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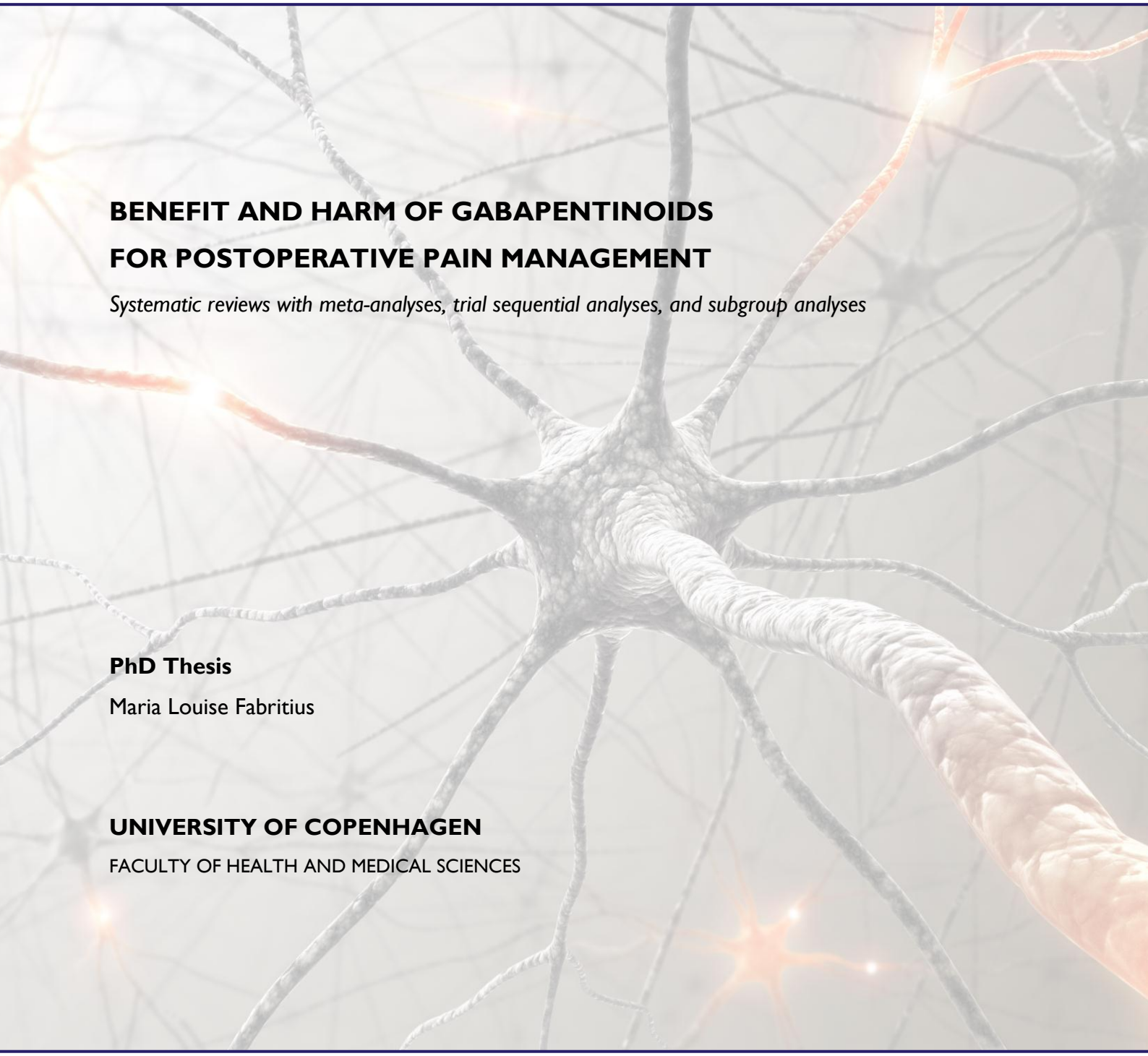

BENEFIT AND HARM OF GABAPENTINOIDS FOR POSTOPERATIVE PAIN MANAGEMENT

Systematic reviews with meta-analyses, trial sequential analyses, and subgroup analyses

PhD Thesis

Maria Louise Fabritius

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PREFACE

My supervisors introduced me to a saying very early on: "When it comes to clinical research – Murphy was an optimist" - I believe, through my tenor, I have proven that to be true for systematic reviews as well. Getting through this process with my optimism intact I am forever grateful to my supervisors, *Jørgen B. Dahl*, *Ole Mathiesen*, and *Jørn Wetterslev*. They have guided me through the clinical and methodological aspects of systematic reviews with great dedication, expertise, support, and humor. I am a fan.

To Jørgen and Ole, the best team, for giving a research novice the chance to conduct this PhD thesis despite a significant lack of beginners luck. They are both dedicated, eminent supervisors, with an extensive experience with- and focus on the clinical aspect of (my) research.

To Jørn for patiently teaching me systematic review methodology through whiteboard-sessions, emails (!) and meetings always with a great sense for details and a humorous approach.

My special thanks goes to *Jakob Trier Møller* for his support, an office space at the research department, and granting me with the great opportunity to work in the exciting and challenging world of trauma, emergency medicine, and anesthesiology, as an junior anesthesiologist.

Furthermore, I extend great thanks to my devoted colleagues, both nurses and doctors at the Department of Anaesthesia, 4231, for their continuous and dedicated education, support, and professional feedback.

I am greatly indebted to all my co-authors for their committed work with data-extraction, bias assessments and valued comments on the manuscripts, especially, *Anja Geisler* and *Pernille Lykke Petersen* for your competent and timely and reponsive help even when deadlines were tight. You have my greatest appreciation.

A heartfelt thanks goes out to all my colleagues at the research department 4231, both senior and junior scientists, who have provided the best, inspirational research environment one could wish for. It has been a fun, educational, and an unforgettable experience, and you all have my deepest gratitude. A warm thanks to *Marianne, Linda*, and *Charlotte* for the support and help with the project, and to *Tina Caludann* for lending me her expert and creative skills in the layout of posters and presentations (and 'TIFFs'). My appreciation also goes to all my colleagues at department Z for their consideration and humor through the last months of this project.

I have to extend my greatest appreciation to my fellow 'research-nerds' whom I have spent (almost) every day with through the last couple of years; *Kamilia, Rebecca, Rikke, Morten, Sandra, Marco, Asger, Marianne, Heidi, Julie, Manuel, Pia* and *Camilla.* It has been wonderful getting to know you and I look forward to future collaborations.

Finally, my deepest and most heartfelt thanks go to my family and friends. To *Anne-Sofie* and *Judith* for their support, celebrating the ups and helping me find a reason to laugh through every down. To *my parents* for their unconditional support in every aspect, and to my sister for simply being *Schwesser*.

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PAPER I Fabritius ML, Geisler A, Petersen PL, Nikolajsen L, Hansen MS, Kontinen V, Hamunen K, Dahl JB, Wetterslev J, Mathiesen O.
Gabapentin for post-operative pain management – a systematic review with meta-analyses and trial sequential analyses. Acta Anaesthesiol Scand. 2016 Oct; 60: 1188-208.

PAPER II Fabritius ML, Geisler A, Petersen PL, Wetterslev J, Mathiesen O, Dahl JB.
Gabapentin in procedure-specific postoperative pain management - preplanned subgroup analyses with meta-analyses and trial sequential analyses. In review.

PAPER III Fabritius ML, Wetterslev J, Mathiesen O, Dahl JB:
Dose-related beneficial and harmful effects of gabapentin in postoperative pain management – Post-hoc analyses with meta-analyses and trial sequential analyses. Submitted.

PAPER IV Fabritius ML, Strøm C, Koyuncu S, Geisler A, Petersen PL, Jæger P, Wetterslev J, Dahl JB, Mathiesen O.
Pregabalin for postoperative pain management – a systematic review with meta-analyses and trial sequential analyses. In review.

LIST OF ABBREVIATIONS

24-h: 24-hour

AE: Adverse Event

AIS: Accrued Information Size

CI: Confidence Interval

FDA: U.S. Food and Drug Administration

FEM: Fixed Effects Model

GPB: Gabapentin

GRADE: Grading of Recommendations Assessment, Development and Evaluation

ICH-GCP: International Committee of Harmonization – Good Clinical Practical practice

NRS: Numeric Rang Scale

NSAID: Non-Steroidal Anti-Inflammatory Drugs

MID: Minimal Important Difference

MD: Mean Difference

OR: Odds Ratio

PETO'S OR: Peto's Odds Ratio

PG: Pregabalin

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

REM: Random Effects Model

RIS: Required Information Size

RR: Risk Ratio

RRR: Relative Risk Reduction

SAE: Serious Adverse Event

SoF: Summary of Finding

T½: Half-life

TSA: Trial Sequential Analysis

VAS: Visual Analogue Scale

LIST OF TABLES AND FIGURES

SUMMARY

Background

Effective postoperative pain management should facilitate rehabilitation of the surgical patient with a minimum of risk. The combination of several different analgesics, known as multimodal analgesia, is commonly used in treatment of postoperative pain. Gabapentin and pregabalin were introduced to postoperative pain management and the multimodal analgesic strategy in 2001 and has been used since then in a great number of combinations. In general, the published randomized clinical trials on gabapentin and pregabalin are small and investigate many combinations with other non-opioid analgesics, doses of gabapentin or pregabalin, and surgical procedures.

It was our aim to assess the benefit and harm of gabapentin and pregabalin in postoperative pain management in systematic reviews with meta-analyses, trial sequential analyses and subgroup analyses.

Methods

We conducted two broad scoped systematic reviews and two subgroup analyses using the Cochrane methodology. We included randomized clinical trials of surgical patients that compared gabapentin or pregabalin to placebo, active placebo or no placebo in the perioperative period. Trial Sequential Analysis adjusted for sparse data and repetitive testing, and Grading of Recommendations, Assessment, Development and Evaluation system (GRADE) methodology assessed the quality of evidence. Subgroup analyses explored the effect of procedure and dose on outcomes. Emphasis was put on trials with overall low risk of bias in results and conclusions.

The co-primary outcomes were 24-hour intravenous morphine, and the risk of serious adverse events. Secondary outcomes were pain intensities at rest and mobilization 6-hours and 24-hours postoperatively, and the risk of adverse events.

Results

In *Paper I* we identified 132 randomized clinical trials with 9,498 patients investigating gabapentin for postoperative pain. Sixteen trials had overall low risk of bias. We found a reduction of 24-hour morphine consumption using gabapentin compared with control interventions with a mean difference of 3.1 mg (95% CI: 0.5, 5.6, $p<0.02$) in the meta-analysis of trials with low risk of bias. This reduction seems negligible when gabapentin is added to a multimodal analgesic regimen, 1.2 mg (95% CI:-0.3, 1.6, $p=0.12$). Trials with low risk of bias suggested an increase in the risk of serious adverse events, 1.6 (95% CI: 0.9, 2.9, $p=0.10$).

In *Paper II*, we explored the effects of gabapentin on six different surgical procedures in preplanned subgroups, data was sparse and we found no differences in beneficial and harmful outcomes between the surgical procedures.
In *Paper III*, we explored the effects of four different doses of gabapentin on beneficial and harmful outcomes in post-hoc analyses. Data were sparse and we could not demonstrate any subgroup differences on the co-primary outcomes reported from trials with low risk of bias.
In *Paper IV*, we included 97 randomized clinical trials with 7,201 patients in the systematic review. Twenty trials had overall low risk of bias. In trials with low risk of bias the cumulative meta-analysis found a reduction in 24-hour morphine consumption of 5.8 mg (95% CI: 3.2, 8.5, $p<0.0001$). The cumulative estimates, from trials with pregabalin added to a multimodal analgesic regimen, found a reduction in 24-hour morphine consumption of 5.3 mg (95% CI: 2.1, 8.5; $p=0.0002$). Trials with low risk of bias suggested increase of serious adverse events with an odds ratio of 2.9 (95% CI: 1.2, 6.8, $p=0.02$). The odds seemed further increased whenever pregabalin was administered more than once, 3.4 (95% CI: 1.3, 9.2; $p= 0.01$) compared with a single administration.

Conclusion

We provide evidence that both gabapentin and pregabalin reduce 24-hour morphine consumption. However, the reduction in 24-hour morphine consumption in the trials investigating gabapentin seems lesser than a minimal (clinically) important difference of 5 mg. The reduction seems almost negligible when added to a multimodal analgesic regimen. We report no firm evidence for a superior dose, or for specific surgical procedures that may benefit more from treatment with gabapentin.
The data suggests increase of serious adverse events with both gabapentin and pregabalin compared with controls.
Based on our results we cannot recommend routine treatment with gabapentinoids in postoperative pain management before firm evidence has documented that benefits outweigh harms of the treatments.

DANSK RESUMÉ

Baggrund

Effektiv postoperativ smertebehandling bør fremme rehabilitering af den kirurgiske patient med den mindste risiko for skade. Kombinationer af forskellige smertestillende farmaka er kendt som multimodale regimer og er typisk brugt i den postoperative smertebehandling. I 2001 blev gabapentin og pregabalin introduceret i den postoperative smertebehandling og det multimodale analgetiske regime. Siden er de blevet brugt i mange forskellige kombinationer i denne sammenhæng. Den publicerede litteratur på området er præget af små forsøg, som undersøger mange forskellige kombinationer af analgetika, involverer forskellige doser af gabapentin og pregabalin og undersøger en bred vifte af kirurgiske indgreb.

Det var vort mål at undersøge de gavnlige og skadelige virkninger af gabapentin og pregabalin i den postoperative smertebehandling ved brug af systematiske litteraturoversigter med metaanalyser og forsøgssekventielle analyser samt subgruppeanalyser.

Metoder

Vi lavede to systematiske litteraturoversigter med subgruppeanalyser og fulgte Cochrane metoden. Vi inkluderede kliniske forsøg med kirurgiske patienter, som sammenligner gabapentin eller pregabalin med placebo, aktiv placebo eller ingen placebo i den perioperative periode. De forsøgssekventielle analyser blev brugt til at justere for manglende data samt gentagen testning. GRADE blev anvendt til at vurdere kvaliteten af evidensen. Subgruppeanalyserne undersøgte om der var forskel på interventionseffekten mellem typerne af de kirurgiske indgreb og mellem de anvendte doser. I resultaterne og konklusionerne har vi lagt vægt på forsøg med lav risiko for bias i samtlige undersøgte bias domæner.

De primære effektmål var 24-timers morfinforbrug samt en risiko for alvorlige skadelige hændelser. De sekundære effektmål var smerteintensitet i hvile og ved mobilisering, både 6 og 24-timer postoperativt, samt skadelige virkninger.

Resultater

I *Projekt I* inkluderede vi 132 randomiserede kliniske forsøg med 9498 patienter, der undersøgte gabapentin i den postoperative smertebehandling. I alt var 16 forsøg klassificeret som havende lav risiko for bias. I metaanalysen af 24-timers iv-morfinforbrug, fra forsøg med lav risiko for bias, fandt vi en reduktion på 3.1 mg morfin (95% CI: 0.5, 5.6, $p<0.02$) under behandling med gabapentin sammenlignet med kontrolgruppen. Denne reduktion var 1.2 mg (95% CI: -0.3, 1.6, $p=0.12$), når gabapentin blev kombineret med andre, non-opioide analgetikae. En risiko for alvorlige hændelser kan være øget ved behandling med gabapentin i forhold til kontrol-behandling, vurderet ud fra forsøg med lav risiko for bias, 1.6 (95% CI: 0.9, 2.9, $p=0.10$).

I *Projekt II* undersøgte vi effekten af kirurgiske indgreb på de primære effektmål. Vi fandt få data fra forsøg med lav risiko for bias og ingen forskel mellem de seks forskellige kirurgiske procedurer på gavnlige og skadelige virkninger.
I *Projekt III* undersøgte vi effekten af dosis på de gavnlige og skadelige virkninger af gabapentin, og fandt ingen forskelle imellem forskellige doser i forsøg med lav risiko for bias.
I *Projekt IV* inkluderede vi 97 randomiserede kliniske forsøg med 7201 patienter i den systematiske litteraturgennemgang. I alt blev 20 forsøg vurderet til at have lav risiko for bias. Forsøgene med lav risiko for bias fandt en reduktion af iv-morfinforbruget over 24 timer på 5.8 mg (95% CI: 3.2, 8.5, p<0.0001). Når pregabalin blev kombineret med andre, non-opioide analgetikae var reduktionen 5.3 mg (95% CI: 2.1, 8.5; p=0.0002) over 24 timer. Forsøg med lav risiko for bias fandt øgede odds for alvorlige hændelser, 2.9 (95% CI: 1.2, 6.8, p=0.02). Disse odds syntes yderligere forøgede, når pregabalin blev givet i mere end en dosis, 3.4 (95% CI: 1.3, 9.2; p= 0.01) sammenlignet med en enkelt dosis.

Konklusion

Vi finder evidens for, at gabapentin og pregabalin reducerer 24-timers morfinforbrug. Reduktionen i 24-timers morfinforbrug overstiger den minimale (kliniske) relevante forskel på 5 mg for pregabalin men ikke for gabapentin. Reduktionen i 24-timers morfinforbrug er næsten ikke-eksisterende, når gabapentin tillægges multimodale analgetiske regimer. Vi kan ikke finde sikker evidens for, at der er en dosis-relateret effekt af gabapentin, eller at specifikke kirurgiske indgreb har mere gavn (eller skade) af gabapentin behandling end andre.
Forekomsten af alvorlige skadelige hændelser kan være øget i behandlingen med gabapentin og pregabalin. Baseret på vore resultater kan vi ikke anbefale gabapentin eller pregabalin som rutine behandling i den postoperative smertebehandling, førend der foreligger sikre beviser for at de gavnlige virkninger overvejer de skadelige virkninger af behandlingen.

INTRODUCTION

Effective treatment of postoperative pain should facilitate early mobilization, fluid- and food intake, and the resumption of normal physical activities.[1] However, effective analgesic treatment remains a challenge. Postoperative pain affects many patients world-wide and the postoperative period includes a high risk of morbidity and mortality some of which may be related to analgesics[2-4].

The surgical patient is often treated with a combination of non-opioid analgesics, referred to as "multimodal analgesia"[1]. The aim of this strategy is to achieve a synergistic or additive beneficial effect with the lowest doses of each analgesic, thus preventing harmful effects while decreasing the use of opioids and consequently, opioid-related adverse events[5,6]. The most commonly used non-opioids in multimodal analgesic treatment are paracetamol, Non-Steroidal Anti Inflammatory Drugs (NSAIDs), steroids, ketamine, local anesthetics, and gabapentinoids[7].

Currently, many different combinations of non-opioid analgesics are employed in clinical practice[5,8]. Our knowledge regarding risks, potential additive or synergistic analgesic effects, and the individual patient response related to such combinations is, however, insufficient[6,9].

During the last couple of years several randomized clinical trials have been published on gabapentinoids in postoperative pain management[10,11]. The trials are diverse, exploring many different drug combinations and doses, and are small in size with a concomitant short follow-up limiting the evidence.
Several systematic reviews have been published on gabapentinoids in postoperative pain management[10-15]. Few of them explore the harms and possible additive/synergistic analgesic effect of postoperative gabapentinoid treatment[15]. Very few of the systematic reviews explore the risk of systematic error on their results, increasing the risk of overestimation of the beneficial outcomes while underestimating the harmful outcomes[10,11]. None of the systematic reviews explore the risk of random error associated with sparse data and repeated updating of cumulative meta-analysis. Consequently, there are both scientific and methodological arguments to systematically explore benefit and harm of gabapentinoids in currently applied analgesic strategies.

Gabapentinoids

Gabapentin and pregabalin are both from the class of drugs named gabapentinoids. They are derivatives of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) that has high affinity for the $\alpha_2\delta$ subunit of voltage-sensitive calcium channels and are chemical analogues of GABA[16]. Their mechanism of action

is not fully understood but it is hypothesized, that the gabapentinoids exhibits their effects through the voltage-dependent calcium channels for which they have high affinity[16].

The characteristics of gabapentinoids are described in *table 1*. Gabapentin and pregabalin seem very similar in the believed mechanisms of action, protein binding capabilities, negligible metabolism, and drug interactions. However, they might differ in the pharmacokinetic and pharmacodynamic properties; absorption, bioavailability, distribution volume, and peak plasma concentration[17].

TABEL 1 CHARACTERISTICS OF GABAPENTIN AND PREGABALIN[17]

	GABAPENTIN	**PREGABALIN**
Mechanisms of action	$\alpha_2\delta$ subunit of presynaptic voltage-gated calcium cannels	$\alpha_2\delta$ subunit of presynaptic voltage-gated calcium cannels
Absorption	Small intestine through in part by active transport and in part by diffusion	Both small intestine through active transport and may have an additional transport system in colon
Bioavailability (%)	Dose-dependent*	≥ 90 %
Volume of distribution	0.8 L/kg	0.5 L/kg
Protein binding	< 1 %	< 1 %
Peak plasma concentration T_{max}	≈3 hours	≤ 1 hour
Half-life T ½	5-7 hours	≈ 6.3 hours
Metabolism	Renal elimination	Renal elimination
Drug interaction	Phenytoin Naproxen Morphine Antacids	Phenytoin Naproxen Morphine Antacids

**GBP oral bioavailability seems inversely dependent on dose. T½: Elimination half-life; T_{max}: time to reach the maximum concentration in blood after oral administration.*

Gabapentinoids exert their analgesic effect differently from other non-opioids analgesics, e.g. NSAIDS, acetaminophen, and local anesthetics, making them interesting adjuncts to multimodal analgesic regimens.

Gabapentinoids seem to possess anti-hyperalgesic effects, which has been documented in both experimental, and clinical trials of healthy volunteers[18,19] laying the ground for several randomized clinical trials and later systematic reviews of gabapentinoids.

Gabapentinoid treatment for medical conditions and chronic pain

Gabapentinoids were first developed and approved for the treatment of epilepsy and neuropathic pain, and generalized anxiety (pregabalin). Very few randomized, clinical trials are included in the reported,

systematic reviews and cumulative analyses of gabapentin and pregabalin for partial epilepsy, anxiety, fibromyalgia, and neuropathic pain disorders[20-26]. Few report on serious adverse events[20,23]. One systematic review focused on the adverse event profile of pregabalin in medical conditions. They found a risk for several AEs but no increased risk of SAEs in pregabalin treatment[23].

A Cochrane review on gabapentin for partial epilepsy finds that more than half of the included trials have a high risk of bias in the incomplete outcome data bias domain[20]. Further, a Cochrane review on pregabalin for partial epilepsy includes solely trials sponsored by the pharmaceutical industry[24]. Both reviews of gabapentin and pregabalin for partial epilepsy consist of trials with high risk of bias, limiting the ability to report trustworthy conclusions[27].

In 2009 Vedula et al[28] explored the outcome reporting in industry-sponsored trials of gabapentin for off-label indications. The off-label indications for gabapentin treatment were migraine, bipolar disorders, neuropathic pain, and nociceptive pain. They found selective outcome reporting bias of the reported outcomes and of the included trials and concluded, that this may threaten the validity of evidence in off-label interventions[28].

In general there are problems with the methodology of the systematic reviews and in the included randomized clinical trials investigating gabapentinoids in medical conditions. This limits the conclusion on benefit and harm.

Gabapentin in pain management

In 2002 it was demonstrated that gabapentin had a postoperative analgesic effect in mastectomy patients,[7] which has since spurred several, often small randomized clinical trials investigating gabapentin in a diversity of surgical procedures, doses, and combinations with other non-opioid analgesics.

Several systematic reviews with meta-analyses of randomized clinical trials have been published investigating gabapentin's postoperative analgesic effect[10,14,15,29-32]. The most recent published systematic review by Doleman et al. reported a beneficial effect of gabapentin peri-operatively[10] in agreement with the previously published systematic reviews[15,29].

Pregabalin in pain management

Pregabalin was developed later than gabapentin but was introduced in postoperative pain management around the same time[33]. Pregabalin has been described as a more potent successor to gabapentin[11], and associated with fewer adverse events[13].

The literature investigating pregabalin is mostly dominated by smaller clinical trials investigating pregabalin's postoperative effects in a wide range of different surgical procedures, doses, and multimodal analgesic treatments similar to the published literature on gabapentin.

All reviews are narrow scoped reviews investigating pregabalin with focus on different surgical procedures[13,34], acute and persistent postoperative pain[11,12], and non- or pro-nociceptive-pain[11] mainly focusing on and reporting a beneficial effect of pregabalin in postoperative pain management.

Evidence-based medicine in gabapentinoid research

Numerous factors may influence clinical decision-making and there are many threats to the validity of evidence. Clinicians are faced with an increasing challenge to ensure the best treatment of patients weighing benefit and harms. In doing so clinicians should have access to the best evidence with a minimal risk of systematic- and random error, and with relevant research questions in order to conduct evidence-based medicine[35].
Randomized clinical trials and systematic reviews are considered the best methodologies in minimizing bias and are thus the strongest methodologies to base future recommendations on[35].

The published research of gabapentin and pregabalin for postoperative pain management displays some threats to the validity of evidence. Very few systematic reviews focus on the risk of systematic error[10,12,30] and none explore the risk of random error. Further, in the randomized clinical trials and systematic reviews on gabapentinoids, patient centered questions such as the risk of serious adverse events are poorly reported[11,30]. Consequently, this limits any ability to decide on the best treatment weighing benefit and harm of gabapentinoids.
These are the arguments for conducting this thesis and exploring benefit and harm of gabapentinoids for postoperative pain management focusing on the risk of systematic- and random error in current published literature.

AIM AND HYPOTHESIS

This thesis aimed to investigate the benefit and harms of gabapentinoids for postoperative pain management through two systematic reviews and four papers with the following aim and hypothesis:

PAPER I The aim of this systematic review was to assess the beneficial and harmful outcomes of perioperative gabapentin.

PAPER II The aim of these pre-planned subgroup analyses was to explore the benefit and harm of perioperative gabapentin in six different surgical procedures.

PAPER III The aim of these post-hoc analyses was to explore the effect of different gabapentin treatment dose on beneficial and harmful outcomes.

PAPER IV The aim of this systematic review was to evaluate the benefit and harms of perioperative pregabalin treatment in postoperative pain management.

It was our hypothesis that the administration of gabapentin or pregabalin in postoperative pain management would reduce 24-hour opioid consumption compared with controls. We hypothesized that the use of gabapentinoids would reduce adverse events related to opioid consumption. Further, it was our hypothesis that the risks of adverse and serious adverse events would not lead to a recommendation of discontinued treatment. Moreover, we expected high degree of heterogeneity in the systematic reviews.

METHODOLOGY

Paper I and IV are systematic reviews with meta-analyses and trial sequential analyses performed according to Cochrane recommendations[36]. The protocols are published at the International Prospective Register of Systematic Reviews (PROSPERO, www.crd.york.ac.uk/PROSPERO)[37].
Paper II and III are subgroup analyses with meta-analyses, trial sequential analyses and test of subgroup differences derived from Paper I. Paper II is a predefined subgroup analysis published in the PROSPERO protocol from the original review, while Paper III consists of a post-hoc analysis.
(More detailed descriptions of the methodology can be viewed in Papers I-IV)

Eligibility criteria

We included randomized clinical trials in all four papers (observational studies and quasi-randomized studies were also included for the evaluation of harm in Paper I). All trials investigated gabapentin or pregabalin compared with placebo, active placebo, or no placebo in surgical patients of 18 years or older. The intervention should be administered perioperatively.
We excluded trials investigating gabapentin or pregabalin for chronic pain, medical conditions, and in healthy volunteers.

Search

A trial search coordinator developed our search strategy that included The Cochrane Library's CENTRAL, PubMed, EMBASE, and Science Citation Index Expanded. All trials and systematic reviews were hand searched for additional trials. The search strategy was systematic and sensitive to identify relevant trials with no language or date restrictions. The search was updated and not older than 6 months upon submitting the manuscript to a journal.

Study selection, data extraction and risk of bias assessment

Two independent authors selected the studies, extracted data and assessed bias using a data extraction form.
The co-primary outcomes are reduction in 24-hour intravenous morphine consumption and Serious Adverse Events (SAEs). SAEs are defined by the International Committee of Harmonization – Good Clinical Practice (ICH-GCP) as medical events that may be life threatening, resulting in death, disability or significant loss of function; causing hospital admission or prolonged hospitalization[38].
The secondary outcomes are: VAS pain intensities 6- and 24-hours postoperatively both at rest and mobilization, and any adverse event reported by the trialists.

All opioids were converted to intravenous morphine based upon equivalency, and all pain intensity scales reporting pain levels between 0 and 10 were converted to the Visual Analogue Scale (VAS) going from 0-100 mm.

The assessment of bias was conducted using the Cochrane risk of bias assessment tool based on six domains: Sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and 'other sources of bias' (e.g. financial and confirmatory bias). Two independent authors critically assessed every included trial and a third author settled any disagreements.

The corresponding author was contacted whenever data was insufficiently reported or a bias domain assessed as unclear risk of bias. The contact was repeated within 14 days of initial contact if there was no answer. If there was no contact from the author the bias domains remained unclear.

Subgroups analyses

In order to explore the clinical and methodological heterogeneity and to answer specific questions regarding the intervention and participants groups, subgroups analyses were planned in the protocol of Paper I and IV.

In Paper I the following subgroup analyses were planned:

- Trials with (low) vs. (unclear + high) risk of bias
- Surgical procedure, e.g. hysterectomy, mastectomy, spinal surgery and cholecystectomy
- Gabapentin in trials without multimodal analgesic treatment vs. gabapentin in trials with multimodal analgesic treatment

In Paper IV the following subgroup analyses were planned:

- Trials with (low) vs. (unclear + high) risk of bias
- Pregabalin in trials without multimodal analgesic treatment vs. pregabalin in trials with multimodal analgesic treatment
- Single dose pregabalin vs. multiple doses of pregabalin

Post-hoc analyses were also conducted. In Paper I-IV all randomized clinical trials in the systematic reviews were divided into three groups based on the number of patients included in each group. The three groups were </= 50 patients, > 50-100 and more than 200 patients in the groups. We have

stated that the majority of randomized clinical trials include few patients and are thus small. The post-hoc analyses of the randomized clinical trial size were meant to confirm and quantify the statement.
Paper III consisted of post-hoc analysis of the dose effect on beneficial and harmful outcomes investigating four different doses of gabapentin. The trials included in the gabapentin review ranged in dose from 100 mg to 1800 mg per day. The analyses were meant to create hypotheses for future trials narrowing down the possible optimal dose of gabapentin for postoperative pain management.

Statistical analyses

We used conventional cumulative meta-analytic statistics to calculate the pooled estimates of each outcome. The meta-analyses were carried out using the guidelines from the Cochrane Handbook for Systematic Reviews of Interventions. Review Manager (RevMan) [Computer program], Version 5.1.6, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 was used for statistical analyses.
For all included trials, mean difference (MD) and Risk Ratio (RR) with 95% CI were calculated whenever two or more trials were included with continuous or dichotomous data in the respective outcomes. Peto's Odd Ratio (Peto's OR) was used in rare events to provide the best confidence interval coverage with a CI of 95%[39].
Random-effects model (REM) and fixed-effects models (FEM) were used whenever two or more trials were included in the meta-analyses of an outcome. The expectation was that substantial heterogeneity was present in the included trials; thus results from random-effects models were underlined. Whenever I^2 was zero both FEM and REM were used for the analysis and the most conservative estimation was presented[39].

In both dichotomous and continuous data a p-value of less than 0.05 was considered statistically significant.

We used TSA to re-assess the level of statistical significance by combining the required information size estimation (required cumulated sample size of included trials) with an adjusted threshold for statistical significance in the cumulative meta-analysis, the trial sequential monitoring boundaries[40,41]. This reduces the risk of making a false positive or negative conclusion[40].
In all four papers the minimal important difference (MID) of 5 mg for 24-hour morphine consumption was used to calculate the required information size with an alpha of 5% and beta of 10%, and appropriate adjustments for heterogeneity (diversity adjustments). In the co-primary outcome, SAE,

the relative risk reduction (RRR) of 50% was chosen. The MID in pain intensities was 10 mm VAS, while RRR of the adverse events was 30%.
Whenever the accrued information size was less than 5% of the required information size, trial sequential monitoring boundaries[40,41] could not be calculated due to lack of data.
The trial sequential analyses were carried out using the TSA software 0.9.5.5. Beta[42].

Grading of Recommendations Assessment, Development and Evaluation

Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used on all outcomes to rate the quality of evidence and strength of recommendations. Quality of evidence was classified as very low, low, moderate or high quality of evidence[43]. Emphasize is put on trials assessed and classified as overall 'low risk of bias' from which the conclusions are based.

RESULTS

These sections present an overall view of the results from the co-primary outcomes and secondary outcomes based on trials with overall low risk of bias from the systematic reviews. In the subgroup analyses estimates from both low risk of bias and all trials are reported on co-primary outcomes.
A more detailed presentation is found in the manuscripts of the four papers.

PAPER I: Gabapentin for postoperative pain – A systematic review with meta-analyses and trial sequential analyses

Trial characteristics

We screened 16,303 titles, and 132 randomized clinical trials with 9,498 patients were included in the review, with 16 trials classified as 'low risk of bias'[44-59]. Ninety percent of the included trials has less than 50 patients in each group, while thirteen trials had more than 50 patients in each group and four had more than 200 patients included in the trial. (*Paper I and Figure 1*)

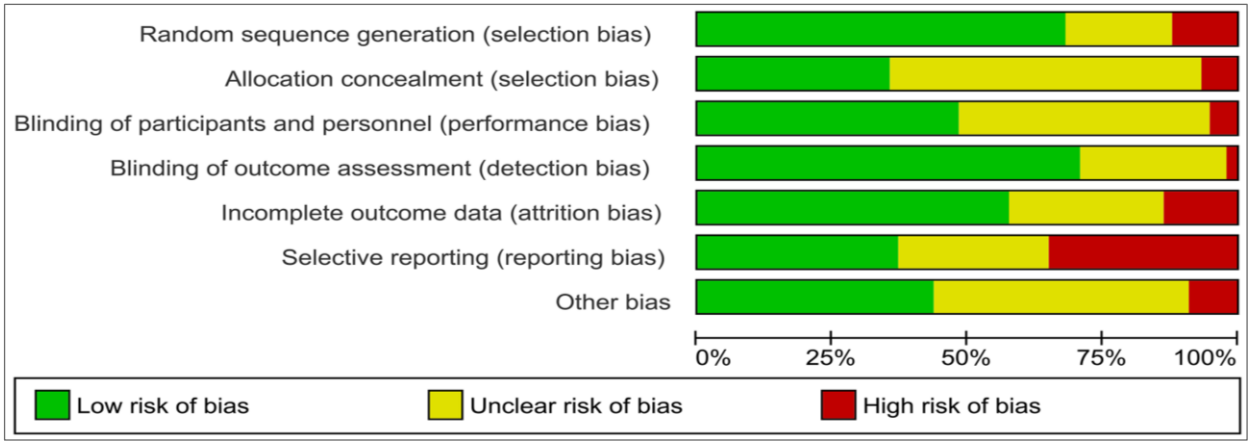

Figure 1 *Bias graph of the six bias domains. The Other bias domain consists of 'vested interests'; financial and confirmatory bias.*

Primary outcomes

Primary and secondary outcomes are presented in *table 2*. In trials reporting 24-hour morphine consumption, the reduction of morphine (3.1 mg (0.5 to 5.6, 0.02)) may be less than the predefined minimal clinical difference of 5 mg per 24-hours. *Figure 2* reports that the reduction in 24-hour morphine consumption from trials with low risk of bias is lower than the reduction from all trials estimate.

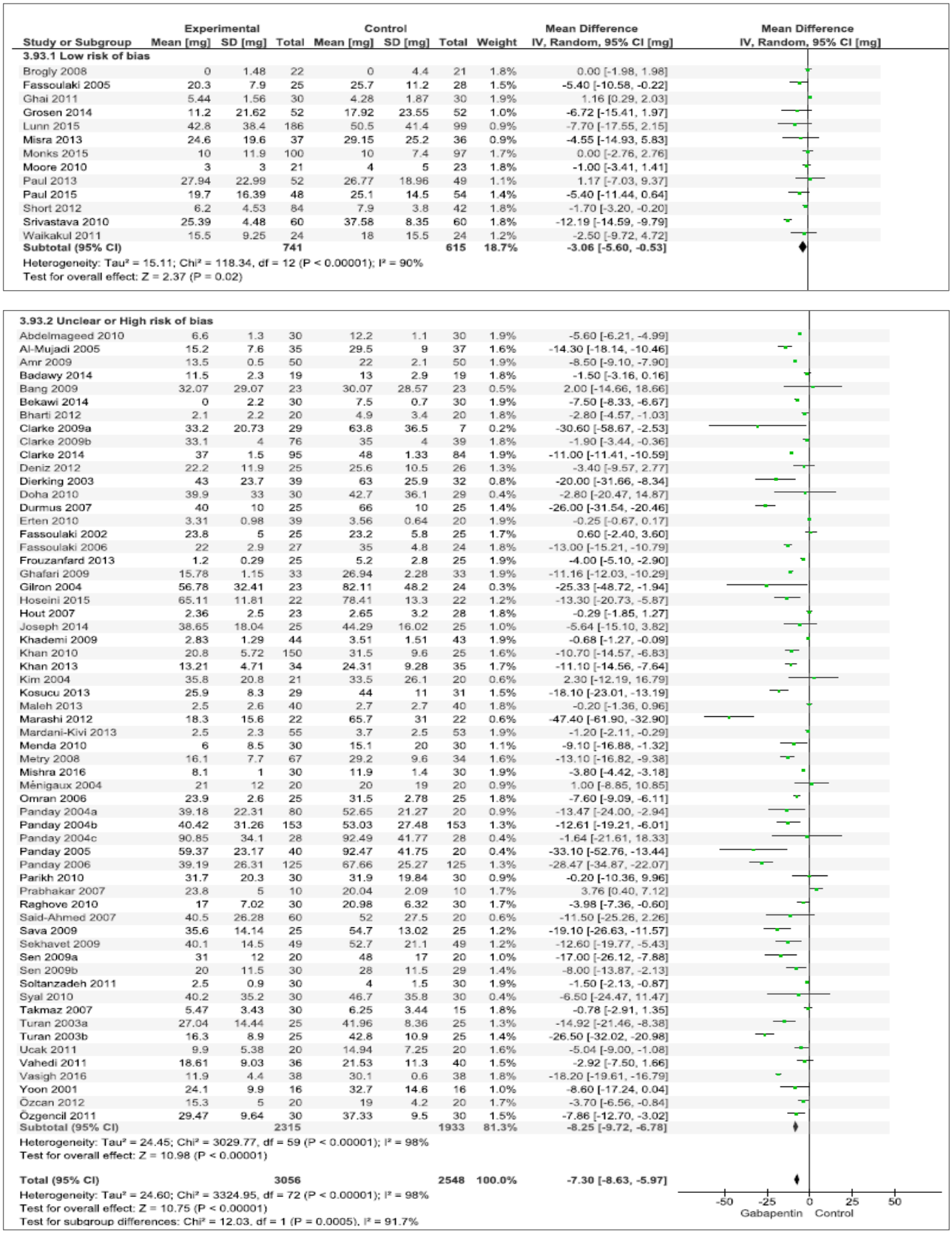

Figure 2 *Forest plot of 24-hour morphine consumption with subgroup analysis of trials with low vs. unclear and high risk of bias and test for subgroup differences.*

The 24-hour morphine consumption indicated a reduction in trials with gabapentin combined with other non-opioid analgesics, 1.2 mg (REM: 95% CI -0.3, 2.6; P = 0.12; I^2: 61%; 11 trials; 1194 patients, TSA adjusted CI -0.3, 2.6; RIS: 281 patients; GRADE: moderate), compared with trials without any other non-opioids analgesic, 8.0 mg (REM: 95% CI -1.5, 17.4; P = 0.10; I^2: 84%; 2 trials; 168 participants, TSA adjusted CI -15.5, 23.3; RIS: 1636; GRADE: low).

TABEL 2: PRIMARY AND SECONDARY OUTCOMES FROM TRIALS WITH LOW RISK OF BIAS

	Mean Difference / Relative Risk *(95% CI, p-value)*	**TSA adj. CI**	**No. of trials** *(Participants / RIS)*	**GRADE**
PRIMARY OUTCOME MEASURES* **				
24-h morphine consumption	3.1 mg (0.5 to 5.6, 0.02)	(0.5 to 5.6)	13 (1356 / 959)	LOW
Serious Adverse Events	1.61 (0.9 to 2.9, 0.10)	(0.6 to 4.6)	9 (1014 / 3139)	LOW
SECONDARY OUTCOME MEASURES* **				
VAS 6-h at rest	9 mm (-1 to 19, 0.07)	(-1.3 to 18.6)	9 (739 / 2061)	VERY LOW
VAS 6-h at mobilization	9 mm (4 to 13, <0.0002)	(4 to 13)	7 (566 / 327)	LOW
VAS 24-h at rest	3 mm (-0 to 6, 0.07)	(-0 to 6)	11 (1021 / 282)	LOW
VAS 24-h at mobilization	5 mm (-2 to 11; 0.15)	(-2 to 11)	8 (789 / 816)	VERY LOW
AE: Nausea	0.83 (0.6 to 1.1, 0.21)	(0.6 to 1.1)	6 (524 / 1350)	MODERATE
AE: Vomiting	1.04 (0.7 to 1.5, 0.85)	(0.5 to 2.2)	4 (352 / 1318)	LOW
AE: Sedation	1.08 (0.9 to 1.2, 0.29)	(0.9 to 1.2)	10 (858 / 1982)	LOW
AE: Dizziness	1.04 (0.8 to 1.2, 0.64)	(0.8 to 1.3)	9 (741 / 1066)	LOW

Cumulated estimates from conventional meta-analyses and trial sequential analyses. GRADE: Quality of evidence can be classified as very low, low, moderate or high quality of evidence.
RIS; Required Information Size; TSA adj. CI: Trial Sequential analyses adjusted Confidence Interval
Reduction in morphine consumption or pain intensities The risk of SAEs or AEs.*

In the nine trials with low risk of bias, 47 SAEs were reported, representing 68% of the total number of the reported SAEs[44,45,47-49,53,55,57,58]. The findings from the nine trials indicated an increase in the risk of serious adverse events, *table 2*. The risk of SAE seems lower in the all trials estimates, 1.14 (95% CI 0.71, 1.81; p = 0.6; I^2: 7%; 26 trials; 2042 participants; TSA adj. CI 0.6, 2.1; GRADE: very low) compared to the estimate from trials with low risk of bias (*table 2*), test for subgroup differences $p<0.05$.

Trial sequential analysis showed that firm evidence for the reduction in 24-hour morphine consumption was reached but data is still lacking in the evaluation of risk of SAEs (*figure 3*).

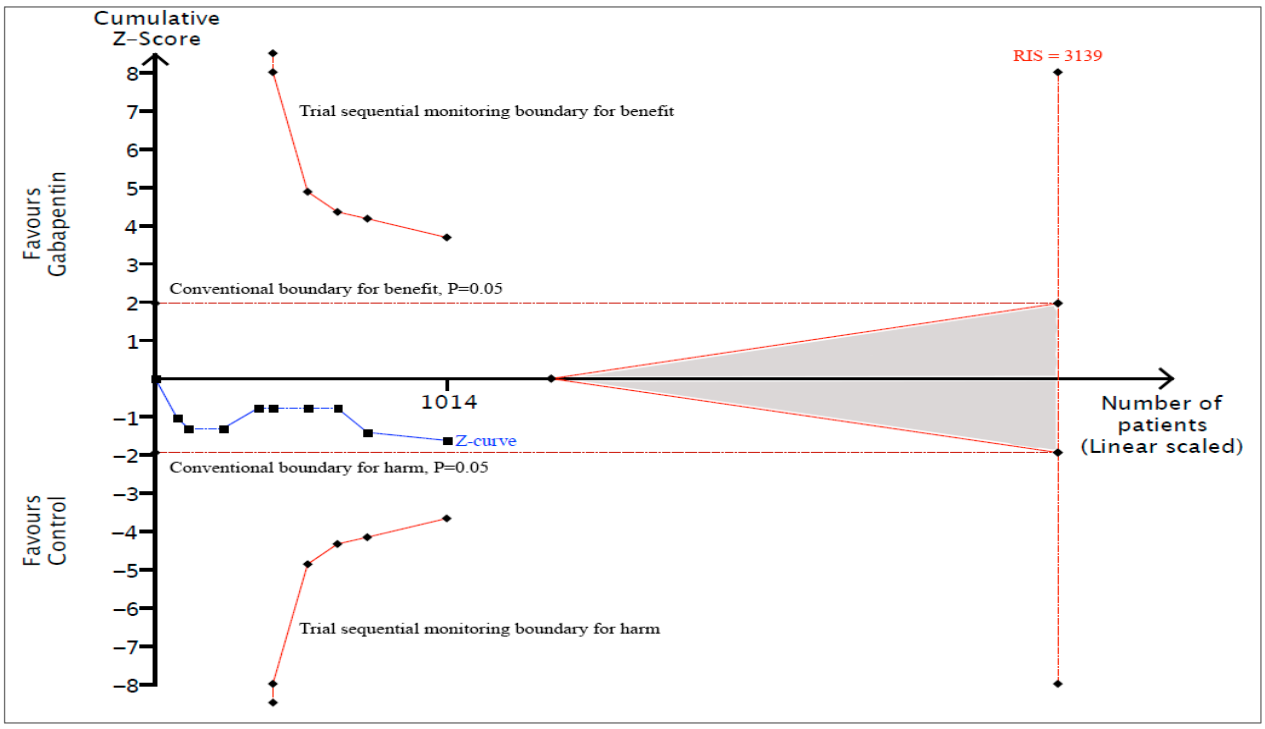

Figure 3 *TSA of the risk of SAE from trials with low risk of bias. TSA of gabapentin vs. controls from nine trials with low risk of bias reporting SAE, including zero-events trials, with RIS of 3139 patients to detect or discard a RRR of 50% and a diversity of 0%. Alpha = 0.05 and beta = 0.10 (power 90%). The number of accrued patients is 1014 and TSA adj. CI for the RR of patients with one or more SAE is 1.61 (0.57 to 4.57). In conclusion, the z-curve does not cross the boundary for harm or reach the futility area, and firm conclusion cannot be made.*

Erratum

Due to a bug in the previous TSA software the RIS was calculated as twice the correct size. The error has been corrected in the erratum published in 2017, and the correct RIS is reported in the results section of this thesis.

Secondary outcomes

Results on pain intensities at rest and mobilization and at 6- and 24-hour postoperatively indicated a reduction in VAS pain. All results for pain intensities except at rest at 6 hours postoperatively were firm, according to TSA.

In trials reporting adverse events, the significant reduction in risk of nausea was a firm result confirmed by TSA. The other adverse events, including vomiting, sedation, and dizziness do not seem to differ between groups. Data on these outcomes is lacking and trustworthy results have not been reached according to TSA.

The quality of evidence of the secondary outcomes according to GRADE is reported in *table 2*.

PAPER II: Gabapentin in procedure-specific postoperative pain management – Preplanned subgroup analyses from a systematic review with meta-analyses and trial sequential analyses

Trial characteristics

The 132 randomized clinical trials from Paper I were sorted according to surgical procedure, and 74 trials with 5,645 participants were included in the six surgical subgroups: Cholecystectomy, hysterectomy, mastectomy, orthopedic arthroplasty surgery, spinal surgery, and thoracic surgery (*Paper II*). Eight trials were low risk of bias[46-49,53,54,57,59] leaving 89% of the trials with unclear or high risk of bias.

Primary outcomes from trials with low risk of bias

Cumulative estimates with trials with low risk of bias from four out of the six surgical subgroups indicated a reduction in 24-hour morphine consumption, *table 3*. Though the point estimate varied between groups, neither the hysterectomy, nor the orthopedic arthroplasty subgroup found a subgroup difference (p=0.21and p=0.75) in the comparison to the remaining groups. None of the subgroups reached firm evidence tested by TSA.

Only one third of the subgroups of trials with low risk of bias reported serious adverse events. None found a subgroup difference, p=0.49. In both the orthopedic arthroplasty- and thoracic surgery subgroups, results indicated increased odds of SAEs. The outcomes consisted of very few data and none reached more than the 5% of RIS in the TSA.

Primary outcomes from all trials

The estimates from all trials reported significant reductions in 24-hour morphine consumption in all surgical subgroups. Half the subgroups reached firm evidence according to TSA. The cumulative meta-analysis from the mastectomy-, orthopedic arthroplasty surgery- and spinal surgery subgroups did not reach firm evidence. None of the subgroups reported a subgroup difference, *table 3*.

The odds of SAEs were reported in all subgroups. There was no difference between subgroups, but all subgroups lacked data and did not reach firm evidence confirmed by TSA.

TABEL 3: PRIMARY OUTCOMES FROM LOW RISK OF TRIALS AND ALL TRIALS

	Mean Difference / Odds Ratio *(95% CI, p-value)*	**TSA adj. CI**	**No. of trials** *(Participants / RIS)*	**Test for subgroup difference** *p-value*
24-H MORPHINE CONSUMPTION (REDUCTION)				
LOW RISK OF BIAS				
Cholecystectomy	12.2 mg (9.8 to 14.6, *p*-)	-	1 trial (120/-)	-
Hysterectomy	1.6 mg (-4.8 to 8.0, 0.62)	(-11.2 to 17.1)	2 trials (113/545)	*P*=0.21
Mastectomy	-	-	-	-
Orthopedic arthroplasty surgery	4.0 mg (-0.8 to 8.7, 0.1)	(-4.1 to 12.0)	3 trials (488/1190)	*P*=0.75
Spinal surgery	-	-	-	-
Thoracic surgery	6.7 mg (-2.0 to 15.4, *p*-)	-	1 trial (104/-)	-
ALL TRIALS				
Cholecystectomy	7.3 mg (4.6 to 9.9, <0.00001)	(4.6 to 9.9)	10 trials (1114/892)	*P*=0.9
Hysterectomy	10.5 mg (6.7 to 14.4, <0.00001)	(6.7 to 14.4)	14 trials (793/1315)	*P*=0.16
Mastectomy	5.2 mg (0.9 to 9.5, 0.02)	(-1.6 to 12.0)	6 trials (391/804)	*P*=0.15
Orthopedic arthroplasty surgery	6.1 mg (0.2 to 12.1, 0.04)	(-7.1 to 19.4)	6 trials (818/3323)	*P*=0.47
Spinal Surgery	10.6 mg (2.1 to 19.0, 0.01)	(-24.1 to 45.2)	8 trials (652/5607)	*P*=0.52
Thoracic surgery	6.3 mg (2.9 to 9.8, 0.0003)	(2.9 to 9.8)	7 trials (425/575)	*P*=0.25
SERIOUS ADVERSE EVENTS (OR)				
LOW RISK OF BIAS				
Cholecystectomy	Not estimable	-	1 trials (120/-)	-
Hysterectomy	-	-	-	-
Mastectomy	-	-	-	-
Orthopedic arthroplasty surgery	2.98 (0.36 to 24.41, 0.31)	TSA adj. CI < 5%	2 trials (375/-)	*P*=0.49
Spinal surgery	-	-	-	-
Thoracic surgery	1.35 (0.57 to 1.74, 0.81)	TSA adj. CI < 5%	2 trials (224/-)	*P*=0.49
ALL TRIALS				
Cholecystectomy	Not estimable	-	1 trials (120/-)	-
Hysterectomy	0.55 (0.1 to 5.6, 0.61)	TSA adj. CI < 5%	5 trials (371/-)	*P*=0.16
Mastectomy	Not estimable	-	2 trials (115/-)	-
Orthopedic arthroplasty surgery	2.98 (0.4 to 24.4, 0.31)	TSA adj. CI < 5%	2 trials (375/-)	*P*=0.30
Spinal surgery	Not estimable	-	1 trials (76/-)	-
Thoracic surgery	1.0 (0.6 to 2.1, 0.81)	(0.3 to 3.6)	4 trials (320/963)	*P*=0.72

Cumulated estimates from conventional meta-analyses and trial sequential analyses.
RIS; Required Information Size; TSA adj. CI: Trial Sequential Analysis adjusted Confidence Interval; OR: Odds Ratio; 95% CI: 95% Confidence Interval.

PAPER III: Dose-related beneficial and harmful effects of gabapentin in postoperative pain management – post-hoc analyses from a systematic review with meta-analyses and trial sequential analyses

Trial characteristics

Trials were included from Paper I. Ten dose-finding trials with more than one intervention group were excluded because they did not have 20 patients or more in the control group after dividing the groups (*Paper III*). Of the 122 trials included in the subgroup analyses, 16 trials were low risk of bias[44-59].

Primary outcomes from trials with low risk of bias

In trials reporting 24-hour morphine consumption, the point estimates varied from a reduction to an increase in morphine consumption, however, not compliant with an association between dose and effect. In the subgroup 701-1050 mg, a subgroup difference was found comparing the point estimate with the rest of the subgroups, p=0.002 (*table 4)*. The remaining subgroups all indicated a reduction in 24-hour morphine consumption, but no subgroup differences were found.

The subgroups reported 40 SAEs, most of which were found in the > 1050 mg subgroup. The subgroups 351-700 mg, and 701-1050 mg, reported decreased odds of SAEs while the subgroup > 1050 mg reported increased odds, *table 4.* No subgroup differences were demonstrated. TSA found that none of the subgroups reported firm evidence.

Primary outcomes from all trials

The subgroups 0-350 mg, 351-700 mg, and > 1050 mg all found significant reductions in 24-hour morphine consumption in the gabapentin group compared to controls. The reductions in 24-hour morphine consumption did not increase with increasing doses of gabapentin. The TSA of cumulated meta-analyses confirmed firm evidence. The tests for subgroup differences were significant in three of four dose-subgroups, *table 4.*

All subgroups reported SAEs. However, none reported any subgroup differences. There was not enough data to reach firm evidence according to the TSA in any subgroup, *table 4*.

TABEL 4: PRIMARY OUTCOMES FROM TRIALS WITH LOW RISK OF BIAS AND ALL TRIALS

	Mean Difference / Odd ratio *(95% CI, p-value)*	**TSA adj. CI**	**No. of trials** *(Participants / RIS)*	**Test for subgroup differences** *p-value*
24-HOUR MORPHINE CONSUMPTION (REDUCTION)				
LOW RISK OF BIAS				
0-350 mg	2.2 mg (0.1 to 4.4, 0.04)	(-0.1 to 4.6)	2 trials (111/58)	*P*=0.69
351-700 mg	4.0 mg (-0.6 to 8.5, 0.09)	(-3.3 to 11.6)	6 trials (599/1360)	*P*=0.25
701-1050 mg	-1.1 mg (0.3 to 2.0, 0.009)	(0.3 to 2.0)	2 trials (181/15)	*P*=0.002
> 1050 mg	2.1 mg (-1.1 to 5.3, 0.2)	(-1.4 to 5.6)	5 trials (427/499)	*P*=0.70
ALL TRIALS				
0-350 mg	8.0 mg (6.2 to 9.8, <0.0001)	(6.2 to 9.8)	11 trials (1070/495)	*P*=0.25
351-700 mg	4.6 mg (3.1 to 6.1, <0.0001)	(3.1 to 6.1)	20 trials (1811/466)	*P*=0.004
701-1050 mg	2.6 mg (-1.4 to 6.6, 0.2)	(-2.9 to 8.2)	7 trials (375/652)	*P*=0.03
> 1050 mg	9.1 mg (7.2 to 11.0, <0.0001)	(7.2 to 11.0)	27 trials (1595/637)	*P*=0.02
SERIOUS ADVERSE EVENTS (OR)				
LOW RISK OF BIAS				
0-350 mg	Not estimable	-	2 trials (113/-)	-
351-700 mg	0.9 (0.2 to 3.4, 0.85)	(0.0 to 220.8)	4 trials (404/2227)	*P*=0.44
701-1050 mg	0.6 (0.04 to 8.6, 0.70)	-	1 trial (121/-)	*P*=0.52
> 1050 mg	2.0 (0.9 to 4.5, 0.1)	(0.1 to 40.0)	3 trials (287/1633)	*P*=0.29
ALL TRIALS				
0-350 mg	Not estimable	-	3 trials (179/ -)	-
351-700 mg	0.9 (0.2 to 3.4, 0.85)	(0.1 to 11.7)	8 trials (682/2981)	*P*=0.44
701-1050 mg	0.6 (0.04 to 6.7, 0.70)	(TSA adj. CI < 5%)	3 trials (221/10413)	*P*=0.52
> 1050 mg	1.3 (0.8 to 2.4, 0.33)	(0.6 to 3.6)	13 trials (876/1973)	*P*=0.29

Cumulated estimates from conventional meta-analyses and trial sequential analyses.
RIS; Required Information Size; TSA adj. CI: Trial Sequential Analysis adjusted Confidence Interval; OR: Odds Ratio; 95% CI: 95% Confidence Interval.

PAPER IV: Pregabalin for postoperative pain management – A systematic review with meta-analyses and trial sequential analyses

Trial characteristics

We screened 4,430 titles and included 97 randomized clinical trials with 7,201 participants, and 20 trials were assessed as having overall low risk of bias[59-78]. Ninety-four percent of the included trials had less than 50 patients in each group, while five trials included more than 50 patients in each group and one trial included more than 200 patients.(*From Paper IV and Figure 4)*

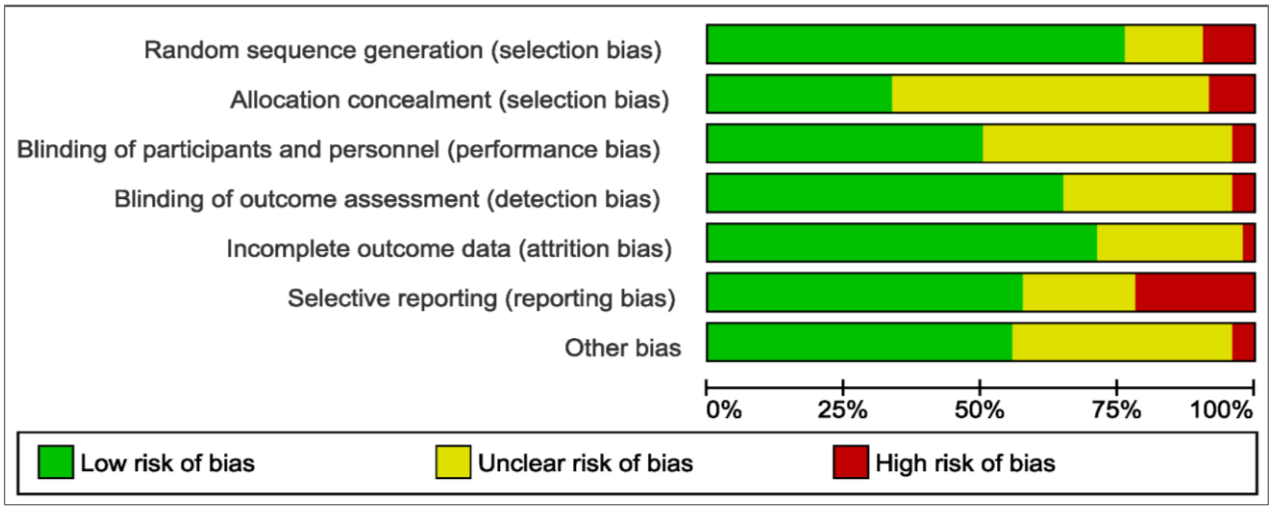

Figure 4 *Bias graph of the six bias domains. The Other bias domain consists of 'vested interests'; financial and confirmatory bias.*

Primary outcomes

Primary and secondary outcomes in trials with low risk of bias are presented in *table 5*. There is a significant reduction in 24-hour morphine consumption (5.8 mg (3.2 to 8.5, <0.0001)). The trial sequential analysis of this outcome confirms that the meta-analysis provides firm evidence for a reduction in 24-hour morphine consumption (*figure 5)*.

The reduction in 24-hour morphine consumption was less in the estimate from trials with low risk of bias compared with all trials estimates, which demonstrated a reduction of 12.5 mg (REM 95% CI: 9.4, 15.5, p<0.0001; 26 trials; 1718 participants). Moreover, a significant subgroup difference was found, p=0.0001.

The subgroup analysis of pregabalin combined with other non-opioid analgesics demonstrated a reduction in 24-hour morphine consumption of 5.3 mg (REM 95% CI: 2.1, 8.5; p=0.0002; TSA adj. CI: 2.1, 8.5; 8 trials; 499 participants; RIS: 571; GRADE: low). The subgroup analysis of pregabalin without other non-opioid analgesics report a reduction of 13.7 mg (REM 95% CI: 9.6, 17.8; p<0.00001; TSA adj. CI: 9.6, 17.8; 2 trials; 120 participants; RIS: 222; GRADE: low). There was a significant subgroup difference, p=0.002.

TABEL 5: PRIMARY AND SECONDARY OUTCOMES FROM TRIALS WITH LOW RISK OF BIAS

	MD / RR / Peto's OR *(95% CI, p-value)*	**TSA adjusted CI**	**No. of trials** *(Participants / RIS)*	**GRADE**
**PRIMARY OUTCOME MEASURES* ** **				
24-h morphine consumption	5.8 mg (3.2 to 8.5, <0.0001)	(3.2 to 8.5)	11 (705 /553)	LOW
Serious Adverse Events	2.9 (1.2 to 6.8, 0.02)	(0.1 to 97.1)	10 (730 / 8312)	MODERATE
SECONDARY OUTCOME MEASURES* **				
VAS 6-h at rest	7.7 mm (2.2 to 13.3, 0.007)	(3.6 to 19.0)	9 (588 / 1996)	LOW
VAS 6-h at mobilization	16.3 mm (-9.9 to 42.6, 0.22)	(TSA adj. 95% CI: -)	5 (323 / 24419)	VERY LOW
VAS 24-h at rest	1.4 mm (-2.7 to 5.5, 0.5)	(-4.6 to 7.4)	15 (1123/2059)	LOW
VAS 24-h at mobilization	3.7 mm (-1.5 to 8.9, 0.16)	(-6 to 13.4)	7 (502 / 1469)	LOW
AE: Nausea	0.8 (0.6 to 1.2, 0.34)	(0.4 to 1.7)	8 (631 / 1895)	LOW
AE: Vomiting	1.3 (0.7 to 2.7, 0.04)	(0.1 to 15.4)	6 (461 / 6325)	LOW
AE: Sedation	1.1 (0.9 to 1.3, 0.45)	(TSA adj. 95%CI: -)	10 (671 / -)	VERY LOW
AE: Dizziness	2.1 (1.1 to 3.9, 0.02)	(0.8 to 1.0)	11 (661 / 5439)	LOW

Cumulated estimates from conventional meta-analyses and trial sequential analyses. GRADE: Quality of evidence can be classified as very low, low, moderate or high quality of evidence.
RIS; Required Information Size; TSA adj. CI: Trial Sequential analyses adjusted Confidence Interval
Reduction in morphine consumption or pain intensities The risk of SAEs or AEs.*

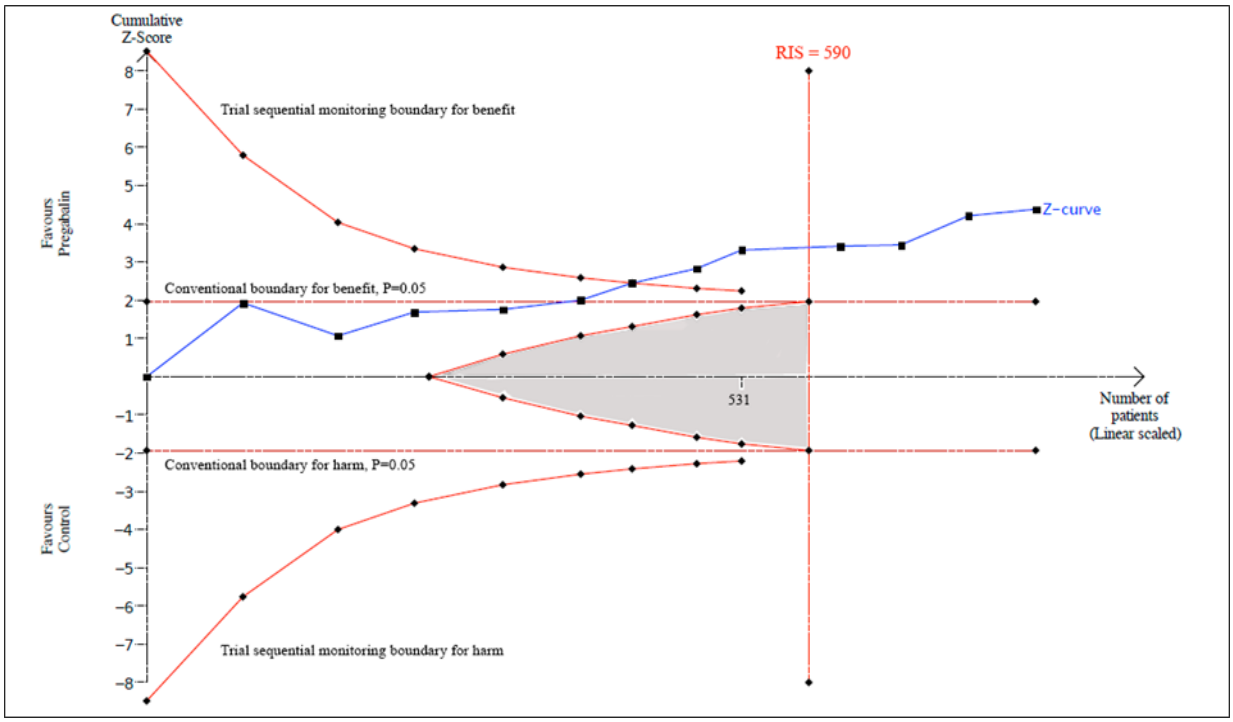

Figure 5 *TSA of the effect of pregabalin on morphine consumption. An estimated RIS of 590 patients to detect or discard a sparing effect of 5 mg morphine was calculated using the actual diversity between trials of 85%, a random-effects meta-analysis, an alpha of 0.05, and a beta of 0.10. After six trials the z-curve crosses the trial sequential monitory boundary for benefit and the RIS is surpassed leading to a TSA adj. CI as the naïve CI (TSA adj. CI 3.2 to 8.5). The number of actually accrued patients is 705, which is 119% of the RIS. In conclusion, the z-curve does surpass the RIS and an opioid sparing effect greater than 8.5 mg is highly unlikely.*

A total of 55 SAEs were reported from all the included trials. Twenty-two SAEs were reported from trials with low risk of bias and the meta-analysis suggests increased odds of SAE in the pregabalin group compared with controls (*figure 6*). More data is needed to confirm this finding according to the TSA. The odds of SAEs with single administration pregabalin, OR1.6 (FEM 95% CI: 0.3, 9.5; p= 0.63; TSA adj. CI: -; trials 4; participants 243; RIS: 7325; GRADE: very low), compared with multiple administration of pregabalin, OR 3.4 (FEM 95% CI: 1.3, 9.2; p= 0.01; TSA adj. CI: 0.1, 190.7; trials 6; participants 487; RIS: 8912; GRADE: moderate), find increased odds of SAE in both subgroups.

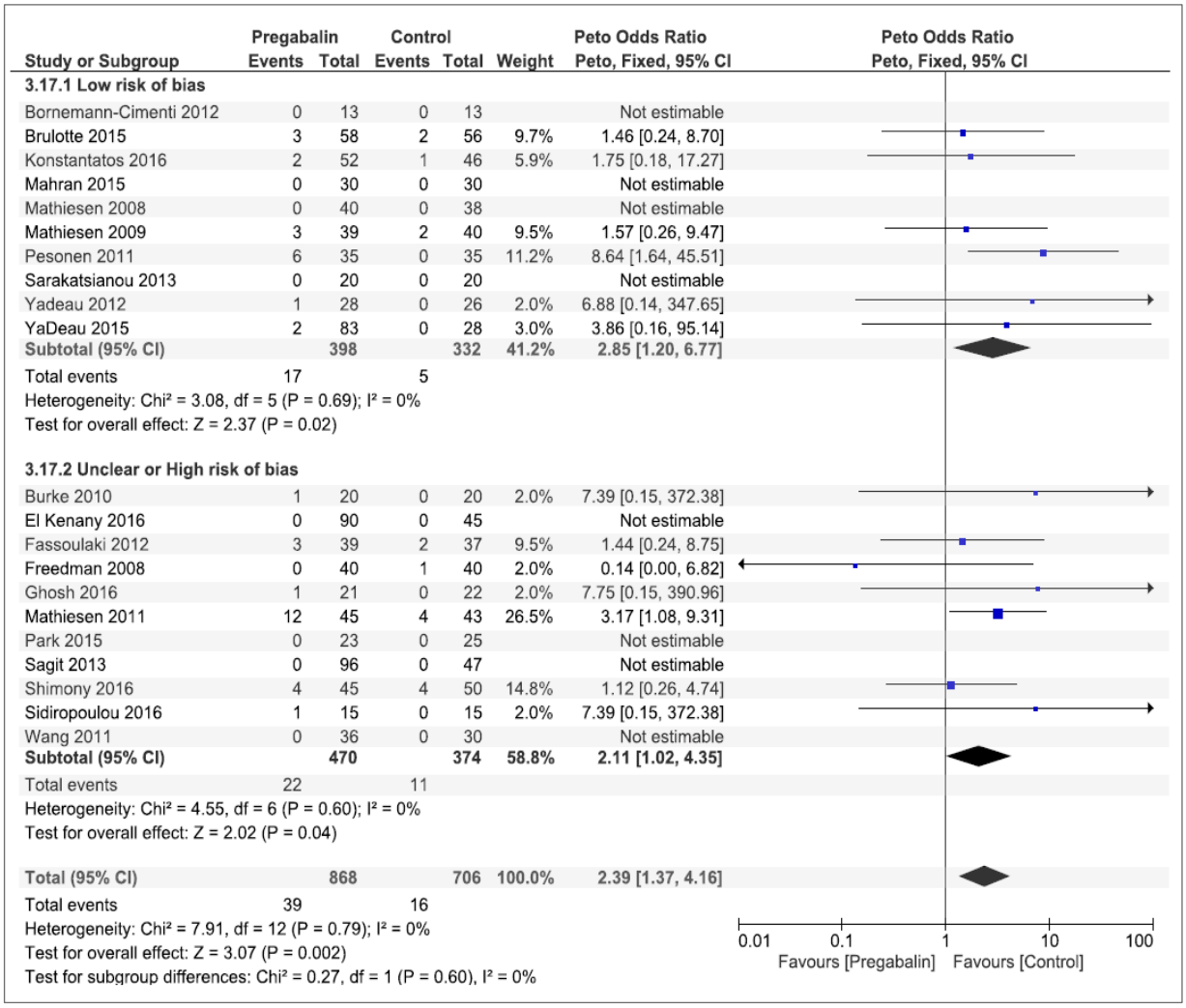

Figure 6 *Forest plot of SAE with subgroup analysis of trials with low risk of bias vs. trials with unclear and high risk of bias.*

Secondary outcomes

All pain intensities at rest and mobilization, at 6- and 24-hour postoperatively indicate a reduction in VAS, *Table 5*. None of the results were firm results according to the TSA.

In trials reporting AE a significant increased risk of vomiting and dizziness is found. While the risk of nausea may be reduced in the pregabalin group compared with controls, the risk of dizziness seem increased. However data is lacking in all meta-analyses of adverse events and is not sufficient to provide firm evidence according to TSA.

Quality of evidence on secondary outcomes according to GRADE is reported in *table 5*.

DISCUSSION

PRINCIPAL FINDINGS

In **Paper I** we found a reduction in 24-hour morphine consumption and an increase in risk of SAEs. However, the reduction in 24-hour morphine consumption in gabapentin treated patients compared to controls is most likely lower than the MID of 5 mg, (3.1 mg, 95%CI: - 0.2 to 6.3; *p*=0.02). When gabapentin is added to other non-opioid analgesics, the benefit seems negligible. The trials with low risk of bias indicated an increased risk of SAE of 61% in patients treated with gabapentin. Based on GRADE the quality of evidence is very low to low.

In **Paper II** very few trials were overall low risk of bias, limiting any firm conclusions. We could not find evidence supporting a difference in beneficial or harmful effects of gabapentin in different surgical procedures, but data is too few to reach firm evidence, according to TSA.

In **Paper III** we found no differences between different doses of gabapentin on the reduction in 24-hour morphine consumption, or the odds of SAEs in trials with low risk of bias. A suggestion of an optimal treatment dose cannot be made. According to the TSA, more data is needed to reach firm evidence.

In **Paper IV** we found firm evidence of a reduction in 24-hour morphine consumption in treatment with pregabalin, reaching the minimal important difference of 5 mg. The reduction does not seem to diminish when pregabalin is added to other non-opioid analgesics. Only few SAEs were reported. Results indicate increased odds of SAEs, which may increase further with multiple doses of pregabalin. Based on GRADE, the quality of evidence is low to moderate.

We found that both gabapentin and pregabalin reduced 24-hour opioid consumption, thus confirming our hypothesis. However, the reduction in 24-hour opioid consumption with gabapentin was lower than the MID, and almost non-existent, when gabapentin was added to other non-opioid analgesics. The risks or odds of serious adverse events with gabapentin and pregabalin seem increased, indicating the opposite of our initial hypothesis, that there would be no major harm in treatment with gabapentinoids for postoperative pain.

We found a high degree of heterogeneity confirming our expectations. Exploring the heterogeneity using the pre-planned subgroup analyses, we found a subgroup difference on outcomes from trials with low vs. unclear and high risk of bias, indicating a methodological heterogeneity. We could not explain the clinical heterogeneity by different procedures or dose, however, this may be due to lack of data.

STRENGHTS AND LIMITATIONS

General strength and limitations of the papers

Outcomes

We chose the co-primary outcomes of 24-hour morphine consumption and the risk of SAEs to explore the benefits and harms of gabapentin and pregabalin treatment in postoperative pain management.
A reduction in 24-hour opioid consumption would, theoretically be a response to an effective intervention meaning that patient would need fewer doses of opioids to achieve pain relief. However, due to fear of adverse events e.g. nausea or sedation, some patients may not consume the amount of opioids really needed to achieve sufficient pain relief, thus blurring the results, which is a limitation to this outcome. Further it is difficult to classify twenty-for hour morphine consumption as a patient-important outcome which is defined as e.g. death, disability, or quality of life[35].

Our choice of the risk of SAEs as a co-primary outcome is, in our opinion, advantageous. We combine several rare events into one composite outcome. This approach increases statistical power, which is a strength of this outcome. The interpretation of a composite outcome can, however, be difficult. Each component of the composite outcome may indicate different or opposite directions of the outcome. Ideally, every component of the outcome should be analyzed separately to properly interpret the direction of the outcome. However, this approach risks repetitive testing and lack of data, which is a potential limitation in the use of composite outcomes[35].

Preventing threats caused by systematic error

In the conclusions of our systematic reviews we put emphasis on trials with low risk of bias which we believe is a considerable strength. The methodological quality of trials may impact estimates of interventions substantially, and thus the conclusions and validity of the systematic reviews[35]. Bias in systematic reviews is often referred to as systematic error that may favor one intervention over others[79-81]. Both Paper I and IV report a high number of trials with unclear or high risk of bias in the domains: Allocation concealment, reporting of outcomes, and vested interests, e.g. financial bias[27]. Paper I and IV include very few trials with low risk of bias, 12% in Paper I and 21% in Paper IV. The high number of trials with unclear and high risk of bias may lead to an overestimation of the reduction of 24-hour morphine consumption, and underestimation of serious adverse events, which is confirmed in our findings from Paper I. Paper IV finds an overestimation of 24-hour morphine consumption in trials with unclear and high risk of bias compared with estimates from trials with low risk of bias in the test-of subgroup difference, p=0.001. The odds ratio of serious adverse events seems higher with pregabalin in the subgroup of trials with low risk of bias compared to trials with unclear or high risk of bias, but no

subgroup difference is found for this outcome. It is our argument that trials with low risk of bias must be emphasized in the conclusions, which is the recommended approach, to ensure validity in conclusions[35].

However, putting emphasis on trials with low risk of bias in conclusions also impose some limitations. Firm evidence has been reached in the primary continuous outcomes of morphine consumption within 24 hours from trials with overall low risk of bias while the increased risk of SAEs did not reach firm evidence in neither Paper I or IV. Arguments could be made that the benefits of power and precision achieved by including estimates from all trials regardless of bias assessments outweigh the risks of excluding data from conclusions. In Paper I, trials with overall low risk of bias report more than half of the SAEs. Further, the estimates from trials with unclear and high risk of bias may underestimate risk of SAEs compared with trials with low risk of bias, p=0.05. In Paper IV, less than half of the SAEs are reported in trials with low risk of bias, *figure 6.* Point estimates from Paper IV suggests an underestimation of the odds of SAEs from trials with unclear and high risk of bias as compared with trials with low risk of bias, however, no subgroup difference was found. Furthermore, we do not find firm evidence of the risks of SAEs from trials with low risk or unclear and high risk of bias. Overall, data on the risk of serious adverse events are lacking, and the conclusions are made on the best quality of trials in order to reduce the risk of underestimation and the threats of validity.

Strengths and limitations of the systematic reviews

The strengths of the systematic reviews, **Paper I** and **Paper IV,** include adherence to Cochrane methodology and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines in the reporting of the systematic reviews[82]. Further strengths are the pre-published protocol at PROSPERO, an updated extensive literature search strategy without limitation, independent screening of titles, full-texts, and bias assessment, and contact to corresponding author upon unclear bias domain or insufficient reporting of data. We used a validated and standardized method (GRADE) to assess the quality of the results[43].

In the planning of our reviews we believed that SAEs would be poorly reported in the gabapentinoid literature. Therefore we did not restrict our reviews based on factors which may impose heterogeneity in the reviews. Theoretically, this gives us the potential power and precision in the pooled meta-analyses of rare events, decreased risk of type II errors, and the possibility to explore the variation of clinical impact, e.g. surgical procedures or increasing dose, on outcomes.

Another strength is the use of TSA to adjust for the risk of random error due to sparse data and repetitive testing of accumulating data[40,41]. One of our arguments to utilize the broad scope systematic

review was that it increases power and precision. However it has been found that many meta-analyses are underpowered and reach flawed conclusions when they do not reach the required information size, which is why the TSA has been used on all outcomes from the four papers[83,84].
The required information size was calculated and used in assessment of the strength of the p-value from the conventional meta-analyses. We defined the risk of type I and II errors, the minimal important difference and relative risk reduction a priori in the protocols. It is debatable whether the minimal important difference of 5 mg for the co-primary outcome, 24-hour morphine consumption, is clinical relevant. We chose this minimal important difference based on a published systematic review investigating other non-opioid analgesics, reporting a reduction in 24-hour morphine consumption of 10 mg or less[85].

Utilizing the broad scope systematic review methodology is a strength, however, it does have some limitations. These include the lack of ability to conclude whether any effect of a specific treatment or in a specific study population, is present based on our results. The broad scope systematic reviews also risk high levels of heterogeneity, which was present in both systematic reviews. This can be derived from the broad inclusion of surgical procedure, study populations, additional non-opioid analgesics, and the intervention regardless of dose, administration intervals and time points. The conversion of pain intensity scores to VAS and opioids to intravenous morphine using equi-analgesic doses may also contribute to the heterogeneity.

