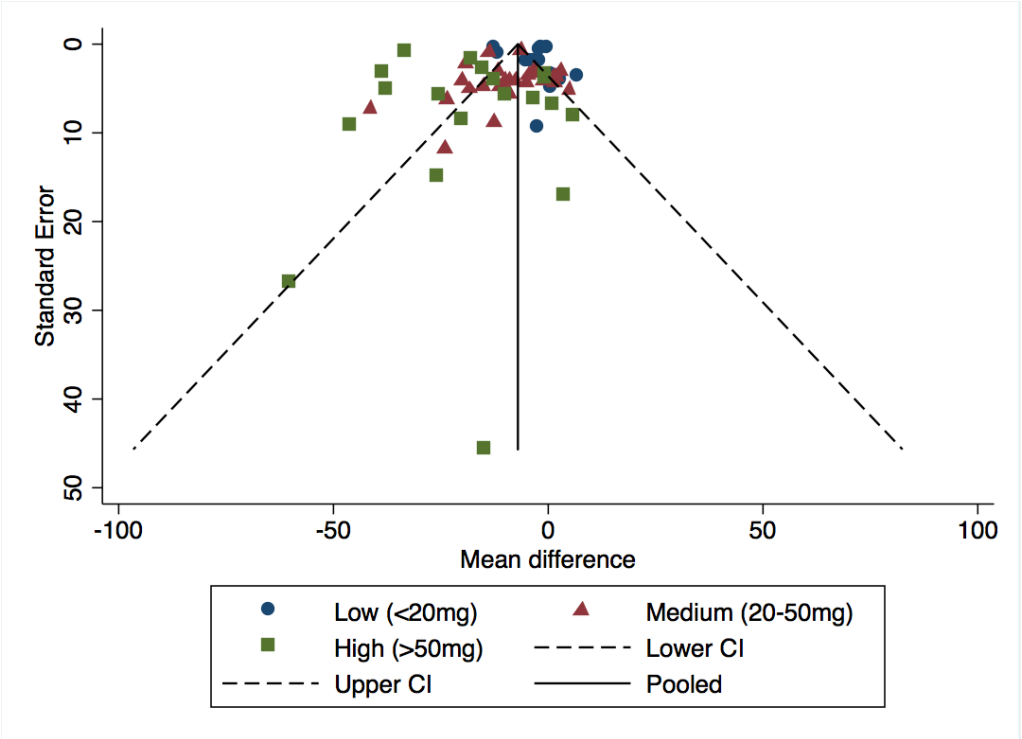


Figure 7.6: Funnel plot of ketamine. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.5 Alpha-2 agonists (clonidine and dexmedetomidine)

The alpha-2 agonists analysis included 33 RCTs. There was evidence of funnel plot asymmetry with a statistically significant Egger's linear regression test (p=0.02). Contour-enhanced funnel plots showed most studies were located in regions of statistical significance suggesting publication bias rather than other causes (Figure 7.7).

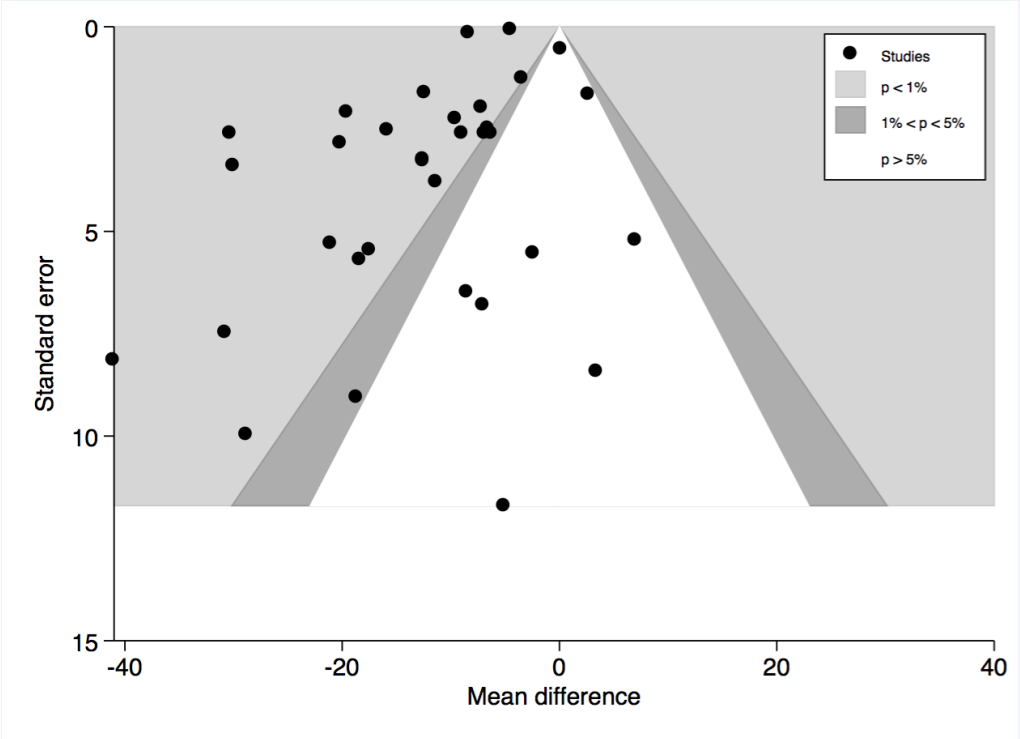


Figure 7.7: Contour-enhanced funnel plot for alpha-2 agonists. Areas represent: statistical non-significance (p>0.05; white) and areas of statistical significance (p<0.05; dark grey and p<0.01; light grey).

Again, when studies were sub-grouped based on the degree of control group morphine consumption, there appeared to be a relationship between morphine consumption and standard errors, with larger consumption having larger standard errors (Figure 7.8). Linear regression analysis showed control group morphine consumption was a significant predictor of standard errors (R^2=55%; p<0.001). On testing regression assumptions, there was some positive skew on residual histograms although there was no evidence of heteroscedasticity. One study had a studentised residual of more than three although no study had a Cook's distance of more than one. When analysing with trim and fill analysis, six studies were trimmed which decreased effect estimates by 22%.

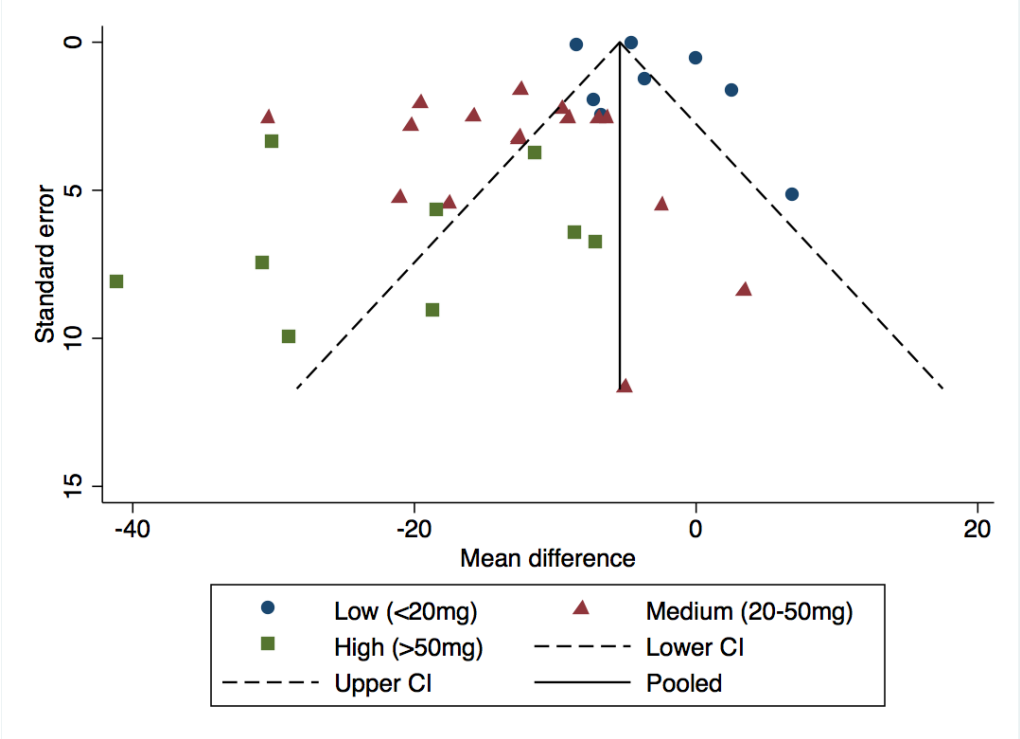


Figure 7.8: Funnel plot of alpha-2 agonists. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.6 Gabapentin

The gabapentin analysis included 67 RCTs. There was evidence of funnel plot asymmetry with a statistically significant Egger's linear regression test ($p<0.001$). Contour-enhanced funnel plots showed more studies in regions of statistical significance, suggesting publication bias as a cause rather than other causes (Figure 7.9).

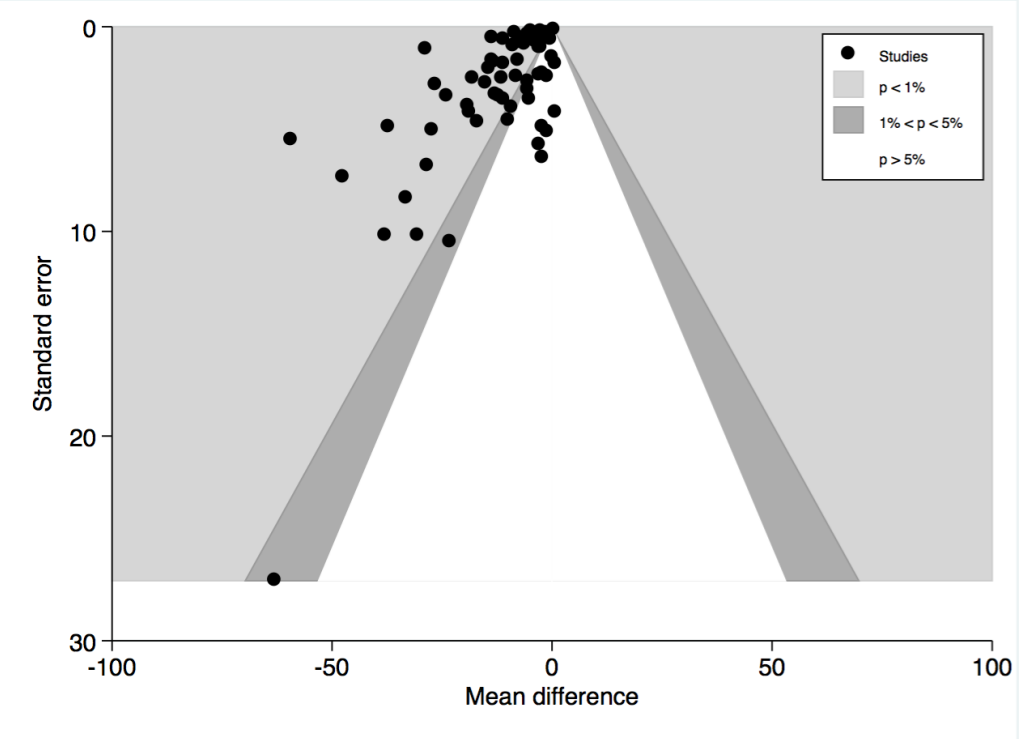


Figure 7.9: Contour-enhanced funnel plot for gabapentin. Areas represent: statistical non-significance ($p>0.05$; white) and areas of statistical significance ($p<0.05$; dark grey and $p<0.01$; light grey).

When re-examining funnel plots with studies sub-grouped on the basis of control group morphine consumption, there appeared to be a relationship between the degree of consumption and larger standard errors (Figure 7.10). On linear regression analysis, control group morphine consumption was a significant predictor of standard errors (R^2=60%; p<0.001). On testing regression assumptions, residuals were normally distributed and there was no evidence of heteroscedasticity. Two studies had a studentised residual of more than three and one study had a Cook's distance of more than one. However, deleting this study had no effect on the results. When analysing using trim and fill analysis, six studies were trimmed which decreased effect estimates by 12%.

