

BENEFIT AND HARM OF GABAPENTINOIDS FOR POSTOPERATIVE PAIN MANAGEMENT

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

PhD Thesis

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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.

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emails (!) and meetings always with a great sense for details and a humorous approach.

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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
T ¹ /2: Half-life
TSA: Trial Sequential Analysis
VAS: Visual Analogue Scale

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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% Cl: 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% Cl:-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% Cl: 0.9, 2.9, p=0.10).

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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, nonopioide 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% Cl: 3.2, 8.5, p<0.0001). Når pregabalin blev kombineret med andre, non-opioide analgetikae var reduktionen 5.3 mg (95% Cl: 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% Cl: 1.2, 6.8, p=0.02). Disse odds syntes yderligere forøgede, når pregabalin blev givet i mere end en dosis, 3.4 (95% Cl: 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 24timers 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 analgesics²⁻⁴.

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 gabapentinoids⁷.

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 management¹⁰⁻¹⁵. Few of them explore the harms and possible additive/synergistic analgesic effect of postoperative gabapentinoid treatment¹⁵. 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 GABA¹⁶. 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 affinity¹⁶.

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 concentration¹⁷.

	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	≈3 hours	≤1 hour
T _{max} Half-life T ½	5-7 hours	≈ 6.3 hours
Metabolism	Renal elimination	Renal elimination
Drug interaction	Phenytoin	Phenytoin
	Naproxen	Naproxen
	Morphine	Morphine
	Antacids	Antacids

TABEL 1 CHARACTERISTICS OF GABAPENTIN AND PREGABALIN¹⁷

*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 disorders²⁰⁻²⁶. 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 treatment²³.

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 domain²⁰. Further, a Cochrane review on pregabalin for partial epilepsy includes solely trials sponsored by the pharmaceutical industry²⁴. Both reviews of gabapentin and pregabalin for partial epilepsy consist of trials with high risk of bias, limiting the ability to report trustworthy conclusions²⁷.

In 2009 Vedula et al²⁸ explored the outcome reporting in industry-sponsored trials of gabapentin for offlabel 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 offlabel interventions²⁸.

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-operatively¹⁰ 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 time³³. Pregabalin has been described as a more potent successor to gabapentin¹¹, and associated with fewer adverse events¹³.

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-pain¹¹ 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 medicine³⁵.

Randomized clinical trials and systematic reviews are considered the best methodologies in minimizing bias and are thus the strongest methodologies to base future recommendations on³⁵.

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 recommendations³⁶. 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 hospitalization³⁸.

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 I² was zero both FEM and REM were used for the analysis and the most conservative estimation was presented³⁹.

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 conclusion⁴⁰.

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. Beta⁴².

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 evidence⁴³. 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 I*)

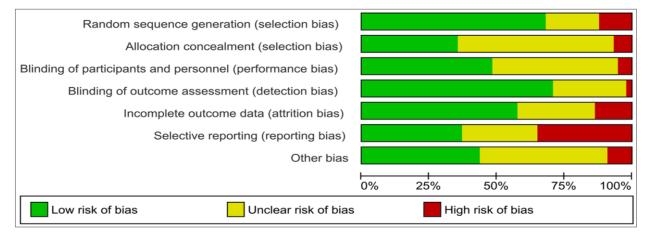


Figure 1 Bias graph of the six bias domains. The Other bias domain consists of 'vested interests'; financial and confirmatory bias.

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.

Study or Subgroup		imental SD [mg]	Total	Con Mean [mg] \$		Total	Weight	Mean Difference IV, Random, 95% CI [mg]	Mean Difference IV, Random, 95% CI [mg]
.93.1 Low risk of bias		25 [uið]		mean [mg] s	(m91		naight		,
Brogly 2008	0	1.48	22	0	4.4	21	1.8%	0.00 [-1.98, 1.98]	+
Fassoulaki 2005	20.3	7.9	25	25.7	11.2	28	1.5%	-5.40 [-10.58, -0.22]	
		1.56	30			30			
Ghai 2011	5.44			4.28	1.87		1.9%	1.16 [0.29, 2.03]	
Grosen 2014	11.2	21.62	52	17.92	23.55	52	1.0%	-6.72 [-15.41, 1.97]	
Lunn 2015	42.8	38.4	186	50.5	41.4	99	0.9%	-7.70 [-17.55, 2.15]	
Misra 2013	24.6	19.6	37	29.15	25.2	36	0.9%	-4.55 [-14.93, 5.83]	-+
Monks 2015	10	11.9	100	10	7.4	97	1.7%	0.00 [-2.76, 2.76]	+
Moore 2010	3	3	21	4	5	23	1.8%	-1.00 [-3.41, 1.41]	+
Paul 2013	27.94	22.99	52	26.77	18.96	49	1.1%	1.17 [-7.03, 9.37]	
Paul 2015	19.7	16.39	48	25.1	14.5	54	1.4%	-5.40 [-11.44, 0.64]	
Short 2012	6.2	4.53	84	7.9	3.8	42	1.8%	-1.70 [-3.20, -0.20]	
Srivastava 2010	25.39	4.48	60	37.58	8.35	60	1.8%	-12.19 [-14.59, -9.79]	*
Waikakul 2011	15.5	9.25	24	18	15.5	24	1.2%	-2.50 [-9.72, 4.72]	
Subtotal (95% CI) Heterogeneity: Tau ² = 1 Test for overall effect: Z			741 = 12 (P	< 0.00001); l²	= 90%	615	18.7%	-3.06 [-5.60, -0.53]	•
.93.2 Unclear or High	risk of bias								
Abdelmageed 2010	6.6	1.3	30	12.2	1.1	30	1.9%	-5.60 [-6.21, -4.99]	
						30			-
Al-Mujadi 2005	15.2	7.6	35	29.5	9		1.6%	-14.30 [-18.14, -10.46]	
Amr 2009	13.5	0.5	50	22	2.1	50	1.9%	-8.50 [-9.10, -7.90]	•
Badawy 2014	11.5	2.3	19	13	2.9	19	1.8%	-1.50 [-3.16, 0.16]	1
Bang 2009	32.07	29.07	23	30.07	28.57	23	0.5%	2.00 [-14.66, 18.66]	
3ekawi 2014	0	2.2	30	7.5	0.7	30	1.9%	-7.50 [-8.33, -6.67]	-
Bharti 2012	2.1	2.2	20	4.9	3.4	20	1.8%	-2.80 [-4.57, -1.03]	H
Clarke 2009a	33.2	20.73	29	63.8	36.5	7	0.2%	-30.60 [-58.67, -2.53]	
Clarke 2009b	33.1	4	76	35	4	39	1.8%	-1.90 [-3.44, -0.36]	-
Clarke 2014	37	1.5	95	48	1.33	84	1.9%	-11.00 [-11.41, -10.59]	
Deniz 2012	22.2	11.9	25	25.6	10.5	26	1.3%	-3.40 [-9.57, 2.77]	+
Dierking 2003	43	23.7	39	63	25.9	32	0.8%	-20.00 [-31.66, -8.34]	
Doha 2010	39.9		39		25.9	29	0.8%	-2.80 [-20.47, 14.87]	
		33		42.7				1 I I I I I I I I I I I I I I I I I I I	
Durmus 2007	40	10	25	66	10	25	1.4%	-26.00 [-31.54, -20.46]	
Erten 2010	3.31	0.98	39	3.56	0.64	20	1.9%	-0.25 [-0.67, 0.17]	
assoulaki 2002	23.8	5	25	23.2	5.8	25	1.7%	0.60 [-2.40, 3.60]	t
assoulaki 2006	22	2.9	27	35	4.8	24	1.8%	-13.00 [-15.21, -10.79]	÷ .
Frouzanfard 2013	1.2	0.29	25	5.2	2.8	25	1.9%	-4.00 [-5.10, -2.90]	-
Shafari 2009	15.78	1.15	33	26.94	2.28	33	1.9%	-11.16 [-12.03, -10.29]	
Silron 2004	56.78	32.41	23	82.11	48.2	24	0.3%	-25.33 [-48.72, -1.94]	
loseini 2015	65.11	11.81	22	78.41	13.3	22	1.2%	-13.30 [-20.73, -5.87]	
Hout 2007	2.36	2.5	23	2.65	3.2	28	1.8%	-0.29 [-1.85, 1.27]	+
loseph 2014	38.65	18.04	25	44.29	16.02	25	1.0%		
								-5.64 [-15.10, 3.82]	
Khademi 2009	2.83	1.29	44	3.51	1.51	43	1.9%	-0.68 [-1.27, -0.09]	1
Khan 2010	20.8	5.72	150	31.5	9.6	25	1.6%	-10.70 [-14.57, -6.83]	-
Khan 2013	13.21	4.71	34	24.31	9.28	35	1.7%	-11.10 [-14.56, -7.64]	-
Kim 2004	35.8	20.8	21	33.5	26.1	20	0.6%	2.30 [-12.19, 16.79]	
Kosucu 2013	25.9	8.3	29	44	11	31	1.5%	-18.10 [-23.01, -13.19]	
Maleh 2013	2.5	2.6	40	2.7	2.7	40	1.8%	-0.20 [-1.36, 0.96]	+
Marashi 2012	18.3	15.6	22	65.7	31	22	0.6%	-47.40 [-61.90, -32.90]	
Mardani-Kivi 2013	2.5	2.3	55	3.7	2.5	53	1.9%	-1.20 [-2.11, -0.29]	4
Menda 2010	2.5	8.5	30	15.1	2.5	30	1.1%		
								-9.10 [-16.88, -1.32]	_
Metry 2008	16.1	7.7	67	29.2	9.6	34	1.6%	-13.10 [-16.82, -9.38]	
Mishra 2016	8.1	1	30	11.9	1.4	30	1.9%	-3.80 [-4.42, -3.18]	•
Ménigaux 2004	21	12	20	20	19	20	0.9%	1.00 [-8.85, 10.85]	
Omran 2006	23.9	2.6	25	31.5	2.78	25	1.8%	-7.60 [-9.09, -6.11]	*
Panday 2004a	39.18	22.31	80	52.65	21.27	20	0.9%	-13.47 [-24.00, -2.94]	
Panday 2004b	40.42	31.26	153	53.03	27.48	153	1.3%	-12.61 [-19.21, -6.01]	
Panday 2004c	90.85	34.1	28	92.49	41.77	28	0.4%	-1.64 [-21.61, 18.33]	
Panday 20040	59.37	23.17	40	92.45	41.75	20	0.4%	-33.10 [-52.76, -13.44]	
				67.66	25.27	125	1.3%		
Panday 2006	39.19	26.31	125					-28.47 [-34.87, -22.07]	
Parikh 2010	31.7	20.3	30	31.9	19.84	30	0.9%	-0.20 [-10.36, 9.96]	
Prabhakar 2007	23.8	5	10	20.04	2.09	10	1.7%	3.76 [0.40, 7.12]	
Raghove 2010	17	7.02	30	20.98	6.32	30	1.7%	-3.98 [-7.36, -0.60]	
Said-Ahmed 2007	40.5	26.28	60	52	27.5	20	0.6%	-11.50 [-25.26, 2.26]	
Sava 2009	35.6	14.14	25	54.7	13.02	25	1.2%	-19.10 [-26.63, -11.57]	
Sekhavet 2009	40.1	14.5	49	52.7	21.1	49	1.2%	-12.60 [-19.77, -5.43]	
Sen 2009a	31	12	20	48	17	20	1.0%	-17.00 [-26.12, -7.88]	
Sen 2009b	20	11.5	30	28	11.5	29	1.4%	-8.00 [-13.87, -2.13]	
Soltanzadeh 2011	2.5	0.9	30	4	1.5	30	1.9%	-1.50 [-2.13, -0.87]	-
Syal 2010	40.2	35.2	30	46.7	35.8	30	0.4%	-6.50 [-24.47, 11.47]	
Fakmaz 2007	5.47		30	6.25	3.44	15	1.8%		1
		3.43						-0.78 [-2.91, 1.35]	—]
furan 2003a	27.04	14.44	25	41.96	8.36	25	1.3%	-14.92 [-21.46, -8.38]	
uran 2003b	16.3	8.9	25	42.8	10.9	25	1.4%	-26.50 [-32.02, -20.98]	
Jcak 2011	9.9	5.38	20	14.94	7.25	20	1.6%	-5.04 [-9.00, -1.08]	
/ahedi 2011	18.61	9.03	36	21.53	11.3	40	1.5%	-2.92 [-7.50, 1.66]	-+
/asigh 2016	11.9	4.4	38	30.1	0.6	38	1.8%	-18.20 [-19.61, -16.79]	-
roon 2001	24.1	9.9	16	32.7	14.6	16	1.0%	-8.60 [-17.24, 0.04]	
Dzcan 2012	15.3	5	20	19	4.2	20	1.7%	-3.70 [-6.56, -0.84]	-
Özgencil 2011						30	1.5%	-7.86 [-12.70, -3.02]	
	29.47	9.64	30	37.33	9.5				Ā
	45: Chi ² = 3	029.77, d	2315 If = 59 (F	P < 0.00001);	² = 98%	1933	81.3%	-8.25 [-9.72, -6.78]	Ŧ
Subtotal (95% CI) Heterogeneity: Tau ² = 24 Fest for overall effect: Z		0.00001)							
leterogeneity: Tau ² = 24 est for overall effect: Z		0.00001)	3056			2548	100.0%	-7.30 [-8.63, -5.97]	•
leterogeneity: Tau ² = 24	= 10.98 (P <			< 0.00001\· I	² = 98%	2548	100.0%	-7.30 [-8.63, -5.97]	-50 -25 0 25 50

٦

Γ

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; I²: 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; I²: 84%; 2 trials; 168 participants, TSA adjusted CI -15.5, 23.3; RIS: 1636; GRADE: low).

	Mean Difference /			
	Relative Risk (95% Cl, p-value)	TSA adj. CI	No. of trials (Participants / RIS)	GRADE
PRIMARY OUTCOME MEAS	SURES* **			
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 M	EASURES* **			
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

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

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; l²: 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*).

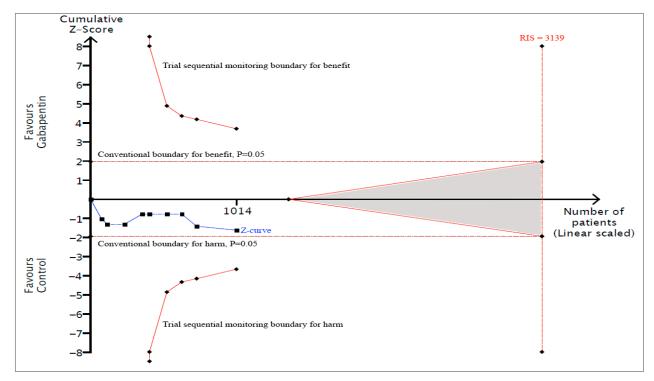


Figure 3 TSA of the risk of SAE from trials with low risk of bias. TSA of gabapentin vs. controls from nine trials with low risk of bias reporting SAE, including zero-events trials, with RIS of 3139 patients to detect or discard a RRR of 50% and a diversity of 0%. Alpha = 0.05 and beta = 0.10 (power 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=0.21 and 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.