Strengths and Limitations of the subgroup analyses
The strengths and limitations of the subgroup analyses mirror those of the systematic reviews. One of the limitations of the subgroups is the very small number of trials with low risk of bias that limits our ability to conclude firmly using the best quality trials. The subgroup effects may be due to small trial effect or lacking power to detect a large effect. This is the reason why we present both estimates from low risk of bias and all trials. Although all trials estimates may risk systematic error they increase power and precision in the single subgroup, making it possible to test for subgroup differences. This will imply careful consideration of the results, which may be over- or underestimated due to systematic error. Subgroup analyses must be perceived as observational studies and we interpreted them as such[86].

Paper II is one of a limited number of planned subgroups from Paper I. We chose this subgroup analysis to explore the hypothesis that different analgesics may have different effects depending on the surgical procedure[5,87]. This was a preplanned (except for 2 surgical procedures) subgroup analysis from a PROSPERO published protocol.

According to the developed credibility criteria from Oxman and Guyatt[88] and Yin Sun et al.[89], further limitations must be considered: That no a-priori direction of subgroup effect has been published; there is no firm evidence that the subgroup can be considered independent and that the effects of the subgroup analyses do not consequently re-occur in the closely related outcomes.

Paper III consists of subgroup analyses planned post-hoc, and should be interpreted with caution. Only a few published, randomized clinical trials have investigated the dose-response effect of gabapentin. Some of those trials suggest that a higher dose of gabapentin is more efficient than the lower dose treatments. It is difficult to form a hypothesis based on the very diverse results reported. This is why we chose to explore the dose effect in thesepost hoc analyses. Beside the post hoc character of Paper III the limitations of this subgroup analyses are similar to those of Paper II.

CURRENT EVIDENCE AND CLINICAL IMPLICATIONS

Quality in the gabapentinoid literature

Systematic reviews investigating gabapentinoids in a perioperative setting

Most systematic reviews on gabapentin and pregabalin have focused on the analgesic effect and reported some AEs[10,12-15,29,33,34,90]. Very few systematic reviews explore[11,30], and none report, the risk of SAEs. The published systematic reviews have not focused on trials with low risk of bias, or adjusted for risk of random error, due to sparse data and repetitive testing. This can be considered general limitations in the utilized methodology and limits any comparison to the results from this thesis, *table 6 and 7*. Only some of the currently published systematic reviews apply GRADE in assessment of the quality of evidence, which aids the interpretation of confidence in the estimate of the intervention effects of the outcomes[43]. Based on GRADE, the quality of evidence on outcomes from trials with low risk of bias in both Paper I and IV have very low to moderate quality of evidence. The results are downgraded based on imprecision, indirectness in some outcomes and inconsistency.

The mentioned limitations are general, methodological weaknesses in the published systematic review literature, which can limit the evidence-based decisions on the use of gabapentinoids in the clinical setting.

Randomized clinical trials investigating gabapentinoids in a perioperative setting

The vast majority of the published randomized clinical trials on gabapentinoids were small. Ninety percent of the gabapentin trials and ninety-four percent of the pregabalin trials have less than 50 patients in each group. In a systematic review of acetaminophen, McNicol et all reported that all of the included trials were small[91]. This indicates that the issue of small trials is not unique for the gabapentinoid literature, but most likely a more generalized problem in analgesic research.

Most of the gabapentinoid trials have a short follow-up time, which risk an under-reporting, and consequently an underestimation of harmful events. This can limit any weighing of benefit versus harm in treatment with gabapentin and pregabalin. None of the included trials have been designed to detect a risk of serious adverse events, and the vast majority is designed to detect a difference in either 24-hour opioid consumption, or pain intensity, as primary outcomes.

Not only did most of the included trials in the systematic reviews have few included patients and a short follow-up period, the majority of trials also had unclear or high risk of bias in bias evaluations. The number of trials with low risk of bias from Paper I is similar to the findings from a recently published review on gabapentin for postoperative pain management[10]. The systematic review of acetaminophen

also found very few trials classified as overall low risk of bias,[91] confirming that this issue does not seem to be limited to the gabapentinoid research but a more general methodological problem in the research of non-opioid analgesics for postoperative pain management.

The beneficial effect of gabapentinoids in postoperative pain management

Gabapentinoids

To explore the overall effect of gabapentinoids in a post-hoc analysis, we merged trials with low risk of bias from the gabapentin- and pregabalin review. The combined mean difference of gabapentinoids for postoperative pain demonstrated a reduced 24-hour morphine consumption of 4.2 mg (95% CI: 2.4, 5.9; $p<0.00001$), *Figure 7*.

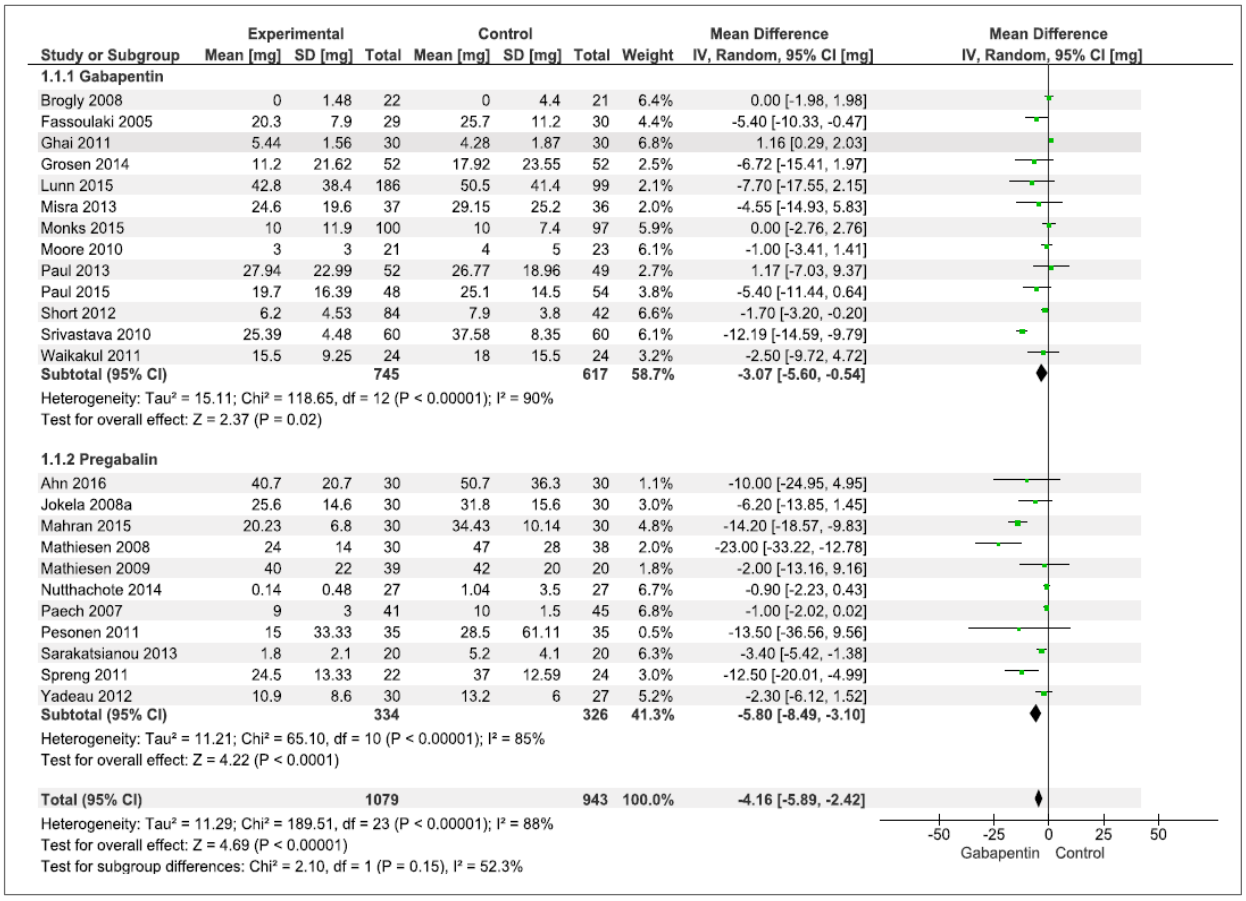

Figure 7 *Forest plot of 24-hour morphine consumption from trials with overall low risk of bias and with subgroups of gabapentin vs. pregabalin trials.*

Also, odds of SAE are significantly increased for the combined gabapentinoid group compared with controls, OR 2.0 (95% CI: 1.2, 3.2; TSA adj. CI: 0.8, 5.2). However, there is not enough data to reach firm evidence on the odds of SAE according to trial sequential analysis (*Figure 8*).

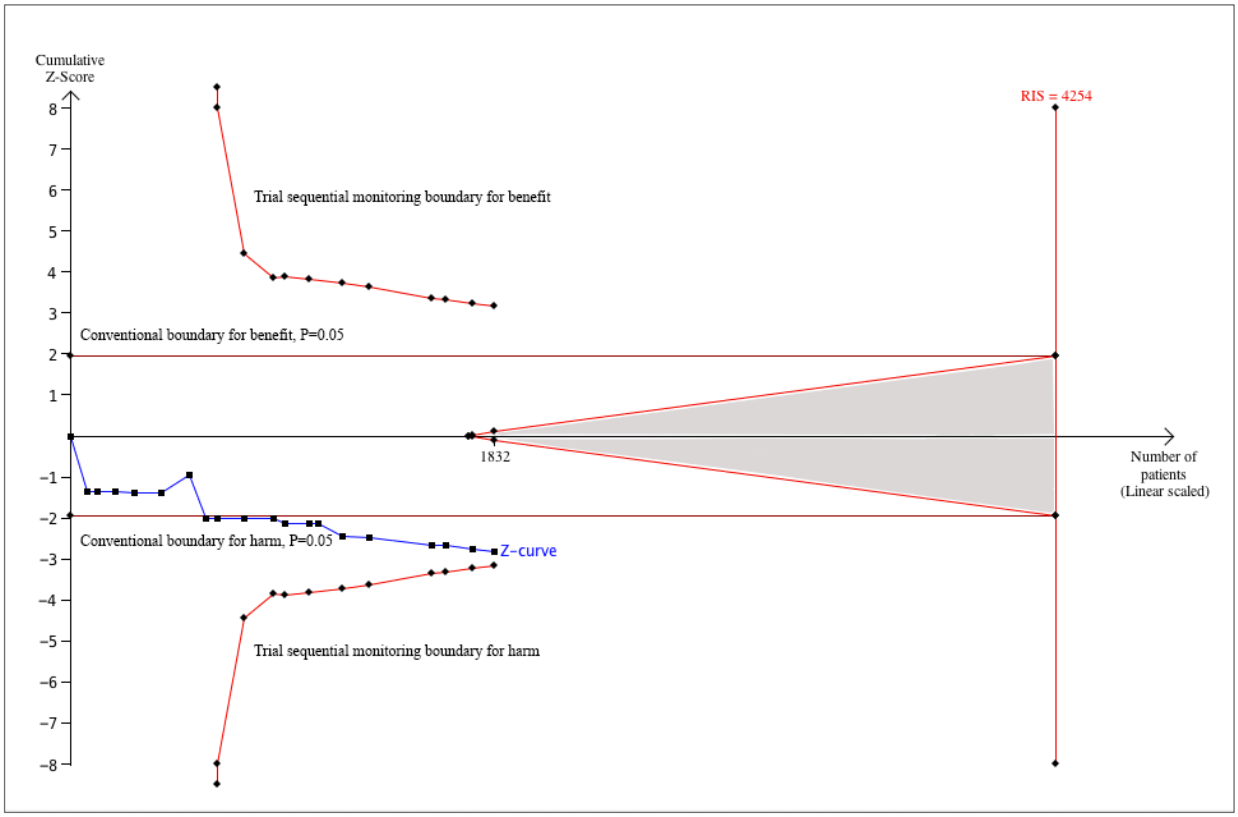

Figure 8 *TSA of the risk of SAE from trials with low risk of bias investigating gabapentinoids. TSA of gabapentinoids vs. controls in includes 19 trials with low risk of bias reporting SAE, including zero-events trials, with RIS of 4254 patients to detect or discard a RRR of 50% and a diversity of 0%. Alpha = 0.05 and beta = 0.10 (power 90%). The number of accrued patients is 1832 and TSA adj. CI for the RR of patients with one or more SAE is 2.0 (0.8, 5.2). In conclusion, the z-curve does not cross the boundary for harm or reach the futility area, and firm conclusion cannot be made.*

The beneficial effect of gabapentinoids may be present, but small, and the increase of serious adverse events should lead to careful considerations of the indications of gabapentinoids in postoperative pain management. No systematic review has previously explored the effect of the combined gabapentinoids on beneficial and harmful outcomes.

Gabapentin

Several reviews have explored the effect of gabapentin on postoperative pain[10,14,15,29,30]. Most of the published systematic reviews on gabapentin in a postoperative setting demonstrated a reduction in pain intensities both early and late, which is similar to the results from the all trials estimates from Paper I[14,15,29]. Doleman et al published a systematic review in 2015 investigating gabapentin for postoperative pain management[10]. The number of included trials, trials with low risk of bias, and 24-hour morphine consumption from all trials estimates seem to be comparable with those reported from Paper I.

The reduction in 24-hour opioid consumption from all trial estimates is smaller in the more recently published reviews[10], including Paper I, compared to the rest[15,29,32], *table 6*. These findings may suggest a reporting bias, the time-lag bias, which finds that more recently published trials report less reduction in 24-hour morphine consumption. This must be taking into account upon evaluation of the indication for gabapentin in postoperative pain management.

The beneficial effect of gabapentin may be less than the predefined MID of 5 mg and the pain intensities are marginally reduced. This must be weighed against the risk of harm in the treatment with gabapentin before clinical implementation.

TABLE 6 COMPARISON OF OUTCOMES AND ESTIMATES FROM GABAPENTIN SYSTEMATIC REVIEWS

GABAPENTIN REVIEWS					
Estimate (MD/RR/OR) *(REM/FEM; 95% CI; p-value; TSA adj. CI)*	**STUDY I**	**Dolemann et al.[10]** ***	**Seib et al.[29]** ***	**Straube et al.[30]** ***	**Ho et al.[15]** ***
LOW RISK OF BIAS* **					
24-h opioid consumption	3.1 mg (0.5 to 5.6; <0.02; 0.5 to 5.6)	Note[1]	Not available	Note[2]	Not available
24-h opioid consumption + add-on	1.2 mg (-0.3 to 2.6; 0.12; -0.3 to 2.6)	Not available	Not available	Not available	Note[4]
24- opioid consumption - add-on	8.0 mg (-1.5 to 17.4; 0.10; -30.5 to 46.3)	Not available	Not available	Not available	Not available
Serious Adverse Events	RR 1.61 (0.5 to 5.6, 0.10; TSA adj. CI: 0.5 to 5.6)	Not available	Not available	Not available	Not available
ALL TRIALS* **					
24-h opioid consumption	7.3 mg (5.9 to 8.8; < 0.00001; 5.9 to 8.8)	8.4 mg (7.3 to 9.6; p<0.0001)*	14.7 mg (9.4 to 20.0; p<0.00001)*	Not available	16.0 mg (24.3 to 31.5; p<0.0001)*
Serious Adverse Events	RR 1.14 (0.71 to 1.81; 0.59; 0.6 to 2.1)	Not available	Not available	Note[3]	Not available

All trials estimates are from results section of Paper I.
MD: mean difference; WMD: weighted mean difference; RR; risk ratio; OR: odds ratio; FEM: fixed effects model; REM: random effects model; TSA: trial sequential analysis
Reduction in morphine consumption or pain intensities. The risk of SAEs.***No TSA conducted*
[1]Authors state: 'The absolute effect may be overestimated due to bias'. [2]No sensitivity analysis since all trials had maximum quality according to the Oxford Quality Scale. [3]Described in text no cumulative estimate reported.[4] Use standardized mean difference, Hedge's g.

Pregabalin

The results on pregabalin in postoperative pain management are similar to the results from Paper I. We found a reduction in 24-hour morphine consumption that only just reached the MID and is smaller than reported in the previous systematic reviews. The difference in estimates from this thesis and the

published systematic reviews may be caused by the methodological differences mentioned previously and in *table 7*. Most of the systematic reviews confirmed a reduction in morphine consumption and pain intensity scores[11-13]. However, the estimates on beneficial outcomes are reported from systematic reviews exploring the effect of procedure[13], pro-nociceptive pain[11], and dose,[90] therefore any direct comparison to the results from this thesis is difficult.

The results from this thesis are the first to evaluate pregabalin in a broad scope systematic review, with emphasize on trials with low risk of bias. We find that based on trials with low risk of bias pregabalin display a beneficial effect that should be weighed against the risk of harm in the future implementation in postoperative pain management.

TABEL 7 COMPARISON OF OUTCOMES AND ESTIMATES FROM PREGABALIN SYSTEMATIC REVIEWS

PREGABALIN REVIEWS

Estimate (MD/RR/OR) *(REM/FEM; 95% CI; p-value; TSA adj. CI)*	**STUDY IV**	**Mishriky et. al.[12]******	**Lam et al.[13] *****	**Zhang et al.[90] *****	**Eipe et al.[11] *****
LOW RISK OF BIAS					
24-h opioid consumption*	5.8 mg (3.2, 8.5; < 0.0001; 3.2, 8.5)	Note[1]	Not available	Not available	Not available
24-h opioid consumption* + add-on	5.3 mg (2.1, 8.5; 0.001; 2.1, 8.5)	Not available	Not available	Not available	Not available
24-h opioid consumption* - add-on	13.7 mg (9.6, 17.8; <0.00001; 9.6. 17.8)	Not available	Not available	Not available	Not available
Serious Adverse Events**	2.9 (1.2, 6.8; 0.02; 0.1, 97.1)	Not available	Not available	Not available	Not available
ALL TRIALS					
24-h opioid consumption *	10.8 mg (8.5, 13.2; <0.00001; 8.5, 13.2)	8.3 mg (6.5 to 10.1; p<0.00001)[*]	Note	Note[2]	Not available
Serious Adverse Events**	2.4 (1.4, 4.2; 0.002; 0.9, 6.33)	Not available	Not available	Not available	Note[3]

All trials estimates are from the results section of Paper IV.
MD: mean difference; WMD: weighted mean difference; RR; risk ratio; OR: odds ratio; FEM: fixed effects model; REM: random effects model; TSA: trial sequential analysis.
Reduction in morphine consumption or pain intensities. **The odds of SAEs and risks of AEs.*No TSA conducted.*
[1]No bias effect found in sensitivity analysis.[2]Used a modified Oxford Scale in quality assessment of the included trials and trials with Oxford Scale score of ≥ 3 were included. [3]Authors state: 'sparse evidence'. [4] Use standardized mean difference, Hedge's g.

Gabapentinoids in multimodal analgesic treatments

Fifty-one percent of the trials from the gabapentin review and seventy-six percent of the trials from the pregabalin review explore the effect of the gabapentinoids in multimodal analgesic treatments, that is, combined with other, non-opioid analgesics. It seems that the gabapentinoids are more commonly

utilized in a multimodal analgesia than as mono-therapy. Surprisingly, none of the published systematic reviews explores the impact of gabapentinoids in treatments with other non-opioid analgesics.
In trials, where gabapentinoids are added to other, non-opioid analgesics, the reduction in 24-hour morphine consumption is barely 5 mg in Paper IV and almost non-existent in Paper 1. However, the multimodal analgesic regimens are diverse and include both a simple regimen of either gabapentin or pregabalin and acetaminophen or a greater regimen of three or four non-opioid analgesics and regional analgesic techniques, as reported in the trial characteristics of Paper I and IV. We have not explored the effect of different variations of multimodal analgesia on the outcomes. In future research there is a need for a systematic exploration of the optimal non-opioid analgesic combinations in treatment of postoperative pain. Multimodal analgesia is the most common approach in postoperative pain management, but there is still very little knowledge of additive or synergistic effects, optimal doses and combinations of non-opioid analgesics including the gabapentinoids.
It seems that pregabalin might still exhibit a beneficial effect when combined with other, non-opioid analgesics. The arguments for the use of gabapentin in a multimodal analgesic regimen seem to diminish based on the results reported in this thesis. The lack of benefit for gabapentin in postoperative multimodal analgesia should lead to careful consideration of the routine use of gabapentin in such combinations.

Adverse events of gabapentinoids in postoperative pain management

Hoffer et al showed that the reporting of adverse events are lacking in randomized clinical trials investigating gabapentin and pregabalin[92]. Most of the included trials in our reviews have a short follow-up time that may cause an underestimation of adverse- and serious adverse events. Only 20% of the trials in the gabapentin review and 22% of the trials in the pregabalin review reported on the incidence of SAEs. In both systematic reviews one of the bias domains with the highest number of unclear and high risk of bias evaluations is the reporting bias domain.
These findings are similar to those of the systematic reviews investigating gabapentin and pregabalin for medical conditions[20-22,25,26,93]. Even though the treatment and follow-up time is generally longer in such trials, few randomized clinical trials report SAEs[20,93]. It may be presumed that, with longer treatment periods and follow-up, the risks of SAEs in treatment with gabapentinoids for medical conditions would be described in greater detail and include more data, however, this does not seem to be the case.
Zaccara et al. found, in an effort to clarify the adverse event (AE) profile of pregabalin, no difference in the risk of SAEs between pregabalin and controls in medical conditions[23]. Further they reported a dose-response relationship between AEs that were related to higher cortical functions and brainstem functions e.g. dizziness and somnolence. Some of the described SAEs were due to falls and fractures

related to falls[23]. We did not explore the dose-response of SAEs in Paper IV, but did find results which suggested an increase of SAEs with more than one administrations of pregabalin. It is worth considering in future research, whether the AEs with high dose or multiple doses of pregabalin may be a contributing factor to the potential increased odds of SAEs reported with multiple dosing reported from Paper IV. The systematic review[23] was limited by their use of the diverse definition of SAEs, which was defined by the individual authors, and the lack of exploration of the effect of the systematic or random errors on their results.

The general lack of data on the risk of SAEs, regardless of indication, makes it difficult to provide any certain interpretation on this risk. Further it is difficult to assess any overrepresentation of SAEs there may be at a specific point during treatment, treatment administration, or in any specific patient population. In both systematic reviews of gabapentin and pregabalin, we found an increase of SAEs with gabapentinoid treatment. Although we have not enough data to reach firm evidence, the risks of SAEs must be taking into consideration when using gabapentin and pregabalin for postoperative pain management.

The risk of sedation, dizziness, nausea, and vomiting are the most common adverse events investigated in the gabapentinoid literature[9]. Overall the risks of the adverse events are reported very diversely in the gabapentinoid literature[92] and no clear consensus is found on the risks of AE in gabapentinoid treatment for postoperative pain management. The contradictions and diversity in the literature on gabapentinoids and concomitant in Paper I and IV confirm the findings by Hoffer et al.[92]. This underreporting and underestimation of adverse and serious adverse events make it difficult to balance the harm and benefit of perioperative gabapentinoid treatment in future evidence-based decisions.

Gabapentin in procedure-specific pain management

Only one published systematic review has focused on gabapentin for procedure specific pain management[31]. Mathiesen et al reported reductions in 24-hour opioid consumption that seemed greatest in the abdominal hysterectomy and spinal surgery groups. They did not test for subgroup differences, and included fewer trials with no emphasis on trials with low risk of bias, limiting a comparison to the results from Paper II[31]. Several reviews have focused on surgical procedures[31,94,95]. Some of the systematic reviews report favorable findings, in treatment with gabapentin for postoperative pain, which is similar to those of the subgroups from all trials estimates. Each of the subgroups, with all trials regardless of bias classification, include more trials than that of the independent systematic reviews, increasing the power and precision of the estimates from Paper II compared to those of the independent systematic reviews.

A systematic review found no effect of surgical procedure on their outcomes[10]. However, they use meta-regression and not subgroup analyses to explore the theoretical clinical heterogeneity, which different surgical procedures may inflict on cumulative estimates.
There is so far no firm evidence of beneficial or harmful effects of gabapentin in the concept of procedure-specific analgesia. Therefore, no recommendation on, which surgical procedures may benefit the most with the least amount of harm, can be made.

Optimal dose of gabapentin in postoperative pain management

No systematic review has been published on gabapentin treatment, with a primarily focus on the effect of different doses on beneficial and harmful outcomes in postoperative pain treatment. The published dose-finding, randomized clinical trials report contradicting results, arguing both beneficial effects of gabapentin with increasing dose, and no such effects[49,96,97]. Overall, there is very little focus on the risk of SAEs.
We found no clear association between dose and beneficial or harmful effect of gabapentin in our review. The diverse results may be related to the bioavailability or anti-hyperalgesic properties of gabapentin, or simply insufficient dosing to achieve analgesic efficacy[17,98]. The most SAEs were reported in the highest dose group. However, it must be speculated if increasing the dose of gabapentin may lead to increased risks of SAEs. Only few SAEs were reported, limiting any conclusion based on this outcome. Based on our review, it is not possible to recommend any specific dose for future treatment and trials of gabapentin for postoperative pain management.

CONCLUSIONS AND FUTURE PERSPECTIVES

The four papers explore the benefits and harms of perioperative gabapentin and pregabalin, with conclusions based primarily on trials with low risk of bias.
Both gabapentin and pregabalin seems to reduce 24-hour morphine consumption, but the evidence for both drugs is of low quality. The morphine sparing effect may be most pronounced for pregabalin. When gabapentin is administered as an adjunct to other non-opioid analgesics, the reduction is clinically insignificant.
The exploratory subgroup analyses did not suggest any optimal dose, or specific surgical procedure, that patients might benefit or risk the most in treatment with gabapentin.
Both gabapentin (GRADE low) and pregabalin (GRADE moderate) treatment seems to increase serious adverse events. In postoperative pain management with pregabalin, SAEs may increase further with multiple administrations.

Overall, the risk of harm may outweigh the potential beneficial effects of gabapentin and pregabalin in postoperative pain management. Consequently, the routine use of gabapentin and pregabalin cannot be recommended, until there is firm, high quality evidence regarding risk of serious adverse events, and beneficial effects. Further, optimal dosages, and subgroups of patients that might achieve a greater benefit of gabapentinoids for postoperative pain, should be identified.

Future perspectives

The use of gabapentinoids for postoperative pain management is common. After 229 randomized clinical trials, and with 16,699 patients included in two systematic reviews of gabapentin and pregabalin, we still have limited knowledge of benefit and harm of the two medications. Further, our knowledge of optimal dosing, surgical procedure-specific effects, and beneficial and harmful effects in combination with other non-opioid analgesics, is very limited.
In our effort to systematically assess the methodological quality of the published literature of gabapentinoids in postoperative pain management, we found several methodological weaknesses. These must be corrected in future trials, to ensure a high level of quality evidence.
Treatment of patients should strive to be evidence-based, and should include a thorough weighing of benefit and harm of the intended intervention. The benefits should outweigh the risk of harm. Future trials investigating gabapentinoids (and other analgesics) for postoperative pain management should not only focus on benefit, as they have in the past, but equally, or primarily, on harm.
We have identified four areas of possible errors from our systematic assessments of the gabapentinoid literature; the risk of systematic error, the risk of random error, choice of outcomes,

and the length of follow-up. Future trialists must consider and design their trials to accommodate these areas and ensure the best evidence and thus treatments in postoperative management with gabapentinoids (*table 8)*.

TABEL 8 RECOMMENDATION FOR FUTURE TRIALS EXPLORING GABAPENTINOIDS FOR POSTOPERATIVE PAIN MANAGEMENT

ITEM	RECOMMENDATION
To avoid the risk of systematic error (bias)	The reports of the results must adhere to CONSORT statements with an increased focus on minimizing allocation concealment, reporting of all outcomes, and vested interests e.g. financial bias.
To minimize the risk of random error	The sample size should be calculated using the risk of SAE as a primary or co-primary outcome adjusting for statistical multiplicity when analyzed.
To avoid design error	Investigate one surgical procedure and not groups of surgical procedures, e.g. 'lower limb surgery' .Ensure that the multimodal regimens of non-opioid analgesics are used similarly in both the control- and intervention groups when used.
Comparator intervention	The gabapentinoids could be compared in a multi-group design to assess both the effects of mono-and poly-intervention including the potential additive or synergistic effects as Thybo et al plan to do in the PANSAID[99] trial.
To evaluate benefit	Prioritize direct and not surrogate outcomes to prevent downgrading quality of evidence. Consider COMET (Core Outcome measures in Effectiveness Trials) and designed core sets of outcomes.
To evaluate harm	Prioritize this outcome to properly evaluate the risk of gabapentinoids. Ensure the follow-up is sufficient to prevent under-reporting and using a clear definition of SAE e.g. the ICH-GCP's definition or a COMET defined core set of outcomes.

In order to ensure the best treatment weighing benefit and harms future gabapentin randomized clinical trials must focus on the risk of SAEs and be powered to reach firm evidence breaking through the boundary for benefit, harm, or futility. Methods should compensate for previous lack in quality of evidence by taking into account indirectness, imprecision, and inconsistency according to the GRADE methodology.

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JW reports that he is a member of the task force at Copenhagen Trial Unit to develop the software and manual for doing Trial Sequential Analysis. None of the remaining authors declares a conflict of interest.

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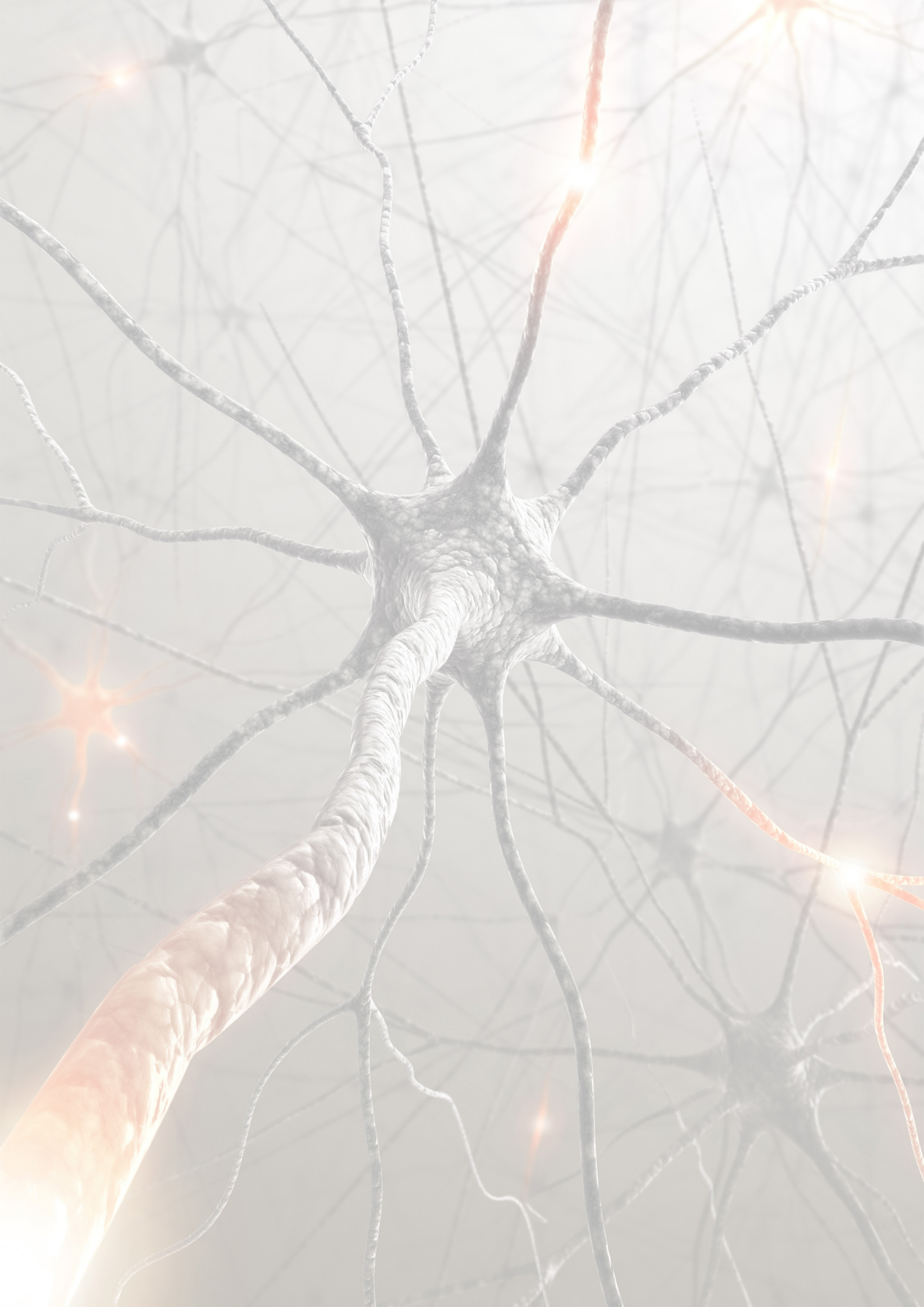

PAPERS

PAPER I **Gabapentin for post-operative pain management – a systematic review with meta-analyses and trial sequential analyses**. Fabritius ML, Fabritius ML, Geisler A, Petersen PL, Nikolajsen L, Hansen MS, Kontinen V, Hamunen K, Dahl JB, Wetterslev J, Mathiesen O. Acta Anaesthesiol Scand. 2016 Oct;60:1188-208.

PAPER II **Gabapentin in procedure-specific postoperative pain management - preplanned subgroup analyses with meta-analyses and trial sequential analyses.** Fabritius ML, Geisler A, Petersen PL, Wetterslev J, Mathiesen O, Dahl JB. In review.

PAPER III **Dose-related beneficial and harmful effects of gabapentin in postoperative pain management – Post-hoc analyses with meta-analyses and trial sequential analyses**. Fabritius ML, Wetterslev J, Mathiesen O, Dahl JB. Submitted.

PAPER IV **Pregabalin for postoperative pain management – a systematic review with meta-analyses and trial sequential analyses.** Fabritius ML, Strøm C, Koyuncu S, Geisler A, Petersen PL, Jæger P, Wetterslev J, Dahl JB, Mathiesen O. In review.

PAPER I

REVIEW ARTICLE

Gabapentin for post-operative pain management – a systematic review with meta-analyses and trial sequential analyses

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Conflict of interest
All authors have completed the ICMJE disclosure form available upon request from corresponding author. VK reports personal fees from Grünenthal, Janssen-Cilag, MSD, Mundipharma, Orion, Pfizer and Steripolar outside of the submitted work. JW reports that he is a member of the task force at Copenhagen Trial Unit to develop the software and manual for doing trial sequential analysis (TSA). AG, PLP, MSH, LN, KH, JBD, OM, and MLF have no conflicts of interests to declare.

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Background: Perioperative pain treatment often consist of combinations of non-opioid and opioid analgesics, 'multimodal analgesia', in which gabapentin is currently used. The aim was to document beneficial and harmful effects of perioperative gabapentin treatment.
Methods: Randomized clinical trials comparing gabapentin vs. placebo or active placebo in adult surgical patients receiving gabapentin perioperatively were included. This review was conducted using Cochrane standards, trial sequential analysis (TSA), and Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The primary outcomes were 24-h opioid consumption and incidence of serious adverse events (SAE).
Results: One hundred and thirty-two trials with 9498 patients were included. Thirteen trials with low risk of bias reported a reduction in 24-h opioid consumption of 3.1 mg [0.5, 5.6; TSA-adjusted CI: −0.2, 6.3]. In the analysis of gabapentin as add-on analgesic to another non-opioid analgesic regimen, a mean reduction in 24-h morphine consumption of 1.2 mg [−0.3, 2.6; TSA-adjusted CI: −0.4, 2.8] in trials with low risk of bias was found. Nine trials with low risk of bias reported a risk ratio of SAEs of 1.61 [0.91; 2.86; TSA-adjusted CI: 0.57, 4.57].
Conclusion: Based on GRADE assessment of the primary outcomes in trials with low risk of bias, the results are low or very low quality of evidence due to imprecision, inconsistency, and in some outcomes indirectness. Firm evidence for use of gabapentin is lacking as clinically relevant beneficial effect of gabapentin may be absent and harm is imminent, especially when added to multimodal analgesia.

Editorial Comment
In this trustworthy systematic review, use of gabapentin for post-operative pain management was scrutinized. In summary, the quality of evidence for a clinically relevant benefit of gabapentin is low, and, importantly, harm may be present.

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The World Health Organization (WHO) estimated that 321.5 million surgical procedures were needed in 2010 to meet the burden of diseases in the global population.[1] Optimal management of post-operative pain is a critical component in care of the surgical patient and is often performed by combinations of non-opioid and opioid analgesics, referred to as 'multimodal analgesia'.[2–4] At present, a diversity of combinations of analgesics is used in clinical practice.

Gabapentin was introduced as an anti-epileptic and has been recommended for treatment of chronic neuropathic pain conditions.[5] It is presumed that gabapentin exhibits its effects through α2δ-subunits of voltage-gated calcium channels causing a decrease in excitatory neurotransmitters, e.g., glutamate, substance P, and calcitonin gene-related peptide (CGRP).[6–8] The anti-hyperalgesic effect of gabapentin has been demonstrated in several experimental and clinical trials.[9–12] The potential post-operative analgesic effects have been investigated in a growing number of randomized clinical trials (RCTs). Gabapentin is becoming an established component in multimodal post-operative analgesia.[13] Therefore, an updated systematic documentation of benefit and harm of perioperative gabapentin treatment is needed. It was our hypothesis that gabapentin would reduce 24-h opioid consumption and that adverse events would not be of a severity which will prevent treatment with gabapentin.

This systematic review aim to evaluate the effects of perioperative gabapentin on post-operative opioid consumption, pain intensity, and adverse and serious adverse effects in surgical patients receiving gabapentin for post-operative pain management with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology for rating quality of evidence.[14]

Methods

This systematic review followed the methodology recommended by the Cochrane Collaboration and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15,16] The protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/PROSPERO) registration no. CRD42013006538.

Search strategy and selection criteria

We searched the Cochrane Library's CENTRAL, PubMed, EMBASE and Science Citation Index Expanded databases for eligible trials using the search terms and MeSH descriptors 'Amines', 'gamma-Aminobutyric Acid', 'gaba* or neurontin* or neurotonin* or horizant*', and 'pain'. Language was not a restriction. Relevant publications were also identified from reference lists of previous reviews and Google Scholar. Unpublished trials were identified through the following trial registries: www.clinicaltrials.gov; www.controlled-trials.com; www.centerwatch.com; www.eudraCT.com; and at the homepage of the US Food and Drug Administration (FDA). The electronic search was last updated 12 April 2016 (Supplemental digital content 1: search strategies).

Randomized clinical trials investigating perioperative gabapentin intervention vs. placebo or an active placebo group mimicking the sedative effect of gabapentin were considered

eligible. Prospective observational and quasi-randomized trials were included for evaluation of harm and detection of rare serious adverse events but not for benefit. The prospective observational and quasi-randomized trials are not included in any of the meta-analyses of outcomes.

The study population included surgical patients of 18 years or above who received gabapentin for post-operative pain. Trials were included regardless of dosage, administration intervals, duration of treatment, or type of surgery.

Exclusion criteria were trials of non-surgical pain conditions, experimental pain models, chronic pain conditions, or different analgesic co-interventions in compared groups.

Study selection

Two authors (MLF, AG) independently screened titles and abstracts for inclusion after removal of duplicates. MLF and one other independent author (AG, MSH, PLP, LN) assessed full texts. Non-English articles were translated to English.

Data extraction

Two authors [MLF (all trials), AG, PLP, MSH, and LN] independently extracted data and assessed bias of the included trials using a data extraction form. The extracted data included participant and trial characteristics: Year of publication, number of participants, type of surgery, follow-up period and dose regimen, consumption of opioid and non-opioid escape medication, pain intensity, any adverse effects described in the trials, including serious adverse events (SAEs) defined according to the International Conference of Harmonization – Good Clinical Practice (ICH-GCP) definitions as medical events being either life-threatening, resulting in death, disability or significant loss of function, and causing hospital admission or prolonged hospitalization.[17]

The corresponding author was contacted whenever data were insufficiently reported and contact was repeated after 14 days. In case of no response, the involved bias domains were classified as unclear.

Risk of bias assessment

The included trials were assessed for risk of bias according to the Cochrane Handbook and we decided a priori to report and conclude based on primarily results from trials classified as low risk of bias.[18,19] The following domains were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias, including funding and confirmation bias.[20] Each domain was categorized as low, unclear, or high risk of bias. If one or more domains were categorized as high risk of bias, the trial was classified as overall high risk of bias. When one or more domains were categorized as unclear, trials were added to high risk of bias trials in the meta-analyses and subgroup analyses as we aimed for estimates based on the trials with reliable low risk of bias.

Any discrepancies in study selection, data extraction, or bias assessment were resolved by OM, JBD, or JW.

Outcomes

The co-primary outcomes were 24-h post-operative opioid consumption and incidence of serious adverse events (SAE).

Secondary outcomes were pain at rest and during mobilization at 6 and 24 h after surgery, opioid-related adverse effects, and all other adverse events.

All opioids were converted to intravenous morphine based upon equivalency (Supplemental digital content 2: Opioid conversion). Various scales were used to report pain intensity in the trials. All pain intensity scales reporting pain levels between 0 and 10 were converted to the Visual Analog Scale (VAS) 0 to 100 mm.

Statistical analysis

Review Manager (RevMan) [Computer program], Version 5.1.6, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 was used for statistical analyses as predefined in the protocol.

In trials with more than one active treatment arm, including trials testing doses delivered pre- and immediate post-operatively, means and

standard deviations were combined for the intervention groups.[21]

Mean and standard deviations were estimated from median and range values according to the method described by Hozo et al.[22] Standard deviations were calculated by dividing the difference in interquartile ranges with 1.35.[23]

Longer ordinal scales were analyzed as continuous data. For dichotomous data, RR with a 95% confidence interval was calculated.

We examined the heterogeneity between trials using chi-squared test. The heterogeneity was measured by I^2, which quantifies inconsistencies and D^2 for information size adjustments. If the I^2 was greater than zero, the results were calculated using both a fixed effect model (FEM) and random effect model (REM) and the most conservative estimation was presented.[24,25] Whenever FEM resulted in a significant result with an estimate lower than REM, this was reported.

Predefined subgroup analyses were calculated investigating the risk of bias in low vs. unclear and high risk of bias; pain intensity at rest vs. during mobilization; pain intensity at different time points (early pain vs. late pain); add-on treatment (trials investigating gabapentin as add-on to other analgesic regimens vs. trials investigating gabapentin as single analgesic). We hypothesized that the estimates of effect would be lower in subgroups of trials with low risk of bias, late pain and pain at rest, and gabapentin as add-on treatment compared with the corresponding subgroups.

Sensitivity analyses were undertaken to explore whether choice of summary statistic and selection of the event category was critical for the conclusions of the meta-analysis.

To adjust the confidence intervals due to sparse data and repeated testing in cumulative meta-analyses, trial sequential analysis (TSA) program version 0.9 beta (www.ctu.dk/tsa) was used.[26,27] We performed the TSA analyses to preserve the risk of type-1 and two errors within 5% and 90%, respectively considering sparse data and sequential testing in a cumulative meta-analysis with repeated testing after each new trial is added.[28] We used a priori definition for opioid sparing effect of 5 mg of morphine equivalent as the minimally clinical relevant effect, the pooled standard deviation, and the diversity calculated from the actual meta-analyses, for estimating the required information size and the TSA-adjusted CI on all outcomes.

Minimal relevant difference was defined as 5 mg reduction in 24-h intravenous morphine consumption. This cut-off was used to detect even a small beneficial effect in light of previous reviews of other non-opioid analgesics demonstrating less than 10 mg reduction in 24-h opioid consumption.[3] The relative risk reduction (RRR) used for categorical outcomes in the TSA was 30% for adverse events and for SAE 50%.

Grading of recommendations assessment, development, and evaluation (GRADE)

We used GRADE to rate the quality of evidence and strength of recommendations for individual outcomes of the review, based on estimates from trials with 'low risk of bias'.[29] The recommendations are presented in a summary of findings table (SoF).

Results

The search result is summarized in the PRISMA flowchart (Fig. 1: PRISMA flowchart). One hundred and forty-seven articles were included for full-text evaluation. Forty-eight full-text articles were excluded based on the following: Not retrievable, non-surgical procedure, inadequately described analgesic regimen, patient age < 18 years, chronic pain trials, no placebo or only active comparator, review article, and double publication.

Trial characteristics

A total of 135 studies were included.[30–164] One hundred and thirty-two trials with 9498 patients were included for the evaluation of benefit and furthermore, three non-randomized studies[154–156] were included for the evaluation of harm.

Gabapentin treatment ranged from 100 to 1200 mg in trials with single-dose therapy (n = 96), and from 900 to 2400 mg/day in trials with multiple doses (n = 36). Initiation of gabapentin treatment varied from 30 min to 48 h pre-operatively.

Included trials investigated gabapentin intervention in a range of surgical procedures

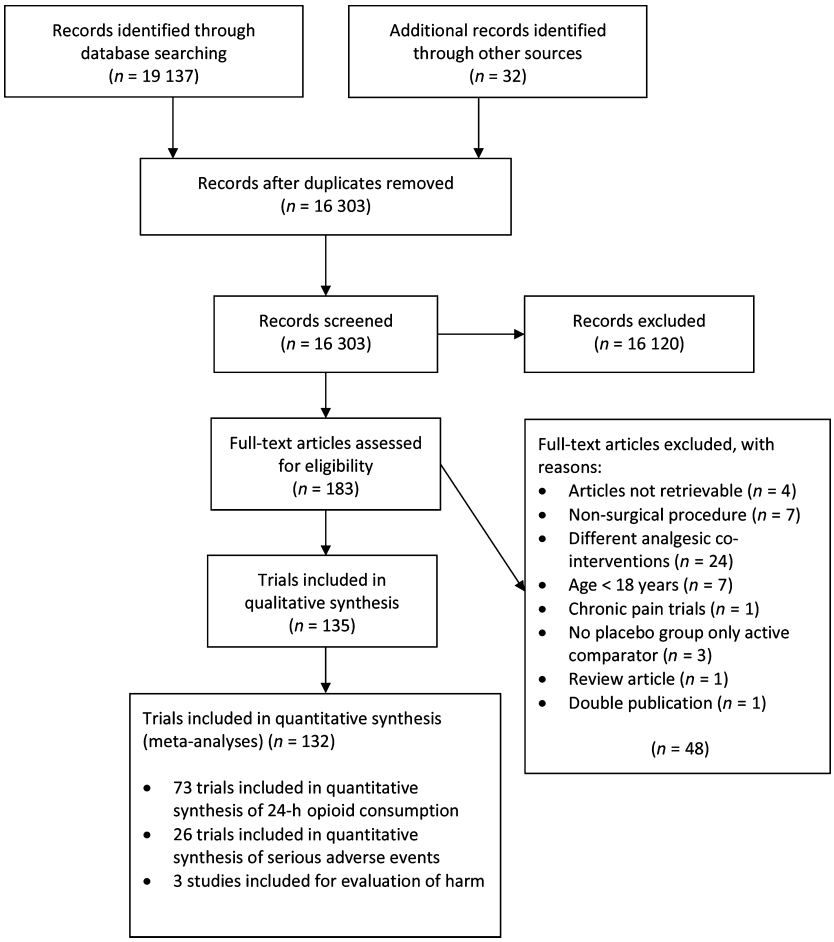

Fig. 1. PRISMA flowchart.

(Supplemental digital content 3: Characteristics of included trials). Number of included patients in the trials ranged from 20 to 306.

The follow-up period for acute pain of the trials varied from 2 h to 6 weeks, with 24 h as the most frequent assessment period (58 trials).

Bias risk assessment

Sixteen trials had overall low risk of bias.[30,45,61,65,68,82,89,98,102,103,116,117,133,136,137,151] Seventy-seven trials had high[32–34,36,39,41,43,47–49,51,53–56,59,62,63,67,69–71,73,76,78,83,84,86–88,90,93,95,96,99–101,104,106,109,112–115,118–127,129,130,135,138,139,142–149,153,157–164] and 39 trials unclear risk of bias.[31,35,37,38,40,42,44,46,50,52,57,58,60,64,66,72,74,75,77,79–81,85,92,94,97,105,107,108,110,111,128,131,134,140,141,150,152]

Reasons for unclear and high risk of bias were mainly 'selective outcome reporting' or 'other bias' (Fig. 2: Bias graph and Supplemental digital content 4: Bias assessment).

Opioid consumption

Trials with low risk of bias (for all trials reporting the outcome, please see Table 1)

Thirteen trials with low risk of bias reported on opioid consumption,[45,61,65,68,89,98,102,103,116,117,133,137,151] which indicates a reduction in 24-h post-operative morphine consumption of 3.1 mg (REM: 95% CI 0.5, 5.6; $P < 0.02$; $I^2 = 90\%$; 13 trials; 1362 patients; TSA-adjusted CI: −0.2, 6.3; Required information size: 1919 patients; Accrued percentage of required information size: 71%; FEM: Reduction 0.8 mg [−0.2, 1.4, $P = 0.01$]; GRADE = very low) (Table 1: Subgroup

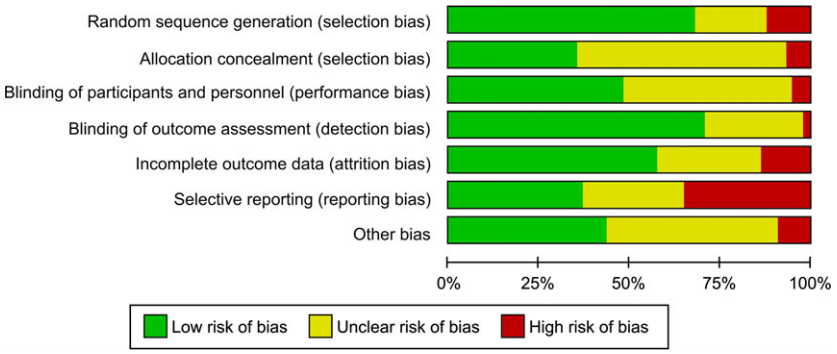

Fig. 2. Bias graph: The 'Other' bias domain consists of an evaluation of risk of financial bias and confirmatory bias.

analyses and all trial analyses, Fig. 3: Forest plot of 24-h morphine consumption, Fig. 4: Trial sequential analysis of trials with low risk of bias on 24-h opioid consumption and Supplemental digital content 5: SoF and GRADE of trials with low risk of bias, Supplemental digital content 6: Trial Sequential Analysis of all trials on 24-h morphine consumption, Supplemental digital content 7: SoF of all trials).

Add-on effect (for all trials reporting the outcome, please see Table 1)

For trials with low risk of bias, the predefined subgroup analysis of gabapentin as add-on analgesic to another non-opioid analgesic regimen indicated a mean reduction in 24-h morphine consumption of 1.2 mg (REM: 95% CI −0.3, 2.6; $P < 0.12$; $I^2 = 61\%$; 11 trials; 1194 patients, TSA-adjusted CI −0.4, 2.8; Required information size: 562 patients; Accrued percentage of required information size: 47%) (Table 1: Subgroup analyses and all trial analyses, Supplemental digital content 8: Forest plot of add-on effect).[45,61,65,68,89,98,102,103,116,117,133]

Trials with no non-opioid basic analgesic treatment did not indicate a statistically significant reduction in the 24-h morphine consumption in trials with low risk of bias [8.0 mg (REM: 95% CI −1.5, 17.4; $P = 0.10$; $I^2 = 84\%$; 2 trials; 168 patients, TSA-adjusted CI −30.5, 46.3; Required information size: 3271 patients; Accrued percentage of required information size: 5%)].[137,151] (Table 1: Subgroup analyses and all trial analyses, Supplemental digital content 9: Forest plot of no-add-on treatment).

Bias effect

For trials with low risk of bias in the domain 'other risk of bias' (confirmatory and funding bias), a mean reduction of 3.8 mg (REM: 95% CI 2.1, 5.5; $P < 0.0001$; $I^2 = 92\%$; 30 trials; 2285 patients; TSA-adjusted CI 2.1, 5.5; Required information size 1968 patients; Accrued percentage of required information size: 116%)[42,44,45,53,54,56,60,61,65,68,73,78,81,84,89,95,98,102,103,114,116–118,120,133,137,139,148,151,160] as compared to a mean reduction in trials with unclear or high risk of bias of 9.9 mg (REM: 95% CI 8.1, 11.7; $P < 0.00001$; $I^2 = 99\%$; 43 trials; 3345 patients; TSA-adjusted CI: 8.1, 11.7; Required information size: 2522 patients; Accrued percentage of required information size: 132%; FEM: Reduction 5.2 mg [5.1, 5.4]) was found on 24-h morphine consumption (Supplemental digital content 10: Forest plot of bias effect in the 'other' bias domain).[31,34,35,37,38,49,50,52,57,59,62–64,67,71,76,78,91–94,96,105–107,109–113,126–128,130,131,135,138,142,143,147,152,159,164]

Serious adverse events

Twenty-six trials reported on incidences of SAEs.[30,33,45,54,55,60,62,67,68,71,74,78,82,88,89,115,116,118,120,121,133,137,147,148,151,153] Seven trials found a total of 69 SAEs,[30,67,68,71,82,89,147] whereas 19 RCTs reported no SAEs during the trial period.[33,45,54,55,60,62,74,78,88,115,116,118,120,121,133,137,148,151,153] The reported SAEs were: death, pneumonia, readmission or prolonged admission to hospital, admission to intensive care unit, respiratory arrest, atrial fibrillation, vein thrombosis, major

Table 1 Analyses of subgroup and all trial analyses.

	Subgroup: Trials with overall Low Risk of Bias					All Trials reporting the outcome			
Outcome Subgroup analysis	Estimate MD/RR (REM) (95% CI; TSA-adjusted 95% CI)	*P*-value	I^2	N Trials/ Participants/ Required information size	*P*-value for test of interaction between trials with low vs. high or unclear risk of bias*	Estimate MD/RR (REM) (95% CI; TSA-adjusted 95% CI)	*P*-value	I^2	N Trials/ Participants/ Required information size
Subgroup analyses of beneficial outcomes									
24-h opioid consumption	3.1 mg (0.5 to 5.6; −0.2 to 6.3)	0.02	90%	13/1362/1919	0.0005	7.3 mg (5.9 to 8.8; 5.9 to 8.8)	< 0.00001	98%	73/5630/2194
24-h opioid consumption + add-on regimen	1.2 mg (−0.3 to 2.6; −0.4 to 2.8)	0.12	61%	11/1194/562	0.002	4.4 mg (2.4 to 6.5; 2.4 to 6.5)	< 0.00001	98%	36/2727/2131
24-h opioid consumption − add-on regimen	8.0 mg (−1.5 to 17.4; −30.5 to 46.3)	0.10	84%	2/168/3271	0.57	10.6 mg (8.4 to 12.8; 8.4 to 12.8)	< 0.00001	97%	37/2903/2591
24-h opioid consumption − Other bias domain	3.8 mg (2.1 to 5.5; 2.1 to 5.5)	< 0.0001	92%	30/2285/1918	< 0.00001	9.9 mg (8.1 to 11.7; 8.1 to 11.7)	< 0.00001	99%	43/3345/2522
VAS 6 h at rest	9 mm (−1 to 19; −13 to 30)	0.07	87%	9/745/4114	0.47	12 mm (9 to 13; 9 to 13)	< 0.00001	96%	71/4556/1907
VAS 6 h at mobilization	9 mm (4 to 13; 4 to 18)	< 0.0002	82%	7/572/636	0.63	8 mm (5 to 11; 5 to 11)	< 0.0001	59%	25/1552/599
VAS 24 h at rest	3 mm (−0 to 6; −1 to 6)	0.07	87%	11/1027/554	0.006	8 mm (5 to 10; 5 to 10)	< 0.0001	93%	68/4319/922
VAS 24 h at mobilization	5 mm (−2 to 11; −5 to 14)	0.15	94%	8/795/1629	0.71	5 mm (−0 to 11; −0 to 11)	0.05	97%	25/1760/582
Subgroup analyses of harmful outcomes									
Serious adverse events	RR 1.61 (0.9 to 2.9; 0.6 to 4.6)	0.10	0%	9/1014/3139	0.05	RR 1.14 (0.71 to 1.81; 0.6 to 2.1)	0.59	7%	26/2051/3973
Nausea	RR 0.83 (0.6 to 1.1; 0.6 to 1.1)	0.21	53%	6/524/3075	0.93	RR 0.82 (0.7 to 0.9; 0.7 to 0.9)	0.0003	9%	56/3756/1004
Vomiting	RR 1.04 (0.7 to 1.5; 0.5 to 2.2)	0.85	0%	4/352/1299	0.11	RR 0.80 (0.7 to 0.9; 0.7 to 0.9)	0.002	0%	51/3446/1648
Sedation	RR 1.08 (0.9 to 1.2; 0.9 to 1.2)	0.29	0%	10/858/1931	0.03	RR 1.33 (1.0 to 1.3; 1.0 to 1.3)	0.005	60%	51/4003/3751
Dizziness	RR 1.04 (0.8 to 1.2; 0.8 to 1.3)	0.64	0%	9/747/2422	0.71	RR 1.02 (0.9 to 1.1; 0.9 to 1.1)	0.77	0%	58/4510/2401

MD: mean difference; RR: relative risk; REM: random effects model; TSA: trial sequential analysis; RIS; required information size; *Test for subgroup differences.

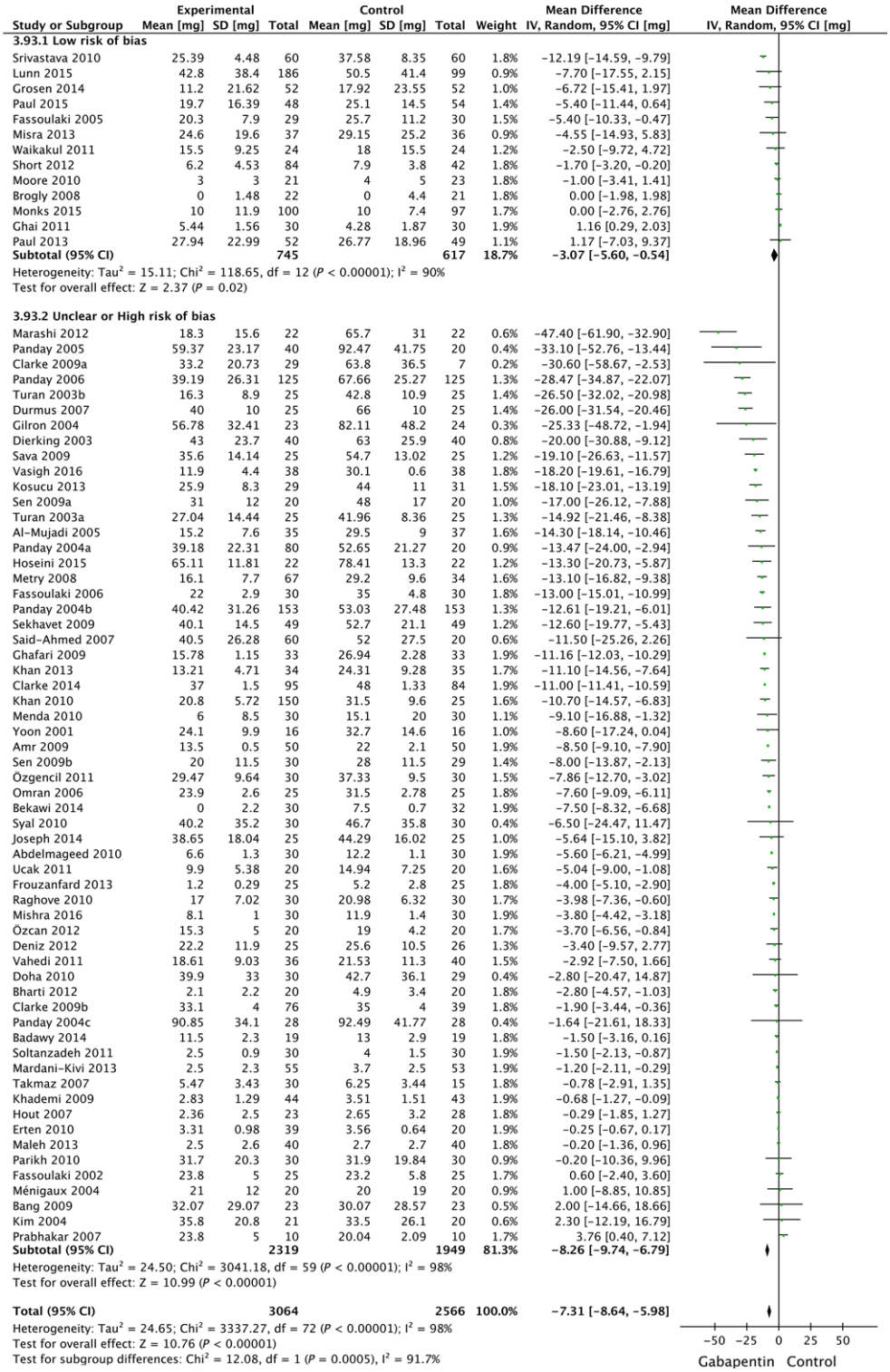

Fig. 3. Forest plot of mean difference in 24-h morphine consumption.

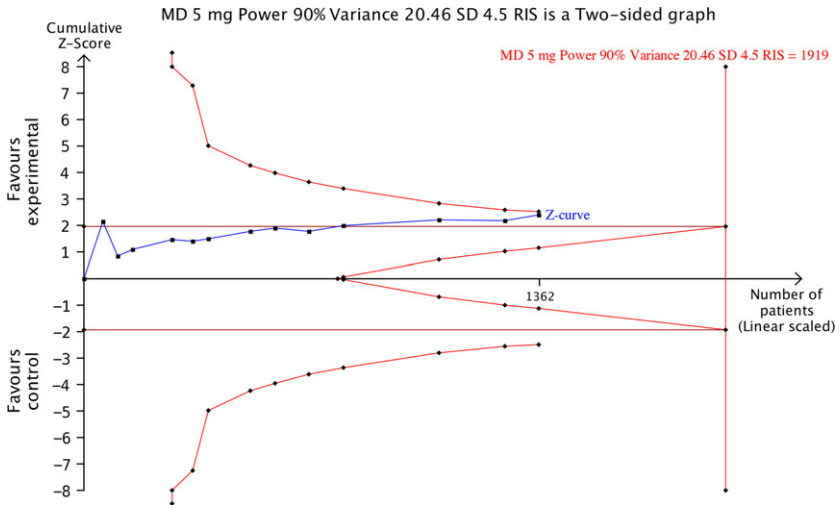

Fig. 4. Trial sequential analysis of trials with low risk of bias on 24-h morphine consumption: TSA of the effect of gabapentin on morphine consumption using the pooled SD of 4.5 mg. An estimated required information size (RIS) of 1919 patients to detect or discard a sparing effect of 5 mg morphine was calculated using the actual diversity between trials of 90%, a random-effects meta-analysis, an α of 0.05, and a β of 0.10. After 13 trials, the cumulative *z*-curve does cross the traditional boundary for benefit ($z = 1.96$ or $P = 0.05$) 95% CI 0.5 to 5.6), but not the trial sequential boundary for benefit (TSA-adjusted CI −0.2 to 6.3). In conclusion, the *z*-curve does not surpass the boundary for benefit and a firm conclusion cannot be made, however an effect beyond 6.3 mg is unlikely.

bleeding, urticarial rash, pleura effusion, and atelectasis.

Trials with low risk of bias reporting SAE (for all trials reporting the outcome, please see Table 1)
The RR of SAE of patients treated with gabapentin vs. placebo was 1.61 (REM: 95% CI 0.91, 2.86; $P < 0.10$; $I^2 = 0\%$; nine trials, 1014 patients; TSA-adjusted CI 0.57, 4.57; Required information size: 2408 patients; Accrued percentage of required information size: 42%; GRADE = low)[30,45,68,82,89,116,133,137,151] (Table 1: Subgroup analyses and all trial analyses, Fig. 5: Forest plot of serious adverse events, Fig. 6: Trial Sequential Analysis of trials with low risk of bias on serious adverse events, Supplemental digital content 11: Trial sequential analysis of all trials reporting serious adverse events).

Pain

Trials with low risk of bias (for all trials reporting the outcome, please see Table 1)
At 6-h post-operatively, pain at rest was not significantly reduced,[30,45,61,68,82,103,133,137,151] whereas pain during mobilization was reduced.[30,45,61,68,103,133,137]

At 24-h post-operatively, neither pain at rest[45,61,68,82,102,103,117,133,136,137,151] nor pain during mobilization were significantly reduced (Table 1: Subgroup analyses and all trial analyses and Supplemental digital content 12–15: Forest plot of pain intensity 6 and 24 h at rest and mobilization).[45,61,68,102,103,117,133,137]

Adverse effects

Trials with low risk of bias (for all trials reporting the outcome, please see Table 1)
Risk of nausea, vomiting, sedation, and risk of dizziness were not significantly different between groups (Table 1: Subgroup analyses and all trial analyses and Supplemental digital content 16–19: Forest plot adverse events: nausea, vomiting, sedation, and dizziness).

Other studies
Three non-randomized clinical studies[154–156] were included for the evaluation of harm and reported one patient with delirium and three with urinary retention in the control groups. In the gabapentin groups, the following adverse effects were reported: One patient with numbness of fingers, tongue, and mouth, three

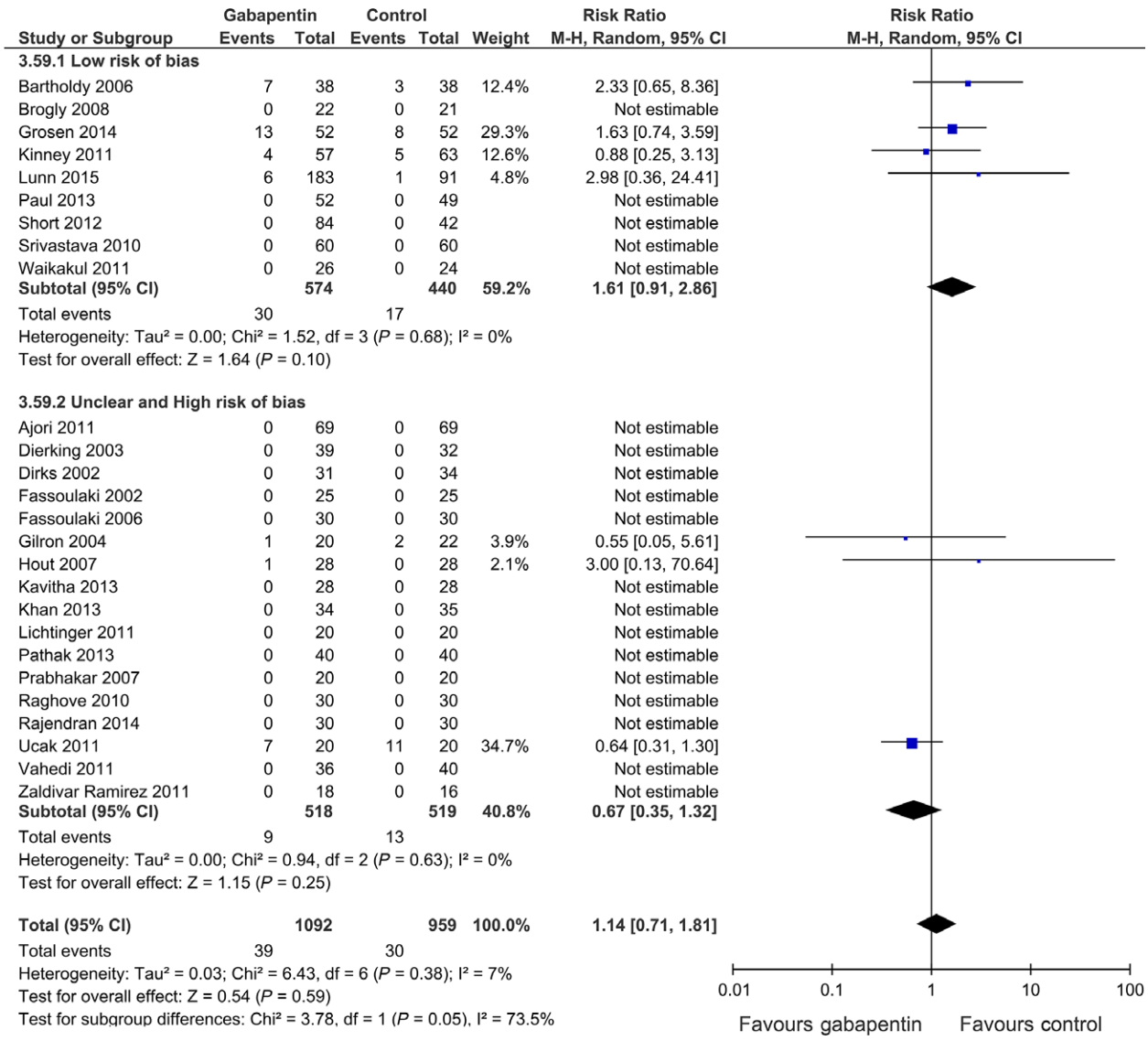

Fig. 5. Forest plot of serious adverse events.

patients with urinary retention, and one patient feeling jittery.

The small trial size effect on primary outcomes

One hundred and nineteen trials had less than 50 patients in each group and were defined as small trials.[30–32,34–47,49,50,52–67,70–81,83–88,90–92,94–101,103–109,111,112,114–120,122–136,138,139,141–153,158–163]

Thirteen trials had more than 50 patients included in each group.[33,48,51,68,82,89,93,102,110,113,137,140,157] Only four trials included more than 200 patients in their trial.[89,110,113,140]

In a post hoc sensitivity analysis, the effect of small trial size on 24-h morphine consumption showed a reduction of 1.1 mg (REM: −0.5, 2.6; $P = 0.18$; $I^2 = 62\%$; 9 trials; 656 patients) in trials with low risk of bias (Supplemental digital content 20: post hoc analysis of small trial size effect on 24-h morphine consumption in trials with low risk of bias).[45,61,65,98,103,116,117,133,151]

In trials with low risk of bias, the post hoc sensitivity analysis of small size trial effect on SAE demonstrated a risk ratio of 2.33 (REM:

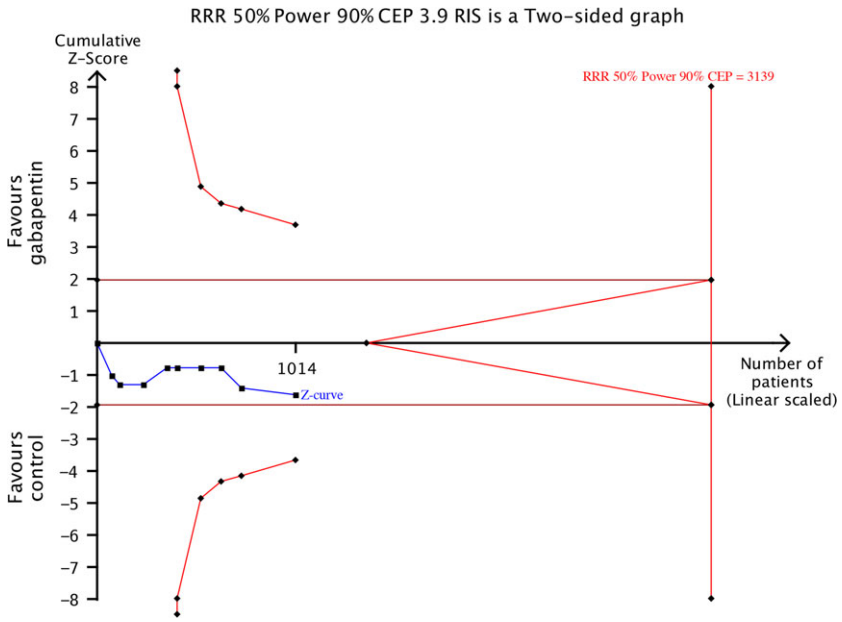

Fig. 6. Trial sequential analysis of trials with low risk of bias on serious adverse events: Trial sequential analysis (TSA) of gabapentin vs. controls in nine trials with low risk of bias reporting serious adverse events, including zero-events trials with a required information size (RIS) of 3139 patients to detect or discard a RRR of 50% and a diversity of 0%. $\alpha = 0.05$ and $\beta = 0.10$ (power 0.90). The number of accrued patients is 1014 and the TSA-adjusted confidence interval for the RR of patients with one or more SAE is 1.61 [0.57 to 4.57]. In conclusion, the *z*-curve does not cross the boundary for harm or reach futility area and a firm conclusion cannot be made.

0.65, 8.36; $P = 0.19$; 5 trials; 396 patients) (Supplemental digital content 21: post hoc analysis of small size trial effect on SAE in trials with low risk of bias).[30,45,116,133,151]

Numbers needed to treat and no more than mild pain

Data from all trials on numbers needed to treat and no more than mild pain calculations were extracted post hoc. None of the included randomized controlled trials planned to analyze or reported number needed to treat. Only one trial reported data on no more than mild pain defined as NRS ≤ 3.[101]

Discussion

Based on trials with overall low risk of bias, the benefits of perioperative gabapentin seems almost absent. The TSA of opioid requirements demonstrate that the accrued information size is only about two-thirds of that required for firm evidence, and the trial sequential boundary for benefit is not crossed. The GRADE-rated quality of evidence is low. Serious adverse events are poorly reported, and the incidence may increase with use of gabapentin.

Strength and limitations of the study

Our systematic review has several strengths. It was based on a PROSPERO pre-study registered protocol and is compliant with the Cochrane methodology and reported according to PRISMA. We applied a comprehensive literature search with no language restrictions, independent screening of all titles, and data extraction and bias assessment by two authors. The risk of random errors was evaluated using TSA on all outcomes. Bias evaluation assessed risk of systematic error, and conclusions were presented using GRADE to document the liability of our findings.

The limitations of our review mirror the limitations of the included trials. The vast majority of trials were classified as unclear or high risk of bias, and trial size was small leading to high risk of imprecision. A minority of the included trials reported on SAE, thus limiting reliable conclusions. Heterogeneity of reporting was present. Trials were included regardless of dose or

duration, type of surgery, and type of additional analgesics. Furthermore, different opioid analgesics were converted to their morphine-equivalent dose, which may have introduced heterogeneity and imprecision of the results.

The different pain intensity scores were all converted to VAS range of 0 to 100 mm, implying some imprecision of the outcomes. However, the sensitivity analyses did not indicate differences between trials where pain scores were converted to VAS, and trials where VAS was reported.

The limitations in choosing 24-h opioid consumption as an outcome are the use of mean, standard deviation, or standard error, despite the non-Gaussian distribution and the use of parametric statistics.[165] The outcome is classified as indirect according to GRADE recommendations and the results on 24-h opioid consumption have been downgraded accordingly.

Strength and weakness in relation to other reviews

A number of systematic reviews with meta-analyses on gabapentin for post-operative pain treatment have previously been published.[166–170] Most reported a more favorable outcome for gabapentin treatment, including reduced opioid consumption, pain levels, and opioid-related adverse effects, than the present review. Doleman et al. found in a recently published review, an opioid-reducing effect of gabapentin similar to the all trials estimate from the present review, but the authors did not focus on best evidence defined as trials with low risk of bias and did not address harmful effects of gabapentin.[171] The authors hypothesized that their results may be due to a small trial size effect. Post hoc analyses on the small trial size effect in meta-analysis of trials included in the present review could not confirm this hypothesis. We did, however, find a bias effect in 24-h opioid consumption, which is greatest in the 'other' bias domain. This indicates that conclusions based on all trials, including trials with unclear or high risk of bias, may lead to an overestimation of benefits and underestimation of adverse effects from intervention with gabapentin perhaps due to outcome reporting bias and other bias, e.g. financial or confirmatory bias[21]. The present review uses a systematic review methodology including GRADE-rated recommendations based on high-quality trials.

Impact of the study

The bias effect on the primary outcome of 24-h morphine consumption was explored on each of the seven bias domains and in the funnel plot. Analyses of trials with low risk of bias demonstrate a clear bias impact on this outcome primarily based on risk of 'other bias', as this bias domain showed a relatively large difference in morphine consumption between the trials with 'low risk of bias 'and the trials with 'unclear or high' risk of bias. The 'other' bias domain includes confirmatory bias and funding bias, and especially lack of information regarding funding is an issue in a large number of the included trials. This bias effect was not demonstrated for any other domains.

TSA on trials with low risk of bias demonstrated that neither boundaries for benefit or futility were crossed for detecting a predefined clinically relevant reduction of morphine consumption of 5 mg. The TSA of 24-h morphine consumption for all trials, including trials with high and unclear risk of bias, showed a statistically significant reduction, which may be a result of bias. Consequently, there is not enough information in the trials with low risk of bias to establish firm evidence for either the presence or absence of a clinically relevant morphine sparing effect with gabapentin.

The morphine sparing effect of combining gabapentin with other analgesics appears even less. It is close to absent in the trials with low risk of bias with less effect than 5 mg and a TSA-adjusted CI (−0.4 to 2.8 mg), which is hardly clinically relevant.

Trials with low risk of bias found a reduction in pain intensity at mobilization 6-h post-operatively. Gabapentin reduced pain levels both 6 and 24 h after surgery in all trials.

Trials with low risk of bias indicated excess of SAEs in the gabapentin group and report twice as many SAEs compared to trials with unclear and high risk of bias. The pooled analysis of all trials reporting SAEs was inconclusive. However, the analysis was influenced by trials of poor quality with high risk of systematic error. TSA widened the confidence intervals of

the conventional meta-analysis and the cumulated *z*-curve reached the futility area. The follow-up period in the majority of trials was short, typically 24 h, which may increase the risk of underestimating incidences of SAEs. The included non-randomized studies did not report previously undescribed SAEs.

The adverse effects nausea and vomiting were not reduced with gabapentin in trials with low risk of bias, but reduced in all trials. Risk of sedation and dizziness were not increased in the trials with low risk of bias. In all trials, the risk of sedation was increased in the gabapentin group. However, reporting of adverse events in the trials with high or unclear risk of bias was only one half of that reported in trials with low risk of bias, and a high percentage of the trials achieved a high risk of 'reporting bias' because of incomplete reporting of the adverse effects although intentionally declared in their method section. Furthermore, most trials only reported on adverse effects for a short period post-operatively, which may be insufficient for a full evaluation. The inconsequent and diverse reporting of adverse events complicates a reliable evaluation.

Conclusion

GRADE assessment of the primary outcome from trials with low risk of bias show that the evidence for perioperative gabapentin treatment is of low or very low quality due to imprecision and inconsistency and for some outcomes indirectness. The SAEs were poorly reported limiting our ability to conclude. The reduction in 24-h morphine consumption is apparently less than the predefined minimal clinical effect of 5 mg, and as add-on therapy, the beneficial effect seems non-existent. Firm evidence for the use of gabapentin in post-operative pain management is lacking. Thus, clinically relevant beneficial effect of gabapentin seems absent and harm is pending. Future trialists must ensure that their trials can be classified as low risk of bias, have sufficient power to detect relevant beneficial effects, and explore the risks of harmful effects.

Systematic review registration

PROSPERO registration number: CRD420 13006538.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Data S1. Supplemental Digital Content 1–21.

Erratum

Fabritius, M.L., Geisler, A., Petersen, P.L., Nikolajsen, L., Hansen, M.S., Kontinen, V., Hamunen, K., Dahl, J.B., Wetterslev, J., & Mathiesen, O. (2016). Gabapentin for postoperative pain management – a systematic review with meta-analyses and trial sequential analyses. *Acta Anaesthesiology Scandinavica,* 60 (9), 1188–1208. DOI: 10.1111/aas.12766.