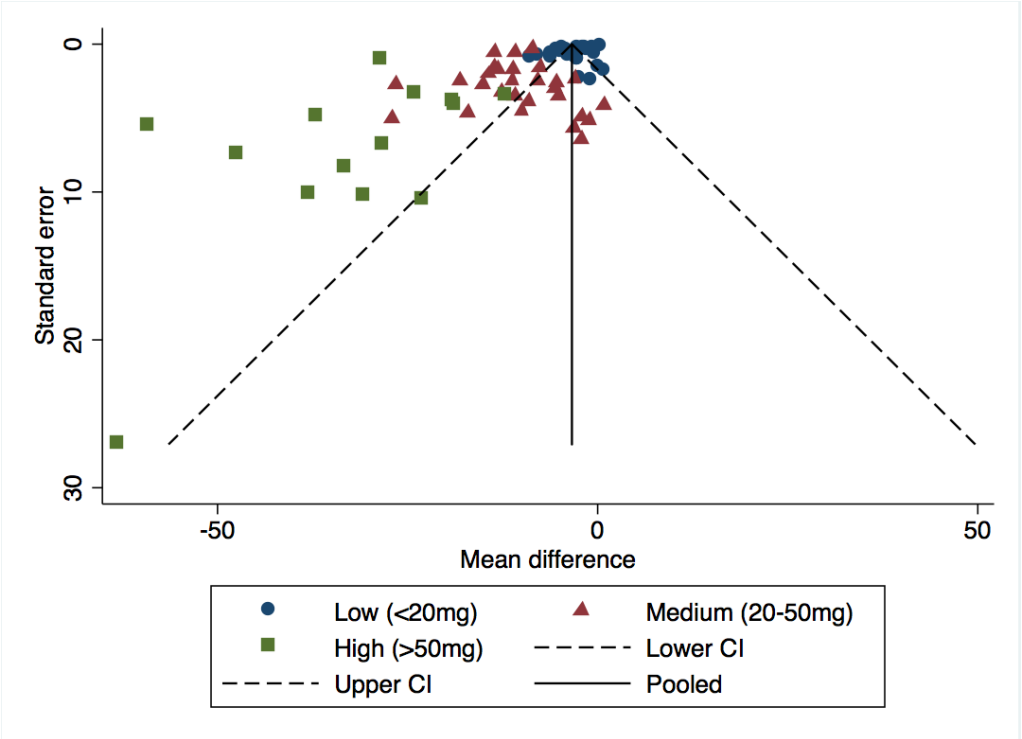


Figure 7.10: Funnel plot of gabapentin. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.7 Pregabalin

The pregabalin analysis included 34 RCTs. There was evidence of funnel plot asymmetry with a statistically significant Egger's linear regression test ($p<0.001$). Contour-enhanced funnel plots showed most studies were located in regions of statistical significance suggesting publication bias as a cause rather than other factors (Figure 7.11).

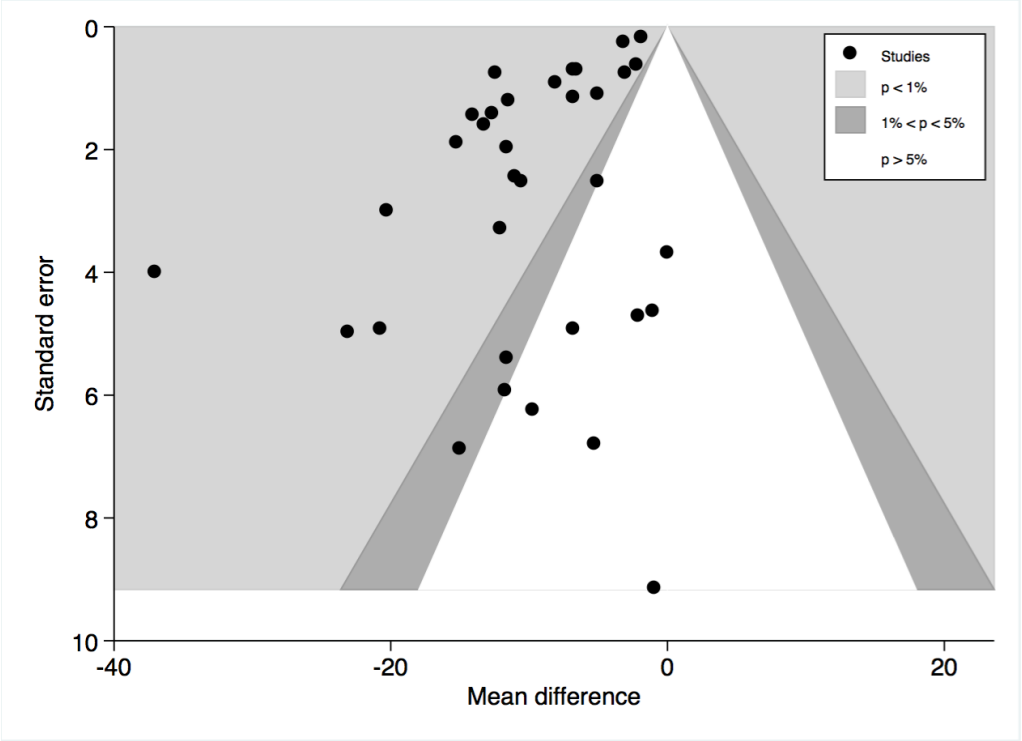


Figure 7.11: Contour-enhanced funnel plot for pregabalin. Areas represent: statistical non-significance ($p>0.05$; white) and areas of statistical significance ($p<0.05$; dark grey and $p<0.01$; light grey).

When re-examining funnel plots with studies sub-grouped on the basis of control group morphine consumption, there appeared to be a relationship between higher consumption and higher standard errors (Figure 7.12). On linear regression analysis, control group morphine consumption was a significant predictor of standard errors (R^2=48%; p<0.001). On testing assumptions, residuals were normally distributed although there was some evidence of heteroscedasticity. No study had a studentised residual of more than three and no study had a Cook's distance of more than one. When analysing using trim and fill analysis, two studies were trimmed although this increased effect estimates by 3%.

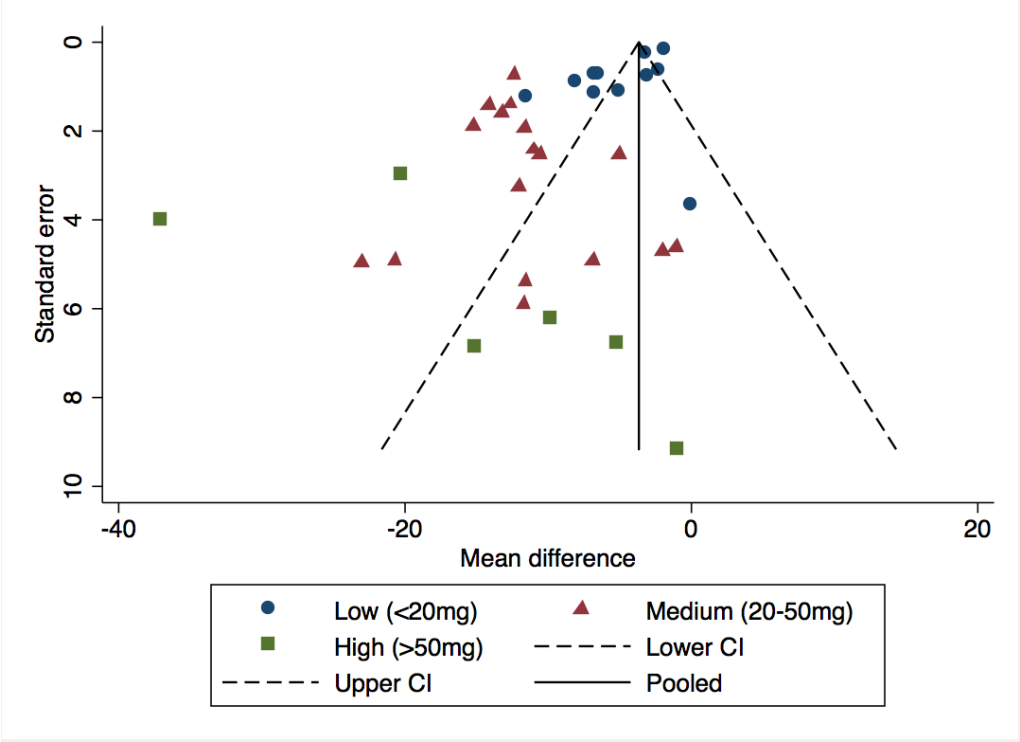


Figure 7.12: Funnel plot of pregabalin. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.8 Nefopam

There were too few studies to investigate publication bias for nefopam.

7.3.9 Lidocaine

In the lidocaine analysis there were 22 RCTs. There was evidence of funnel plot asymmetry with a statistically significant Egger's linear regression test (p=0.02). Contour-enhanced funnel plots showed most studies were in regions of statistical non-significance, suggesting other causes than publication bias (Figure 7.13).

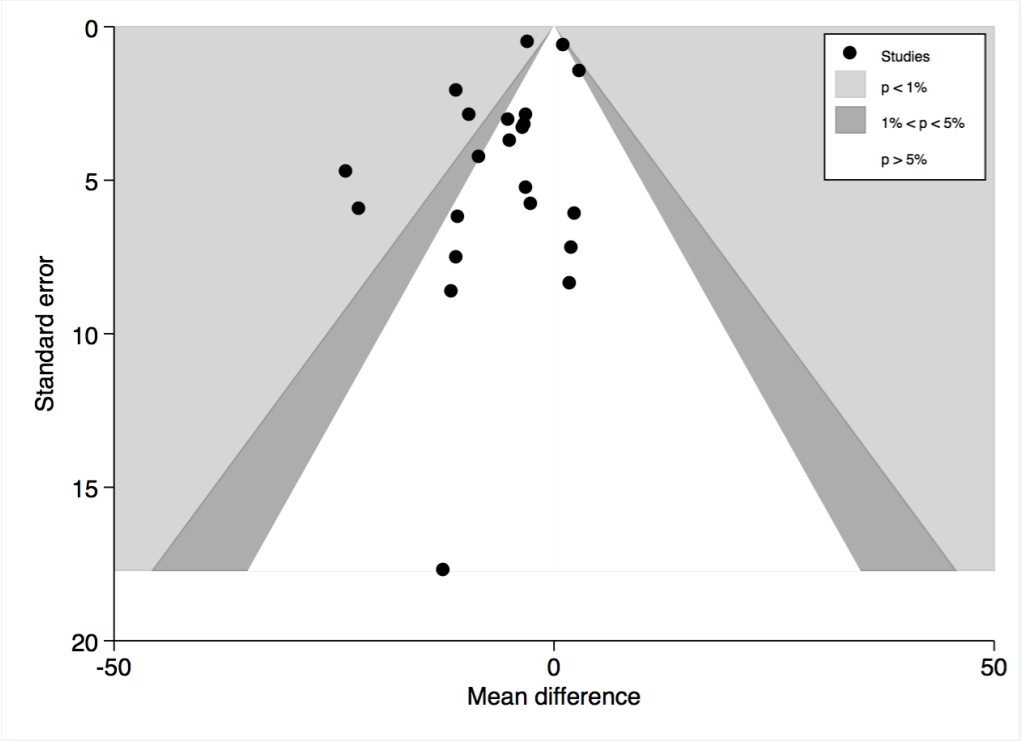


Figure 7.13: Contour-enhanced funnel plot for lidocaine. Areas represent: statistical non-significance (p>0.05; white) and areas of statistical significance (p<0.05; dark grey and p<0.01; light grey).

When re-examining funnel plots with studies sub-grouped on the basis of control group morphine consumption, there again appeared to be a relationship between higher consumptions and higher standard errors, although less so than with other analyses (Figure 7.14). On linear regression analysis, control group morphine consumption was a significant predictor of standard errors (R^2=31%; p=0.007). On testing regression assumptions, there was some positive skew on residual histograms although there was no evidence of heteroscedasticity. One study had a studentised residual of more than three although no study had a Cook's distance of more than one. When analysing using trim and fill analysis, no studies were trimmed.