	Mean Difference / Odds Ratio (95% CI, p-value)	TSA adj. Cl	No. of trials (Participants / RIS)	Test for subgroup difference p-value
			(**************************************	P
24-H MORPHINE CON LOW RISK OF BIAS	SUMPTION (REDUCTION)			
Cholecystectomy	12.2 mg (9.8 to 14.6, <i>p</i> -)	-	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	-	(-11.2 (0 17.1)	2 (11ais (115/545)	-0.21
Orthopedic	4.0 mg (-0.8 to 8.7, 0.1)	(-4.1 to 12.0)	3 trials (488/1190)	<i>P</i> =0.75
arthroplasty surgery	4.0 mg (0.0 to 0.7, 0.1)	(4.1 (0 12.0)	5 (103 (400/1150)	1-0.75
Spinal surgery	_	-	-	-
Thoracic surgery	6.7 mg (-2.0 to 15.4, <i>p</i> -)	-	1 trial (104/-)	-
ALL TRIALS	oi, iig (210 to 1011) p /			
Cholecystectomy	7.3 mg (4.6 to 9.9, <0.00001)	(4.6 to 9.9)	10 trials (1114/892)	<i>P=</i> 0.9
Hysterectomy	10.5 mg (6.7 to 14.4, <0.00001)	(6.7 to 14.4)	14 trials (793/1315)	<i>P=</i> 0.16
Mastectomy	5.2 mg (0.9 to 9.5, 0.02)	(-1.6 to 12.0)	6 trials (391/804)	<i>P=</i> 0.15
Orthopedic	6.1 mg (0.2 to 12.1, 0.04)	(-7.1 to 19.4)	6 trials (818/3323)	<i>P=</i> 0.47
arthroplasty surgery		, , , , , , , , , , , , , , , , , , ,		
Spinal Surgery	10.6 mg (2.1 to 19.0, 0.01)	(-24.1 to 45.2)	8 trials (652/5607)	<i>P=</i> 0.52
Thoracic surgery	6.3 mg (2.9 to 9.8, 0.0003)	(2.9 to 9.8)	7 trials (425/575)	<i>P=</i> 0.25
	· · · · ·	•	· · ·	
SERIOUS ADVERSE EV	ENTS (OR)			
LOW RISK OF BIAS				
Cholecystectomy	Not estimable	-	1 trials (120/-)	-
Hysterectomy	-	-	-	-
Mastectomy	-	-	-	-

LOW RISK OF BIAS				
Cholecystectomy	Not estimable	-	1 trials (120/-)	-
Hysterectomy	-	-	-	-
Mastectomy	-	-	-	-
Orthopedic	2.98 (0.36 to 24.41, 0.31)	TSA adj. CI < 5%	2 trials (375/-)	<i>P=</i> 0.49
arthroplasty surgery				
Spinal surgery	-	-	-	-
Thoracic surgery	1.35 (0.57 to 1.74, 0.81)	TSA adj. CI < 5%	2 trials (224/-)	<i>P=</i> 0.49
ALL TRIALS				
Cholecystectomy	Not estimable	-	1 trials (120/-)	-

Cholecystectomy	Not estimable	-	1 trials (120/-)	-
Hysterectomy	0.55 (0.1 to 5.6, 0.61)	TSA adj. CI < 5%	5 trials (371/-)	<i>P=</i> 0.16
Mastectomy	Not estimable	-	2 trials (115/-)	-
Orthopedic	2.98 (0.4 to 24.4, 0.31)	TSA adj. CI < 5%	2 trials (375/-)	<i>P=</i> 0.30
arthroplasty surgery				
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)	<i>P</i> =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 bias⁴⁴⁻⁵⁹.

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*.

	Mean Difference / Odd ratio (95% CI, p-value)	TSA adj. Cl	No. of trials (Participants / RIS)	Test for subgroup differences p-value
24-HOUR MORPHIN	E 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)	<i>P=</i> 0.69
351-700 mg	4.0 mg (-0.6 to 8.5, 0.09)	(-3.3 to 11.6)	6 trials (599/1360)	<i>P=</i> 0.25
701-1050 mg	-1.1 mg (0.3 to 2.0, 0.009)	(0.3 to 2.0)	2 trials (181/15)	<i>P=</i> 0.002
> 1050 mg	2.1 mg (-1.1 to 5.3, 0.2)	(-1.4 to 5.6)	5 trials (427/499)	<i>P=</i> 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)	<i>P=</i> 0.25
351-700 mg	4.6 mg (3.1 to 6.1, <0.0001)	(3.1 to 6.1)	20 trials (1811/466)	<i>P=</i> 0.004
701-1050 mg	2.6 mg (-1.4 to 6.6, 0.2)	(-2.9 to 8.2)	7 trials (375/652)	<i>P=</i> 0.03
> 1050 mg	9.1 mg (7.2 to 11.0, <0.0001)	(7.2 to 11.0)	27 trials (1595/637)	<i>P=</i> 0.02
SERIOUS ADVERSE E	VENTS (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)	<i>P=</i> 0.44
701-1050 mg	0.6 (0.04 to 8.6, 0.70)	-	1 trial (121/-)	<i>P=</i> 0.52
> 1050 mg	2.0 (0.9 to 4.5, 0.1)	(0.1 to 40.0)	3 trials (287/1633)	<i>P=</i> 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)	<i>P=</i> 0.44
701-1050 mg	0.6 (0.04 to 6.7, 0.70)	(TSA adj. CI < 5%)	3 trials (221/10413)	<i>P=</i> 0.52
> 1050 mg	1.3 (0.8 to 2.4, 0.33)	(0.6 to 3.6)	13 trials (876/1973)	<i>P=</i> 0.29

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

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 bias⁵⁹⁻⁷⁸. 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*)

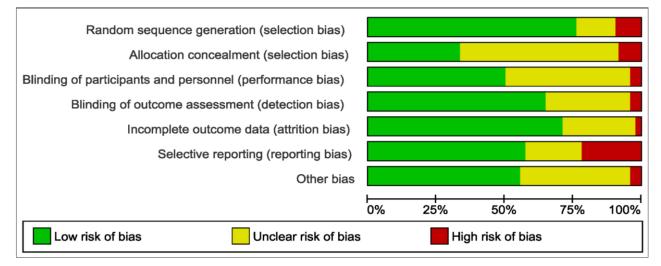


Figure 4 Bias graph of the six bias domains. The Other bias domain consists of 'vested interests'; financial and confirmatory bias.

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.

	MD / RR / Peto's OR (95% Cl, p-value)	TSA adjusted Cl	No. of trials (Participants / RIS)	GRADE
PRIMARY OUTCOME MEAS				010.02
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 M		(2.6.to 10.0)	0 (588 / 1006)	
VAS 6-h at rest	EASURES* ** 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

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

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.

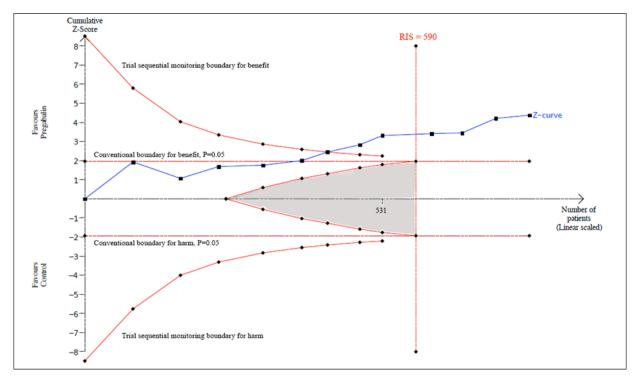
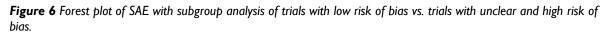


Figure 5 TSA of the effect of pregabalin on morphine consumption. An estimated RIS of 590 patients to detect or discard a sparing effect of 5 mg morphine was calculated using the actual diversity between trials of 85%, a random-effects metaanalysis, an alpha of 0.05, and a beta of 0.10. After six trials 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, OR 1.6 (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.

	Pregaba		Contr			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
3.17.1 Low risk of bias							
Bornemann-Cimenti 2012	0	13	0	13		Not estimable	
Brulotte 2015	3	58	2	56	9.7%	1.46 [0.24, 8.70]	
Konstantatos 2016	2	52	1	46	5.9%	1.75 [0.18, 17.27]	
Mahran 2015	0	30	0	30		Not estimable	
Mathiesen 2008	0	40	0	38		Not estimable	
Mathiesen 2009	3	39	2	40	9.5%	1.57 [0.26, 9.47]	
Pesonen 2011	6	35	0	35	11.2%	8.64 [1.64, 45.51]	
Sarakatsianou 2013	0	20	0	20		Not estimable	
Yadeau 2012	1	28	0	26	2.0%	6.88 [0.14, 347.65]	
YaDeau 2015	2	83	0	28	3.0%	3.86 [0.16, 95.14]	
Subtotal (95% CI)		398		332	41.2%	2.85 [1.20, 6.77]	
Total events Heterogeneity: Chi² = 3.08, Test for overall effect: Z = 2	· ·	· · ·	5 ² = 0%				
3.17.2 Unclear or High ris	k of bias						
Burke 2010	1	20	0	20	2.0%	7.39 [0.15, 372.38]	· · · · · · · · · · · · · · · · · · ·
El Kenany 2016	0	90	0	45		Not estimable	
Fassoulaki 2012	3	39	2	37	9.5%	1.44 [0.24, 8.75]	
Freedman 2008	0	40	1	40	2.0%	0.14 [0.00, 6.82]	· · · · ·
Ghosh 2016	1	21	0	22	2.0%	7.75 [0.15, 390.96]	
		45	4	43	26.5%	3.17 [1.08, 9.31]	
Mathiesen 2011	12	40					
	12 0	23	0	25		Not estimable	
Park 2015				25 47		Not estimable Not estimable	
Park 2015 Sagit 2013	0	23	0		14.8%		
Mathiesen 2011 Park 2015 Sagit 2013 Shimony 2016 Sidiropoulou 2016	0	23 96	0	47	14.8% 2.0%	Not estimable	
Park 2015 Sagit 2013 Shimony 2016 Sidiropoulou 2016	0 0 4	23 96 45	0 0 4	47 50		Not estimable 1.12 [0.26, 4.74]	
Park 2015 Sagit 2013 Shimony 2016 Sidiropoulou 2016 Wang 2011	0 0 4 1	23 96 45 15	0 0 4 0	47 50 15		Not estimable 1.12 [0.26, 4.74] 7.39 [0.15, 372.38]	
Park 2015 Sagit 2013 Shimony 2016 Sidiropoulou 2016 Wang 2011 Subtotal (95% CI)	0 0 4 1	23 96 45 15 36	0 0 4 0	47 50 15 30	2.0%	Not estimable 1.12 [0.26, 4.74] 7.39 [0.15, 372.38] Not estimable	
Park 2015 Sagit 2013 Shimony 2016 Sidiropoulou 2016 Wang 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4.55,	0 4 1 0 22 , df = 6 (P =	23 96 45 15 36 470 : 0.60);	0 0 4 0 0	47 50 15 30	2.0%	Not estimable 1.12 [0.26, 4.74] 7.39 [0.15, 372.38] Not estimable	
Park 2015 Sagit 2013 Shimony 2016 Sidiropoulou 2016 Wang 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4.55, Test for overall effect: Z = 2	0 4 1 0 22 , df = 6 (P =	23 96 45 15 36 470 : 0.60);	0 0 4 0 0	47 50 15 30 374	2.0%	Not estimable 1.12 [0.26, 4.74] 7.39 [0.15, 372.38] Not estimable	
Park 2015 Sagit 2013 Shimony 2016	0 4 1 0 22 , df = 6 (P =	23 96 45 15 36 470 = 0.60); 04)	0 0 4 0 0	47 50 15 30 374	2.0% 58.8%	Not estimable 1.12 [0.26, 4.74] 7.39 [0.15, 372.38] Not estimable 2.11 [1.02, 4.35]	



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 24hour 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 patientimportant outcome which is defined as e.g. death, disability, or quality of life³⁵.

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 outcomes³⁵.

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 reviews³⁵. Bias in systematic reviews is often referred to as systematic error that may favor one intervention over others⁷⁹⁻⁸¹. 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 bias²⁷. 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 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 conclusions³⁵.

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, 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, figure 6. Point estimate and high risk of bias as compared with 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 reviews⁸². 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 results⁴³.

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 less⁸⁵.

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 such⁸⁶.

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 Guyatt⁸⁸ 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 outcomes⁴³. 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 small⁹¹. 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 management¹⁰. 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*.

		rimental			ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [mg]	SD [mg]	Total	Mean [mg]	SD [mg]	Total	Weight	IV, Random, 95% CI [mg]	IV, Random, 95% CI [mg]
1.1.1 Gabapentin									
Brogly 2008	0	1.48	22	0	4.4	21	6.4%	0.00 [-1.98, 1.98]	+
Fassoulaki 2005	20.3	7.9	29	25.7	11.2	30	4.4%	-5.40 [-10.33, -0.47]	
Ghai 2011	5.44	1.56	30	4.28	1.87	30	6.8%	1.16 [0.29, 2.03]	-
Grosen 2014	11.2	21.62	52	17.92	23.55	52	2.5%	-6.72 [-15.41, 1.97]	
Lunn 2015	42.8	38.4	186	50.5	41.4	99	2.1%	-7.70 [-17.55, 2.15]	
Misra 2013	24.6	19.6	37	29.15	25.2	36	2.0%	-4.55 [-14.93, 5.83]	
Monks 2015	10	11.9	100	10	7.4	97	5.9%	0.00 [-2.76, 2.76]	+
Moore 2010	3	3	21	4	5	23	6.1%	-1.00 [-3.41, 1.41]	*
Paul 2013	27.94	22.99	52	26.77	18.96	49	2.7%	1.17 [-7.03, 9.37]	+
Paul 2015	19.7	16.39	48	25.1	14.5	54	3.8%	-5.40 [-11.44, 0.64]	
Short 2012	6.2	4.53	84	7.9	3.8	42	6.6%	-1.70 [-3.20, -0.20]	•
Srivastava 2010	25.39	4.48	60	37.58	8.35	60	6.1%	-12.19 [-14.59, -9.79]	-
Waikakul 2011	15.5	9.25	24	18	15.5	24	3.2%	-2.50 [-9.72, 4.72]	
Subtotal (95% CI)			745			617	58.7%	-3.07 [-5.60, -0.54]	◆
Ahn 2016	40.7	20.7	30	50.7	36.3	30	1.1%	-10.00 [-24.95, 4.95]	
1.1.2 Pregabalin	40.7	20.7	20	50.7	26.2	20	1 10/	10.00 [24.95, 4.95]	
Jokela 2008a	25.6	14.6	30		15.6	30	3.0%	-6.20 [-13.85, 1.45]	
Mahran 2015	20.23	6.8	30	34.43	10.14	30	4.8%	-14.20 [-18.57, -9.83]	+
Mathiesen 2008	24	14	30	47	28	38	2.0%	-23.00 [-33.22, -12.78]	
Mathiesen 2009	40	22	39	42	20	20	1.8%	-2.00 [-13.16, 9.16]	
Nutthachote 2014	0.14	0.48	27	1.04	3.5	27	6.7%	-0.90 [-2.23, 0.43]	+
Paech 2007	9	3	41	10	1.5	45	6.8%	-1.00 [-2.02, 0.02]	
Pesonen 2011	15	33.33	35	28.5	61.11	35	0.5%	-13.50 [-36.56, 9.56]	
Sarakatsianou 2013	1.8	2.1	20	5.2	4.1	20	6.3%	-3.40 [-5.42, -1.38]	*
Spreng 2011	24.5	13.33	22	37	12.59	24	3.0%	-12.50 [-20.01, -4.99]	
Yadeau 2012	10.9	8.6	30	13.2	6	27	5.2%	-2.30 [-6.12, 1.52]	
Subtotal (95% CI)			334			326	41.3%	-5.80 [-8.49, -3.10]	◆
Heterogeneity: Tau ² = Test for overall effect:	,		= 10 (P	< 0.00001); l ^a	² = 85%				
Total (95% CI)			1079			943	100.0%	-4.16 [-5.89, -2.42]	•
Heterogeneity: Tau ² =	11 29: Chi ² =	189.51 df		< 0 00001).	1 ² = 88%				
Test for overall effect: Test for subgroup diffe	Z = 4.69 (P <	0.00001)							-50 -25 0 25 Gabapentin Control

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*).