This article included Trial Sequential Analyses (TSA) of the random-effects models used to adjust the confidence intervals (CI) for possible sparse data and repetitive testing. Unfortunately, due to a bug in the TSA program, the required information size (RIS) for continuous outcomes were calculated twice the correct value. There was no error in the calculations of RIS for dichotomous outcomes. However, even with an upgrade of the GRADE evaluation of the effect on the co-primary outcome of 24 hrs morphine consumption from 'very low' to 'low' the conclusions still hold and should not be changed. Accordingly, the authors present corrections for the following passages in the article:

In the Abstract, Results section:

.."Thirteen trials with low risk of bias reported a reduction in 24-h opioid consumption of 3.1 mg [0.5, 5.6; TSA adjusted CI: −0.2, 6.3]. In the analysis of gabapentin as add-on analgesic to another non-opioid analgesic regimen found a mean reduction in 24-h morphine consumption of 1.2 mg [−0.3, 2.6; TSA adjusted CI: −0.4, 2.8] in trials with low risk of bias."...

Should be replaced with:

...."Thirteen trials with low risk of bias reported a reduction in 24-h opioid consumption of 3.1 mg [0.5, 5.6; TSA adjusted CI: 0.5, 5.6]. In the analysis of gabapentin as add-on analgesic to another non-opioid analgesic regimen found a mean reduction in 24-h morphine consumption of 1.2 mg [−0.3, 2.6; TSA adjusted CI: −0.3, 2.6] in trials with low risk of bias."...

In the Results section:

In Opioid consumption:

"Thirteen trials with low risk of bias reported on opioid consumption,[45,61,65,68,89,98,102,103,116,117,133,137,151] which indicates a reduction in 24-h postoperative morphine consumption of 3.1 mg (REM: 95% CI 0.5 to 5.6; $P < 0.02$; $I^2 = 90\%$; 13 trials; 1362 patients; TSA adj. CI: −0.2 to 6.3; Required information size: 1919 patients; Accrued percentage of required information size: 71%)"

Should be replaced with:

"Thirteen trials with low risk of bias reported on opioid consumption,[45,61,65,68,89,98,102,103,116,117,133,137,151] which indicates a reduction in 24-h postoperative morphine consumption of 3.1 mg (REM: 95% CI 0.5 to 5.6; $P < 0.02$; $I^2 = 90\%$; 13 trials; 1362 patients; TSA adj. CI: 0.5 to 5.6; Required information size: 959 patients; Accrued percentage of required information size: 142%)"

In Add-on Effect (for all trials reporting the outcome, please see table 1.):

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"For trials with low risk of bias, the predefined subgroup analysis of gabapentin as add-on analgesic to another non-opioid analgesic regimen indicated a mean reduction in 24-h morphine consumption of 1.2 mg (REM: 95% CI −0.3 to 2.6; $P < 0.12$; $I^2 = 61\%$; 11 trials; 1194 patients, TSA adjusted CI −0.4 to 2.8; Required information size: 562 patients; Accrued percentage of required information size: 47%).[45,61,65,68,89,98,102,103,116,117,133]"

Should be replaced with:

"For trials with low risk of bias, the predefined subgroup analysis of gabapentin as add-on analgesic to another non-opioid analgesic regimen indicated a mean reduction in 24-h morphine consumption of 1.2 mg (REM: 95% CI −0.3 to 2.6; $P < 0.12$; $I^2 = 61\%$; 11 trials; 1194 patients, TSA adjusted CI −0.3 to 2.6; Required information size: 281 patients; Accrued percentage of required information size: 425%).[45,61,65,68,89,98,102,103,116,117,133]"

And

"Trials with no non-opioid basic analgesic treatment did not indicate a statistically significant reduction in the 24-h morphine consumption in trials with low risk of bias [8.0 mg (REM: 95% CI −1.5 to 17.4; $P = 0.10$; $I^2 = 84\%$; 2 trials; 168 patients, TSA adjusted CI −30.5 to 46.3; Required information size: 3271 patients; Accrued percentage of required information size: 5%)].[137,151]

Should be replaced with:

"Trials with no non-opioid basic analgesic treatment did not indicate a statistically significant reduction in the 24-h morphine consumption in trials with low risk of bias [8.0 mg (REM: 95% CI −1.5 to 17.4; $P = 0.10$; $I^2 = 84\%$; 2 trials; 168 patients, TSA adjusted CI −15.5 to 23.3; Required information size: 1636 patients; Accrued percentage of required information size: 10%)].[137,151]

In Bias Effect

For trials with low risk of bias in the domain 'other risk of bias' (confirmatory and funding bias), a mean reduction of 3.8 mg (REM: 95% CI 2.1 to 5.5; $P < 0.0001$; $I^2 = 92\%$; 30 trials; 2285 patients; TSA adjusted CI 1.6 to 6.1; Required information size 1918 patients; Accrued percentage of required information size: 116%)[42,44,45,53,54,56,60,61,65,68,73,78,81,84,89,95,98,102,103,114,116-118,120,133,137,139,148,151] as compared to a mean reduction in trials with unclear or high risk of bias of 9.9 mg (REM: 95% CI 8.1 to 11.7; $P < 0.00001$; $I^2 = 99\%$; 43 trials; 3345 patients; TSA adjusted CI: 7.6 to 11.6; Required information size: 2398 patients; Accrued percentage of required information size: 134%)

Should be replaced with:

For trials with low risk of bias in the domain 'other risk of bias' (confirmatory and funding bias), a mean reduction of 3.8 mg (REM: 95% CI 2.1 to 5.5; $P < 0.0001$; $I^2 = 92\%$; 30 trials; 2285 patients; TSA adjusted CI 2.1 to 5.5; Required information size 959 patients; Accrued percentage of required information size: 232%)[42,44,45,53,54,56,60,61,65,68,73,78,81,84,89,95,98,102,103,114,116-118,120,133,137,139,148,151] as compared to a mean reduction in trials with unclear or high risk of bias of 9.9 mg (REM: 95% CI 8.1 to 11.7; $P < 0.00001$; $I^2 = 99\%$; 43 trials; 3345 patients; TSA adjusted CI: 8.1 to 11.7; Required information size: 1199 patients; Accrued percentage of required information size: 268%)

Figure 4 including legend shall be changed to:

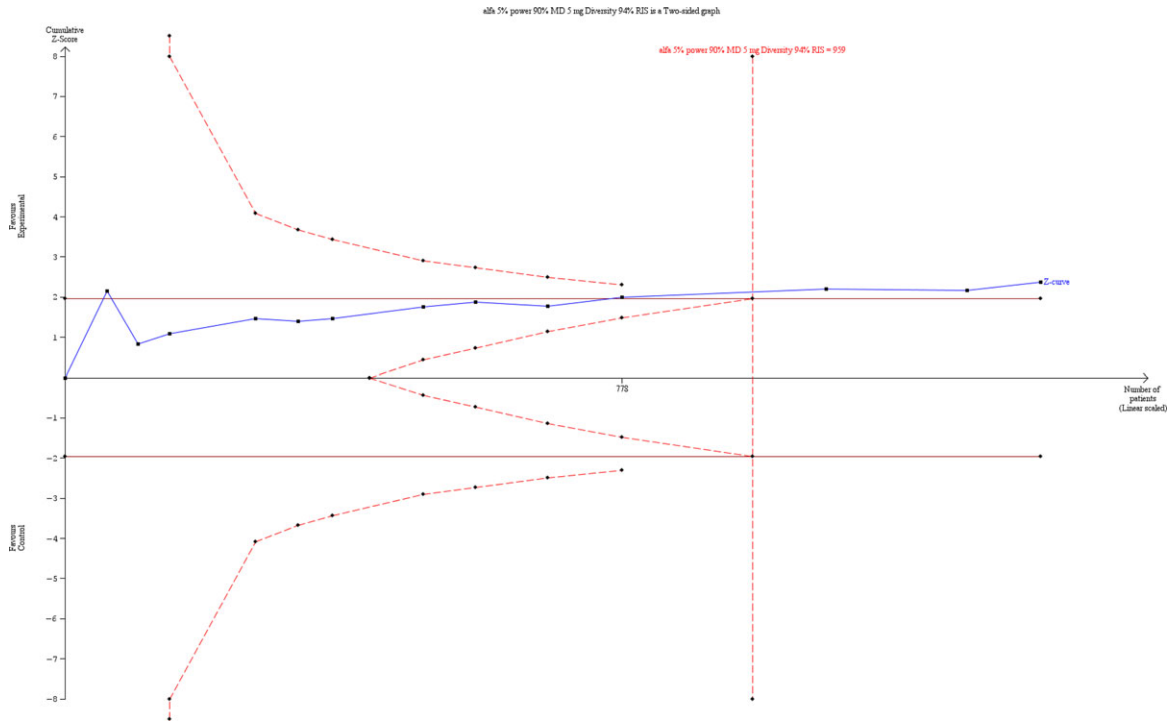


Fig. 4. Trial sequential analysis of trials with low risk of bias on 24-h morphine consumption: TSA of the effect of Gabapentin on morphine consumption using the pooled SD of 5.8 mg. An estimated required information size (RIS) of 959 patients to detect or discard a sparing effect of 5 mg morphine was calculated using the actual diversity between trials of 94%, a random-effects meta-analysis, an α of 0.05, and a β of 0.10. After 11 trials, the cumulative z-curve does cross the traditional boundary for benefit ($z = 1.96$ or $P = 0.05$) 95% CI 0.5 to 5.6) and the required information size is surpassed leading to a TSA-adjusted CI as the naive CI (TSA adj. CI 0.5 to 5.6). The number of actually accrued patients is 1362 which is 142% of the RIS. In conclusion, the z-curve does surpass the required information size and a 5.6-mg opioid sparing effect or more is highly unlikely. [Colour figure can be viewed at wileyonlinelibrary.com]

The Supporting Information Digital Content 5 and Digital Content 6 have also been resupplied and corrected in the online version of this article.

We sincerely apologize for the inconvenience caused.

APPENDIX PAPER I

Appendix 1 Search strategies

Preliminary searches performed 13 November 2013
Total number of references identified: 16895 references
Number of duplicates removed: 3189 references
Number of references in final list: 13706 references

Batch name: 131113_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL)(Issue 10 of 12, 2013) in The Cochrane Library (2411 hits in CENTRAL)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP)(1946 to November 2013)(7072 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to November 2013)(3653 hits)
1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]

3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (http://apps.webofknowledge.com)(1900 to November 2013)(3759 hits)
#3 3,759 #2 AND #1
#2 385,187 TS=(pain*)
#1 68,630 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 30 June 2014
Total number of references identified: 16861 references
Number of duplicates removed: 3592 references
Number of references in final list: 13569 references
Number of new references: 789 references

Batch name: 140701_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL)(Issue 6 of 12, 2014) in The Cochrane Library (2619 hits in CENTRAL)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP)(1946 to July 2014)(6319 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]

3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to July 2014)(3847 hits)
1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (http://apps.webofknowledge.com)(1900 to July 2014)(4076 hits)
#3 4,076 #2 AND #1
#2 417,945 TS=(pain*)
#1 72,059 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 14 November 2014
Total number of references identified: 17315 references
Number of duplicates removed: 4105 references
Number of references in final list: 13210 references
Number of new references: 462 references

Batch name: 141114_J Wetterslev_GABA NEW

Cochrane Central Register of Controlled Trials (CENTRAL)(Issue 11 of 12, 2014) (2645 hits)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]

#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP)(1946 to November 2014)(6549 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to November 2014)(3962 hits)
1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (1900 to November 2014)(4159 hits)
#3 4,159 #2 AND #1
#2 417,588 TS=(pain*)
#1 72,305 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 9 April 2015
Total number of references identified: 17466 references
Number of duplicates removed: 4042 references
Number of references in final list: 13424 references
Number of new references: 126 references

Batch name: 150409_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3 of 12, 2015) (2629 hits)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP)(1946 to April 2015) (6432 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to April 2015) (4081 hits)

1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (1900 to April 2015) (4324 hits)

#3 4,324 #2 AND #1
#2 430,421 TS=(pain*)
#1 73,791 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 23rd September 2015

Total number of references identified: 18200 references
Number of duplicates removed: 4184 references
Number of references in final list: 14016 references
Number of new references: 1188 references

Batch name: 150915_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8 of 12, 2015) (2798 hits)

#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP) (1946 to September 2015) (6621 hits)

1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to September 2015) (4289 hits)

1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (1900 to September 2015) (4492 hits)

#3 4,492 #2 AND #1
#2 445,898 TS=(pain*)
#1 75,431 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 12th April 2016

Total number of references identified:	references
Number of duplicates removed:	references
Number of references in final list:	references
Number of new references:	references

Batch name: 160412_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 4 of 12, 2015) (2993 hits)

#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP) (1946 to April 2016) (6625 hits)

1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to April 2016) (4474 hits)

1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7

9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (1900 to April 2016) (4717 hits)
#3 #2 AND #1
#2 TS=(pain*)
#1 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Google Scholar search
After the 1st search, 13th November 2013
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

After the 2nd search, 30th June 2014
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st November 2013 and on

After the 3rd search, 14th November 2014
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st June 2014 and on

After the 4th search, 9th April 2015
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st November 2014 and on

After the 5th search, 23rd September 2015
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st April 2015 and on

After the 6th search, 12th April 2016
Gabapentin AND Postoperative pain

Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st September 2015 and on

Appendix 2: Opioid conversion

Opioid	Administration	Opioid: Intravenous morphine
1 mg Fentanyl	i.v.	100 mg morphine
1 mg Hydromorphone	i.v.	5 mg morphine
1 mg Morphine oral	oral	0.33 mg morphine
1 mg Nalbuphine	i.v.	1 mg morphine
1 mg Pethidine/Meperidine	i.v.	0.13 mg morphine
1 mg Propoxyphene	i.v.	5 mg morphine
1 mg Tramadol oral	oral	0.07 mg morphine

Appendix 3: Characteristics of included trials

Trial	No* of patients	Surgical Procedures	Treatment (dose)**	Analgesic regimen (add-on therapy)	Follow-up***
Abdelmageed 2010 [29]	60	Tonsillectomy	1200 mg	None	24 h
Adam 2006 [30]	53	Arthroscopic shoulder surgery	800 mg	NSAID; Nerve block	48 h
Ajori 2011 [31]	138	Abdominal hysterectomy	600 mg	None	24 h
Al-Mujadi 2005 [32]	72	Elective thyroid surgery	1200 mg	None	24 h
Amr 2009 [33]	100	Radical or partial mastectomy	300 mg (300 mg/day)	Acetaminophen; Codeine	10 day
Azemati 2013 [34]	100	Mastectomy or quandrandectomy and axillary node dissection	600 mg	Acetaminophen	8 h
Badawy 2014 [35]	40	Abdominal hysterectomy	800 mg	Acetaminophen	24 h
Bafna 2014 [148]	60	Gynecological surgery	600 mg	NSAID; Spinal anesthesia	24 h
Bakry 2011 [37]	60	Cataract surgery	1200 mg	Nerve block	-
Bang 2009 [36]	46	Arthroscopic shoulder surgery	300 mg	NSAID	24 h
Bartholdy 2006 [28]	76	Sterilization laparoscopic with Filshie clips	1200 mg	NSAID	4 h
Bashir 2009 [38]	100	Laparoscopic cholecystectomy	600 mg	None	24 h
Behdad 2012 [39]	61	Hysterectomy	100 mg (300 mg/day)	None	24 h
Bekawi 2014 [40]	60	Laparoscopic cholecystectomy	1200 mg (1200 mg/day)	NSAID; Tramadol	48 h
Bhandari [41]	40	Laparoscopic cholecystectomy	600 mg	NSAID	24 h
Bharti 2012 [42]	40	Total mastectomy with axillary node dissection	600 mg	NSAID	24 h
Brogly 2008 [43]	43	Total or partial thyroidectomy	1200 mg	Acetaminophen; Nerve block	24 h (6 months)
Butt 2010 [44]	100	Mastectomy	1200 mg	None	12 h
Celebi 2013 [45]	60	Gynecological laparoscopy	600 mg	NSAID	96 h (3 months)
Chowdhury 2010 [46]	200	Gynecological surgery	300 mg	NSAID	6 h
Clarke 2009a [47]	36	Total knee arthroplasty	600 mg (300/600/900 mg/day)	NSAID; Nerve block	4 days
Clarke 2009b [48]	115	Total hip arthroplasty	600 mg	Acetaminophen; NSAID; Glucocorticoids	48 h (6 months)
Clarke 2013 [49]	44	General-, gynecological-, plastic and ENT surgery	1200 mg	None	2 h
Clarke 2014 [50]	179	Total knee arthroplasty	600 mg	NSAID; Nerve block	4 days (3 months)
Deniz 2012 [51]	51	Radical Retropubic Prostatectomy	900 mg	Acetaminophen; NSAID	24 h

Dierking 2003 [52]	80	Abdominal hysterectomy and salphinooophrectomy	600 mg (2400 mg/day)	None	24 h
Dirks 2002 [53]	65	Unilateral radical mastectomy with axillary dissection	1200 mg	None	4 h
Doha 2010 [54]	59	Radical Mastectomy	1200 mg	NSAID	24 h
Durmus 2006 [55]	50	Total abdominal hysterectomy	1200 mg	None	24 h
Ercan 2014 [56]	34	Carotid Endartectomy	600 mg	Acetaminophen; NSAID	24 h
Erten 2010 [57]	59	Laminectomy	900 mg/ 1200 mg	NSAID	24 h
Fassoulaki 2002 [58]	50	Radical mastectomy or lobectomy with axillary lymph node dissection	1200 mg (1200 mg/day)	Acetaminophen	10 days (3 months)
Fassoulaki 2005 [59]	59	Abdominal hysterectomy	400 mg (1600 mg/day)	Acetaminophen	5 day (1 month)
Fassoulaki 2006 [60]	60	Abdominal hysterectomy	800 mg (1600 mg/day)	Acetaminophen	48 h (1 month)
Farzi 2015 [157]	103	Septorhinoplasty	900 mg	Local anesthesia	End of operation
Frouzanfard 2013 [61]	50	Abdominal hysterectomy	1200 mg	NSAID	24 h
Ghafari 2009 [62]	66	Abdominal hysterectomy and salphinooophrectomy	300 mg(300 mg/day)	None	48 h
Ghai 2011 [63]	60	Abdominal hysterectomy	900 mg	NSAID	24 h
Ghai 2012 [64]	60	Abdominal hysterectomy	900 mg	None	12 h
Gilron 2004 [65]	47	Abdominal hysterectomy	600 mg (1800 mg/day)	None	48 h (1 month)
Gosai 2015 [158]	60	Mastectomy	600 mg	None	12 h
Grosen 2014 [66]	104	Thoracotomy for malignancy	1200 mg (1200 mg/day)	Acetaminophen; NSAID; Epidural	5 day (6 month)
Grover 2009 [67]	46	Total mastectomy with axillary node dissection	600 mg	None	12 h
Hassani 2014 [68]	40	Laparoscopic gastric bypass	100 mg	None	6 h
Hoseini 2015 [159]	44	Cholecystectomy	600 mg	None	12 h
Hout 2007 [69]	51	Exploratory thoracotomy, pneumonectomy, lobectomy, segmentectomy, biopsy	1200 mg	Epidural	24 h
Jajeda 2014 [70]	50	Upper abdominal surgery	1200 mg	NSAID	24 h
Joseph 2014 [71]	50	Abdominal hysterectomy	600 mg (600 mg)	None	24 h
Kavitha 2013 [72]	56	Intraocular surgery/cataract	600 mg	Nerve block	6 h
Kazak 2009 [73]	60	Nasal septal, nasal sinus surgery	600 mg	NSAID; Local anesthesia	24 h
Khademi 2009 [74]	87	Open cholecystectomy	600 mg	None	24 h
Khan 2010 [75]	175	Single lumbar laminectomy	600mg/900mg/1200 mg	None	24 h

Khan 2013 [76]	69	Abdominal hysterectomy	1200 mg	None	24 h
Khezri 2013 [77]	80	Cataract surgery	600 mg	Nerve block	5 h
Khurana 2013 [78]	60	Lumbar discectomy	300 mg (300 mg/day)	NSAID	48 h (3 months)
Kim 2004 [79]	41	Mastectomy	900 mg	None	24 h
Kinney 2011 [80]	125	Thoracotectomy; lobectomy; pneumonectomy; chest wall resection	600 mg	Acetaminophen; NSAID; Epidural	48 h (3 months)
Koc 2007 [81]	40	Varicocele	800 mg	NSAID	24 h
Kosucu 2013 [82]	60	Posterolateral or lateral thoracotomy	1200 mg	NSAID	48 h
Kuhnle 2010 [83]	82	PRK Myopia surgery	300 mg	Acetaminophen; NSAID	4 days
Kumar 2013 [84]	87	Abdominal hysterectomy	300/600/900 mg	None	24 h
Leung 2006 [85]	21	Spine surgery	900 mg (900 mg/day)	None	72 h
Lichtinger 2011 [86]	40	Bilateral photorefractive keratectomy	300 mg (600 mg)	Glucocorticoids	7 days
Lunn 2015 [87]	274	Total knee arthroplasty	900 mg(600 mg/day) 1300 mg(900 mg/day)	Acetaminophen; NSAID; Local anesthesia	7 days (3 months)
Manhoori 2014 [88]	50	Unilateral herniorrhaphy	400 mg	None	24 h
Maleh 2013 [89]	80	Laparoscopic surgery	600 mg	None	72 h
Marashi 2012 [90]	44	Thyroidectomy	900 mg	None	24 h
Mardani-Kivi 2013 [91]	108	Anterior Collateral Ligament reconstruction	600 mg	None	24 h
Menda 2010 [92]	60	Coronary Artery Bypass Graft	600 mg	Acetaminophen	48 h
Ménigaux 2004 [93]	40	Arthroscopic anterior cruciate ligament	1200 mg	None	48 h
Metry 2008 [94]	68	Unilateral radical mastectomy and axillary dissection	1200 mg (600 mg)	None	24 h
Mikkelsen 2006 [95]	51	Tonsillectomy	1200 mg (1800 mg/day)	NSAID; Ketobemidone	5 days
Mishra 2016 [160]	60	Laparoscopic cholecystectomy	900 mg	None	24 h
Misra 2013 [96]	73	Craniotomy for intracranial tumor	600 mg	Acetaminophen; Glucocorticoids	24 h
Mohammed 2012 [97]	80	Functional endoscopic sinus surgery	1200 mg	None	8 h
Mohammadi 2008 [98]	70	Assisted reproductive techniques	300 mg	None	2 h
Mohammadi 2009 [99]	80	Abdominal surgery/gynecological surgery	300 mg	None	6 h
Monks 2015 [100]	197	Cesarean section	600 mg (600 mg/day)	Acetaminophen; NSAID	48 h (6 weeks)
Moore 2010 [101]	44	Cesarean section	600 mg (600 mg/day)	Acetaminophen; NSAID	48 h (3 months)
Neogi 2012 [102]	60	Laparoscopic cholecystectomy	900 mg	None	?

Omran 2005 [103]	50	Posterolateral thoracotomy for lobectomy	1200 mg (1200 mg/day)	None	48 h
Özcan 2011 [104]	40	Supratentorial tumor surgery	600 mg	NSAID	24 h
Özgenzil 2011 [105]	60	Decompressive lumbar laminectomy and discectomy	600 mg (1800 mg/day)	None	24 h
Pakravan 2012 [106]	100	Post photorefractive keratectomy surgery	300 mg (900 mg/day)	Acetaminophen	3 days
Pandey 2004a [107]	100	Single lumber disc surgery	300mg/600mg/900mg/1200mg	None	24 h
Pandey 2004b [108]	306	Laparoscopic cholecystectomy	300 mg	None	24 h
Pandey 2004c [109]	56	Single level lumbar disc surgery	300 mg	None	24 h
Pandey 2005 [110]	60	Open donor nephrectomy	600 mg	None	24 h
Pandey 2006 [111]	250	Laparoscopic cholecystectomy	600 mg	None	24 h
Parikh 2010 [112]	60	Elective surgery	600 mg	NSAID	24 h
Pathak 2014 [113]	80	Cholecystectomy	1200 mg	None	12 h
Paul 2013 [114]	101	Total knee arthroplasty	1200 mg	Acetaminophen; NSAID	72 h
Paul 2015 [115]	102	Total hip arthroplasty	600 mg (600 mg/day)	Acetaminophen; NSAID	72 h
Prabhakar 2007 [116]	20	Elective brachial plexus exploration	800 mg	NSAID	24 h
Radhakrishnan 2005 [117]	30	Lumbar laminectomy or lumbar discectomy	400 mg (800 mg/day)	None	8 h
Raghove 2010 [118]	60	Single lower limb surgery under anesthesia	600 mg/ 1200 mg	None	72 h
Rajendran 2014 [119]	60	Small gastrointestinal procedures	900 mg	None	72 h
Ram 2015 [161]	60	Abdominal hysterectomy	900 mg	None	24 h
Ray 2015 [162]	60	Abdominal hysterectomy	300 mg	NSAID	48 h
Rapchuk 2009 [120]	54	Cardiac surgery	1200 mg	None	72 h
Rimaz 2014 [121]	60	Dacryocystorhinostomy	900 mg	Nerve block	24 h
Rorarius 2004 [122]	90	Vaginal hysterectomy	1200 mg	None	20 h
Saeed 2013 [123]	100	Laparoscopic cholecystectomy	600 mg	NSAID	24 h
Said-Ahmed 2007 [124]	80	Myomectomy	300 mg/600mg/1200mg	None	24 h
Sava 2009 [125]	50	Colorectal surgery	600 mg	None	24 h
Sekhavet 2009 [126]	98	Abdominal hysterectomy	600 mg	NSAID	72 h
Semira 2013 [127]	60	Laparoscopic cholecystectomy	600 mg	None	24 h
Sen 2009a [128]	40	Abdominal hysterectomy and salphinooophrectomy	1200 mg	Acetaminophen	6 months

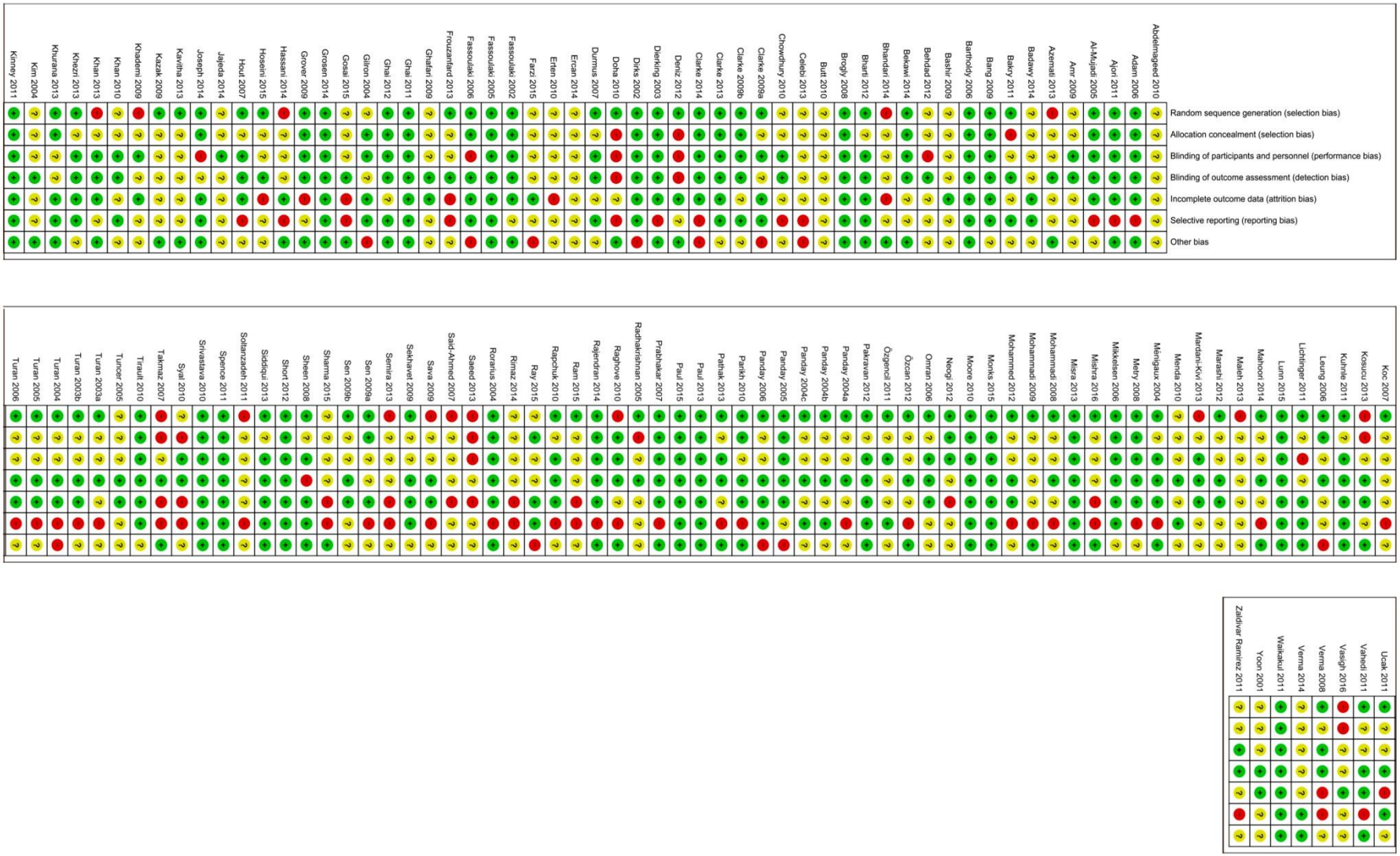
Sen 2009b [129]	59	Unilateral inguinal herniotomy	1200 mg	Acetaminophen; NSAID	6 months
Sharma 2015 [163]	40	Laparoscopic cholecystectomy	600 mg	None	48 h
Sheen 2008 [130]	80	Orthopedic surgeries	1200 mg	None	24 h
Short 2012 [131]	126	Caesarean section	300mg/600 mg	Acetaminophen; NSAID	3 months
Siddiqui 2013 [132]	72	Major bowel surgery	600 mg	None	2 days
Soltanzadeh 2011 [133]	60	Coronary Artery Bypass Grafting	800 mg (400 mg)	None	24 h
Spence 2011 [134]	57	Shoulder arthroscopy	300mg	Acetaminophen; Local anesthesia	48 h
Srivastava 2009 [135]	120	Open cholecystectomy	600 mg	None	48 h
Syal 2010 [136]	60	Open cholecystectomy	1200 mg	None	24 h
Takmaz 2007 [137]	45	Open cholecystectomy	900mg/1200 mg	None	24 h
Tirault 2010 [138]	135	Ear-nose and throat-, general-, orthopedic-, and gynecologic surgery	1200 mg	None	24 h
Tuncer 2005 [139]	30	Major orthopedic surgery	900 mg/1200 mg	None	4 h
Turan 2003a [140]	50	Abdominal hysterectomy and salphinooophrectomy	1200 mg	None	24h
Turan 2003b [141]	50	Discectomy spinal fusion surgery	1200 mg	None	24 h
Turan 2004 [142]	50	Ear Nose and Throat surgery	1200 mg	NSAID; Local anesthesia	24 h
Turan 2005 [143]	40	Lower limb surgery	1200mg (1200 mg/day)	Acetaminophen; Epidural	72 h
Turan 2006 [144]	50	Abdominal hysterectomy and salphinooophrectomy	1200 mg (1200 mg/day)	Acetaminophen	72 h
Ucak 2011 [145]	40	Coronary Artery Bypass Graft	1200 mg (1200 mg/day)	Acetaminophen	3 months
Vahedi 2011 [146]	76	Lumbar laminectomy and discectomy	300 mg	None	24 h
Vasigh 2016 [164]	76	Laminectomy	600 mg (300 mg)	None	24 h
Verma 2008 [147]	50	Abdominal hysterectomy	300 mg	None	24 h
Waikakul 2011 [149]	48	Spine, major joint, tumor and major limb surgery	400 mg (300 mg/day)	None	24 h
Yoon 2001 [150]	32	Hysterectomy	400 mg (300 mg/day)	None	24 h
Zaldivar-Ramirez 2011 [151]	34	Nissen laparoscopic fundoperation	300 mg (600 mg/day)	NSAID	120 days

* From the intervention and control group

** First dose gabapentin (second dose or dose per day)

*** Follow-up at the end of intervention (follow-up at end of observation period)

Appendix 4: Bias assessment



Appendix 5: SoF of All outcomes from trials with low risk of bias

Quality assessment						N Patients (Trials)	Effect Estimate MD/RR (95% CI; TSA adj. CI)			Quality
Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative effect**	**Absolute effect**	**P-value**	**I^2**	
Serious adverse events											
RCT	Not serious [1]	Serious [2]	Not serious [3]	Serious [4]	None	1014 (9 trials)	**RR 1.61** (0.91 to 2.86; 0.55 to 4.51)	**24 more per 1,000** (from 3 fewer to 72 more)	<0.1	0%	⊕⊕◯◯ LOW
24-hour Morphine consumption											
RCT	Not serious [1]	Serious [5]	Serious [6]	Serious [4]	Publication bias strongly suspected [7]	1356 (13 trials)	-	**3.1 mg reduction** (0.5 to 5.6; 0.5 to 5.6)	0.02	90%	⊕⊕◯◯ LOW
6-hour VAS at rest											
RCT	Not serious [1]	Very serious [8]	Not serious [3]	Serious [4]	None	739 (9)	-	**9 mm reduction** (-1 to 19; -13 to 30)	0.07	87%	⊕◯◯◯ VERY LOW
6-hour VAS at mobilization											
RCT	Not serious [1]	Serious [9]	Not serious [3]	Not serious	Publication bias strongly suspected [7]	566 (7)	-	**9 mm reduction** (4 to 13; 4 to 18)	<0.0002	82%	⊕⊕◯◯ LOW
24-hour VAS at rest											
RCT	Not serious [1]	Serious [10]	Not serious [3]	Serious [4]	None	1021 (11)	-	**3 mm reduction** (-0 to 6; -1 to 6)	<0.07	87%	⊕⊕◯◯ LOW
24-hour VAS at mobilization											

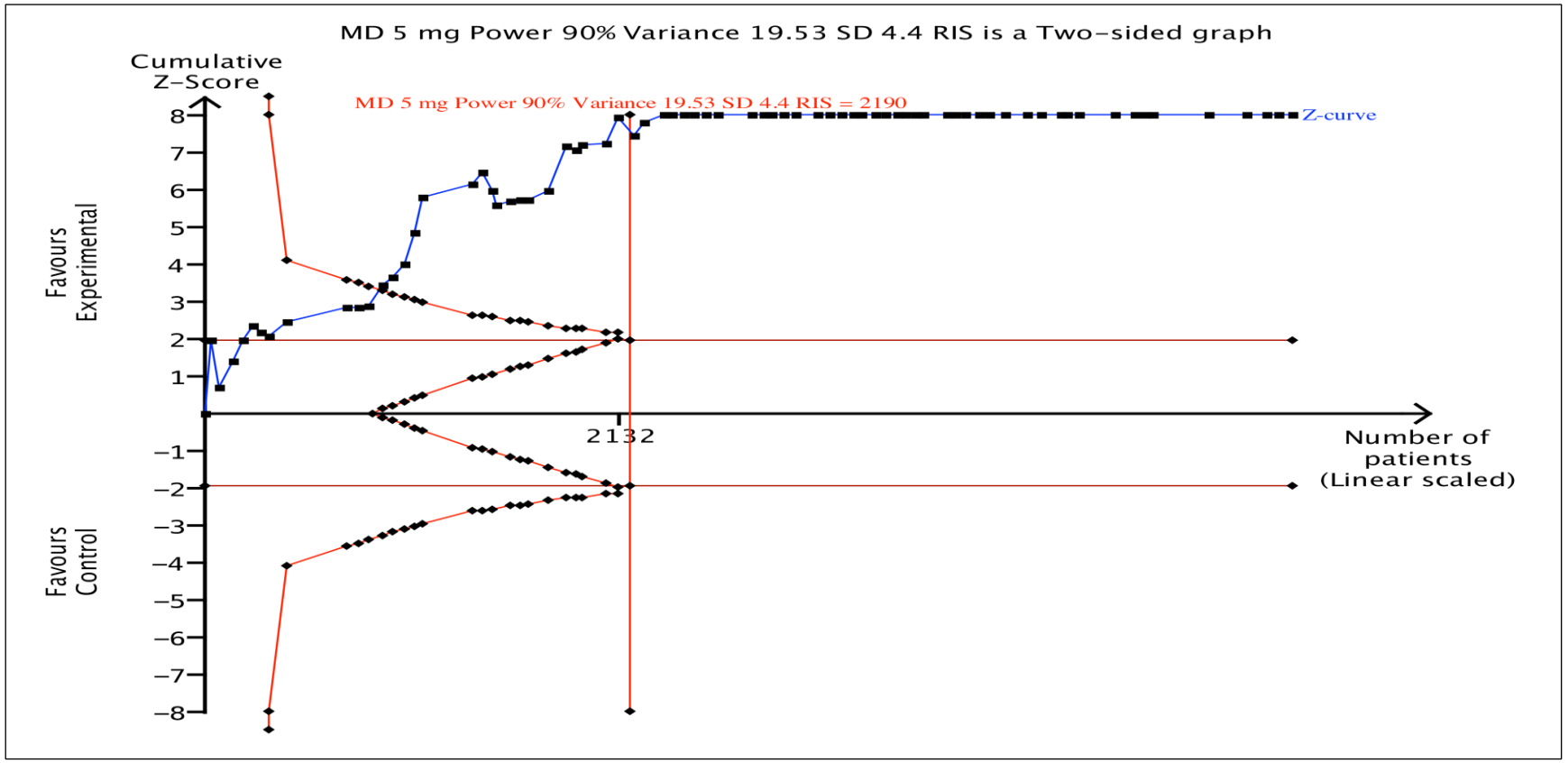
Quality assessment						N Patients (Trials)	Effect Estimate MD/RR (95% CI; TSA adj. CI)				Quality
Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative effect**	**Absolute effect**	**P-value**	**I^2**	
RCT	Not serious [1]	Very serious [11]	Not serious [3]	Serious [4]	None	789 (8)	**-**	**5 mm reduction** (-2 to 11; -5 to 14)	0.15	94%	⊕◯◯◯ VERY LOW
Nausea											
RCT	Not serious [1]	Not serious	Not serious [3]	Serious [4]	None	524 (7)	**RR 0.83** (0.62 to 1.11; 0.63 to 1.09)	**87 fewer per 1,000** (from 56 more to 194 fewer) **121 fewer per 1,000** (from 78 mores to 270 fewer)	0.21	53%	⊕⊕⊕◯ MODERATE
Vomiting											
RCT	Not serious [1]	Not serious	Not serious [3]	Serious [4]	Publication bias strongly suspected [7]	352 (4)	**RR 1.04** (0.73 to 1.47; 0.50 to 2.16)	**10 more per 1,000** (from 65 fewer to 84 more) **7 more per 1,000** (from 48 fewer to 84 more)	0.85	0%	⊕⊕◯◯ LOW
Sedation											
RCT	Not serious [1]	Not serious	Not serious [3]	Serious [4]	Publication bias strongly suspected [7]	858 (10)	**RR 1.29** (1.06 to 1.57; 0.97 to 1.27)	**29 more per 1,000** (from 21 fewer to 82 more) **30 more per 1,000** (from 22 fewer to 85 more)	0.29	0%	⊕⊕◯◯ LOW
Dizziness											

Quality assessment						N Patients (Trials)	Effect Estimate MD/RR (95% CI; TSA adj. CI)				Quality
Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative effect**	**Absolute effect**	**P-value**	**I^2**	
RCT	Not serious [1]	Serious [12]	Not serious [3]	Serious [4]	None	741 (9)	**RR 1.04** (0.84 to 1.22; 0.81 to 1.33)	**11 more per 1,000** (from 34 fewer to 62 more) **6 more per 1,000** (from 19 fewer to 35 more)	0.64	0%	⊕⊕◯◯ LOW

CI: *Confidence interval;* ***RR:*** *Risk ratio;* ***MD:*** *Mean difference;* ***RCT****: randomized clinical trial*

1. *Bias assessed using Cochrane methodology*
2. *I-square = 0% low, overlap in confidence intervals, heterogeneity: p=0.68, small trial size, inconsistency may be explained by bias*
3. *The intervention investigated in the patient population of interest with patient important outcome*
4. *CI does not cross decision threshold, required information size in Trial Sequential Analysis not met*
5. *I-square = 90%, may be substantial, overlap in confidence intervals, heterogeneity: p < 0.0001, small trial size*
6. *Surrogate outcome*
7. *Funnel plot demonstrates skewed distribution of trials and many small trials are included*
8. *I-square = 98%, may be considerable, not all confidence intervals overlap, heterogeneity: p< 0.0001, small trial size*
9. *I-square = 82%, may be substantial, overlap in confidence intervals, heterogeneity: p < 0.0001, small trial size*
10. *I-square = 87%, may be substantial, overlap in confidence intervals, heterogeneity < 0.0001, small trial size*
11. *I-square = 94%, may be substantial, not all confidence intervals overlap, heterogeneity < 0.0001, small trial size*
12. *I-square = 0%, may be low, confidence overlap, heterogeneity: p= 0.59, small trial size*

Appendix 6: TSA of 24-hour morphine consumption of all trials



***Appendix 6**: Trial Sequential Analysis of all trials on 24-hour morphine consumption: Trial sequential analysis (TSA) of gabapentin vs. controls in all 73 trials for a morphine sparing effect of 5 mg with a pooled SD of 4.4 mg. An estimated required information size (RIS) of 2190 patients using the actual diversity between trials of 98%, a random-effects meta-analysis, an α of 0.05, and a β of 0.10. After 11 trials the cumulative z-curve does cross the trial sequential boundary for benefit. The TSA adjusted confidence interval (CI) for a sparing effect of 7.3 mg morphine is similar to the 95% CI in a traditional random-effects meta-analysis of [6.0 to 8.6]. In conclusion the Z-curve crosses the boundary for benefit and the required information size is reached and a firm conclusion can be deducted, however this conclusion may be affected by bias.*

Appendix 7: SoF table of all outcomes from all trials

Quality assessment						N Patients (Trials)	Effect Estimate MD/RR (95% CI; TSA adj. CI)				Quality
Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative effect**	**Absolute effect**	**P-value**	**I^2**	
Serious adverse events											
RCT	very serious [1]	serious [5]	not serious	serious [6]	none	2042 (26)	**RR 1.14** (0.7 to 1.8; 0.6 to 2.0)	**4 per 1000** (from 9 fewer to 25 more)	0.59	7%	⊕◯◯◯ VERY LOW
24h Morphine consumption											
RCT	very serious [1]	very serious [2]	serious [3]	not serious	publication bias strongly suspected [11]	5604 (73)	-	**7.3 mg reduction** (5.9 to 8.8; 5.9 to 8.8)	< 0.00001	98%	⊕◯◯◯ VERY LOW
6h VAS at rest											
RCT	very serious [1]	very serious [4]	not serious	not serious	none	4532 (71)	-	**12 mm reduction** (9 to 13; 9 to 13)	< 0.00001	96%	⊕◯◯◯ VERY LOW
6h VAS at mobilization											
RCT	very serious [1]	serious [7]	not serious	not serious	publication bias strongly suspected [11]	1528 (25)	-	**8 mm reduction** (5 to 12; 5 to 12)	< 0.0001	59%	⊕◯◯◯ VERY LOW
24h VAS at rest											
RCT	very serious [1]	very serious [8]	not serious	not serious	none	4302 (68)	-	**8 mm reduction** (5 to 10; 5 to 10)	< 0.0001	93%	⊕◯◯◯ VERY LOW
24h VAS at mobilization											
RCT	very serious [1]	very serious [9]	not serious	serious [6]	none	1745 (25)	-	**5 mm reduction** (-0 to 11; -0 to 11)	0.05	97%	⊕◯◯◯ VERY LOW
Nausea											

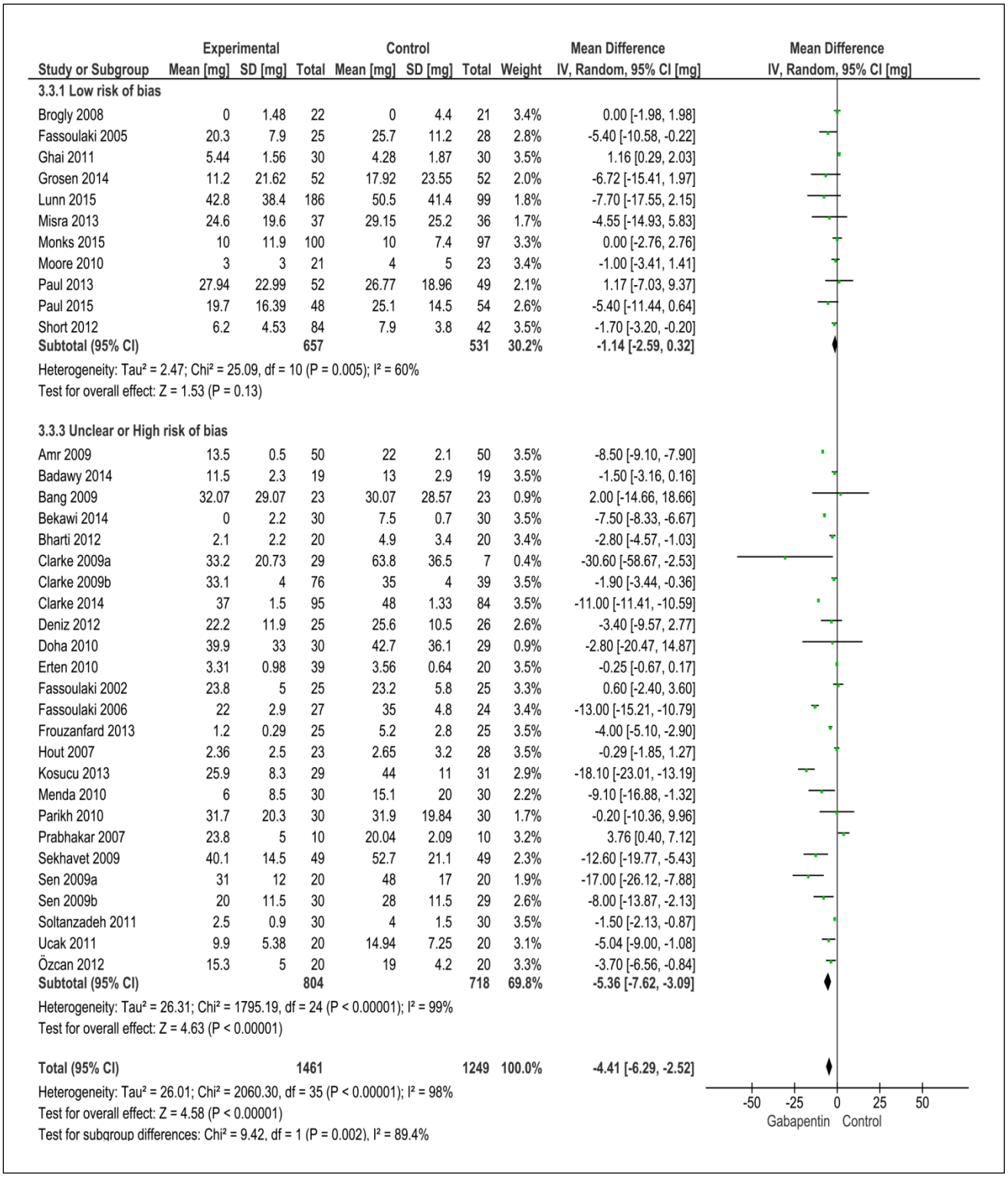
Quality assessment						N Patients (Trials)	Effect Estimate MD/RR (95% CI; TSA adj. CI)				Quality
Study design	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative effect**	**Absolute effect**	**P-value**	**I^2**	
RCT	very serious [1]	not serious	not serious	not serious	none	3756 (57)	**RR 0.82** (0.7 to 0.9; 0.7 to 0.9)	**53 fewer per 1000** (from 27 fewer to 80 fewer) **42 fewer per 1000** (from 21 fewer to 63 fewer)	0.0003	9%	⊕⊕◯◯ LOW
Vomiting											
RCT	very serious [1]	not serious	not serious	not serious	publication bias strongly suspected [11]	3446 (51)	**RR 0.80** (0.7 to 0.9; 0.7 to 0.9)	**40 fewer per 1000** (from 16 fewer to 62 fewer) **32 fewer per 1000** (from 13 fewer to 50 fewer)	0.002	0%	⊕◯◯◯ VERY LOW
Sedation											
RCT	very serious [1]	serious [10]	not serious	not serious	publication bias strongly suspected [11]	4003 (51)	**RR 1.33** (1.0 to 1.3; 1.0 to 1.3)	**15 more per 1000** (from 13 fewer to 20 more)	0.01	71%	⊕◯◯◯ VERY LOW
Dizziness											
RCT	very serious [1]	not serious	not serious	serious [6]	none	4624 (60)	**RR 1.02** (0.9 to 1.1; 0.9 to 1.1)	**3 more per 1000** (from 13 fewer to 20 more) **2 more per 1000** (from 9 fewer to 14 more)	0.77	0%	⊕◯◯◯ VERY LOW

CI: *Confidence interval;* ***MD:*** *Mean difference;* ***RR:*** *Risk ratio*

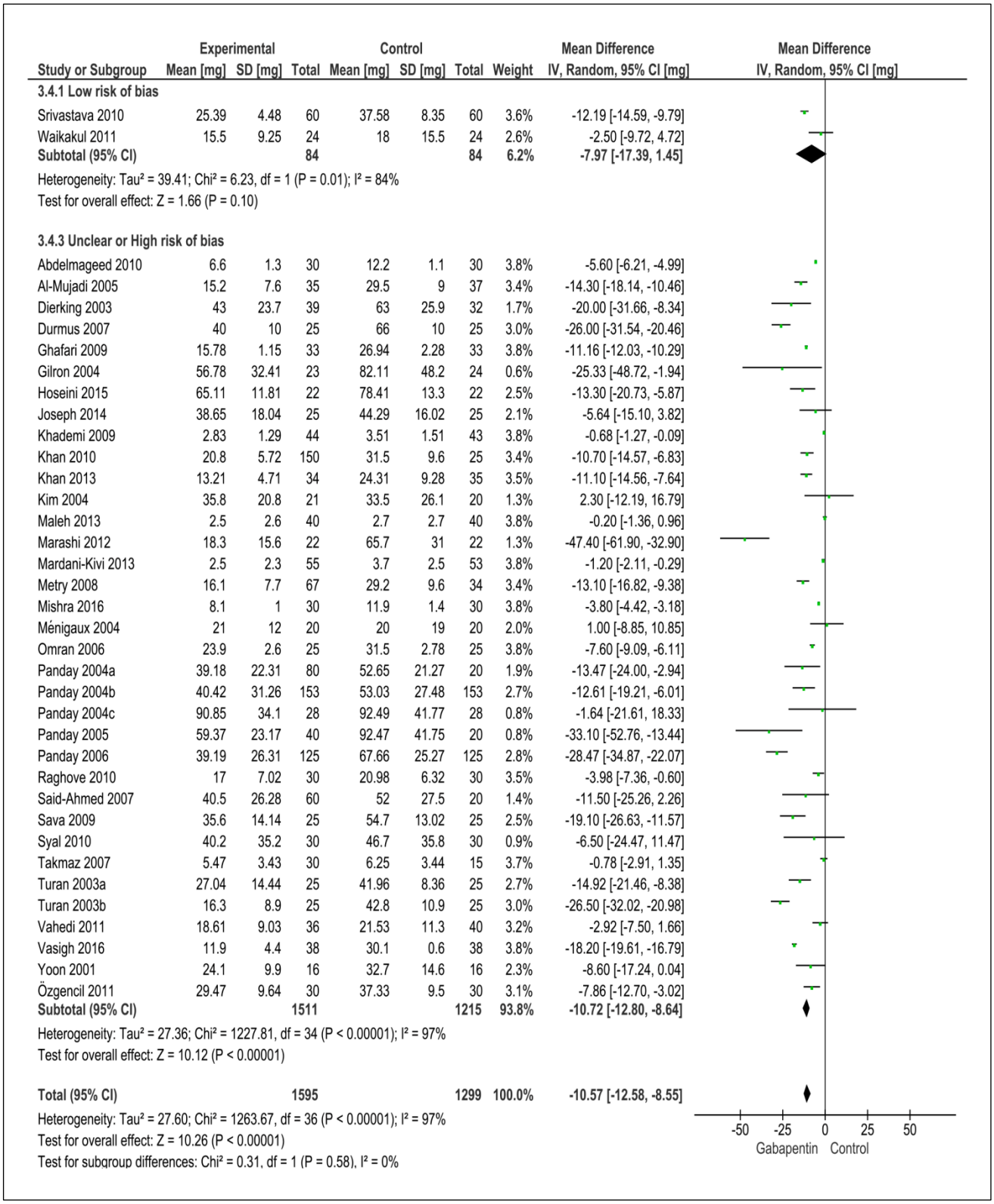
1. *Assessed according to Cochrane methodology*
2. *I-square = 98%, may be considerable, overlap in confidence intervals, small trial size*
3. *Surrogate outcomes*
4. *I-square 96%, may be considerable, overlap in confidence intervals, small trial size*
5. *I-square = 7%, may be low, overlap in confidence intervals, small trial size*
6. *CI does not cross decision threshold, required information size in Trial Sequential Analyses not met*

7. *I-square = 59%, may be moderate, overlap in confidence intervals, small trial size*
8. *I-square = 93%, may be considerable, overlap in confidence intervals, small trial size*
9. *I-square = 97%, may be considerable, overlap in confidence intervals, small trial size*
10. *I-square = 60%, may be moderate, not all confidence intervals overlap, small trial size*
11. *Funnel plot demonstrates skewed distribution of trials and many small trials are included*

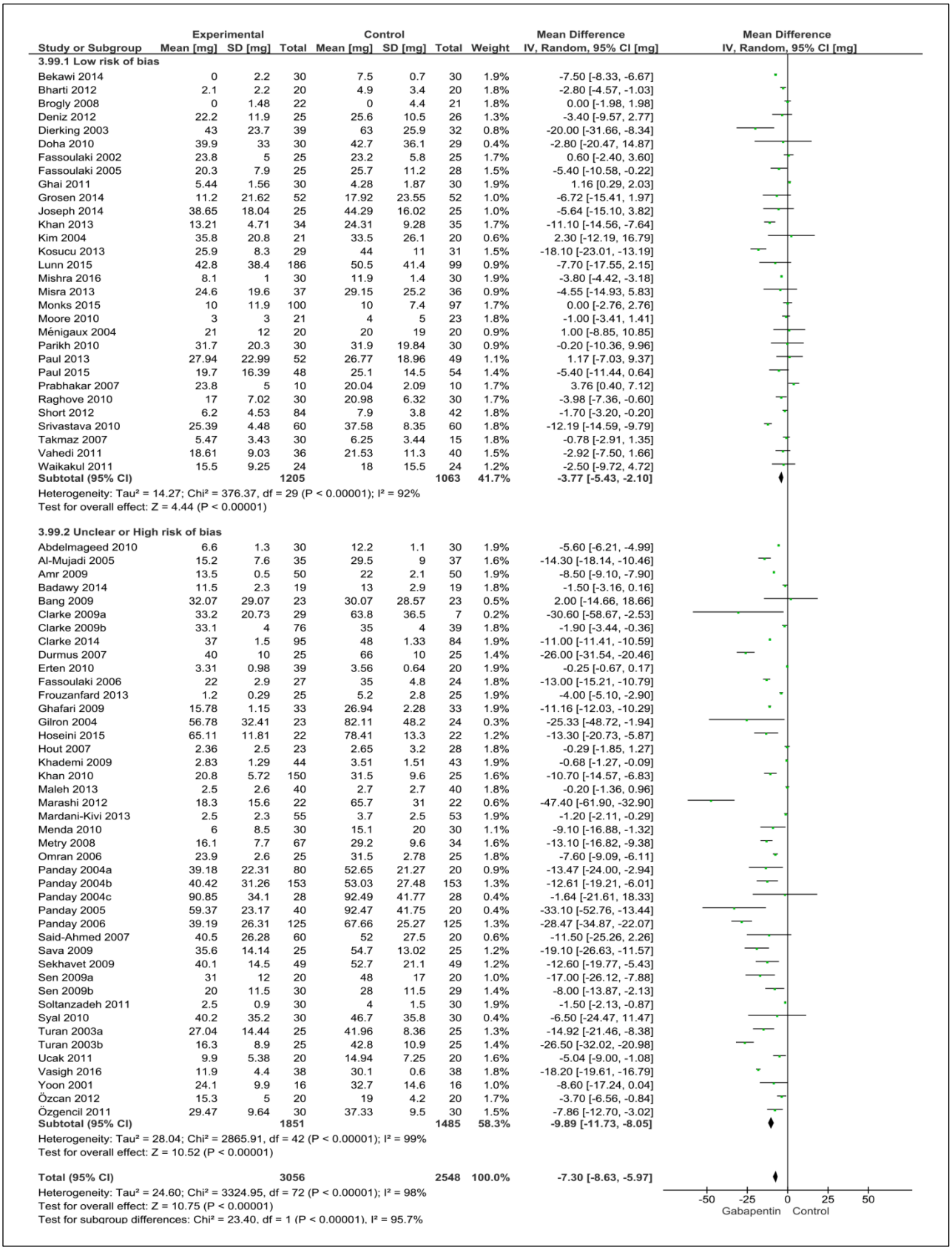
Appendix 8: Forest plot of add-on effect



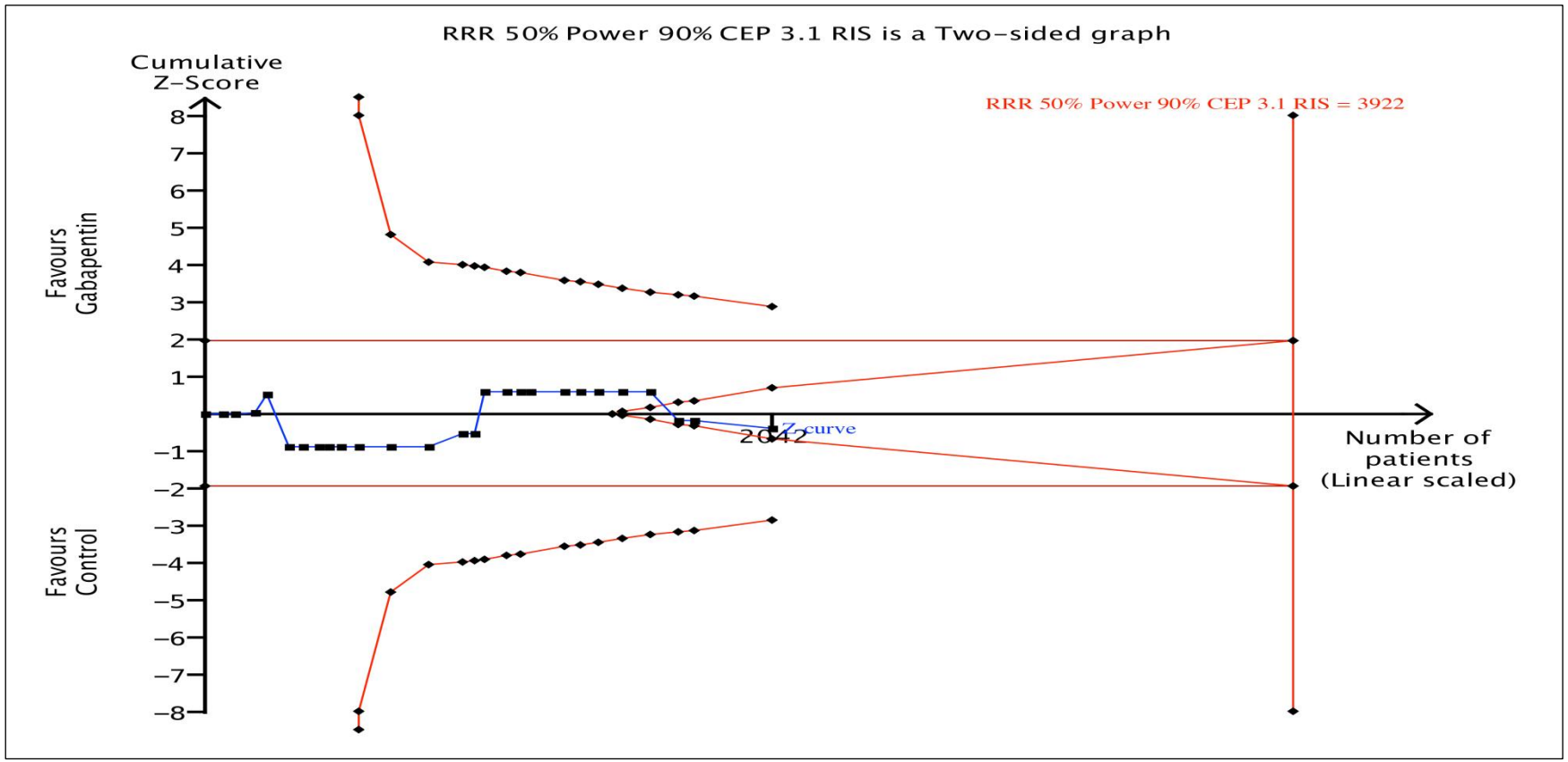
Appendix 9: Forest plot of no add-on effect



Appendix 10: Forest plot of bias effect in the 'other' bias domain

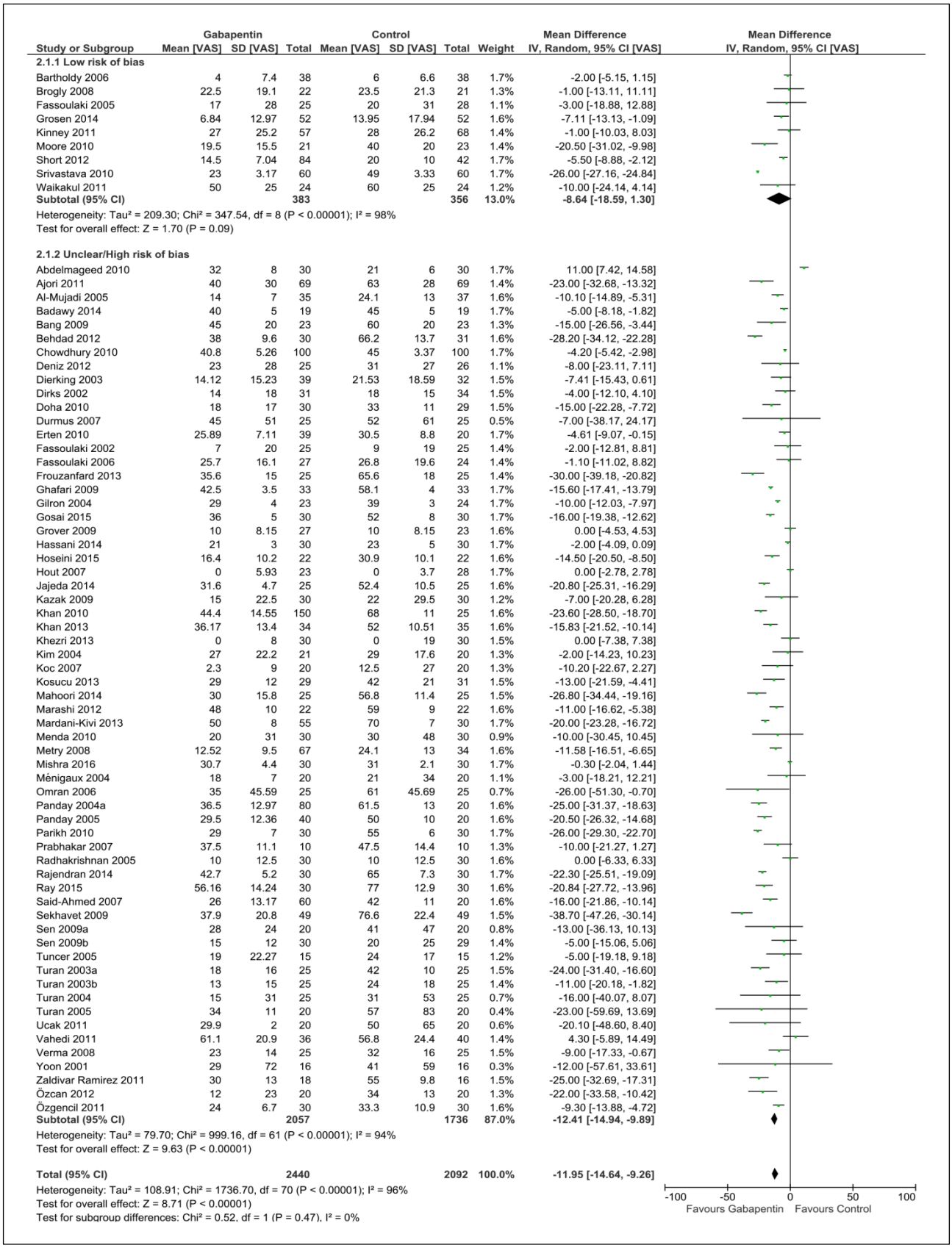


Appendix 11: TSA of all trials reporting serious adverse events

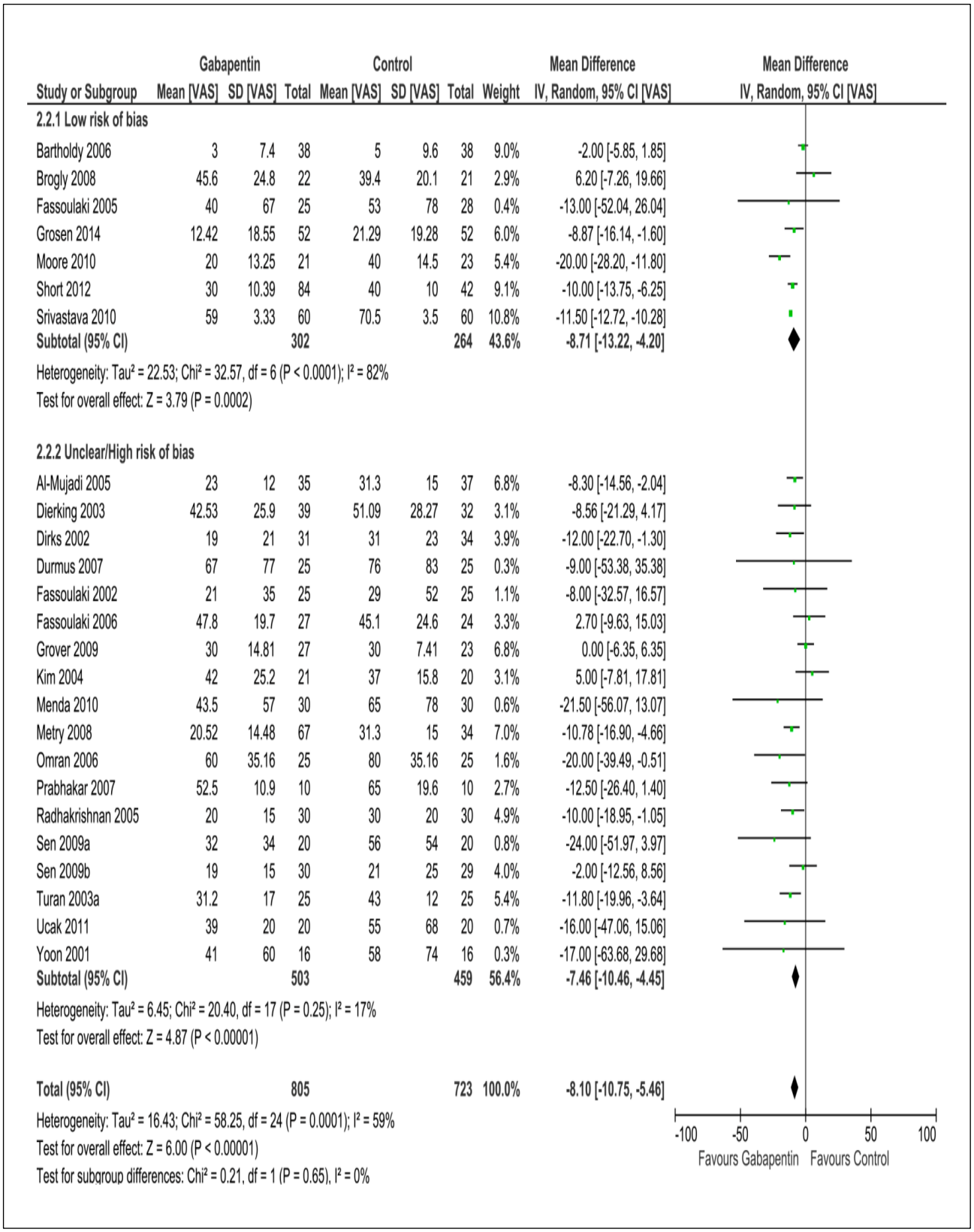


Appendix 11*: Trial sequential analysis of all trials reporting serious adverse events: Trial sequential analysis (TSA) of gabapentin vs. controls in all 26 trials reporting serious adverse events including zero-events trials and despite risk of bias with a required information size (RIS) of 3922 patients and a diversity of 0%. Alfa =0.05 and beta=0.10 (power 0.90). The number of accrued patients is 2042 and the TSA adjusted confidence interval for the RR of patients with one or more SAE is 1.14 [0.63 to 1.90]). In conclusion the z-curve crosses the futility boundary indicating no effect, however, this conclusion may be affected by bias.*

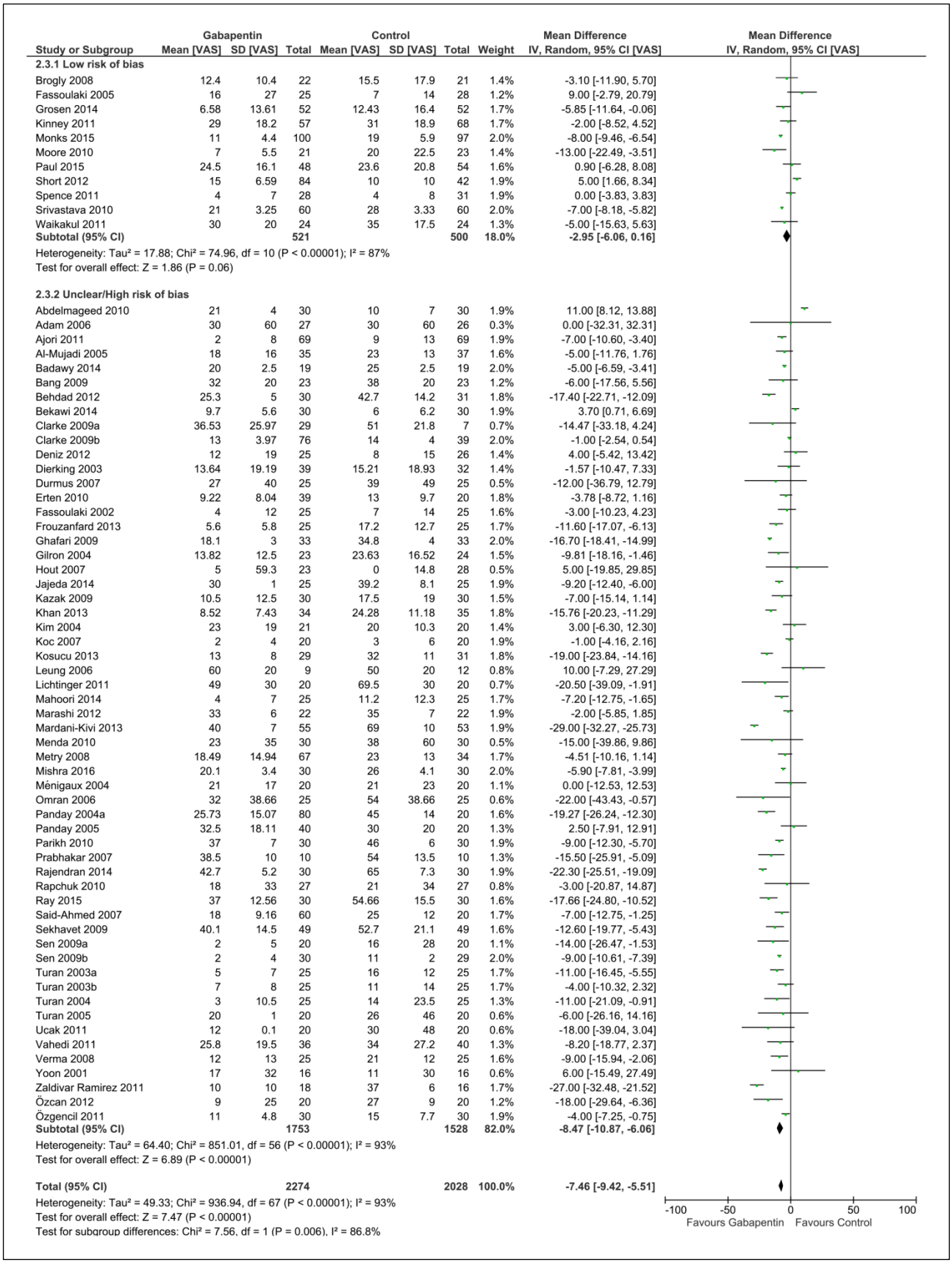
Appendix 12: Forest plot of pain intensity 6 hours postoperative at rest



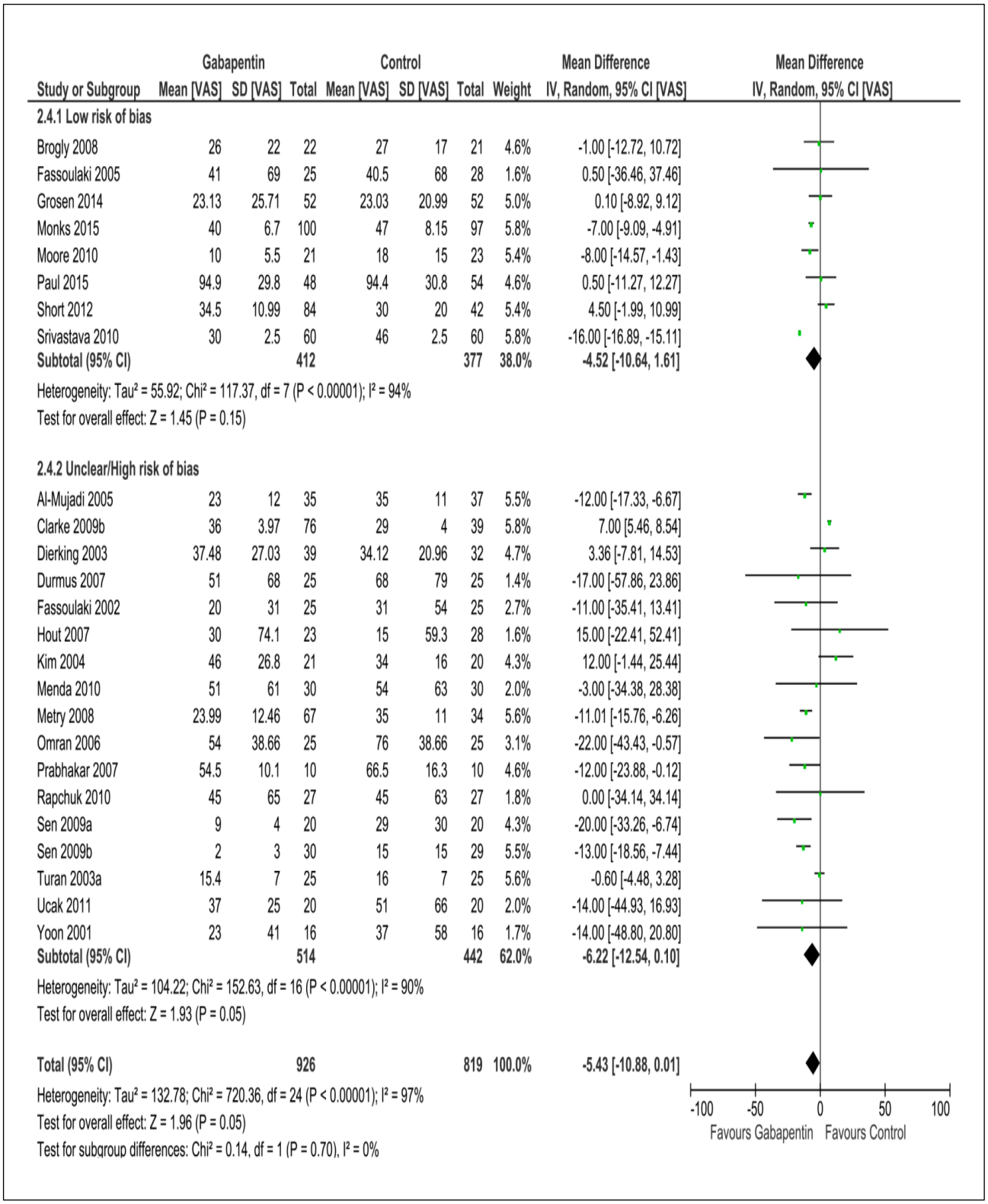
Appendix 13: Forest plot of pain intensity 6 hours postoperative at mobilization



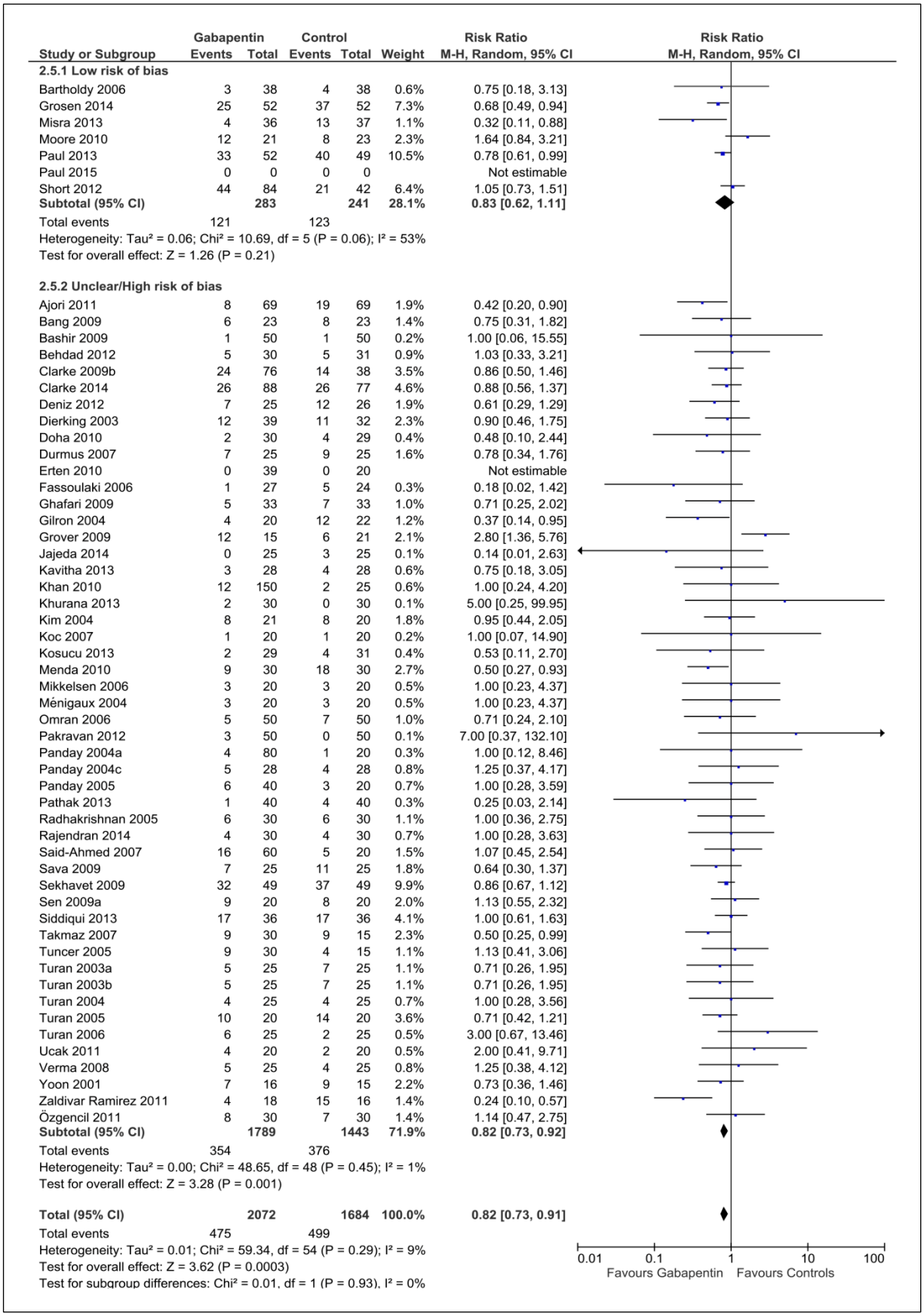
Appendix 14: Forest plot of pain intensity 24 hours postoperative at rest