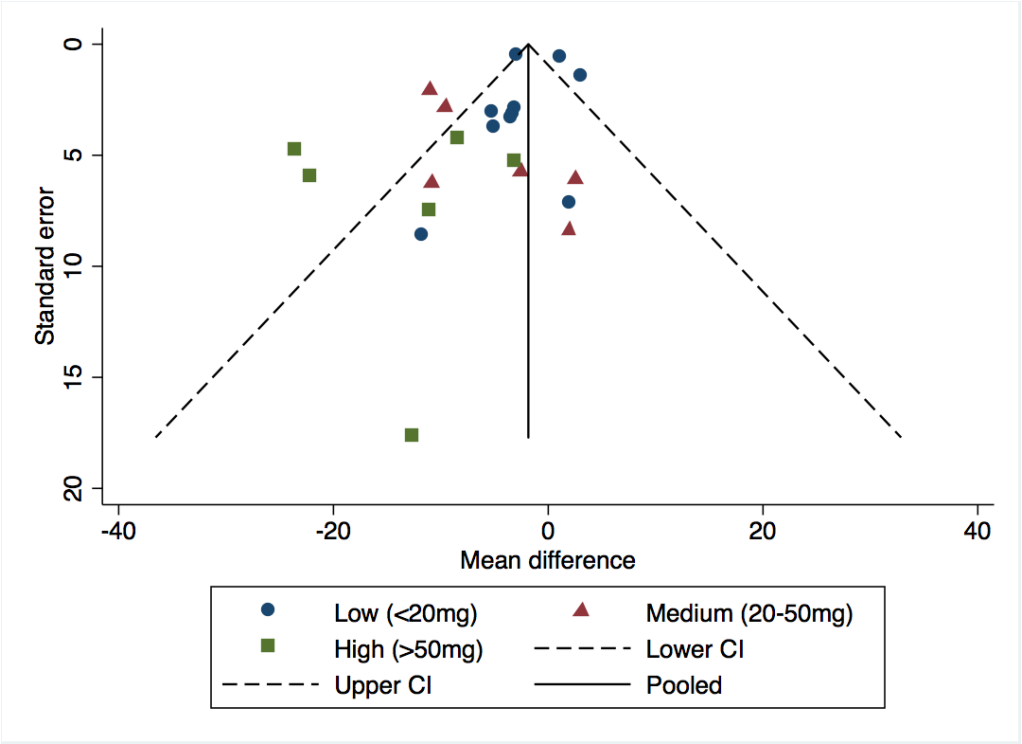


Figure 7.14: Funnel plot of lidocaine. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.10 Dexamethasone

In the dexamethasone analysis there were 16 RCTs. There was evidence of funnel plot asymmetry with a statistically significant Egger's linear regression test (p=0.09). However, when examining contour-enhanced funnel plots, most studies were in regions of statistical non-significance suggesting other causes than publication bias (Figure 7.15).

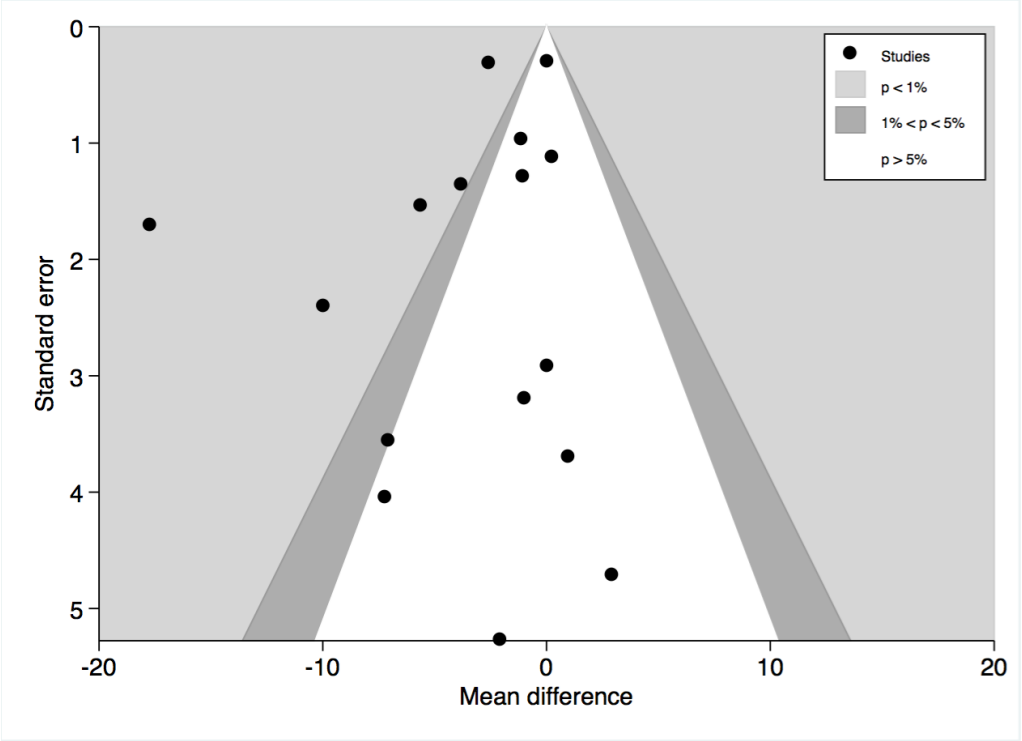


Figure 7.15: Contour-enhanced funnel plot for dexamethasone. Areas represent: statistical non-significance (p>0.05; white) and areas of statistical significance (p<0.05; dark grey and p<0.01; light grey).

When re-examining funnel plots sub-grouped on the degree of control group morphine consumption there appeared to be a relationship between higher consumption and higher standard errors, although medium consumption (20-50mg) appeared to have the largest standard errors (Figure 7.16). However, on linear regression analysis, control group morphine consumption was not a significant predictor of standard errors (R^2=18%; p=0.1). On testing regression assumptions, residuals were normally distributed although the data appeared to violate the assumption of linearity. No study had a studentised residual of more than three although one study had a Cook's distance of more than one. Deleting this study resulted in a significant prediction (R^2=40%; p=0.01). When analysing using trim and fill analysis, two studies were trimmed which increased effect estimates by 11%.

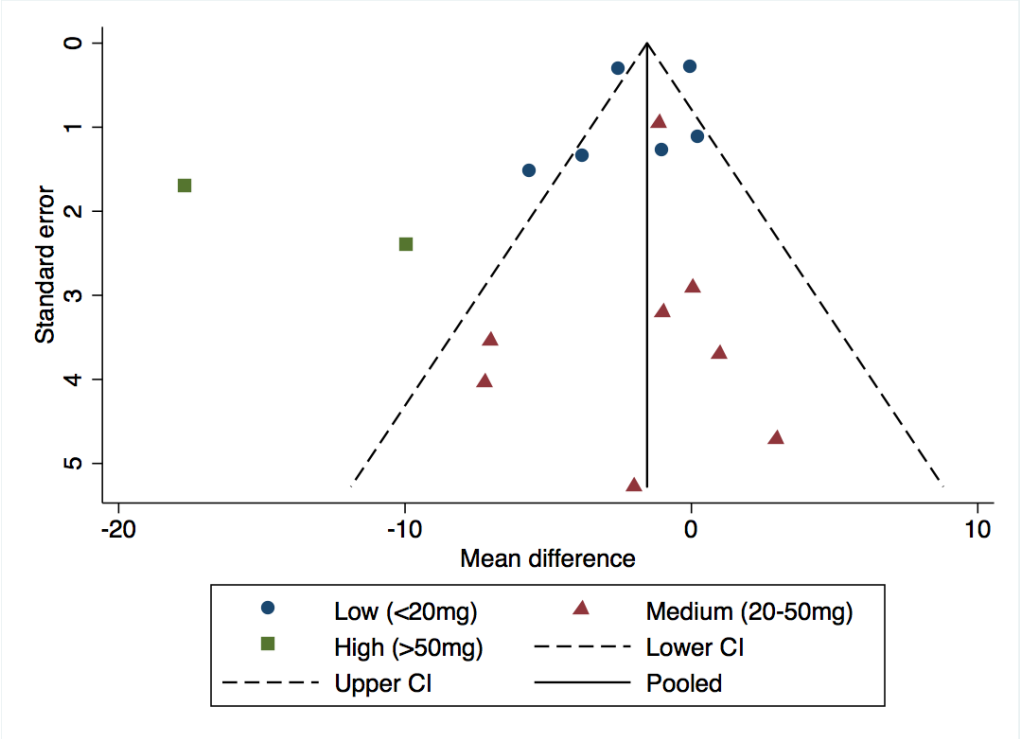


Figure 7.16: Funnel plot of dexamethasone. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.11 Magnesium

The magnesium analysis included 22 RCTs. There was some evidence of funnel plot asymmetry although Egger's linear regression test was not statistically significant (p=0.21) (Figure 7.17). Most studies were in regions of statistical significance.

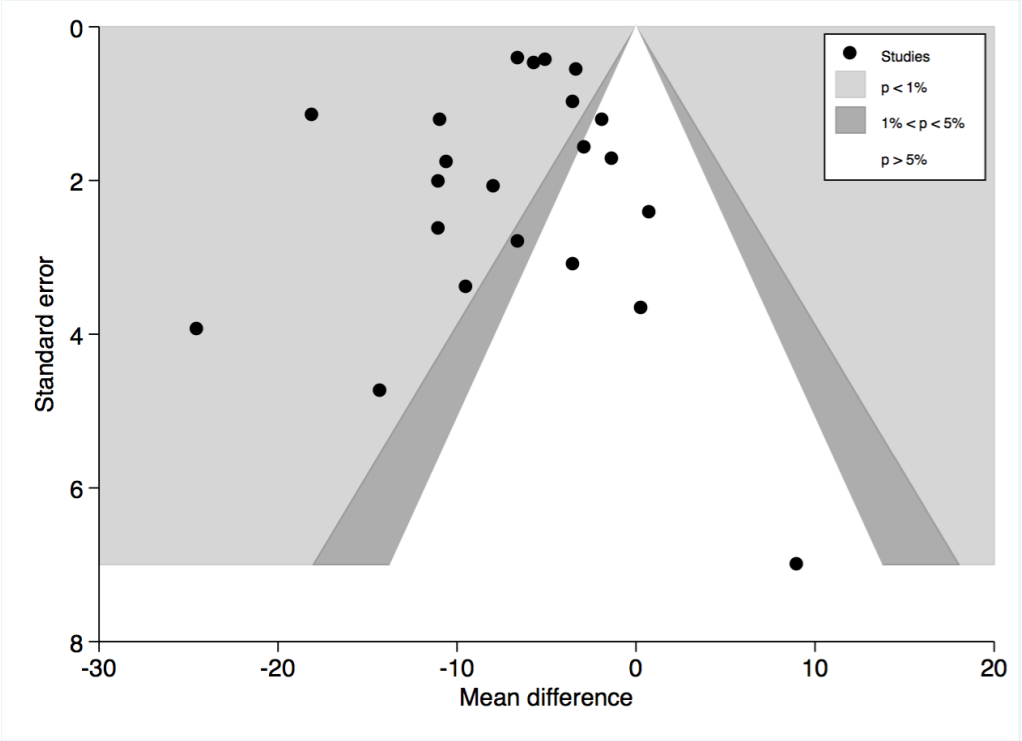


Figure 7.17: Contour-enhanced funnel plot for magnesium. Areas represent: statistical non-significance (p>0.05; white) and areas of statistical significance (p<0.05; dark grey and p<0.01; light grey).

When re-examining funnel plots sub-grouped on control group morphine consumption, there was a relationship between higher consumption and higher standard errors (Figure 7.18). However, on linear regression analysis control group morphine consumption was not a significant predictor of standard errors (R^2=5%; p=0.34). On testing regression assumptions, residuals were positively skewed although there was no evidence of heteroscedasticity. One study had a studentised residual of more than three although no study had a Cook's distance of more than one. When analysing using trim and fill analysis, one study was trimmed which increased effect estimates by 3%.

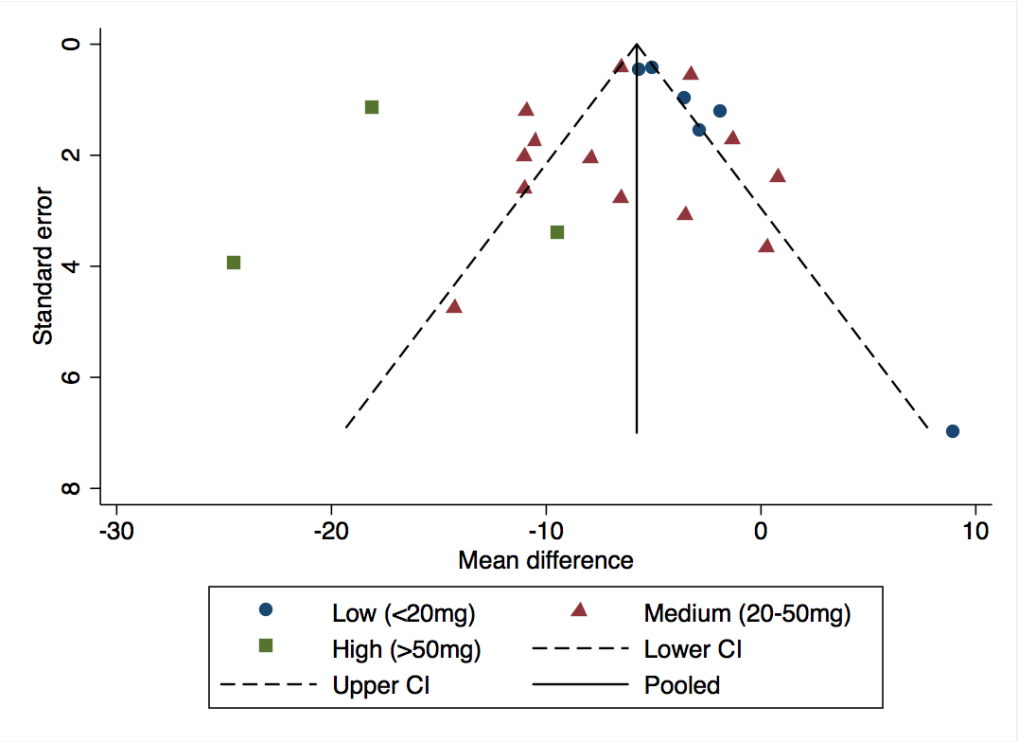


Figure 7.18: Funnel plot of magnesium. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.12 Tramadol

The tramadol analysis included 11 RCTs. There was some evidence of funnel plot asymmetry although Egger's linear regression test was not statistically significant (p=0.23) (Figure 7.19). Most studies were in regions of statistical significance.