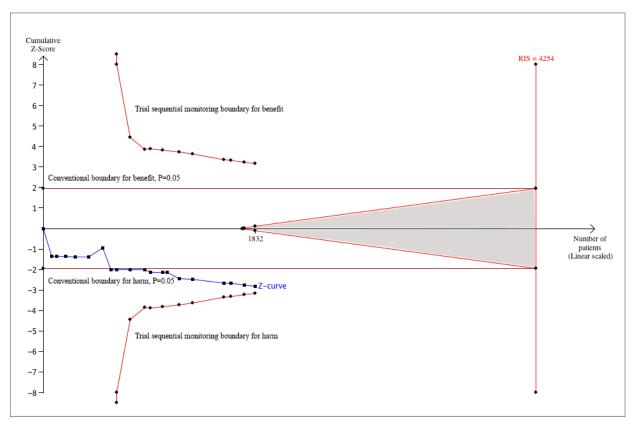


Figure 8 TSA of the risk of SAE from trials with low risk of bias investigating gabapentinoids. TSA of gabapentinoids vs. controls in includes 19 trials with low risk of bias reporting SAE, including zero-events trials, with RIS of 4254 patients to detect or discard a RRR of 50% and a diversity of 0%. 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 management¹⁰. 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 reviews¹⁰, 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 REV	IEWS				
Estimate	STUDY I	Dolemann et	Seib et al. ²⁹	Straube	Ho et al. ¹⁵
(MD/RR/OR)		al. ¹⁰ ***	***	et al. ³⁰	***
(REM/FEM; 95% CI;				***	
p-value; TSA adj. CI)					
LOW RISK OF BIAS* **	k				
24-h opioid	3.1 mg	Note ¹	Not	Note ²	Not available
consumption	(0.5 to 5.6; <0.02; 0.5 to 5.6)		available		
24-h opioid	1.2 mg	Not available	Not	Not	Note ⁴
consumption	(-0.3 to 2.6; 0.12; -0.3 to 2.6)		available	available	
+ add-on					
24- opioid	8.0 mg	Not available	Not	Not	Not available
consumption	(-1.5 to 17.4; 0.10; -30.5 to		available	available	
- add-on	46.3)				
Serious Adverse	RR 1.61	Not available	Not	Not	Not available
Events	(0.5 to 5.6, 0.10; TSA adj. CI:		available	available	
	0.5 to 5.6)				
ALL TRIALS* **					
24-h opioid	7.3 mg	8.4 mg	14.7 mg	Not	16.0 mg
consumption	(5.9 to 8.8; < 0.00001; 5.9 to	(7.3 to 9.6;	(9.4 to 20.0;	available	(24.3 to 31.5;
	8.8)	<i>p</i> <0.0001)*	<i>p<</i> 0.00001)*		<i>p<</i> 0.0001)*
Serious Adverse	RR 1.14	Not available	Not	Note ³	Not available
Events	(0.71 to 1.81; 0.59; 0.6 to 2.1)		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

¹Authors state: 'The absolute effect may be overestimated due to bias'. ²No sensitivity analysis since all trials had maximum quality according to the Oxford Quality Scale. ³Described 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 scores¹¹⁻¹³. However, the estimates on beneficial outcomes are reported from systematic reviews exploring the effect of procedure¹³, pro-nociceptive pain¹¹, 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 REVIE	WS				
Estimate (MD/RR/OR)	STUDY IV	Mishriky et.	Lam et	Zhang et	Eipe et
(REM/FEM; 95% Cl; p-		al. ¹² ***	al. ¹³ ***	al. ⁹⁰ ***	al. ¹¹ ***
value; TSA adj. Cl)					
LOW RISK OF BIAS					
24-h opioid	5.8 mg	Note ¹	Not	Not	Not
consumption*	(3.2, 8.5; < 0.0001; 3.2, 8.5)		available	available	available
24-h opioid	5.3 mg	Not available	Not	Not	Not
consumption*	(2.1, 8.5; 0.001; 2.1, 8.5)		available	available	available
+ add-on					
24-h opioid	13.7 mg	Not available	Not	Not	Not
consumption*	(9.6, 17.8; <0.00001; 9.6. 17.8)		available	available	available
- add-on					
Serious Adverse	2.9	Not available	Not	Not	Not
Events**	(1.2, 6.8; 0.02; 0.1, 97.1)		available	available	available
ALL TRIALS					
24-h opioid	10.8 mg	8.3 mg	Note	Note ²	Not
consumption *	(8.5, 13.2; <0.00001; 8.5, 13.2)	(6.5 to 10.1;			available
		<i>p</i> <0.00001) [*]			
Serious Adverse	2.4	Not available	Not	Not	Note ³
Events**	(1.4, 4.2; 0.002; 0.9, 6.33)		available	available	

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.

¹No bias effect found in sensitivity analysis.²Used a modified Oxford Scale in quality assessment of the included trials and trials with Oxford Scale score of \geq 3 were included. ³Authors 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 I. 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 pregabalin⁹². Most of the included trials in our reviews have a short followup 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 conditions²³. 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 falls²³. 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 review²³ 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 literature⁹. Overall the risks of the adverse events are reported very diversely in the gabapentinoid literature⁹² 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 management³¹. 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 II³¹. 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 outcomes¹⁰. 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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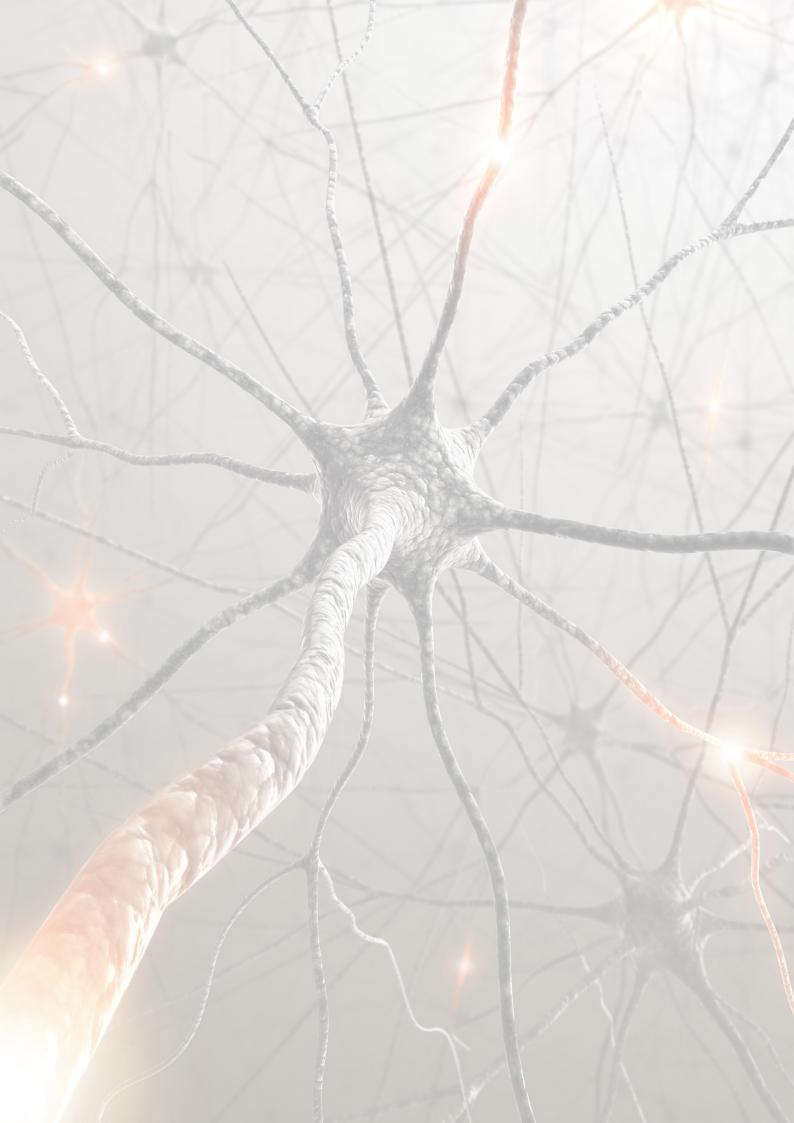
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PAPERS

- PAPER IGabapentin for post-operative pain management a
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- PAPER II Gabapentin in procedure-specific postoperative pain management - preplanned subgroup analyses with metaanalyses 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

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 $\alpha 2\delta$ -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 postoperative opioid consumption, pain intensity, and adverse and serious adverse effects in surgical patients receiving gabapentin for postoperative 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

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eligible. Prospective observational and quasirandomized 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.¹

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, inade-quately 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

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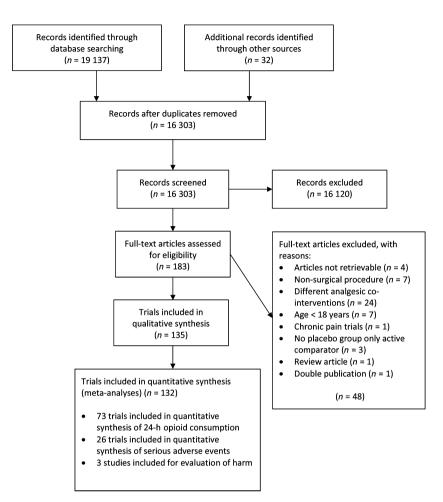


Fig. 1. PRISMA flowchart.

(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

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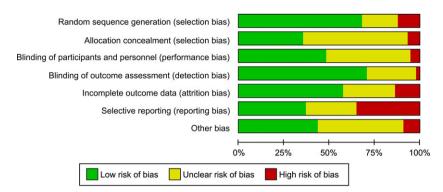


Fig. 2. Bias graph: The 'Other' bias domain consists of an evaluation of risk of financial bias and confirmatory bias.

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 size: of required information percentage 116%)42,44,45,53,54,56,60,61,65,68,73,78,81,84,89,95,98,102, 116%) 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 hos-}}

nia, readmission or prolonged admission to hospital, admission to intensive care unit, respiratory arrest, atrial fibrillation, vein thrombosis, major

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Table 1 Analyses of subgroup and all trial analyses.	l trial analyses.								
	Subgroup: Trials with overall Low Risk of Bias	verall Low	Risk of	Bias		All Trials reporting the outcome	e outcome		
Outcome Subgroup analysis	Estimate MD/RR (REM) (95% Cl; TSA-adjusted 95% Cl)	P-value	12	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% Cl; TSA-adjusted 95% Cl)	P-value	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	%06	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	-	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	00	0.10	84%	2/168/3271	0.57	10.6 mg (8.4 to	< 0.00001	97%	37/2903/2591
regimen	-30.5 to 46.3)					12.8; 8.4 to 12.8)			
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	%66	43/3345/2522
VAS 6 h at rest	9 mm (-1 to	0.07	87%	9/745/4114	0.47	12 mm (9 to	< 0.00001	896%	71/4556/1907
	19; -13 to 30)					13; 9 to 13)			
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	0.07	87%	11/1027/554	0.006	8 mm (5 to	< 0.0001	93%	68/4319/922
	6; -1 to 6)					10; 5 to 10)			
VAS 24 h at mobilization	5 mm (-2 to	0.15	94%	8/795/1629	0.71	5 mm (-0 to	0.05	%26	25/1760/582
Subgroup analyses of harmful outcomes	11; -5 to 14) les					11; -0 to 11)			
Serious adverse events	ш.	0.10	%0	9/1014/3139	0.05	RR 1.14 (0.71 to	0.59	7%	26/2051/3973
:	2.9; 0.6 to 4.6)	0	č		0000	1.81; 0.6 to 2.1)		õ	
Nausea	KK U.83 (U.0 T0 1 1· 0 6 to 1 1)	0.21	23%	G/N5/4/30/0	0.93	KK U.82 (U./ TO U.9; 0.7 to 0.01	0.0003	%6	4001/05/26/0C
Vomiting	RR 1.04 (0.7 to	0.85	%0	4/352/1299	0.11	RR 0.80 (0.7 to 0.9;	0.002	%0	51/3446/1648
)	1.5; 0.5 to 2.2)					0.7 to 0.9)			
Sedation	RR 1.08 (0.9 to	0.29	%0	10/858/1931	0.03	RR 1.33 (1.0 to 1.3;	0.005	%09	51/4003/3751
	1.2; 0.9 to 1.2)					1.0 to 1.3)			
Dizziness	RR 1.04 (0.8 to	0.64	%0	9/747/2422	0.71	RR 1.02 (0.9 to 1.1;	0.77	%0	58/4510/2401
	1.2; 0.8 to 1.3)					0.9 to 1.1)			
MD: mean difference; RR: relative risk; REM: random effects model; TSA: trial sequential analysis; RIS; required information size; *Test for subgroup differences.	; REM: random effects mod	del; TSA: tri	al sequ	ential analysis; RIS	; required information siz	e; *Test for subgroup o	differences.		