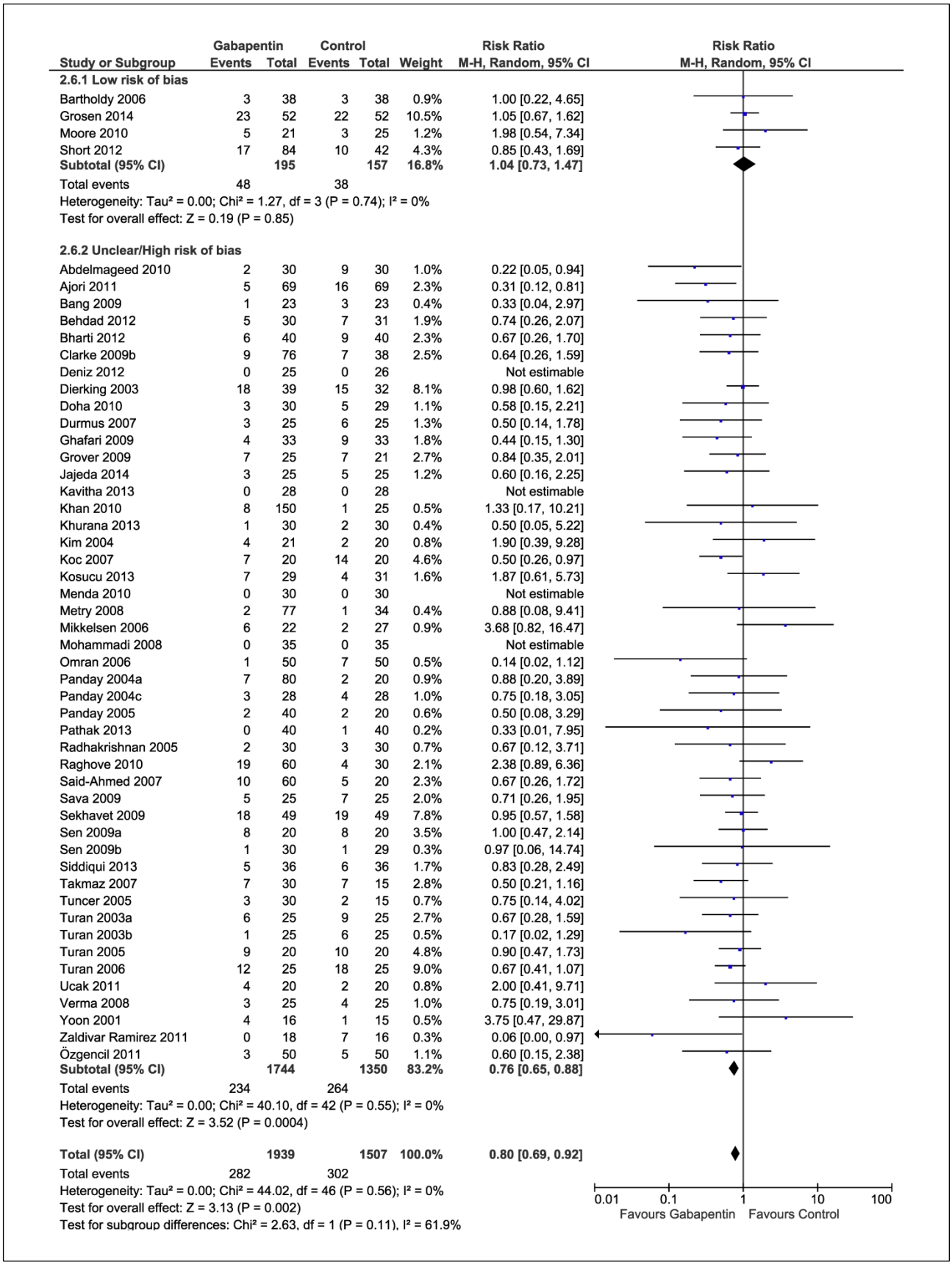
Appendix 15: Forest plot of pain intensity 24 hours postoperative at mobilization



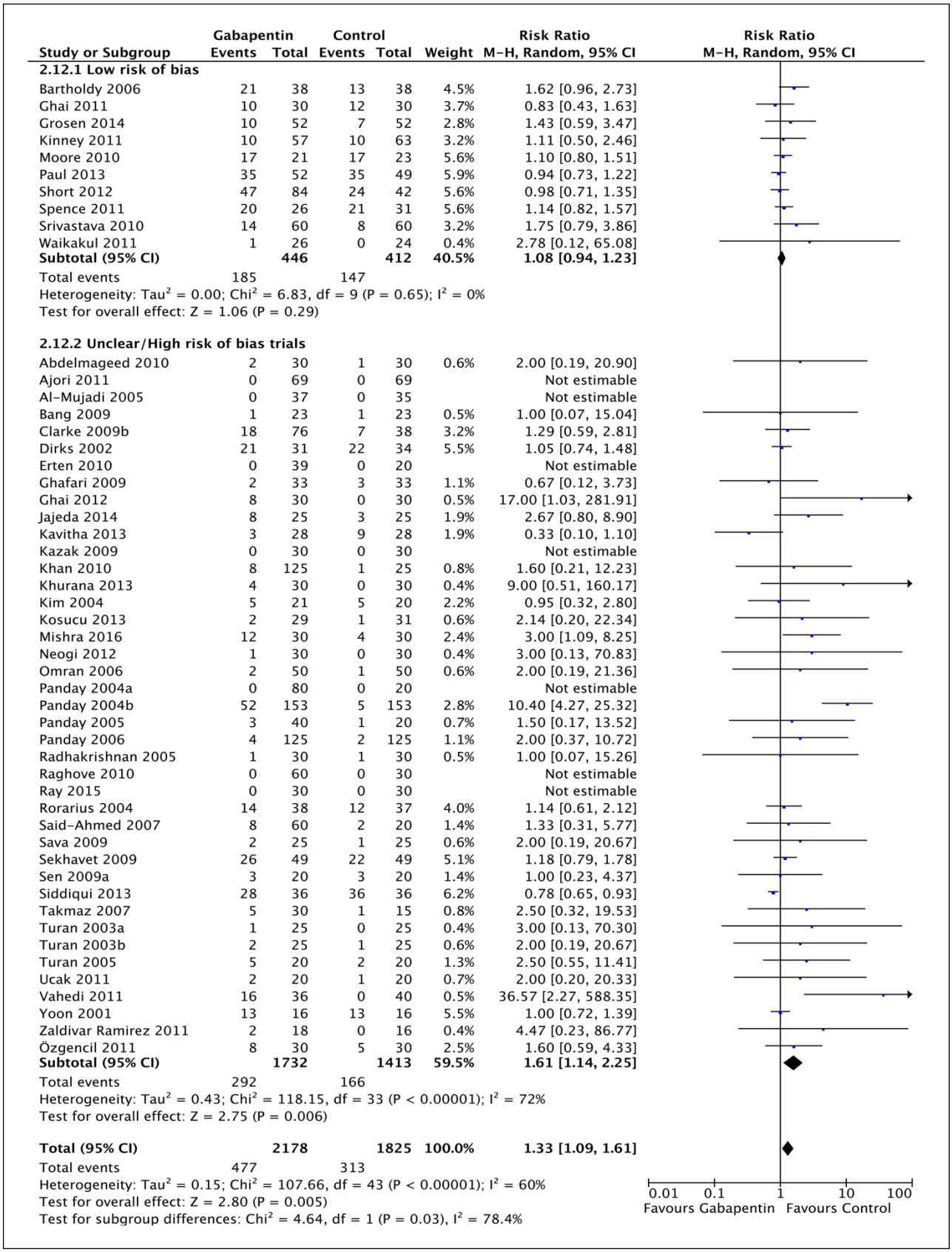
Appendix 16: Forest plot of adverse events nausea



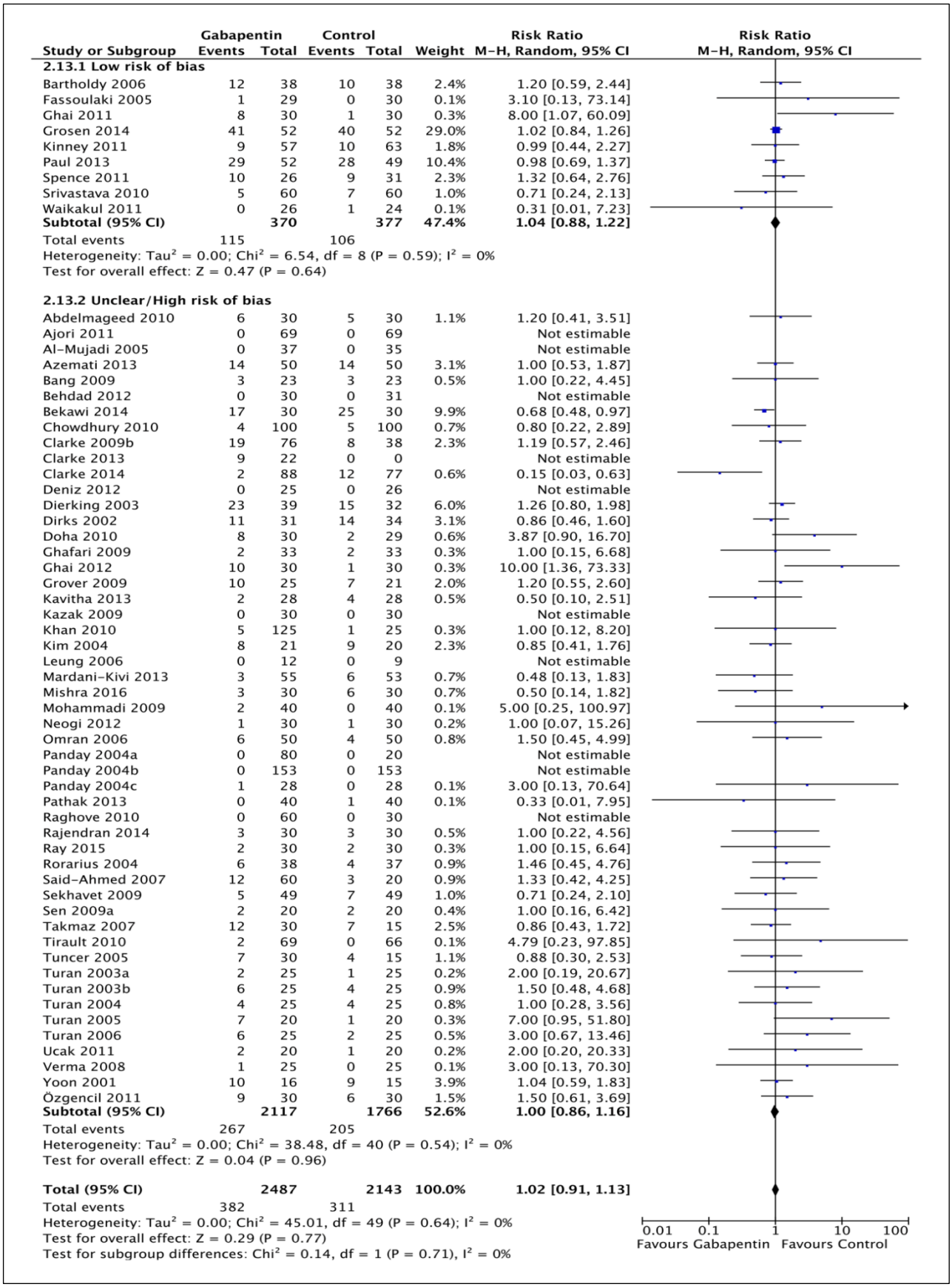
Appendix 17: Forest plot of adverse events vomiting



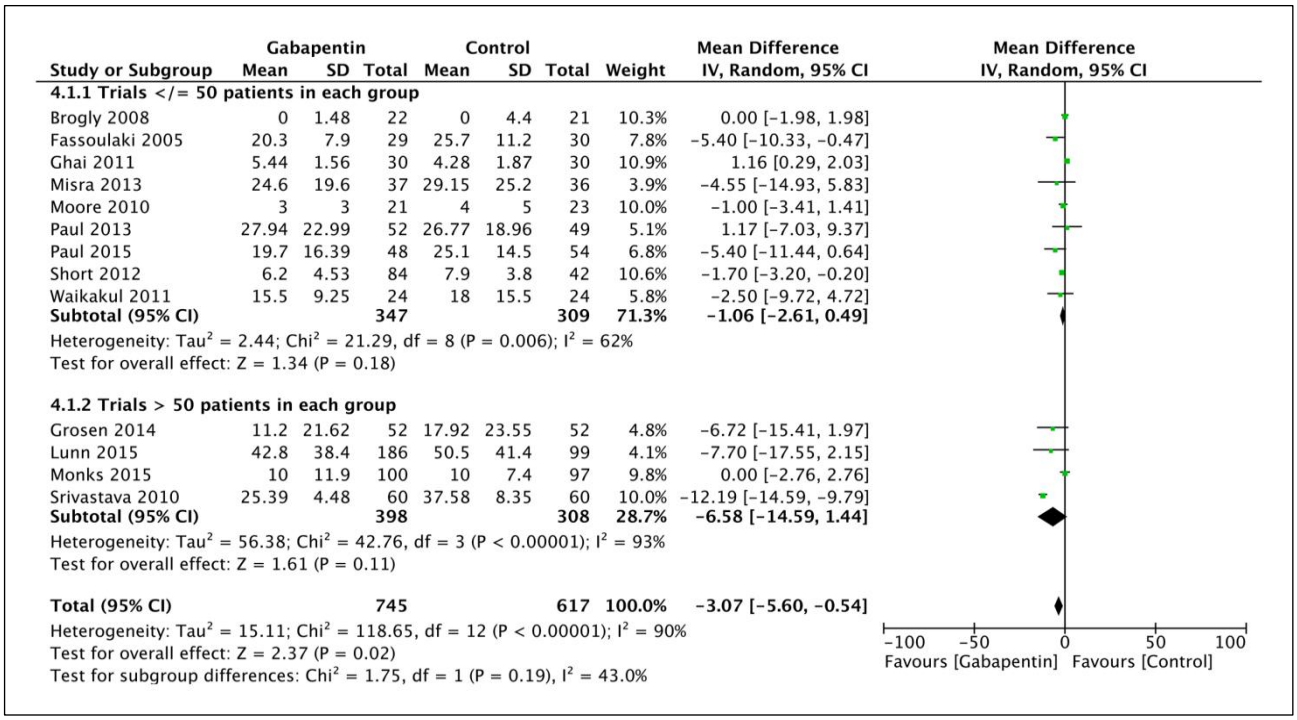
Appendix 18: Forest plot of adverse events sedation



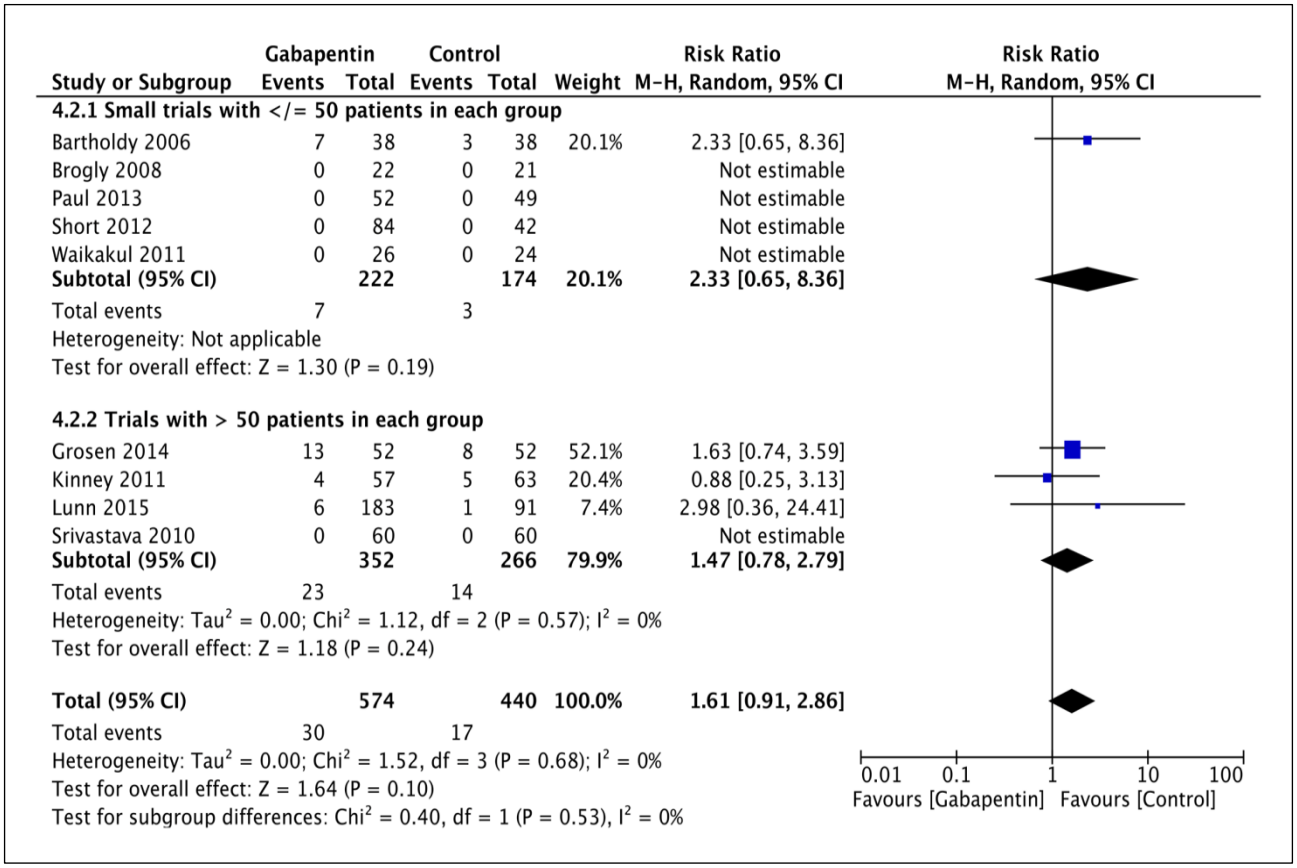
Appendix 19: Forest plot of adverse events dizziness



Appendix 20: Post hoc analysis of small trial size effect on 24-hour morphine consumption in trials with low risk of bias



Appendix 21: Post hoc analysis of small trial size effect on SAEs in trials with low risk of bias



PAPER II

Gabapentin in procedure-specific postoperative pain management
– Preplanned subgroup analyses with meta-analyses and trial sequential analyses

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ABSTRACT

Background

It has been argued that postoperative pain treatment should be "procedure-specific", since different analgesics may have specific effects dependent on the surgical procedure. The aim of these subgroup analyses was to compare the beneficial and harmful effects of perioperative gabapentin treatment in different surgical procedures.

Methods

Relevant database were searched for randomized clinical trials (RCTs) comparing gabapentin versus placebo. Two authors independently screened titles and abstracts, extracted data and assessed risk of bias. The primary outcomes were differences in 24-hour morphine consumption and serious adverse events (SAE) between surgical procedures. These subgroup analyses were predefined in a PRISMA compliant systematic review registered at PROSPERO (ID: CRD42013006538).

Results

Seventy-four RCTs with 5,645 patients were included assessing benefit and harm in cholecystectomy, hysterectomy, mastectomy, and arthroplasty surgery, spinal surgery and thoracic surgery.

Only eight of 74 trials were classified as overall low risk of bias limiting our ability to conclude on the estimates in most meta-analyses. Fifty-one trials with 4,193 patients, including all trials regardless risk of bias, reported on 24-hour opioid consumption. The difference between surgical procedures was not statistically significant when tested for subgroup differences. Fifteen trials with 1,377 patients reported a total of 59 SAEs, most of which were observed in thoracic surgery.

Conclusion

Both beneficial and harmful effects in these subgroup analyses were influenced by bias and insufficient data limiting conclusions. With these limitations, we could not demonstrate major differences in beneficial or adverse outcomes between six surgical subgroups undergoing perioperative gabapentin treatment.

BACKGROUND

Pain management is a crucial component in postoperative care of the surgical patient. The combination of non-opioid and opioid analgesics, known as multimodal analgesia, is a cornerstone in the treatment of postoperative pain. Gabapentin has recently become a part of a wide array of postoperative multimodal analgesic regimens.[1-3]

It has been argued that postoperative pain treatment should be "procedure-specific", that is adapted to the particular surgical procedure, since different analgesics may have specific effects dependent on the nature of the surgery.[4,5]

Gabapentin has been used in postoperative pain management since 2002. It is an anti-epileptic drug presumed to affect the nociceptive process through α 2δ -subunits of voltage gated calcium channels and thereby causing decrease in excitatory neurotransmitters, e.g. glutamate, substance P and calcitonin gene-related peptide (CGRP).[6,7] The anti-hyperalgesic properties of gabapentin have been investigated in several experimental and clinical trials.[8-11]

In a recent systematic review we pooled data from all clinical trials and different surgical interventions with gabapentin. In these preplanned subgroup analyses and post hoc analyses we aim to compare the procedure-specific effects of peri-operative gabapentin on postoperative opioid consumption, pain intensity, and adverse- and serious adverse events in six different surgical procedures. It was our hypothesis that the reduction in 24-hour morphine consumption and incidence of SAE´s would differ between surgical procedures.

METHODS

These are preplanned subgroup analyses and post hoc analyses from a systematic review following the methodology recommended by the Cochrane Collaboration. The protocol is published in the International Prospective Register of Systematic Reviews (PROSPERO) (www.crd.york.ac.uk/PROSPERO) registration no. CRD42013006538.[12]

Search strategy

The search was planned by a trial search coordinator using the Cochrane Library's CENTRAL, PubMed, EMBASE, and Science Citation Index Expanded databases. The previous reviews, reference lists and Google Scholar were hand-searched for eligible trials. Www.clinicaltrials.gov; www.controlled-trials.com; www.centerwatch.com; www.eudraCT.com, and at the homepage of the US Food and Drug Administration (FDA) were searched for unpublished trials. Non-English articles were translated to English. The electronic search (Appendix 1: search strategies) was last updated April 12th, 2016.

Data extraction

After removal of duplicates, titles and abstracts were screened by two independent authors (MLF, AG). MLF and one other independent author (AG, MSH, PLP, LN) assessed full texts, extracted data and assessed bias. The following characteristics were extracted from the trials using a data extraction form: Year of publication, number of participants, type of surgery, follow-up period and dose regimen, consumption of opioid and non-opioid medication, pain intensity, and any adverse effects described in the trials, including serious adverse events (SAEs).

The corresponding author was contacted whenever data were insufficiently reported and contact was repeated after 14 days. In case of no response, the involved bias domains were classified as unclear. All authors were contacted.

Risk of bias assessment

Risk of bias was assessed using The Cochrane Handbook guidelines. All trials classified as low, unclear or high risk of bias using the following domains: Random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other bias, including funding and confirmatory bias. It was a pre-planned and protocolled decision that conclusions of the review would primarily be based on trials with low risk of bias.

Disagreements between authors on study selection, data extraction or bias assessment were solved by OM, JBD or JW.

Small trial size

All trials were evaluated in this post hoc analysis and allocated to the corresponding group according to the numbers of participants included in the analyses. Small trials were defined as trials with less than 50 patients included in each group. Trials were allocated to the remaining two groups if they included either more than 50 patients, or more than 200 patients.[13]

Analyses

These subgroup analyses of surgical procedures were predefined in the protocol investigating the effect of different surgical procedures: Cholecystectomy, hysterectomy, mastectomy, orthopedic arthroplasty surgery and thoracic surgery on the primary and secondary outcomes. Analyses of thoracic surgery and orthopedic arthroplasty surgery have been added post hoc.[12]

The planning and interpretation of the subgroup analyses followed the direction of the Cochrane Handbook. [17]

Outcomes

The primary outcomes were difference in 24-hour postoperative opioid sparing effect and reported serious adverse events (SAE) between surgical procedures. SAE´s were defined according to the International Conference of Harmonization – Good Clinical Practice (ICH-GCP) definitions: Medical events being either life threatening, resulting in death, disability or significant loss of function, or causing hospital admission or prolonged hospitalization.[14]

Secondary outcomes were differences in early (6-hours) and late (24-hour) pain postoperatively, both at rest and during mobilization, and all other adverse events, between surgical procedures.

All opioids were converted to intravenous morphine based upon equivalency as presented in Appendix 2. Various scales were used to report pain intensity in the trials. All pain intensity scales reporting pain levels between 0 and 10 were converted to the Visual Analogue Scale (VAS) 0 to 100 mm.

Statistical analysis

Review Manager (RevMan) [Computer program], Version 5.1.6, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 was used for statistical analyses as predefined in the protocol.

In trials with more than one active treatment arm, including trials testing doses delivered pre- and immediate postoperatively, means and standard deviations were combined for the intervention groups.

Mean and standard deviations were estimated from median and range values according to the method described by Hozo et al.[15] Standard deviations were calculated by dividing the difference in interquartile ranges with 1.35. [16]

Longer ordinal scales were analyzed as continuous data. For dichotomous data, RR with a 95% confidence interval was calculated.

We examined the heterogeneity between trials using chi-squared test. The heterogeneity was measured by I^2, which quantifies inconsistencies. If the I^2 was greater than zero the results were calculated using both a fixed effect model (FEM) and random effect model (REM) and the most conservative estimation was used.[17,18] In the case of very few and rare events, Peto's odd ratio was used to provide the best coverage of confidence intervals.[19,20]

Estimates were pooled in meta-analyses whenever more than one trial was included for the outcome. Test for subgroup differences was carried out for all surgical procedures on all outcomes whenever a meta-analysis was possible. Using RevMan, the method to test for subgroup differences was implemented for all types of meta-analyses.[21]

We used Trial Sequential Analysis (TSA) in post hoc analyses to adjust the confidence intervals for sparse data and repetitive testing. Minimal clinical relevant differences were defined as in our main review.[13] In the event that the accrued information size was less than 5% of the required information size, no TSA is reported, as the TSA program is unable to calculate trial sequential monitoring boundaries in this situation.

RESULTS

The search strategies revealed 19,137 titles. Duplicates were removed and 16,303 titles were sorted according to inclusion- and exclusion criteria. One-hundred-thirty-five randomized controlled trials and observational studies were included in the original systematic review. After excluding 61 trials investigating other surgical procedures, a total of 74 randomized controlled trials with 5,645 patients were included in the present analyses. [22-96]

Characteristics of included trials

Trial characteristics are presented in table 1. Eight trials were classified as overall low risk of bias, [41,45,48,58,61,74,75,87] 18 trials were overall unclear risk of bias [23,25,26,28,30,31,33,38,40,44,54,56,57,63,67,68,70,71,82] and 48 trials were classified as high risk of bias [22,24,27,29,32,34-37,39,42,43,46,47,49-53,55,59,60,62,64-66,69,72,73,76-81,83-86,88-96], (figure 1: Bias assessment). Allocation concealment, selective outcome reporting and "other bias" were the domains with most unclear or high risk of bias evaluations (figure 2: Risk of bias graph).

Sixty-six trials were classified as small trials,[23-29,31-33,35-47,49-57,59,60,63-66,68,69,71,73-83,85,86,88-96] five had more than 50 participants in each group[22,34,48,58,87] and three included more than 200 patients.[61,70,72]

The gabapentin dose in the included trials ranged from 100 mg to 1800 mg, and was mostly administered as a single dose (46 trials). [22,24-26,30-34,36-39,43,45,47,49-53,55,57-59,63-66,69-73,77,79-81,83,84,87-92,94,96]In 30 trials, gabapentin was administered in combination with a basic, non-opioid/opioid analgesic regimen [22,24,25,28,30,32-34,39-43,45,48,51,56,58,59,61,63,74,75,78,81,82,84,89,92,93]. In 44 trials, gabapentin was administered together with an opioid as the only analgesic.[22,27,29,31,35-38,46,47,49,50,52-55,57,60,64-73,76,77,79,80,85-88,90,91,94-96] In five trials, gabapentin was administered in combination with a NSAID, [29,47,77,79,85], and in two trials, the postoperative analgesic regimen was not described. [26,83]

Bias assessments in surgical subgroups

Eight trials were classified as overall low risk of bias. None from the mastectomy subgroup and one trial from the cholecystectomy group was overall low risk of bias.[87] In the subgroups hysterectomy, [41,45] and thoracic surgery [48,58] two trials were low risk of bias in each group and three trials were classified as low risk of bias in the orthopedic arthroplasty subgroup.[61,74,75]

Below, we present analyses from trials with low risk of bias, and from all trials, separately. (Table 2 Primary outcomes from trials with low risk of bias and all trials estimates and Table 3: Secondary outcomes from trials with low risk of bias and all trials estimate).

Primary outcomes (table 2: The intervention effect estimated from trials with low risk of bias and from all trials despite risk of bias)

24-hour morphine consumption

24-hour morphine consumption was reported in 51 trials with 4,193 patients. [23,25,28,30,32-35,37-46,48,50-55,57,59,61-65,67-72,74,75,82,84,86-91,93-95] Of the 51 trials, 7 were classified as overall low risk of bias. [41,45,48,61,74,75,87]

Low risk of bias: In cholecystectomy, one trial reported a reduction of 12.2 mg [9.8, 14.6] in 24-hour morphine consumption in the gabapentin treatment group compared to controls,[87] two trials in hysterectomy found a reduction of 1.6 mg [-4.8, 8.0],[41,45] and three trials in orthopedic arthroplasty demonstrated a reduction of 4.0 mg [-0.8, 8.7].[61,74,75] Finally, one trial in thoracic surgery reported a reduction of 6.7 mg [-2.0, 15.4].[48]

All trials: Differences between surgical procedures were not statistically significant when tested for subgroup differences.

A statistically significant reduction in 24-hour morphine consumption was demonstrated in all surgical procedures, ranging from a reduction of 5.2 mg/24 h after mastectomy, to 10.6 mg/24 h after spinal surgery, compared with controls.

In the TSA analyses, the z-curve crossed the trial sequential monitoring boundary for benefit in cholecystectomy, hysterectomy and thoracic surgery. The trial sequential analyses reached the required information size only in the cholecystectomy group (Figure 3: Forest plot of 24-hour morphine consumption).

Serious adverse events

Fifteen trials with 1,377 patients reported SAEs [22,35,36,40,41,46,48,51,55,58,61,74,87,93,94]. Of the 15 trials, 5 were classified as overall low risk of bias.[48,58,61,74,87]

Low risk of bias: A comparison of pooled-estimates in test for subgroup differences from trials with low risk of bias indicated no difference between groups, p = 0.49. (Appendix 9: Forest plot SAE low risk of bias)

One cholecystectomy trial, two orthopedic arthroplasty trials, and two thoracic surgery trials were classified as overall low risk of bias. [48,58,61,74,87] In the trials with low risk of bias, the risk of SAEs were 2.98 [0.36, 24.41] in the orthopedic arthroplasty subgroup[61,74] and 1.35 [0.69, 2.63] the thoracic subgroup.[48,58] (Appendix 3: Forest plot of SAEs in trials with low risk of bias)

All trials: A total of 59 SAEs were reported from all trials despite bias classification, 49 were reported in the thoracic surgery trials [48,51,58,93], seven in the orthopedic arthroplasty trials [61,74], and three in the hysterectomy trials [22,35,41,46,55]. The cholecystectomy, mastectomy and spinal surgery trials reported no SAEs[36,40,87,94].

A comparison of pooled-estimates in test for subgroup differences from all trials indicated no difference between groups, p = 0.16, p = 0.3 and p = 0.72 for hysterectomy, orthopedic arthroplasty surgery, and thoracic surgery, respectively.

The risk of SAEs varied from 0.55 in hysterectomy, to 1.00 in thoracic surgery, and 2.98 in orthopedic arthroplasty surgery. In thoracic surgery, the z-curve reached the futility area of no difference with a RRR of 50%. None of the other subgroups reported sufficient events for the accrued information size to reach beyond the 5% threshold of the required information size (Figure 4: Forest plot of SAEs; Appendix 4: TSA of SAEs in the thoracic surgery subgroup).

Secondary outcomes (table 3: The intervention effect estimated from trials with low risk of bias and from all trials despite risk of bias)

Results from analyses of early and late pain intensity at rest and during mobilization, and adverse events, in trials with low risk of bias, and from all trials, are summarized in table 3.

Pain intensity

In general, only few data were available from trials with low risk of bias, rendering tests for subgroup differences impossible and/or unreliable. Results from data including all trials are divergent across surgical subgroups, with few and inconsistent differences between surgical procedures.

(Appendix 5-8: Forest plot of VAS 6 hours postoperative at rest and mobilization, 24 hours postoperative at rest and mobilization).

Adverse events

No subgroup difference was demonstrated in any adverse event in trials with low risk of bias.

As with data on pain intensity, results from data including all trials are divergent across surgical subgroups, with no consistent differences in adverse events between surgical procedures.

(Appendix 9-12; Forest plot of nausea, vomiting, sedation and dizziness).

DISCUSSION

It has been argued that postoperative pain treatment should be "procedure-specific", since different analgesics may have specific effects dependent on the surgical procedure.[4,5] In these preplanned subgroup analyses, we aimed to compare the effects of perioperative gabapentin on postoperative opioid consumption, pain intensity, and adverse- and serious adverse events in six different surgical procedures. Our primary outcome was 24-hour morphine consumption and SAE´s.

Our results are limited by the fact that overall, only eight trials were classified as low risk of bias, limiting our ability to test for subgroup differences and to pool estimates in meta-analyses of these eight trials. When interpreting the results from the all trials analyses, it should be noted that about two-thirds of these trials had overall high risk of bias, which is a severe limitation to any conclusion on the outcomes.

In trials with low risk of bias, 24-hour morphine consumption varied, and only the cholecystectomy subgroup indicated a difference between groups. With only one trial in this subgroup, the result has not been reproduced and is difficult to interpret.

For the analysis of all trials, the difference in 24-hour morphine consumption between surgical procedures was not statistically significant, when tested for subgroup differences. A reduction in 24-hour morphine consumption was demonstrated for all surgical procedures, compared with controls. However, the TSA did only reach required information size in the cholecystectomy group. Consequently, the effects observed in the individual procedures may be due to both random and systematic error, as indicated in the main systematic review.[13]

SAEs were primarily reported in the thoracic surgery trials but overall, since SAE´s were very poorly reported and data sparse, it is not possible to conclude on this outcome.

For pain intensity outcomes, only very few data were available from trials with low risk of bias. In the analyses of data from all trials, the results were divergent across surgical subgroups, and it is difficult to interpret the direction and authenticity in the test for subgroup differences.

No subgroup difference was demonstrated in any adverse event in trials with low risk of bias, and results from data including all trials were divergent across surgical subgroups, with no consistent differences in adverse events between surgical procedures. This indicates a similar adverse event profile of gabapentin for postoperative pain management irrespective of surgical procedure. Much like the previous outcomes, there is far too few data to make any firm conclusions based on these results. Poor reporting and high risk of bias limits any interpretation.

<u>Strengths and limitations of the subgroup analyses</u>

These subgroup analyses have some strength. The analysis was planned in a PROSPERO published protocol and was derived from a PRISMA compliant systematic review adhering to Cochrane standards in methodology and bias assessment. Our selection of surgical subgroups was based on a clinical hypothesis reported by previous studies [4,97], and several systematic reviews report similar findings.[98-101]

The trials have been critically assessed using the Cochrane bias assessment tools and where possible, conclusions are based on trials with low risk of bias, which is unlike most of the previous systematic reviews. The TSA has been added to adjust for sparse data and repetitive resting, which is a risk when the vast majority of included trials are small, that is < 50 patients in each group.[98-101]

The limitations of this analysis mirror those of the included trials, and the limitations of the general methodology in subgroup analyses. Subgroup comparisons are to be perceived as observational because we compare pre-existing non-randomized groups, and must be interpreted as such.[102]

The critical assessment of the trial methodology shows a very small number of trials with overall low risk of bias. Eighty-nine percent of the included trials have unclear or high risk of bias in one of the bias domains or more, risking an overestimation of beneficial -, and underestimation of harmful outcomes.

Despite the larger number of included trials in each subgroup compared to previous published systematic reviews, there is still a risk of spurious results due to lack of sufficient data. The lack of statistical significant p-values in these subgroup analyses may be due to a small effect size, or poor power to detect a large effect.

According to Oxman and Guyatt,[103] Xin Sun et al[104] and their criteria to evaluate the credibility of subgroup analyses, we have to consider further limitations such as: If the subgroup can be considered independent; no a-priori direction of the subgroup effect has been published; the subgroup effects found in our analyses does not seem to consequently manifest in closely related outcomes.

Relation to the previously published systematic reviews

A number of systematic reviews investigating individual surgical procedures, or with a procedure specific approach, have been published.[98-101,105-107] Most of these systematic reviews report favorable results for gabapentin treatment similar to the findings in our all trials analyses.

In comparison with the systematic reviews of gabapentin for hysterectomy, cholecystectomy and thoracic surgeries[98,101,105] more trials have been included in our subgroups. Due to different inclusion criteria and subgroup analyses in the systematic reviews, it is not possible to conduct a full comparison of estimates.

None of the systematic reviews above have investigated the risk of SAEs, limiting the ability to weigh the benefit and harm of gabapentin in perioperative pain management.[98-101,105]

Impact of the analyses

We observed no systematic differences in postoperative opioid consumption, pain intensity, or adverse- or serious adverse effects between six different surgical procedures treated with peri-operative gabapentin.

SAEs were very poorly reported, and only half the subgroups reported this outcome. More than 80% of the SAEs were reported in the thoracic surgery trials making it impossible to rely on the risk and subgroup differences between the surgical procedures. In the original review excess SAEs were reported in the gabapentin versus control groups and approximately twice as many SAEs were found in trials with low risk of bias compared with all trials.[13] Most trials have a short follow-up period, and only report on SAEs and

adverse effects for a short period postoperatively, which seems insufficient for a full evaluation. The inconsequent and diverse reporting of SAEs and adverse events complicates any reliable evaluation of these outcomes.

CONCLUSION

Both beneficial and harmful effects in these subgroup analyses are influenced by bias and insufficient amount of data, limiting any conclusions. The very poorly reported incidence of SAEs limits any conclusion based on this outcome.

With these limitations, we did not find any major differences in beneficial or adverse outcomes between various surgical subgroups with gabapentin for postoperative pain. Consequently, our analyses do not support the concept of a procedure specific postoperative pain management with gabapentin.

DECLARATIONS

Ethics approval and consent to participate

Not relevant.

Consent for publication

Not relevant.

Availability of data and material

The datasets used and/or analyzed during the current study available from the corresponding author on request.

These are preplanned, protocolled subgroup analyses from a systematic review with meta-analyses and trial sequential analyses: Fabritius ML, Geisler A, Hansen MS, Nikolajsen L, Hamunen K, Kontinen V, Wetterslev J, Dahl JB, Mathiesen O. Gabapentin for post-operative pain management - a systematic review with meta-analyses and trial sequential analyses. Acta Anaesthesiol Scand 2016; 60: 1188-208.

Competing interests

All authors declare no financial competing interests. JW reports that he is a member of the task force at Copenhagen Trial Unit to develop the software and manual for doing Trial Sequential Analysis (TSA). AG, PLP, JBD, OM and MLF have no conflicts of interests to declare.

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Authors' contributions

All authors have made substantive intellectual contributions to this systematic review adhering to the International Committee of Medical Journal Editors (ICMJE) guidelines. OM, JW and JBD have all made substantial contributions to the original idea and design, analyses and interpretation of data as well as revising the manuscript and all have given final approval to the submitted version of the manuscript.

AG and PLP made substantial contribution to acquisition of data, revising the manuscript critically and have given final approval to the submitted version of the manuscript.

MLF made substantial contributions to design, acquisition of data, analysis and interpretation of data, drafting the manuscript and given final approval of the submitted manuscript.

All authors have agreed to be accountable for all aspects of the work.

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TABLE 1 TRIAL CHARACTERISTICS

Reference *(Author and year)*	Surgical procedure	N *Gabapentin /Control*	Intervention *Dose (mg) (mg/day*)*	*Single/ Continuous*	Postoperative analgesia	Anesthetic technique	Bias assessment
Cholecystectomy trials							
Bashir 2009	Laparoscopic cholecystectomy	50/50	600 mg	Single	Not described	GA	Unclear
Bekawi 2014	Laparoscopic cholecystectomy	30/30	1200 mg (400 mg)	Continuous	NSAID/Pethidine/Tramadol	GA	Unclear
Bhandari 2014	Laparoscopic cholecystectomy	20/20	600 mg (600 mg)	Continuous	NSAID	GA	High
Hoseini 2015	Laparoscopic cholecystectomy	22/22	600 mg	Single	Morphine	GA	High
Khademi 2009	Open cholecystectomy	44/43	600 mg	Single	Pethidine	GA	High
Mishra 2016	Laparoscopic cholecystectomy	30/30	900 mg	Single	Tramadol	GA	High
Neogi 2012	Laparoscopic cholecystectomy	30/30	900 mg	Single	Tramadol	GA	High
Panday 2004b	Laparoscopic cholecystectomy	153/153	300 mg	Single	Fentanyl	GA	Unclear
Panday 2006	Laparoscopic cholecystectomy	125/125	600 mg	Single	Fentanyl	GA	High
Pathak 2013	Open cholecystectomy	40/40	1200 mg	Single	Pethidine	GA	High
Saeed 2013	Laparoscopic cholecystectomy	50/50	600 mg	Single	Pethidine/NSAID	GA	High
Semira 2013	Laparoscopic cholecystectomy	30/30	600 mg	Single	Not described	GA	High
Sharma 2015	Laparoscopic cholecystectomy	20/20	600 mg (600 mg)	Continuous	NSAID	GA	High
Srivastava 2009	Open cholecystectomy	60/60	600 mg	Single	Tramadol	GA	Low
Syal 2010	Open cholecystectomy	30/30	1200 mg	Single	Tramadol	GA	High
Takmaz 2009	Open cholecystectomy	30/15	900/1200 mg	Single	Tramadol/Meripedine	GA	High
Hysterectomy trials							
Ajori 2011	Abdominal hysterectomy	69/69	600 mg	Single	Meripedine	GA	High
Badawy 2014	Hysterectomy	20/20	800 mg	Single	Meripedine/Acetaminophen	GA	Unclear
Behdad 2012	Hysterectomy	30/31	100 mg (300 mg/d)	Continuous	An opioid	GA	High
Dierking 2003	Abdominal hysterectomy	40/40	1200 mg (1800mg/d)	Continuous	Morphine	GA	High

Durmus 2006	Hysterectomy	25/25	1200 mg	Single	Morphine	GA	Unclear
Fassoulaki 2005	Abdominal hysterectomy	29/30	400 mg (1600 mg/d)	Continuous	Morphine/Paracetamol/Codeine	GA	Low
Fassoulaki 2006	Abdominal hysterectomy	30/30	400 mg (1600 mg/d)	Continuous	Morphine/Paracetamol/Codeine/LA	GA	High
Frouzanfard 2013	Abdominal hysterectomy	25/25	1200 mg	Single	Morphine /NSAID	GA	High
Ghafari 2009	Abdominal hysterectomy	33/33	300 mg (300 mg/d)	Continuous	Morphine	GA	Unclear
Ghai 2011	Abdominal hysterectomy	30/30	900 mg	Single	Morphine/NSAID	GA	Low
Gilron 2004	Abdominal hysterectomy	23/24	1800 mg (1800 mg/d)	Continuous	Morphine	GA	High
Joseph 2014	Abdominal hysterectomy	25/25	600 mg	Single	Morphine	GA	High
Khan 2013	Abdominal hysterectomy	34/35	1200 mg	Single	Nalbuphine	GA	High
Ram 2015	Abdominal hysterectomy	30/30	900 mg	Single	NSAID	Spinal anesthesia	High
Ray 2015	Abdominal hysterectomy	30/30	300 mg	Single	NSAID	Spinal anesthesia	High
Rorarius 2004	Vaginal hysterectomy	45/45	600 mg	Single	Fentanyl	GA	High
Sekhavet 2009	Abdominal hysterectomy	49/49	600 mg (300 mg/d)	Continuous	Morphine/NSAID	GA	Unclear
Sen 2009a	Abdominal hysterectomy	20/20	1200 mg	Single	Morphine/Acetaminophen/Codeine	GA	High
Turan 2003a	Abdominal hysterectomy	25/25	1200 mg	Single	Tramadol	GA	High
Turan 2006	Abdominal hysterectomy	25/25	1200 mg (1200 mg/d)	Continuous	Acetaminophen/Codeine	GA	High
Verma 2008	Abdominal hysterectomy	25/25	300 mg	Single	Epidural analgesia	Spinal-epidural anesthesia	High
Mastectomy trials							
Amr 2009	Radical or partial mastectomy	50/50	300 mg (300 mg/d)	Continuous	Morphine/Acetaminophen/Codeine	GA	Unclear
Azemati 2013	Radical mastectomy or quandrandectomy	50/50	600 mg	Single	Pethidine/Acetaminophen	GA	High
Bharti 2012	Total mastectomy	20/20	600 mg	Single	Morphine/NSAID	GA	Unclear
Butt 2010	Mastectomy	50/50	1200 mg	Single	Morphine	GA	Unclear
Dirks 2002	Unilateral radical	31/34	1200 mg	Single	Morphine	GA	High
Doha 2010	Radical mastectomy	30/30	1200 mg	Single	Tramadol/NSAID	GA	High
Fassoulaki 2002	Radical mastectomy or lobectomy	25/25	400 mg (1200 mg/d)	Continuous	Propoxyphene/Acetaminophen/Codeine	GA	High
Gosai 2015	Radical mastectomy	30/30	600 mg	Single	NSAID	GA	High
Grover 2009	Total mastectomy	27/23	600 mg	Single	Morphine	GA	High
Kim 2004	Mastectomy	21/20	900 mg	Single	Fentanyl	GA	Unclear
Metry 2008	Unilateral radical mastectomy	67/34	1200 mg	Single	Morphine	GA	High
Orthopedic arthroplasty surgery trials							
Clarke 2009a	Total knee arthroplasty	29/7	600 mg(300/600	Single	Morphine/NSAID	Spinal	High

			/900 mg/d)	/continuous	Regional anesthesia	anesthesia and sedation	
Clarke 2009b	Total hip arthroplasty	76/39	600 mg	Single	Morphine/NSAID/Acetaminophen/ Dexamethasone	Spinal anesthesia	Unclear
Clarke 2014	Total knee arthroplasty	95/84	600 mg	Single	Morphine/NSAID/Regional anesthesia	Spinal anesthesia and sedation	High
Lunn 2015	Total knee arthroplasty	186/99	900/600mg (1300/900mg/d)	Continuous	Sufentanil /Oxycodone/NSAID /Acetaminophen/LIA	Spinal anesthesia and sedation	Low
Paul 2013	Total hip arthroplasty	52/49	600 mg (600 mg)	Continuous	Morphine/NSAID/Acetaminophen	Spinal anesthesia and sedation	Low
Paul 2015	Total hip arthroplasty	48/54	600 mg/(600 mg)	Continuous	Morphine/NSAID/Acetaminophen	Spinal anesthesia and sedation	Low
Spinal surgery trials							
Erten 2010	Laminectomy	39/20	900/1200 mg	Single	Tramadol/Pethidine/NSAID	GA	High
Khan 2010	Laminectomy	150/25	600/900/1200mg (600/900/1200 mg)	Continuous	Morphine	GA	Unclear
Khurana 2013	Discoidectomy	30/30	300 mg (900 mg/d)	Continuous	Tramadol/NSAID	GA	Unclear
Leung 2006	Spine surgery	9/12	900 mg (900mg/d)	Continuous	Hydromorphine	GA	Unclear
Özgencil 2011	Laminectomy or discoidectomy	30/30	1800 mg (1200 mg/d)	Continuous	Morphine	GA	Unclear
Panday 2004a	Discoidectomy	80/20	300/600/900/1200 mg	Single	Fentanyl	GA	High
Panday 2004c	Discoidectomy	28/28	300 mg	Single	Fentanyl	GA	Unclear
Radhakrishnan 2005	Laminectomy or discoidectomy	30/30	800 mg (800 mg/d)	Continuous	Morphine	GA	High
Turan 2003b	Discoidectomy or spinal fusion	25/25	1200 mg	Single	Morphine	GA	High
Vahedi 2011	Laminectomy or discoidectomy	36/40	300 mg	Single	Morphine	GA	High
Vasigh 2015	Laminectomy	38/38	600 mg (900 mg/d)	Continuous	Morphine	GA	High
Thoracic surgery trials							
Grosen 2014	Thoracotomy for malignancies	52/52	1200 mg (1200mg/d)	Continuous	Morphine/NSAID/Acetaminophen Epidural analgesia	GA	Low
Hout 2007	Exploratory thoracotomy,	23/28	1200 mg	Single	Hydromorphine/Epidural analgesia	GA	High

	pneumonectomy, lobectomy, segmentectomy, biopsy						
Kinney 2011	Thoratectomy; Lobectomy; Wedge resection; Segmentectomy; Pneumonectomy; Chest wall resection	57/68	600 mg	Single	Fentanyl/NSAID/Acetaminophen Epidural analgesia	GA	Low
Kosucu 2013	Posterolateral or lateral thoracotomy	29/31	1200 mg	Single	Morphine/Meriphidine/NSAID	GA	High
Menda 2010	Coronary artery bypass graft	30/30	600 mg	Single	Morphine/Acetaminophen	GA	Unclear
Omran 2005	Posterolateral thoracotomy for lobectomy	25/25	1200 mg (1200 mg/d)	Continuous	Morphine	GA	Unclear
Rapchuk 2009	Cardiac surgery via Sternum	27/27	1200 mg (600 mg/d)	Continuous	Fentanyl/Acetaminophen	GA	High
Soltanzadeh 2011	Coronary artery bypass graft	30/30	800 mg (400 mg/d)	Continuous	Morphine	GA	High
Ucak 2011	Coronary artery bypass graft	20/20	1200 mg (1200 mg/d)	Continuous	Tramadol/Acetaminophen	GA	High

**The continuous treatment is defined as more than one administration of gabapentin. The mg/day is the dose of gabapentin per day in the treatments that extends one administration.*

TABLE 2 PRIMARY OUTCOMES FROM TRIALS WITH LOW RISK OF BIAS AND ALL TRIALS ESTIMATES

Surgical procedure	**Cholecystectomy**		**Hysterectomy**		**Mastectomy**		**Orthopedic arthroplasty surgery**		**Spinal Surgery**		**Thoracic surgery**	
Outcomes	Reduction (mg) /RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mg) /RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mg) /RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mg) /RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mg) /RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mg) /RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*
BENEFICIAL OUTCOMES												
24-hour morphine consumption *Low risk of bias*	**12.2 mg** (95% CI: 9.8, 14.6; p = -; 1 trial; TSA adj. CI: -)	-	**1.6 mg** (95% CI: -4.8, 8.0; 2 trials; p = 0.62; TSA adj. CI: -11.2, 17.1; 20.6%)	P = 0.21	-	-	**4.0 mg** (95% CI: -0.8, 8.7; p = 0.1; 3 trials; TSA adj. CI: -4.1, 12.0; 41.0%)	P = 0.75	-	-	**6.7 mg** (95% CI: -2.0, 15.4; p = -; 1 trial; TSA adj. CI: -)	-
24-hour morphine consumption *All trials*	**7.3 mg** (95% CI: 4.6, 9.9; p < 0.00001; 10 trials; TSA adj. CI: 4.6, 9.9; 124.9%)	P= 0.9	**10.5 mg** (95% CI: 6.7, 14.4; p < 0.00001; 14 trials; TSA adj. CI: 6.7; 14.4 67.8%)	P=0.16	**5.2 mg** (95% CI: 0.9, 9.5; p= 0.02; 6 trials; TSA adj. CI: -1.6, 12.0; 26.7%)	P=0.15	**6.1 mg** (95% CI: 0.2, 12.1; p = 0.04; 6 trials; TSA adj. CI: -7.1, 19.4; 24.6%)	P=0.47	**10.6 mg** (95% CI: 2.1, 19.0; p = 0.01; 8 trials; TSA adj. CI: -24.1, 45.2; 11.6 %)	P=0.52	**6.3 mg** (95% CI: 2.9, 9.8; p = 0.0003; 7 trials; TSA adj. CI: 2.9, 9.8; 7.39%)	P=0.25
HARMFUL OUTCOMES												
Serious adverse events *Low risk of bias*	Not estimable	-	-	-	-	-	**2.98** (95% CI: 0.36, 24.41; 2 trials; TSA adj. CI: -)	P= 0.49	-	-	**1.35** (95% CI: 0.69, 2.63; 2 trials; TSA adj. CI: -)	P = 0.49
Serious adverse events *All trials*	Not estimable	-	**0.55** (95% CI: 0.05, 5.61; p 0.61; 5 trials; TSA adj. CI -; 3.3%)	P=0.16	Not estimable	-	**2.98** (95% CI: 0.36, 24.41; p = 0.31; 2 trials; TSA adj. CI: - ; 2.1%)	P=0.3	Not estimable	-	**1.0** (95% CI: 0.57, 1.74; p= 0.81; 4 trials; TSA adj.CI: 0.5, 2.1; 55.9%)	P=0.72

REM: Random Effects Model; FEM: Fixed Effects Model; RR: Risk Ratio; Peto's OR; Peto's Odds Ratio; TSA adj. CI: Trial Sequential Analysis adjusted Confidence Interval

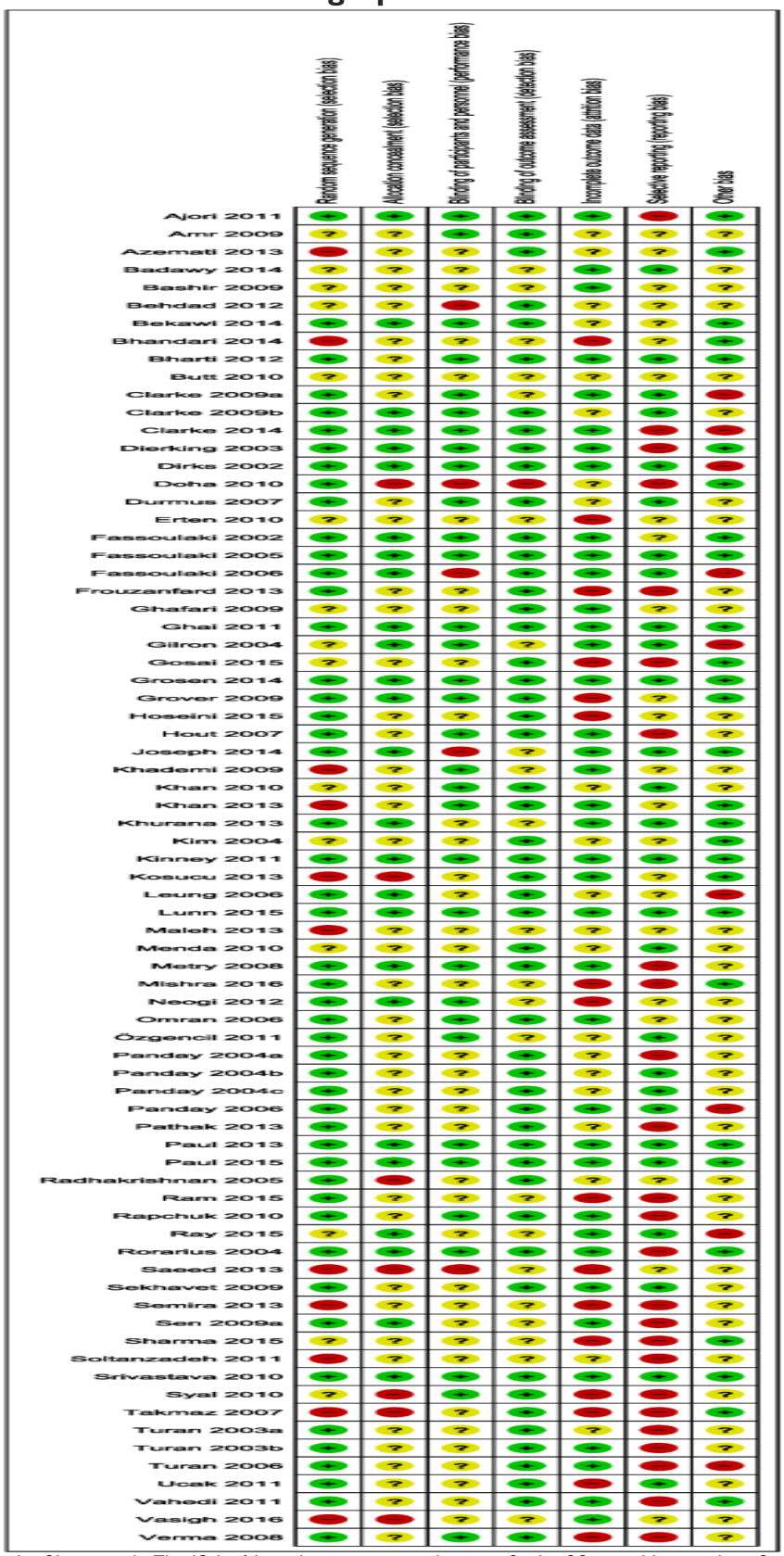
TABLE 3 SECONDARY OUTCOMES FROM TRIALS WITH LOW RISK OF BIAS AND ALL

Surgical procedure	**Cholecystectomy**		**Hysterectomy**		**Mastectomy**		**Orthopedic arthroplasty surgery**		**Spinal Surgery**		**Thoracic surgery**	
Outcomes	Reduction (mm) / RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mm) / RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mm) / RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mm) / RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mm) / RR *Estimate (95% CI; p-value; trials)*	Test for subgroup difference *P-value*	Reduction (mm) / RR Estimate (95% CI; p-value; trials)	Test for subgroup difference *P-value*
BENEFICIAL OUTCOMES												
6-hour VAS at rest *Low risk of bias*	**26.0 mm** (95% CI: 24.8, 27.2; p = -; 1 trial; TSA adj. CI: -)	-	**3.0 mm** (95% CI: -12.9, 18.9; p = -; 1 trial; TSA adj. CI: -)	-	-	-	-	-	-	-	**5.0 mm** (95% CI: -0.7, 10.7; p = 0.08; 2 trials; TSA adj. CI: -2.6, 12.6; 112.8%)	P = 0.36
6-hour VAS at rest *All trials*	**13.6 mm** (95% CI: -6.2, 33.4; p = 0.18; 3 trials; TSA adj. CI: -21.8, 94.3; 8.7%)	P=0.87	**16.4 mm** (95% CI: 11.9, 21.0; p < 0.00001; 16 trials; TSA adj. CI: 11.9, 21.0; 208.5%)	P=0.05	**7.8 mm** (95% CI: 1.9, 13.7; p = 0.01; 7 trials; TSA adj. CI: 1.9, 13.7; 103.3%)	P=0.15	Not estimable	-	**10.2 mm** (95% CI: 2.3, 18.0; p = 0.01; 7 trials; TSA adj. CI: -0.9, 21.2; 58.8%)	P=0.59	**4.6 mm** (95% CI: 0.9, 10.2; p = 0.1; 6 trials; TSA adj. CI: -1.5, 10.8; 118.5%)	P=0.02
6-hour VAS at mobilization *Low risk of bias*	**11.5 mm** (95% CI: 10.3, 12.7; p = -; 1 trial; TSA adj. CI: -)	-	**13.0 mm** (95% CI: -26.0, 52.0; p = -; 1 trial; TSA adj. CI: -)	-	-	-	-	-	-	-	**8.9 mm** (95% CI: 1.6, 16.1; p = -; 1 trial; TSA adj. CI: -)	-
6-hour VAS at mobilization *All trials*	**11.5 mm** (95%CI: 10.3, 12.7; p = -; 1 trial; TSA adj. CI: -)	P=0.04	**8.5 mm** (95%CI: 2.8, 14.2; p = 0.004; 6 trials; TSA adj.CI: 2.8, 14.2; 112.1%)	P=0.97	**5.2 mm** (95%CI: -1.6, 12.0; p = 0.14; 6 trials; TSA adj. CI: -9.5, 20.1; 22.4%)	P=0.07	Not estimable	-	**10.0 mm** (95%CI: 1.1, 19.0; p = 0.03; 1 trial; TSA adj. CI: -)	P=0.73	**10.9 mm** (95%CI: 4.4, 17.4; p = 0.001; 4 trials; TSA adj. CI: 4.4, 17.4; 85.5%)	P=0.41
24-hour VAS at rest *Low risk of bias*	**7.0 mm** (95% CI: 5.8, 8.2; 1 trial; TSA adj. CI: -)	-	**9.0 mm** (95% CI: -2.8, 20.8; 1 trial; TSA adj. CI: -)	-	-	-	**0.9 mm** (95% CI: -6.3, 8.1; 1 trial; TSA adj. CI: -)	-	-	-	**4.2 mm** (95% CI: -0.2, 8.5; 2 trials; TSA adj. CI: -)	P = 0.06

24-hour VAS at rest *All trials*	**3.2 mm** (95% CI: -1.9, 8.4; p = 0.22; 3 trials; TSA adj. CI: -3.2, 9.7; 138.3%)	P=0.1	**10.5 mm** (95% CI: 6.9, 14.2; p < 0.00001; 15 trials; TSA adj. CI: 6.9, 14.2; 266.9%)	P=0.02	**2.6 mm** (95% CI: -3.2, 8.5; p = 0.2; 3 trials; TSA adj. CI: -2.9, 8.2; 225.9%)	P=0.02	**1.0 mm** (95% CI: -1.7, 3.7; p = 0.45; 3 trials; TSA adj. CI: -2.3, 4.4; 496.1%)	P=0.001	**6.2 mm** (95% CI: 0.9, 11.6; p = 0.02; 6 trials; TSA adj. CI: 0.0, 12.4; 77.9%)	P=0.61	**9.7 mm** (95% CI: 2.4, 17.1; p = 0.01; 8 trials; TSA adj. CI: 2.4, 17.1; 66.9%)	P=0.51
24-hour VAS at mobilization *Low risk of bias*	**16.0 mm** (95% CI: 15.1, 16.9; 1 trial; TSA adj. CI: -)	-	**0.5 mm** (95% CI: -36.5, 37.5; 1 trial; TSA adj. CI: -)	-	-	-	**0.5 mm** (95% CI: -11.4, 12.3; 1 trial; TSA adj. CI: -)	-	-	-	**0.1 mm** (95% CI: -8.9, 9.1; 1 trial; TSA adj. CI: -)	-
24-hour VAS at mobilization *All trials*	**16.0 mm** (95% CI: 15.1, 16.9; p < 0.0001; 1 trial; TSA adj. CI: -)	P <0.00001	**4.5 mm** (95% CI: -4.5, 13.5; p = 0.34; 5 trials; TSA adj. CI: -1.0, 19.1; 45.0%)	P=0.91	**3.1 mm** (95% CI: -13.6, 19.8; p = 0.72; 3 trials; -65.1, 71.3; 13.1%)	P=0.87	**- 6.5 mm** (95% CI: 3.0, 9.9; p = 0.0002; 2 trials; TSA adj.CI: 2.5, 10.5; 150.7%)	P=0.0008	Not estimable	-	**3.0 mm** (95% CI: -4.5, 10.4; p = 0.43; 6 trials; TSA adj. CI: -6.7,12.6; 66.1%)	P=0.86
HARMFUL OUTCOMES												
Nausea *Low risk of bias*	-	-	-	-	-	-	**0.8** (95% CI: 0.6,1.0; 2 trials)	P = 0.5	-	-	**0.7** (95% CI: 0.5, 0.9; 1 trial)	-
Nausea *All trials*	**0.5** (95% CI: 0.25, 0.99; p = 0.05; 1 trial; TSA adj. CI: -)	P=0.16	**0.77** (95% CI: 0.63, 0.95; p = 0.01; 11 trials; TSA adj. CI: 0.6, 1.1; 49.4%)	P=0.73	**1.38** (95% CI: 0.85, 2.23; p = 0.19; 3 trials; TSA adj. CI: -; 2.69%)	P=0.33	**0.83** (95% CI: 0.66, 1.03; p = 0.08; 4 trials; TSA adj. CI: - ; 79.7%)	P=0.91	**1.07** (95% CI: 0.68, 1.68; p = 0.78; 8 trials; TSA adj. CI: 0.4, 3.2; 22.8%)	P=0.29	**0.66** (95% CI: 0.5, 0.88; p = 0.005; 5 trials; TSA adj. CI: 0.4, 1.0; 49.9%)	P=0.1
Vomiting *Low risk of bias*	-	-	-	-	-	-	-	-	-	-	**1.1** (95% CI: 0.7, 1.6; 1 trial)	-
Vomiting *All trials*	**0.5** (95%CI: 0.21, 1.16; p = 0.11; 1 trial; TSA adj. CI: -)	P=0.28	**0.71** (95% CI: 0.57, 0.9; p = 0.005; 9 trials; TSA adj. CI: 0.5, 1.0; 71.7%)	P=0.61	**0.81** (95% CI: 0.48, 1.37; p = 0.44; 5 trials; TSA adj. CI: 0.1, 6.9; 16.5%)	P=0.92	**0.64** (95% CI: 0.26, 1.59; p = 0.34; 1 trial; TSA adj. CI: -)	P=0.66	**0.61** (95% CI: 0.33, 1.12; p = 0.11; 7 trials; TSA adj. CI: 0.2, 2.3; 18.6%)	P=0.51	**1.01** (95% CI: 0.69, 1.49; p = 0.96; 5 trials; TSA adj. CI: 0.2, 4.9; 8.0%)	P=0.32

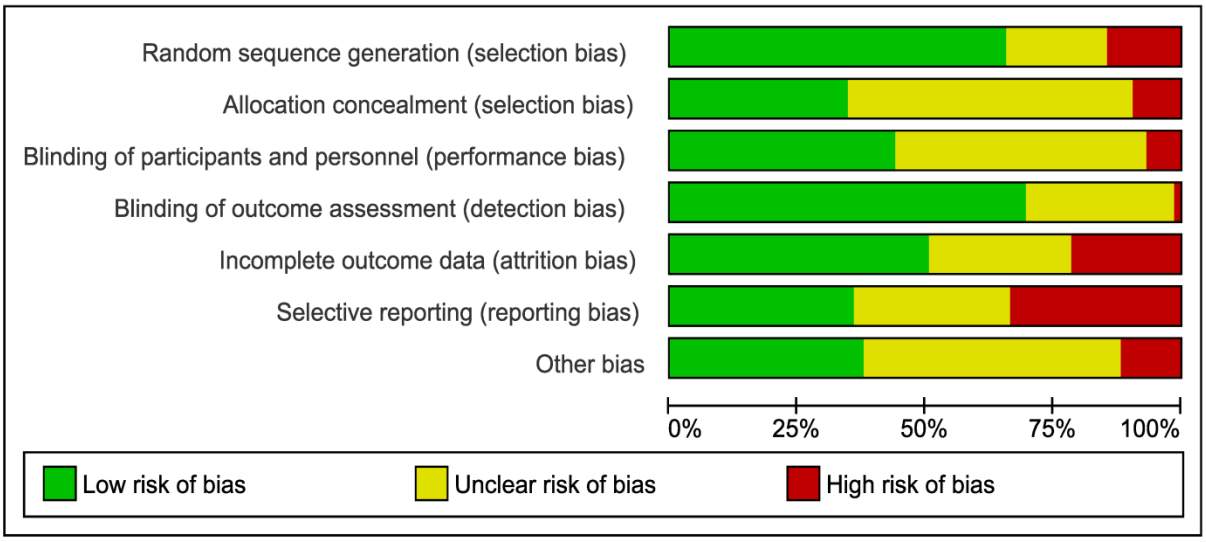
Sedation *Low risk of bias*	**1.8** (95% CI: 0.8, 3.9; 1 trial; TSA adj. CI)	-	**0.8** (95% CI: 0.4, 1.6; 1 trial; TSA adj. CI)	-	-	-	**0.9** (95% CI: 0.7, 1.2; 1 trial; TSA adj. CI)	-	-	-	**1.2** (95% CI: 0.7, 2.3; 2 trials; TSA adj. CI)	P = 0.55
Sedation *All trials*	**3.28** (95% CI: 1.55, 6.94; p = 0.002; 5 trials; TSA adj. CI: -; 3.9%)	P=0.009	**1.08** (95% CI: 0.81, 1.45; p = 0.61; 7 trials; TSA adj. CI: 0.5, 2.2; 23.2%)	P=0.06	**1.04** (95% CI: 0.75, 1.44; p = 0.83; 2 trials; TSA adj. CI: - ; 4.8%)	P=0.06	**0.97** (95% CI: 0.76, 1.24; p = 0.82; 2 trials; TSA adj. CI: 0.7, 1.6; 44.3%)	P=0.01	**2.65** (95% CI: 0.94, 7.52; p = 0.07; 7 trials; TSA adj. CI: - ; 2.3%)	P=0.19	**1.34** (95% CI: 0.78, 2.32; p = 0.29; 5 trials; TSA adj. CI: 0.1, 12.5; 10.8%)	P=0.68
Dizziness *Low risk of bias*	**1.0** (95% CI: 0.7, 1.4; 1 trial; TSA adj. CI)	-	**6.2** (95% CI: 1.1, 34.0; 1 trial; TSA adj. CI)	-	-	-	**0.7** (95% CI: 0.2, 2.1; 1 trial; TSA adj. CI)	-	-	-	**1.0** (95% CI: 0.8, 1.3; 2 trials; TSA adj. CI)	P = 0.64
Dizziness *All trials*	**0.7** (95% CI: 0.52, 0.94; p = 0.02; 6 trials; TSA adj. CI: 0.2, 2.6; 27.1%)	P=0.01	**1.34** (95% CI: 0.95, 1.89; p = 0.1; 11 trials; TSA adj. CI: 0.3, 5.6; 16.8%)	P=0.2	**1.03** (95% CI: 0.74, 1.43; p = 0.88; 5 trials; TSA adj. CI: 0.6, 2.1; 31.4%)	P=0.84	**0.72** (95% CI: 0.32, 1.66; p = 0.45; 3 trials; TSA adj. CI: 0.0, 18.1; 5.6%)	P=0.44	**1.03** (95% CI: 0.74, 1.43; p = 0.88; 5 trials; TSA adj. CI: 0.6, 2.1; 31.4%)	P=0.22	**1.04** (95% CI: 0.85, 1.26; p = 0.7; 4 trials; TSA adj. CI: 0.7, 1.5; 36.4%)	P=0.66

FIGURE 1 Risk of bias graph



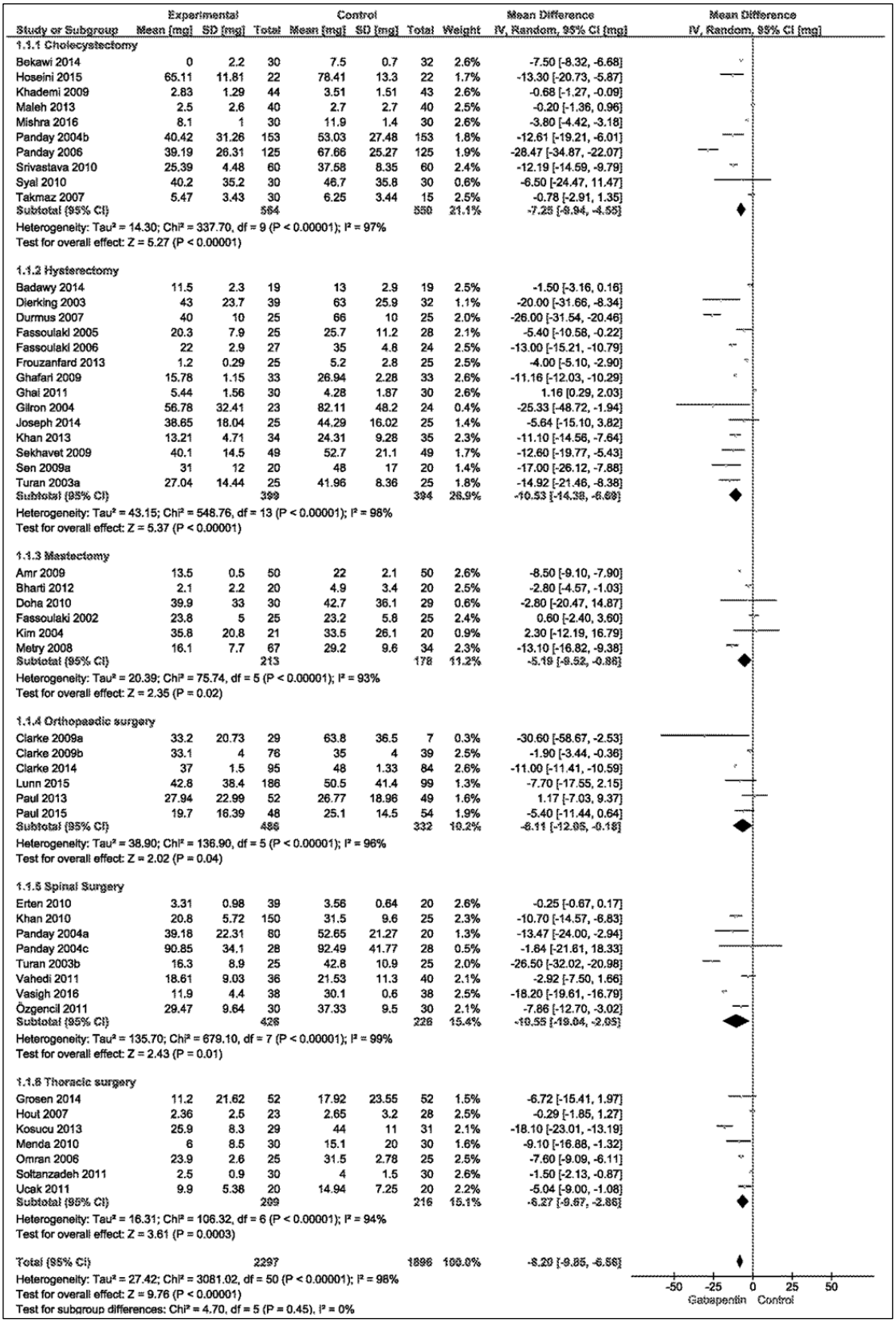
Risk of bias graph: The 'Other' bias domain is an evaluation of risk of financial bias and confirmatory bias

FIGURE 2 Bias summary



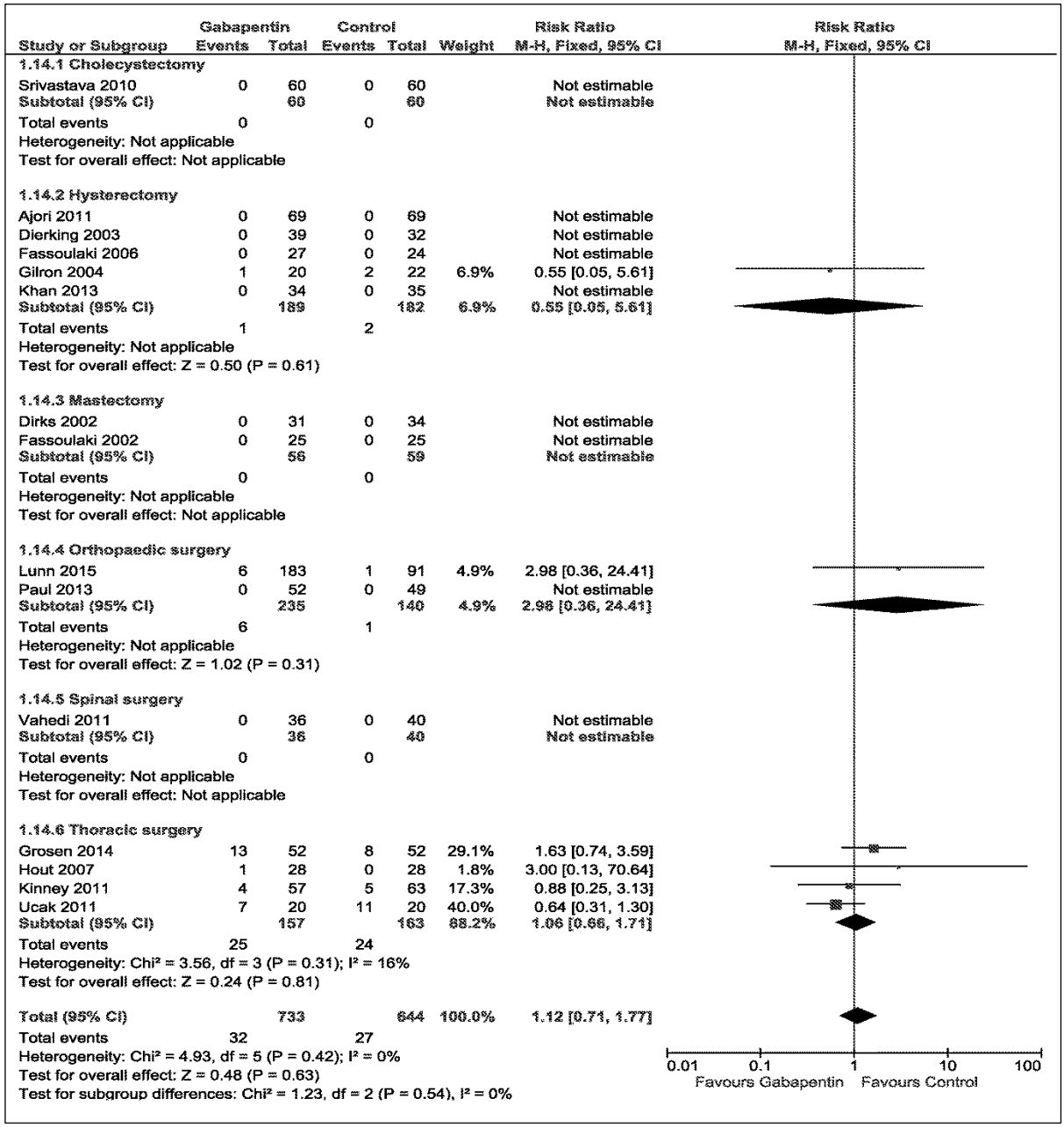
Risk of bias summary: *The 'Other' bias domain is an evaluation of risk of financial bias and confirmatory bias*

FIGURE 3 Forest plot of 24-hour morphine consumption



Forest plot of 24-hour morphine consumption

FIGURE 4 Forest plot of Serious Adverse Events



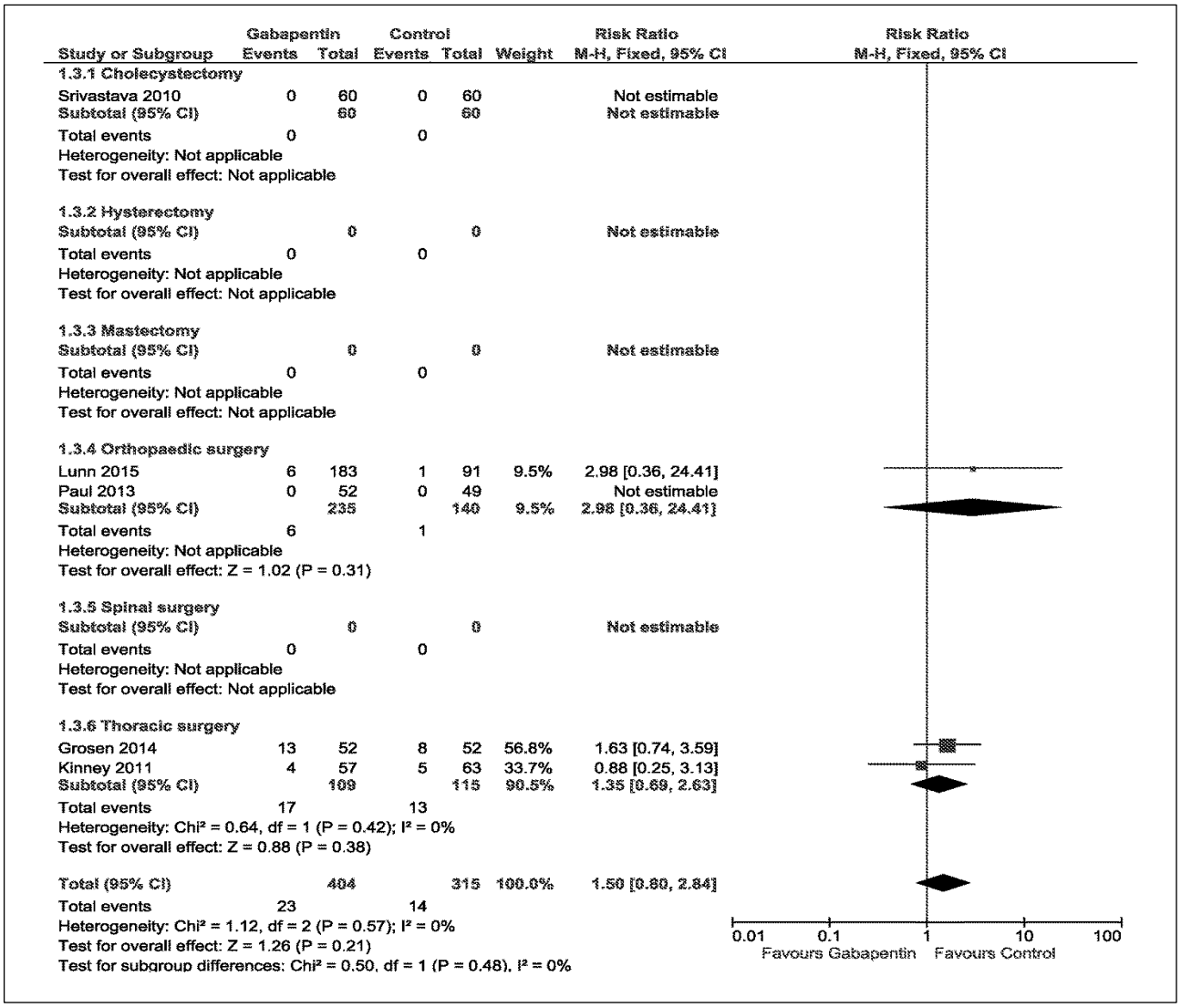
Forest plot of Serious Adverse Events

APPENDIX PAPER II

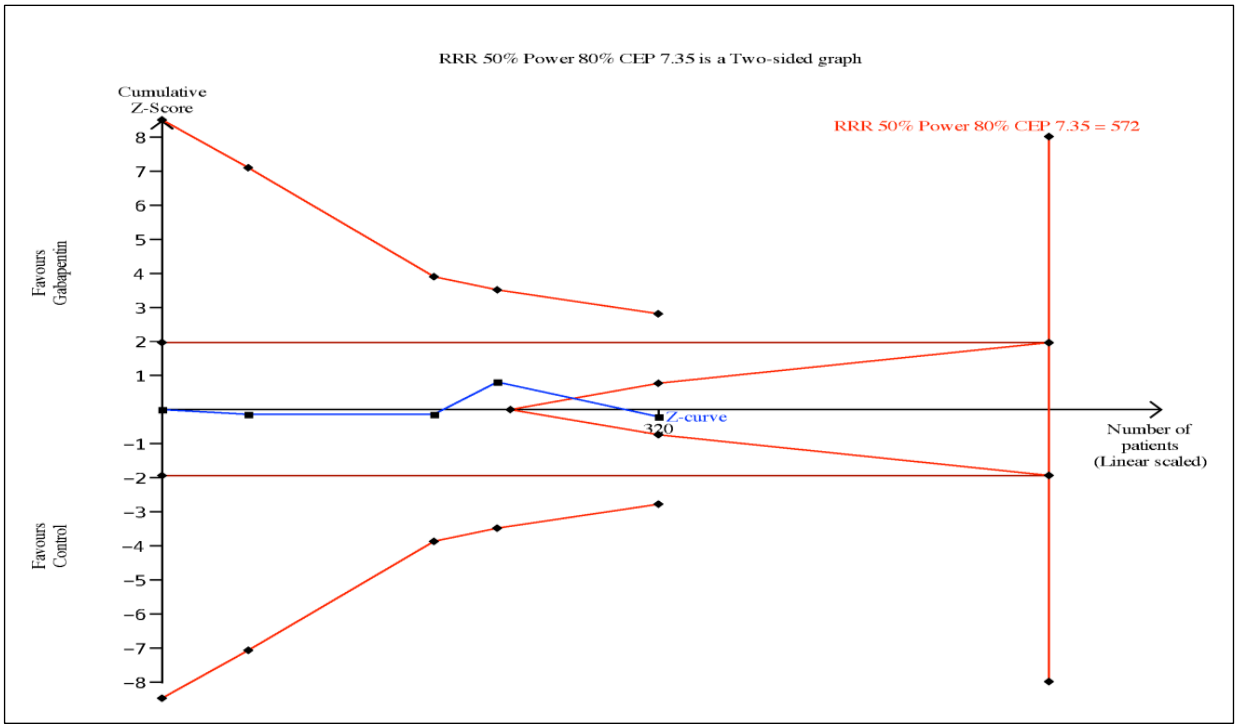
Appendix 1: Search strategies
Appendix from PAPER I.