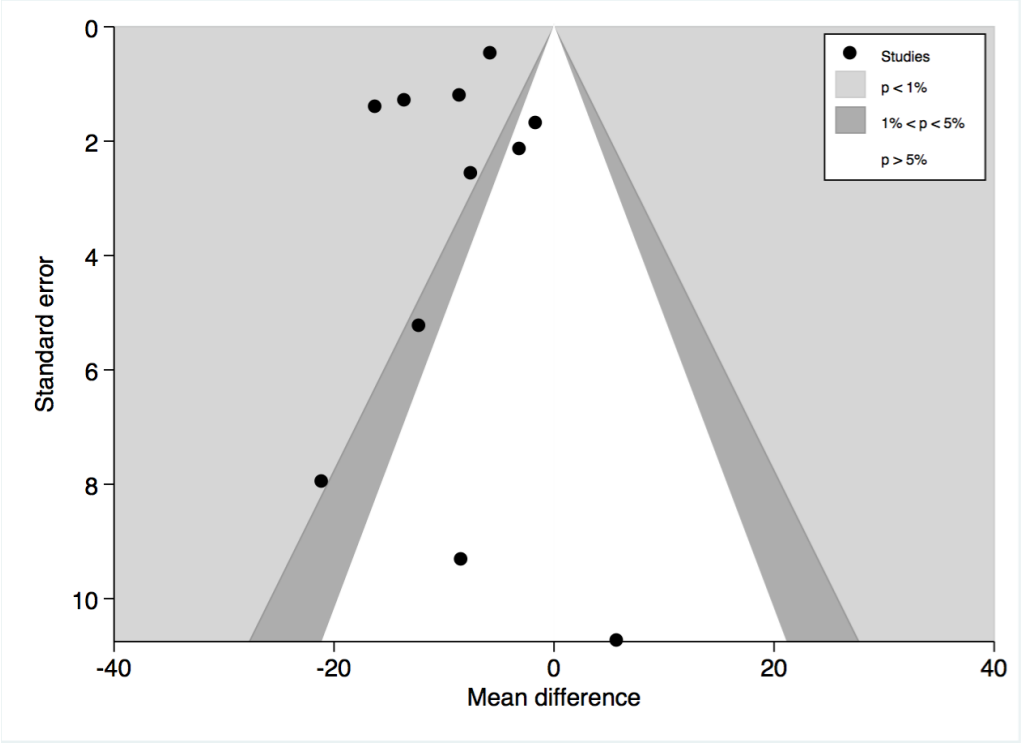


Figure 7.19: Contour-enhanced funnel plot for tramadol. Areas represent: statistical non-significance (p>0.05; white) and areas of statistical significance (p<0.05; dark grey and p<0.01; light grey).

When re-examining funnel plots sub-grouped on the basis of control group morphine consumption, there appeared to be a relationship between higher consumption and higher standard errors (Figure 7.20). However, on linear regression analysis, control group morphine consumption was not a significant predictor of standard errors (R^2=23%; p=0.14). On testing regression assumptions, there was some positive skew on residual histograms although there was no evidence of heteroscedasticity. No study had a studentised residual of more than three and no study had a Cook's distance of more than one. When analysing using trim and fill analysis, no studies were trimmed.

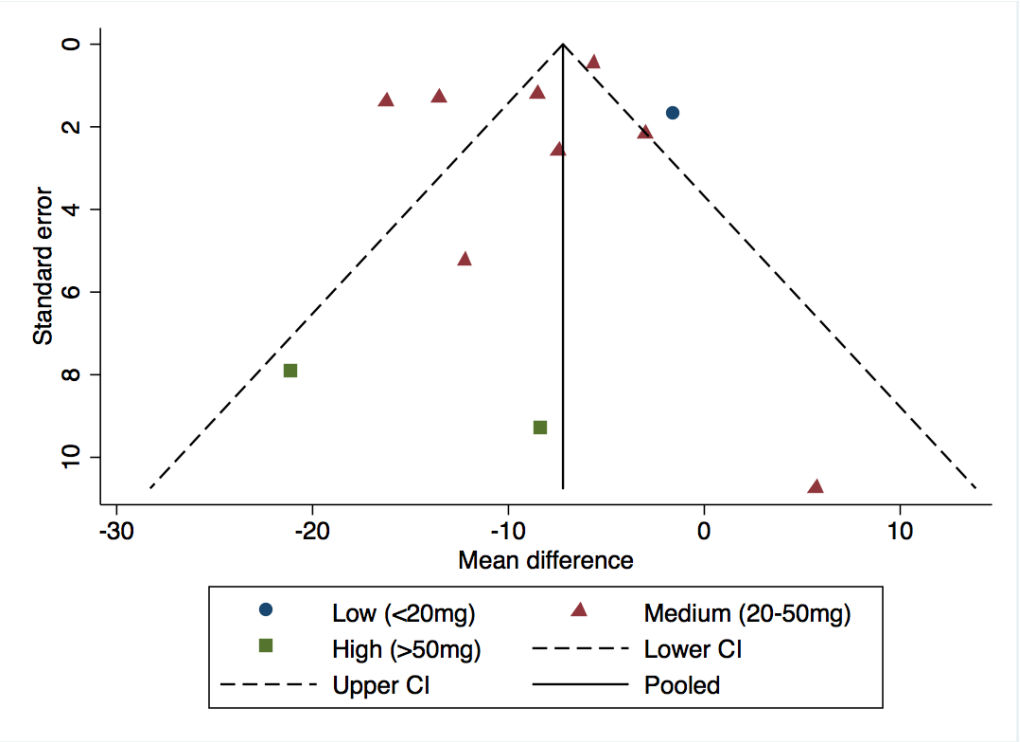


Figure 7.20: Funnel plot of tramadol. Studies are sub-grouped based on control group morphine consumption (see legend).

7.3.13 Simulated meta-analyses

We simulated eight meta-analyses with no publication bias where both effect sizes and standard deviations were dependent on baseline risk (Figure 7.21; analysis performed in collaboration with Professor Alex Sutton). When observing the figure below (from top left), funnel plots using mean differences on the X-axis and standard errors (on a reverse scale) on the Y axis (A on Figure 7.21) demonstrate funnel plot asymmetry (all p<0.001 on Egger's linear regression test). The corresponding meta-analyses using residual values on the X axis (B on Figure 7.21) resolve this asymmetry (p=0.1 to p=0.99).

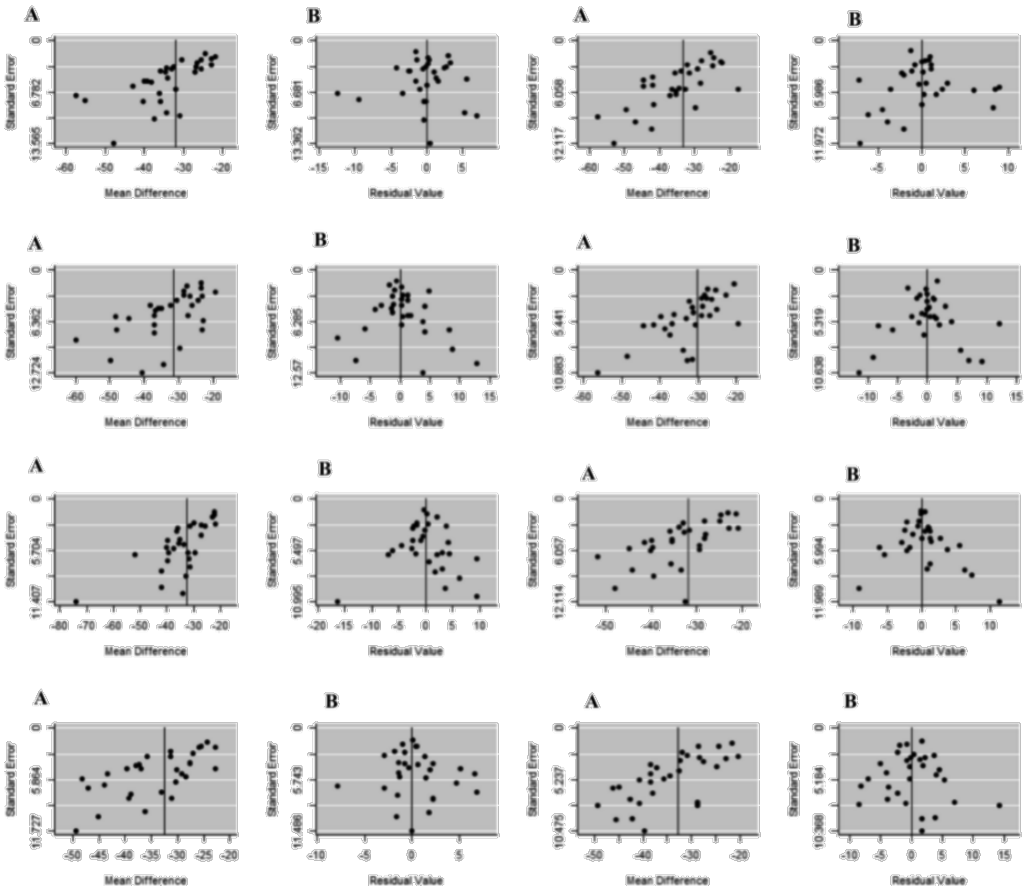


Figure 7.21: Funnel plots of simulated meta-analyses. Shows both traditional axes using mean differences and standard errors (A) and novel axes using residuals and standard errors (B).

7.4 Discussion

7.4.1 Summary of results

This chapter has identified widespread evidence of imprecise study effects (using traditional methods) in meta-analyses of analgesic adjuncts, despite the use of various search strategies and wide inclusion criteria in our review. We found evidence that only a small proportion of included reviews employed methods aimed at preventing possible publication bias despite around half employing methods to identify imprecise study effects. When adjusted for a symmetric funnel plot, in some cases effect estimates were adjusted by a large degree. However, when examining the relationship between control group morphine consumption (baseline risk) and imprecision, for most analgesics there was a significant relationship between baseline risk and standard errors implying that funnel plots may be an inaccurate method to assess publication bias where values are dependent on baseline risk. Indeed, when we simulated similar meta-analyses where no publication bias was present, funnel plot asymmetry was evident for all analyses ($p<0.001$). Moreover, we have presented a novel method to correct this artifactual asymmetry using meta-regression residuals.

7.4.2 Links with other research

The prevalence of publication bias within meta-analyses is estimated to be around 25%-40% (Egger *et al.* 1997a; Sterne, Gavaghan and Egger 2000). Within the anaesthesia literature, using a sample of systematic reviews from leading anaesthetic journals, the prevalence of publication bias has been estimated to be 50-80% (Hedin *et al.* 2016). This has important implications for the validity of systematic review findings, as publication bias has been found to be the cause when meta-analyses and subsequent large RCTs disagree (Egger *et al.* 1997a). Meta-analyses are frequently used to inform clinical decision-making and guidelines; therefore using invalid data may lead to the use of ineffective or even harmful interventions in clinical practice.

Due to the consequences of publication bias, methods were developed to help identify it. We found that only around 50% of included reviews attempted to detect potential publication bias. However, of more concern is the small number of included reviews that employed methods aimed at preventing publication bias. Only 16% of reviews searched unpublished clinical trial databases and 9% searched conference proceedings. Prevention is the most important step in reducing the effects of publication bias and therefore future reviews need to ensure such methods are employed to produce more valid findings. Despite the employment of the above methods for preventing publication bias, these methods would only be successful if trial investigators registered their studies on clinical trial databases. Taking a sample of studies published since 2010 (to allow a decade for conduct and publication since the inception of clinicaltrials.gov), only 23% were registered on such databases. Methods for preventing publication bias can only succeed if all trials are registered. Thankfully, leading journals are now using clinical trial registration as a condition of publication. However, this requirement also needs to be universally adopted by lower impact journals.