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GABAPENTIN FOR POST-OPERATIVE PAIN MANAGEMENT

		mental SD [mg]	Total	Con Mean [mg]		Total	Weight	Mean Difference IV, Random, 95% CI [mg]	Mean Difference IV, Random, 95% CI [mg]
3.93.1 Low risk of bias									
Frivastava 2010	25.39	4.48	60	37.58	8.35	60	1.8%	-12.19 [-14.59, -9.79]	-
unn 2015	42.8	38.4	186	50.5	41.4	99	0.9%	-7.70 [-17.55, 2.15]	
rosen 2014	11.2	21.62	52	17.92	23.55	52	1.0%	-6.72 [-15.41, 1.97]	
aul 2015	19.7	16.39	48	25.1	14.5	54	1.4%	-5.40 [-11.44, 0.64]	-
assoulaki 2005	20.3	7.9	29	25.7	11.2	30	1.5%	-5.40 [-10.33, -0.47]	
lisra 2013	24.6	19.6	37	29.15	25.2	36	0.9%	-4.55 [-14.93, 5.83]	-+
/aikakul 2011	15.5	9.25	24	18	15.5	24	1.2%	-2.50 [-9.72, 4.72]	-
hort 2012	6.2	4.53	84	7.9	3.8	42	1.8%	-1.70 [-3.20, -0.20]	1
loore 2010	3	3	21	4	5.0	23	1.8%	-1.00 [-3.41, 1.41]	1
	0	1.48	22	4	4.4	23	1.8%		1
rogly 2008								0.00 [-1.98, 1.98]	I
lonks 2015	10	11.9	100	10	7.4	97	1.7%	0.00 [-2.76, 2.76]	T
hai 2011	5.44	1.56	30	4.28	1.87	30	1.9%	1.16 [0.29, 2.03]	1
aul 2013	27.94	22.99	52	26.77	18.96	49	1.1%	1.17 [-7.03, 9.37]	
ubtotal (95% CI)			745			617	18.7%	-3.07 [-5.60, -0.54]	•
eterogeneity: Tau ² = 15 est for overall effect: Z =			df = 12	(P < 0.0000)	1); I ² = 90	0%			
.93.2 Unclear or High r									
larashi 2012	18.3	15.6	22	65.7	31	22	0.6%	-47.40 [-61.90, -32.90]	<u> </u>
anday 2005	59.37	23.17	40	92.47	41.75	20	0.4%	-33.10 [-52.76, -13.44]	
larke 2009a	33.2	20.73	29	63.8	36.5	7	0.2%	-30.60 [-58.67, -2.53]	
anday 2006	39.19	26.31	125	67.66	25.27	125	1.3%	-28.47 [-34.87, -22.07]	I
uran 2003b	16.3	8.9	25	42.8	10.9	25	1.4%	-26.50 [-32.02, -20.98]	-
urmus 2007	40	10	25	42.8	10.9	25	1.4%		I
								-26.00 [-31.54, -20.46]	
ilron 2004	56.78	32.41	23	82.11	48.2	24	0.3%	-25.33 [-48.72, -1.94]	
ierking 2003	43	23.7	40	63	25.9	40	0.8%	-20.00 [-30.88, -9.12]	
ava 2009	35.6	14.14	25	54.7	13.02	25	1.2%	-19.10 [-26.63, -11.57]	-
asigh 2016	11.9	4.4	38	30.1	0.6	38	1.8%	-18.20 [-19.61, -16.79]	
osucu 2013	25.9	8.3	29	44	11	31	1.5%	-18.10 [-23.01, -13.19]	-
en 2009a	31	12	20	48	17	20	1.0%	-17.00 [-26.12, -7.88]	
uran 2003a	27.04	14.44	25	41.96	8.36	25	1.3%	-14.92 [-21.46, -8.38]	
I-Mujadi 2005	15.2	7.6	35	29.5	9	37	1.6%	-14.30 [-18.14, -10.46]	-
anday 2004a	39.18	22.31	80	52.65	21.27	20	0.9%	-13.47 [-24.00, -2.94]	
,									
oseini 2015	65.11	11.81	22	78.41	13.3	22	1.2%	-13.30 [-20.73, -5.87]	
letry 2008	16.1	7.7	67	29.2	9.6	34	1.6%	-13.10 [-16.82, -9.38]	Ţ
assoulaki 2006	22	2.9	30	35	4.8	30	1.8%	-13.00 [-15.01, -10.99]	-
anday 2004b	40.42	31.26	153	53.03	27.48	153	1.3%	-12.61 [-19.21, -6.01]	
ekhavet 2009	40.1	14.5	49	52.7	21.1	49	1.2%	-12.60 [-19.77, -5.43]	
aid-Ahmed 2007	40.5	26.28	60	52	27.5	20	0.6%	-11.50 [-25.26, 2.26]	
hafari 2009	15.78	1.15	33	26.94	2.28	33	1.9%	-11.16 [-12.03, -10.29]	•
han 2013	13.21	4.71	34	24.31	9.28	35	1.7%	-11.10 [-14.56, -7.64]	-
larke 2014	37	1.5	95	48	1.33	84	1.9%	-11.00 [-11.41, -10.59]	
									_
han 2010	20.8	5.72	150	31.5	9.6	25	1.6%	-10.70 [-14.57, -6.83]	-
lenda 2010	6	8.5	30	15.1	20	30	1.1%	-9.10 [-16.88, -1.32]	
oon 2001	24.1	9.9	16	32.7	14.6	16	1.0%	-8.60 [-17.24, 0.04]	
mr 2009	13.5	0.5	50	22	2.1	50	1.9%	-8.50 [-9.10, -7.90]	•
en 2009b	20	11.5	30	28	11.5	29	1.4%	-8.00 [-13.87, -2.13]	
zgencil 2011	29.47	9.64	30	37.33	9.5	30	1.5%	-7.86 [-12.70, -3.02]	-
Omran 2006	23.9	2.6	25	31.5	2.78	25	1.8%	-7.60 [-9.09, -6.11]	-
ekawi 2014	0	2.2	30	7.5	0.7	32	1.9%	-7.50 [-8.32, -6.68]	
yal 2010	40.2	35.2	30	46.7	35.8	30	0.4%	-6.50 [-24.47, 11.47]	
oseph 2014	38.65	18.04	25	44.29	16.02	25	1.0%	-5.64 [-15.10, 3.82]	T
bdelmageed 2010	6.6	1.3	30	12.2	1.1	30	1.9%	-5.60 [-6.21, -4.99]	.1
cak 2011	9.9	5.38	20	14.94	7.25	20	1.6%	-5.04 [-9.00, -1.08]	~
rouzanfard 2013	1.2	0.29	25	5.2	2.8	25	1.8%	-4.00 [-5.10, -2.90]	•
aghove 2010	17	7.02	30	20.98	6.32	30	1.7%	-3.98 [-7.36, -0.60]	7
lishra 2016	8.1	1	30	11.9	1.4	30	1.9%	-3.80 [-4.42, -3.18]	•
zcan 2012	15.3	5	20	19	4.2	20	1.7%	-3.70 [-6.56, -0.84]	-
eniz 2012	22.2	11.9	25	25.6	10.5	26	1.3%	-3.40 [-9.57, 2.77]	-+
ahedi 2011	18.61	9.03	36	21.53	11.3	40	1.5%	-2.92 [-7.50, 1.66]	
		33	30	42.7	36.1	29	0.4%		
oha 2010 harti 2012	39.9							-2.80 [-20.47, 14.87]	<u> </u>
	2.1	2.2	20	4.9	3.4	20	1.8%	-2.80 [-4.57, -1.03]]
larke 2009b	33.1	4	76	35	4	39	1.8%	-1.90 [-3.44, -0.36]	1
anday 2004c	90.85	34.1	28	92.49	41.77	28	0.4%	-1.64 [-21.61, 18.33]	
adawy 2014	11.5	2.3	19	13	2.9	19	1.8%	-1.50 [-3.16, 0.16]	1
oltanzadeh 2011	2.5	0.9	30	4	1.5	30	1.9%	-1.50 [-2.13, -0.87]	1
1ardani-Kivi 2013	2.5	2.3	55	3.7	2.5	53	1.9%	-1.20 [-2.11, -0.29]	4
akmaz 2007	5.47	3.43	30	6.25	3.44	15	1.8%	-0.78 [-2.91, 1.35]	+
hademi 2009	2.83	1.29	44	3.51	1.51	43	1.9%	-0.68 [-1.27, -0.09]	4
lout 2007	2.36	2.5	23	2.65	3.2	28	1.8%	-0.29 [-1.85, 1.27]	1
rten 2010	3.31	0.98	39	3.56	0.64	20	1.9%	-0.25 [-0.67, 0.17]	1
									1
laleh 2013	2.5	2.6	40	2.7	2.7	40	1.8%	-0.20 [-1.36, 0.96]	_ I
arikh 2010	31.7	20.3	30	31.9	19.84	30	0.9%	-0.20 [-10.36, 9.96]	+
assoulaki 2002	23.8	5	25	23.2	5.8	25	1.7%	0.60 [-2.40, 3.60]	†
lénigaux 2004	21	12	20	20	19	20	0.9%	1.00 [-8.85, 10.85]	+
ang 2009	32.07	29.07	23	30.07	28.57	23	0.5%	2.00 [-14.66, 18.66]	_
im 2004	35.8	20.8	21	33.5	26.1	20	0.6%	2.30 [-12.19, 16.79]	_ _
rabhakar 2007			10						Ĺ.
	23.8	5		20.04	2.09	10	1.7%	3.76 [0.40, 7.12]	<u>،</u> ۲
ubtotal (95% CI)			2319			1949	81.3%	-8.26 [-9.74, -6.79]	•
eterogeneity: Tau ² = 24 est for overall effect: Z =				9 (P < 0.000	01); $I^2 = 9$	98%			
									, [
otal (95% CI)			3064			2566	100.0%	-7.31 [-8.64, -5.98]	•
	65. Chi2 -	3337.27	. df = 7	2 (P < 0.000)	$(01): ^2 = 9$	98%			
eterogeneity: Tau ² = 24	.05, CIII =								
eterogeneity: Tau ² = 24 est for overall effect: Z =					// -				-50 -25 0 25 50



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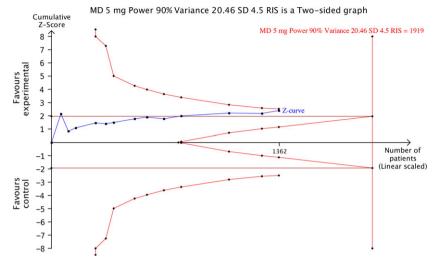


Fig. 4. Trial sequential analysis of trials with low risk of bias on 24-h morphine consumption: TSA of the effect of gabapentin on morphine consumption using the pooled SD of 4.5 mg. An estimated required information size (RIS) of 1919 patients to detect or discard a sparing effect of 5 mg morphine was 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

GABAPENTIN FOR POST-OPERATIVE PAIN MANAGEMENT

	Gabape		Contr			Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	1	М-Н,	Random, 95% Cl		
3.59.1 Low risk of bias											
Bartholdy 2006	7	38	3	38	12.4%	2.33 [0.65, 8.36]				-	
Brogly 2008	0	22	0	21		Not estimable					
Grosen 2014	13	52	8	52	29.3%	1.63 [0.74, 3.59]			+		
Kinney 2011	4	57	5	63	12.6%	0.88 [0.25, 3.13]		_			
Lunn 2015	6	183	1	91	4.8%	2.98 [0.36, 24.41]					
Paul 2013	0	52	0	49		Not estimable					
Short 2012	0	84	0	42		Not estimable					
Srivastava 2010	0	60	0	60		Not estimable					
Waikakul 2011 Subtotal (95% CI)	0	26 574	0	24 440	59.2%	Not estimable 1.61 [0.91, 2.86]			•		
Total events	30		17								
Heterogeneity: Tau ² = 0.0	00; Chi² =	1.52, df	= 3 (P =	0.68); I	² = 0%						
Test for overall effect: Z =	= 1.64 (<i>P</i> =	= 0.10)									
3.59.2 Unclear and High											
Ajori 2011	0	69	0	69		Not estimable					
Dierking 2003	0	39	0	32		Not estimable					
Dirks 2002	0	31	0	34		Not estimable					
Fassoulaki 2002	0	25	0	25		Not estimable					
Fassoulaki 2006	0	30	0	30		Not estimable					
Gilron 2004	1	20	2	22	3.9%	0.55 [0.05, 5.61]			-		
Hout 2007	1	28	0	28	2.1%	3.00 [0.13, 70.64]					_
Kavitha 2013	0	28	0	28		Not estimable					
Khan 2013	0	34	0	35		Not estimable					
Lichtinger 2011	0	20	0	20		Not estimable					
Pathak 2013	0	40	0	40		Not estimable					
Prabhakar 2007	0	20	0	20		Not estimable					
Raghove 2010	0	30	0	30		Not estimable					
Rajendran 2014	0	30	0	30		Not estimable			_		
Ucak 2011	7	20	11	20	34.7%	0.64 [0.31, 1.30]		-			
Vahedi 2011	0	36	0	40		Not estimable					
Zaldivar Ramirez 2011 Subtotal (95% Cl)	0	18 518	0	16 519	40.8%	Not estimable 0.67 [0.35, 1.32]			•		
Total events	9		13								
Heterogeneity: Tau ² = 0.0 Test for overall effect: Z =			= 2 (P =	0.63); I	² = 0%						
Total (95% CI)		1092		959	100.0%	1.14 [0.71, 1.81]			•		
Total events	39		30						-		
Heterogeneity: Tau ² = 0.0		6.43. df		0.38) I	² = 7%		—			+	
Test for overall effect: Z =			- v, -	0.00), 1	1 /0		0.01	0.1	1	10	1
Test for subgroup differen	· ·		df = 1 (D	- 0.05	12 - 70 5	0/		urs gabape		rs contro	

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. ^{33,4}	8,51,68,8	2,89,93,	102,110,1	13,137,1	40,157	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:

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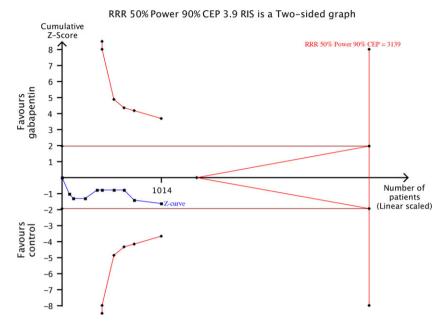


Fig. 6. Trial sequential analysis of trials with low risk of bias on serious adverse events: Trial sequential analysis (TSA) of gabapentin vs. controls in nine trials with low risk of bias reporting serious adverse events, including zero-events trials with a required information size (RIS) of 3139 patients 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 analvses 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 bias²¹. 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

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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 24h 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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Acta Anaesthesiologica Scandinavica **60** (2016) 1188–1208 © 2016 The Acta Anaesthesiologica Scandinavica Foundation. Published by John Wiley & Sons Ltd gabapentin on acute and chronic pain after inguinal herniorrhaphy. Eur J Anaesthesiol 2009; 26: 772–6.