Appendix 2: Opioid conversion table
Appendix from PAPER 1.

Appendix 3: Forest plot SAE low risk of bias

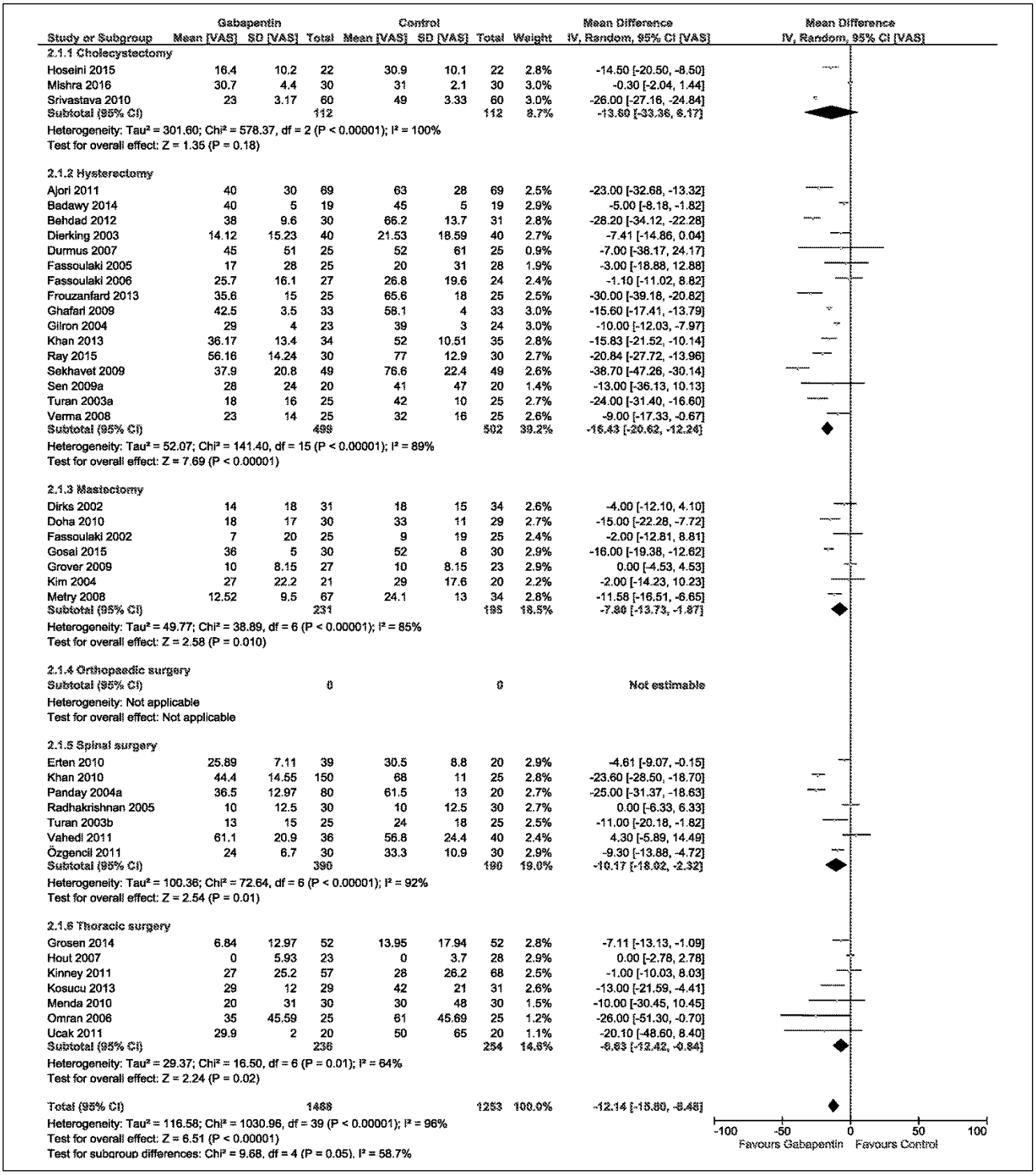


Appendix 4: TSA thoracic surgery SAE

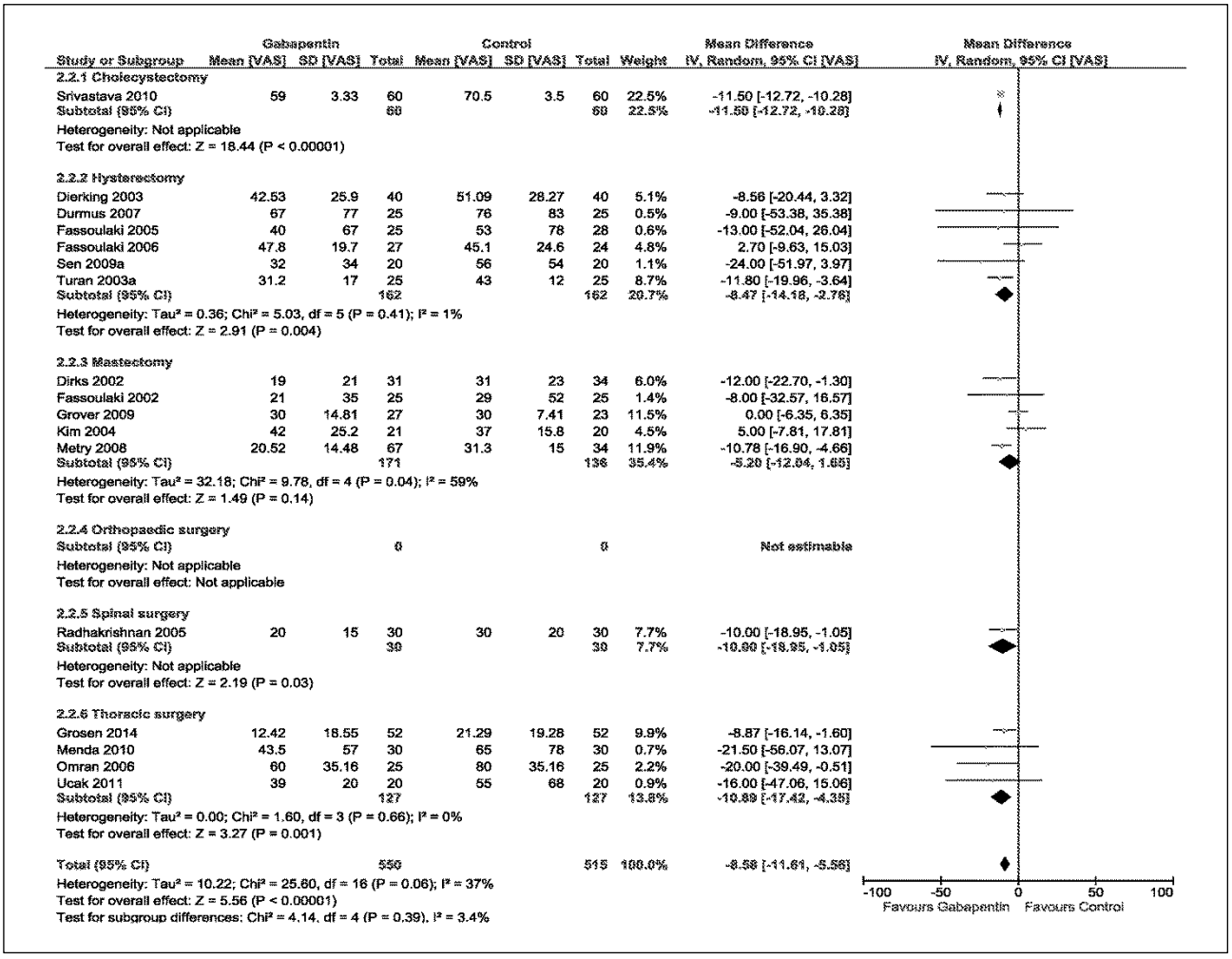


Appendix 4: *Trial sequential analysis of all thoracic trials regardless of bias classification on serious adverse events: TSA of the effect of Gabapentin on SAEs using a RRR of 50% and an α of 0.05, and a $\beta$of 0.20. An estimated required information size (RIS) of 572 patients was calculated to detect or discard a RRR of 50%. After three trials the cumulative z-curve does cross into the futility area. In conclusion the z-curve reaches futility areas enabling us to conclude that gabapentin does not seem to increase the number of SAE with 50% or more compared with the control intervention, however we cannot based on the acquired data exclude an increase in SAE's of less than 50%. However, this is data from all trial estimates risking an underestimation of harmful outcomes due to systematic error.*

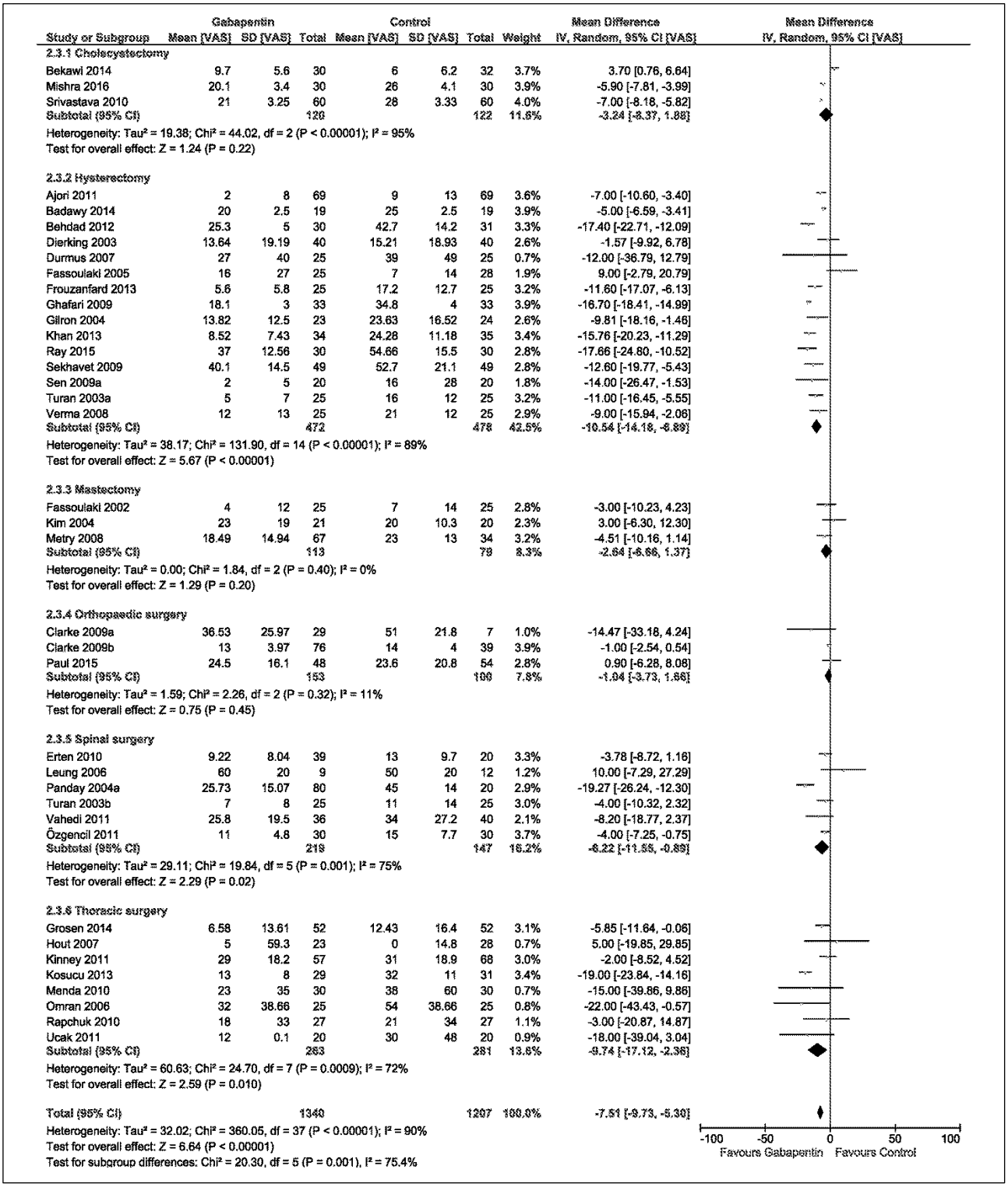
Appendix 5: Forest plot 6 hour VAS rest



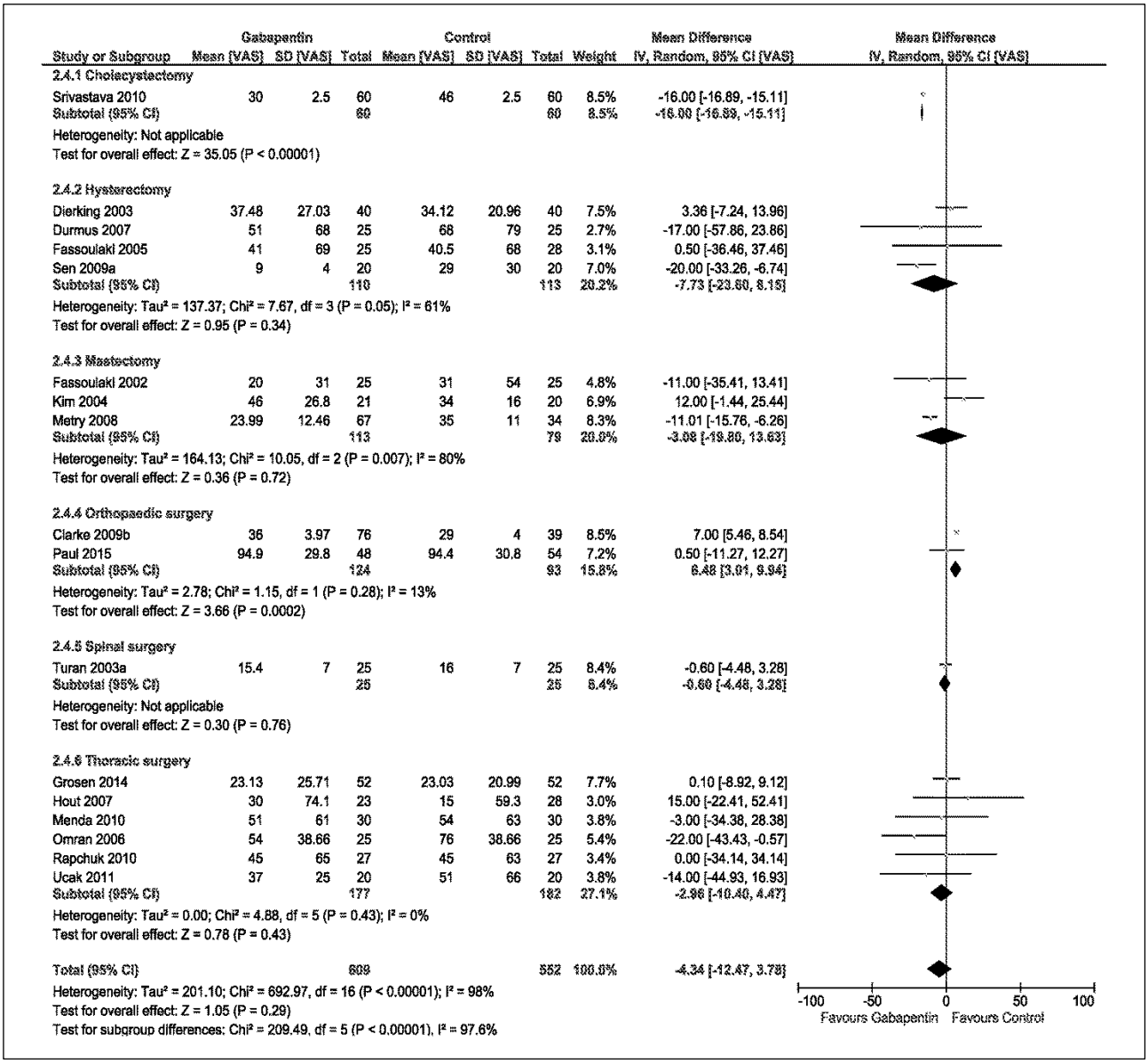
Appendix 6: Forest plot 6 hour VAS mobilization



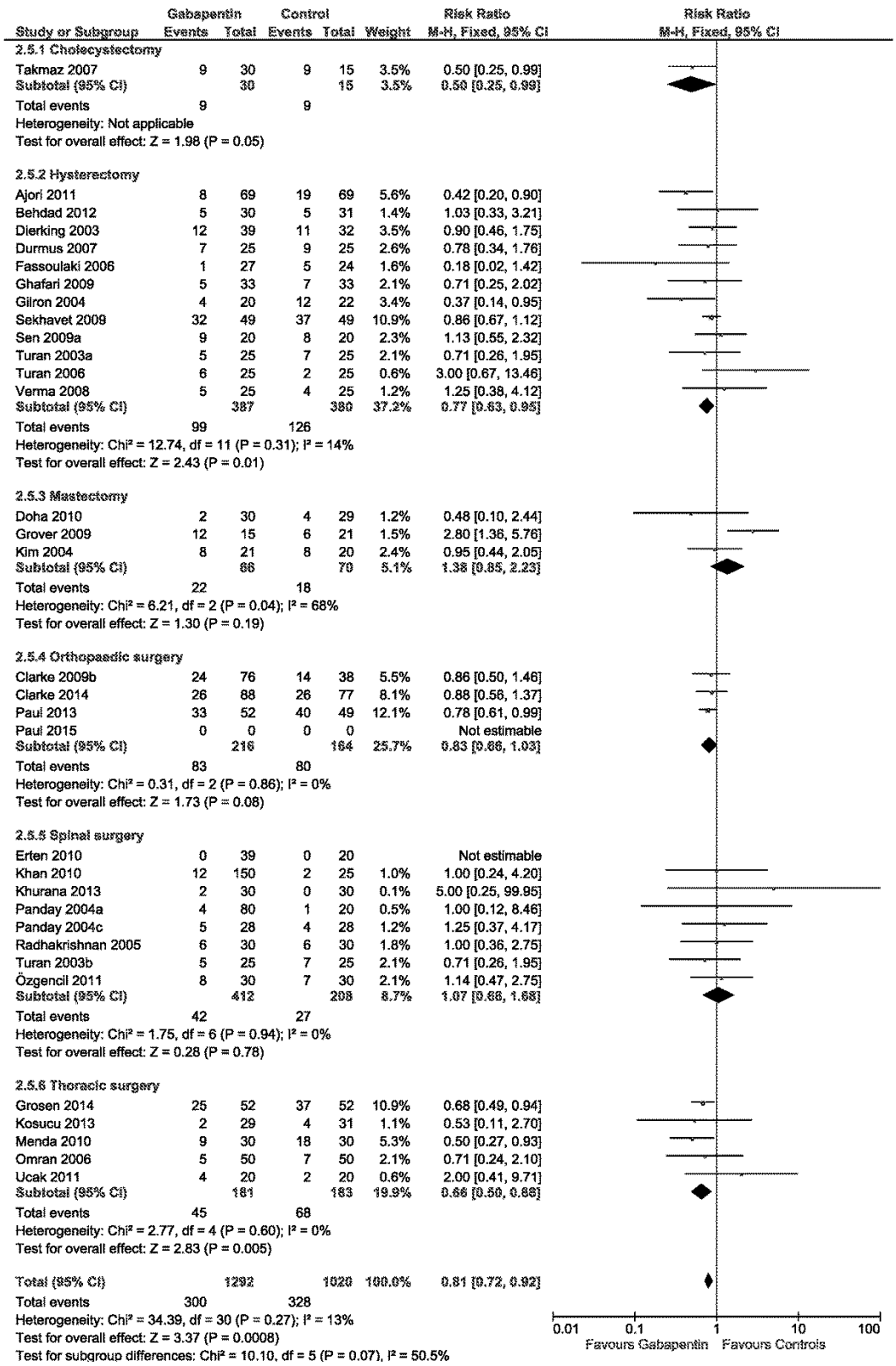
Appendix 7: Forest plot 24 hour VAS rest



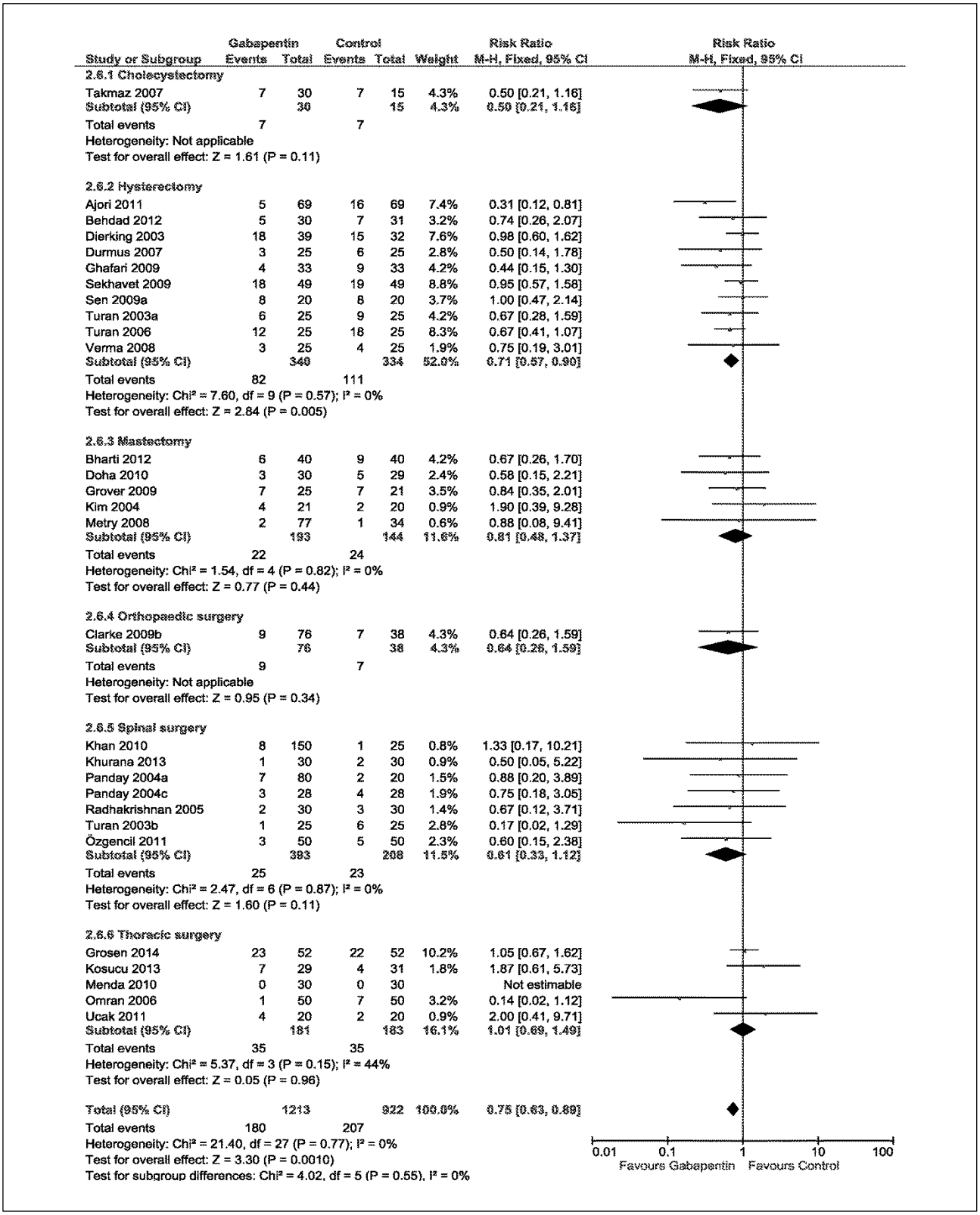
Appendix 8: Forest plot 24 hour VAS mobilization



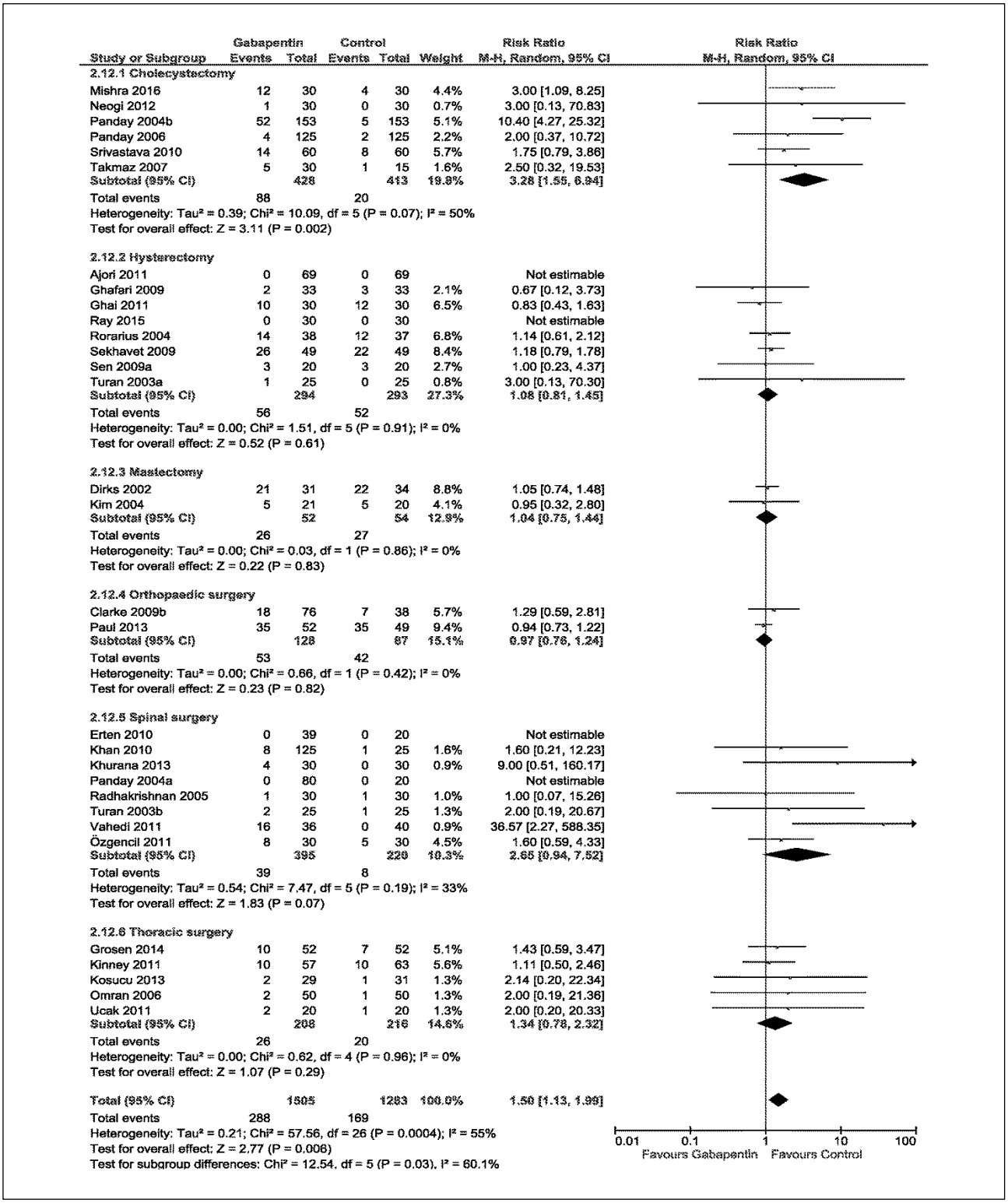
Appendix 9: Forest plot Nausea



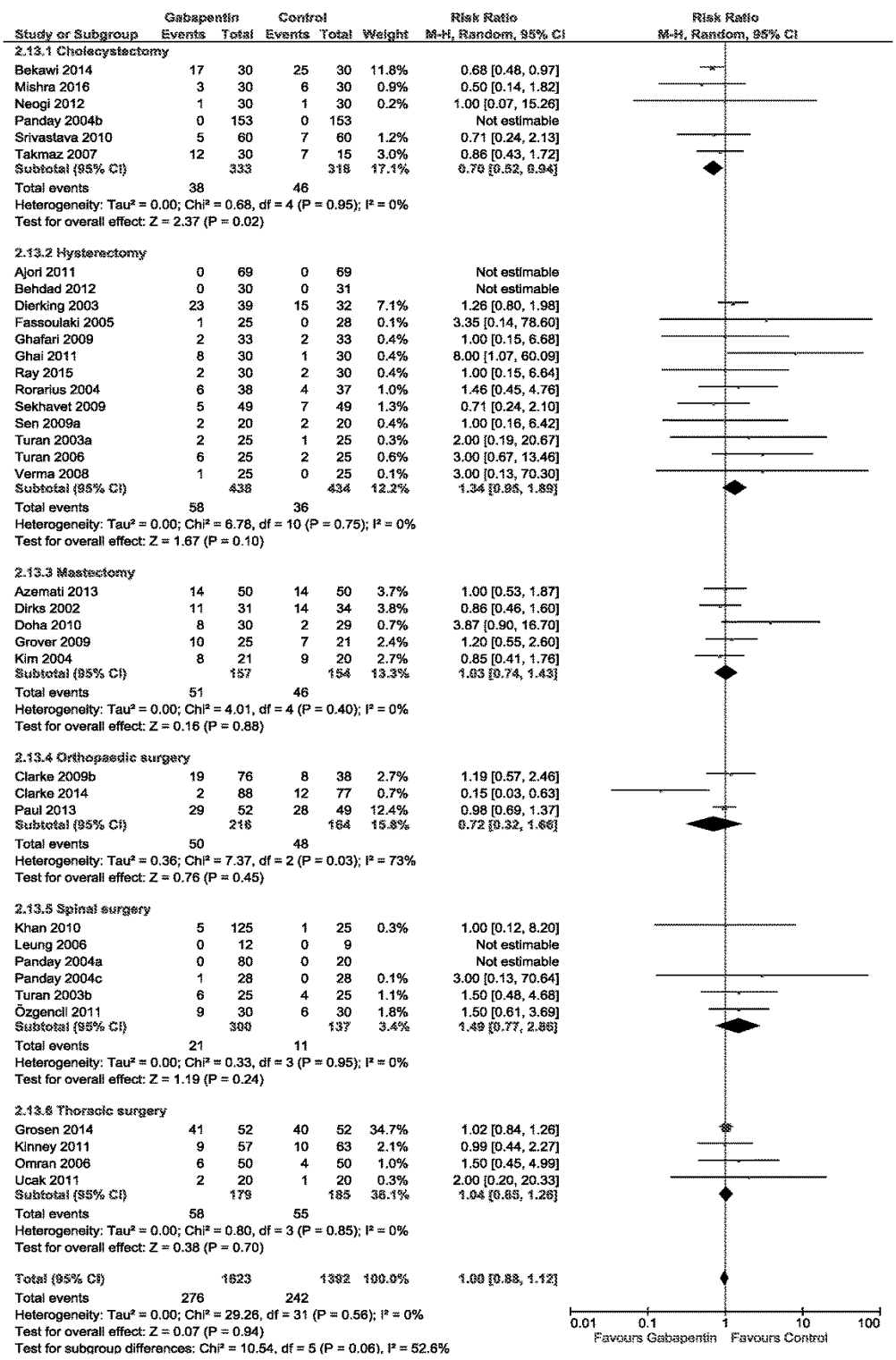
Appendix 10: Forest plot Vomiting



Appendix 11: Forest plot Sedation



Appendix 12: Forest plot Dizziness



PAPER III

Dose-related beneficial and harmful effects of gabapentin in postoperative pain management

–Post-hoc analyses from a systematic review with meta-analyses and trial sequential analyses

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ABSTRACT

This systematic review aimed to explore the beneficial and harmful effects of various doses of gabapentin, administered to surgical patients. The methods followed Cochrane guidelines. Four dose-intervals were investigated: 0-350 mg, 351-700 mg, 701-1050 mg and > 1050 mg.

Primary co-outcomes were 24-hour morphine consumption and serious adverse events.

One-hundred-and-twenty-two randomized clinical trials, with 8.466 patients, were included. Sixteen were overall low risk of bias. No consistent increased morphine-sparing effect was observed with increasing doses of gabapentin from trials with low risk of bias. Analyzing all trials, the smallest and the highest dose subgroups demonstrated the numerical most prominent reductions in morphine consumption.

Twenty-seven trials reported 72 SAEs, of which 83 % were reported in the > 1050 mg subgroup. No systematic increase in SAE´s was observed with increasing doses of gabapentin.

We were not able to demonstrate a relationship between dosage of gabapentin, and opioid-sparing or harmful effects.

BACKGROUND

During the last 15 years, gabapentin has become an established component of post-operative analgesia. Gabapentin has been employed in a wide range of doses, but little is known about the optimal dose, providing the best balance between benefit and harm in post-operative pain treatment.

The number of published, dose-finding gabapentin trials in postoperative pain treatment is limited,[1-12] and the results are inconsistent. It is well-established, however, that oral gabapentin is absorbed in part by diffusion, and in part by a carrier-mediated saturable transport mechanism system.[13] Thus, the bioavailability of oral gabapentin is not linear, but inversely dependent on the dose,[14] ranging from approximately 60% for a 300 mg dose to approximately 30% with doses of 1600 mg. [15-19]

Consequently, the optimal dosing of gabapentin, providing the best balance between benefit and harm, may not be obvious. In this post-hoc subgroup analysis we aimed to explore the relative effects of different doses of gabapentin, on 24-hour morphine consumption, pain intensity, risk of serious adverse events, and other adverse events.

We hypothesized that increasing doses of gabapentin would lead to increasing reductions in 24-hour morphine consumption and/or pain intensity, decreasing opioid-related adverse effects, but probably also increasing risks of serious adverse events and other drug-specific adverse events. We realized, however, that the possible increase in beneficial and harmful effects with increasing doses of gabapentin would probably not be linear, due to the non-linear bioavailability of oral gabapentin.

METHODS

The present review includes exploratory post-hoc analyses from an original systematic review, employing the Cochrane Collaboration methodology. The protocol of the original PRISMA-compliant review is published at the International Prospective Register of Systematic Reviews (PROSPERO) website (www.crd.york.ac.uk/PROSPERO) with the registration no. CRD42013006538 12.[20]

Literature search

Our comprehensive search strategy was planned by a trial search coordinator and reported in the published systematic review[21] and Appendix 1: Search strategies.

The Cochrane Library's CENTRAL, PubMed, EMBASE, Science Citation Index Expanded, Google Scholar and FDA database were searched for relevant trials. Unpublished trials were searched in relevant databases. Randomized controlled trials comparing gabapentin versus placebo, irrespective of publication type, status, publication year and language, were included. All Non-English articles were translated to English. We updated the search strategy April 12th 2016.

Data

MLF and one of the independent authors (AG, MSH, PLP, LN) screened titles and abstracts, evaluated the risk of bias and extracted data. Extracted data included: Article publication year, number of participants, surgical procedure, follow-up period and gabapentin dose administered, consumption of morphine (intravenous morphine based on equivalency, Appendix 2) and other non-opioid analgesics, pain intensity, and any adverse effects reported, including serious adverse events (SAEs).

Pain intensity was reported in different scales in the original trials. All pain intensity scales using intensity scores between 0 and 10 were converted to the Visual Analogue Scale (VAS) 0 to 100 mm.

SAE´s were classified according to the International Conference of Harmonization – Good Clinical Practice (ICH-GCP) definitions: Medical events being either life threatening, resulting in death, disability or significant loss of function, or causing hospital admission, or prolonged hospitalization.[22]

If data were incomplete or bias assessment was unclear, the corresponding author was contacted. This contact was repeated after two weeks in case of no response to initial contact. If the corresponding author did not reply, the involved bias domains were classified as unclear.

Assessment of risk of bias

The risk of bias assessment adhered to the Cochrane Handbook methodology.[23] All the included trials were assessed as low, unclear or high risk of bias, using the six bias domains described in the Handbook. The "other" bias domain consisted of financial and confirmatory bias evaluations.[24] Any difference in evaluations between authors on any part of the data extraction and evaluations process was solved by OM, JBD or JW.

It was protocolled that the review and conclusions would primarily be based on trials with low risk of bias.

Small trial size

This post-hoc analysis assessed the number of patients included in each original trial as defined in the original systematic review.[21] Trials with less than 50 participants were defined as small trials, trials with more than 50 participants in each group included a second group, and the trials with more than 200 participants made up the final group.

Analyses

The dose treatments of gabapentin were divided into 4 groups: 0-350 mg, 351-700 mg, 701-1050 mg, and more than 1050 mg. The defined groups represent the four most commonly used dose treatments in gabapentin research, which are 300 mg, 600 mg, 900 mg and 1200 mg.

All doses are considered as 24-hour treatments, regardless of single or multiple administrations, pre- or postoperative treatments, or the duration of the treatment.

If an original trial investigated more than one dose, the control group receiving placebo was divided into the corresponding number of intervention groups. In trials where the divided control groups included less than 20 participants, the trials were excluded. The individual dose-finding trials were counted as one trial in all summary statistics. Whenever the trials were included in cumulative analyses, the trials were viewed as separate trials.

Outcomes

Twenty-four-hour morphine consumption represented the beneficial primary outcome, and serious adverse events (SAE) represented the harmful primary outcome.

The secondary outcomes were divided into beneficial outcomes: Reduction in early (6-hour) and late (24-hour) pain postoperatively, both at rest and during mobilization, and harmful outcomes: All other adverse events.

Statistical analysis

Review Manager (RevMan) [Computer program], Version 5.1.6 was used in the cumulated analyses and subgroup analyses.

The handling of median and range (or interquartile range), longer ordinal scales and dichotomous data, examination of heterogeneity, employment of fixed or random effect models (FEM/REM), Peto's Odds Ratio, and handling of few and rare events, was done according to the PROSPERO published protocol and described in the published PRISMA-compliant systematic review.[20,21]

If more than one trial was included in the outcome, the estimates were pooled in meta-analyses and test for subgroup analyses was performed using RevMan in which the method to test for subgroup differences was implemented.

All trials with one intervention group and one control group were included. Handling of trials investigating more than one dose is described above. The mean and standard deviation of divided control groups was divided using the methodology from the Cochrane handbook.[25]

Trial Sequential Analysis (TSA) was used to adjust for sparse data and repetitive testing in the cumulative analyses.[26,27] Minimal relevant clinical differences were defined as in the published systematic review.[21] TSA is only reported if the accrued information size was 5% or more of the required information size (RIS), since the TSA program is only able to report trial sequential monitoring boundaries if this is the case.

RESULTS

In the original published systematic review, 19,137 titles were located, and after removal of duplicates, 16,303 titles were screened for in-and exclusion criteria. The original systematic review included 135 randomized clinical trials, including three observational studies.[21]

For the purpose of the present review, the three observational studies, and ten dose-finding trials with less than 20 patients in the split control groups, were excluded,[1-4,7,8,10-12,28] leaving 122 trials with 8,466 participants for analyses (Appendix 3: Trial characteristics).[5,9,28-147]

Trial characteristics

In the present analyses, 16 trials demonstrated overall low risk of bias,[5,9,38,44,59,62,66,80,95,99,100,111,112,131,132,144] 36 trials unclear risk of bias,[28,29,33,35,37,39,41,43,45,48,54,55,58,61,63,71,73,74,77-79,83,88,90,93,102,104,105,107,123,126,128,129,134,143,145,147] and 70 high risk of bias (figure 1: Bias evaluation; Appendix 4: Risk of bias graph).[6,8,12,30-32,34,36,40,42,46,47,49-53,56,57,60,64,65,67-70,72,75,76,81,82,84-87,89,91,92,94,96-98,101,103,106,109,110,113-122,124,125,127,128,130,133,135,136,138-142,146]

We found that 105 trials were "small trials",[12,28-30,32-46,48,50-55,57-65,67,69-79,81-88,90-98,100-105,108-110,113-131,133,135-146] 14 trials included more than 50 participants in each group,[9,31,47,49,56,66,80,89,99,111,112,132,134,147] and only 2 trials included more than 200 participants.[5,106]

Treatment with gabapentin included both single dose (84 trials)[9,12,28-32,34-39,43-48,50,52-56,60,62,63,65,67,69-71,73-77,79-82,86-90,92,94-98,100,101,103,106-110,113,115-122,124-126,128,129,132-135,137,140,142,143,147] and multiple dose administration (38 trials).[5,33,40-42,49,51,57-59,61,64,66,72,78,83-85,93,99,102,104,105,111,112,114,123,127,130,131,136,138,139,141,144-146] For further information about individual trials, see appendix 3: Trial characteristics.

Primary outcomes *(Table 1: The estimates of primary outcomes from trials with low risk of bias, and from all trials, despite risk of bias).*

Total 24-hour morphine consumption

Sixty-five trials with 4,851 patients reported 24-hour opioid consumption, and 15 trials (1318 participants) were classified as overall low risk of bias.

Trials with low risk of bias:
In the 0-350 mg subgroup, a reduction in 24-hour morphine consumption of 2.2 mg (0.1, 4.4; p = 0.04)[9,144] was reported with gabapentin versus control. The 351-700 mg subgroup demonstrated a reduction of 3.4 mg (0.9, 8.5; p = 0.12)[9,95,99,100,111,112,132], the 701-1050 mg subgroup an increase in consumption of 24-hour morphine consumption of 1.1 mg (0.3, 2.0; p = 0.01)[5,44,59,62,66], and the subgroup > 1050 mg reported a reduction of 2.9 mg (-1.1, 6.9; p = 0.2)[5,44,59,66] (table 1).
The test for subgroup differences was significant for the 701-1050 mg subgroup compared with the other subgroups (p = 0.002), but no systematic increase in morphine sparing effect was observed with increasing doses of gabapentin. With TSA, half the subgroup meta-analyses reached the futility area with the predefined minimal clinical difference, (MCD) and alfa and beta, while the other half did not report firm results.
(Figure 2: Forest plot of 24-hour morphine consumption from trials with low risk of bias and table 1).

All trials:
All subgroups demonstrated a reduction in 24-hour morphine consumption (table 2). Differences between the different dose intervals were statistically significant in test for subgroup differences between the 350-700 mg, 701-1050 mg, and >1050 mg subgroups. The 0-350 mg subgroup, and the > 1050 mg subgroup, demonstrated the numerical most pronounced reductions in morphine consumption, but no systematic increase in morphine-sparing effect was observed with increasing doses of gabapentin. Only the meta-analysis for the subgroup 701-1050 did not report firm evidence according to TSA.
(Figure 3: Forest plot of 24-hour morphine consumption from all trials estimates and table 1).

Serious adverse events

Twenty-seven trials with 1,958 participants reported 72 SAEs, of which 83 % were reported in the > 1050 mg subgroup. Of the 27 trials, eight were classified as overall low risk of bias[5,9,44,66,80,111,132,144], and these eight trials reported more than half the SAEs.

Trials with low risk of bias:
In the 0-350 mg subgroup[9,144], Peto's OR and TSA were not estimable. In the remaining subgroups, the risk of SAE´s were: 351-700 mg subgroup: OR 0.9 (0.2, 3.4; p = 0.85)[9,80,111,132]; 700-1050 mg subgroup: OR 0.6 (0.04, 8.6; p = 0.70)[5]; > 1050 mg subgroup: OR 2.0 (0.9, 4.5; p = 0.1)[5,44,66]. No subgroup differences were demonstrated for this outcome, and no systematic increase in SAE´s was observed with increasing doses of gabapentin. It was only possible to conduct TSA on two subgroups (351-700 mg, and > 1050 mg), and both subgroups had less than 20% of required information size, and none reported firm evidence.
(Figure 4: Forest plot of SAE from trials with low risk of bias and table 1).
All trials:
None of the gabapentin subgroups demonstrated statistically significant increases in SAE´s compared with controls. No significant differences between the different dose intervals were demonstrated, and no systematic increase in SAE´s was observed with increasing doses of gabapentin (table 2). TSA showed that none of the three subgroups, 351-700 mg, 701-1050 mg, and > 1050 mg, reached firm evidence, nor did they reach more than 5% of RIS. (Figure 5: Forest plot of SAE from all trials estimates)

Secondary outcomes

Pain intensity

Few data were reported from trials with low risk of bias, limiting the reliability of the test for subgroup differences. No consistent dose-related trends or subgroup differences were demonstrated in the all trials estimates (table 2 and Appendix 5-12 Forest plots of pain intensities).

Adverse events

No consistent dose-related trends or subgroup differences were demonstrated neither in data from trials with low risk of bias, nor in the all trials estimates (table 3). None of the meta-analyses of trials with low risk of bias reporting risk of AE reached firm evidence according to TSA. (Appendix 13-20 Forest plot of AE)

DISCUSSION

In this review, we aimed to explore the effect of increasing doses of gabapentin on post-operative morphine consumption, SAE´s, pain intensity, opioid-related- and drug-specific adverse events, in four groups of trials that included the most commonly used doses of gabapentin for perioperative pain management: 300 mg, 600 mg, 900 mg and 1200 mg.

For the primary beneficial outcome, 24-hour morphine consumption, no consistent increase in morphine-sparing effect was observed with increasing doses of gabapentin, neither in the analysis of trials with low risk of bias, nor in the all trials analysis. On the contrary, the smallest (0-350 mg), and the largest (> 1050 mg) dose-regimens demonstrated comparable, and the most pronounced reductions in morphine consumption in the all trials analysis.

Only few SAEs were reported, limiting any reliable conclusion on this outcome. Of 72 stated SAEs, 83 % were reported in the > 1050 mg subgroup, indicating an increased risk of SAEs with increasing doses. Of the 27 trials reporting SAEs, 10 were classified as overall low risk of bias, and these 10 trials reported more than half the SAEs.

For the secondary outcomes, pain intensity and adverse events, no consistent dose-related trends or subgroup differences were demonstrated, neither in data from trials with low risk of bias, nor in the all trials estimates.

We could not find any clear indication of a dose related effect of gabapentin. A possible explanation may by the fact that higher doses of gabapentin lead to relatively smaller increases in blood concentrations because of the saturable absorption of gabapentin after oral administration.[15-17] This may potentially provide an upper limit to the effect of beneficial outcomes and adverse events. However, none of our results indicated a clear upper limit or difference between subgroups, confirming this hypothesis. The non-linear absorption may be the main reason of the less predictable clinical effect of increased doses, but other explanations also have to be considered.

The analgesic effect of gabapentin is considered to be related to its anti-hyperalgesic properties, as demonstrated for both single and multiple dosing in human volunteer pain models.[149-151] In such models, gabapentin did not affect nociceptive pain per se.[149,150,152] Furthermore, gabapentin demonstrated dose-dependent anti-hyperalgesic effects in rat pain models,[153] which however, has not been investigated in humans. It is therefore unknown if increasing doses of gabapentin display increasing anti-hyperalgesic effects in humans, and it is unknown if such a dose-response relationship is linear. This may contribute significantly to the shortcoming of detecting a dose-response effect in postoperative pain patients. Furthermore, postoperative pain is related to multiple pain mechanisms, of which hyperalgesia is only one. It is, though, unknown how important the hyperalgesic component is for the total sum of experienced pain. This may, in part, also explain the shortcomings of detecting a dose-response relationship for postoperative gabapentin treatment.

The optimal dose for postoperative pain treatment has been investigated in a few original clinical trials.[2-11,147] The study by Van Elstraete and coworkers,[154] found a relatively high median effective analgesic dose of 21.7 mg/kg gabapentin in spinal fusion surgery. Considering this result, it is possible that the investigated

doses in general are too low for analgesic efficacy, although higher doses (> 1200 mg) most likely will produce profound adverse effects.

Most included trials were small in size, and 86% of the trials included less than 50 participants in each group, which can be a limitation. The large number of small sized trials leads to repetitive testing in the cumulative meta-analyses, increasing the risk of random error. Accordingly, we applied TSA to compensate for this limitation. The majority of cumulative subgroup analyses of trials with low risk of bias did not reach firm evidence, or the required information size. This limits any firm evidence and conclusions. In addition, the lack of data may cause a type II error.

The strengths of the present subgroup analyses are related to the primary systematic review that was carried out using Cochrane methodology, and reported according to PRISMA guidelines. All trials were critically assessed using the Cochrane bias evaluation tools, and the risk of random error was assessed using trial sequential analysis, to adjust for sparse data and repetitive testing.

However, there are substantial limitations to our results. The conclusions based on our results are generally weakened by the low number of trials classified as overall low risk of bias, which limits the test for subgroup differences, and pooled estimates in meta-analyses. The few number of trials with low risk of bias means that all trials estimates must be factored into the evaluation, and interpretation of these subgroup analyses. It is well described, that estimates from trials with unclear and high risk of bias have an inherent risk of overestimating beneficial outcomes, and underestimating harmful events, which must be taken into account upon conclusions, and further use in future hypothesis based on these analyses.[148]

Few of the included trials reported serious adverse events, and most of the trials exhibited a short follow-up period, further limiting the analyses exploring the risks of gabapentin treatment.[21]

Further, the present review consists of post-hoc analyses, which limit the reliability of the results. The subgroups of our analyses must be interpreted as observational studies, with the inherent limitations of such studies: Confounding by other study characteristics may bias the analyses.

Our post-hoc analysis was meant to explore the dose-effect of gabapentin in published randomized clinical trials, since no previously published systematic review has been published on the topic. Based on the combined analyses, we cannot recommend a specific dose or regimen, if any, for perioperative gabapentin treatment. We hope, that our analyses may inspire the hypotheses of future trials.

CONCLUSION

Data were sparse in all subgroups, and the small number of trials with low risk of bias is a major limitation for firm conclusions. Taking these limitations into account, we were not able to demonstrate a clear relationship between dosage of gabapentin, and opioid-sparing or harmful effects. Numerically, most SAE´s were reported in the higher dosing groups, and trials with low risk of bias reported the most SAE´s. The present subgroup analyses are exploratory, and hypothesis generating for future trialists.

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Ethics statement

Not relevant.

Dual Publication

These are post-hoc subgroup analyses from a systematic review with meta-analyses and trial sequential analyses: Fabritius ML, Geisler A, Hansen MS, Nikolajsen L, Hamunen K, Kontinen V, Wetterslev J, Dahl JB, Mathiesen O. Gabapentin for post-operative pain management - a systematic review with meta-analyses and trial sequential analyses. Acta Anaesthesiol Scand 2016; 60: 1188-208.

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TABLE 1: The estimates on primary outcomes from trials with low risk of bias and from all trials despite risk of bias

Surgical procedure	**Dose 0-350 mg**		**Dose 351-700 mg**		**701-1050 mg**		**>1050 mg**	
Outcomes	Reduction (mg) MD or Peto's OR *(Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	Reduction (mg) MD or Peto's OR *(Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	Reduction (mg) MD or Peto's OR *(Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	Reduction (mg) MD or Peto's OR *(Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*
BENEFICIAL OUTCOMES								
24-hour morphine consumption *Trials with low risk of bias*	**2.2 mg** (0.1, 4.4; p= 0.04; 2 trials; 111 participants; TSA adj. CI: .0.1, 4.6; 191%)	P = 0.69	**3.4 mg** (0.9, 7.7; p=0.12; 7 trials; 700 participants; TSA adj. CI: -3.3, 11.6; 44%)	P = 0.33	**- 1.1 mg** (-0.3, -2.0; p=0.01; 2 trials; 181 participants; TSA adj. CI: 0.3, 2.0; 329%)	P = 0.002	**2.9 mg** (1.1, 6.9; p=0.2; 4 trials; 326 participants; TSA adj. CI: -1.4, 5.6; 89.6%)	P = 0.9
24-hour morphine consumption *All trials*	**8.0 mg** (6.2, 9.8; p<0.00001; 11 trials; 1070 participants; TSA adj. CI: 6.2, 9.8; 263.5%)	P = 0.25	**4.6 mg** (3.1 6.1; p<0.0001; 20 trials; 1811 participants; TSA adj. CI: 3.1, 6.1; 389%)	P = 0.004	**2.6 mg** (-1.4, 6.6; p=0.2; 7 trials; 375 participants; TSA adj. CI: -2.9, 8.2; 57.5%)	P = 0.03	**9.0 mg** (7.1, 10.9; p<0.00001; 27 trials, 1595 participants; TSA adj. CI: 7.2, 11; 245.6%)	P = 0.02
HARMFUL OUTCOMES								
Serious adverse events *Trials with low risk of bias*	**Not estimable** (2 trials, 113 participants)	-	**0.9** (0.2, 3.4; P= 0.85; 4 trials; 404 participants; TSA adj. CI: 0.0, 220.8; 18.1%)	P = 0.44	**0.6** (0.04, 8.6; p = 0.70; 1 trial; 121 patients; TSA adj. -)	P = 0.52	**2.0** (0.9, 4.5; p=0.1; 3 trials; 287 participants; TSA adj. CI: 0.1, 40.0; 17.8%)	P = 0.29
Serious adverse events *All trials*	**Not estimable** (3 trials, 179 participants)	-	**0.9** (0.2, 3.4; P= 0.85; 8 trials; 682 participants TSA adj. CI: 0.1, 11.7; 22.9%)	P = 0.44	**0.6** (0.04, 8.6; p=0.70; 3 trials; 221 participants; TSA adj. CI: <5%)	0.52	**1.3** (0.8, 2.4; p=0.33; 13 trials; 876 participants; TSA adj. CI: 0.6, 3.6; 44.4%)	P = 0.29

REM: Random Effects Model; FEM: Fixed Effects Model; RR: Risk Ratio; Peto's OR; Peto's Odds Ratio; TSA adj. CI: Trial Sequential Analysis adjusted Confidence Interval

TABLE 2: The Beneficial secondary outcomes from trials with low risk of bias and all trials

BENEFICIAL OUTCOMES	**0-350 mg**		**351-700 mg**		**701-1050 mg**		**> 1050 mg**	
	Reduction (mm) MD *Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	Reduction (mm) MD *Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	Reduction (mm) MD *Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	Reduction (mm) MD *Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*
6-h VAS at rest *Low risk of bias*	**6.4 mm** (-1.9, 11.0; p = 0.006; 2 trial; 111 participants; TSA adj. CI: -5.8, 11.4; 73%)	P = 0.98	**13.2 mm** (-1.1, 27.6; p = 0.07; 3 trials; 289 participants; TSA adj. CI: -28.5, 55.0; 17.8%)	P = 0.23	-	-	**5.6 mm** (0.5, 10.7; p = 0.03; 3 trials; 206 participants; TSA adj. CI: -0.8, 11.9; 141%)	P = 0.20
6-h VAS at rest *All trials*	**13.7 mm** (7.1, 20.0; p < 0.0001; 10 trials; 740 participants; TSA adj. CI: 7.1, 20.0; 83.7%)	P = 0.53	**15.3 mm** (10.7, 20.0; p < 0.00001; 18 trials; 1275 participants; TSA adj. CI: 10.7, 20.0; 175%)	P = 0.05	**6.0 mm** (2.7, 9.3; p = 0.0003; 7 trials; 294 participants; TSA adj. CI: 0.9, 11.1; 330%)	P = 0.006	**9.4 mm** (5.6, 13.3; p < 0.00001; 27 trials; 1519 participants; TSA adj. CI: 5.6, 13.3; 241.1%)	P = 0.19
6-h VAS at mobilization *Low risk of bias*	**11 mm** (5.7, 16.3; p < 0.00001; 1 trial; 63 participants; TSA adj. CI -)	-	**12.4 mm** (8.0; 16.8 p <0.0001; 3 trials; 227 participants; TSA adj. CI: 8.0, 16.1; 258%)	P = 0.16	-	-	**3.8 mm** (-7.9, 15.4; p=0.53; 3 trials; 206 participants; TSA adj. CI: -21.1, 28.6; 26.8%)	P = 0.19
6-h VAS at mobilization *All trials*	**11.1 mm** (5.8, 16.4; p < 0.0001; 2 trials; 95 participants; TSA adj. CI: -13.1, 19.7; 130.1%)	P = 0.30	**10.2 mm** (5.7, 14.7; p < 0.0001; 6 trials; 438 participants; TSA adj. CI: 5.1, 15.3; 176.6%)	P = 0.24	**6.1 mm** (-3.9, 16.2; p = 0.23; 3 trials; 121 participants; TSA adj. CI: -12.2; 24.4; 36.1%)	P = 0.67	**6.3 mm** (3.1, 9.6; p = 0.0001; 15 trials; 898 participants; TSA adj. CI: 3.1, 9.6; 342.7%)	P = 0.16
24-h VAS at rest *Low risk of bias*	**0.6 mm** (-3.0, 4.2; p = 0.75; 2 trials; 107 participants; TSA adj. CI: -)	P = 0.02	**3.9 mm** (-0.1, 7.9; p = 0.05; 5 trials; 526 participants; TSA adj. CI: -0.1, 7.9; 268%)	P = 0.005	-	-	**1.8 mm** (-3.4, 7.0; p = 0.51; 4 trials; 331 participants; TSA adj. CI: -3.7; 7.2%)	P = 0.21
24-h VAS at rest *All trials*	**7.3 mm** (1.7, 12.8; p = 0.01; 13 trials; 806 participants; TSA adj. CI: 1.7, 12.8; 115.9%)	P = 0.77	**8.9 mm** (4.8, 12.9; p < 0.0001; 15 trials; 1315 participants; TSA adj. CI: 4.8, 12.9; 224.8%)	P = 0.19	**2.2 mm** (-1.1, 5.6; p = 0.19; 7 trials; 255 participants; TSA adj. CI: -1.7, 6.2; 318.8%)	P = 0.02	**6.1 mm** (2.5, 9.7; p = 0.0009; 27 trials; 1493 participants; TSA adj. CI: 2.5, 9.7; 280.6%)	P = 0.23
24-h VAS at mobilization *Low risk of bias*	**-2.0 mm** (7.2, 11.2; p = 0.67; 1 trial, 63 participants; TSA adj. CI:	-	**5.9 mm** (-0.9, 12.8; p = 0.09; 5 trials; 526 participants; TSA adj.	P = 0.16	**-1.0 mm** (-3.3, 5.3; p= 0.65; 1 trial; 121 participants; TSA adj.	-	**0.8 mm** (-2.9, 4.5; p = 0.67; 4 trials; 326 participants; TSA adj.	P = 0.39

	-)		CI: -2.4, 14.3; 74%)		CI: -)		CI: -2.7, 4.3; 300%)	
24-h VAS at mobilization *All trials*	**-1.0 mm** (-7.9, 9.8; p = 0.8; 2 trial; 95 participants; TSA adj. CI: -13.1, 15.0; 46.1%)	P = 0.27	**2.5 mm** (-6.4, 11.4; p = 0.58; 9 trials; 843 participants; TSA adj. CI: -17.4, 11.3; 17.4; 45.1%)	P = 0.59	**5.1 mm** (-5.4, 15.5; p = 0.34; 2 trial; 141 participants; TSA adj. CI: -14.6, 24.8; 33%)	P = 0.92	**5.9 mm** (-1.5, 10.3; p = 0.009; 15 trials; 922 participants; TSA adj. CI: -3.6, 10.9; 87.0%)	P = 0.52

REM: Random Effects Model; FEM: Fixed Effects Model; RR: Risk Ratio; Peto's OR; Peto's Odds Ratio; TSA adj. CI: Trial Sequential Analysis adjusted Confidence Interval

TABLE 3: The harmful secondary outcomes from trials with low risk of bias and all trials

HARMFULL OUTCOMES	0-350 mg		351-700 mg		701-1050 mg		> 1050 mg	
	RR *Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	RR *Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	RR *Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*	RR *Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)*	Test for subgroup difference *P-value*
Nausea *Low risk of bias*	-	-	**0.8** (0.4, 1.6; p = 0.54; 3 trials; 218 participants; TSA adj. CI: 1.9, 15.6; 72.9%)	P = 0.66	-	-	**0.7** (0.5, 0.9; p =0.02; 2 trials; 180 participants; TSA adj. CI: 0.1, 1.2; 33.7%)	P = 0.66
Nausea *All trials*	**0.9** (0.7, 1.1; p = 0.16; 9 trials; 633 participants; TSA adj. CI: 0.7, 1.1; 70.6%)	P = 0.42	**0.8** (0.6, 1.1; p = 0.10; 15 trials; 1019 participants; TSA adj. CI: 0.5, 1.3; 40.0%)	P = 0.82	**0.8** (0.5, 1.4; p = 0.51; 4 trials; 271 participants; TSA adj. CI: 0.1, 7.2; 12.8%)	P = 0.91	**0.8** (0.6, 0.9; p = 0.003; 21 trials; 1203 participants; TSA adj. CI: 0.3, 1.8; 50.4%)	P = 0.47
Vomiting *Low risk of bias*	-	-	**2.0** (0.5, 7.3; p = 0.3; 1 trial; 46 participants; TSA adj. CI: -)	-	-	-	**1.0** (0.7, 1.6; p = 0.85; 2 trials, 180 participants; TSA adj. CI: 0.2, 5.9; 16.5%)	P = 0.36
Vomiting *All trials*	**0.8** (0.6, 1.2; p = 0.26; 9 trials; 538 participants; TSA adj. CI: 04, 1.7; 29.2%)	P = 0.82	**0.7** (0.5, 0.9; p = 0.007; 14 trials; 948 participants; TSA adj. CI: 0.4, 1.1; 54.8%)	P = 0.17	**0.7** (0.1, 3.7; p = 0.64; 2 trials; 111 participants; TSA adj. CI: 0.1. 7.2; 12.8%)	P = 0.85	**0.8** (0.7, 1.1; p = 0.002; 19 trials; 1188 participants; TSA adj. CI: 0.1, 6.1; 71.4%)	P = 0.33
Sedation *Low risk of bias*	**1.2** (0.8, 1.6; p = 0.4; 2 trials; 107 participants; TSA adj. CI: 0.3, 4.2; 15.2%)	P = 0.79	**1.0** (0.9, 1.3; p 0 =0.69; 4 trials; 385 participants; TSA adj. CI: 0.4, 1.1; 54.8%)	P = 0.35	**0.8** (0.4, 1.6; p = 0.59; 1 trial; 60 participants; TSA adj. CI: -)	-	**1.6** (1.0, 2.5; p = 0.05; 2 trials; 180 participants; TSA adj. CI: 0.2, 9.9; 12.4%)	P = 0.10
Sedation *All trials*	**2.5** (0.9, 7.1; p = 0.08; 8 trials; 734 participants; TSA adj. CI: < 5%)	P = 0.13	1.0 (0.8, 1.2; p = 0.97; 15 trials; 1317 participants; TSA adj. CI: 0.8, 1.2; 98.7%)	P = 0.009	**1.9** (0.4, 8.7; p = 0.43; 4 trials; 240 participants; TSA adj. CI: < 5%)	P = 0.67	**1.3** (1.0, 1.6; p = 0.02; 15 trials; 942 participants; TSA adj. CI: 0.9, 1.9; 41.7%)	P = 0.94
Dizziness *Low risk of bias*	**1.2** (0.6, 2.5; p = 0.57; 2 trials; 107 participants; TSA adj. CI: 0.1, 26.5; 5.8%)	P = 0.64	**1.0** (0.7, 1.3; p = 0.77; 3 trials; 341 participants; TSA adj. CI: 0.5, 1.8; 28.9%)	P = 0.37	**8.0** (1.1, 60.1; p = 0.04; 1 trial; 60 participants; TSA adj. CI: -)	-	**1.0** (0.9, 1.3; p = 0.68; 3 trials; 239 participants; TSA adj. CI: 0.7, 1.7; 21.9%)	P = 0.95

Dizziness *All trials*	**0.8** (0.5, 1.3; p = 0.45; 12 trials; 1209 participants; TSA adj. CI: 0.2, 4.4; 14.6%)	P = 0.34	**1.0** (0.8, 1.2; p = 0.89; 13 trials; 1101 participants; TSA adj. CI: 0.7, 1.3; 64.8%)	P = 0.36	**3.0** (0.8, 11.2; p = 0.10; 6 trials; 312 participants; TSA adj. CI: <5%)	P = 0.11	**1.2** (1.0, 1.5; p = 0.11; 21 trials; 1400 participants; TSA adj. CI: 0.9, 1.2; 87.2%)	P = 0.20

REM: Random Effects Model; FEM: Fixed Effects Model; RR: Risk Ratio; Peto's OR; Peto's Odds Ratio; TSA adj. CI: Trial Sequential Analysis adjusted Confidence Interval

FIGURE 1 Bias graph

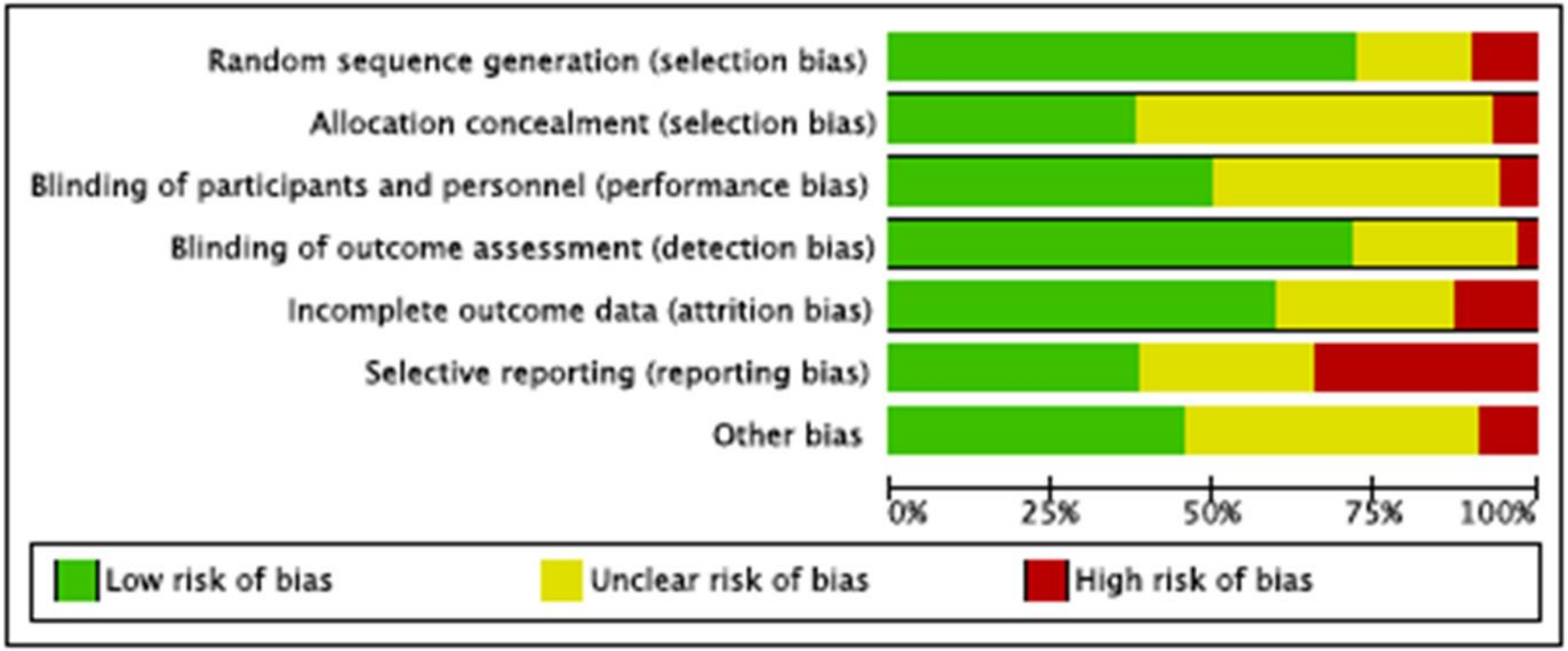
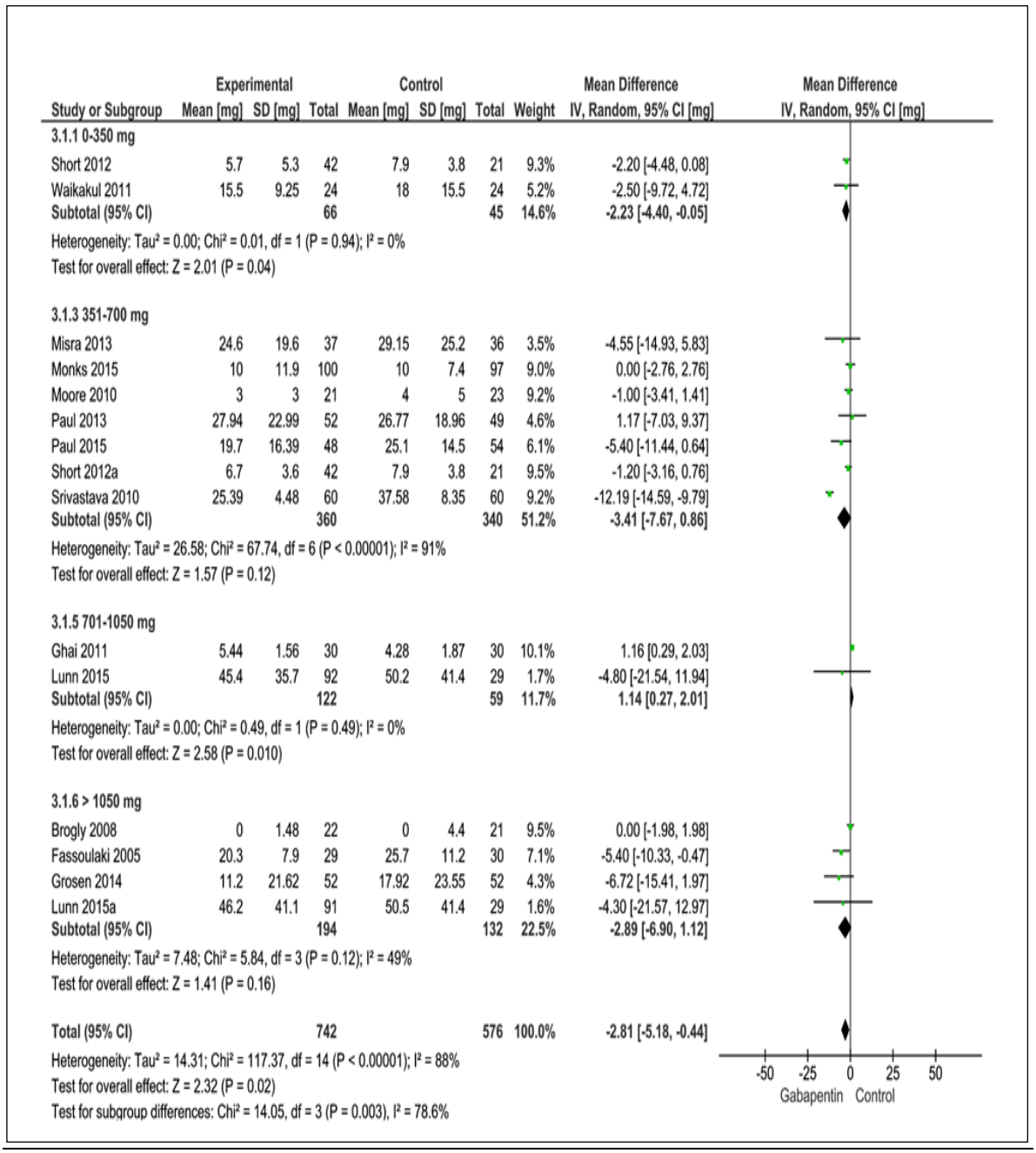
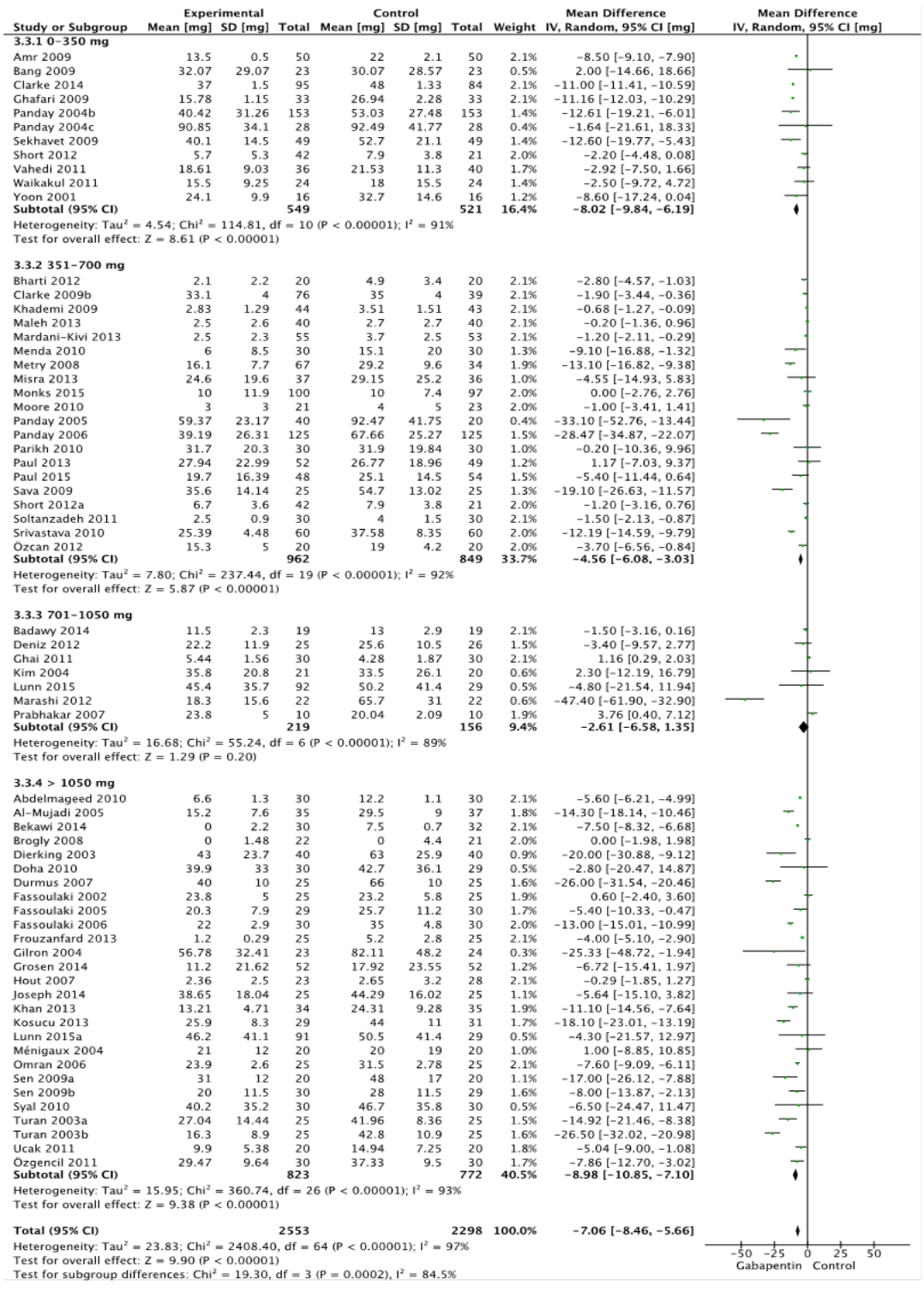


FIGURE 2 Forest plot of 24-hour morphine consumption



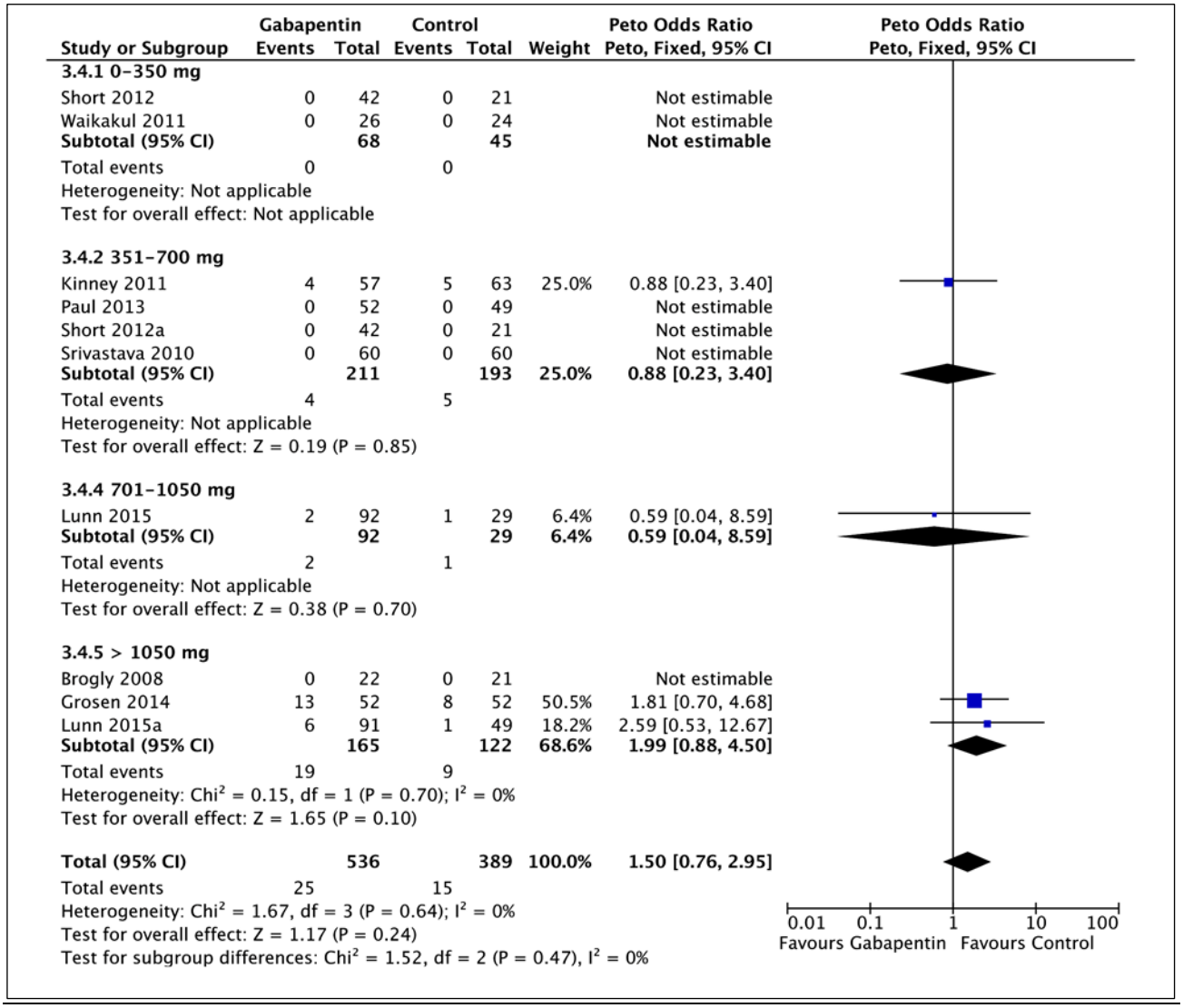
Forest plot of 24-hour morphine consumption from trials with overall low risk of bias

FIGURE 3 Forest plot of 24-hour morphine consumption



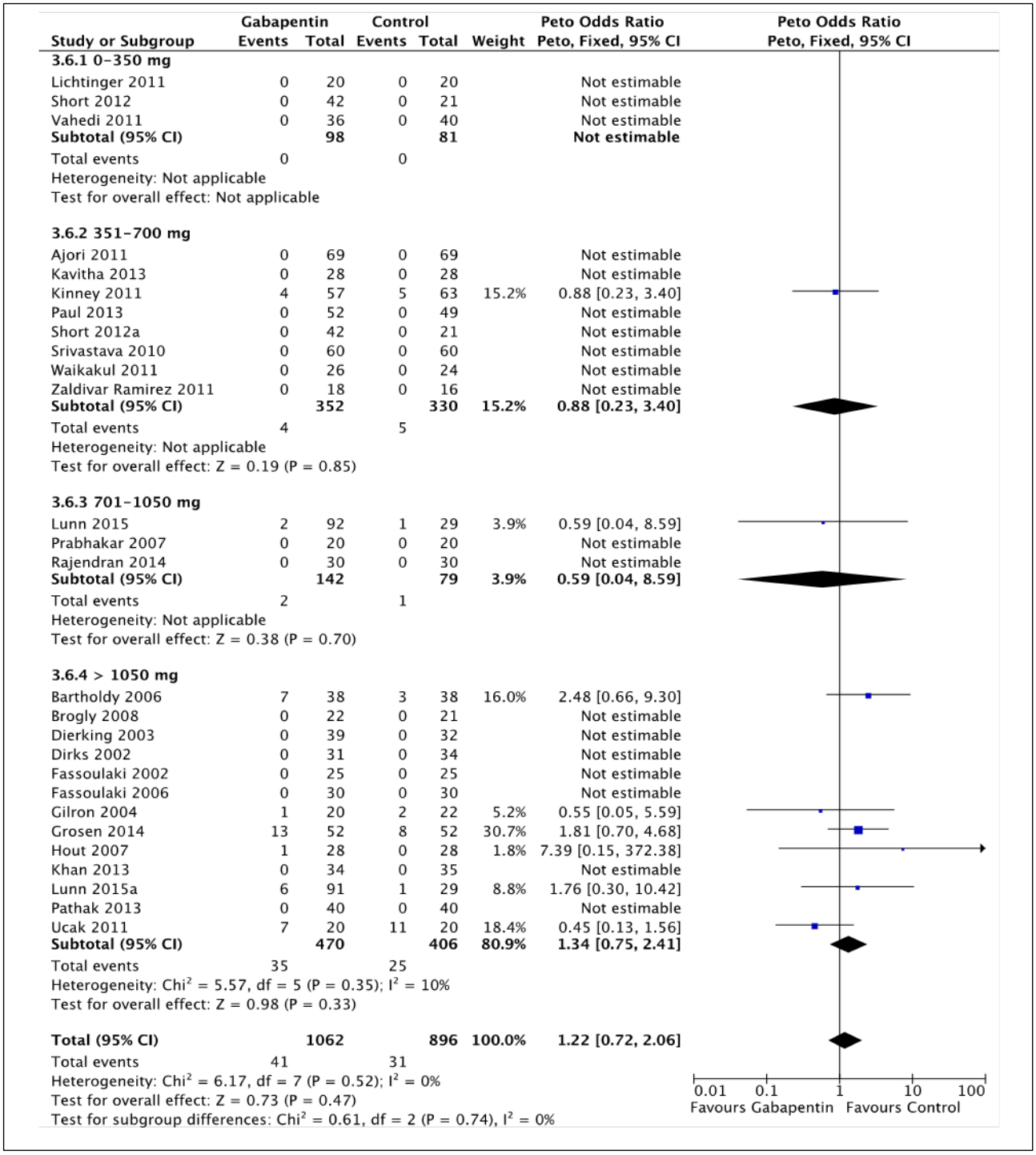
Forest plot of 24-hour morphine consumption from all trials estimates regardless of bias evaluations

FIGURE 4 Forest plot of SAE



Forest plot of the odds of serious adverse events from trials with overall low risk of bias.