Although there is a wealth of research into the use of funnel plots and quantitative tests for the detection of imprecise study effects, little work has been conducted on research using continuous outcomes such as morphine consumption (Higgins and Green 2008). Moreover, less work has been undertaken examining continuous outcomes with considerable heterogeneity and variation in effect estimates dependent on baseline risk. The construction of conventional funnel plots uses effect estimates on the x-axis and standard errors (in reverse order) on the y-axis as a measure of imprecision. The theory is that smaller studies (with higher standard errors) are more likely to show exaggerated results and as study size gets larger (and hence standard error smaller), the results should converge closer to the mean effect derived from the meta-analysis. Therefore, unpublished smaller studies can be identified as missing from one side of the base of the funnel plot, suggesting possible publication bias.

However, the outcome of morphine consumption presents problems for this underlying assumption. We have previously demonstrated that the results from any one study are dependent on control group morphine consumption (with higher baseline risk having larger reductions in morphine consumption). In addition, the trials included in our meta-analyses are often small (50-100 participants) and therefore standard error calculations will be more dependent on standard deviations than for larger studies (as SE = SD / √N). As there is a tendency for studies with higher control group morphine consumption to have larger standard deviations there is a dependency between the mean difference (larger with higher baseline risk) and the standard errors (larger with higher baseline risk). This could create an asymmetric funnel plot even in the presence of no publication bias (analogous to a rotated scatter plot). Indeed, for most analyses, baseline risk was a significant predictor of standard errors on linear regression analysis. Moreover, when we simulated meta-analyses where no publication bias was present, funnel plot asymmetry was evident in all analyses. Therefore, we would argue that traditional funnel plots are not a reliable method to detect imprecise study effects for morphine consumption and that this finding may also extend to other, similar continuous outcomes whose results are dependent on baseline risk (such as pain scores).

This dependency can also present issues for meta-analyses of continuous outcomes. If the results from a meta-analysis vary with baseline risk, this will cause issues with the weighting of individual studies when calculating pooled effect estimates. As studies with lower baseline risk (lower control group morphine consumption) with have lower standard errors, they will receive a higher percentage weight than studies with higher baseline risk (using the inverse-variance method). This will mean effect estimates will be lower than the true average effect, leading to an underestimation of efficacy. Therefore, this further suggests meta-regression estimates from a fixed consumption of morphine may give a more accurate representation of efficacy than mean differences.

Assuming that funnel plot asymmetry is secondary to publication bias using conventional analyses may have serious consequences for the results of a meta-

analysis. For example, when performing tests to adjust for funnel plot asymmetry (trim and fill analysis), effect estimates changed for some analyses by 12-60%. This has the potential to have a significant effect on meta-analysis conclusions. However, it should be noted that our findings of funnel plot asymmetry did not extend to all analgesic adjuncts. For tramadol, magnesium and ketamine there was no evidence of imprecise study effects.

7.4.3 Implications for research and clinical practice

Clearly, the issues highlighted above have implications for the interpretation of results derived from meta-analyses. Incorrect conclusions regarding the presence of publication bias could lead to unnecessary downgrading of evidence as per GRADE (Guyatt *et al.* 2008). In addition, the conduct of trim and fill analysis could reduce effect estimates and significantly alter a reviews conclusions, which may be inappropriate. These factors need to be considered when performing meta-analyses using postoperative morphine consumption. Furthermore, these findings may also extend to similar outcomes, such as pain scores, which may also be dependent on baseline risk (Doleman *et al.* 2015a).

In terms of conduct of future meta-analyses, as we have demonstrated that traditional funnel plots may be an inaccurate method for assessing publication bias in analyses dependent on baseline risk, we suggest future reviews utilise the methods presented in this chapter. Namely, funnel plots should be constructed using meta-regression residual values on the X-axis and standard errors on the Y-axis. These can then be formally tested using Egger's linear regression test. However, further simulation studies are required to test this novel method under a variety of assumptions.

Finally, in terms of future primary and secondary study conduct, more reviews should aim to employ methods that aim to prevent potential publication bias by searching clinical trial databases, conference proceedings and grey literature databases. However, this also requires RCTs to register on clinical trial databases and trial investigators to engage with review authors when unpublished trial data is requested. Furthermore, the practice of journals

making clinical trial registration a condition of publication should be extended to all journals in order to help reduce publication bias.

7.4.4 Limitations

The first limitation of this chapter is the use of previously published reviews with variable search strategies. The fact that only a small number of included reviews searched for unpublished studies means our sample would be more likely susceptible to publication bias. However, our aim was to both perform a meta-epidemiological study of existing reviews and identify any publication bias present in the current literature, which made our search strategy appropriate for this aim. Secondly, some of our analyses contained a low number of primary studies, which may render quantitative tests for publication bias underpowered. Finally, trim and fill analysis may perform poorly under the conditions of large between-study heterogeneity, which was present in our review (Peters *et al*. 2007).

7.4.5 Conclusions

We found that only a small amount of included reviews used methods aimed at preventing publication bias and around half used methods aimed at detecting it. Using conventional methods, we found evidence of widespread imprecise study effects for most analgesics used to prevent postoperative pain. However, due to an association between baseline risk and standard errors, this finding may be a result of statistical artefact as demonstrated in our simulations of meta-analyses where no publication bias was present. Therefore, future reviews should employ our alternative methods presented in this chapter.

Chapter 8

Type I and II errors in reviews of analgesics: a trial sequential analysis of low risk of bias studies

8.1 Introduction

Type I and II errors have received widespread attention when conducting primary research studies. Sample size calculations can ensure that studies have sufficient power to detect true differences between groups and reduce type II errors (Moher, Dulberg and Wells 1994), while avoiding (or correcting for) multiple comparisons can help reduce type I errors (Bender and Lange 2001). However, such issues with error have only recently received attention for systematic reviews and meta-analyses. Trial sequential analysis, which is based on group sequential methods for primary RCTs, can both calculate an adequate IS (analogous to sample size calculations) and adjust for multiple comparisons that can occur if hypothetic reviews are performed after the publication of each subsequent trial (analogous to adjustment for multiple comparisons) (Borm and Donders 2009; Imberger *et al.* 2015; Pogue and Yusuf 1998; Thorlund *et al.* 2009).

Although we have previously identified 344 published RCTs evaluating multimodal analgesic agents, these were of varying risk of bias. While we can confidently infer that sufficient data exist to limit type I and type II errors, it is as yet unclear whether there exists sufficient data from low risk of bias trials. We have previously shown that measures of internal validity such as allocation concealment (Schultz and Grimes 2002a), blinding (Schultz and Grimes 2002b) and attrition bias can exaggerate effect estimates. Therefore, it is necessary to establish the evidence base for trials at low risk of bias. With this in mind, the aim of this chapter is to evaluate whether sufficient evidence exists to exclude type I and type II errors in analyses of low risk of bias trials for analgesic adjuncts.

8.2 Methods

8.2.1 Search strategy and data extraction

The search strategy for this analysis is discussed elsewhere (Section 6.2.1). We did not register this review, as it was a *post hoc* analysis based on previous observations and results. We extracted data from previous results in chapter six. Risk of bias for each study has been reported previously (Figure 6.2 to 6.11). We regarded trials at low risk of bias if they received low risk for randomisation, allocation concealment (Schultz and Grimes 2002a), blinding (Schultz and Grimes 2002b) and attrition bias (Juni and Egger 2005), while not receiving any high risk of bias for other elements.

8.2.2 Statistical analysis

We performed a trial sequential analysis for all analgesics included in chapter six. The outcome of interest was 24-hour morphine consumption. If alternative opioids were reported, these were converted to morphine-equivalents using the previously reported conversion factors (Section 6.2.3). As we have previously identified that reductions in morphine consumption are dependent on control group consumption, we used empirical mean differences from the included studies rather than specify clinically significant differences based on mean values. We used empirical estimates of variance and heterogeneity corrections (D^2) from the included studies in the analysis. If this figure was <50%, we conducted sensitivity analysis using heterogeneity corrections of 50% and 80%. These corrections would incorporate the uncertainty from the included studies to increase a required IS in the presence of high between-study heterogeneity (reduce type II errors). We constructed alpha spending monitoring boundaries using the O'Brien-Fleming method with a significance level of $p<0.05$ (reduce type I errors). We used the DerSimonian and Laird method for calculating random-effects estimates. We also constructed futility boundaries using a $1-\beta=0.80$ where possible. We conducted all analyses using TSA software from the Copenhagen Trial Unit (version 0.9.5.5 beta).

8.3 Results

8.3.1 Paracetamol

There were two low risk of bias trials included in the analysis. The results from these trials failed to cross either the conventional or O'Brien-Fleming boundary for statistical significance (Figure 8.1). In addition, the results failed to reach the required IS for a definitive answer (386 participants).

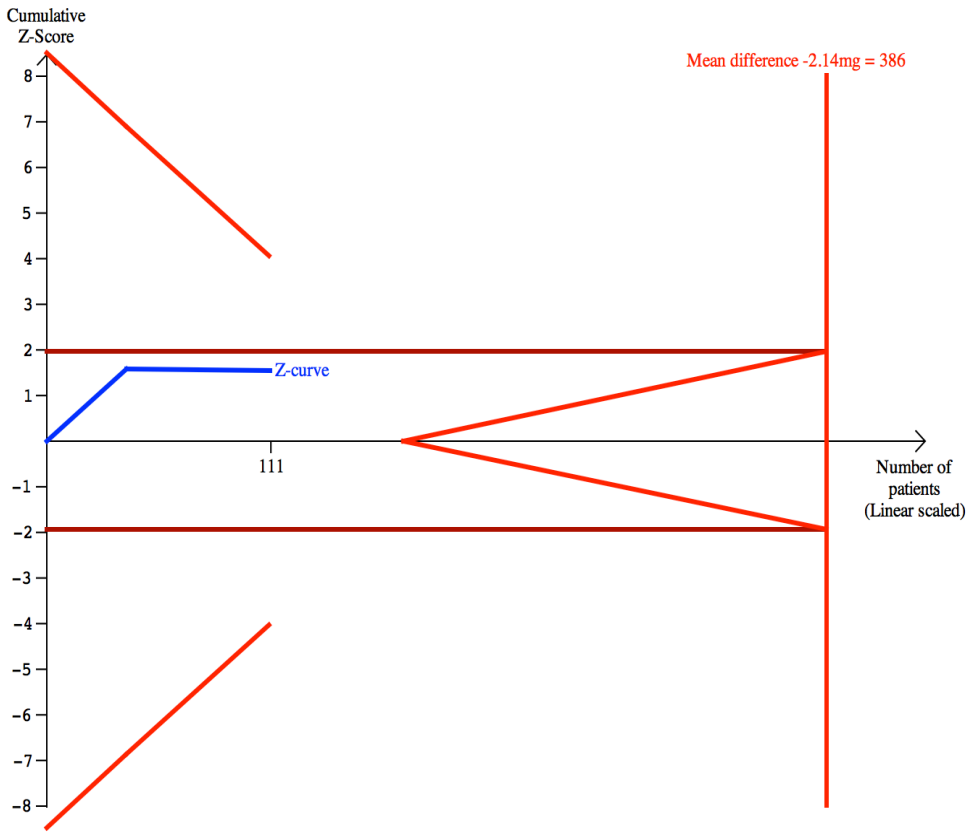


Figure 8.1: Trial sequential analysis of low risk of bias trials for paracetamol. Performed assuming an empirical MD of -2.14mg, variance of 9.4, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 83.2. Blue line indicates cumulative Z score with values more than 0 indicating benefit with paracetamol.

8.3.2 NSAIDS and COX-2 inhibitors

The NSAIDS and COX-2 inhibitors analysis included three low risk of bias trials. The results failed to cross the conventional or O'Brien-Fleming boundary for statistical significance (Figure 8.2). In addition, the results failed to reach the required IS (534 participants).