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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}"

"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; $l^2 = 84\%$; 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; $l^2 = 92\%$; 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; $l^2 = 99\%$; 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:

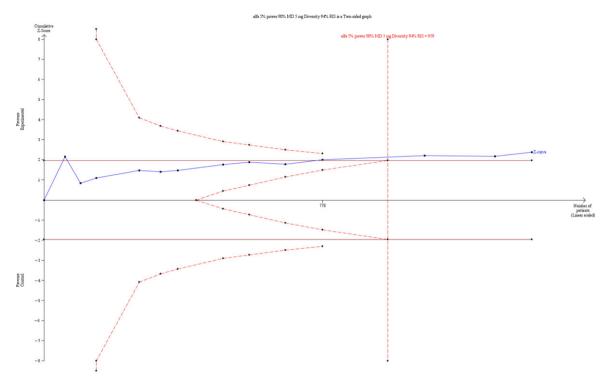


Fig. 4. Trial sequential analysis of trials with low risk of bias on 24-h morphine consumption: TSA of the effect of Gabapentin on morphine consumption using the pooled SD of 5.8 mg. An estimated required information size (RIS) of 959 patients to detect or discard a sparing effect of 5 mg morphine was 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 I 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: I3III3_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)

I. 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. I 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)

I. 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. I 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: I40701_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL)(Issue 6 of 12, 2014) in The Cochrane Library (2619 hits in CENTRAL) #I MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU1 #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)

I. 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. I 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)

I. 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. I 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: I4III4_J Wetterslev_GABA NEW

<u>Cochrane Central Register of Controlled Trials</u> (CENTRAL)(Issue 11 of 12, 2014) (2645 hits) #I 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)

I. 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. I 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)

I. 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. I 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: I 50409_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)

I. 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. I 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)

I. 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. I 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)
#I 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)

- I. 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. I 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)

I. 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. I 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

<u>Cochrane C</u>	<u>entral Register of Controlled Trials (CENTRAL) (Issue 4 of 12, 2015) (2993 hits)</u>
#I	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 eff	ects - AE, Therapeutic use - TU]
# 4	(gaba* or neurontin* or neurotonin* or horizant*)
#5	#I 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)

I. 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. I 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)

I. 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. I 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 I^{st} 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 $1^{\,\mbox{st}}$ September 2015 and on

Appendix 2: Opioid conversion

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

Trial	No* of patients	Surgical Procedures	Treatment (dose)**	Analgesic regimen (add-on therapy)	Follow-up***
Abdelmageed 2010	patients		(4050)		
[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
		Mastectomy or quandrandectomy and axillary		I <i>'</i>	,
Azemati 2013 [34]	100	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
				Acetaminophen; NSAID;	
Clarke 2009b [48]	115	Total hip arthroplasty	600 mg	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

Appendix 3: Characteristics of included trials

		Abdominal hysterectomy and			
Dierking 2003 [52]	80	salphinooophrectomy	600 mg (2400 mg/day)	None	24 h
		Unilateral radical mastectomy with axillary			
Dirks 2002 [53]	65	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
		Radical mastectomy or lobectomy with axillary			
Fassoulaki 2002 [58]	50	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 (I month)
Farzi 2015 [157]	103	Septorhinoplasty	900 mg	Local anesthesia	End of operation
Frouzanfard 2013 [61]	50	Abdominal hysterectomy	1200 mg	NSAID	24 h
		Abdominal hysterectomy and	-		
Ghafari 2009 [62]	66	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	I2 h
Gilron 2004 [65]	47	Abdominal hysterectomy	600 mg (1800 mg/day)	None	48 h (I month)
Gosai 2015 [158]	60	Mastectomy	600 mg	None	l2 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	I2 h
Hassani 2014 [68]	40	Laparoscopic gastric bypass	100 mg	None	6 h
Hoseini 2015 [159]	44	Cholecystectomy	600 mg	None	l2 h
		Exploratory thoracotomy, pneumonectomy,			
Hout 2007 [69]	51	lobectomy, segmentectomy, biopsy	1200 mg	Epidural	24 h
Jajeda 2014 [70]	50	Upper abdominal surgery	I 200 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
		- ,	-		

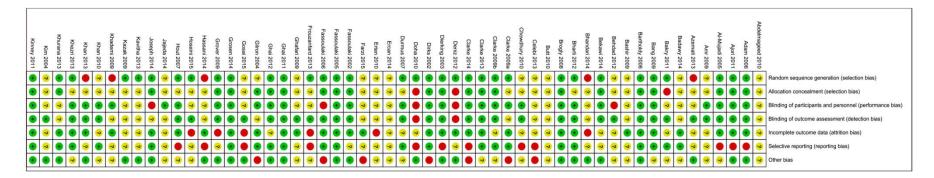
Khan 2013 [76]	69	Abdominal hysterectomy	I 200 mg	None	24 h
Khezri 2013 [77]	80	Cataract surgery	600 mg	Nerve block	5 h
Khurana 2013 [78]	60	Lumbar discectomy	300 mg (300 mg/day)	NSAID	48 h (3 months)
Kim 2004 [79]	41	Mastectomy	900 mg	None	24 h
		Thoracotectomy; lobectomy; pneumonectomy;			
Kinney 2011 [80]	125	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
			900 mg(600 mg/day)	Acetaminophen; NSAID; Local	
Lunn 2015 [87]	274	Total knee arthroplasty	1300 mg(900 mg/day)	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
		Unilateral radical mastectomy and axillary	-		
Metry 2008 [94]	68	dissection	l 200 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	?
		, , ,	č		

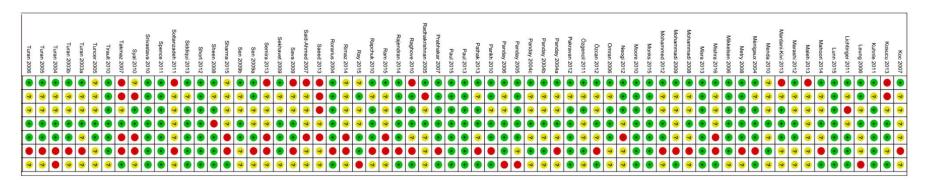
Omran 2005 [103]	50	Posterolateral thoracotomy for lobectomy	1200 mg (1200 mg/day)	None	48 h
Özcan 2011 [104]	40	Supratentorial tumor surgery	600 mg	NSAID	24 h
		Decompressive lumbar laminectomy and			
Özgenzil 2011 [105]	60	discectomy	600 mg (1800 mg/day)	None	24 h
Pakravan 2012 [106]	100	Post photorefractive 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	I2 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
		Abdominal hysterectomy and			
Sen 2009a [128]	40	salphinooophrectomy	1200 mg	Acetaminophen	6 months

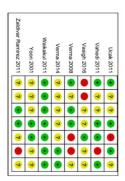
Sen 2009b [129]59Unilateral inguinal herniotomy1200 mgAcetaminophen; NSAID6 monthsSharma 2015 [163]40Laparoscopic cholecystectomy600 mgNone48 hSheen 2008 [130]80Orthopedic surgeries1200 mgNone24 hShort 2012 [131]126Caesarean section300mg/600 mgAcetaminophen; NSAID3 monthsSiddiqui 2013 [132]72Major bowel surgery600 mgNone2 daysSoltanzadeh 2011Karana and Acetaminophen2 days2 days
Sheen 2008 [130]80Orthopedic surgeries1200 mgNone24 hShort 2012 [131]126Caesarean section300mg/600 mgAcetaminophen; NSAID3 monthsSiddiqui 2013 [132]72Major bowel surgery600 mgNone2 days
Short 2012 [131]126Caesarean section300mg/600 mgAcetaminophen; NSAID3 monthsSiddiqui 2013 [132]72Major bowel surgery600 mgNone2 days
Siddiqui 2013 [132]72Major bowel surgery600 mgNone2 days
[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
Ear-nose and throat-, general-, orthopedic-, and
Tirault 2010 [138] 135 gynecologic surgery 1200 mg None 24 h
Tuncer 2005 [139] 30 Major orthopedic surgery 900 mg/1200 mg None 4 h
Abdominal hysterectomy and
Turan 2003a [140]50salphinooophrectomy1200 mgNone24h
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]40Lower limb surgeryI 200mg (1200 mg/day)Acetaminophen; Epidural72 h
Abdominal hysterectomy and
Turan 2006 [144]50salphinooophrectomy1200 mg (1200 mg/day)Acetaminophen72 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]50Abdominal hysterectomy300 mgNone24 h
Waikakul 2011 [149]48Spine, major joint, tumor and major limb surgery400 mg (300 mg/day)None24 h
Yoon 2001 [150] 32 Hysterectomy 400 mg (300 mg/day) None 24 h
Zaldivar-Ramirez 2011
[151]34Nissen laparoscopic fundoperation300 mg (600 mg/day)NSAID120 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

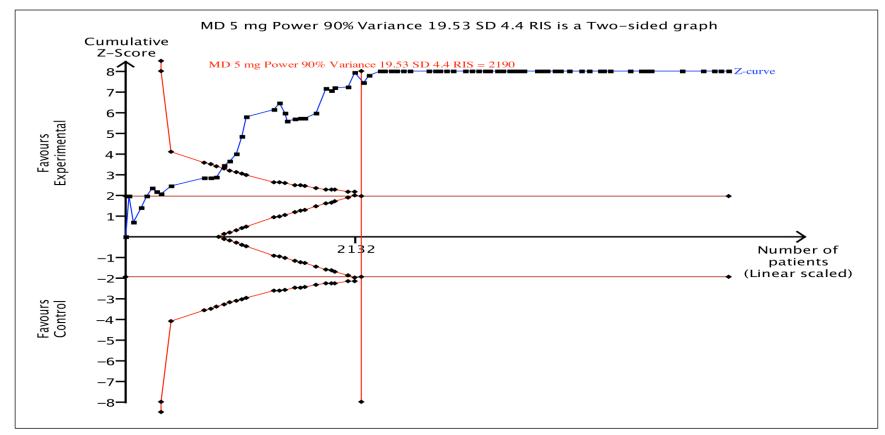
Quality assessment						N	Effect Estimate MD/RR (95% CI; TSA adj. CI)				Quality
Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	- Patients (Trials)	Relative effect	Absolute effect	P-value	l ²	
Serious	adverse eve	nts									
RCT	Not serious	Serious ²	Not serious 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-hou	r Morphine c	onsumption									
RCT	Not serious	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	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 mob	ilization				·				<u>.</u>	·
RCT	Not serious	Serious ⁹	Not serious ³	Not serious	Publication bias strongly suspected ⁷	566 (7)	-	9 mm reduction (4 to 3; 4 to 8)	<0.0002	82%	⊕⊕⊖⊖ LOW
24-hou	r VAS at rest	:									
RCT	Not serious	Serious 10	Not serious 3	Serious ⁴	None	1021 (11)	-	3 mm reduction (-0 to 6; -1 to 6)	<0.07	87%	⊕⊕⊖⊖ LOW

Quality assessment						N	Effect Estimate MD/I	Effect Estimate MD/RR (95% CI; TSA adj. CI)			
Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	- Patients (Trials)	Relative effect	Absolute effect			
RCT	Not serious	Very serious	Not serious	Serious ⁴	None	789 (8)	-	5 mm reduction (-2 to 11; -5 to 14)	0.15	94%	
Nausea	ı										
RCT	Not serious	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)	0.21	53%	⊕⊕⊕⊖ MODERAT E
								121 fewer per 1,000 (from 78 mores to 270 fewer)			
Vomiti	ng										
RCT	Not serious	Not serious	Not serious 3	Serious ⁴	Publication bias strongly	352 (4)	RR 1.04 (0.73 to 1.47;	10 more per 1,000 (from 65 fewer to 84 more)	0.85	0%	⊕⊕⊖⊖ LOW
					suspected ⁷		0.50 to 2.16) 7 more per 1,000 (from 48 fewer to 84 more)				
Sedatio	on										
RCT	Not serious	Not serious	Not serious	Serious ⁴	Publication bias strongly	858 (10)	RR 1.29 (1.06 to 1.57;	29 more per 1,000 (from 21 fewer to 82 more)	0.29	0%	⊕⊕⊖⊖ LOW
					suspected ⁷		0.97 to 1.27) 30 more per 1,000 (from 22 fewer to 85 more)				

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

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	Effect Estimate MD/RR (95% CI; TSA adj. CI)				Quality	
Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	- Patients (Trials)	Relative effect	Absolute effect	P-value	l ²	- Quality
Serious	adverse event	s	·						•		
RCT	very serious '	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%	
24h Mo	rphine consum	ption									
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 LOV
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%	
6h VAS	at mobilizatio	n									
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%	
24h VA	S 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%	
24h VA	S at mobilizati	on									
RCT	very serious ¹	very serious ⁹	not serious	serious ⁶	none	1745 (25)	-	5 mm reduction (-0 to ; -0 to)	0.05	97%	

Quality assessment						N Patients	Effect Estimate MD/RR (95% CI; TSA adj. CI)				- Quality
Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	(Trials)	Relative effect	Absolute effect	P-value	I ²	Quanty
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)	0.0003	9%	⊕⊕⊖⊖ LOW
								42 fewer per 1000 (from 21 fewer to 63 fewer)			
Vomiti	ng										
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)	0.002	0%	
								32 fewer per 1000 (from 13 fewer to 50 fewer)			
Sedatio	n										
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)	I5 more per 1000 (from 13 fewer to 20 more)	0.01	71%	⊕⊖⊖⊖ VERY LOW
Dizzine	SS										
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)	0.77	0%	⊕⊖⊖⊖ VERY LOW
								2 more per 1000 (from 9 fewer to 14 more)			