FIGURE 5 Forest plot of SAE



Forest plot of the odds of serious adverse events from all trials estimates regardless of bias evaluations

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APPENDIX PAPER III

Appendix 1 Search strategies

See search strategy from paper I

Appendix 2 Opioid conversion

See opioid conversion from paper I.

Appendix 3 Trial characteristics

Trial	No* of patients	Surgical Procedures	Dose *mg/day (bolus mg)*	Treatment *Single / Multiple dose*	Total 24-hour morphine consumption *Intra venous morphine (mg)*	
					Intervention (mg) *(Mean SD)*	**Control (mg)** *(Mean SD)*
Amr 2009[32]	100	Radical or partial mastectomy	300 mg/day (300 mg)	Multiple dose	13.5 (0.5)	22.0 (2.1)
Bang 2009[36]	46	Arthroscopic shoulder surgery	300 mg/day	Single dose	32.1 (29.1)	30.1 (28.67)
Behdad 2012[39]	61	Hysterectomy	300 mg/day (100 mg)	Multiple dose	-	-
Chowdhury 2010[46]	200	Gynecological surgery	300 mg/day	Single dose	-	-
Clarke 2014[48]	179	Total knee arthroplasty	200 mg /day (600 mg)	Multiple dose	37 (1.5)	48 (1.3)
Ghafari 2009[60]	66	Abdominal hysterectomy and salphingooophrectomy	300 mg/day (300 mg)	Multiple dose	15.8 (1.2)	26.9 (2.3)
Hassani 2014[67]	60	Laparoscopic gastric by-pass	100 mg/day	Single dose	-	-
Khurana 2013[77]	60	Lumbar discectomy	300 mg/day (300 mg)	Multiple dose	-	-
Mohammadi 2008[95]	70	Assisted reproductive techniques	300 mg/day	Single dose	-	-
Mohammadi 2009[96]	80	Abdominal surgery/gynecological surgery	300 mg/day	Single dose	-	-
Lichtinger 2011[84]	40	Bilateral photorefractive keratectomy	300 mg/day (600 mg)	Multiple dose	-	-
Pandey 2004c[107]	56	Single level lumbar disc surgery	300 mg/day	Single dose	90.9 (34.1)	92.5 (41.8)
Ray 2015[118]	60	Abdominal hysterectomy	300 mg/day	Single dose	-	-
Sekhavet 2009[123]	98	Abdominal hysterectomy	300 mg /day (600 mg)	Multiple dose	40.1 (14.5)	52.7 (21.1)
Spence 2011[131]	57	Shoulder arthroscopy	300mg/day (300 mg)	Multiple dose	-	-
Vahedi 2011[140]	76	Lumbar laminectomy and discectomy	300 mg/day	Single dose	18.6 (9.0)	21.5 (11.3)
Vasigh 2016[141]	76	Laminectomy	300 mg/day (600 mg)	Multiple dose	-	-
Verma 2008[142]	50	Abdominal hysterectomy	300 mg/day	Single dose	-	-
Waikakul 2011[144]	48	Spine, major joint, tumor and major limb surgery	300 mg/day (400 mg)	Multiple dose	15.5 (9.3)	18 (15.5)
Yoon 2001[145]	32	Hysterectomy	300 mg/day (400 mg)	Multiple dose	24.1 (9.9)	32.7 (14.6)

Ajori 2011[30]	138	Abdominal hysterectomy	600 mg/day	Single dose	-	-
Azemati 2013[33]	100	Mastectomy or quandrandectomy and axillary node dissection	600 mg/day	Single dose	-	-
Bafna 2014[143]	60	Gynecological surgery	600 mg/day	Single dose	-	-
Bashir 2009[38]	100	Laparoscopic cholecystectomy	600 mg/day	Single dose	-	-
Bhandari 2014[41]	40	Laparoscopic cholecystectomy	600 mg/day (600 mg)	Multiple dose	-	-
Bharti 2012[42]	40	Total mastectomy with axillary node dissection	600 mg/day	Single dose	2.1 (2.2)	4.9 (3.4)
Celebi 2013[45]	60	Gynecological laparoscopy	600 mg/day	Single dose	-	-
Clarke 2009b[147]	115	Total hip arthroplasty	600 mg/day	Single dose	37.0 (1.5)	48 (1.3)
Ercan 2014[54]	34	Carotid Endartectomy	600 mg/day	Single dose	-	-
Gosai 2015[64]	60	Mastectomy	600 mg/day	Single dose	-	-
Grover 2009[66]	46	Total mastectomy with axillary node dissection	600 mg/day	Single dose	-	-
Hoseini 2015[68]	44	Cholecystectomy	600 mg/day	Single dose	-	-
Joseph 2014[71]	50	Abdominal hysterectomy	600 mg/day (600 mg)	Multiple dose	38.7 (18.0)	44.3 (16.0)
Kavitha 2013[72]	56	Intraocular surgery/cataract	600 mg/day	Single dose	-	-
Kazak 2009[73]	60	Nasal septal, nasal sinus surgery	600 mg/day	Single dose	-	-
Khademi 2009[74]	87	Open cholecystectomy	600 mg/day	Single dose	2.8 (1.3)	3.5 (1.5)
Khezri 2013[76]	80	Cataract surgery	600 mg/day	Single dose	-	-
Kinney 2011[79]	125	Thoratectomy; lobectomy; pneumonectomy; chest wall resection	600 mg/day	Single dose	-	-
Manhoori 2014[85]	50	Unilateral herniorrhaphy	400 mg/day	Single dose	-	-
Maleh 2013[86]	80	Laparoscopic surgery	600 mg/day	Single dose	2.5 (2.6)	2.7 (2.7) 3.7 (2.5)
Mardani-Kivi 2013[88]	108	Anterior Collateral Ligament reconstruction	600 mg/day	Single dose	2.5 (2.3)	
Menda 2010[89]	60	Coronary Artery Bypass Graft	600 mg/day	Single dose	6.0 (8.5)	15.1 (20)
Metry 2008[91]	68	Unilateral radical mastectomy and axillary dissection	600 mg/day (1200 mg)	Single dose	16.1 (7.7)	29.2 (9.6)
Misra 2013[94]	73	Craniotomy for intracranial tumor	600 mg/day	Single dose	24.6 (19.6)	29.2 (25.2)
Monks 2015[98]	197	Cesarean section	600 mg/day (600 mg)	Multiple dose	10.0 (11.9)	10.0 (7.4)
Moore 2010[99]	44	Cesarean section	600 mg/day	Single dose	3.0 (3.0)	4.0 (5.0)
Özcan 2011[102]	40	Supratentorial tumor surgery	600 mg/day	Single dose	15.0 (5.0)	19.0 (4.2)
Pandey 2005[108]	60	Open donor nephrectomy	600 mg/day	Single dose	59.4 (23.2)	92.5 (41.8)
Pandey 2006[105]	250	Laparoscopic cholecystectomy	600 mg/day	Single dose	39.2 (26.3)	67.7 (25.3)
Parikh 2010[109]	60	Elective surgery	600 mg/day	Single dose	31.7 (20.3)	31.9 (19.8)
Paul 2013[111]	101	Total knee arthroplasty	600 mg/day (200 mg)	Multiple dose	27.9 (23.0)	26.8 (19.0)
Paul 2015[112]	102	Total hip arthroplasty	600 mg/day		19.7 (16.4)	

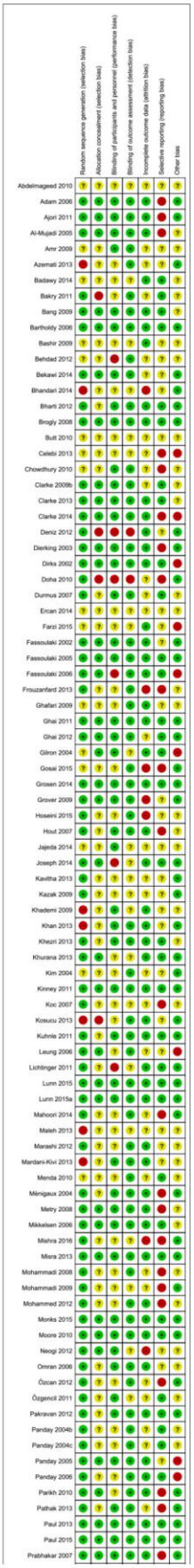
			(600 mg)	Multiple dose		25.1 (14.5)
Saeed 2013[121]	100	Laparoscopic cholecystectomy	600 mg/day	Single dose	-	-
Sava 2009[122]	50	Colorectal surgery	600 mg/day	Single dose	35.6 (14.1)	54.7 (13.0)
Semira 2013[124]	60	Laparoscopic cholecystectomy	600 mg/day	Single dose	-	-
			600 mg/day			
Sharma 2015[127]	40	Laparoscopic cholecystectomy	(600 mg)	Multiple dose	-	-
Short 2012[9]	63	Cecaerean section	300 mg	Single dose	5.7 (5.3)	7.9 (3.8)
Siddiqui 2013[129]	72	Major bowel surgery	600 mg/day	Single dose	-	-
			400 mg/day			
Soltanzadeh 2011[130]	60	Coronary Artery Bypass Grafting	(800 mg)	Multiple dose	2.5 (0.9)	4.0 (1.5)
Srivastava 2009[132]	120	Open cholecystectomy	600 mg/day	Single dose	25.4 (4.5)	37.6 (8.4)
			600 mg/day			
Zaldivar-Ramirez 2011[146]	34	Nissen laparoscopic fund-operation	(300 mg)	Multiple dose	-	-
Adam 2006[29]	53	Arthroscopic shoulder surgery	800 mg/day	Single dose	-	-
Badawy 2014[34]	40	Abdominal hysterectomy	800 mg/day	Single dose	11.5 (2.3)	13.0 (2.9)
Deniz 2012[49]	51	Radical Retropubic Prostatectomy	900 mg/day	Single dose	22.2 (11.9)	25.6 (10.5)
Farzi 2015[55]	103	Septorhinoplasty	900 mg/day	Single dose	-	-
Ghai 2011[61]	60	Abdominal hysterectomy	900 mg/day	Single dose	5.4 (1.6)	4.3 (1.9)
Ghai 2012[62]	60	Abdominal hysterectomy	900 mg/day	Single dose	-	-
			900 mg /day			
Kuhnle 2010[82]	82	PRK Myopia surgery	(300 mg)	Multiple dose	-	-
Kim 2004[78]	41	Mastectomy	900 mg/day	Single dose	35.8 (20.8)	33.5 (26.1)
Koc 2007[80]	40	Varicocele	800 mg/day	Single dose	-	-
			900 mg/day			
Leung 2006[83]	21	Spine surgery	(900 mg)	Multiple dose	-	-
Lunn 2015[5]	140	Total knee arthroplasty	900 mg/day	Multiple dose	45.4 (35.7)	50.5 (41.4)
Marashi 2012[87]	44	Thyroidectomy	900 mg/day	Single dose	18.3 (15.6)	65.7 (31.0)
Mishra 2016[93]	60	Laparoscopic cholecystectomy	900 mg/day	Single dose	-	-
Neogi 2012[100]	60	Laparoscopic cholecystectomy	900 mg/day	Single dose	-	-
			900 mg/day			
Pakravan 2012[104]	100	Post photorefractive keratectomy surgery	(300 mg)	Multiple dose	-	-
Prabhakar 2007[113]	20	Elective brachial plexus exploration	800 mg/day	Single dose	23.8 (5.0)	20.0 (2.1)
			800 mg/day			
Radhakrishnan 2005[114]	30	Lumbar laminectomy or lumbar discectomy	(400 mg)	Multiple dose	-	-
Rajendran 2014[116]	60	Small gastrointestinal procedures	900 mg/day	Single dose	-	-
Ram 2015[115]	60	Abdominal hysterectomy	900 mg/day	Single dose	-	-
Rimaz 2014[119]	60	Dacryocystorhinostomy	900 mg/day	Single dose	-	-
Short 2012a[9]	63	Cesarean section	600 mg	Single dose	6.7 (3.6)	7.9 (3.8)
Abdelmageed 2010[28]	60	Tonsillectomy	1200 mg/day	Single dose	6.6 (1.3)	12.2 (1.1)
Al-Mujadi 2005[31]	72	Elective thyroid surgery	1200 mg/day	Single dose	15.2 (7.6)	29.5 (9)

Bartholdy 2006[37]	76	Sterilization laparoscopic with Filshie clips	1200 mg/day	Single dose	-	-
Bakry 2011[35]	60	Cataract surgery	1200 mg/day	Single dose	-	-
Bekawi 2014[40]	60	Laparoscopic cholecystectomy	1200 mg/day (1200 mg)	Multiple dose	0 (2.2)	7.5 (0.7)
Brogly 2008[43]	43	Total or partial thyroidectomy	1200 mg/day	Single dose	0 (1.48)	0 (4.4)
Butt 2010[44]	100	Mastectomy	1200 mg/day	Single dose	-	-
Clarke 2013[47]	44	General-, gynecological-, plastic and ENT surgery	1200 mg/day	Single dose	-	-
Dierking 2003[50]	80	Abdominal hysterectomy and salphingooophrectomy	2400 mg/day (600 mg)	Multiple dose	43.0 (23.7)	63.0 (25.9)
Dirks 2002[51]	65	Unilateral radical mastectomy with axillary dissection	1200 mg/day	Single dose	-	-
Doha 2010[52]	59	Radical Mastectomy	1200 mg/day	Single dose	39.9 (33.0)	42.7 (36.1)
Durmus 2006[53]	50	Total abdominal hysterectomy	1200 mg/day	Single dose	40.0 (10.0)	66.0 (10.0)
Fassoulaki 2002[57]	50	Radical mastectomy or lobectomy with axillary node dissection	1200 mg/day (1200 mg)	Multiple dose	23.8 (5.0)	23.2 (5.8)
Fassoulaki 2005[58]	59	Abdominal hysterectomy	1600 mg/day 400 mg	Multiple dose	20.3 (7.9)	25.7 (11.2)
Fassoulaki 2006[56]	60	Abdominal hysterectomy	1600 mg/day 800 mg	Multiple dose	22.0 (2.9)	35.0 (4.8)
Frouzanfard 2013[59]	50	Abdominal hysterectomy	1200 mg/day	Single dose	1.2 (0.2)	5.2 (2.8)
Gilron 2004[63]	47	Abdominal hysterectomy	1800 mg/day 600 mg	Multiple dose	56.8 (32.4)	82.1 (48.2)
Grosen 2014[65]	104	Thoracotomy for malignancy	1200 mg/day (1200 mg)	Multiple dose	11.2 (21.6)	17.9 (23.69)
Hout 2007[69]	51	Exploratory thoracotomy, pneumonectomy, lobectomy, segmentectomy, biopsy	1200 mg/day	Single dose	2.4 (2.5)	2.7 (3.2)
Jajeda 2014[70]	50	Upper abdominal surgery	1200 mg/day	Single dose	-	-
Khan 2013[75]	69	Abdominal hysterectomy	1200 mg/day	Single dose	13.1 (4.7)	24.3 (9.3)
Kosucu 2013[81]	60	Posterolateral or lateral thoracotomy	1200 mg/day	Single dose	25.9 (8.3)	44.0 (11.0)
Lunn 2015a[5]	141	Total knee arthroplasty	1300 mg/day	Multiple dose	46.2 (41.0)	50.5 (41.4)
Ménigaux 2004[90]	40	Arthroscopic anterior cruciate ligament	1200 mg/day	Single dose	21.0 (12.0)	20.0 (19.0)
Mikkelsen 2006[92]	51	Tonsillectomy	1800 mg/day (1200 mg)	Multiple dose	-	-
Mohammed 2012[97]	80	Functional endoscopic sinus surgery	1200 mg/day	Single dose	-	-
Omran 2005[101]	50	Posterolateral thoracotomy for lobectomy	1200 mg/day (1200 mg)	Multiple dose	23.9 (2.6)	31.5 (2.8)
Özgenzil 2011[103]	60	Decompressive lumbar laminectomy and discectomy	1800 mg/day 600 mg	Multiple dose	29.5 (9.6)	37.3 (9.5)
Pathak 2014[110]	80	Cholecystectomy	1200 mg/day	Single dose	-	-
Rapchuk 2009[117]	54	Cardiac surgery	1200 mg/day	Single dose	-	-

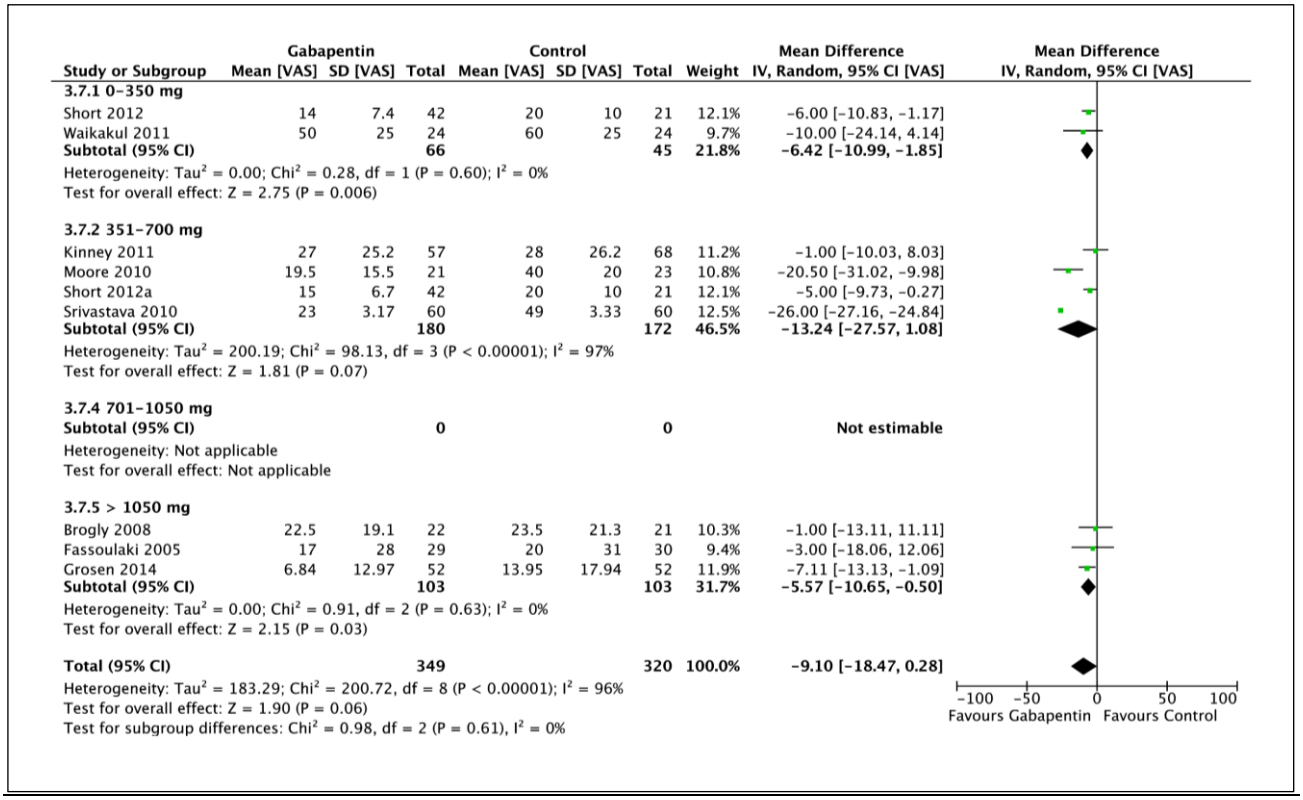
Rorarius 2004[102]	90	Vaginal hysterectomy	1200 mg/day	Single dose	-	-
Sen 2009a[125]	40	Abdominal hysterectomy and salphingooophrectomy	1200 mg/day	Single dose	31.0 (12.0)	48.0 (17.0)
Sen 2009b[126]	59	Unilateral inguinal herniotomy	1200 mg/day	Single dose	20.0 (11.5)	28.0 (11.5)
Sheen 2008[128]	80	Orthopedic surgeries	1200 mg/day	Single dose	-	-
Syal 2010[133]	60	Open cholecystectomy	1200 mg/day	Single dose	40.2 (35.2)	46.7 (35.8)
Tirault 2010[134]	135	Ear-nose and throat-, general-, orthopedic-, and gynecologic surgery	1200 mg/day	Single dose	-	-
Turan 2003a[12]	50	Abdominal hysterectomy and salphingooophrectomy	1200 mg/day	Single dose	27.0 (14.4)	42.0 (8.4)
Turan 2003b[135]	50	Discectomy spinal fusion surgery	1200 mg/day	Single dose	16.3 (8.9)	42.8 (10.9)
Turan 2004[137]	50	Ear Nose and Throat surgery	1200 mg/day	Single dose	-	-
Turan 2005[136]	40	Lower limb surgery	1200 mg/day (1200 mg)	Multiple dose	-	-
Turan 2006[138]	50	Abdominal hysterectomy and salphingooophrectomy	1200 mg/day (1200 mg)	Multiple dose	-	-
Ucak 2011[139]	40	Coronary Artery Bypass Graft	1200 mg/day (1200 mg)	Multiple dose	9.9 (5.4)	14.9 (7.3)

The multiple dose is defined as more than one administration of gabapentin. The mg/day is the dose of gabapentin per day in the treatments that extends one administration.

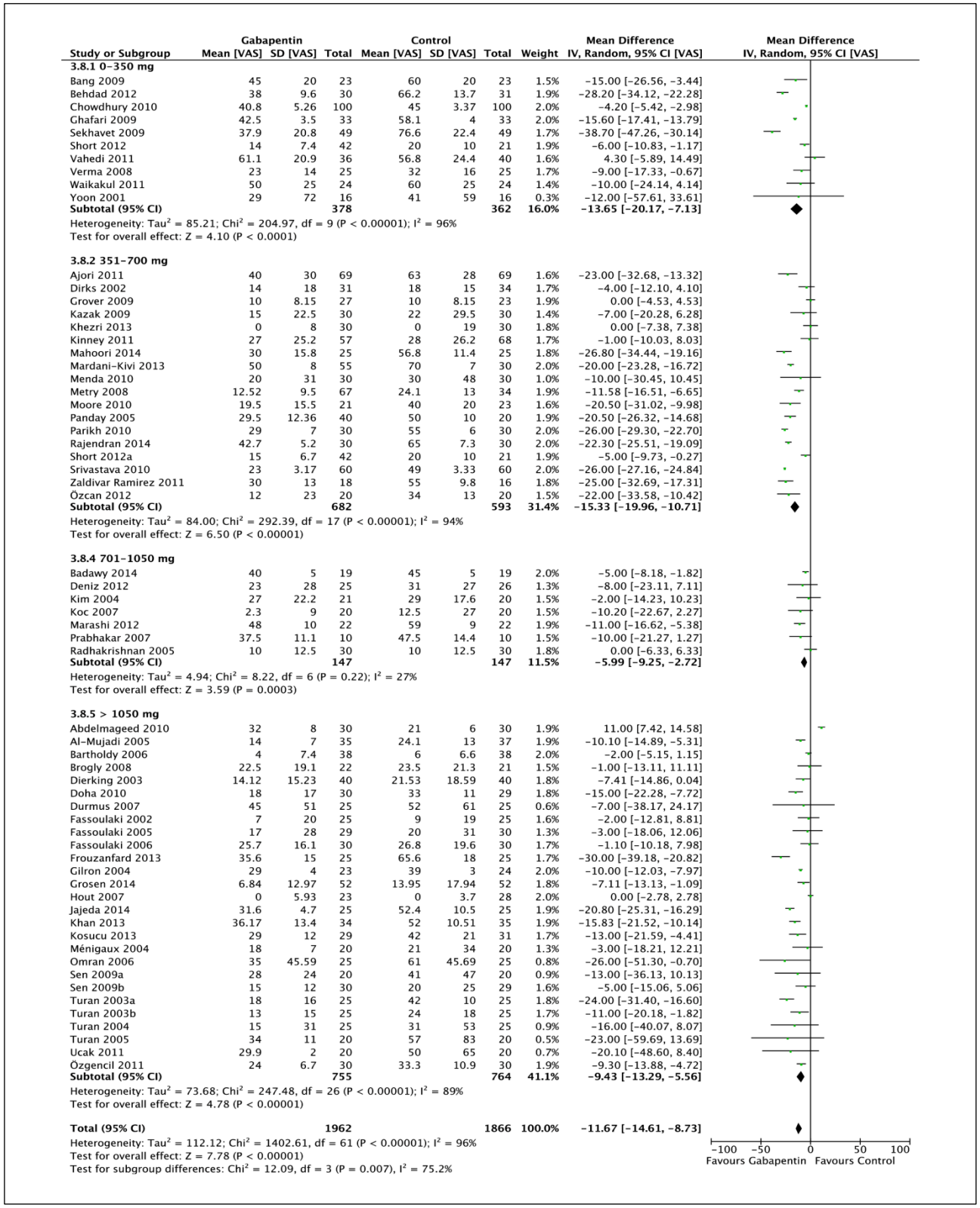
Appendix 4: Bias evaluations



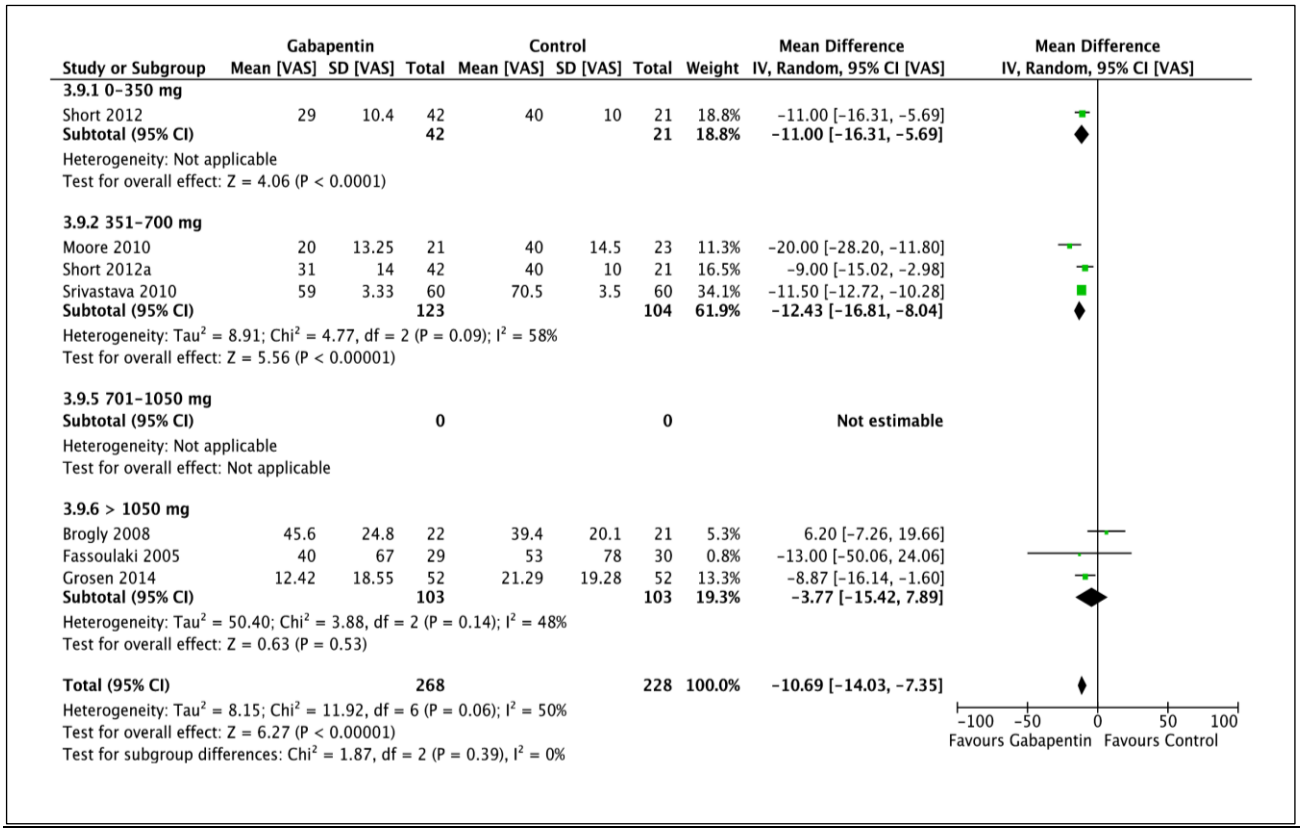
Appendix 5 Forest plot of VAS 6h rest from trials with low risk of bias



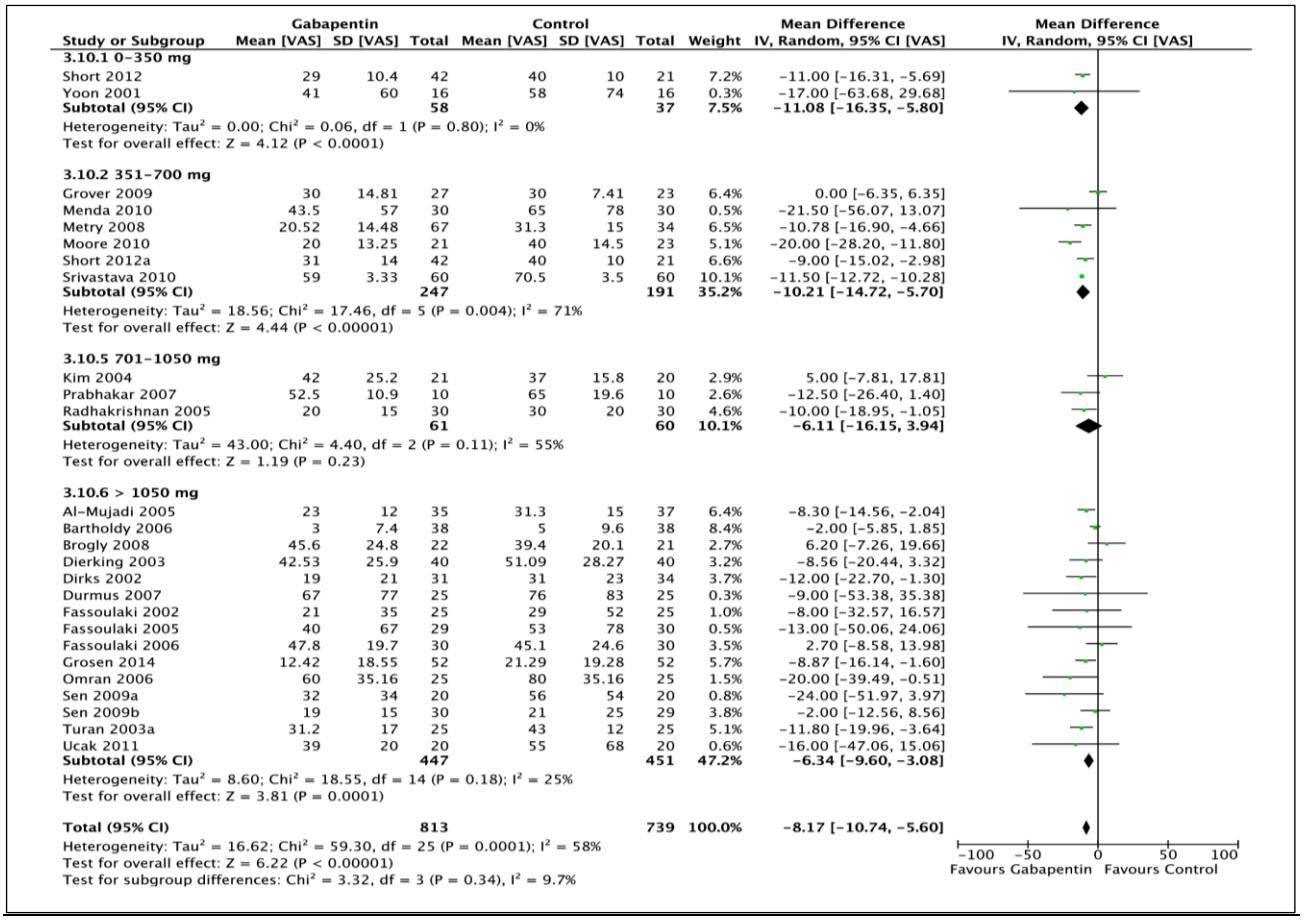
Appendix 6 Forest plot of VAS 6h rest from all trials estimates



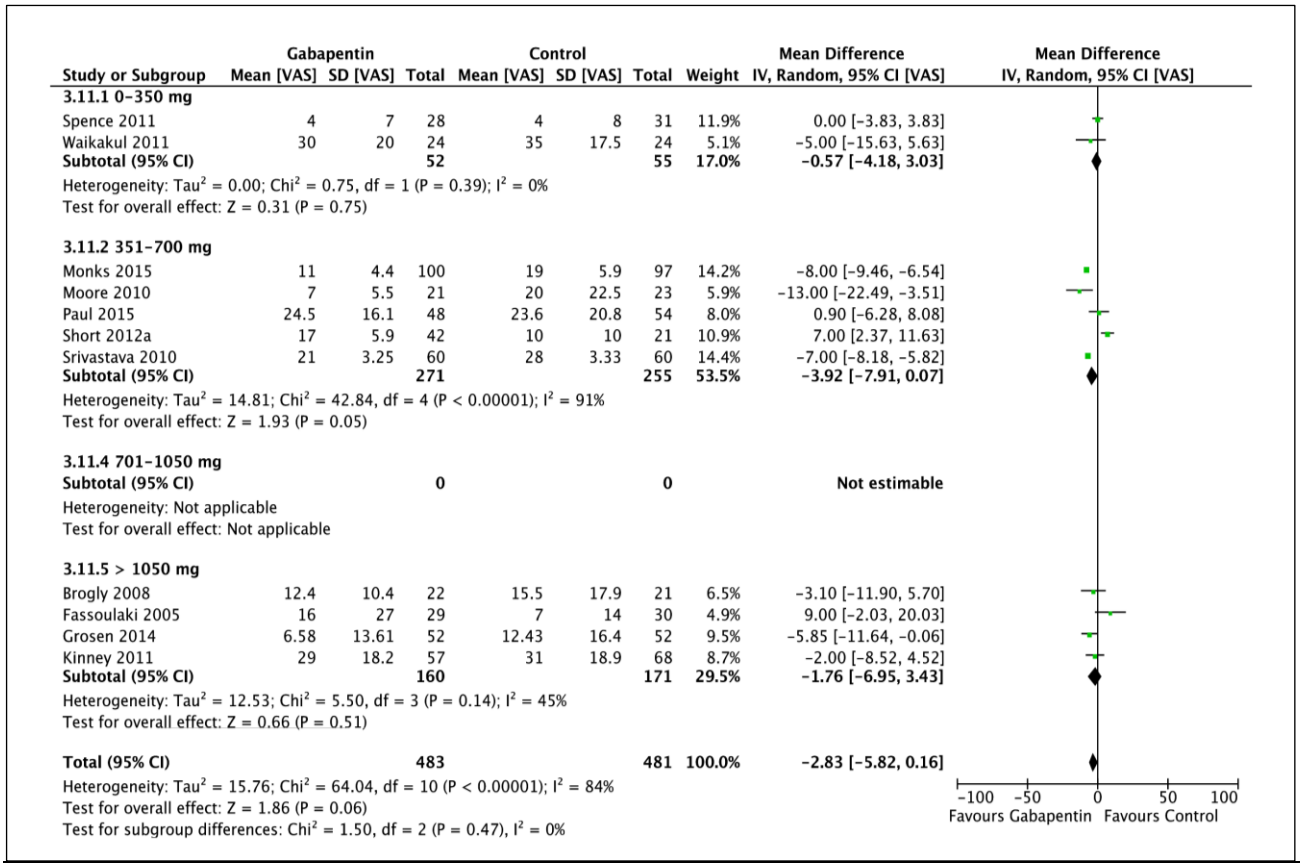
Appendix 7 Forest plot of VAS 6h mobilization from trials with low risk of bias



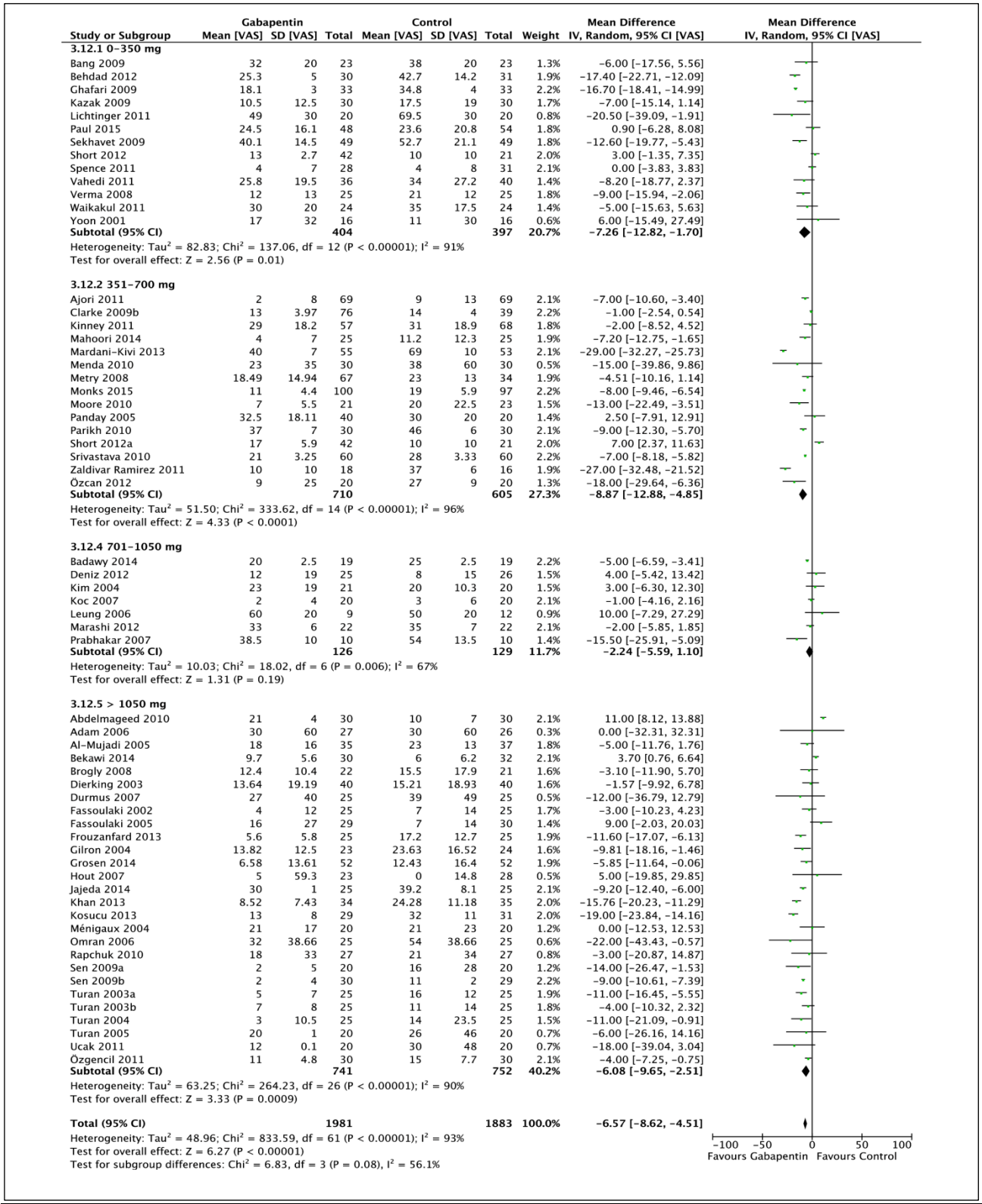
Appendix 8 Forest plot of VAS 6h mobilization from all trials estimates



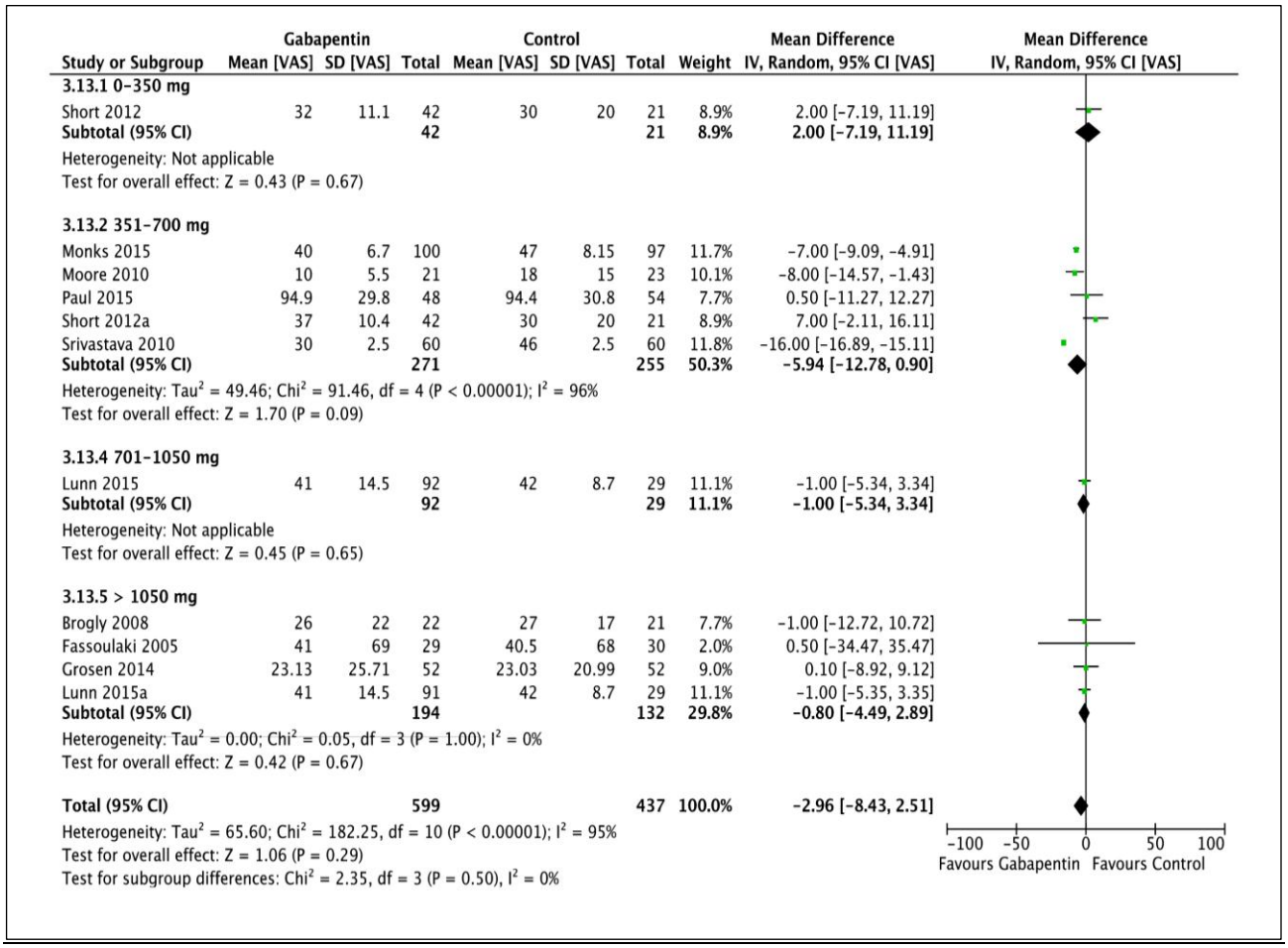
Appendix 9 Forest plot of VAS 24h rest from trials with low risk of bias



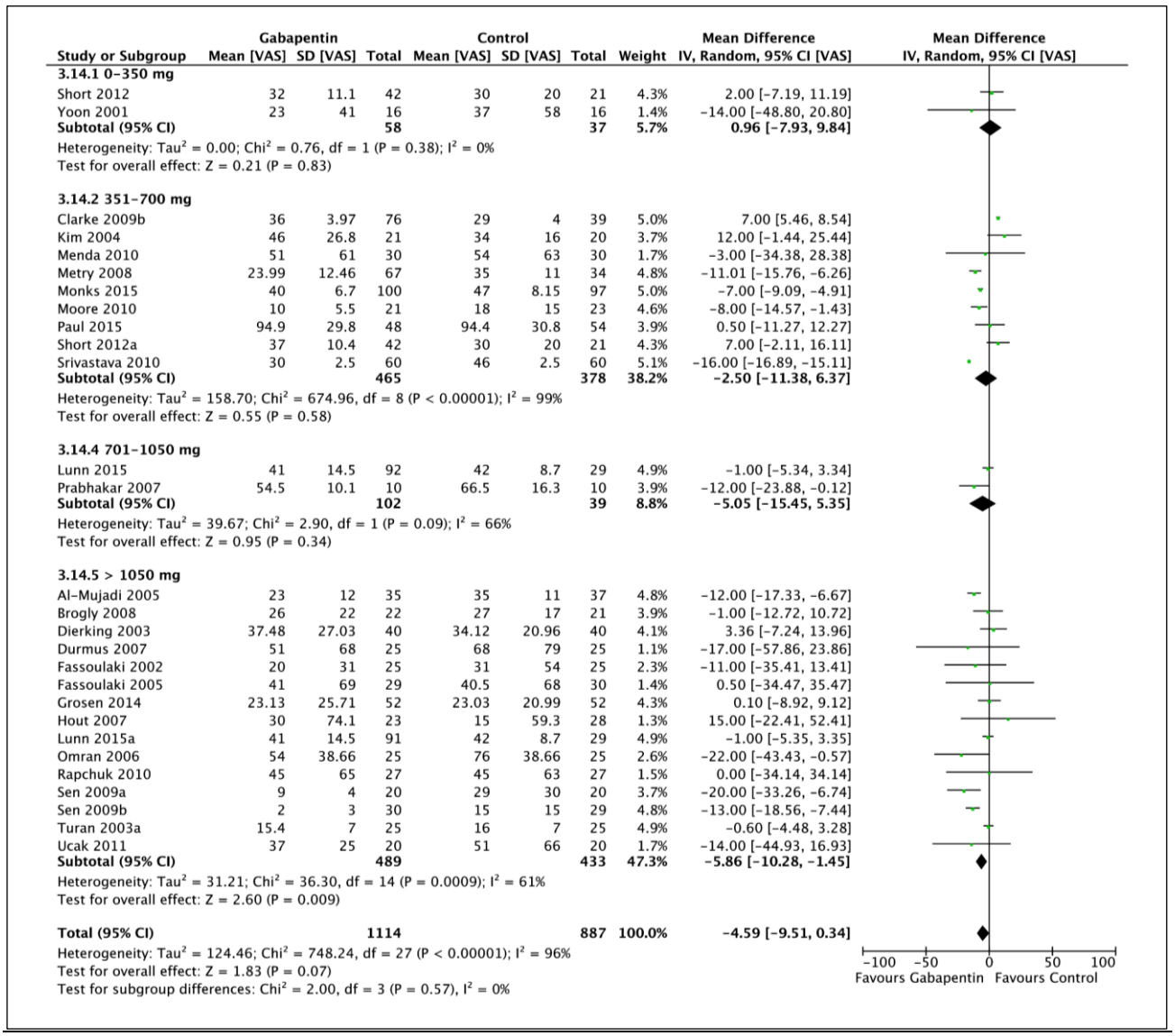
Appendix 10 Forest plot of VAS 24h rest from all trials estimates



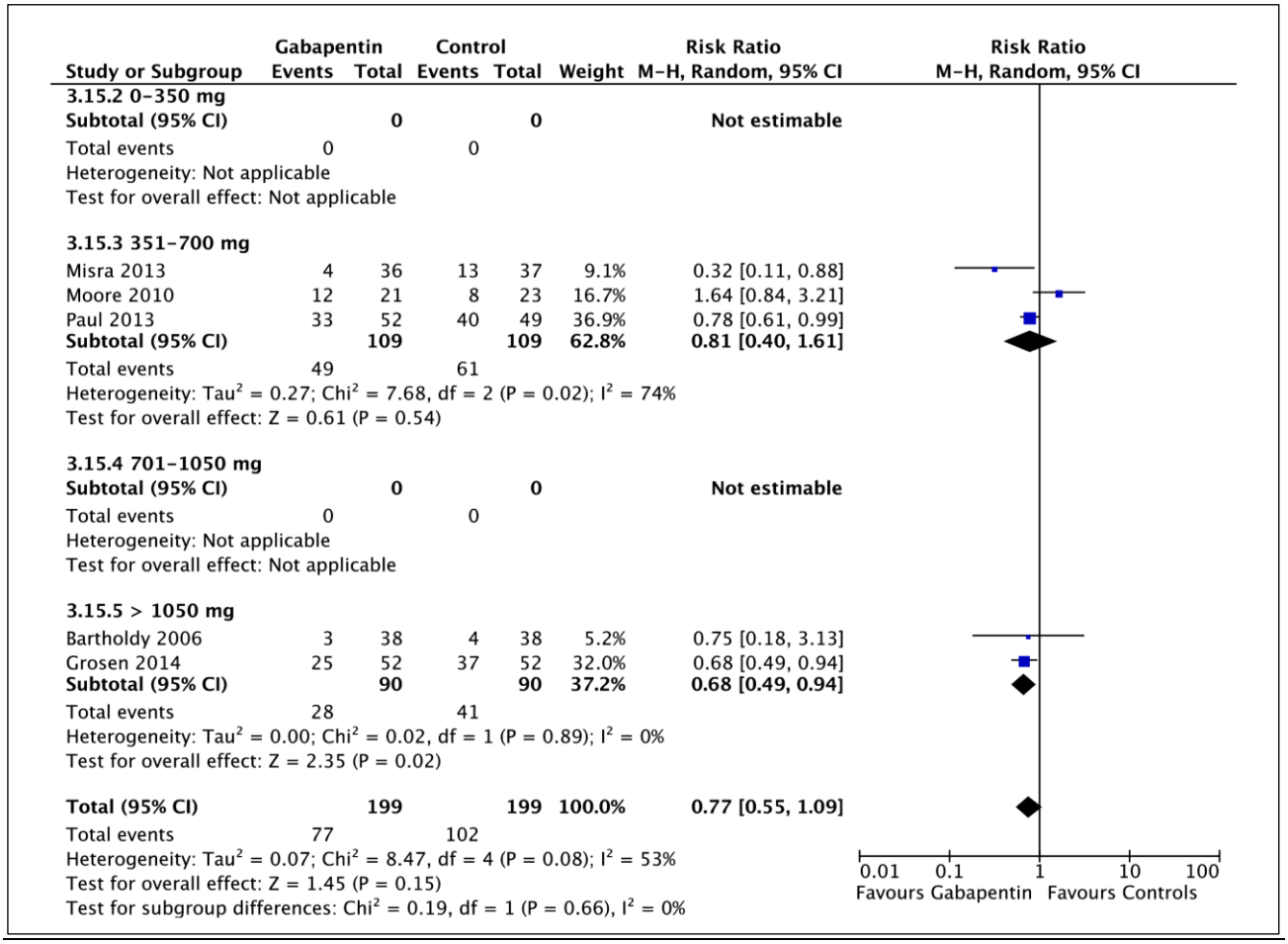
Appendix 11 Forest plot of VAS 24h mobilization from trials with low risk of bias



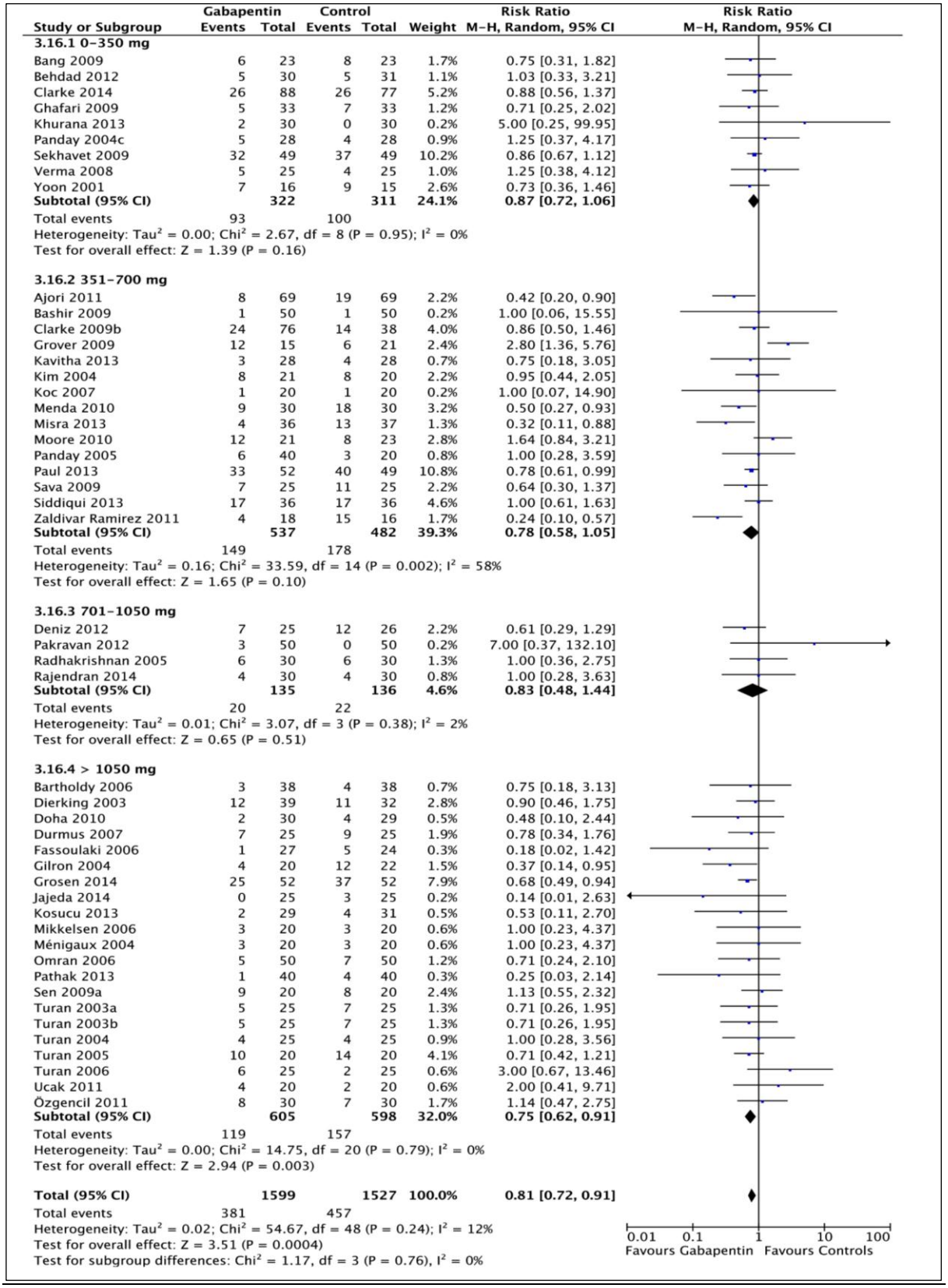
Appendix 12 Forest plot of VAS 24h mobilization from all trials estimates



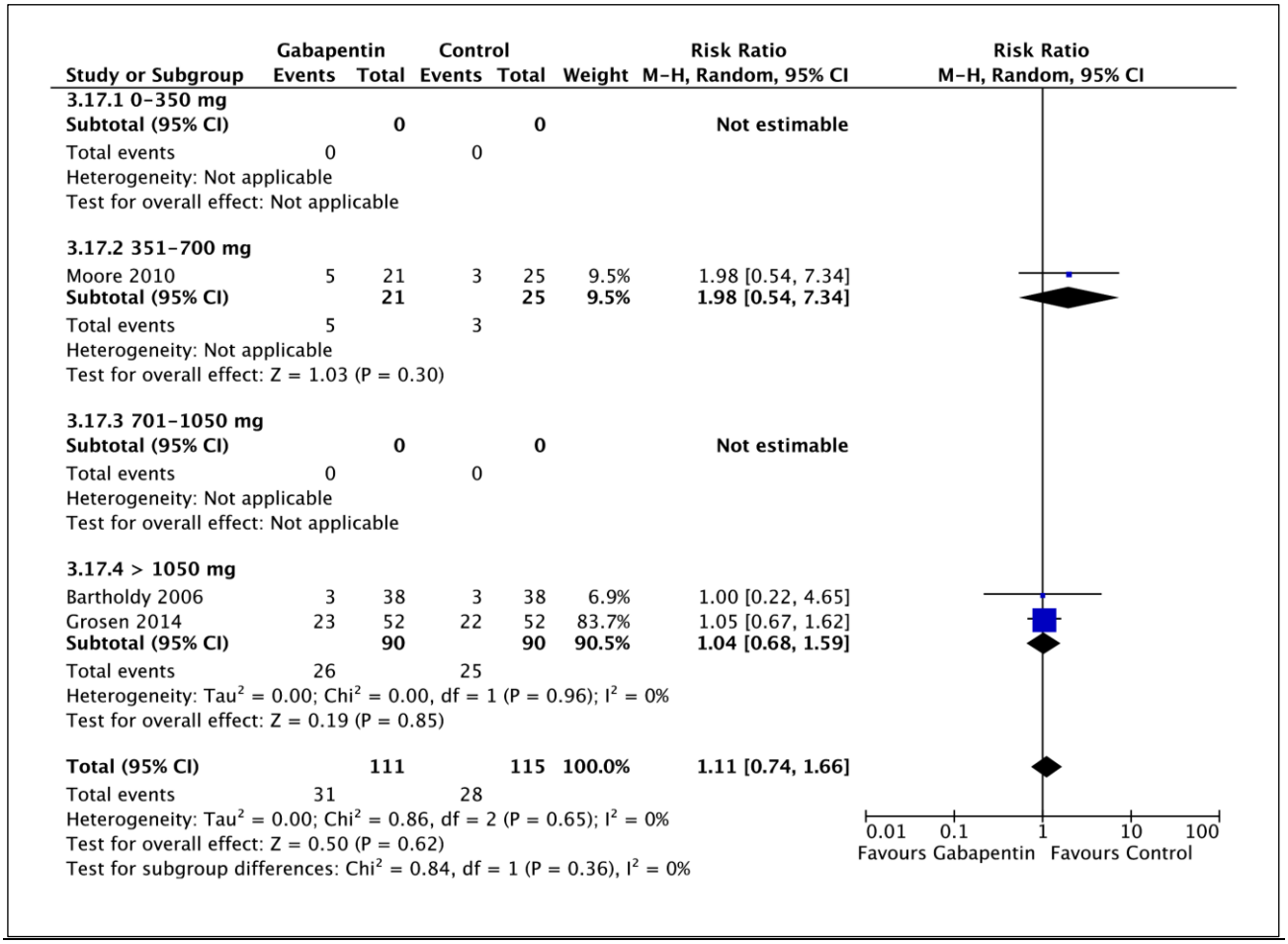
Appendix 13 Forest plot of nausea from trials with low risk of bias



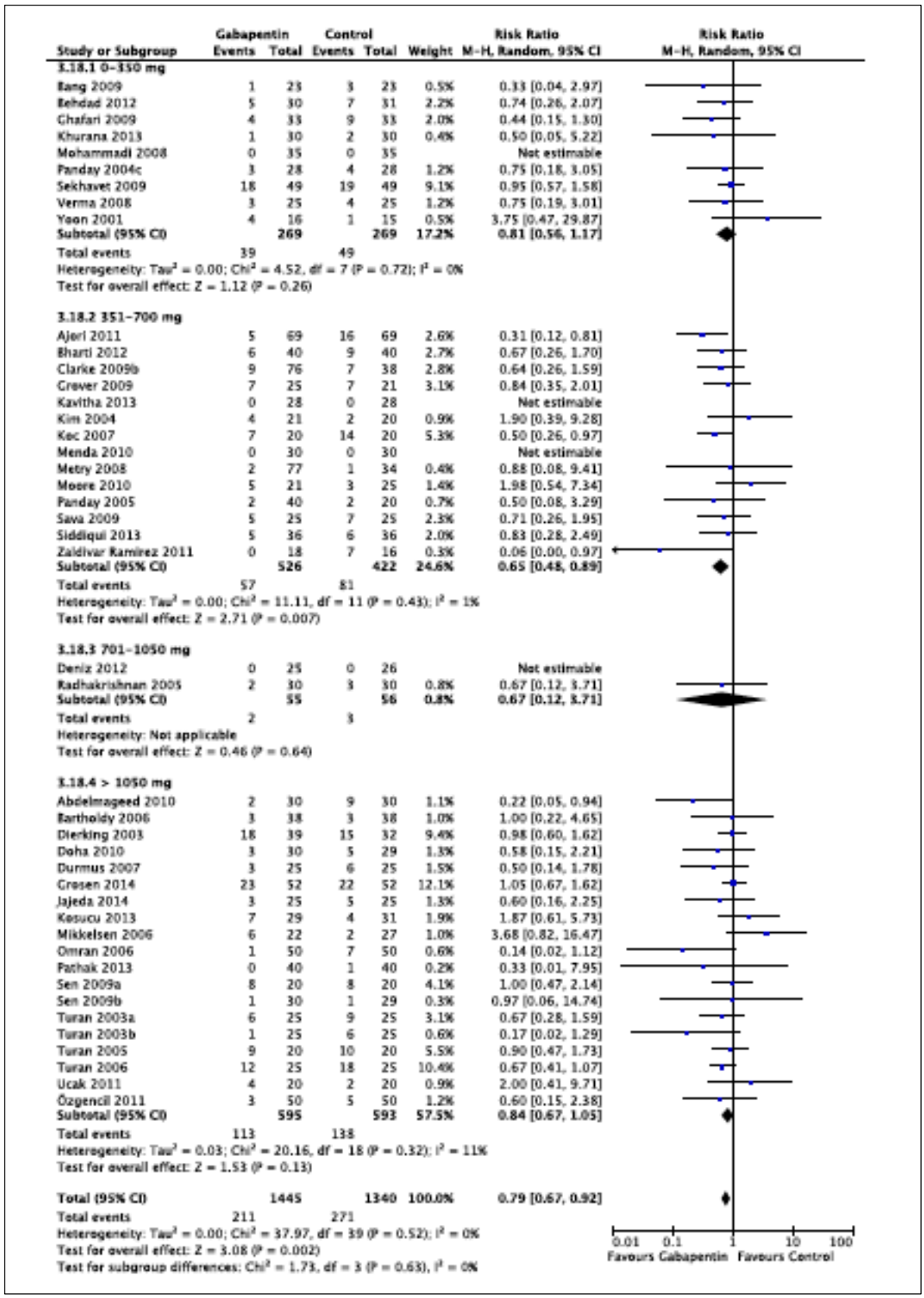
Appendix 14 Forest plot of nausea from all trials estimates



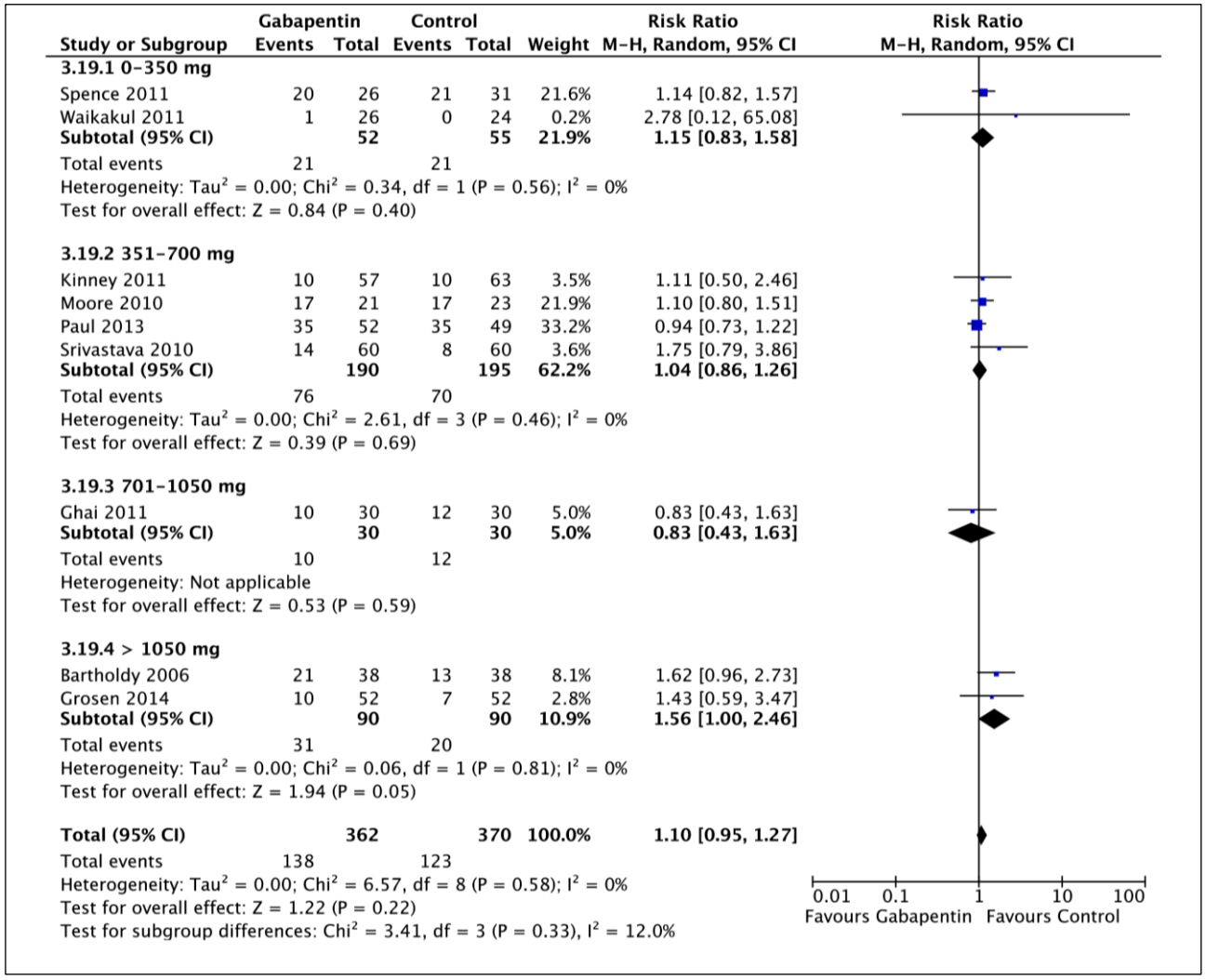
Appendix 15 Forest plot of vomiting from trials with low risk of bias



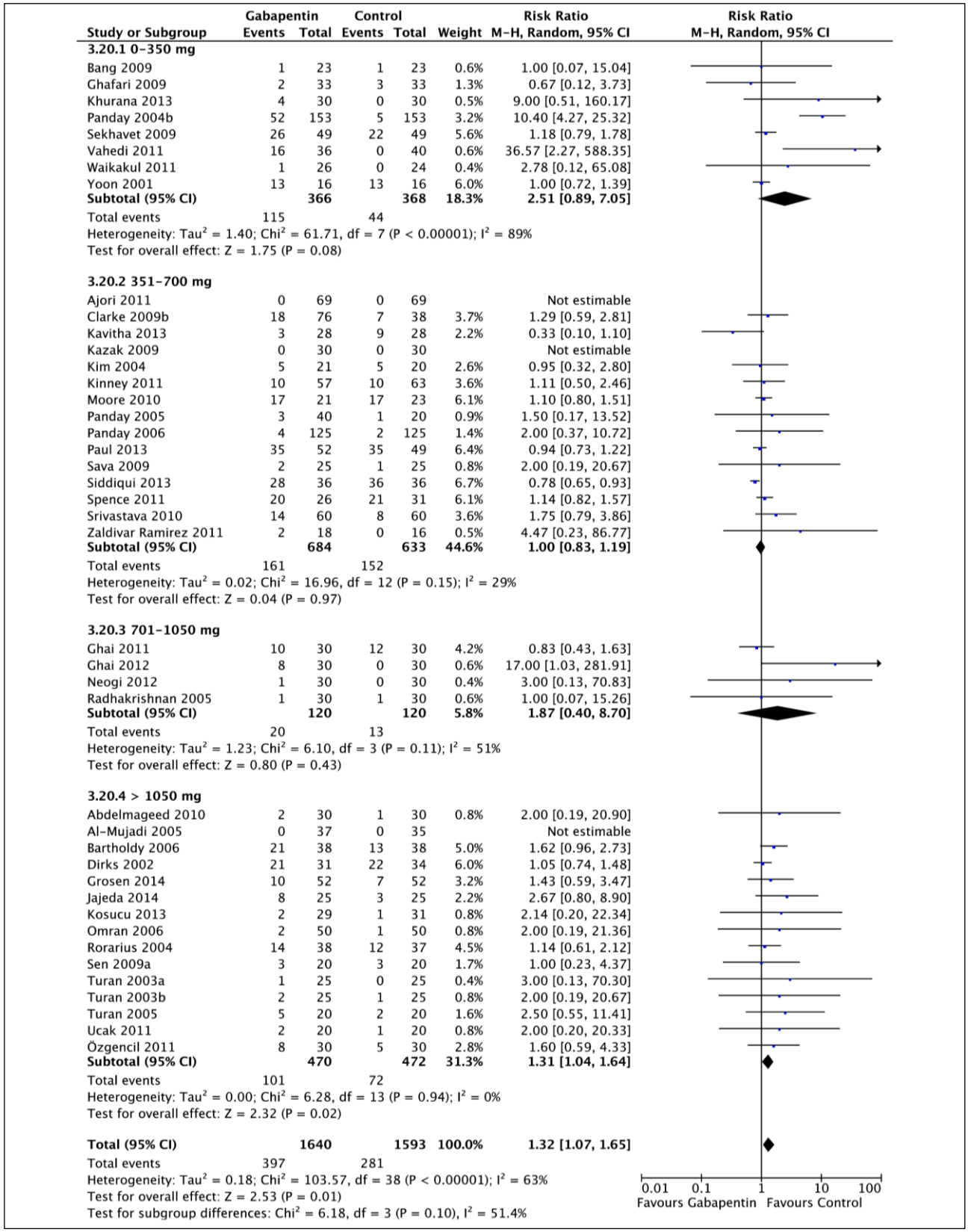
Appendix 16 Forest plot of vomiting from all trials estimates



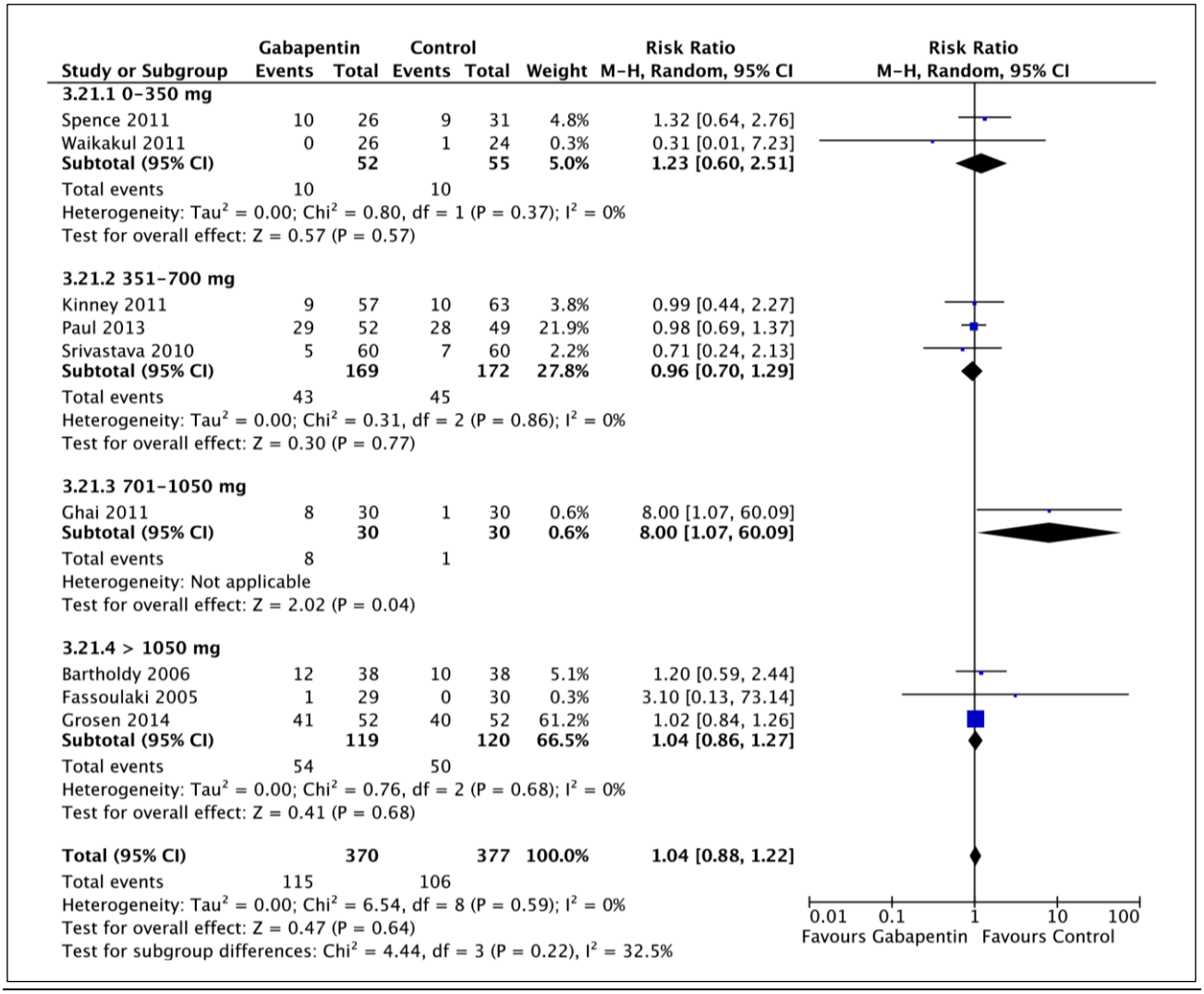
Appendix 17 Forest plot of sedation from trials with low risk of bias



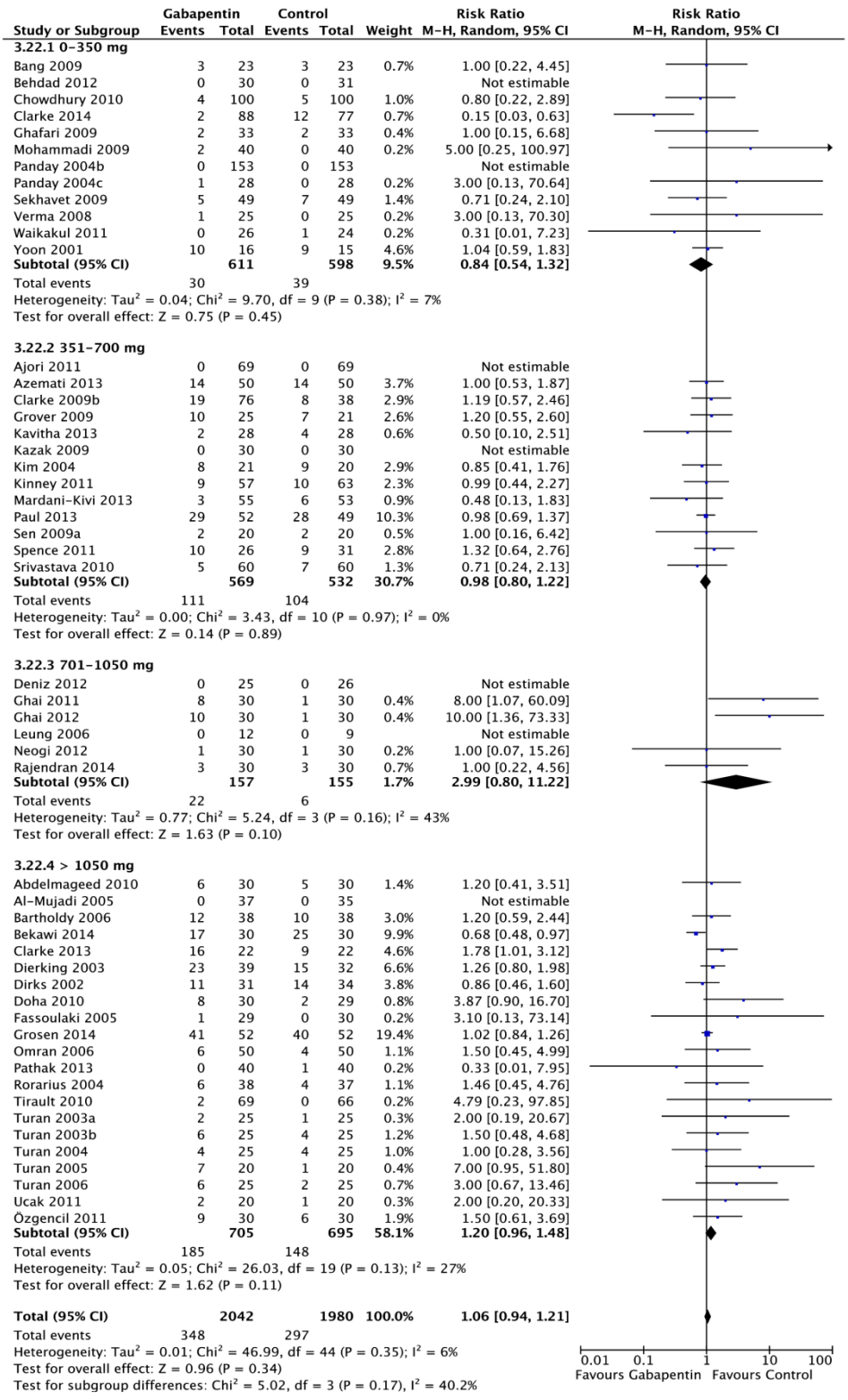
Appendix 18 Forest plot of sedation from all trials estimates



Appendix 19 Forest plot of dizziness from trials with low risk of bias



Appendix 20 Forest plot of dizziness from all trials estimates



PAPER IV

Pregabalin in postoperative pain management

– a systematic review with meta-analyses and trial sequential analyses

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ABSTRACT

Background

Pregabalin has demonstrated anti-hyperalgesic properties, similar to gabapentin, and was introduced for treatment of acute pain in 2001. Our aim was to evaluate the beneficial and harmful effects of pregabalin in postoperative pain management.