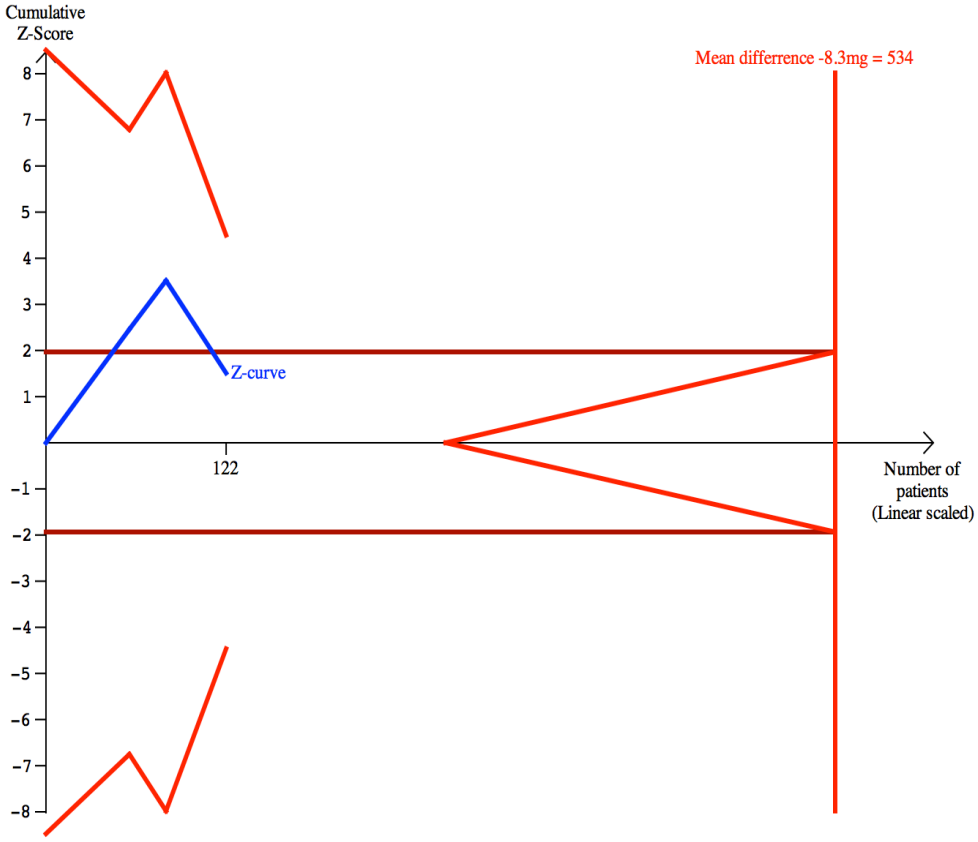


Figure 8.2: Trial sequential analysis of low risk of bias trials for NSAIDS and COX-2 inhibitors. Performed assuming an empirical MD of -8.3mg, variance of 6.9, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 99.3. Blue line indicates cumulative Z score with values more than 0 indicating benefit with NSAIDS and COX-2 inhibitors.

8.3.3 Ketamine

The ketamine analysis included 11 trials at low risk of bias. Although the ketamine analysis crossed the boundary for conventional statistical significance, it did not cross the adjusted O'Brien-Fleming boundary for statistical significance (Figure 8.3). In addition, the ketamine analysis failed to reach the required IS for a definitive answer (1602 participants).

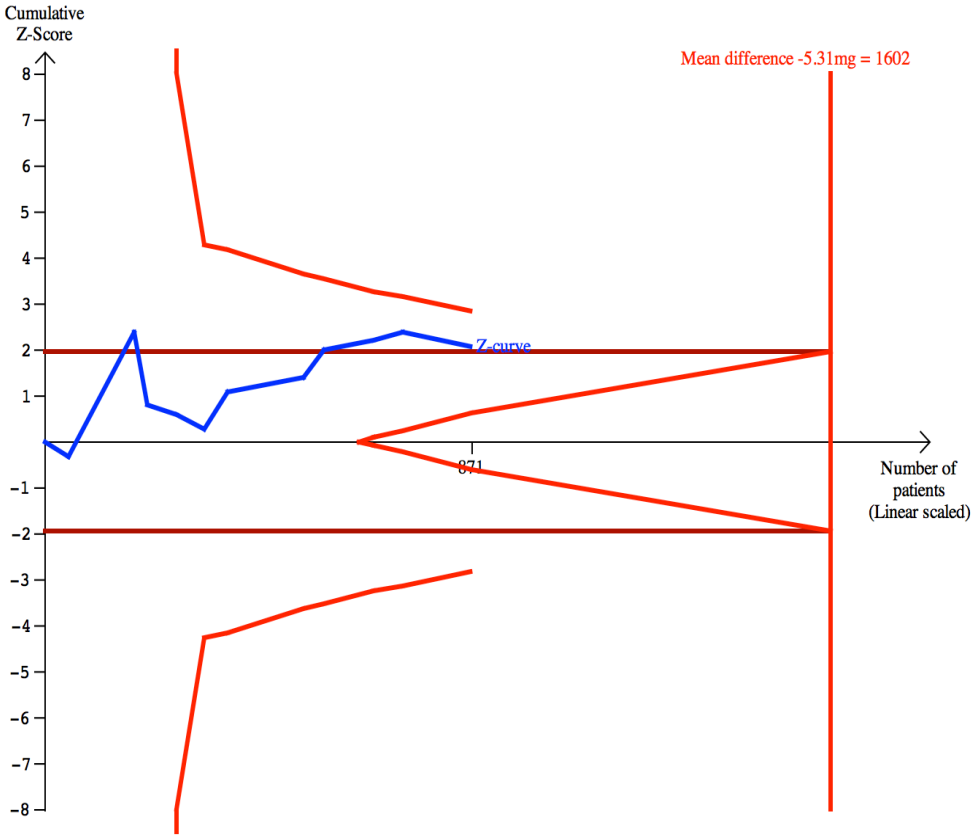


Figure 8.3: Trial sequential analysis of low risk of bias trials for ketamine. Performed assuming an empirical MD of -5.31mg, variance of 41, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 97.1. Blue line indicates cumulative Z score with values more than 0 indicating benefit with ketamine.

8.3.4 Alpha-2 agonists

The alpha-2 agonists analysis included only one RCT. The results crossed the conventional boundary for statistical significance (Figure 8.4). However, O'Brien-Fleming and boundaries for futility or IS could not be calculated due to too few information.

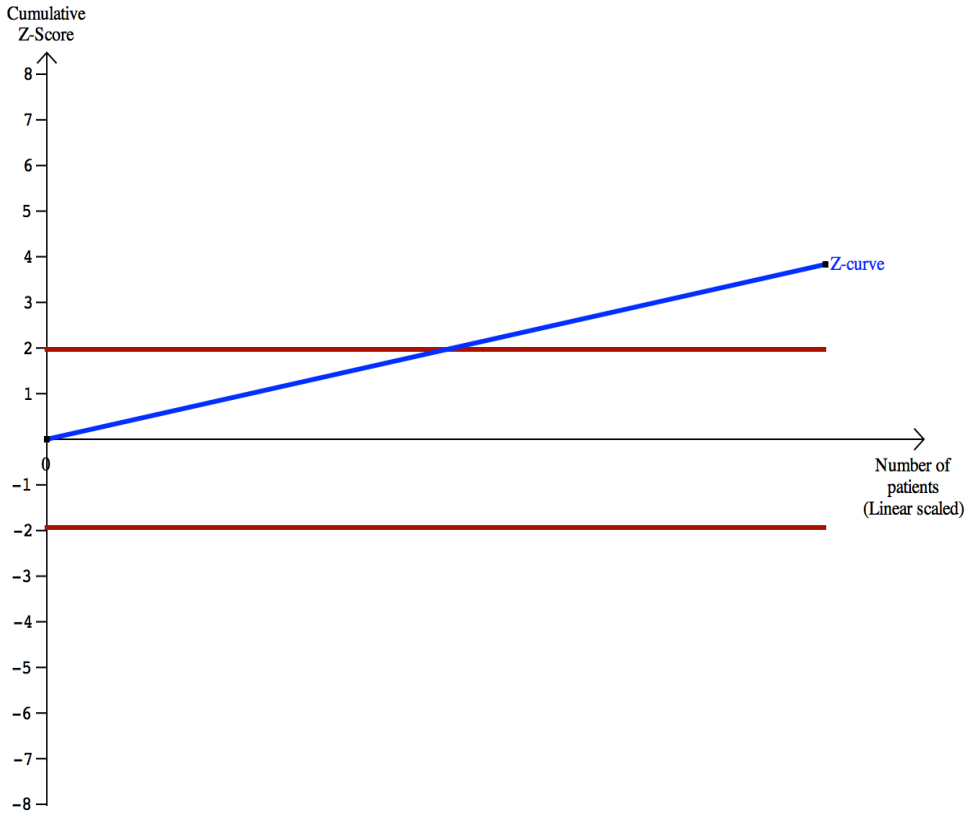


Figure 8.4: Trial sequential analysis of low risk of bias trials for alpha-2 agonists. Performed assuming an empirical MD of -12.5mg, variance of 162, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with alpha-2 agonists.

8.3.5 Gabapentin

The gabapentin analysis included seven RCTs. The results crossed both the conventional boundary for statistical significance and the O'Brien-Fleming boundary (Figure 8.5) and also reached the required IS (341 participants).

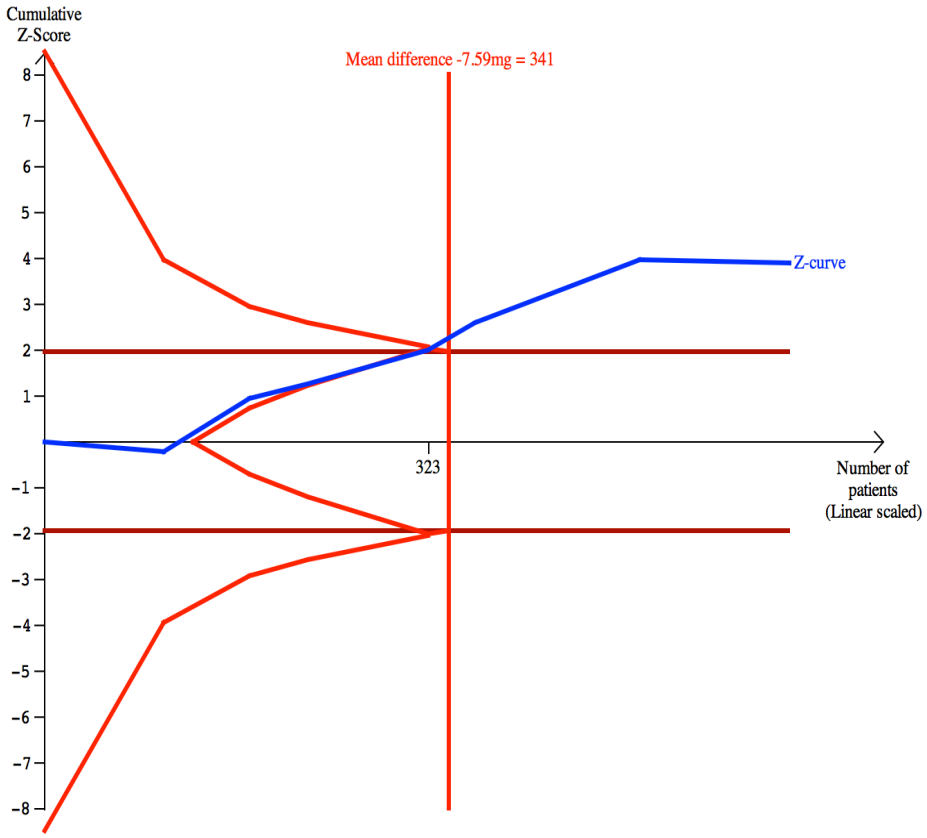


Figure 8.5: Trial sequential analysis of low risk of bias trials for gabapentin. Performed assuming an empirical MD of -7.59mg, variance of 33, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 94.4. Blue line indicates cumulative Z score with values more than 0 indicating benefit with gabapentin.

8.3.6 Pregabalin

The pregabalin analysis included three RCTs. O'Brien-Fleming boundaries could not be constructed for an empirical MD of -11.04mg (Figure 8.6). However, the results crossed the conventional boundary for statistical significance.