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

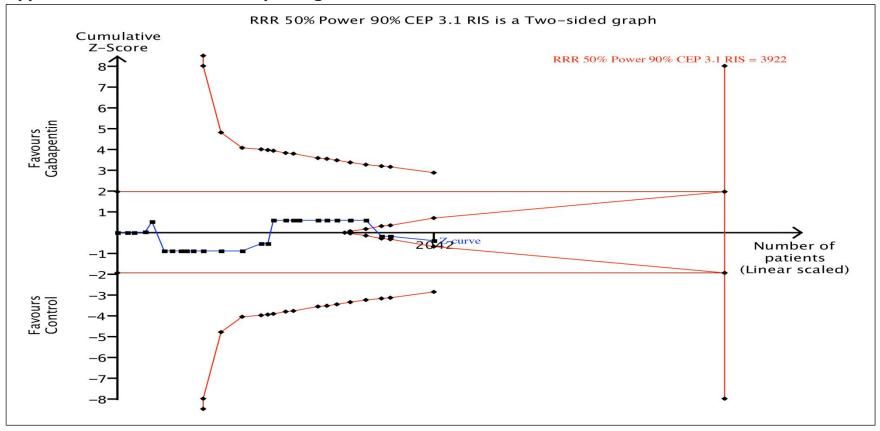
		rimental			ontrol			Mean Difference	Mean Difference
Study or Subgroup		SD [mg]	Total	Mean [mg]	SD [mg]	Total	Weight	IV, Random, 95% CI [mg]	IV, Random, 95% CI [mg]
3.3.1 Low risk of bias									
Brogly 2008	0	1.48	22	0	4.4	21	3.4%	0.00 [-1.98, 1.98]	Ť
Fassoulaki 2005	20.3	7.9	25	25.7	11.2	28	2.8%	-5.40 [-10.58, -0.22]	
Ghai 2011	5.44	1.56	30	4.28	1.87	30	3.5%	1.16 [0.29, 2.03]	t t
Grosen 2014	11.2	21.62	52	17.92	23.55	52	2.0%	-6.72 [-15.41, 1.97]	
Lunn 2015	42.8	38.4	186	50.5	41.4	99	1.8%	-7.70 [-17.55, 2.15]	
Misra 2013	24.6	19.6	37	29.15	25.2	36	1.7%	-4.55 [-14.93, 5.83]	-+
Monks 2015	10	11.9	100	10	7.4	97	3.3%	0.00 [-2.76, 2.76]	†
Moore 2010	3	3	21	4	5	23	3.4%	-1.00 [-3.41, 1.41]	+
Paul 2013	27.94	22.99	52	26.77	18.96	49	2.1%	1.17 [-7.03, 9.37]	
Paul 2015	19.7	16.39	48	25.1	14.5	54	2.6%	-5.40 [-11.44, 0.64]	
Short 2012	6.2	4.53	84	7.9	3.8	42	3.5%	-1.70 [-3.20, -0.20]	1
Subtotal (95% CI)			657			531	30.2%	-1.14 [-2.59, 0.32]	•
Heterogeneity: Tau ² =	2.47; Chi² = 2	5.09, df =	10 (P =	0.005); l ² = 6	0%				
Test for overall effect:	Z = 1.53 (P =	0.13)							
3.3.3 Unclear or High		0.5	50			50	2 50/	0 50 1 0 40 7 001	
Amr 2009	13.5	0.5	50	22	2.1	50	3.5%	-8.50 [-9.10, -7.90]	·
Badawy 2014	11.5	2.3	19	13	2.9	19	3.5%	-1.50 [-3.16, 0.16]	
Bang 2009	32.07	29.07	23	30.07	28.57	23	0.9%	2.00 [-14.66, 18.66]	
Bekawi 2014	0	2.2	30	7.5	0.7	30	3.5%	-7.50 [-8.33, -6.67]	
Bharti 2012	2.1	2.2	20	4.9	3.4	20	3.4%	-2.80 [-4.57, -1.03]	
Clarke 2009a	33.2	20.73	29	63.8	36.5	7	0.4%	-30.60 [-58.67, -2.53]	
Clarke 2009b	33.1	4	76	35	4	39	3.5%	-1.90 [-3.44, -0.36]	1
Clarke 2014	37	1.5	95	48	1.33	84	3.5%	-11.00 [-11.41, -10.59]	•
Deniz 2012	22.2	11.9	25	25.6	10.5	26	2.6%	-3.40 [-9.57, 2.77]	
Doha 2010	39.9	33	30	42.7	36.1	29	0.9%	-2.80 [-20.47, 14.87]	
Erten 2010	3.31	0.98	39	3.56	0.64	20	3.5%	-0.25 [-0.67, 0.17]	1
Fassoulaki 2002	23.8	5	25	23.2	5.8	25	3.3%	0.60 [-2.40, 3.60]	Ť
Fassoulaki 2006	22	2.9	27	35	4.8	24	3.4%	-13.00 [-15.21, -10.79]	
Frouzanfard 2013	1.2	0.29	25	5.2	2.8	25	3.5%	-4.00 [-5.10, -2.90]	•
Hout 2007	2.36	2.5	23	2.65	3.2	28	3.5%	-0.29 [-1.85, 1.27]	†
Kosucu 2013	25.9	8.3	29	44	11	31	2.9%	-18.10 [-23.01, -13.19]	-
Menda 2010	6	8.5	30	15.1	20	30	2.2%	-9.10 [-16.88, -1.32]	
Parikh 2010	31.7	20.3	30	31.9	19.84	30	1.7%	-0.20 [-10.36, 9.96]	
Prabhakar 2007	23.8	5	10	20.04	2.09	10	3.2%	3.76 [0.40, 7.12]	-
Sekhavet 2009	40.1	14.5	49	52.7	21.1	49	2.3%	-12.60 [-19.77, -5.43]	
Sen 2009a	31	12	20	48	17	20	1.9%	-17.00 [-26.12, -7.88]	
Sen 2009b	20	11.5	30	28	11.5	29	2.6%	-8.00 [-13.87, -2.13]	
Soltanzadeh 2011	2.5	0.9	30	4	1.5	30	3.5%	-1.50 [-2.13, -0.87]	1
Ucak 2011	9.9	5.38	20	14.94	7.25	20	3.1%	-5.04 [-9.00, -1.08]	-
Özcan 2012	15.3	5	20	19	4.2	20	3.3%	-3.70 [-6.56, -0.84]	
Subtotal (95% CI)			804			718	69.8%	-5.36 [-7.62, -3.09]	♦
Heterogeneity: Tau ² =	26.31; Chi ² =	1795.19, c	lf = 24	(P < 0.00001)	; l² = 99%				
Test for overall effect:				,					
Total (95% CI)			1461			1249	100.0%	-4.41 [-6.29, -2.52]	▼
Heterogeneity: Tau ² =			if = 35	(P < 0.00001)	; ² = 98%				-50 -25 0 25 50
Test for overall effect:	Z = 4.58 (P <	0.00001)							Gabapentin Control

Appendix 9: Forest plot of no add-on effect

	•	rimental			ontrol			Mean Difference	Mean Difference
Study or Subgroup		SD [mg]	Total	Mean [mg]	SD [mg]	Total	Weight	IV, Random, 95% CI [mg]	IV, Random, 95% CI [mg]
3.4.1 Low risk of bias									
Srivastava 2010	25.39	4.48	60	37.58	8.35	60	3.6%	-12.19 [-14.59, -9.79]	-
Waikakul 2011 Subtotal (95% CI)	15.5	9.25	24 84	18	15.5	24 84	2.6% 6.2%	-2.50 [-9.72, 4.72] -7.97 [-17.39, 1.45]	•
Heterogeneity: Tau ² =	39 41 · Chi ² =	623 df=	1 (P = () ()1)· 2 = 849	6				•
Test for overall effect:	-	,	. (•				
3.4.3 Unclear or High	risk of bias								
Abdelmageed 2010	6.6	1.3	30	12.2	1.1	30	3.8%	-5.60 [-6.21, -4.99]	•
Al-Mujadi 2005	15.2	7.6	35	29.5	9	37	3.4%	-14.30 [-18.14, -10.46]	-
Dierking 2003	43	23.7	39	63	25.9	32	1.7%	-20.00 [-31.66, -8.34]	
Durmus 2007	40	10	25	66	10	25	3.0%	-26.00 [-31.54, -20.46]	
Ghafari 2009	15.78	1.15	33	26.94	2.28	33	3.8%	-11.16 [-12.03, -10.29]	•
Gilron 2004	56.78	32.41	23	82.11	48.2	24	0.6%	-25.33 [-48.72, -1.94]	
Hoseini 2015	65.11	11.81	22	78.41	13.3	22	2.5%	-13.30 [-20.73, -5.87]	
Joseph 2014	38.65	18.04	25	44.29	16.02	25	2.1%	-5.64 [-15.10, 3.82]	-+
Khademi 2009	2.83	1.29	44	3.51	1.51	43	3.8%	-0.68 [-1.27, -0.09]	4
Khan 2010	20.8	5.72	150	31.5	9.6	25	3.4%	-10.70 [-14.57, -6.83]	-
Khan 2013	13.21	4.71	34	24.31	9.28	35	3.5%	-11.10 [-14.56, -7.64]	-
Kim 2004	35.8	20.8	21	33.5	26.1	20	1.3%	2.30 [-12.19, 16.79]	
Valeh 2013	2.5	2.6	40	2.7	2.7	40	3.8%	-0.20 [-1.36, 0.96]	ł
Marashi 2012	18.3	15.6	22	65.7	31	22	1.3%	-47.40 [-61.90, -32.90]	<u> </u>
Mardani-Kivi 2013	2.5	2.3	55	3.7	2.5	53	3.8%	-1.20 [-2.11, -0.29]	
Metry 2008	16.1	7.7	67	29.2	9.6	34	3.4%	-13.10 [-16.82, -9.38]	-
Vishra 2016	8.1	1	30	11.9	1.4	30	3.8%	-3.80 [-4.42, -3.18]	
Vénigaux 2004	21	. 12	20	20	19	20	2.0%	1.00 [-8.85, 10.85]	_ _
Omran 2006	23.9	2.6	25	31.5	2.78	25	3.8%	-7.60 [-9.09, -6.11]	-
Panday 2004a	39.18	22.31	80	52.65	21.27	20	1.9%	-13.47 [-24.00, -2.94]	
Panday 2004b	40.42	31.26	153	53.03	27.48	153	2.7%	-12.61 [-19.21, -6.01]	
Panday 2004c	90.85	34.1	28	92.49	41.77	28	0.8%	-1.64 [-21.61, 18.33]	
Panday 2005	59.37	23.17	40	92.47	41.75	20	0.8%	-33.10 [-52.76, -13.44]	
Panday 2006	39.19	26.31	125	67.66	25.27	125	2.8%	-28.47 [-34.87, -22.07]	
Raghove 2010	17	7.02	30	20.98	6.32	30	3.5%	-3.98 [-7.36, -0.60]	-
Said-Ahmed 2007	40.5	26.28	60	52	27.5	20	1.4%	-11.50 [-25.26, 2.26]	
Sava 2009	35.6	14.14	25	54.7	13.02	25	2.5%	-19.10 [-26.63, -11.57]	<u> </u>
Sava 2009 Syal 2010	40.2	35.2	20 30	46.7	35.8	20 30	0.9%	-6.50 [-24.47, 11.47]	
Takmaz 2007	40.2 5.47	3.43	30 30	6.25	3.44	30 15	0.9% 3.7%	-0.78 [-2.91, 1.35]	ļ
Turan 2003a	27.04	3.43 14.44	30 25	41.96	3.44 8.36	25	2.7%	-0.78 [-2.91, 1.35] -14.92 [-21.46, -8.38]	<u> </u>
Turan 2003a Turan 2003b	27.04	14.44	25 25	41.96	8.36 10.9	25 25	2.7%	-14.92 [-21.46, -8.38] -26.50 [-32.02, -20.98]	<u> </u>
ahedi 2003b Zahedi 2011	18.61		25 36	42.8 21.53	10.9				4
Vanedi 2011 Vasigh 2016	18.61	9.03 4.4		30.1	0.6	40	3.2% 3.8%	-2.92 [-7.50, 1.66]	• T
Yoon 2001		4.4 9.9	38	30.1		38		-18.20 [-19.61, -16.79]	
	24.1		16		14.6	16	2.3%	-8.60 [-17.24, 0.04]	
Özgencil 2011 Subtotal (95% CI)	29.47	9.64	30 1511	37.33	9.5	30 1215	3.1% 93.8 %	-7.86 [-12.70, -3.02] -10.72 [-12.80, -8.64]	♦
Heterogeneity: Tau ² = Test for overall effect:				(P < 0.00001)	; l² = 97%				
Total (95% CI)			1595			1299	100.0%	-10.57 [-12.58, -8.55]	•
Heterogeneity: Tau ² = Test for overall effect:				(P < 0.00001)	; l² = 97%			-	