Methods

We included randomised, clinical trials investigating perioperative pregabalin treatment in adult surgical patients. The review followed Cochrane methodology including Grading of Recommendations Assessment, Development and Evaluation (GRADE) and used trial sequential analyses (TSA).

The primary outcomes were 24-hour intravenous morphine consumption and the incidence of Serious Adverse Events (SAE) defined by International Conference of Harmonisation – Good Clinical Practice (ICH-GCP) guidelines. Conclusions were based primarily on low risk of bias trials.

Results

A total of 97 randomised, clinical trials with 7201 patients were included. Twenty-four-hour morphine consumption was reported in 11 trials with overall low risk of bias finding a reduction of 5.8 mg (3.2, 8.5; TSA adj. CI: 3.2, 8.5).

Incidence of SAEs was reported in 21 trials, with 55 SAEs reported in 12 of these trials, and 22 SAEs reported in 10 trials with overall low risk of bias. In trials with overall low risk of bias Peto's OR was 2.9 (1.2, 6.8; TSA adj. CI: 0.1, 97.1).

Conclusion

Based on the GRADE evaluations the results from trials with low risk of bias had moderate to very low quality of evidence. A clinical relevant beneficial effect of pregabalin may be present (GRADE low). The risk of harm seems imminent but quality of evidence is weak (GRADE moderate).

INTRODUCTION

Pregabalin was synthesised in 1991 and approved for the treatment of neuropathic pain and refractory epilepsy in 2004 and 2005.[1] It is one of two available α_2-δ ligands, pregabalin and gabapentin, known as the gabapentinoids. Pregabalin and gabapentin share similar mechanism of action, and the use of gabapentinoids in experimental pain models have demonstrated anti-hyperalgesic analgesic effects. This effect is mediated through binding to α2-δ subunits in presynaptic voltage-gated calcium channels thereby inhibiting calcium influx and the subsequent release of excitatory neurotransmitters.[2] Differences between gabapentin and pregabalin are mainly related to pharmacokinetic and pharmacodynamic characteristics,[3 4] and pregabalin has a faster onset time and a more predictable absorption profile than gabapentin.[5]

Since the first published clinical trial in 2001, the literature continues to suggest a beneficial effect of pregabalin in acute postoperative pain management. Furthermore, an increasing number of systematic reviews with meta-analyses have been published, suggesting that pregabalin has both opioid-sparing and pain-reducing effects.[6-8] However, the published reviews have only limited focus on the risk of random and systematic error in the published reviews and also, the possible introduction of serious adverse events are sparsely investigated.

Therefore, the aim of this systematic review was to evaluate 24-hour opioid consumption, serious adverse events, pain intensity and adverse events of perioperative pregabalin compared with placebo or active placebo in adult surgical patients from randomised, clinical trials. The results and conclusions will primarily be based on meta-analyses of the best evidence, defined as trials with overall low risk of bias and furthermore, the risk of random error will be explored using trial sequential analyses on all outcomes. Finally, the results will be evaluated and graded according to their quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[9]

METHODS

Search, eligibility criteria and study selection

This PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) compliant systematic review followed the methodology recommended by the Cochrane Collaboration. The review protocol was published at the homepage of the International Prospective Register of Systematic Reviews (PROSPERO): CRD42015025282.[10]

Literature search

The search was planned and carried out by a trial search coordinator searching the Cochrane Library's CENTRAL, PubMed, EMBASE and Science Citation Index Expanded databases for eligible trials using the search terms and MeSH descriptors "Amines", "gamma-Aminobutyric Acid", "pregabalin* or lyrica*" and "pain". Published systematic reviews and articles were hand-searched for eligible trials. We searched for unpublished trials in: www.clinicaltrials.gov; www.controlled-trials.com; www.centerwatch.com; www.eudraCT.com, and at the homepage of the US Food and Drug Administration (FDA). Non-indexed journals and their published articles were found searching Google Scholar. The electronic search was last updated October 28th, 2016 (Appendix 1: search strategies).

Inclusion criteria

We included randomised clinical trials evaluating pregabalin for postoperative pain management versus a placebo or an active placebo that imitates the sedative effect of pregabalin. Participants were adult (≥ 18 years) surgical patients who received pregabalin regardless of dosage, administration intervals, duration of intervention and surgical procedure. All trials irrespective of language, publication status and year of publication were included. Non-English trials were translated to English. Exclusion criteria were non-randomised trials, non-surgical patients, and experimental pain models, pregabalin treatment for chronic pain conditions and analgesic co-interventions that was different in the compared groups. Two authors (MLF and CS) screened title and abstracts for eligibility using the pre-defined in- and exclusion criteria.

Data extraction

Two authors assessed full texts independently; MF (all trials) and one other author (CS, SK, AG, PJ, PLP) extracted data and assessed bias using a data extraction form. The extracted data included: Participant and trial characteristics such as publication year, number of participants, surgical procedure, follow-up period, pregabalin dose administration regimen, opioid consumption and consumption of non-opioid analgesics, pain intensity, any adverse event and serious adverse events (SAE).

If data was missing or bias evaluation was classified as unclear in one or more domains the corresponding author from the trial was contacted to confirm or obtain data. After a fourteen-day interval authors were contacted again if they did not respond to initial contact.

Risk of bias classification

All included trials were evaluated using the Cochrane Handbook risk of bias classification guidelines. Random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other bias, including financial and confirmation bias, were independently evaluated by two authors.[11] Bias domains were classified as high, unclear or low risk of bias. If one or more domains were classified as high risk of bias, the overall bias classification was high.[12] If one or more bias domains were deemed unclear, the trial were classified as overall unclear risk of bias and the trial was pooled together with trials with high risk of bias in meta- analyses and subgroup analyses. Conclusions in the review were based on low risk of bias trials according to protocol.[10]

Any disagreements in screening, study selection, data extraction or bias assessments were resolved by OM, JBD or JW.

Outcomes

The review had two co-primary outcomes: 24-hour intravenous opioid consumption and SAE defined according to the International Conference of Harmonization – Good Clinical Practice (ICH-GCP) definitions as medical events being either life threatening, resulting in death, disability or significant loss of function; causing hospital admission or prolonged hospitalisation.[13] The secondary outcomes were: Pain intensity at rest and mobilisation 6-hours and 24-hour postoperatively, and any adverse events reported.

All opioids were converted to intravenous morphine based upon equivalency (Appendix 2: Opioid conversion). All pain intensity scales reporting pain levels between 0 and 10 were converted to the Visual Analogue Scale (VAS) 0 to 100 mm.

Statistical analyses

We used the Review Manager (RevMan) [Computer program], Version 5.1.6, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 for the statistical analyses as predefined in the protocol. The Trial Sequential Analysis (TSA) program version 0.9 beta (www.ctu.dk/tsa) was used for trial sequential analyses on all outcomes.

In trials with more than one treatment arm, we combined means and standard deviations in the intervention groups.[14] Median and range values were converted to mean and standard deviations using the method described by Hozo et all.[15] Interquartile ranges were divided with 1.35 to define the standard deviation.[16] Long ordinal scales were analysed as continuous data. Risk Ratio (RR) with a 95% confidence interval was calculated for dichotomous data.[16]

To assess whether the observed differences in results are compatible with chance alone, we used Chi-squared test to examine the heterogeneity between trials. The heterogeneity was assessed by I^2 that quantifies the observed differences and D^2 for information size adjustments in the trial sequential analyses.

Whenever I^2 was greater than zero the results were calculated with both fixed effect model (FEM) and random effect model (REM) and the most conservative estimate was used.[17,18] In case of rare and few adverse events Peto's Odds ratio was used to provide the best confidence interval coverage.[14,19,20]

In order to explore heterogeneity, the following pre-planned subgroup analyses were used to investigate the risk of bias in low vs. unclear and high risk of bias: Pain intensity at rest vs. during mobilisation; pain intensity at 6 hours postoperatively vs. 24 hours postoperatively; single dose pregabalin vs. multiple doses of pregabalin; add-on treatment (trials investigating pregabalin added to other non-opioid analgesics vs. trials investigating pregabalin without any other non-opioid analgesics). We hypothesised that estimates from subgroups with low risk of bias, pain at rest and late pain, as well as pregabalin as add-on treatment would be lower than those from the corresponding subgroups.

We used sensitivity analyses to explore whether choice of summary statistics and choices made through the review process such as selection of event category were critical for the conclusions of the meta-analyses.

Trial Sequential Analyses (TSA) was used, with the risks of type-1 and 2 errors of 5% and 90% respectively, adjustment of the confidence intervals of intervention effects due to sparse data and repetitive testing in the cumulative meta-analyses.[18,21] If the accrued information size was smaller than 5% of the required information size, using the TSA was not possible due to insufficient amount of data.

Our a priori definition of a minimal clinical relevant effect in 24-hour opioid consumption was 5 mg of intravenous morphine. This minimal clinical relevant effect was chosen to detect or reject even a small beneficial effect. Previous systematic reviews of pregabalin and a recent review of gabapentin demonstrated an opioid-sparing effect of less than 10 mg.[6,10,22] The relative risk reduction (RRR) was set to 30% for adverse events and 50% for SAE in the TSA.

Trial size effect

This post-hoc analysis explores the effect of small trials on primary outcomes. The trials will be divided according to the following definition: ≤ 50 patients in each group, > 50 to 100 patients in each group, and ≥ 100 patients in each group.

Grading of recommendations assessment, development, and evaluation (GRADE)

GRADE was used to rate the quality of evidence and strength of recommendations for all outcomes in the systematic review. According to our protocol, the conclusions are based on estimates from trials classified as overall low risk of bias. The recommendations are presented in summary of findings tables (SoF).[9]

RESULTS

The number of trials screened, assessed for eligibility and included in the review is presented in the PRISMA flow diagram (Figure 1). One hundred and thirty four articles were considered for full text evaluation of the review. We excluded 37 trials due to chronic pain conditions, non-surgical procedures, different analgesic co-interventions, age < 18 years, double publications, intervention initiated > 48 hours preoperatively, observational methodology, study population was healthy adults, abstracts without reply from author, and a trial that investigated gabapentin as an intervention.

Trial characteristics

A total of 97 randomised clinical trials with 7201 patients were included in the systematic review.[23-119] Perioperative analgesic treatment with a single dose of pregabalin was investigated in 69 trials and dosage ranged from 50 mg to 300 mg.[23-30,32,35-37,39-43,48-53,55,56,62,63,65-73,76,79,81,84-87,90-94,96,98-100,102,105,107,109,110,112-115,118] In treatments with more than one dose of pregabalin, accumulated doses ranged from 100 mg/day to 600 mg/day in 28 trials.[31,33-35,38,44-47,50,54,57-61,64,74,75,77,78,80,82,83,88,89,95,97,101,103,108,116,117,119] Postoperative follow-up time varied from 6 hours to 1 year with the most common period being 24 hours (n=39).[23-31,36,39,41-44,48,49,51-53,55,56,62,66,68,69,71-73,75,78,79,84,86-89,95,96,98,102,107,109,110,112-115]

The number of patients included in each trial ranged from 26 to 228. Various surgical procedures were investigated with the majority of trials using general anaesthesia (n=73) for the included patients.[23-25,27,28,30-33,36-53,55-61,63-70,72,73,77-79,81-83,87,89-93,95,96,98-101,103,106-109,112,116,117,119] (Appendix 3: Trial Characteristics).

Bias assessment

Twenty trials were classified as having overall low risk of bias.[32,48,56,57,68,70-72,74,77,79,83,89,90,94,97,100,101,108,111] Forty-two trials were classified as overall unclear risk of bias[23,24,26,28,31,34,36-38,40,42,49,50,54,63-66,73,76,78,80,81,84,92,95,96,98,102-107,110,112-115,117] and 35 trials were classified as having an overall high risk of bias.[25,27,30,33,35,39,41,43-47,51-53,55,58-62,67,69,75,82,85-88,91,93,99,109,116-119]

Allocation concealment and selective outcome reporting were the most frequent reasons for unclear and high risk of bias assessments. (Figure 2: Bias graph, Appendix 4: Bias assessments).

The following sections will summarize meta-analyses of trials with overall low risk of bias. For all trials reporting the outcomes, please see table 1.

Morphine consumption

Trials with low risk of bias (for all trials reporting the outcomes, please see Table 1)
Twenty-four hour morphine consumption was reported in 11 trials with overall low risk of bias.[57,68,71,72,77,79,83,89,90,97,100] The reported data found a reduction in 24-hour morphine consumption of 5.8 mg (REM 95% CI: 3.2, 8.5; p < 0.0001; TSA adj. 95% CI: 3.2, 8.5; trials 11; 705 participants; percentage of RIS: 127.5%; GRADE: low). Results from all trials estimates are presented in table 1: All trials estimates and subgroup analyses. (Figure 3: Forest plot of 24-hour morphine consumption, Figure 4: Trial sequential analysis of 24-hour morphine consumption in trials with low risk of bias; Appendix 5: SoF and GRADE of trials with low risk of bias).

<u>Add-on effect</u>

In the subgroup analyses of pregabalin as add on to a non-opioid, basic analgesic regimen, the analyses found a mean reduction of 24-hour morphine consumption of 5.3 mg (REM 95% CI: 2.1, 8.5; p=0.0002; TSA adj. CI: 2.1, 8.5; trials 8; participants 499; percentage of RIS: 87.4%; GRADE: low).[57,71,72,77,83,89,90,97] (Appendix 6: Forest plot 24-hour morphine consumption + add-on).

<u>No add-on effect</u>

Two trials with overall low risk of bias investigating pregabalin without other non-opioid analgesics reported a reduction in 24-hour morphine consumption of 13.7 mg (REM 95% CI: 9.6, 17.8; p = <0.00001; TSA adj. CI: 9.6, 17.8; trials 2; participants 120; percentage of RIS: 54.0%; GRADE: low).[68,100]

(Appendix 7: Forest plot 24-hour morphine consumption – add-on).

Single dose vs. multiple dose treatments

In the subgroup analyses exploring the effect of a single dose pregabalin on 24-hour morphine consumption, 6 trials with overall low risk of bias found a reduction of 10.1 mg (REM 95%CI: 2.4, 17.8; p=0.01; TSA adj. 95% CI: -21.3, 41.5; trials 6; participants 399; percentage of RIS 15.1%; GRADE: low).[68,71,72,79,90,100] Five trials with overall low risk of bias investigating multiple dose administration of pregabalin found a reduction of 2.4 mg (REM 95% CI: 0.6, 4.9; p= 0.01; TSA adj. CI: 0.6, 4.9; trials 5; participants 306; percentage of RIS 66.7%; GRADE: low).[57,77,83,89,97] (Appendix 8: Forest plot 24-hour morphine consumption single vs. multiple dose treatments).

Serious adverse events

Trials with low risk of bias (for all trials reporting the outcomes, please see Table 1)
Incidence of SAEs was reported in 21 trials.[32,33,45,46,68,71-73,81,83,87,89,94,97,101,105,107,111,116-118] A total of 55 SAEs were reported from 13 trials[33,45,46,72,73,94,97,101,107,111,116-118] and 22 of these were reported in 10 trials with low risk of bias.[32,68,71,72,83,89,94,97,101,111] Eight trials reported zero-events.[32,68,71,81,87,89,105,118] The reported SAEs were: Readmission to hospital, prolonged hospital stay, postponed operation due to sedation from pregabalin, allergic reaction, stroke, pulmonary embolism, myocardial infarction, acute kidney injury, pneumonia, wound infection, bleeding or hematoma and death.

In trials with overall low risk of bias, the OR of SAEs was 2.9 (FEM 95% CI: 1.2, 6.8; p=0.02; TSA adj. CI: 0.1, 97.1; trials 10; participants 730; percentage of RIS: 8.8%; GRADE: moderate).[32,68,71,72,83,89,94,97,101,111] (Table 1: subgroup analyses, Figure 5: Forest plot of serious adverse events).

Single dose vs. multiple dose treatments

In trials with low risk of bias administrating pregabalin as a single dose, the odd ratio of SAE was 1.6 (FEM 95% CI: 0.3, 9.5; p= 0.63; TSA adj. CI: -; trials 4; participants 243; percentage of RIS: <5 %; GRADE: very low).[32,68,71,72] The OR in trials with multiple administrations of pregabalin was 3.4 (FEM 95% CI: 1.3, 9.2; p= 0.01; TSA adj. CI: 0.1, 190.7; trials 6; participants 487; percentage of RIS: 5.8%; GRADE: moderate).[83,89,94,97,101,111] (Appendix 9: Forest plot SAE single vs. multiple dose treatments).

Pain intensity

Trials with low risk of bias (for all trials reporting the outcomes, please see Table 1)
Early pain intensity at 6 hours postoperatively during mobilisation and late (24h) pain intensity at rest or mobilisation was not significantly reduced in trials with overall low risk of bias. The meta-analysis of VAS 6-hours postoperatively at rest found a reduction in pain intensity of 7.7 mm (REM 95 % CI: 2.2., 13.3; p=0.007; TSA adj. CI: -3.6, 19.0; trials 9; participants 588; percentage of RIS: 29.5%; GRADE: moderate).

(Table 1: subgroup analyses, Appendix 5: SoF and GRADE of trials with low risk of bias; Appendix 10-13: Forest plots of early and late VAS pain at rest and mobilisation).

Adverse events

Trials with low risk of bias (for all trials reporting the outcomes, please see Table 1)
The risk of nausea, sedation, and headache were not significantly different between groups. Trials reporting on PONV indicated a reduction in the pregabalin group compared to the controls, whereas there might be an increase in incidence of vomiting, dizziness and visual disturbance in the pregabalin groups compared with control groups in trials with overall low risk of bias. (Table 1: subgroup analyses, Appendix 5: SoF and GRADE of trials with low risk of bias, Appendix 14-20: Forest plots of adverse events: nausea, vomiting, PONV, sedation, dizziness, headache and visual disturbance).

Small trial effect

This post-hoc analysis showed that out of the 97 included trials, 91 were classified as small trials with 50 patients or less in each group.[23-33,35-73,75-81,83-100,102,105-110,112-115,117-119] Five trials included between 50 and 100 patients in each group,[74,82,101,104,116] and only one trial had more than 200 patients included.[34]

Of all of the trials reporting 24-hour morphine consumption, only one trial had more than 50 participants in each group.[104] In trials reporting serious adverse events one trial had more than 50 participants in each group.[101]

DISCUSSION

Based on the trials with overall low risk of bias there may be a beneficial, but small, effect of pregabalin in postoperative pain management. The predefined minimal clinical relevant difference of 5 mg for 24-hour morphine consumption was demonstrated as the trial sequential boundary for benefit was crossed. Only few trials reported on SAEs limiting our ability to firmly conclude upon these results. The estimates indicate an increased incidence of SAEs in the pregabalin group compared to controls, especially in trials with more than one administration of pregabalin. Pain scores and most adverse events did not differ significantly between groups except for early pain intensity at rest, which was significantly reduced, and risk of dizziness, vomiting, and visual disturbance, which was increased; however, the TSA analyses did not reach firm evidence.

Relation to other reviews

Other recent systematic reviews with meta-analyses have investigated beneficial and harmful effects of pregabalin on acute pain after surgery.[6,8] Eipe et al. included 43 RCTs in their systematic review and investigated perioperative pregabalin with a special focus on dose-response, as well as on pro-nociceptive vs non-nociceptive pain, thereby making it difficult to compare with the outcomes of the present review.[8] They found a similar small number of low risk of bias studies as in the present review, although this was not accounted for in their analyses. Mishriky et al.[6] conducted a systematic review and found a significant reduction in 24-hour morphine consumption (8.27 mg; 95% CI: 6.47, 10.08) based on all trials, regardless of bias, and similar to the all trials estimates from the present review (10.8 mg; 95% CI: 8.5, 13.2). The results from our subgroup analyses (table 1: subgroup analyses) indicated an overestimation of beneficial effects and underestimation of harmful effects in trials with unclear and high risk of bias, compared to those with low risk of bias. Mishriky et al.[6] did explore the bias effect and found no effect from removal of trials with uncertain risk of bias. However, they explored different outcomes than in our review, thus making it difficult to draw a direct comparison of primary outcomes and bias effects between reviews.

The present review is to our knowledge the first and currently largest systematic review investigating both benefit and harm of pregabalin for postoperative pain management, while assessing and addressing both the risk of random and systematic error.

Impact of analyses

Our a priori definition of a minimal clinical relevant effect in 24-hour opioid consumption was 5 mg of intravenous morphine. This predefined estimate was chosen based on previous systematic reviews of gabapentin, indicating that the opioid sparing effect of gabapentin was less than 10 mg.[121,22] Consequently, in order not to ignore any clinical relevant difference in the meta-analyses, the cut-off was set to 5 mg.

It may be argued that 5 mg is too small or irrelevant in a clinical setting. The confidence intervals for trials with low risk of bias, where pregabalin is administered together with other non-opioid analgesics, does not reach 10 mg, thereby excluding a morphine sparing effect of more than 10 mg in this context. Treatment with pregabalin without other non-opioid analgesics indicated a morphine sparing effect greater than 10 mg; however we found only two trials with low risk of bias in this group.

The morphine sparing effect in trials investigating pregabalin together with other non-opioid analgesics was also slightly greater than that of the predefined minimal important difference. Pregabalin treatment with more than one dose compared with a single dose treatment does not seem to increase the opioid sparing effect of pregabalin.

The reduction in 24-hour morphine consumption was generally lower in estimates for trials with low risk of bias compared to all trials, that also included uncertain and high risk of bias trials, thus confirming that trials with high risk of systematic errors often overestimate beneficial effects.

SAEs were infrequently reported, with only 21 trials reporting this outcome. A little more than half of the included trials reported SAEs in the published manuscripts, and the rest found none during their follow-up. The short follow-up periods, and diverse and infrequent registering of SAEs, limit the reliability of our results. However, it does seem that an increased incidence of SAEs is present in the pregabalin group, and the risk may increase with more than one dose treatment of pregabalin.

For trials investigating the effect of pregabalin on early and late pain intensity at rest and mobilisation, we cannot rule out a reduction in pain intensity scores, as the required information size was not reached in any of the TSA's.

The reporting of adverse events was diverse with similar limitations as for the SAE outcome. This problem of incomplete adverse event reporting has recently been addressed and confirmed in another review.[120] The present analyses indicate that pregabalin treatment is associated with increased levels of sedation, dizziness and visual disturbances, and increased risk of vomiting, whereas nausea, PONV and headaches might be reduced. None of the trials with low risk of bias had enough information to withstand the TSA testing. The all trials estimates do indicate a more homogeneous profile with possible reductions in incidences of nausea, vomiting, PONV and headaches, and with an increased risk of sedation, dizziness and visual disturbances.

Comparative effects of pregabalin and gabapentin in postoperative pain management

A comparable systematic review evaluating gabapentin for postoperative pain management has recently been published.[121] Per-protocol it was pre-defined, that conclusions from both the review of gabapentin, and the present review of pregabalin, should primarily be based on meta-analyses of the best evidence, defined as trials with overall low risk of bias.[10, 123] Comparable data from the two reviews on primary beneficial and harmful outcomes are summarized in table 2. Further, table 2 includes available data from meta-analyses of 4 other frequently employed non-opioid analgesics in postoperative pain treatment, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), COX2-inhibitors, and steroids.

With gabapentin, an overall 24-hour morphine-sparing effect of 3.1 mg was demonstrated, which was less than the predefined 5 mg minimal clinical difference. Further, the morphine-sparing effect of gabapentin as mono-therapy (8.0 mg) was not statistically significant different from placebo, but this result is based on only 2 trials with low risk of bias .[121] (table 2).

In contrast, pregabalin reduced overall 24-hour morphine consumption by 5.8 mg, thus reaching the predefined 5 mg minimal clinical difference. Further, the reduction in 24-hour morphine consumption with pregabalin as add-on to other non-opioid analgesics, was 5.3 mg, as opposed to 1.2 mg with gabapentin.

Both results with pregabalin reached firm evidence according to TSA. There is, however, still a major probability that a clinically, relevant beneficial effect is not present with pregabalin.

The risk of SAEs in trials with low risk of bias was increased in both reviews, however, none of the reviews have enough data to reach firm evidence. [121] The gabapentin review demonstrated a 1.6 times increased risk of SAEs, while the current pregabalin review reports almost twice the odds of SAEs, compared with gabapentin: 2.9. Furthermore, multiple administrations of pregabalin further increased the risk of SAEs to 3.4.

Pain was moderately reduced in low risk of bias trials in both reviews, but only in the early postoperative period.

The risk of adverse events differs between the two reviews. While the gabapentin review found no significant differences between groups for risk of nausea, vomiting, sedation, and dizziness,[121] the risk of vomiting and dizziness seemed increased with pregabalin, compared to controls. However, none of these outcomes reached firm evidence, according to TSA.

It should be noted, that no comparable data from meta-analyses of trials with low risk of bias are available in the literature, for four of the most employed non-opioid analgesics, paracetamol, NSAIDs, COX2-inhibitors, and steroids (table 2). It must be anticipated, though, that results similar to those presented in our reviews of pregabalin and gabapentin would be found for low risk of bias trials with other non-opioid analgesics, as indicated in a recent analysis of intravenous paracetamol.[123] In this analysis, only very few trials were considered low risk of bias.[123]

Considerations on gabapentinoids as part of enhanced recovery programs after surgery

Enhanced recovery programs aims to improve postoperative rehabilitation while reducing the risk of complications in surgical populations. Effective pain relief and opioid-sparing with multimodal regimens that often include 2 or more non-opioid analgesics, represents a cornerstone in such programs.

On the basis of the actual reviews, with conclusions based on low risk of bias trials only, gabapentin cannot be recommended for routine, postoperative pain treatment, neither as a single analgesic administered together with opioid, nor as part of multimodal regimens. Opioid-sparing, reduction of opioid-related adverse events, and pain relief is marginal, at best, and the risk of SAEs is imminent.

For pregabalin, a significant, but minimal reduction in opioid consumption seems present, but pain reduction is marginal. Although PONV might be reduced, the risk of both dizziness and especially visual disturbances is increased. Pregabalin may also display a greater risk of SAEs than gabapentin.

In more general terms, our knowledge of benefit and harm regarding "multimodal" analgesic regimens is sparse, and we have very limited, high-quality information of regimens including more than one non-opioid analgesic.[127, 128] Consequently, analgesic regimens using gabapentinoids as part of multimodal analgesic regimens for enhanced recovery programs should only be used in protocolled situations, with careful considerations of benefit and harm. Based on the two reviews, we find little sound evidence from trials with the best research methodology to support the routine use of gabapentinoids in this context.

Strengths and limitations of the review

This systematic review has several strengths. The protocol was pre-study registered at PROSPERO, it is compliant with the latest Cochrane methodology, and the review is reported according to the PRISMA guidelines. Our search strategies were comprehensive without language restrictions. Screening of all titles and full texts, data extraction, and bias assessments, were carried out by two independent authors.

We evaluated the risk of random errors using TSA methodology on all outcomes, and the risk of systematic error was assessed using Cochrane bias evaluation tools. All conclusions were based on trials with overall low risk of bias, using GRADE to document the further liability of our results.

The limitations of the conclusions in this review mirror those of the trials included in the review. The problems identified are that the majority of the included trials are classified as either unclear or high risk of bias, with an inherent risk of systematic error. Very few trials reported on SAEs, and most have a short follow-up period, limiting the ability for firm conclusions and with a huge risk of underestimating incidences of SAE. Major heterogeneity was present as we included all trials regardless of surgical procedure, dosing regimen and type of additional analgesics. The conversion of scales for pain intensity scores and calculations of equi-analgesic doses of opioids might introduce heterogeneity and imprecision.

CONCLUSION

Based on GRADE recommendations from trials with low risk of bias we found that the quality of evidence regarding perioperative treatment with pregabalin for postoperative pain is moderate to very low, primarily due to indirectness and imprecision. A minimal clinical relevant reduction of 5 mg in 24-hour morphine consumption was reached in trials with low risk of bias (GRADE: low), and in trials investigating pregabalin as an adjunct to other non-opioid analgesics. Pregabalin seems to increase SAEs (GRADE: moderate) especially when more than one dose treatment is used; SAEs are, however, infrequently reported, and it is not possible to conclude firmly upon the estimate of harm because of few data.

Future researchers must focus on both harmful and beneficial effects of gabapentinoids for postoperative pain in trials with minimal risk of systematic and random error. Further, more information of beneficial and harmful effects of other non-opioid analgesics is needed in meta-analyses from systematic reviews of trials with low risk of bias.

Declaration of interests

JW reports that he is a member of the task force at Copenhagen Trial Unit to develop the software and manual for doing Trial Sequential Analysis (TSA). PJ has received speaker´s honorarium and funding for a study from Smiths Medical. AG, PLP, CS, SK, JBD, OM and MLF have no conflicts of interests to declare.

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Authors' contributions and authorship

All authors comply with ICMJE recommendations.

JBD, JW and OM have all substantially contributed to the conception and design, interpretation of data, revising the final manuscript draft critically for important intellectual content, approve the final manuscript ready for publishing and agree to be accountable for all aspects of the work.

CS, SK, PLP, AG PJ have all contributed substantially to the acquisition of data, interpretation of data as well as revising the manuscript critically and given their approval of the final version of the manuscript and agree to be accountable for all aspects of the work.

MLF has contributed substantially to the conception and design, acquisition, analysis and interpretation of data, drafting the manuscript, revising the final version of the manuscript, approval of the final version and is as such accountable for all aspects of the work.

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TABLE 1 Subgroup analyses

Outcome *Subgroup analyses*	**Estimates** **Trials with overall low risk of bias**				**Estimates** **All trials**		
	Estimate MD/RR *(REM/FEM/RR/Peto's OR)* *(95% CI; p-value; TSA adj. 95% CI)*	**I^2**	**N** *Trials/ Participants/ Required information size/ Accrued information size*	**Test of interaction** *P-value*	**Estimate MD/RR** *(REM/FEM/RR/Peto's OR)* *(95% CI; p-value; TSA adj. 95% CI)*	**I^2**	**N** *Trials/ Participants/ Required information size/ Accrued information size*
BENEFICIAL OUTCOMES							
24-hour morphine consumption	**5.8 mg reduction** (REM 95% CI: 3.2, 8.5; p < 0.0001; TSA adj. CI: 3.2, 8.5)	85%	11 / 705 /553 /127.5%	P = 0.001	**10.8 mg reduction** (REM 95% CI: 8.5, 13.2; p<0.00001; TSA adj. CI: 8.5, 13.2)	95%	37 /2423 /923 / 262.5%
24-hour morphine consumption - *Add-on*	**5.3 mg reduction** (REM 95% CI: 2.1, 8.5; p=0.0002; TSA adj. CI: 2.1, 8.5)	83%	8 / 499 / 571/87.4%	P = 0.08	**8.9 mg reduction** (REM 95% CI: 6.7, 11.0; p<0.0001; TSA adj. CI: 6.7, 11.0)	92%	21 / 1269 / 923/ 137.5%
24-hour morphine consumption - *No add-on*	**13.7 mg reduction** (REM 95% CI: 9.6, 17.8; p<0.00001; TSA adj. CI: 9.6. 17.8)	0%	2 / 120 / 222 / 54%	P = 0.16	**20.4 mg reduction** (REM 95% CI: 11.1, 34.0; p = 0.0001; TSA adj. CI: -16.6, 56.6)	96%	9 / 560 / 4928 / 17.1%
24-hour morphine consumption - *Single administration*	**10.1 mg** (REM 95%CI: 2.4, 17.8; p=0.01; TSA adj. CI: - 21.3, 41.5)	92%	6/ 399 / 2644 /15.1%	P = 0.93	**9.8 mg reduction** (REM 95% CI: 6.9, 12.6; p<0.00001; TSA adj. CI 6.9, 12.6)	93%	22 / 1331 / 1189/ 111.9%
24-hour morphine consumption - *Multiple administration*	**2.4 mg** (REM 95%CI: 0.6, 4.2; p= 0.01; TSA adj. CI: 0.5, 4.9)	41%	5 / 306 / 459 / 66.7%	P < 0.00001	**12.7 mg reduction** (REM 95% CI: 8.2, 17.1; p<0.00001; TSA adj. CI: 8.2, 17.1)	97%	15 /1092 / 459 / 237.8%
6-hour VAS pain at rest	**7.7 mm reduction** (REM 95% CI: 2.2, 13.3; p=0.007; TSA adj. CI: -3.6, 19.0)	77%	9 / 588 / 1996 / 29.5%	P = 0.61	**9.3 mm reduction** (REM 95% CI: 5.5, 13.1; p < 0.00001; TSA adj. CI: 5.5, 13.1)	98%	55 / 3582 / 1401 / 255.7%
6-hour VAS pain at mobilisation	**16.3 mm reduction** (REM 95% CI: -9.9, 42.6; p=0.22; TSA adj. CI: -)	97%	5 / 323 / 24419 / <5%	P = 0.41	**9.8 mm reduction** (REM 95% CI: 4.7, 14.9; p = 0.0002; TSA adj. CI: 4.7, 14.9)	96%	19 / 1323 / 988/ 133.9 %
24-hour VAS pain at rest	**1.4 mm reduction** (REM 95% CI: -2.7, 5.5; p=0.5; TSA adj. CI: -4.6, 7.4)	89%	15 / 1123 /2059 / 54.5%	P = 0.10	**5.3 mm reduction** (REM 95% CI: 1.6, 9.1; p= 0.005; TSA adj. CI: 1.6, 9.1)	99%	59 / 4105 / 1620 / 253.3 %
24-hour VAS pain at mobilisation	**3.7 mm reduction**	47%	7 / 502 / 1469/	P = 0.83	**4.2 mm reduction**	75%	23 / 1629 / 364 /

	(REM 95% CI: -1.5, 8.9; p=0.16; TSA adj. CI:-6, 13.4)		34.2 %		(REM 95% CI: 1.3, 7.0; p=0.004; TSA adj. CI: 1.3, 7.0)		447.5%
HARMFUL OUTCOMES							
Serious adverse events	**RR 2.9** (Peto's OR 95% CI: 1.2, 6.8; p=0.02; TSA adj. CI: 0.1, 97.1)	0%	10 / 730 / 8312/8.8%	P = 0.60	**RR 2.4** (Peto's OR 95% CI: 1.4, 4.2 p=0.002; TSA adj. CI: 0.9, 6.33)	0%	21 / 1574 / 5388 / 29.2%
Serious adverse events - *Single administration*	**RR 1.6** (Peto's OR 95% CI: 0.3, 9.5; p= 0.63; TSA adj. 95% CI: -)	0%	4 / 243 / 7323 / <5%	P = 0.47	**RR 2.8** (Peto's OR 95% CI: 1.1, 6.9; p=0.03; TSA adj. CI: 0.1, 109.5)	0%	10 / 766 / 6911 / 11.1%
Serious adverse events - *Multiple administration*	**RR 3.4** (Peto's OR 95% CI: 1.3, 9.2; p= 0.01; TSA adj. CI: 0.1, 190.7)	0%	6 / 487 / 8912 / 5.8%	P = 0.20	**RR 2.2** (Peto's OR 95% CI: 1.1, 4.4; p= 0.03; TSA adj. CI: 0.3, 13.5)	0%	11 / 834 / 4576 / 18.2%
Adverse event: Nausea	**RR 0.8** (REM 95% CI: 0.6, 1.2; P= 0.34; TSA adj. CI: 0.4, 1.7)	40%	8 / 631 / 1895 / 33.3%	P= 0.92	**RR 0.8** (REM 95% CI: 0.7, 1.0; p= 0.05; TSA adj. CI: 0.7, 1.1)	49%	34 / 2389 / 2783 / 85.8%%
Adverse event: Vomiting	**RR 1.3** (REM 95% CI: 0.7, 2.7; p= 0.04; TSA adj. CI: 0.1, 15.4)	58%	6 / 461 / 6325 / 7.3%	P = 0.04	**RR 0.7** (REM 95% CI: 0.5, 9.4; p = 0.02; TSA adj. CI: 0.5, 1.1)	53%	29 / 2122 / 3536 /61.7%
Adverse event: PONV	**RR 0.7** (REM 95% CI: 0.5, 1.0; p= 0.04; TSA adj. CI: 0.5,1.2)	25%	9 / 558 / 1141 / 55.3%	P = 0.66	**RR 0.7** (REM 95% CI: 0.6, 0.9; p= 0.05; TSA adj. CI: 0.6, 0.8)	40%	28 / 1914 / 1315 / 145.6%
Adverse event: Sedation	**RR 1.1** (REM 95% CI: 0.9, 1.3; p=0.45; TSA adj. CI: -)	83%	10 / 671 / - / <5%	P = 0.05	**RR 1.4** (REM 95% CI: 1.1, 1.7; p = 0.009; TSA adj. CI:-)	85%	40 / 2764 / - / <5%
Adverse event: Dizziness	**RR 2.1** (REM 95% CI: 1.1, 3.9; p= 0.02; TSA adj. CI: 0.8, 1.0)	49%	11 / 661 / 5439 / 12.1%	P = 0.22	**RR 1.5** (REM 95% CI: 1.2, 1.8; p=0.0007; TSA adj. CI: 1.2, 1.8)	57%	51 / 3461 / 4665 / 74.2%
Adverse event: Headache	**RR 0.7** (REM 95% CI: 0.4, 1.3; p = 0.02; TSA adj. CI: 0.02, 8.0)	38%	5 / 285 / 2263 / 13.3%	P = 0.33	**RR 1.0** (REM 95% CI: 0.8, 1.2); p= 0.7; TSA adj. CI: 0.7, 1.3)	10%	24 / 1462 / 2113 / 69.2%
Adverse event: Visual disturbance	**RR 3.2** (REM 95% CI: 1.2, 8.3; p= 0.02; TSA adj. CI: -)	0%	5 / 299 / - / <5%	P= 0.55	**RR 2.3** (REM 95% CI: 1.3, 4.1); p= 0.003; TSA adj. CI: 0.2, 26.5)	12%	30 / 1973 / 20555 /9.6%

REM: Random Effects Model; FEM: Fixed Effects Model; RR: Risk Ratio; Peto's OR; Peto's Odds Ratio; TSA adj. CI: Trial Sequential Analysis adjusted Confidence Interval

TABLE 2 Comparative data from meta-analyses of pregabalin, gabapentin, paracetamol, NSAIDs, cox2-inhibitors and steroids in postoperative pain management

	Pregabalin	**Gabapentin**	**Paracetamol**	**NSAIDs**	**Cox2-inhibitors**	**Steroids**
	Estimate MD/RR *(REM/Peto's OR)* *(95% CI; p-value; TSA adj. 95% CI)*	**Estimate MD/RR** *(REM/Peto's OR)* *(95% CI; p-value; TSA adj. 95% CI)*	**Estimate MD** *(95% CI; p-value)*	**Estimate MD** *(95% CI; p-value)*	**Estimate MD** *(95% CI; p-value)*	**Estimate MD** *(95% CI; p-value)*
TRIALS WITH OVERALL LOW RISK OF BIAS						
24-hour morphine consumption	5.8 mg reduction (REM 95% CI: 3.2, 8.5; p < 0.0001; TSA adj. CI: 3.2, 8.5) (11 trials)	3.1 mg reduction (REM 95% CI: 0.5, 5.6; p = 0.02; TSA adj. CI: -0.5, 5.6) (13 trials)	No available data	No available data	No available data	No available data
24-hour morphine consumption - *Add-on*	5.3 mg reduction (REM 95% CI: 2.1, 8.5; p = 0.0002; TSA adj. CI: 2.1, 8.5) (8 trials)	1.2 mg reduction (REM 95% CI: -0.3, 2.6; p = 0.12; TSA adj. CI: -0.3, 2.6) (11 trials)	No available data	No available data	No available data	No available data
24-hour morphine consumption - *No add-on*	13.7 mg reduction (REM 95% CI: 9.6, 17.8; p < 0.00001; TSA adj. CI: 9.6. 17.8) (2 trials)	8.0 mg reduction (REM 95% CI: -1.5, 17.4; p = 0.10; TSA adj. CI: -15.5, 23.3) (2 trials)	No available data	No available data	No available data	No available data
ALL TRIALS						
24-hour morphine consumption	10.8 mg reduction (REM 95% CI: 8.5, 13.2; p < 0.00001; TSA adj. CI: 8.5, 13.2) (37 trials)	7.3 mg reduction (REM 95% CI: 5.9, 8.8; p < 0.00001; TSA adj. CI: 5.9, 8.8) (73 trials)	No available data*	No available data*	No available data*	No available data*
24-hour morphine consumption - *Add-on*	8.9 mg reduction (REM 95% CI: 6.7, 11.0; p < 0.0001; TSA adj. CI: 6.7, 11.0) (21 trials)	4.4 mg reduction (REM 95% CI: 2.4, 6.5; p < 0.00001; TSA adj. CI: 2.4, 6.5) (36 trials)	No available data*	No available data*	No available data*	2.33 mg reduction (95% CI: 0.26; 4.39); p = 0.03; **[126]
24-hour morphine consumption - *No add-on*	20.4 mg reduction (REM 95% CI: 11.1, 34.0; p = 0.0001; TSA adj. CI: -16.6,	10.6 mg reduction (REM 95% CI: 8.4 to 12.8; p < 0.00001;	6.3 mg reduction (95% CI: 3.7, 9.0); p < 0.05; **[125]	10.2 mg reduction (95% CI: 8.7, 11.7);	10.9 mg reduction (95% CI: 9.1, 12.8);	No available data*

	56.6) (9 trials)	TSA adj. CI: 8.4, 12.8) (37 trials)		p < 0.05; **[125]	p < 0.05; **[125]	
TRIALS WITH OVERALL LOW RISK OF BIAS						
Serious adverse events	OR 2.9 (Peto's OR 95% CI: 1.2, 6.8; p=0.02; TSA adj. CI: 0.1, 97.1) (10 trials)	RR 1.61 (FEM 95% CI: 0.9, 2.9; p = 0.10 TSA adj. CI: 0.6, 4.6) (9 trials)	No available data*	No available data*	No available data*	No available data*
ALL TRIALS						
Serious adverse events	OR 2.4 (Peto's OR 95% CI: 1.4, 4.2 p=0.002; TSA adj. CI: 0.9, 6.33) (21 trials)	RR 1.14 (FEM 95% CI: 0.71, 1.81; p = 0.59; TSA adj. CI: 0.6, 2.1) (26 trials)	No available data on RR, but see McDaid et al. *[125]	No available data on RR, but see McDaid et al. *[125]	No available data on RR, but see McDaid et al. *[125]	No available data*

*See also[127, 128] **TSA not performed

FIGURE 1 PRISMA diagram

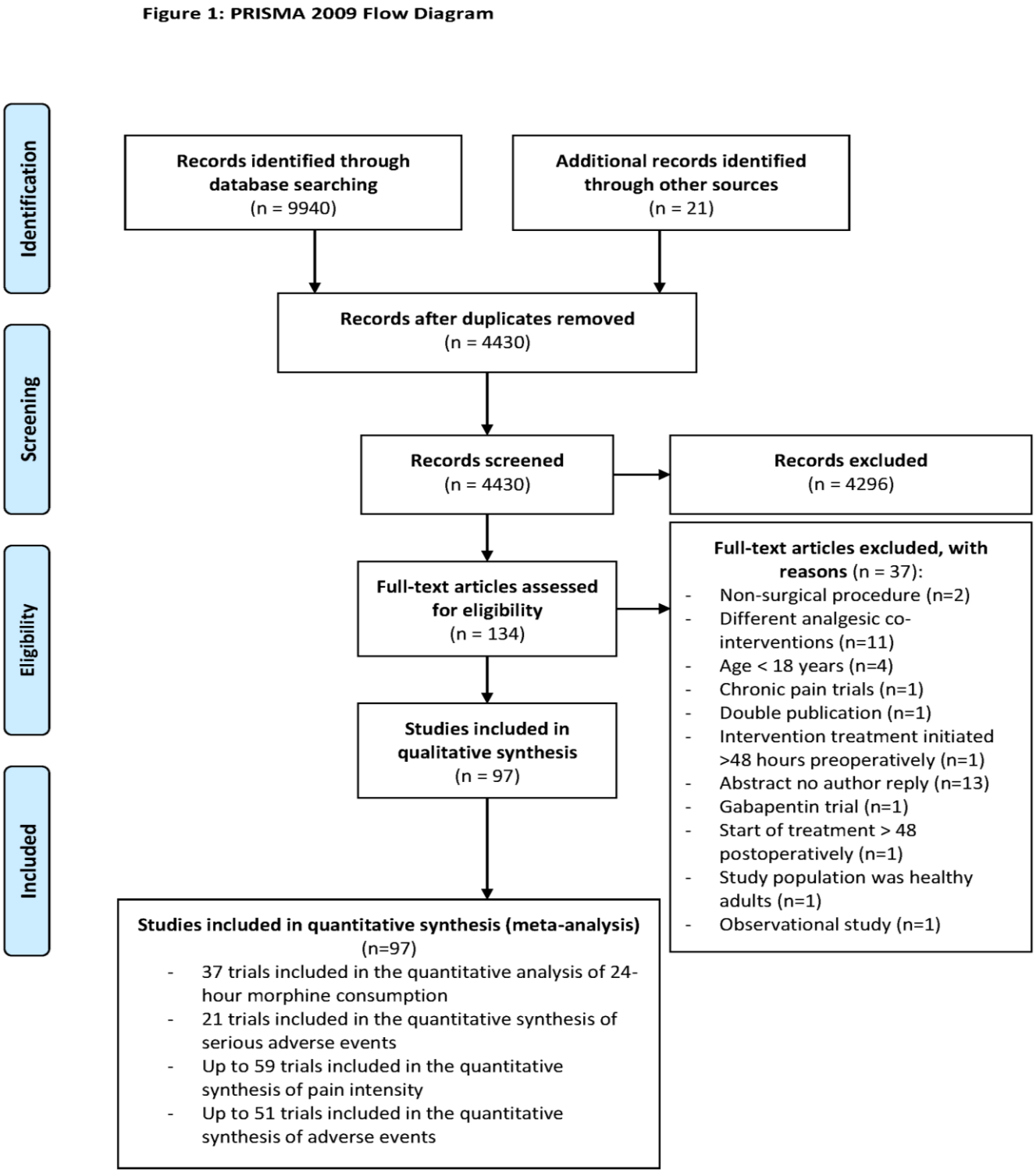
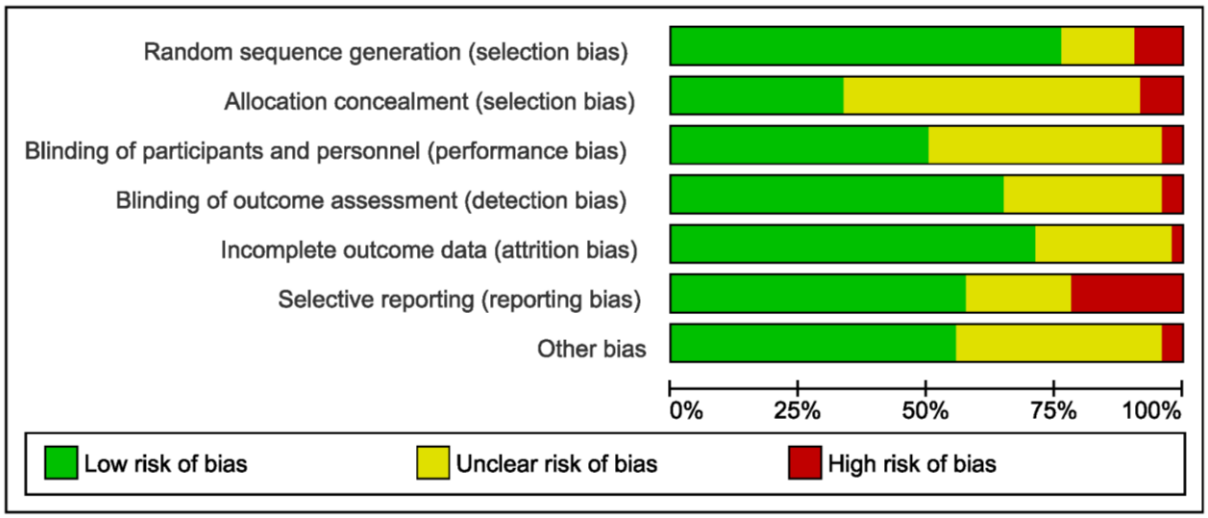
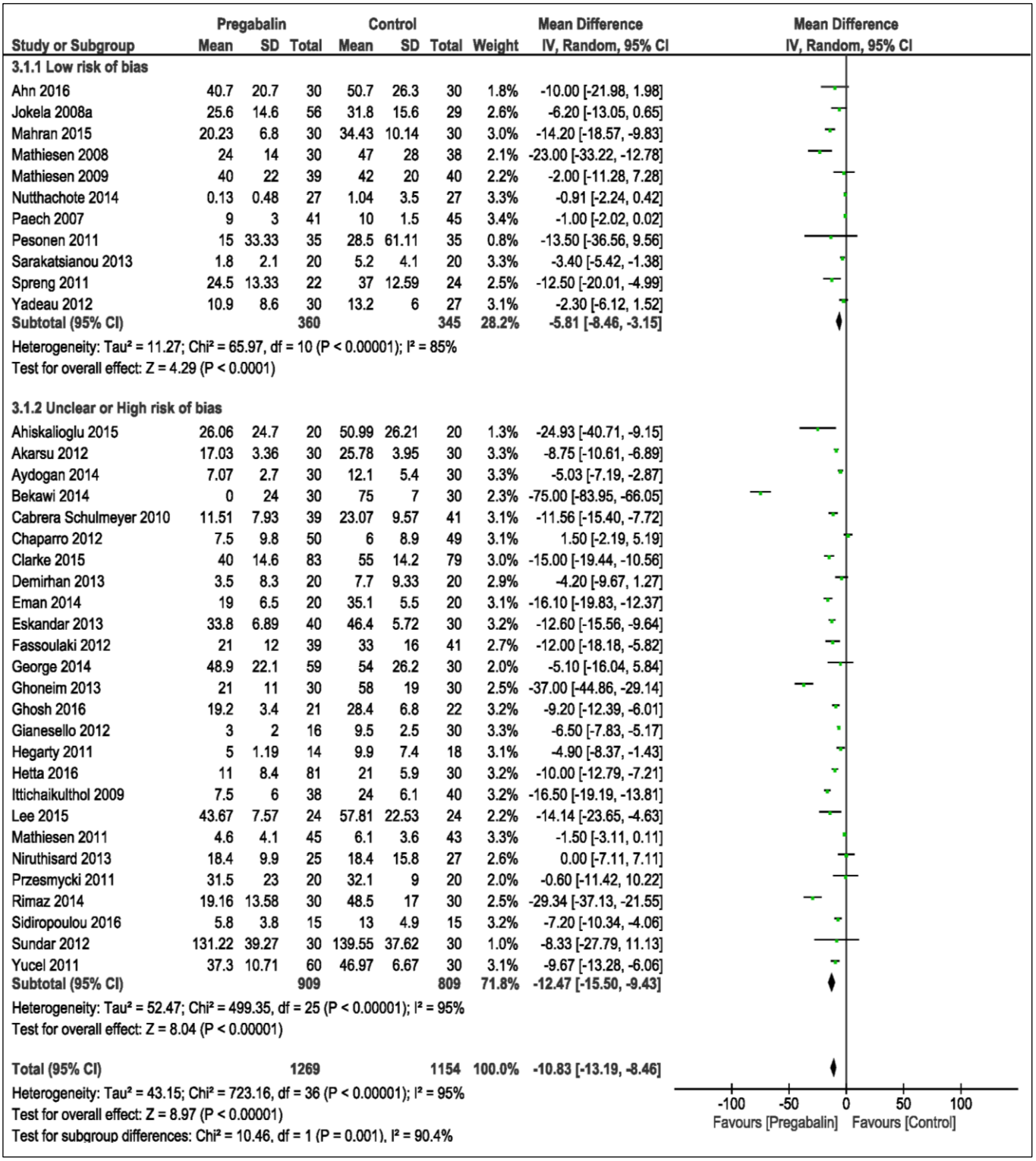


FIGURE 2 Bias graph



Risk of bias summary

FIGURE 3 Forest plot of 24-hour morphine consumption



Forest plot of 24-hour morphine consumption including the subgroup of trials with low risk of bias vs. trials with unclear and high risk of bias.

FIGURE 4 TSA of 24-hour morphine consumption from trials with low risk of bias

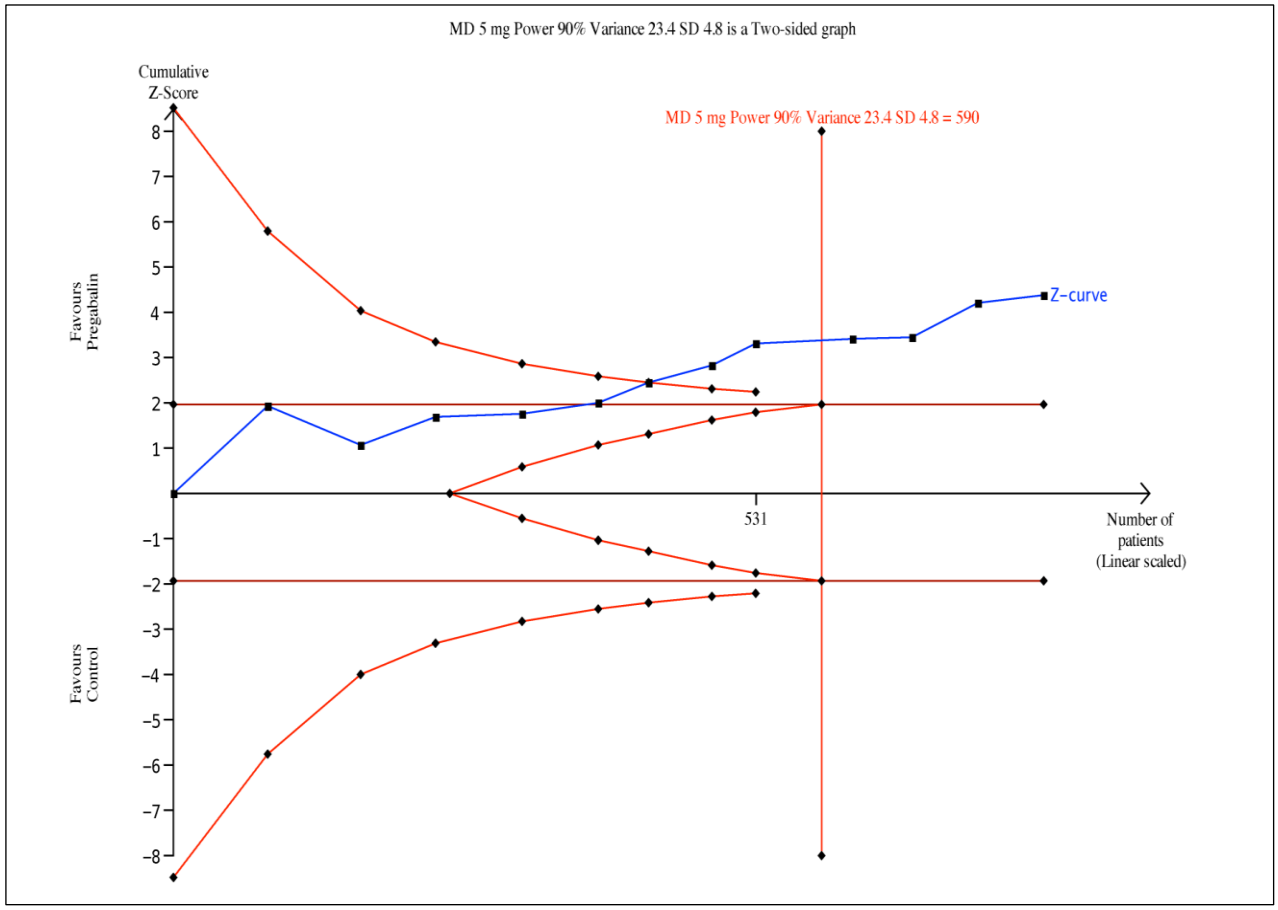
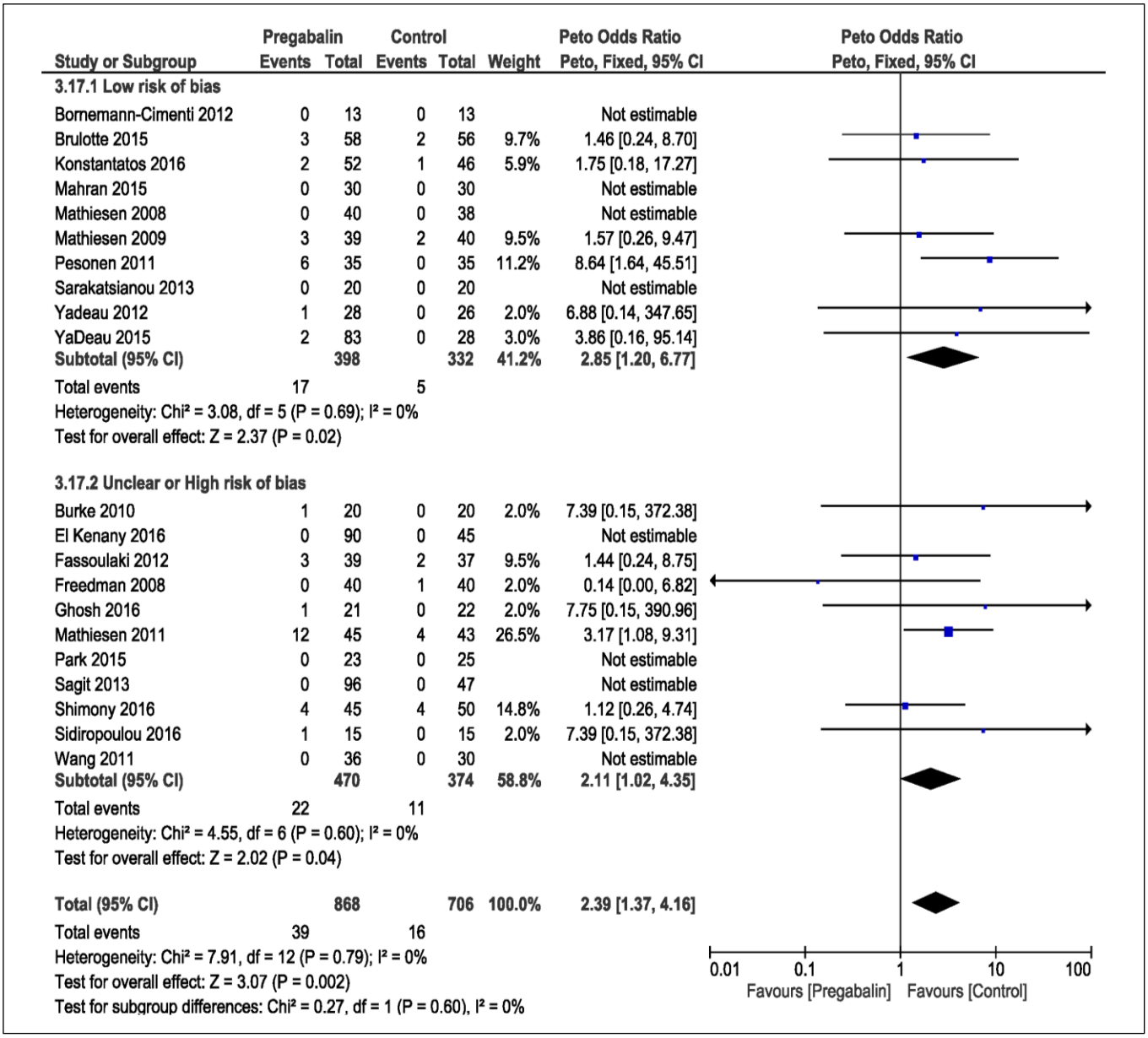


***Figure 4**: Trial sequential analysis of 24-hour morphine consumption from trials with low risk of bias. The minimal clinical difference was 5 mg with an α of 5% and β of 10% the z-curve crosses the monitoring boundary for benefit after six trials and the required information size is met. In conclusion there is firm evidence that pregabalin reduces 24-hour morphine consumption however we cannot rule out a reduction in 24-hour morphine consumption less than the predefined minimal clinical difference of 5 mg as the TSA adj. CI is 3.2 to 8.5 mg.*

FIGURE 5 Forest plot of SAE



Forest plot of SAE including the subgroup of trials with low risk of bias vs. trials with unclear and high risk of bias.