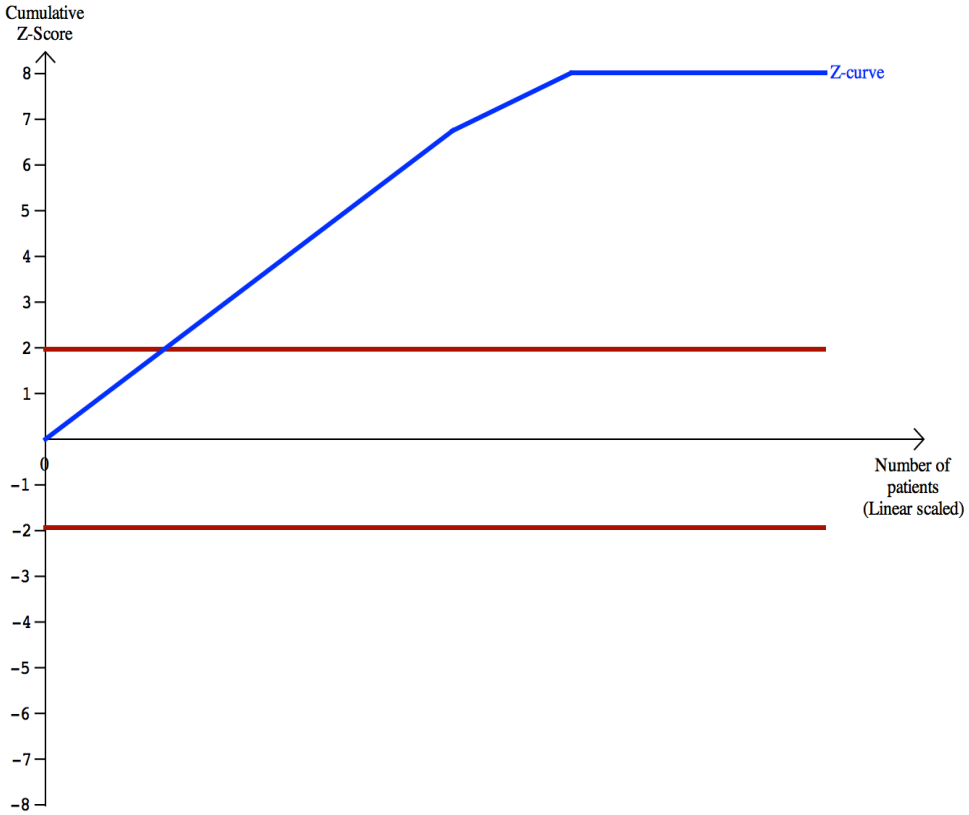


Figure 8.6: Trial sequential analysis of low risk of bias trials for pregabalin. Performed assuming a MD of -11mg, variance of 19.5, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 69.9. Blue line indicates cumulative Z score with values more than 0 indicating benefit with pregabalin.

8.3.7 Nefopam

There was only one low risk of bias trial for nefopam. Boundaries could not be constructed for an empirical MD of -17.5mg (Figure 8.7). However, results did cross the conventional boundary for statistical significance.

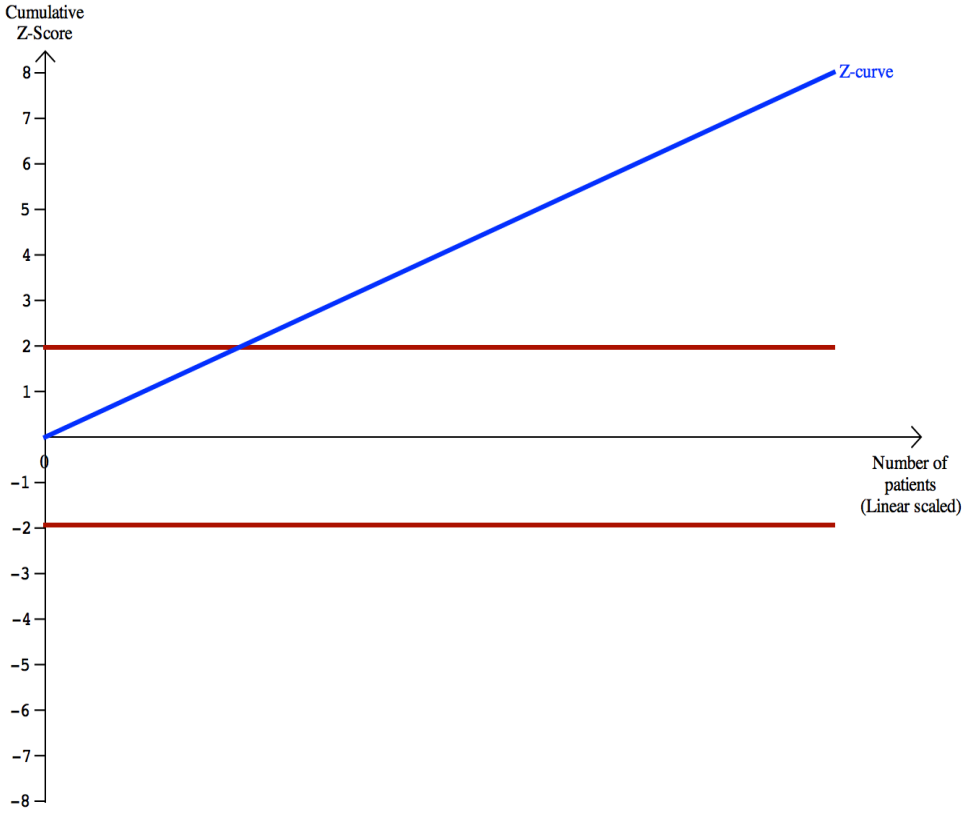


Figure 8.7: Trial sequential analysis of low risk of bias trials for nefopam. Performed assuming a MD of -17.5mg, variance of 41, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with nefopam.

8.3.8 Lidocaine

The lidocaine analysis included six RCTs at low risk of bias. Although the results crossed the conventional boundary for statistical significance, they did not cross the O'Brien-Fleming boundary (Figure 8.8). In addition, the results did not reach the required IS for definitive answer (490 participants). Assuming a heterogeneity correction of 50% and 80%, the required ISs were 980 and 2450 participants respectively.

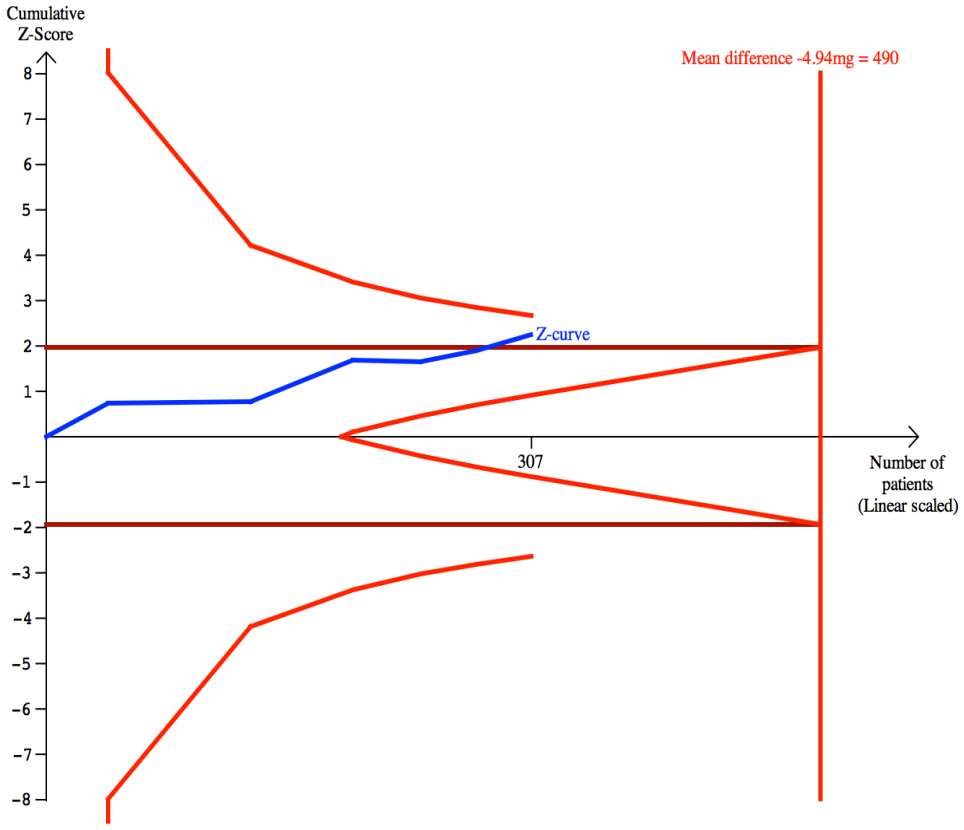


Figure 8.8: Trial sequential analysis of low risk of bias trials for lidocaine. Performed assuming an empirical MD of -4.94mg, variance of 380, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with lidocaine.

8.3.9 Dexamethasone

There was only one low risk of bias trial in the dexamethasone analysis. Although the results crossed the conventional boundary, they did not cross the O'Brien-Fleming boundary for statistical significance. In addition, the results failed to reach the required IS (Figure 8.9). Assuming a heterogeneity correction of 50% and 80% resulted in an IS of 218 and 545 participants respectively.

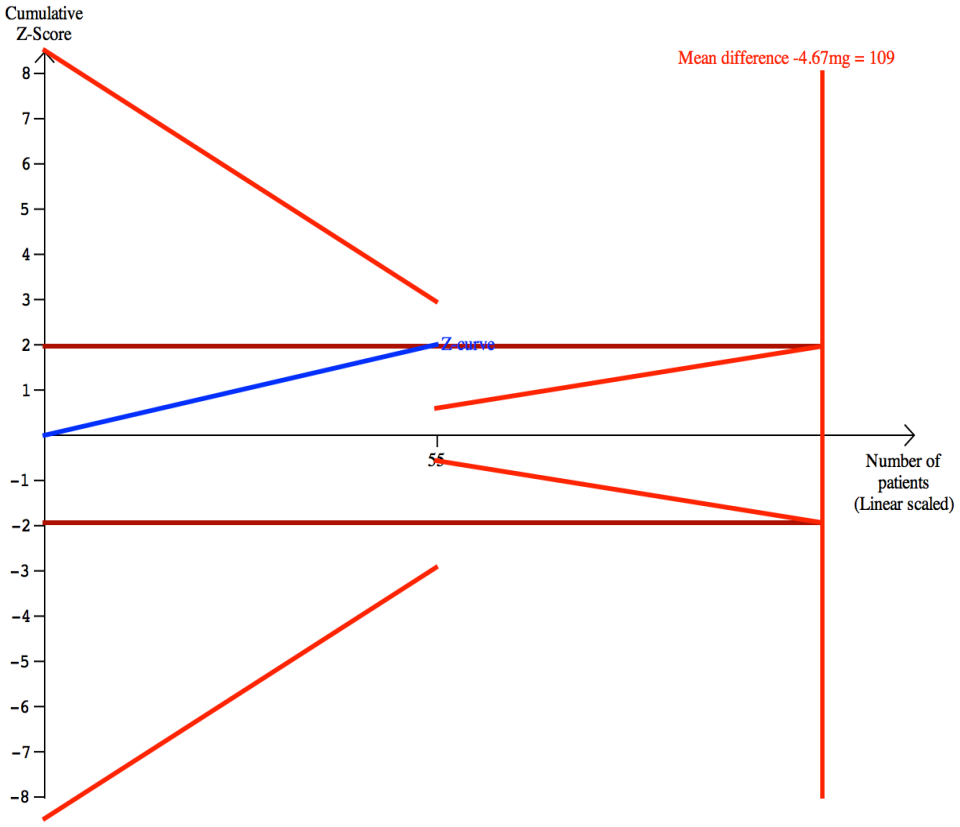


Figure 8.9: Trial sequential analysis of low risk of bias trials for dexamethasone. Performed assuming an empirical MD of -4.67mg, variance of 75, adjusted α=0.05, 1-β=0.80 and a heterogeneity correction of 0. Blue line indicates cumulative Z score with values more than 0 indicating benefit with dexamethasone.

8.3.10 Magnesium

There was only one low risk of bias trial for magnesium. There was too little information from this trial to conduct TSA. The results from this trial did not cross the conventional boundary for statistical significance.

8.3.11 Tramadol

There were no low risk of bias trials for tramadol and therefore TSA could not be performed.

8.4 Discussion

8.4.1 Summary of results

Although a large number of RCTs have been published evaluating multimodal analgesic agents, only 36 RCTs (approximately 10%) were at low risk of bias. Only the results for gabapentin crossed boundaries for benefit adjusted for multiple comparisons (reduce type I errors). In addition, only the results from gabapentin were able to reach the required IS for a definitive answer (reduce type II errors). Ultimately, there is currently insufficient evidence from low risk of bias trials to be confident of the effects of any multimodal analgesic agents currently used in clinical practice.