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

tudy or Subgroup .99.1 Low risk of bia	Mean [mg]	rimental SD [mg]	Total		ntrol SD [mg]	Total	Weight	Mean Difference IV, Random, 95% CI [mg]	Mean Difference IV, Random, 95% CI [mg]
ekawi 2014	0	2.2	30	7.5	0.7	30	1.9%	-7.50 [-8.33, -6.67]	
harti 2012	2.1	2.2	20	4.9	3.4	20	1.8%	-2.80 [-4.57, -1.03]	-
rogly 2008	0	1.48	22	0	4.4	21	1.8%	0.00 [-1.98, 1.98]	+
eniz 2012	22.2	11.9	25	25.6	10.5	26	1.3%	-3.40 [-9.57, 2.77]	-+
ierking 2003	43	23.7	39	63	25.9	32	0.8%	-20.00 [-31.66, -8.34]	
oha 2010	39.9	33	30	42.7	36.1	29	0.4%	-2.80 [-20.47, 14.87]	
assoulaki 2002	23.8	5	25	23.2	5.8	25	1.7%	0.60 [-2.40, 3.60]	+
assoulaki 2005	20.3	7.9	25	25.7	11.2	28	1.5%	-5.40 [-10.58, -0.22]	
Shai 2011	5.44	1.56	30	4.28	1.87	30	1.9%	1.16 [0.29, 2.03]	
Grosen 2014	11.2	21.62	52	17.92	23.55	52	1.0%	-6.72 [-15.41, 1.97]	
oseph 2014	38.65	18.04	25	44.29	16.02	25	1.0%	-5.64 [-15.10, 3.82]	+
han 2013	13.21	4.71	34	24.31	9.28	35	1.7%	-11.10 [-14.56, -7.64]	-
im 2004	35.8	20.8	21	33.5	26.1	20	0.6%	2.30 [-12.19, 16.79]	
osucu 2013	25.9	8.3	29	44	11	31	1.5%	-18.10 [-23.01, -13.19]	
unn 2015	42.8	38.4	186	50.5	41.4	99	0.9%	-7.70 [-17.55, 2.15]	
ishra 2016	8.1	1	30	11.9	1.4	30	1.9%	-3.80 [-4.42, -3.18]	
lisra 2013	24.6	19.6	37	29.15	25.2	36	0.9%	-4.55 [-14.93, 5.83]	
lonks 2015	10	11.9	100	10	7.4	97	1.7%	0.00 [-2.76, 2.76]	+
					7.4	23			1
loore 2010	3	3	21	4			1.8%	-1.00 [-3.41, 1.41]	
lénigaux 2004	21	12	20	20	19	20	0.9%	1.00 [-8.85, 10.85]	
arikh 2010	31.7	20.3	30	31.9	19.84	30	0.9%	-0.20 [-10.36, 9.96]	
aul 2013	27.94	22.99	52	26.77	18.96	49	1.1%	1.17 [-7.03, 9.37]	+-
aul 2015	19.7	16.39	48	25.1	14.5	54	1.4%	-5.40 [-11.44, 0.64]	
rabhakar 2007	23.8	5	10	20.04	2.09	10	1.7%	3.76 [0.40, 7.12]	+
aghove 2010	17	7.02	30	20.98	6.32	30	1.7%	-3.98 [-7.36, -0.60]	-
hort 2012	6.2	4.53	84	7.9	3.8	42	1.8%	-1.70 [-3.20, -0.20]	4
rivastava 2010	25.39	4.48	60	37.58	8.35	60	1.8%	-12.19 [-14.59, -9.79]	-
akmaz 2007	5.47	3.43	30	6.25	3.44	15	1.8%	-0.78 [-2.91, 1.35]	+
ahedi 2011	18.61	9.03	36	21.53	11.3	40	1.5%	-2.92 [-7.50, 1.66]	-+
/aikakul 2011	15.5	9.25	24	18	15.5	24	1.2%	-2.50 [-9.72, 4.72]	-+
ubtotal (95% CI)			1205			1063	41.7%	-3.77 [-5.43, -2.10]	•
leterogeneity: Tau ² = est for overall effect: 2			= 29 (F	e < 0.00001); I	² = 92%				
.99.2 Unclear or High				10.0			1.00/	5 00 1 0 01 1 001	
bdelmageed 2010	6.6	1.3	30	12.2	1.1	30	1.9%	-5.60 [-6.21, -4.99]	
I-Mujadi 2005	15.2	7.6	35	29.5	9	37	1.6%	-14.30 [-18.14, -10.46]	
mr 2009	13.5	0.5	50	22	2.1	50	1.9%	-8.50 [-9.10, -7.90]	•
adawy 2014	11.5	2.3	19	13	2.9	19	1.8%	-1.50 [-3.16, 0.16]	1
ang 2009	32.07	29.07	23	30.07	28.57	23	0.5%	2.00 [-14.66, 18.66]	
larke 2009a	33.2	20.73	29	63.8	36.5	7	0.2%	-30.60 [-58.67, -2.53]	
larke 2009b	33.1	4	76	35	4	39	1.8%	-1.90 [-3.44, -0.36]	-
larke 2014	37	1.5	95	48	1.33	84	1.9%	-11.00 [-11.41, -10.59]	•
urmus 2007	40	10	25	66	10	25	1.4%	-26.00 [-31.54, -20.46]	
rten 2010	3.31	0.98	39	3.56	0.64	20	1.9%	-0.25 [-0.67, 0.17]	•
assoulaki 2006	22	2.9	27	35	4.8	24	1.8%	-13.00 [-15.21, -10.79]	-
rouzanfard 2013	1.2	0.29	25	5.2	2.8	25	1.9%	-4.00 [-5.10, -2.90]	•
Shafari 2009	15.78	1.15	33	26.94	2.28	33	1.9%	-11.16 [-12.03, -10.29]	•
ilron 2004	56.78	32.41	23	82.11	48.2	24	0.3%	-25.33 [-48.72, -1.94]	
oseini 2015	65.11	11.81	22	78.41	13.3	22	1.2%	-13.30 [-20.73, -5.87]	
out 2007	2.36	2.5	23	2.65	3.2	28	1.8%	-0.29 [-1.85, 1.27]	1
hademi 2009	2.83	1.29	44	3.51	1.51	43	1.9%		
								-0.68 [-1.27, -0.09]	-
han 2010	20.8	5.72	150	31.5	9.6	25	1.6%	-10.70 [-14.57, -6.83]	
laleh 2013	2.5	2.6	40	2.7	2.7	40	1.8%	-0.20 [-1.36, 0.96]	I
larashi 2012	18.3	15.6	22	65.7	31	22	0.6%	-47.40 [-61.90, -32.90]	
ardani-Kivi 2013	2.5	2.3	55	3.7	2.5	53	1.9%	-1.20 [-2.11, -0.29]	1
enda 2010	6	8.5	30	15.1	20	30	1.1%	-9.10 [-16.88, -1.32]	
letry 2008	16.1	7.7	67	29.2	9.6	34	1.6%	-13.10 [-16.82, -9.38]	-
mran 2006	23.9	2.6	25	31.5	2.78	25	1.8%	-7.60 [-9.09, -6.11]	•
anday 2004a	39.18	22.31	80	52.65	21.27	20	0.9%	-13.47 [-24.00, -2.94]	
anday 2004b	40.42	31.26	153	53.03	27.48	153	1.3%	-12.61 [-19.21, -6.01]	
anday 2004c	90.85	34.1	28	92.49	41.77	28	0.4%	-1.64 [-21.61, 18.33]	
anday 2005	59.37	23.17	40	92.47	41.75	20	0.4%	-33.10 [-52.76, -13.44]	
anday 2006	39.19	26.31	125	67.66	25.27	125	1.3%	-28.47 [-34.87, -22.07]	
aid-Ahmed 2007	40.5	26.28	60	52	27.5	20	0.6%	-11.50 [-25.26, 2.26]	
ava 2009	35.6	14.14	25	54.7	13.02	25	1.2%	-19.10 [-26.63, -11.57]	<u> </u>
ekhavet 2009	40.1	14.5	49	52.7	21.1	49	1.2%	-12.60 [-19.77, -5.43]	
en 2009a	31	14.5	20	48	17	20	1.0%	-17.00 [-26.12, -7.88]	
en 2009a en 2009b	20	11.5	30	28	11.5	20	1.4%	-8.00 [-13.87, -2.13]	
	2.5			20		29 30		-1.50 [-2.13, -0.87]	
oltanzadeh 2011		0.9	30		1.5		1.9%		
yal 2010	40.2	35.2	30	46.7	35.8	30	0.4%	-6.50 [-24.47, 11.47]	
uran 2003a	27.04	14.44	25	41.96	8.36	25	1.3%	-14.92 [-21.46, -8.38]	-
uran 2003b	16.3	8.9	25	42.8	10.9	25	1.4%	-26.50 [-32.02, -20.98]	
cak 2011	9.9	5.38	20	14.94	7.25	20	1.6%	-5.04 [-9.00, -1.08]	-
	11.9	4.4	38	30.1	0.6	38	1.8%	-18.20 [-19.61, -16.79]	•
	24.1	9.9	16	32.7	14.6	16	1.0%	-8.60 [-17.24, 0.04]	
oon 2001	15.3	5	20	19	4.2	20	1.7%	-3.70 [-6.56, -0.84]	-
oon 2001		9.64	30	37.33	9.5	30	1.5%	-7.86 [-12.70, -3.02]	-
oon 2001 Jzcan 2012	29.47		1851			1485	58.3%	-9.89 [-11.73, -8.05]	♦
'asigh 2016 'oon 2001 Dzcan 2012 Dzgencil 2011 Subtotal (95% CI) leterogeneity: Tau ² = 3		2865.91, c		P < 0.00001);	$I^2 = 99\%$				
oon 2001 Dzcan 2012 Dzgencil 2011 Subtotal (95% CI) leterogeneity: Tau ² = 2 est for overall effect: 2	28.04; Chi² =		if = 42 (P < 0.00001);	I² = 99%				
oon 2001 ozcan 2012 ozgencil 2011 ubtotal (95% CI) leterogeneity: Tau ² = 2	28.04; Chi² =		df = 42 (P < 0.00001);	I ² = 99%	2548	100.0%	-7.30 [-8.63, -5.97]	•
oon 2001 izcan 2012 izgencil 2011 ubtotal (95% CI) eterogeneity: Tau ² = 2 est for overall effect: 2	28.04; Chi² = Z = 10.52 (P •	< 0.00001)	df = 42 (3056			2548	100.0%	-7.30 [-8.63, -5.97]	



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

Study or Subgroup		pentin SD IVAS1	Total	Contr Mean IVAS1 SI		Total	Weight	Mean Difference IV, Random, 95% CI [VAS	Mean Difference IV, Random, 95% CI [VAS]
2.1.1 Low risk of bias	Lioun [TAO]	-5 [FA0]	, Jiai		. [vA0]	, otal	maight	, rundom, 33 /0 OI [4A3	
Bartholdy 2006	4	7.4	38	6	6.6	38	1.7%	-2.00 [-5.15, 1.15]	-
Brogly 2008	22.5	19.1	22	23.5	21.3	21	1.3%	-1.00 [-13.11, 11.11]	
			22		21.3	21		-3.00 [-18.88, 12.88]	
Fassoulaki 2005	17	28		20			1.1%	-7.11 [-13.13, -1.09]	
Grosen 2014	6.84	12.97	52	13.95	17.94	52	1.6%		
Kinney 2011	27	25.2	57	28	26.2	68	1.4%	-1.00 [-10.03, 8.03]	
Moore 2010	19.5	15.5	21	40	20	23	1.4%	-20.50 [-31.02, -9.98]	
Short 2012	14.5	7.04	84	20	10	42	1.7%	-5.50 [-8.88, -2.12]	-
Srivastava 2010	23	3.17	60	49	3.33	60	1.7%	-26.00 [-27.16, -24.84]	•
Waikakul 2011	50	25	24	60	25	24	1.2%	-10.00 [-24.14, 4.14]	
Subtotal (95% CI)			383			356	13.0%	-8.64 [-18.59, 1.30]	\bullet
Heterogeneity: Tau ² = 209 Test for overall effect: Z =			(P < 0.	00001); I² = 98%					
2.1.2 Unclear/High risk o	f bias								
Abdelmageed 2010	32	8	30	21	6	30	1.7%	11.00 [7.42, 14.58]	-
Ajori 2011	40	30	69	63	28	69	1.4%	-23.00 [-32.68, -13.32]	
Al-Mujadi 2005	14	7	35	24.1	13	37	1.6%	-10.10 [-14.89, -5.31]	-
Badawy 2014	40	5	19	45	5	19	1.7%	-5.00 [-8.18, -1.82]	+
Bang 2009	45	20	23	60	20	23	1.3%	-15.00 [-26.56, -3.44]	
									-
Behdad 2012	38	9.6	30	66.2	13.7	31	1.6%	-28.20 [-34.12, -22.28]	_
Chowdhury 2010	40.8	5.26	100	45	3.37	100	1.7%	-4.20 [-5.42, -2.98]	
Deniz 2012	23	28	25	31	27	26	1.1%	-8.00 [-23.11, 7.11]	
Dierking 2003	14.12	15.23	39	21.53	18.59	32	1.5%	-7.41 [-15.43, 0.61]	
Dirks 2002	14	18	31	18	15	34	1.5%	-4.00 [-12.10, 4.10]	-+
Doha 2010	18	17	30	33	11	29	1.5%	-15.00 [-22.28, -7.72]	
Durmus 2007	45	51	25	52	61	25	0.5%	-7.00 [-38.17, 24.17]	
Erten 2010	25.89	7.11	39	30.5	8.8	20	1.7%	-4.61 [-9.07, -0.15]	-
Fassoulaki 2002	7	20	25	9	19	25	1.4%	-2.00 [-12.81, 8.81]	<u> </u>
Fassoulaki 2002	25.7	16.1	27	26.8	19.6	24	1.4%	-1.10 [-11.02, 8.82]	<u> </u>
Frouzanfard 2013	35.6	15	25	65.6	19.6	24	1.4%	-30.00 [-39.18, -20.82]	<u> </u>
									_
Ghafari 2009	42.5	3.5	33	58.1	4	33	1.7%	-15.60 [-17.41, -13.79]	-
Gilron 2004	29	4	23	39	3	24	1.7%	-10.00 [-12.03, -7.97]	*
Gosai 2015	36	5	30	52	8	30	1.7%	-16.00 [-19.38, -12.62]	-
Grover 2009	10	8.15	27	10	8.15	23	1.6%	0.00 [-4.53, 4.53]	+
Hassani 2014	21	3	30	23	5	30	1.7%	-2.00 [-4.09, 0.09]	-
Hoseini 2015	16.4	10.2	22	30.9	10.1	22	1.6%	-14.50 [-20.50, -8.50]	-
Hout 2007	0	5.93	23	0	3.7	28	1.7%	0.00 [-2.78, 2.78]	+
Jajeda 2014	31.6	4.7	25	52.4	10.5	25	1.6%	-20.80 [-25.31, -16.29]	-
Kazak 2009	15	22.5	30	22	29.5	30	1.2%	-7.00 [-20.28, 6.28]	
Khan 2010	44.4	14.55	150	68	11	25	1.6%	-23.60 [-28.50, -18.70]	-
	36.17		34			35			
Khan 2013		13.4		52	10.51		1.6%	-15.83 [-21.52, -10.14]	
Khezri 2013	0	8	30	0	19	30	1.5%	0.00 [-7.38, 7.38]	
Kim 2004	27	22.2	21	29	17.6	20	1.3%	-2.00 [-14.23, 10.23]	
Koc 2007	2.3	9	20	12.5	27	20	1.3%	-10.20 [-22.67, 2.27]	
Kosucu 2013	29	12	29	42	21	31	1.5%	-13.00 [-21.59, -4.41]	
Mahoori 2014	30	15.8	25	56.8	11.4	25	1.5%	-26.80 [-34.44, -19.16]	
Marashi 2012	48	10	22	59	9	22	1.6%	-11.00 [-16.62, -5.38]	
Mardani-Kivi 2013	50	8	55	70	7	30	1.7%	-20.00 [-23.28, -16.72]	-
Menda 2010	20	31	30	30	48	30	0.9%	-10.00 [-30.45, 10.45]	
Metry 2008	12.52	9.5	67	24.1	13	34	1.6%	-11.58 [-16.51, -6.65]	-
Mishra 2016	30.7	4.4	30	31	2.1	30	1.7%	-0.30 [-2.04, 1.44]	Ļ
Ménigaux 2004	18	7	20	21	34	20	1.1%	-3.00 [-18.21, 12.21]	
Omran 2006	35	45.59	25	61	45.69	25	0.7%	-26.00 [-51.30, -0.70]	
Panday 2004a	36.5	12.97	80	61.5	13	20	1.6%	-25.00 [-31.37, -18.63]	
Panday 2005	29.5	12.36	40	50	10	20	1.6%	-20.50 [-26.32, -14.68]	-
Parikh 2010	29	7	30	55	6	30	1.7%	-26.00 [-29.30, -22.70]	-
Prabhakar 2007	37.5	11.1	10	47.5	14.4	10	1.3%	-10.00 [-21.27, 1.27]	
Radhakrishnan 2005	10	12.5	30	10	12.5	30	1.6%	0.00 [-6.33, 6.33]	+
Rajendran 2014	42.7	5.2	30	65	7.3	30	1.7%	-22.30 [-25.51, -19.09]	+
Ray 2015	56.16	14.24	30	77	12.9	30	1.6%	-20.84 [-27.72, -13.96]	
Said-Ahmed 2007	26	13.17	60	42	11	20	1.6%	-16.00 [-21.86, -10.14]	-
Sekhavet 2009		20.8	49	76.6	22.4	20 49	1.5%	-38.70 [-47.26, -30.14]	<u> </u>
	37.9								
Sen 2009a	28	24	20	41	47	20	0.8%	-13.00 [-36.13, 10.13]	<u> </u>
Sen 2009b	15	12	30	20	25	29	1.4%	-5.00 [-15.06, 5.06]	T
Tuncer 2005	19	22.27	15	24	17	15	1.2%	-5.00 [-19.18, 9.18]	
Turan 2003a	18	16	25	42	10	25	1.5%	-24.00 [-31.40, -16.60]	
Furan 2003b	13	15	25	24	18	25	1.4%	-11.00 [-20.18, -1.82]	
Furan 2004	15	31	25	31	53	25	0.7%	-16.00 [-40.07, 8.07]	
Furan 2005	34	11	20	57	83	20	0.4%	-23.00 [-59.69, 13.69]	
Jcak 2011	29.9	2	20	50	65	20	0.6%	-20.10 [-48.60, 8.40]	
/ahedi 2011	61.1	20.9	36	56.8	24.4	40	1.4%	4.30 [-5.89, 14.49]	
/erma 2008	23		25	32	16	25	1.4%	-9.00 [-17.33, -0.67]	
		14							
Yoon 2001	29	72	16	41	59	16	0.3%	-12.00 [-57.61, 33.61]	
Zaldivar Ramirez 2011	30	13	18	55	9.8	16	1.5%	-25.00 [-32.69, -17.31]	
Özcan 2012	12	23	20	34	13	20	1.3%	-22.00 [-33.58, -10.42]	
Özgencil 2011	24	6.7	30	33.3	10.9	30	1.6%	-9.30 [-13.88, -4.72]	
			2057			1736	87.0%	-12.41 [-14.94, -9.89]	♦
Subtotal (95% CI)	70; Chi ² = 999.		(P < 0.	00001); I² = 94%				-	
Subtotal (95% CI) Heterogeneity: Tau² = 79. Test for overall effect: Z =	9.63 (P < 0.000	001)							
Heterogeneity: Tau² = 79. Test for overall effect: Z =	9.63 (P < 0.000	001)	2440			2092	100.0%	-11.95 [-14.649 26]	•
Heterogeneity: Tau ² = 79. ⁻ Test for overall effect: Z = Total (95% CI)	,	,	2440 70 (P <	0 00001\+ 12 = 060	%	2092	100.0%	-11.95 [-14.64, -9.26]	
Heterogeneity: Tau² = 79. Test for overall effect: Z =	.91; Chi² = 173	6.70, df =		0.00001); l ² = 96 ¹	%	2092	100.0%	-11.95 [-14.64, -9.26]	-100 -50 0 50 10 Favours Gabapentin Favours Control