APPENDIX PAPER IV

Appendix 1: Search strategies

Searches performed 18 August 2015

Total number of references identified: 4389 references
Number of duplicates removed: 1148 references
Number of references in final list: 3241 references

Batch name: 150818_J Wetterslev_Pregabalin til postop smertebeh

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 7 of 12, 2015) (399 hits)
#1 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifier(s): [Adverse effects - AE, Therapeutic use - TU]
#2 (pregabalin or lyrica)
#3 #1 or #2
#4 MeSH descriptor: [Pain] explode all trees
#5 pain*
#6 #4 or #5
#7 #3 and #6
#8 adult* or middle age* or aged
#9 #7 and #8

MEDLINE (Ovid SP)(1946 to August 2015) (833 hits)
1. gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
2. (pregabalin or lyrica).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. 1 or 2
4. exp Pain/
5. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. 4 or 5
7. 3 and 6
8. (adult* or middle age* or aged).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. 7 and 8

EMBASE (1974 to August 2015) (1751 hits)
1. exp pregabalin/ae, dt [Adverse Drug Reaction, Drug Therapy]
2. (pregabalin or lyrica).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. 1 or 2
4. exp pain/
5. pain*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. 4 or 5
7. 3 and 6
8. limit 7 to (adult <18 to 64 years> or aged <65+ years>)

Science Citation Index Expanded (1900 to August 2015) (1406 hits)
#3 1,406 #2 AND #1
#2 443,346 TS=pain*
#1 2,693 TS=(pregabalin or lyrica)

Second search 28th October 2016
Total number of references identified: 5551 references
Number of duplicates removed: 1407 references

Number of references in final list: **4144 references**
Number of new references in updated search: **1147 references**

Batch name: 161025_J Wetterslev_Pregabalin til postop smertebeh

Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (2016, Issue 9) (512 hits)

#1 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifier(s): [Adverse effects - AE, Therapeutic use - TU]
#2 (pregabalin or lyrica)
#3 #1 or #2
#4 MeSH descriptor: [Pain] explode all trees
#5 pain*
#6 #4 or #5
#7 #3 and #6
#8 adult* or middle age* or aged
#9 #7 and #8

MEDLINE (OvidSP) (1946 to October 2016) (1016 hits)

1. gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
2. (pregabalin or lyrica).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. 1 or 2
4. exp Pain/
5. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. 4 or 5
7. 3 and 6
8. (adult* or middle age* or aged).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
9. 7 and 8

Embase (OvidSP) (1974 to October 2016) (2396 hits)

1. exp pregabalin/ae, dt [Adverse Drug Reaction, Drug Therapy]
2. (pregabalin or lyrica).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. 1 or 2
4. exp pain/
5. pain*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. 4 or 5
7. 3 and 6
8. limit 7 to (adult <18 to 64 years> or aged <65+ years>)

Science Citation Index Expanded (Web of Science) (1900 to October 2016) (1627 hits)

#3 #2 AND #1
#2 TS=pain*
#1 TS=(pregabalin or lyrica)

Google scholar search

<u>After the 1st search, 18th August 2015</u>
Pregabalin AND Postoperative pain
Pregabalin AND Acute pain management
Pregabalin AND Perioperative pain management

After the 2nd search, 28th October 2016
Pregabalin AND Postoperative pain
Pregabalin AND Acute pain management
Pregabalin AND Perioperative pain management

Limits: titles from 1st August 2015 and on

Appendix 2: Opioid conversion

Opioid	Administration	Opioid: Intravenous morphine
1 mg Fentanyl	i.v.	100 mg morphine
1 mg Hydromorphone	i.v.	5 mg morphine
1 mg Morphine oral	oral	0.33 mg morphine
1 mg Nalbuphine	i.v.	1 mg morphine
1 mg Pethidine/Meperidine	i.v.	0.13 mg morphine
1 mg Propoxyphene	i.v.	5 mg morphine
1 mg Tramadol oral	oral	0.07 mg morphine

Appendix 3: Trial characteristics

Trial characteristics	N*	Surgical procedure	Pregabalin dose + administration	Anesthesia	Postoperative analgesia	Follow-up**
Author (Year)						
Abbasabadi 2015	N=69	Hysterectomy	75mg/150mg Single dose	GA	Morphine (3 mg p.n.)	24 hours
Ahiskalioglu 2015	N=40	Double jaw surgery	150mg Single dose	GA	Fentanyl (PCA)***; NSAID (Dexketoprofen 50 mg); LIA (2% Articain 80 mg)****	24 hours
Ahn 2016	N=60	Anthropic shoulder surgery	150 mg Single dose	GA	Fentanyl (PCA); Ketorolac 30 mg p.n.	48 hours
Akarsu 2012	N=60	Laparoscopic cholecystectomy	300 mg Single dose	GA	Pethidine (0.35mg/kg i.v.); NSAID (Diclofenac 75 mg i.m.)	24 hours
Akhavanakbari 2013	N=60	Lower limb surgery	150 mg Single dose	Spinal anesthesia	Pethidine (50 mg i.v.)	24 hours
Alimian 2012	N=80	Dacryocystorhino-stomy	300 mg Single dose	GA	Pethidine (25 mg i.m.)	24 hours
Aydogan	N=60	Nephrelisthomia	75 mg Single dose	GA	Morphine (PCA); NSAID (Tenoxicam 20 mg i.v.)	24 hours
Bafna 2014	N=60	Gynecological surgery	150 mg Single dose	Spinal anesthesia	NSAID (Diclofenac 75 mg i.m.)	24 hours
Balaban 2012	N=90	Laparoscopic cholecystectomy	150mg/300 mg Single dose	GA	Fentanyl (25 ug i.v. p.n.)	24 hours
Bekawi 2014	N=60	Laparoscopic cholecystectomy	150 mg Continuous dose	GA	Pethidine (1 mg/kg I.m.) Tramadol (1 mg/kg); NSAID (Diclofenac 75 mg i.m. p.n.)	24 hours
Bornemann-Cimenti 2012	N=26	Nephrectomy	300 mg Single dose	GA	Piritramide (PCA 0.2 mg/kg)	48 hours
Brulotte 2015	N=99	Thoracotomy	150 mg (300 mg/d)	GA	Fentanyl (50-100 ug p.n.); Epidural analgesia (0.1%+fentanyl 2 ug/ml); Paracetamol (1300 mg+ 650 mg x 4)	3 months
Burke 2009	N=38	Lumbar Discectomy	300 mg Continuous dose	GA	Morphine (0.1 mg/kg); Codeine, Tramadol; NSAID (Diclofenac 75 mg x2); Paracetamol (1-2 g); LIA (0.25% Bupivacaine)	3 months
Buvanendran 2010	N=228	Total knee arthroplasty	300 mg Continuous dose	Spinal-epidural anesthesia	Opioids (morphine, Oxycodone, Hydromorphone); Epidural analgesia (PCIA Bupivacain 0.75% 1mg/ml + Fentanyl 25 ug) ******; NSAID (Celecoxib 200 mg x 3)	6 months
Buvanendran 2012	N=44	Total knee arthroplasty	150 mg Single/continuous dose	Spinal-epidural anesthesia	Epidural analgesia (PCIA Bupivacain 0.75% 4 ml/h)	32 hours
Cabrera-Schulmeyer 2010	N=80	Sleeve gastrectomy	150 mg Single dose	GA	Morphine (0.1 mg/kg+ 2 mg bolus); NSAID (Ketoprofen 100 mg i.v.+ infusion 300 mg/24h)	24 hours
Cegin 2016	N=80	Upper extremity bone	75 mg/ 150 mg /300	LA	Infraclavicular blok (Levobupicavaine 75 mg)	24 hours

		surgery	mg Single dose			
Chang 2009	N=77	Laparoscopic cholecystectomy	150 mg Single dose	GA	Pethidine (25 mg i.v.); NSAID (30 mg i.v. p.n.)	48 hours
Chaparro 2012	N=106	Cosmetic surgery	150 mg (150 mg/d)	GA	Morphine (0.05 mg/kg); NSAID (Diclofenac 75 mg and/or Dipyrone 2g); Paracetamol (325 or 500 mg); Regional anesthesia (Bupivacain 0.25%)	96 hours
Choi 2013	N=72	Lumbar laminectomy	150 mg Continuous	GA	Fentanyl (0.4 ug/kg/hour); NSAID (Keterolac 30 mg i.v. p.n.)	6 months
Chotten 2014	N=80	Abdominal hysterectomy	150 mg Single dose	GA	NSAID (Keterolac); Paracetamol (1000 mg)	24 hours
Clarke 2016	N=184	Total hip arthroplasty	150 mg Single dose	Spinal anesthesia	Morphine (PCA 1 mg p.n.); Oxycontin (5mg x 4); NSAID (Celecoxib 400 mg)	3 months
Clendenen 2010	N=47	Arthroscopic rotator cuff repair	150 mg Single dose	GA	Oxycodone (5 mg p.n.); NSAID (Celecoxib 400 mg); Paracetamol (325 mg p.n.); Regional anesthesia (Bupivacain 0.5% 30 ml)	48 hours
Demirhan 2013	N=40	Rhinoplasty	300 mg Single dose	GA	Pethidine (50 mg i.v,); Tramadol (50 mg i.v.+ PCA 20 mg bolus); NSAID (Diclofenac 75 mg i.m.); LIA (Lidocaine 20 mg/ml)	24 hours
Demirhan 2014	N=60	Septoplasty	300 mg Single dose	GA	Pethedine (0.5 mg/kg); Tramadol (50 mg i.v.+ PCA 20 mg bolus); NSAID (Diclofenac 75 mg); LIA (Lidocaine 20 mg/ml)	24 hours
Eman 2014	N=40	Abdominal hysterectomy	150 mg Single dose	GA	Morphine (PCA)	24 hours
El Kenany 2016	N=135	Caesarean section	150 mg /300 mg Single dose	Spinal	Morphine (PCA 1 mg i.v. p.n.); Fentanyl (0.5 ug/kg i.v. p.n.);	48 hours
Eskander 2013	N=80	Shoulder arthroscopy	300 mg Continuous	GA	Nalbuphine (4 mg i.v. p.n.); NSAID (Diclofenac 75 mg i.v.); LIA (Bupivacaine 0.25% 10 ml)	24 hours
Fassoulaki 2012	N=67	Abdominal hysterectomy and myomectomy	150 mg Continuous	GA	Morphine (PCA 1 mg/ml); Codeine (30 mg from day 2); Paracetamol (500 mg from day 2)	3 months
Freedman 2008	N=80	Augmentation mammoplasty	75 mg Continuous	GA	Hydromorphone (5 mg p.o.)	7 days
Fujati 2015	N=97	Spinal surgery	75 mg / 150 mg Single dose	GA	Morphine (1mg/ml i.v. p.n.); NSAID (Flurbiprofen 50 mg or Indomethacin 50 mg suppositories)	48 hours
George 2014	N=89	Abdominal hysterectomy	75/150 mg Continuous	GA	Morphine (PCA 1-2 mg); NSAID (Ketorolac 30 mg i.v., Naproxen 1000 mg/day)	6 months
Ghai 2011	N=60	Abdominal hysterectomy	300 mg Single dose	GA	Tramadol (10 mg i.v. p.n.); NSAID (Diclofenac 1 mg/kg i.m.)	24 hours
Ghai 2012	N=60	Abdominal hysterectomy	300 mg Single dose	GA	?	24 hours
Ghosh 2016	N=64	Abdominal hysterectomy	300 mg Single dose	GA	Fentanyl (25 ug i.v. p.n.); Paracetamol (4000 mg/d)	24 hours
Giansello 2012	N=60	Lumbar laminectomy with	300 mg	GA	Morphine (0.01 mg/kg/h); NSAID (ketorolac infusion 2.5 mg/h)	1 year

		spinal fusion	Continuous			
Gonano 2011	N=40	Arthroscopic knee surgery	300 mg Single dose	GA	Piritramide (7.5 mg i.v. and 2 mg i.v. p.n.); NSAID (Mefenamine acid 0.5 g p.o. p.n.)	24 hours
Gupta 2011	N=120	Laparoscopic cholecystectomy	150 mg Single dose	GA	Opioid	?
Gurunathan 2016	N=34	Laparoscopic cholecystectomy	150 mg (150 mg/d)	GA	Fentanyl (PCA)	48 hours
Hegarty 2011	N=32	Lumbar discectomy	300 mg Single dose	GA	Morphine (PCA 2 mg p.n.); NSAID (75 mg i.v.); Paracetamol (1000 mg i.v.); LIA (Bupivacaine 2.5 mg/ml)	24 hours
Hetta 2016	N=111	Mastectomy	75 mg /150 mg /300 mg Single dose	GA	Morphine (0.1 mg/kg i.v.); Paracetamol (1000 mg i.v.)	24 hours
Ittichaikulthol 2009	N=78	Abdominal hysterectomy	300 mg Single dose	GA	Morphine (PCA 1 mg i.v. p.n.)	24 hours
Jain 2012	N=40	Total knee arthroplasty	75 mg Continuous	Spinal-epidural anesthesia	Epidural analgesia (PCIA Bupicavaine 0.25% 5 ml p.n. and morphine 0.005 mg/ml); NSAID (Diclofenac 75 mg p.o. p.n.)	48 hours
Jajada 2014	N=60	Middle ear surgery	150 mg Single dose	GA	Tramadol (50 mg i.v. p.n.); NSAID (Diclofenac 1.5 mg/kg i.v. p.n.)	24 hours
Jokela 2008a	N=85	Laparoscopic hysterectomy	150mg/300mg (300mg/d or 600 mg/d)	GA	Oxycodone (PCA 0.04 mg/kg bolus and 1 mg/ml infusion); NSAID (Ibuprofen 800 mg); Paracetamol /Codeine (tablets p.n.)	5 days
Jokela 2008b	N=84	Laparoscopic gynecologic surgery	75mg/150 mg Single dose	GA	Fentanyl (0.075 mg/kg i.v. single bolus and 0.025 mg i.v. p.n.); NSAID (800 mg p.o.); Paracetamol /Codeine (tablets p.n.)	30 hours
Joshi 2013	N=40	Coronary artery bypass surgery	150 mg (150mg/d)	GA	Tramadol (1 mg/kg); NSAID (Diclofenac 75 mg p.n.); Paracetamol (4000 mg/d)	3 months
Khetarpal 2016	N=60	Lower limb orthopedic surgery	300 mg Single dose	Spinal-epidural anesthesia	Epidural analgesia (0.5% Bupivacaine 3 ml); NSAID (Diclofenac 75 i.m.)	24 hours
Khurana 2014	N=60	Lumbar discectomy	75 mg (225mg/d)	GA	Tramadol (1-2mg/kg); NSAID (75mg Diclofenac)	3 months
Kim 2010	N=94	Robot assisted endoscopic thyroidectomy	150 mg (300mg/d)	GA	Tramadol (50 mg i.m.*** p.n.); Fentanyl (50ug p.n.); NSAID (Ketorolac 30 mg and Ibuprofen 400 mg)	3 months
Kim 2011a	N=84	Mastectomy	75 mg (150mg/d)	GA	Tramadol (50 mg i.m. p.n.); Fentanyl (50 ug p.n.) NSAID (Ketorolac 30 mg and Airtal 200 mg/d)	1 month
Kim 2011b	N=84	Lumbar spinal fusion surgery	75 mg / 150 mg Single	GA	Fentanyl (PCA); NSAID (Ketorolac 120 mg and Ketorolac 30 mg p.n.)	48 hours
Kim 2014	N=47	Septoplasty	75 mg/150mg (150 mg/d and 300 mg/d)	GA	Pethidine (50 ug p.n.); Paracetamol (1950 mg/d)	48 hours
Kohli 2011	N=12	Hysterectomy	150 mg / 300 mg	Spinal anesthesia	Unknown rescue analgesics	24 hours

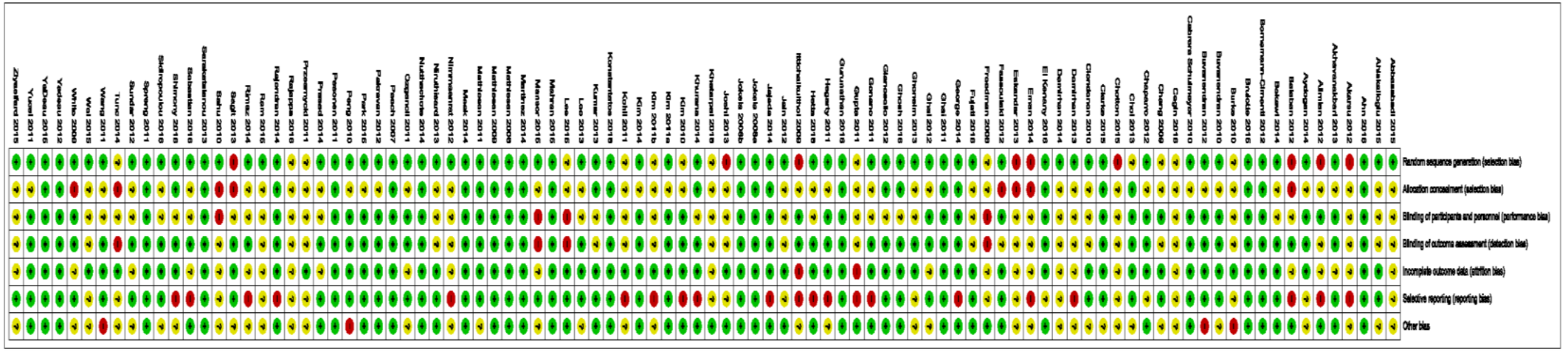
	0		Single dose			
Konstantatos 2016	N010 0	Video-assisted thoracoscopic surgery	300 mg Single dose	GA	Morphine (PCA 1 mg i.v. p.n.); Oxycodone (p.o. p.n.); Paracetamol (4000 mg/d)	9 months
Kumar 2013	N=56	Lumbar discectomy	300 mg Single dose	GA	Fentanyl (50ug p.n.); NSAID (Diclofenac 50 mg p.n.)	6 hours
Lee 2013	N=60	Laparoscopic urologic surgery	300 mg Single dose	GA	Morphine (PCA); NSAID (Ketorolac 150 mg)	24 hours
Lee 2014	M=41	Total knee arthroplasty	150 mg Single dose	GA	Fentanyl (PCA); Tramadol (50 mg i.m. p.n.); Hydromorphone (6 mg/d from day 2) NSAID (Celecoxib 400 mg/d); LIA (Bupivacaine 0.5% 20 ml)	48 hours
Mahran 2011	N=60	Mastectomy	150 mg Single dose	GA	Morphine (PCA)	24 hours
Mansor 2015	N=49	Mastectomy	150 mg Single dose	GA	Morphine (0.1-0.2mg/kg); Tramadol (50 mg p.n.); NSAID (Parecoxib 40 mg and 480 mg/d); Paracetamol (4000 mg/d); LIA (Levibupivacaine 2 mg/kg)	24 hours
Martinez 2013	N=62	Total hip arthroplasty	150 mg Single dose	GA	Morphine (PCA)	3 days
Mathiesen 2008	N=78	Total hip arthroplasty	300 mg Single dose	Spinal anesthesia	Morphine (PCA); Paracetamol (3000 mg/d)	24 hours
Mathiesen 2009	N=79	Abdominal hysterectomy	300 mg Single dose	GA	Morphine (PCA); Paracetamol (4000 mg/d)	24 hours
Mathiesen 2011	N=88	Tonsillectomy	300 mg Single dose	GA	Morphine (2.5 mg i.v. p.n.); Paracetamol (3000 mg/d); Ketobemidone (2.5 mg p.o. p.n.)	24 hours
Meek 2014	N=13 0	Post photorefractive keratectomy	75 mg (150 mg/d)	Local anesthesia	Oxycodone (5 mg p.n.); NSAID (Ketorolac trometamine 0.4% eyedrops, Ibuprofen); Paracetamol (500 mg p.n.)	5 days
Nimmaanrat 2012	N=56	Arthroscopic anterior cruciate ligament repair	75 mg (150 mg/d)	Spinal anesthesia	Morphine (PCA)	24 hours
Niruthisard 2013	N=51	Total knee arthroplasty	150 mg Single dose	Spinal anesthesia	Morphine (PCA)	48 hours
Nutthachote 2014	N=54	Laparoscopic gynecologic surgery	75 mg (150mg/d)	GA	Meripidine (1 mg/kg i.v. p.n.); NSAID (Etoricoxib 120 mg/d); Paracetamol (1000mg p.n.)	48 hours
Özgencil 2011	N=60	Lumbar laminectomy and discectomy	150 mg (300mg/d)	GA	Morphine (PCA); NSAID (Lornoxicam 8 mg p.n.)	24 hours
Paech 2007	N=86	Minor gynecologic surgery	100 mg Single dose	GA	Fentanyl (20-30 ug p.n.), Tramadol (50 mg p.n.), NSAID (Diclofenac 50 mg p.n.); Paracetamol (1000 mg)	24 hours
Pakravan 2012	N=10 0	Post photorefractive keratectomy	75 mg (225 mg/d)	Local anesthesia	Paracetamol /Codeine (300/10 p.o. p.n.), Betamethasone (0.1% eyedrops 4/d)	4 days
Park 2015	N=48	Tonsillectomy	300 mg Single dose	GA	Fentanyl (PCA); Paracetamol (1950 mg/d)	8 days
Peng 2010	N=14 2	Laparoscopic cholecystectomy	50 mg /75 mg (100 mg/d and 150	GA	Fentanyl (25-50 ug p.n.); Acetaminophen (1000 mg); LIA (Bupivacaine 0.25% 20 ml); Paracetamol /Codeine (325/30 mg p.n.)	7 days

			mg/d)			
Pesonen 2011	N=60	Cardiac surgery	150 mg (150 mg/d)	GA	Oxynorm (0.05 mg/kg iv or 0.10-0.15 mg/kg p.o. p.n.); Paracetamol (3000 mg/d)	3 months
Prasad 2014	N=60	Vaginal hysterectomy	150 mg Single dose	Spinal anesthesia	NSAID (Diclofenac 1 mg/kg i.m. p.n.)	24 hours
Przesmycki 2011	N=80	Abdominal hysterectomy	75 mg / 150 mg /300 mg Single dose	GA	Morphine (PCA 5 mg i.v. p.n.); Paracetamol (Paracetamol 1000-2000 mg p.n.)	24 hours
Rajappa 2016	N=135	Vaginal hysterectomy	75 mg /150 mg Single dose	Spinal anesthesia	Tramadol 50 mg i.v. p.n.; NSAID (Diclofenac 75 mg i.v. p.n.); Paracetamol (Paracetamol 3000 mg/d)	24 hours
Rajendran 2014	N=60	Lower abdominal and limb surgery	300 mg Single dose	Spinal anesthesia	Tramadol (100 mg i.m. p.n.)	72 hours
Ram 2015	N=60	Abdominal hysterectomy	300 mg Single dose	Spinal anesthesia	NSAID (Diclofenac 1 mg/kg i.m. p.n.)	24 hours
Rimaz 2014	N=60	Dacryocystorhinostomy	300 mg	LA	Pethidine; LIA (Lidocaine 2% and 0.5% Bupivacaine)	24 hours
Sagit 2013	N=143	Septoplasty	75mg/150 mg	GA	NSAID (Diclofenac 75 mg i.m. p.n.)	24 hours
Sahu 2010	N=70	Below umbilical surgeries	150mg (300mg/d)	Spinal anesthesia	Tramadol (1mg/kg i.v.)	24 hours
Sarakatsianou 2012	N=40	Laparoscopic cholecystectomy	300 mg (600 mg/d)	GA	Morphine (PCA); Paracetamol (4000 mg/d)	24 hours
Sebastian 2016	N=90	Lower limb orthopedic surgery	150 mg Single dose	Spinal anesthesia	NSAID (Diclofenac 75 mg i.m. p.n.)	24 hours
Shimoni 2016	N=100	Supra- or infratentorial tumor surgery	150 mg (300 mg/d)	GA	Morphine (1 mg i.v. p.n. or Tramadol 100 mg i.v. p.n); NSAID (Diclofenac 75 mg i.m. p.n.); Paracetamol (1000 mg i.v.)	3 months
Sidiropoulou 2016	N=30	Thoracotomy	75 mg (150 mg/d)	GA	Morphine (PCA 1mg i.v. p.n.); Paracetamol (4000 mg/d i.v.); Lonagal (Paracetamol 500 mg and Codeine 30 mg after postoperative day 2)	3 months
Spreng 2011	N=46	Discectomy	150 mg Single dose	GA	Morphine (PCA); NSAID (Diclofenac 150 mg/d); Paracetamol (4000 mg/d); LIA (Bupivacaine 0.25% 20 ml)	7 days
Sundar 2012	N=60	Coronary artery bypass surgery	150 mg Single dose	GA	Fentanyl (0.5 ug/kg p.n.); Propofol (1 mg/kg/h continued in intensive care unit until the extubation criteria were met)	24 hours
Tunc 2014	N=40	Thoracotomy	150 mg Single dose	GA	Epidural analgesia (Bupivacaine 0.25% 0.1 ml/kg)	6 months
Wang 2010	N=66	Bunionectomy	300 mg (450 mg/d)	Spinal anesthesia	Hydromorphine (PCA); NSAID (Naproxen: 1100 mg/d); Hydrocordone/ Paracetamol 7.5/500 mg tablets p.o. p.n. after 24 hours); LIA (Lidocaine 2%)	48 hours
Wei 2014	N=49	Eyelid surgery	150 mg Single dose	GA	Acetaminophen (4000 mg/d); LIA (Lidocaine 1% and Bupivacain 0.5%)	48 hours
White 2009	N=108	ENT-, laparoscopic-, urologic- and plastic	75mg/150mg /300mg	GA	Fentanyl (25-50 ug i.v. p.n.)	7 days

		surgery				
YaDeau 2012	N=54	Ankle surgery	200 mg (100 mg/d)	Spinal and epidural anesthesia	Hydromorphone (PCA); Oxycodone- Paracetamol (5/325 mg); Regional analgesia (Bupivacaine 0.375%, Clonidine 100 ug and epinephrine 5 ug/ml); LIA (Bupivacaine 0.5%)	7 days
YaDeau 2015	N=111	Total knee arthroplasty	50mg/100mg /150mg	Spinal and epidural anesthesia	Oxycodone-paracetamol (5 mg/325mg p.n.); Epidural analgesia (Bupivacaine 0.006% and Hydromorphone 10 ug/ml); Regional Analgesia (Bupivacaine 0.25% 30 ml with adrenaline); NSAID (Meloxicam);	16 days
Yucel 2011	N=90	Abdominal hysterectomy	150mg/300mg (300mg/d and 600 mg/d)	GA	Morphine (PCA)	24 hours
Ziyaeifard 2015	N=60	Coronary Artery Bypass surgery	150 mg Single dose	GA	Morphine (1mg/kg i.v. p.n.)	24 hours

**N: number of patients in the pregabalin and control group added; **The longest follow-up described in the article; **PCA: Patient Controlled Analgesia; LIA: Local Infiltration Anesthesia; ****Continuous dose: more than one administration of pregabalin; PCIA: Patient Controlled Intrathecal Analgesia; """" I.M. intra muscular; pn: upon request or at a pain intensity score above a pre-defined cut-off; p.o: oral administration*

Appendix 4: Bias assessments



Appendix 5: SoF and GRADE of trials with low risk of bias

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Controls	Relative (95% CI)	Absolute (95% CI)	
24-hour opioid consumption: Bias - Low risk of bias											
11	Randomised trials	not serious	not serious	serious [a]	serious[d]	none	360	345	-	MD **5.8 lower** (8.5 lower to 3.2 lower)	⊕⊕◯◯ Low
24-hour opioid consumption Multimodal regimen: + add-on - Low risk of bias											
8	Randomised trials	not serious	not serious	serious [c]	serious [d]	none	259	240	-	MD **5.3 lower** (8.5 lower to 2.1 lower)	⊕⊕◯◯ LOW
24-hour opioid consumption Multimodal regimen - add-on, placebo - Low risk of bias											
2	Randomised trials	not serious	not serious	serious [c]	serious [d]	none	60	60	-	MD **13.7 lower** (17.8 lower to 9.6 lower)	⊕⊕◯◯ LOW
24-hour opioid consumption: Single vs Multiple dose - Single dose											
6	Randomised trials	not serious	serious [e]	serious [c]	serious [d]	none	192	207	-	MD **10.1 lower** (17.8 lower to 2.4 lower)	⊕◯◯◯ VERY LOW
24-hour opioid consumption: Single vs Multiple dose Bias - Multiple dose											
5	Randomised trials	not serious	serious [f]	serious	not serious	none	168	138	-	MD **2.4 lower** (4.2 lower to 0.6 lower)	⊕⊕◯◯ LOW
Serious Adverse Events: Bias - Low risk of bias											
10	Randomised trials	not serious	not serious	not serious	serious [d]	none	17/398 (4.3%)	5/332 (1.5%)	**OR 2.85** (1.20 to 6.77)	**27 more per 1.000** (from 3 more to 79 more)	⊕⊕⊕◯ MODERATE
Serious Adverse Events: Single vs Multiple dose - Single dose											
4	Randomised trials	not serious	Serious[f]	not serious	serious [d]	none	3/122 (2.5%)	2/121 (1.7%)	**OR 1.57** (0.26 to 9.47)	**9 more per 1.000** (from 12 fewer to 121 more)	⊕◯◯ VERY LOW
Serious Adverse Events: Single vs Multiple dose - Multiple dose											

Quality assessment							№ of patients		Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Controls	Relative (95% CI)	Absolute (95% CI)	
6	Randomised trials	not serious	not serious	not serious	serious [d]	none	14/276 (5.1%)	3/211 (1.4%)	**OR 3.41** (1.27 to 9.15)	**33 more per 1.000** (from 4 more to 102 more)	⊕⊕⊕◯ MODERATE
Adverse event: Vomiting: Bias - Low risk of bias											
6	Randomised trials	not serious	serious [f]	not serious	serious [d]	none	51/243 (21.0%)	47/218 (21.6%)	**RR 1.34** (0.68 to 2.65)	**73 more per 1.000** (from 69 fewer to 356 more)	⊕⊕◯◯ LOW
Adverse event: PONV: Bias - Low risk of bias											
8	Randomised trials	not serious	not serious	not serious	serious [d]	none	74/271 (27.3%)	88/241 (36.5%)	**RR 0.75** (0.54 to 1.03)	**91 fewer per 1.000** (from 11 more to 168 fewer)	⊕⊕⊕◯ MODERATE
Adverse event: Sedation: Bias - Low risk of bias											
10	Randomised trials	not serious	not serious	not serious	serious [d]	publication bias strongly suspected [c]	207/377 (54.9%)	142/294 (48.3%)	**RR 1.06** (0.91 to 1.25)	**29 more per 1.000** (from 43 fewer to 121 more)	⊕⊕◯◯ LOW
VAS 6h rest Bias - Low risk of bias											
9	Randomised trials	not serious	not serious	not serious	serious [d]	none	322	266	-	MD **7.7 lower** (13.3 lower to 2.2 lower)	⊕⊕⊕◯ MODERATE
VAS 6h mob Bias - Low risk of bias											
5	Randomised trials	not serious	very serious [g]	not serious	serious [d]	none	175	148	-	MD **16.3 lower** (42.6 lower to 9.9 higher)	⊕◯◯◯ VERY LOW
Adverse event: Dizziness: Bias - Low risk of bias											
11	Randomised trials	not serious	not serious	not serious	serious [d]	none	120/342 (35.1%)	56/319 (17.6%)	**RR 2.10** (1.12 to 3.91)	**193 more per 1.000** (from 21 more to 511 more)	⊕⊕⊕◯ MODERATE
Adverse event: Visual disturbance: Bias - Low risk of bias											

Quality assessment							№ of patients		Effect		Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Pregabalin**	**Controls**	**Relative (95% CI)**	**Absolute (95% CI)**	
5	Randomised trials	not serious	not serious	not serious	serious [d]	publication bias strongly suspected [c]	27/163 (16.6%)	4/136 (2.9%)	**RR 3.21** (1.24 to 8.28)	**65 more per 1.000** (from 7 more to 214 more)	⊕⊕◯◯ LOW
VAS 24h rest Bias - Low risk of bias											
15	Randomised trials	not serious	not serious	not serious	serious [d]	none	615	508	-	MD **1.4 lower** (5.5 lower to 2.7 higher)	⊕⊕⊕◯ MODERATE
VAS 24h mob: Bias - Low risk of bias											
7	Randomised trials	not serious	serious [f]	not serious	serious [d]	none	262	240	-	MD **3.7 lower** (8.9 lower to 1.5 higher)	⊕⊕◯◯ LOW
Adverse event: Headache: Bias - Low risk of bias											
5	Randomised trials	not serious	serious [f]	not serious	serious [d]	publication bias strongly suspected [c]	40/156 (25.6%)	38/129 (29.5%)	**RR 0.74** (0.41 to 1.33)	**77 fewer per 1.000** (from 97 more to 174 fewer)	⊕◯◯◯ VERY LOW

CI: *Confidence interval;* ***MD:*** *Mean difference;* ***OR:*** *Odds ratio;* ***RR:*** *Risk ratio*

a. In-direct outcome

b. Some unexplained heterogeneity, I-square: 50-90%, however all CI-intervals overlap, point estimates seem aligned

c. Publication bias suspected, illustrated by Funnel plots

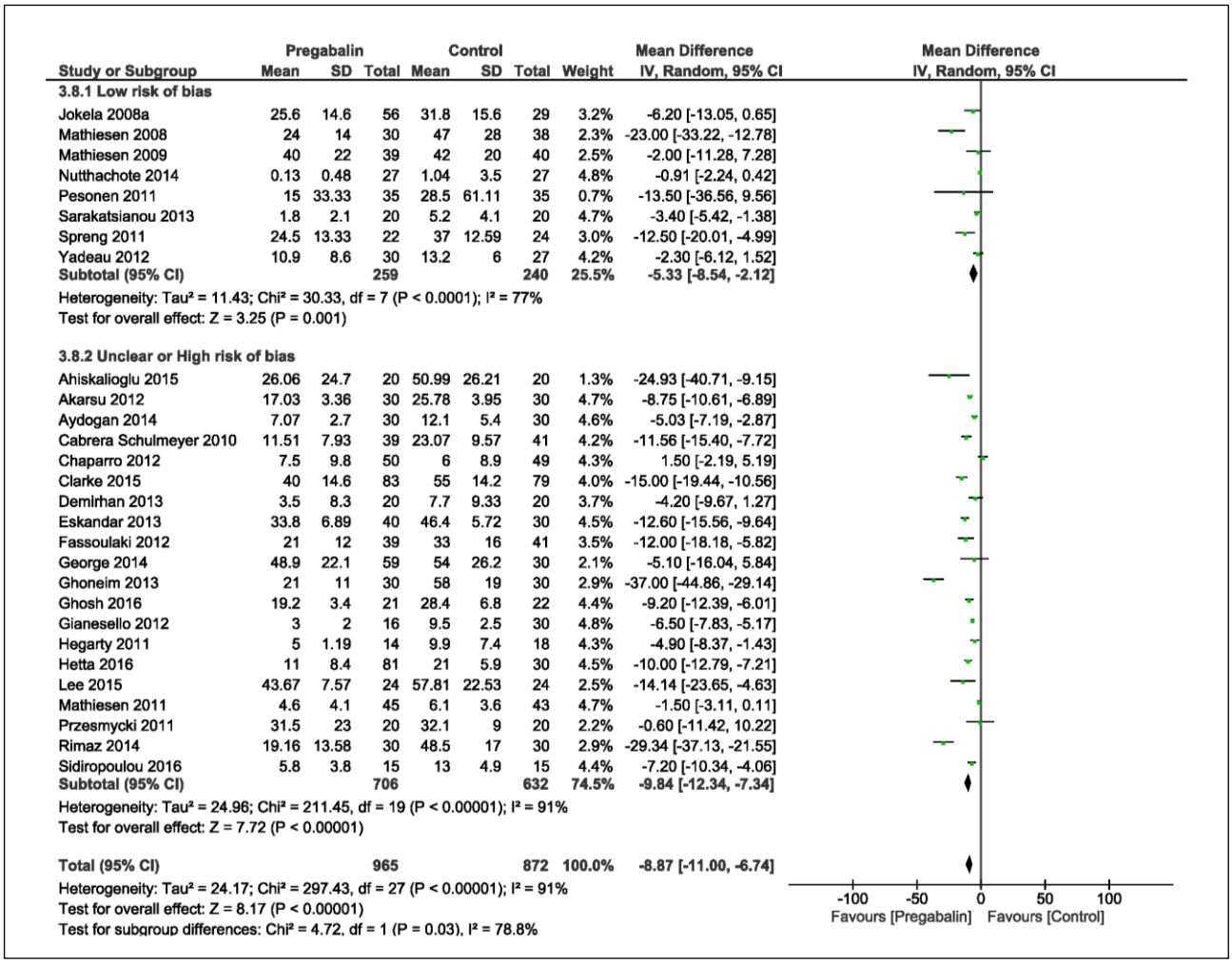
d. The CI crosses the clinical decision threshold between recommending and not recommending treatment, RIS is not met.

e. Some unexplained heterogeneity, I-square: > 90%, however all CI-intervals overlap, and point estimates seem aligned

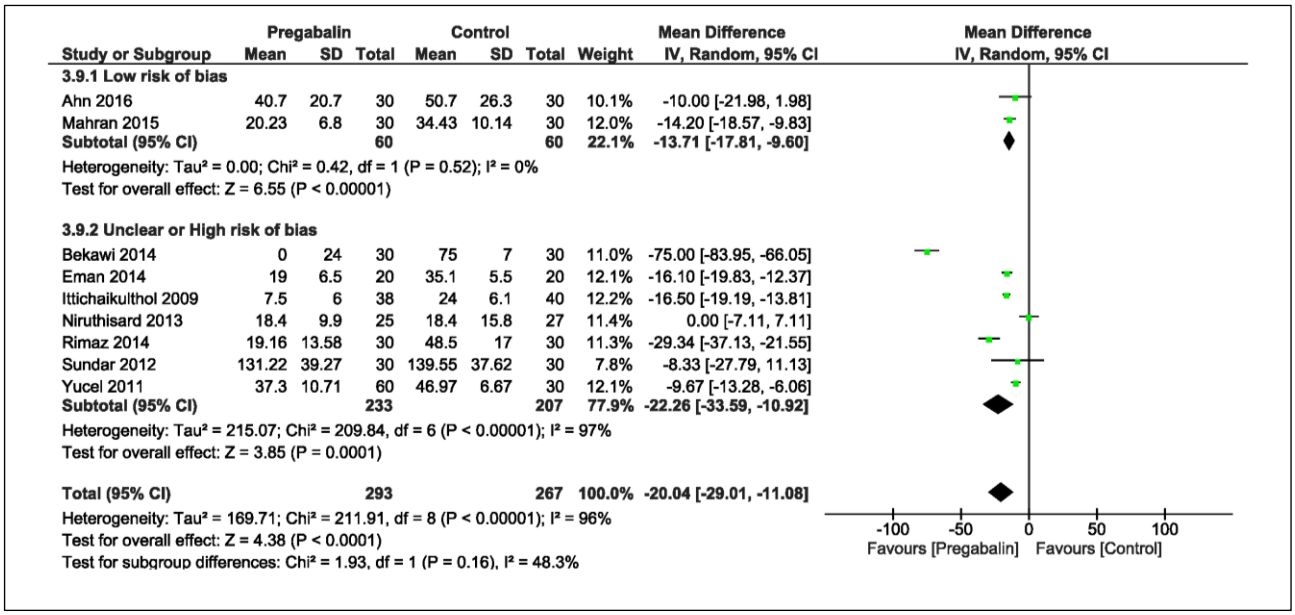
f. Some unexplained heterogeneity, I-square: 30-60%, however all CI-intervals overlap and point estimates seem aligned

g. Some unexplained heterogeneity, I-square > 90%, not all CI-intervals overlap

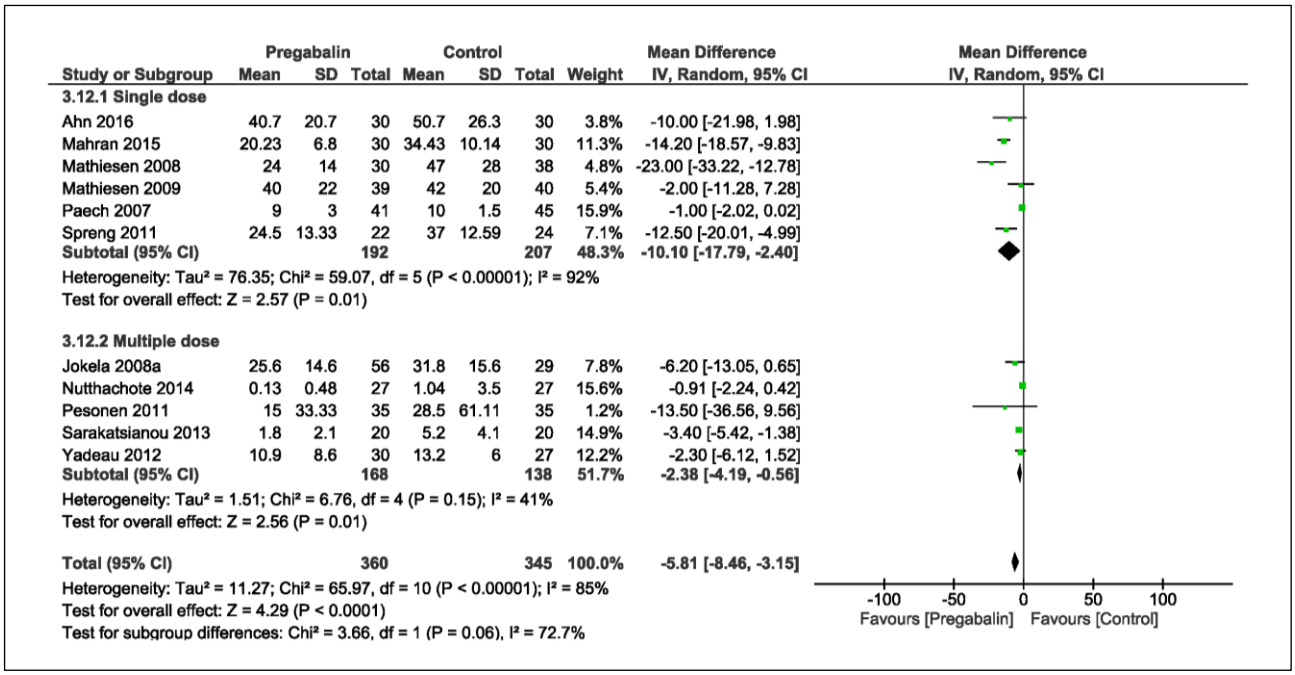
Appendix 6: Forest plot 24-hour morphine consumption + add-on



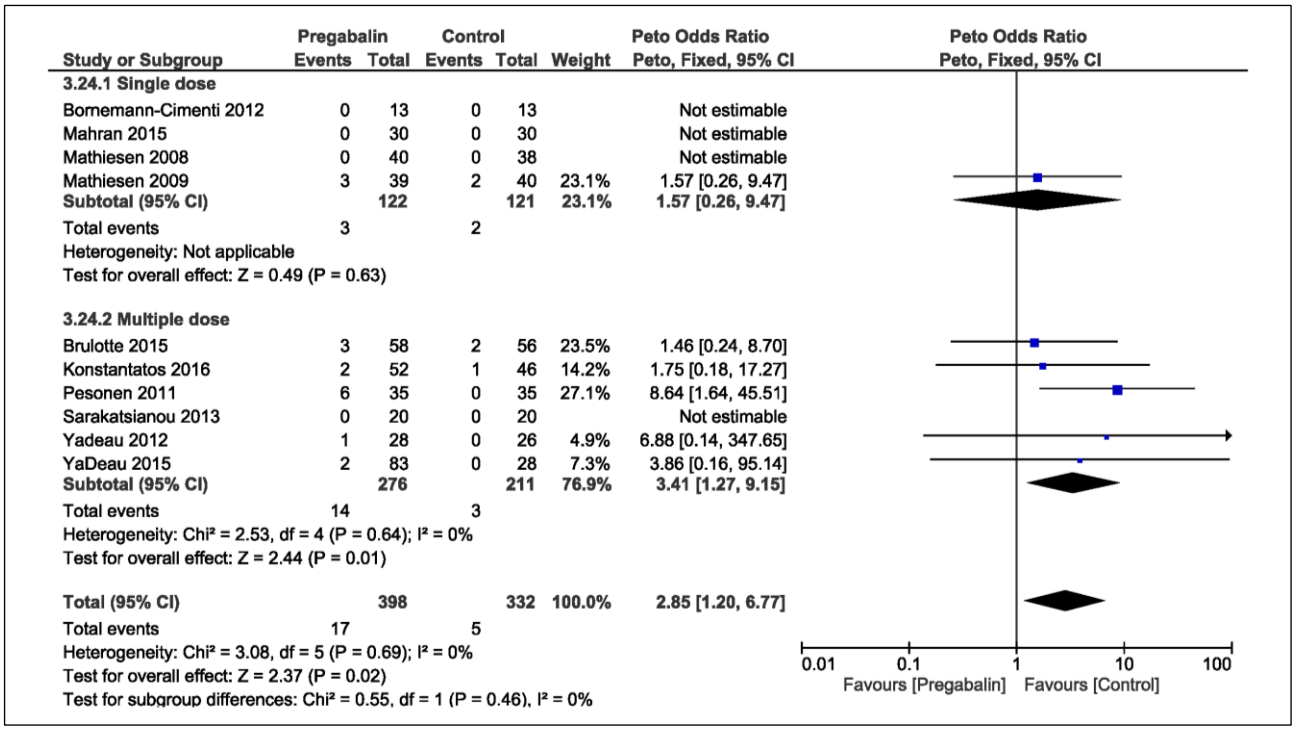
Appendix 7: Forest plot 24-hour morphine consumption – add-on



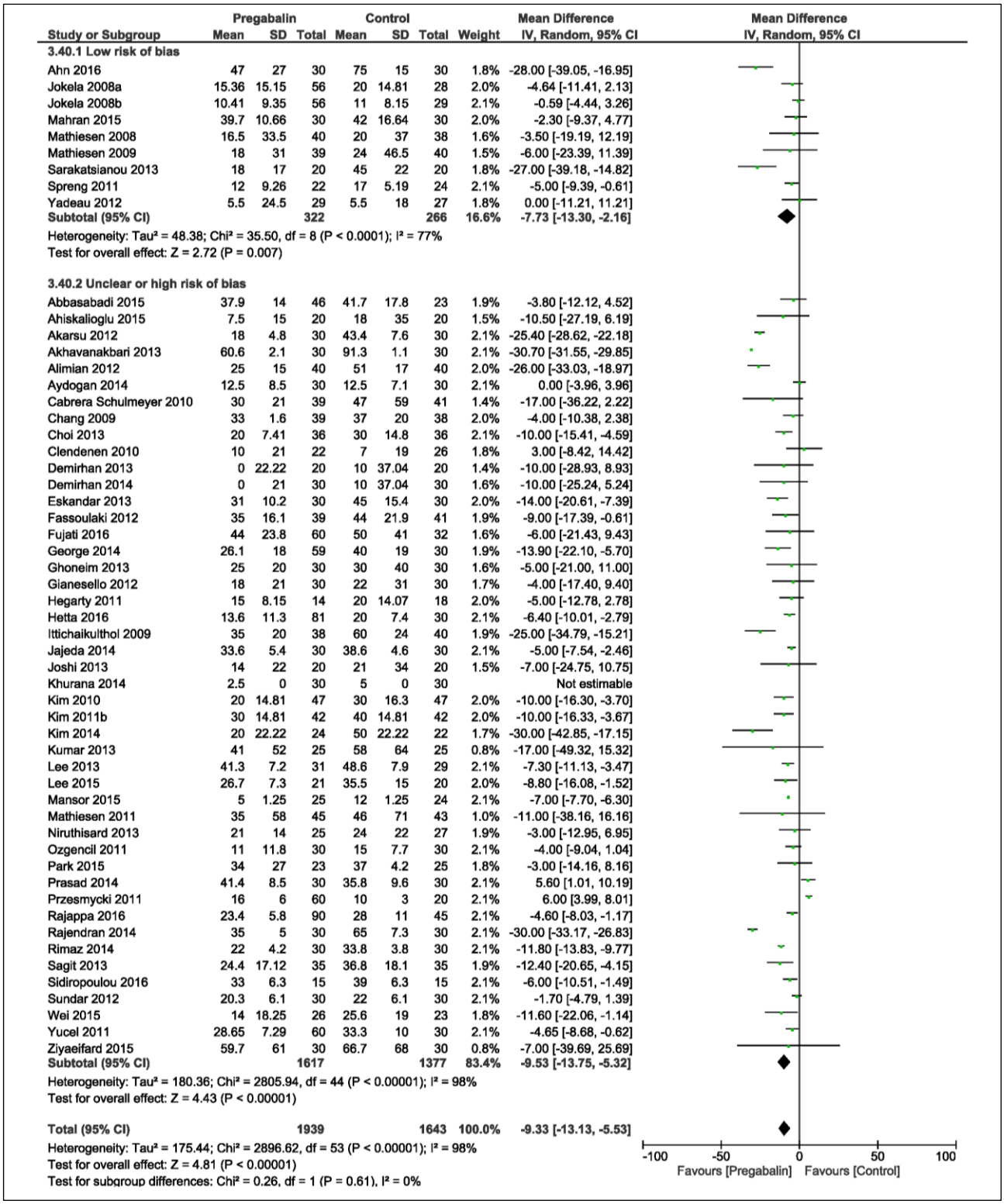
Appendix 8: Single vs multiple dose 24-hour morphine consumption



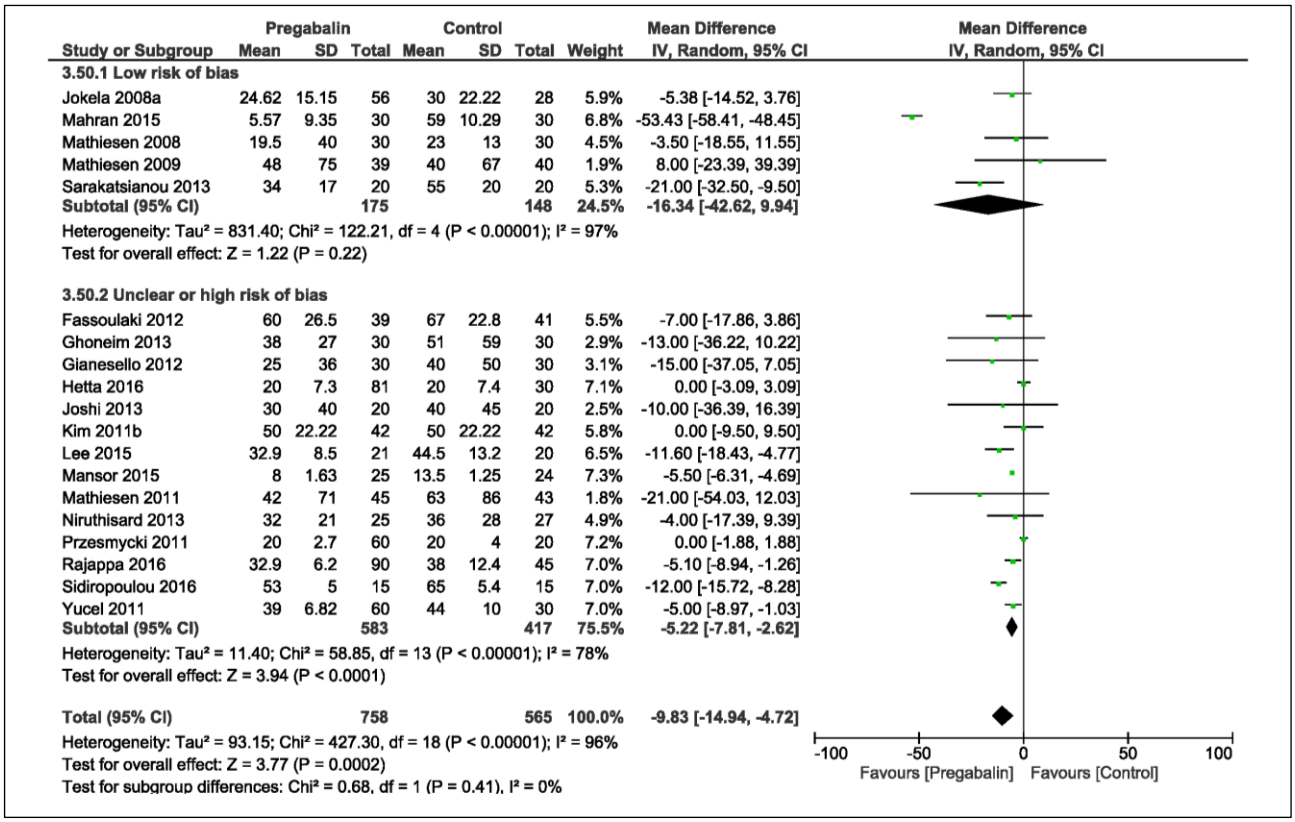
Appendix 9: Single vs. multiple dose SAE



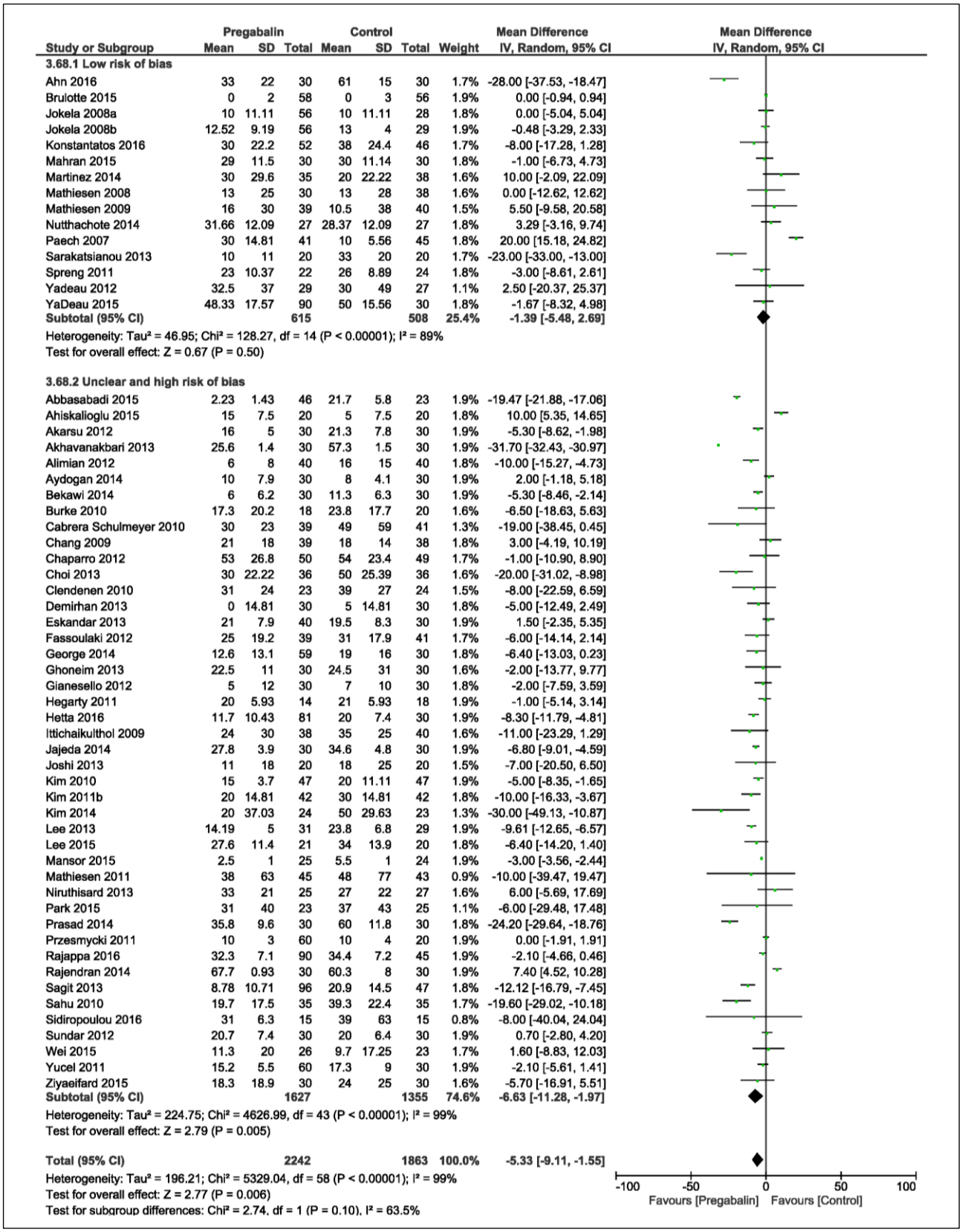
Appendix 10: Forest plots of VAS 6h pain at rest



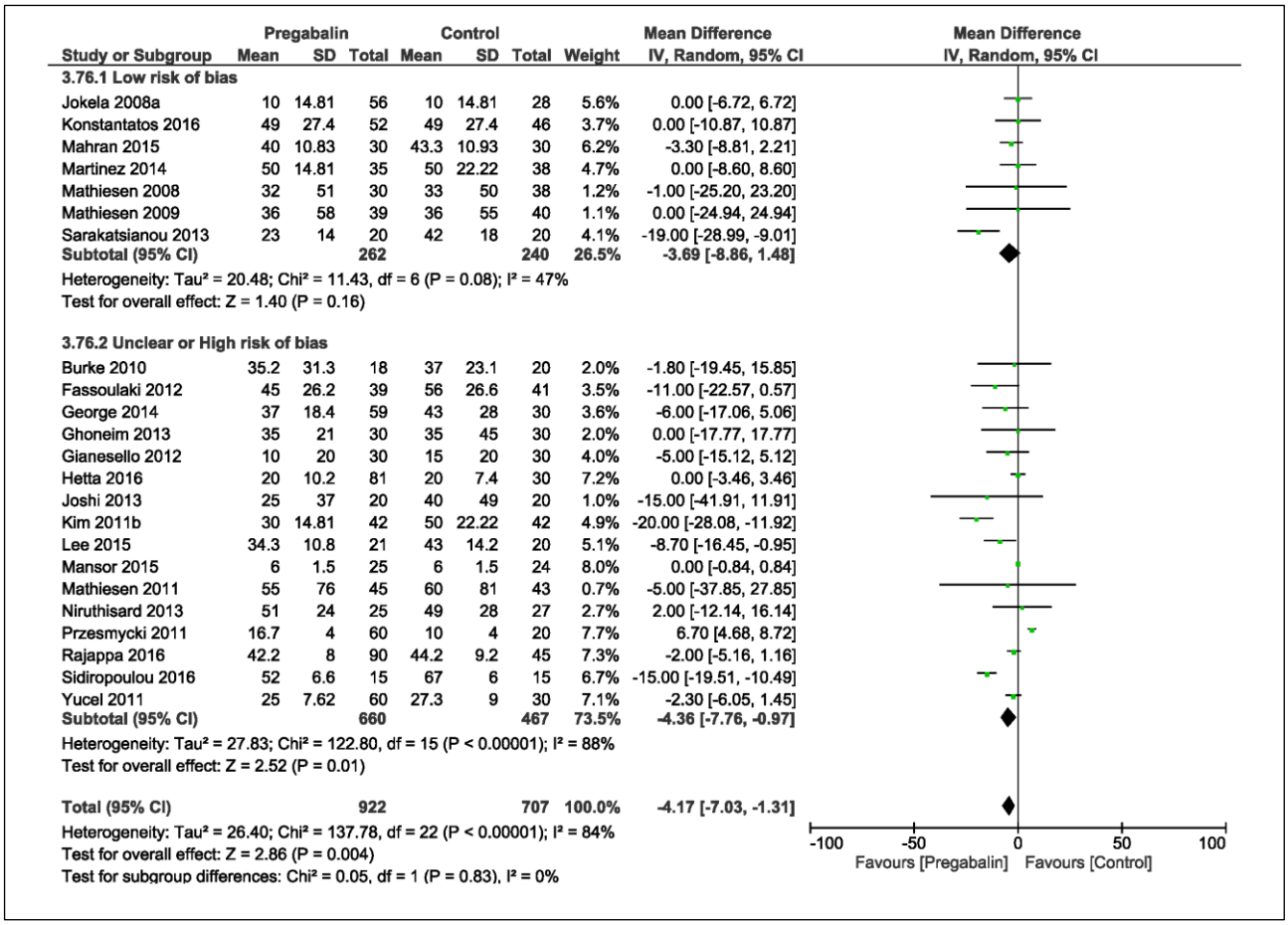
Appendix 11: Forest plots of VAS 6h pain at mobilisation



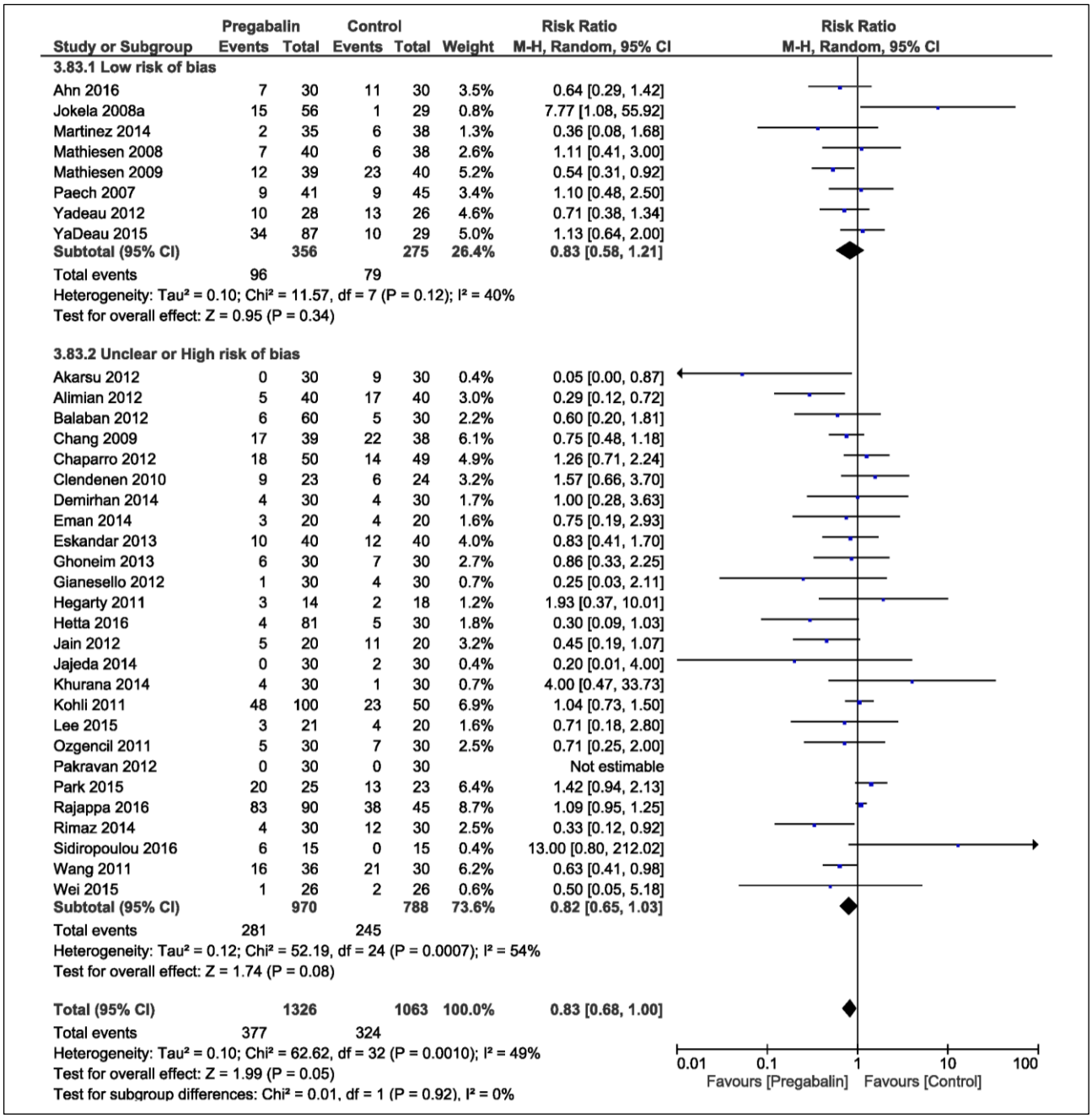
Appendix 12: Forest plots of VAS 24h pain at rest



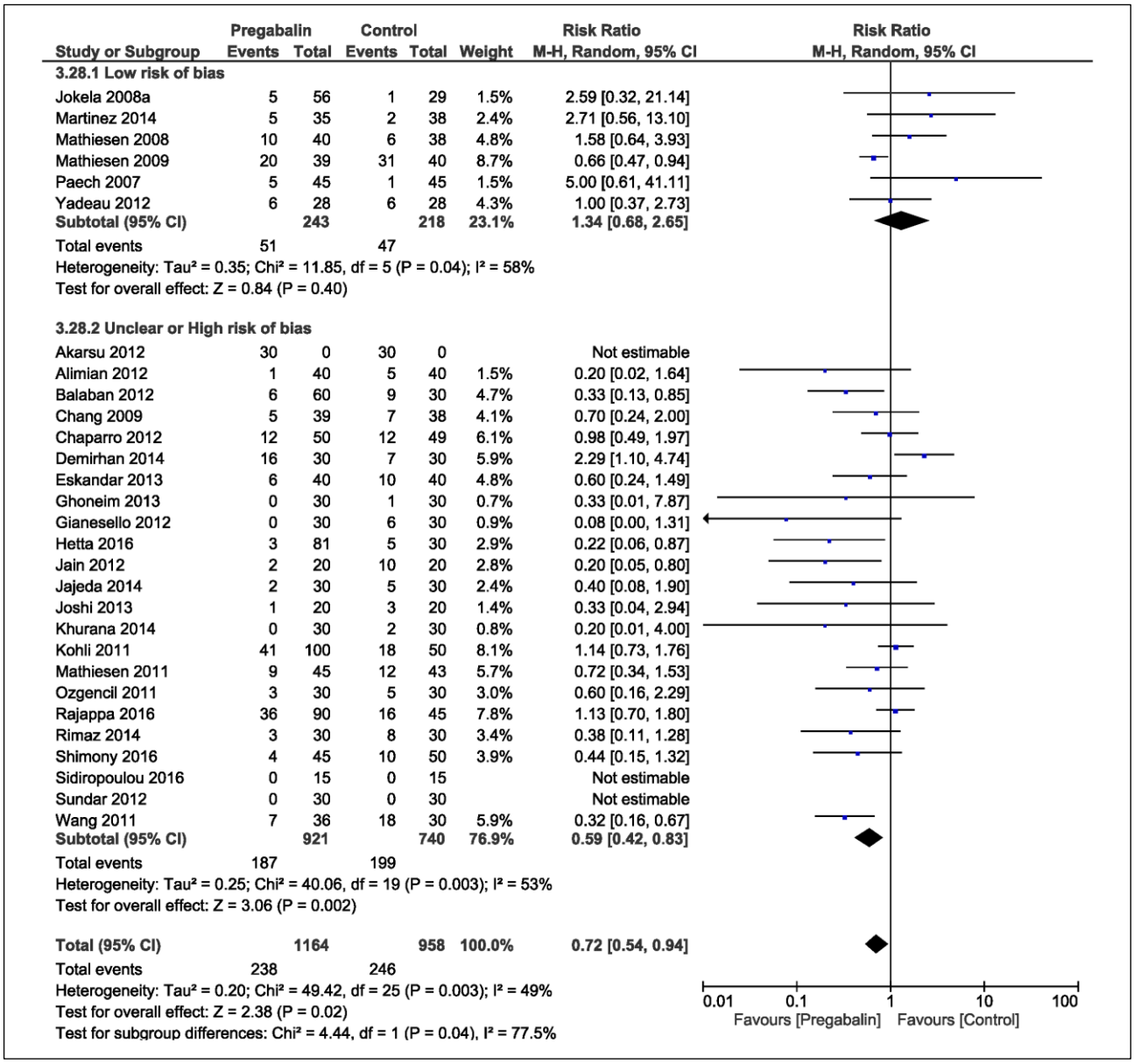
Appendix 13: Forest plots of VAS 24h pain at mobilisation



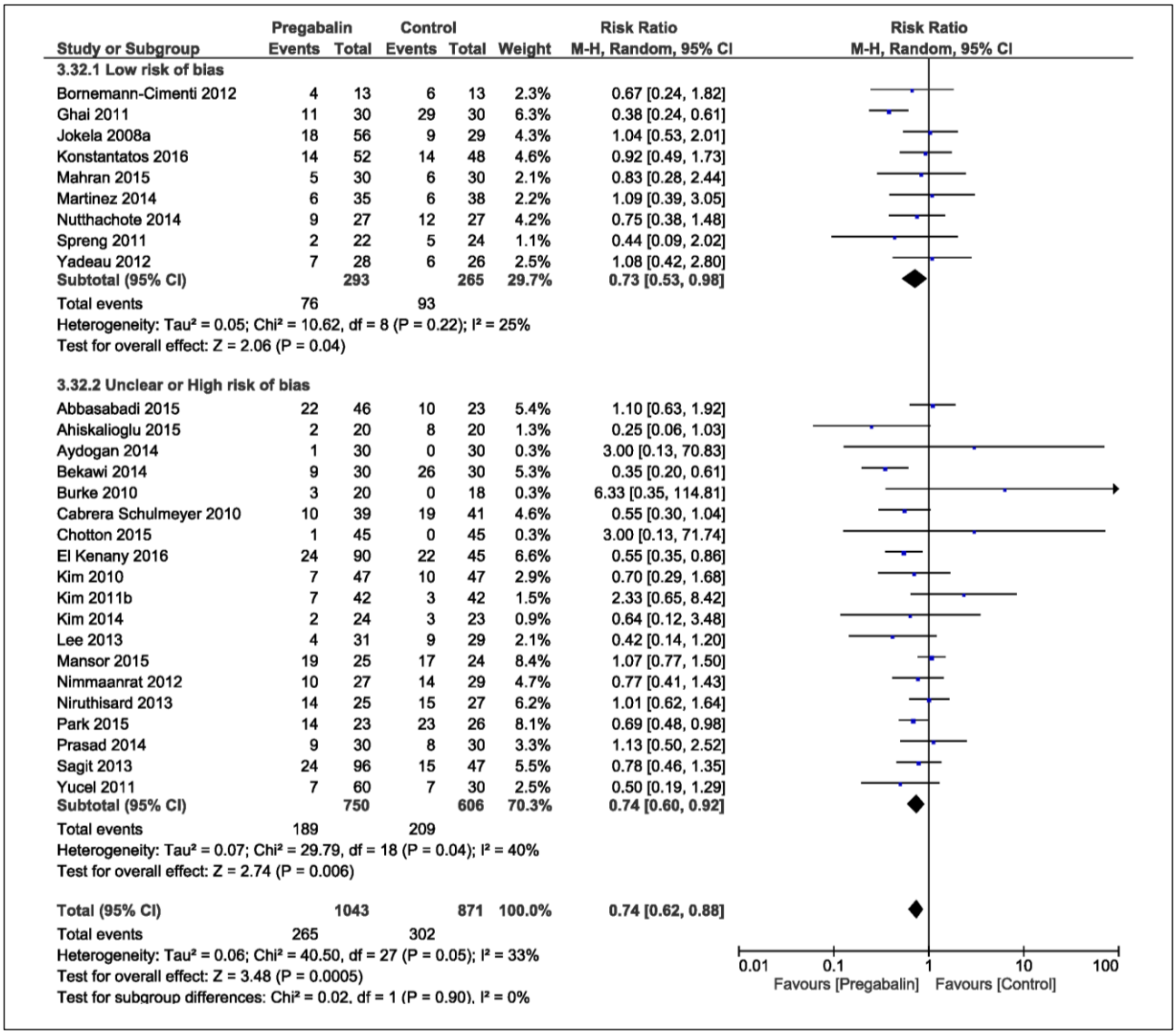
Appendix 14: Forest plots of adverse events: nausea



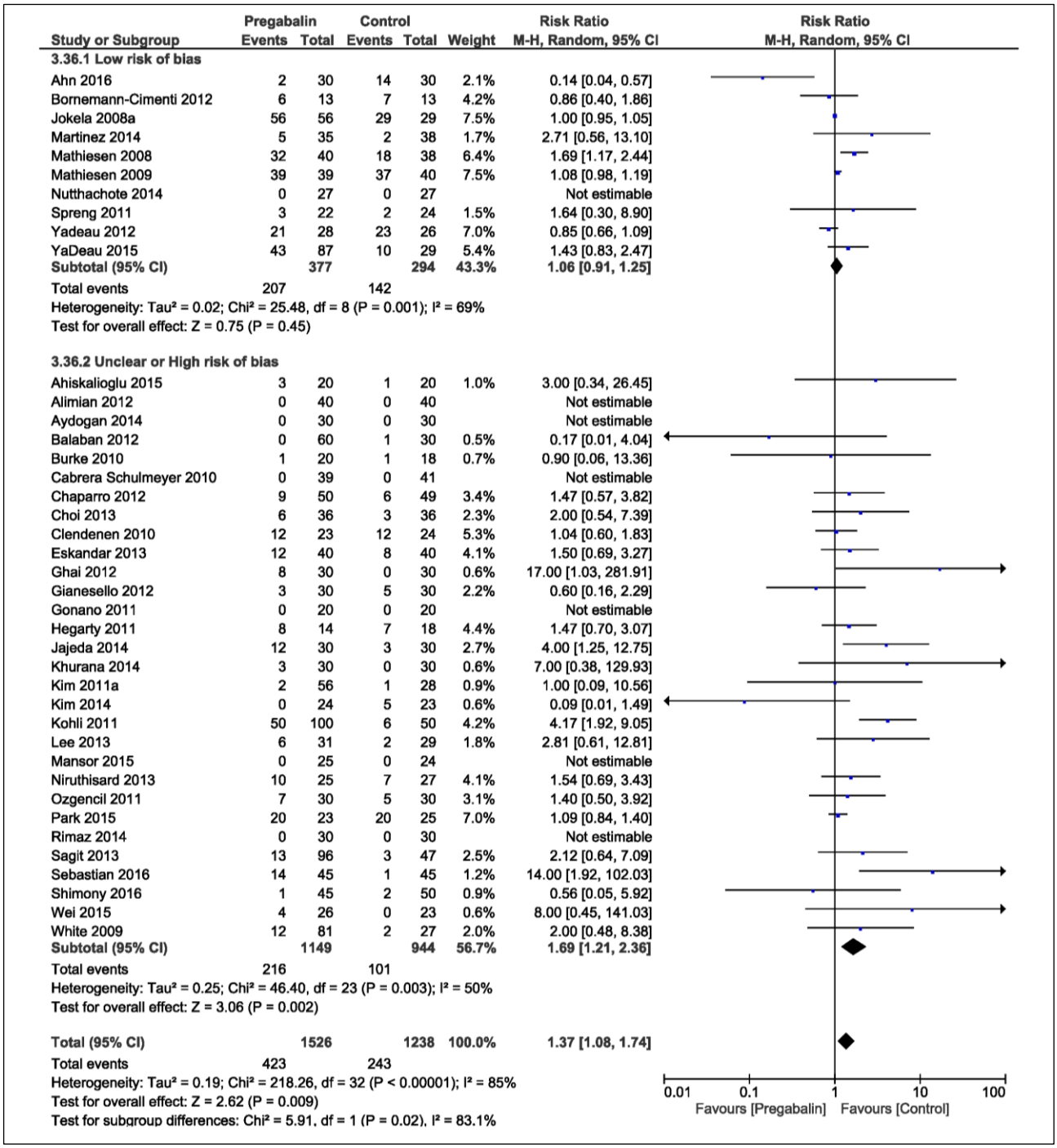
Appendix 15: Forest plots of adverse events: vomiting



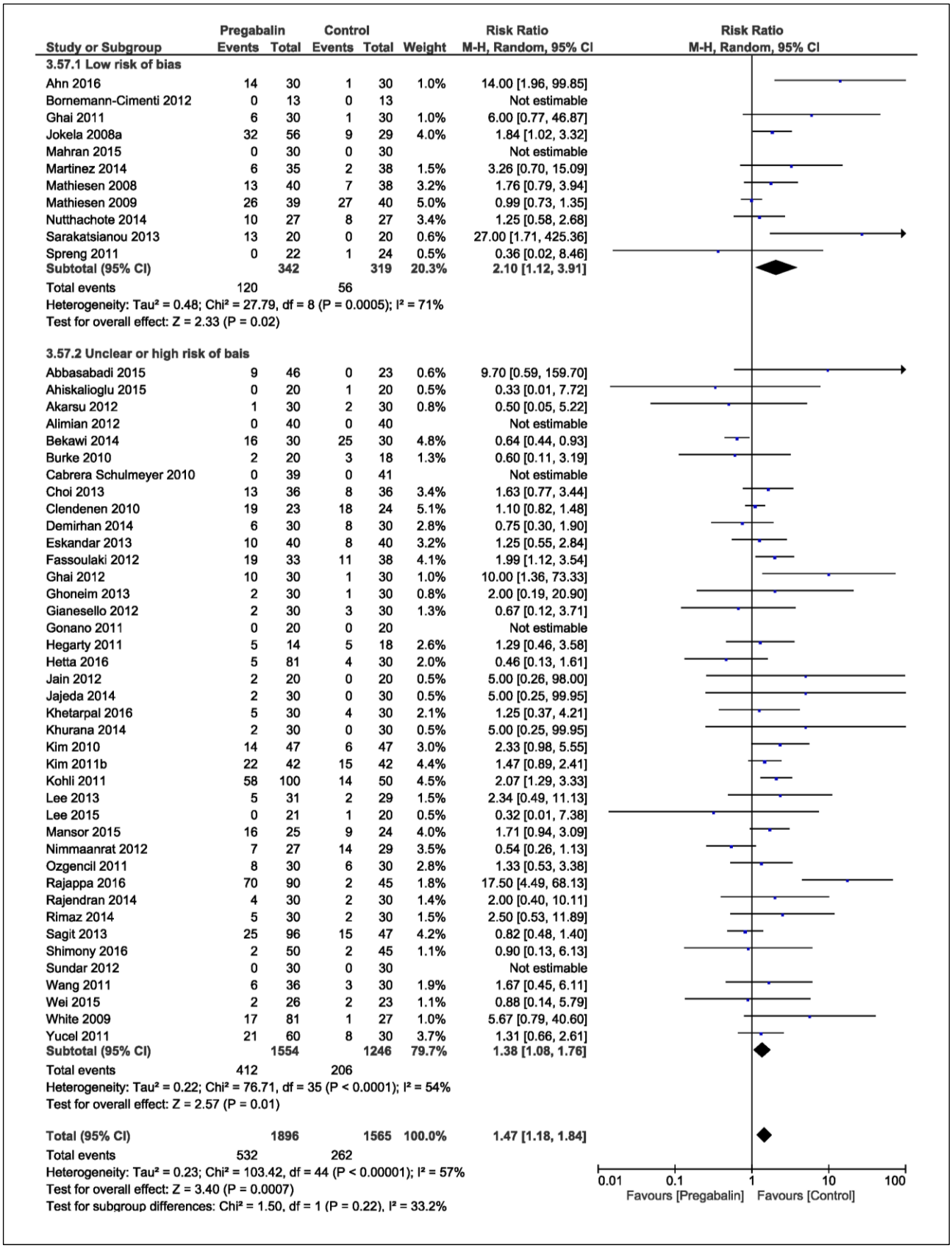
Appendix 16: Forest plots of adverse events: PONV



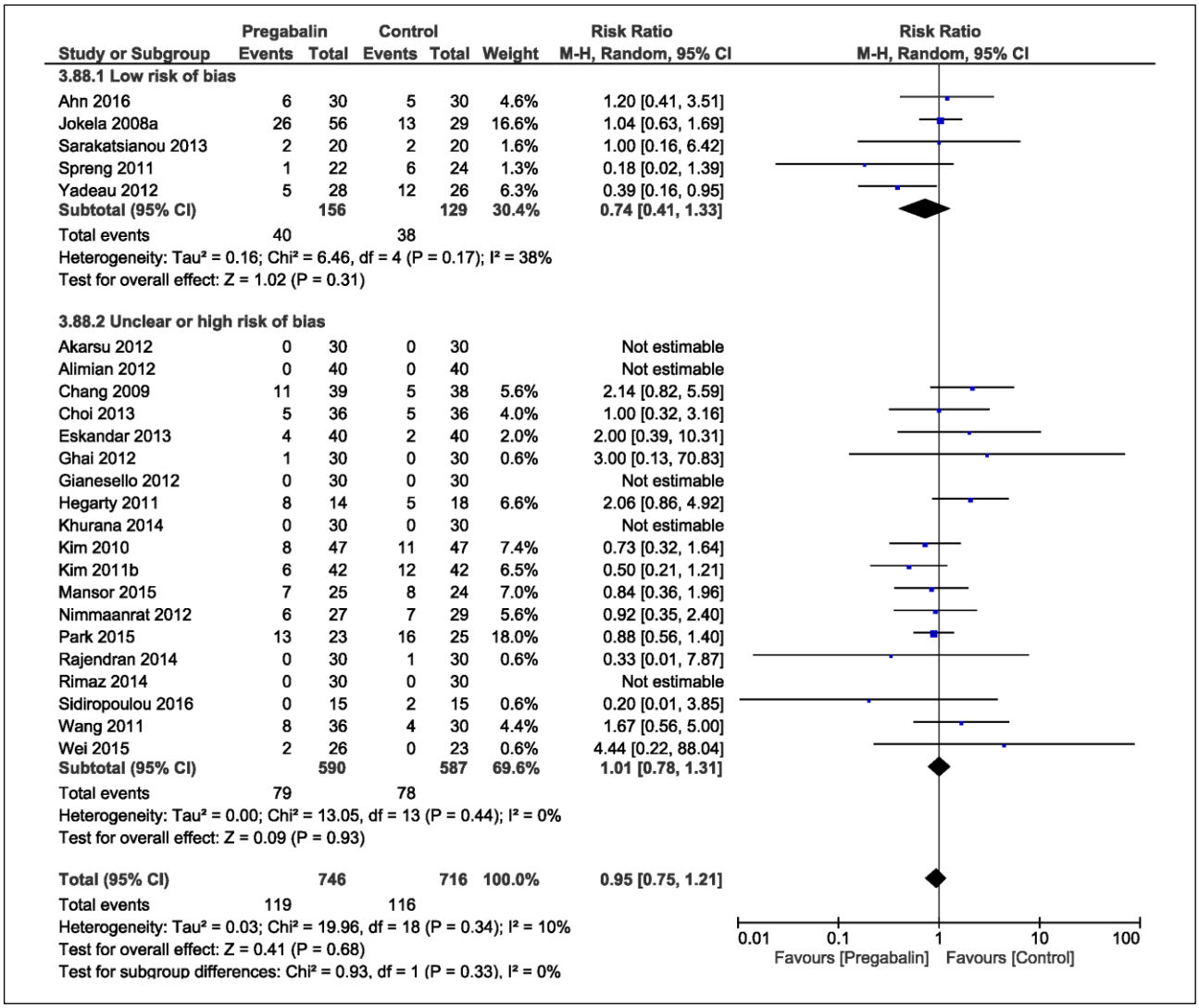
Appendix 17: Forest plots of adverse events: sedation



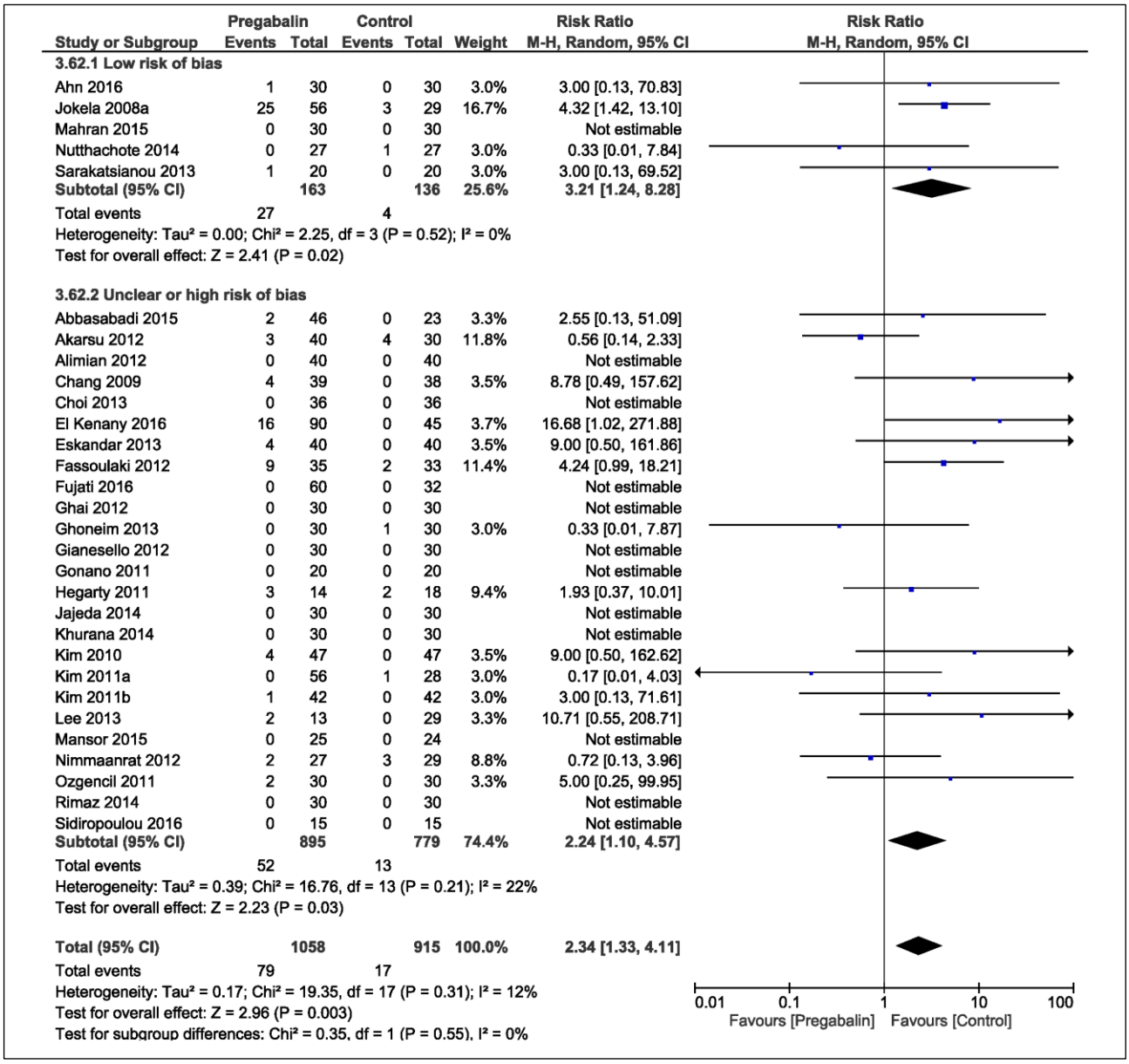
Appendix 18: Forest plots of adverse events: dizziness



Appendix 19: Forest plots of adverse events: headache



Appendix 20: Forest plots of adverse events: visual disturbance



GRADUATE SCHOOL OF HEALTH AND MEDICAL SCIENCES
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Information on PhD student:	
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Principal supervisor	Jørgen Berg Dahl

Title of PhD thesis:
BENEFIT AND HARMS OF GABAPENTINOIDS FOR POSTOPERATIVE PAIN MANAGEMENT

This declaration concerns the following article:
Gabapentin for postoperative pain management – a systematic review with meta-analyses and trial sequential analyses

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1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
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3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	B

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A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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	Morten Sejer Hansen	MD	

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6/2-2017	Morten Sejer Hansen	MD	

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	Katri Hamunen	MD, Dr.MedSci	
	Jørn Wetterslev	MD, PhD	
	Ole Mathiesen	MD, PhD	

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Date: **PhD student:**	**Date:** **Principal supervisor:**

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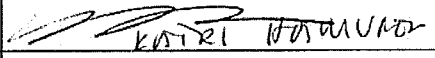
13.2.17	Katri Hamunen	MD, Dr.MedSci	
	Jørn Wetterslev	MD, PhD	
	Ole Mathiesen	MD, PhD	

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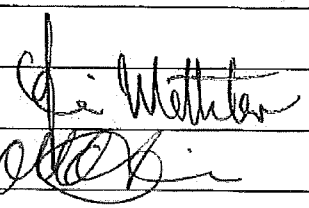
	Vesa Kontinen	MD, Dr.MedSci	
	Katri Hamunen	MD, Dr.MedSci	
13-02-17	Jørn Wetterslev	MD, PhD	
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13-02-17	JØRN WETTERSLEV	MD, PHD	
	OLE MATHIESEN	MD, ASSOCIATE	

13/2-17		PROFESSOR	

Signature of the PhD student and the principal supervisor:	
Date:	**Date:**
PhD student:	**Principal supervisor:**

		PROFESSOR	

Signature of the PhD student and the principal supervisor:	
Date: 5/3 · 17 PhD student:	Date: 13/2 -2017 Principal supervisor:

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Title of PhD thesis:
BENEFIT AND HARMS OF GABAPENTINOIDS FOR POSTOPERATIVE PAIN MANAGEMENT

This declaration concerns the following article:
Dose-related effect of gabapentin in postoperative pain management –Analyses from a systematic review with meta-analyses and trial sequential analyses

The PhD student's contribution to the article: *(please use the scale (A,B,C) below as benchmark*)*	(A,B,C)
1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments	B
2. Planning of the experiments and methodology design, including selection of methods and method development	C
3. Involvement in the experimental work	C
4. Presentation, interpretation and discussion in a journal article format of obtained data	C

**Benchmark scale of the PhD student's contribution to the article*		
A. refers to:	*Has contributed to the co-operation*	*0-33 %*
B. refers to:	*Has contributed considerably to the co-operation*	*34-66 %*
C. refers to:	*Has predominantly executed the work independently*	*67-100 %*

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Pregabalin for postoperative pain management – a systematic review with meta-analyses and trial sequential analyses

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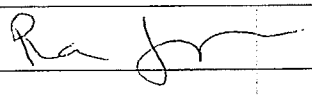
6/3-17	Pia Jæger	MD, PhD	
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	PIA JÆGER	MD, PHD	

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