8.4.2 Links with previous research

Randomised controlled trials are the gold standard for assessing the efficacy of interventions. However, issues with trial conduct have the potential to bias the results from these trials. We have previously demonstrated that this bias has the potential to exaggerate effect estimates using meta-regression analysis. Allocation concealment is a process where researchers cannot foresee the group to which subsequent participants will be allocated and has the potential to cause selection bias. A review of four empirical studies has shown that trials with inadequate or unclear allocation concealment exaggerated effects up to 40% (Schultz *et al.* 1995; Schultz and Grimes 2002a). With regards to blinding, if participants are un-blinded to the intervention, they become subject to placebo effects, which may influence an outcome with a psychological element, such as pain (Turner *et al.* 1994). Indeed, a previous paper has expressed concerns over lack of blinding of outcome assessment, especially for subjective outcomes such as pain scores (Schultz and Grimes 2002b).

An under-recognised problem with meta-analyses is the potential for spurious conclusions due to type I and type II errors. A proposed solution was the use of trial sequential monitoring boundaries and calculation of information sizes to help reduce these errors (Thorlund *et al.* 2008). With a focus on anaesthesia, a previous review of 50 anaesthetic meta-analyses has found that only 12% of

meta-analyses had a power of >80% and only 32% maintained a type I error of <5% using TSA (Imberger *et al.* 2015). Our analysis of low risk of bias trials has demonstrated that despite the multitude of published studies, for most multimodal analgesic agents, there is not enough data to be confident of excluding type I and type II errors.

8.4.3 Limitations

As our classification of risk of bias was determined from published reports, unclear risk of bias assignments may have included, in reality, both trials with high risk and low risk for each element (although high risk are likely to predominate). This may have diluted the true extent of these methodological differences and led to under or overestimations in results. In addition, our sample of RCTs was limited to those published in previous meta-analyses with variable search strategies, therefore the possibility of missing studies limits our results. However, we can be confident that our samples include at least as many studies as the previously published meta-analyses sampled and thus more extensive than the current literature.

8.4.4 Conclusions

In conclusion, we have demonstrated that there is currently insufficient evidence from low risk of bias trials for multimodal analgesic agents to confidently exclude type I and type II errors. Therefore, further adequately powered, low risk of bias trials are required to exclude such errors in current meta-analyses.

Chapter 9

Discussion

9.1 Summary of thesis results

This thesis started with a general discussion surrounding patient-centred outcomes that negatively affect patients around the peri-operative period. These negative outcomes include postoperative pain, vomiting, pruritus, pre-operative anxiety and the associated adverse effects of opioids (Apfelbaum *et al.* 2003). This led to a proposed solution to these outcomes; the use of multimodal analgesia, which aims to both treat postoperative pain and lower opioid consumption with the aim of reducing the adverse effects of opioids. One such multimodal agent is gabapentin, which reduces pain via multiple mechanisms and has found favour in the treatment of postoperative pain, supported by a wealth of clinical trials published over the last decade. Due to the extensive published trials on gabapentin, this thesis used systematic review and meta-analysis as the most appropriate methodology to answer various clinical questions surrounding the use of gabapentin. The chapter concluded with a discussion of various systematic review methodologies that aim to reduce bias and error.

The second chapter of the thesis evaluated the use of gabapentin in treating acute and chronic postoperative pain. Gabapentin had variable effects on pain scores and opioid consumption. Our meta-regression model helped identify clinical situations where gabapentin may be more effective including patients with higher postoperative morphine consumption or pain scores, increasing gabapentin dosages and those undergoing procedures under general anaesthesia. However, we did find evidence of imprecise study effects, which may be caused by publication bias. Despite strong evidence supporting its use in acute postoperative pain, there was little evidence that gabapentin is effective for chronic postoperative pain. Although future trials are required to confirm these findings.

The third chapter aimed to focus on a variety of peri-operative outcomes including gabapentin adverse events and opioid side effects. We found evidence that gabapentin reduced postoperative nausea, vomiting, pruritus and pre-operative anxiety. However, gabapentin increased the risk of postoperative

sedation. Despite this, when focusing on the patient-centred outcome of patient satisfaction, although only a few studies reported this outcome, those patients who had received gabapentin reported higher satisfaction than those who received placebo. To help explain this finding, we cited evidence from the literature that demonstrated sedation is ranked below pain and vomiting for events patients fear the most during anaesthesia (Macario *et al.* 1999). We also highlighted that gabapentin may have other benefits following surgery, although data is limited to a small number of studies, which requires future trials to resolve this. We also found further evidence of imprecise study effects in this chapter. However, for sedation and dizziness, there was a bias against gabapentin suggesting that these effects may be overestimated should the assumption of a symmetric funnel plot hold.

The fourth chapter aimed to examine the optimum timing of gabapentin administration. The theoretical underpinning of pre-emptive analgesia suggests that initiating analgesic interventions before surgical incision can improve postoperative pain compared to the same intervention given after surgical incision. We found a small number of studies focusing on this comparison and found no evidence of a pre-emptive analgesic effect with gabapentin. No studies evaluated a preventive effect of gabapentin (doses continued postoperatively). However, given that oral administration of gabapentin has effects on pre-operative anxiety and can be given with the patient fully alert, pre-operative dosing may be a more convenient time of administration. Although as later identified in chapter five, concerns over adverse intra-operative haemodynamic effects need to be resolved before recommending this as this optimum time to administer gabapentin.

The fifth chapter shifted focus from pain and adverse events and focused on a novel clinical effect of gabapentin in attenuating the haemodynamic response to endotracheal intubation. This haemodynamic response can cause myocardial ischaemia in high-risk patients and may therefore lead to increased postoperative mortality. Although we found evidence of successful attenuation of this haemodynamic response with gabapentin, none of the included studies included high-risk patients or studied clinically relevant outcomes such as

myocardial infarction or mortality. Furthermore, there was little data concerning adverse haemodynamic effects such as bradycardia and hypotension, which have been associated with increased postoperative stroke and mortality. As already discussed, the findings of this chapter have implications for gabapentin use as an analgesic agent, as theoretically, haemodynamic effects could affect important patient outcomes.

Chapter six aimed to extend the principal that the efficacy of analgesic adjuncts is determined by the level of morphine consumption in the control group (baseline risk), by applying meta-regression analysis to published RCTs of multimodal analgesic adjuncts. In addition, we performed a meta-epidemiological study of published reviews and RCTs to check adherence to methods recommended to investigate heterogeneity and measures of internal validity in published RCTs. For the included reviews, we found most studies investigated heterogeneity, although a small number used meta-regression. For the included RCTs, only a third described adequate allocation concealment, which has previously been shown to exaggerate effect estimates (Schultz and Grimes 2002a). On meta-regression analysis, we found evidence that for all of these analgesic adjuncts, a large proportion of the between-study variance could be explained by the control group morphine consumption (baseline risk), a surrogate marker for both how painful the surgery is, participant characteristics and the concurrent analgesics used. We also found evidence of exaggerated effect estimates in the presence of methodological limitations such as inadequate allocation concealment, blinding and attrition bias. Furthermore, we could find little empirical evidence to support the conduct of procedure-specific meta-analyses. Using these findings, we presented a league table of analgesics and presented novel methods to more accurately report opioid consumption that reduces confounding present using current methods.

Chapter seven used the same sample of meta-analyses and RCTs to perform a meta-epidemiological study and a secondary analysis of RCTs to identify the extent of funnel plot asymmetry and thus possible publication bias within the current literature. We found that only a small number of included reviews used methods to prevent publication bias (such as searching grey literature, clinical

trial databases and conference proceedings) and around half used qualitative and quantitative methods to help identify imprecise study effects. On analysing the included RCTs, although there was quantitative and qualitative evidence of funnel plot asymmetry (imprecise study effects) for most analgesic agents, this may be a product of statistical artifact from the association between baseline risk and standard errors. As trials with larger control group morphine consumption have larger associated standard deviations and most trials are of similar sample sizes, funnel plot asymmetry may not reflect true underlying publication bias. Indeed, our simulation studies of meta-analyses where no publication bias was present showed funnel plot asymmetry in all analyses, which was corrected using novel funnel plots of meta-regression residuals on the X axis.

Chapter eight was the final analysis, this chapter used trial sequential analysis of low risk of bias studies to identify whether there was sufficient evidence to reject type I and type II errors on meta-analysis. There is currently insufficient data to exclude such errors and therefore we recommend further conduct of low risk of bias studies. This is especially important following our previous findings of the association between exaggerated effect estimates and limitations in methodological conduct in the included trials.

9.2 Suggestions for future research

Although meta-analytic methods have advantages over primary research studies by including a larger amount of information (thus increasing precision), they have associated disadvantages, such as publication bias. Therefore, larger, prospectively registered RCTs are still required to substantiate the conclusions of this review in regards to postoperative pain, opioid side effects and gabapentin adverse events.

Such trials would need to be larger than those published thus far to be able to detect differences in dichotomous outcomes such as chronic pain, vomiting and sedation. Such studies should ensure adequate randomisation, allocation concealment, blinding and full intention-to-treat analysis to improve on those

published previously. Especially in light of findings of exaggerated effect estimates with trials at higher risk of bias for analgesics used to treat postoperative pain. Such large trials are the only way to resolve issues of publication bias, although such trials would need to ensure prospective registration on clinical trial databases to help reduce problems with not publishing negative study results. We would advise such trials aim to recruit participants undergoing surgery where postoperative morphine consumption is expected to be high, in procedures performed under general anaesthesia and aim to use higher doses of gabapentin (600-1200mg). Such studies should also include other patient-centred outcomes where evidence is scarce, such as those presented in chapter three.

In terms of the haemodynamic effects of gabapentin, as gabapentin in known to reduce heart rate and blood pressure responses to endotracheal intubation and is also known to reduce postoperative pain and catecholamine secretion (all known to increase myocardial demand with links to cardiac complications), future studies should be conducted in high risk patients to identify if gabapentin can reduced myocardial ischaemia, arrhythmias, myocardial infarction and mortality. Such trials will require careful monitoring for adverse haemodynamic effects (such as hypotension and bradycardia), which have the potential to increase mortality. Similar to studies for postoperative pain, such trials need to ensure low risk of bias for measures of internal validity and are adequately powered to detect differences in such dichotomous outcomes. This is especially true for mortality, where postoperative incidence is low and likely to require thousands of participants. Therefore, initial smaller trials may wish to measure surrogate outcomes such as episodes of myocardial ischaemia or arrhythmias on ECG recordings, which would require smaller numbers of patients and help prove the initial concept that gabapentin can reduce myocardial ischaemia in high-risk patients.

With regards to our findings in relation to higher control group consumption predicting larger reductions in postoperative morphine consumption, this has implications for clinical practice, primary research studies and future meta-analyses. Meta-analyses of analgesic adjuncts may wish to use meta-regression

to help explain the inherent statistical heterogeneity present in most of these reviews using the covariates presented in this thesis. This may help increase the quality of the evidence derived from these reviews as per GRADE. Moreover, we recommend future meta-analyses of analgesics report reductions in morphine at one specified time-point and report models based on a fixed consumption of morphine (50mg). An additional advantage of this method is the ability to add other clinical and methodological covariates used in this thesis to reduce confounding. This would also allow clinicians to more appropriately assess the clinical significance of findings from these reviews, as results can be directly compared across interventions.

As previously stated for gabapentin, future RCTs of analgesic adjuncts may wish to target surgeries where morphine consumption is expected to be high to improve the absolute effects of the intervention. Due to the inherent bias and confounding of meta-regression analysis, future primary research may wish to explore the relationship between the efficacy of analgesic adjuncts and the pain experienced by the participant. However, such studies would only be possible when using analgesics to treat established postoperative pain, where baseline pain recordings are possible. Or alternatively, if interventions are given before outcome measurement, trials could recruit participants at high and low risk of severe postoperative pain, then randomise them within these groups and identify whether the intervention causes larger reductions in pain in one group compared to the others (as those in the severe group would be expected to have higher pain scores compared the low risk group).

Our findings of exaggerated effect estimates in studies with lower methodological conduct means future trials should aim to reduce these inherent biases and conduct low risk of bias research. In addition, future meta-analyses of analgesic adjuncts should use TSA to help reduce type I and type II errors in low risk of bias research. Rejection of such errors from low risk of bias trials may be achieved in future reviews as further trial evidence is accrued.

9.4 Conclusion of thesis

This thesis has demonstrated the benefit of gabapentin for preventing acute postoperative pain, lowering opioid consumption, reducing the incidence of a number of opioid adverse events and in attenuating the haemodynamic response to intubation. We have used meta-regression analysis to demonstrate that gabapentin may be more effective in groups of participants at higher baseline risk. In addition, we have shown that this finding extends to other analgesic adjuncts. Furthermore, we have shown how this dependency on baseline risk affects meta-analyses in general by confounding results when presented as mean differences and producing funnel plot asymmetry even in the presence of no publication bias. Moreover, we have presented novel methods of presenting effect estimates and assessing publication bias that resolves the above concerns and recommend use of these methods in future meta-analyses.

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