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

Study or Subgroup		apentin	Total		ntrol SD [VAS]	Total	Woight	Mean Difference IV, Random, 95% CI [VAS]	Mean Difference IV, Random, 95% CI [VAS]
2.2.1 Low risk of bias			Total		00 [170]	Total	Weight		
Bartholdy 2006	3	7.4	38	5	9.6	38	9.0%	-2.00 [-5.85, 1.85]	+
Brogly 2008	45.6	24.8	22	39.4	20.1	21	2.9%	6.20 [-7.26, 19.66]	
Fassoulaki 2005	40	67	25	53	78	28	0.4%	-13.00 [-52.04, 26.04]	
Grosen 2014	12.42	18.55	52	21.29	19.28	52		-8.87 [-16.14, -1.60]	
Moore 2010	20	13.25	21	40	14.5	23	5.4%	-20.00 [-28.20, -11.80]	
Short 2012	30	10.39	84	40	10	42	9.1%	-10.00 [-13.75, -6.25]	+
Srivastava 2010	59	3.33	60	70.5	3.5	60	10.8%	-11.50 [-12.72, -10.28]	•
Subtotal (95% CI)		0.00	302		010	264	43.6%	-8.71 [-13.22, -4.20]	•
Heterogeneity: Tau ² =	22.53: Chi ² = 32	2.57. df = 6	(P < 0.(0001): l² = 82%				• • •	
Test for overall effect:			1						
		,							
2.2.2 Unclear/High ris		10	~-		1.	~-	0.00/	0.0011150.000	
Al-Mujadi 2005	23	12	35	31.3	15	37	6.8%	-8.30 [-14.56, -2.04]	
Dierking 2003	42.53	25.9	39	51.09	28.27	32	3.1%	-8.56 [-21.29, 4.17]	
Dirks 2002	19	21	31	31	23	34	3.9%	-12.00 [-22.70, -1.30]	
Durmus 2007	67	77	25	76	83	25	0.3%	-9.00 [-53.38, 35.38]	
Fassoulaki 2002	21	35	25	29	52	25	1.1%	-8.00 [-32.57, 16.57]	
Fassoulaki 2006	47.8	19.7	27	45.1	24.6	24	3.3%	2.70 [-9.63, 15.03]	
Grover 2009	30	14.81	27	30	7.41	23	6.8%	0.00 [-6.35, 6.35]	Ť
Kim 2004	42	25.2	21	37	15.8	20	3.1%	5.00 [-7.81, 17.81]	
Menda 2010	43.5	57	30	65	78	30	0.6%	-21.50 [-56.07, 13.07]	
Metry 2008	20.52	14.48	67	31.3	15	34	7.0%	-10.78 [-16.90, -4.66]	-
Omran 2006	60	35.16	25	80	35.16	25	1.6%	-20.00 [-39.49, -0.51]	
Prabhakar 2007	52.5	10.9	10	65	19.6	10	2.7%	-12.50 [-26.40, 1.40]	
Radhakrishnan 2005	20	15	30	30	20	30	4.9%	-10.00 [-18.95, -1.05]	
Sen 2009a	32	34	20	56	54	20	0.8%	-24.00 [-51.97, 3.97]	
Sen 2009b	19	15	30	21	25	29	4.0%	-2.00 [-12.56, 8.56]	
Turan 2003a	31.2	17	25	43	12	25	5.4%	-11.80 [-19.96, -3.64]	-
Ucak 2011	39	20	20	55	68	20	0.7%	-16.00 [-47.06, 15.06]	
Yoon 2001	41	60	16	58	74	16	0.3%	-17.00 [-63.68, 29.68]	
Subtotal (95% CI)			503			459	56.4%	-7.46 [-10.46, -4.45]	V
Heterogeneity: Tau ² = Test for overall effect: :			(P = 0.2	25); I² = 17%					
	- יו) וטידי -	00001							
Total (95% CI)			805			723	100.0%	-8.10 [-10.75, -5.46]	•
Heterogeneity: Tau ² =	16.43; Chi ² = 58	3.25, df = 24	4 (P = 0	.0001); l² = 59%	6				-100 -50 0 50 100

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

	Gabar	entin		Contr	ol			Mean Difference	Mean Difference
Study or Subgroup			Total			Total	Weight	IV, Random, 95% CI [VAS]	
2.3.1 Low risk of bias	incuir [1740]		Total	incun [TA0] of		Total	Weight		
Brogly 2008	12.4	10.4	22	15.5	17.9	21	1.4%	-3.10 [-11.90, 5.70]	-+
Fassoulaki 2005	16	27	25	7	14	28	1.2%	9.00 [-2.79, 20.79]	+
Grosen 2014	6.58	13.61	52	12.43	16.4	52	1.7%	-5.85 [-11.64, -0.06]	
Kinney 2011	29	18.2	57	31	18.9	68	1.7%	-2.00 [-8.52, 4.52]	-+
Monks 2015	11	4.4	100	19	5.9	97	2.0%	-8.00 [-9.46, -6.54]	•
Moore 2010	7	5.5	21	20	22.5	23	1.4%	-13.00 [-22.49, -3.51]	
Paul 2015	24.5	16.1	48	23.6	20.8	54	1.6%	0.90 [-6.28, 8.08]	+
Short 2012	15	6.59	84	10	10	42	1.9%	5.00 [1.66, 8.34]	+
Spence 2011	4	7	28	4	8	31	1.9%	0.00 [-3.83, 3.83]	+
Srivastava 2010	21	3.25	60	28	3.33	60	2.0%	-7.00 [-8.18, -5.82]	•
Waikakul 2011	30	20	24	35	17.5	24	1.3%	-5.00 [-15.63, 5.63]	
Subtotal (95% CI)			521			500	18.0%	-2.95 [-6.06, 0.16]	•
Heterogeneity: Tau² = 17 Test for overall effect: Z =		, df = 10 (P < 0.0	0001); l² = 87%					
2.3.2 Unclear/High risk									
Abdelmageed 2010	21	4	30	10	7	30	1.9%	11.00 [8.12, 13.88]	-
Adam 2006	30	60	27	30	60	26	0.3%	0.00 [-32.31, 32.31]	
Ajori 2011	2	8	69	9	13	69	1.9%	-7.00 [-10.60, -3.40]	
Al-Mujadi 2005	18	16	35	23	13	37	1.6%	-5.00 [-11.76, 1.76]	
Badawy 2014	20	2.5	19	25	2.5	19	2.0%	-5.00 [-6.59, -3.41]	•
Bang 2009	32	20	23	38	20	23	1.2%	-6.00 [-17.56, 5.56]	
Behdad 2012	25.3	5	30	42.7	14.2	31	1.8%	-17.40 [-22.71, -12.09]	-
Bekawi 2014	9.7	5.6	30	6	6.2	30	1.9%	3.70 [0.71, 6.69]	
Clarke 2009a	36.53	25.97	29	51	21.8	7	0.7%	-14.47 [-33.18, 4.24]	
Clarke 2009b	13	3.97	76	14	4	39	2.0%	-1.00 [-2.54, 0.54]	1
Deniz 2012	12	19	25	8	15	26	1.4%	4.00 [-5.42, 13.42]	
Dierking 2003	13.64	19.19	39	15.21	18.93	32	1.4%	-1.57 [-10.47, 7.33]	
Durmus 2007 Erten 2010	27 9.22	40 8.04	25 39	39 13	49 9.7	25 20	0.5% 1.8%	-12.00 [-36.79, 12.79]	
				7	9.7 14			-3.78 [-8.72, 1.16] -3.00 [-10.23, 4.23]	
Fassoulaki 2002 Frouzanfard 2013	4 5.6	12 5.8	25 25	7 17.2	12.7	25	1.6% 1.7%		-
Ghafari 2009	18.1	5.6	25 33	34.8	4	25 33	2.0%	-11.60 [-17.07, -6.13] -16.70 [-18.41, -14.99]	
Gilron 2004	13.82	12.5	23	23.63	4 16.52	24	1.5%	-9.81 [-18.16, -1.46]	
Hout 2004	13.62	59.3	23 23	23.63	14.8	24 28	0.5%		
Jajeda 2014	30	59.5	23 25	39.2	8.1	28 25	1.9%	5.00 [-19.85, 29.85]	-
Kazak 2009	10.5	12.5	30	17.5	19	30	1.5%	-9.20 [-12.40, -6.00] -7.00 [-15.14, 1.14]	
Khan 2013	8.52	7.43	30	24.28	11.18	35	1.8%	-15.76 [-20.23, -11.29]	-
Kim 2004	23	19	21	24.28	10.3	20	1.6%		
Kin 2004 Koc 2007	23	4	20	3	6	20	1.9%	3.00 [-6.30, 12.30] -1.00 [-4.16, 2.16]	1
Kosucu 2013	13	8	20	32	11	31	1.8%	-19.00 [-23.84, -14.16]	-
Leung 2006	60	20	23	50	20	12	0.8%	10.00 [-7.29, 27.29]	
Lichtinger 2011	49	30	20	69.5	30	20	0.7%	-20.50 [-39.09, -1.91]	
Mahoori 2014	43	7	25	11.2	12.3	25	1.7%	-7.20 [-12.75, -1.65]	
Marashi 2012	33	6	22	35	7	22	1.9%	-2.00 [-5.85, 1.85]	-
Mardani-Kivi 2013	40	7	55	69	10	53	1.9%	-29.00 [-32.27, -25.73]	-
Menda 2010	23	35	30	38	60	30	0.5%	-15.00 [-39.86, 9.86]	
Metry 2008	18.49	14.94	67	23	13	34	1.7%	-4.51 [-10.16, 1.14]	
Mishra 2016	20.1	3.4	30	26	4.1	30	2.0%	-5.90 [-7.81, -3.99]	+
Ménigaux 2004	21	17	20	21	23	20	1.1%	0.00 [-12.53, 12.53]	
Omran 2006	32	38.66	25	54	38.66	25	0.6%	-22.00 [-43.43, -0.57]	
Panday 2004a	25.73	15.07	80	45	14	20	1.6%	-19.27 [-26.24, -12.30]	
Panday 2005	32.5	18.11	40	30	20	20	1.3%	2.50 [-7.91, 12.91]	+
Parikh 2010	37	7	30	46	6	30	1.9%	-9.00 [-12.30, -5.70]	-
Prabhakar 2007	38.5	10	10	54	13.5	10	1.3%	-15.50 [-25.91, -5.09]	
Rajendran 2014	42.7	5.2	30	65	7.3	30	1.9%	-22.30 [-25.51, -19.09]	-
Rapchuk 2010	18	33	27	21	34	27	0.8%	-3.00 [-20.87, 14.87]	
Ray 2015	37	12.56	30	54.66	15.5	30	1.6%	-17.66 [-24.80, -10.52]	-
Said-Ahmed 2007	18	9.16	60	25	12	20	1.7%	-7.00 [-12.75, -1.25]	
Sekhavet 2009	40.1	14.5	49	52.7	21.1	49	1.6%	-12.60 [-19.77, -5.43]	
Sen 2009a	2	5	20	16	28	20	1.1%	-14.00 [-26.47, -1.53]	
Sen 2009b	2	4	30	11	2	29	2.0%	-9.00 [-10.61, -7.39]	*
Turan 2003a	5	7	25	16	12	25	1.7%	-11.00 [-16.45, -5.55]	-
Turan 2003b	7	8	25	11	14	25	1.7%	-4.00 [-10.32, 2.32]	+
Furan 2004	3	10.5	25	14	23.5	25	1.3%	-11.00 [-21.09, -0.91]	
Furan 2005	20	1	20	26	46	20	0.6%	-6.00 [-26.16, 14.16]	
Jcak 2011	12	0.1	20	30	48	20	0.6%	-18.00 [-39.04, 3.04]	
Vahedi 2011	25.8	19.5	36	34	27.2	40	1.3%	-8.20 [-18.77, 2.37]	+
/erma 2008	12	13	25	21	12	25	1.6%	-9.00 [-15.94, -2.06]	
Yoon 2001	17	32	16	11	30	16	0.6%	6.00 [-15.49, 27.49]	_
Zaldivar Ramirez 2011	10	10	18	37	6	16	1.7%	-27.00 [-32.48, -21.52]	-
Özcan 2012	9	25	20	27	9	20	1.2%	-18.00 [-29.64, -6.36]	
Özgencil 2011	11	4.8	30	15	7.7	30	1.9%	-4.00 [-7.25, -0.75]	_ _
Subtotal (95% CI)			1753			1528	82.0%	-8.47 [-10.87, -6.06]	♥
Heterogeneity: Tau ² = 64 Fest for overall effect: Z =			(P < 0.	00001); l ² = 93%					
Total (95% CI)			2274			2028	100.0%	-7.46 [-9.42, -5.51]	
		4 16 07	(D < 0)	00001) 12 - 020/					
Heterogeneity: Tau ² = 49	.33; Chi² = 936.9	4, df = 67	(P < 0.	00001); 1 93%					-100 -50 0 50 100

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

Study or Subgroup		apentin	Total		ntrol SD IVASI	Total	Weight	Mean Difference IV, Random, 95% CI [VAS	Mean Difference IV, Random, 95% CI [VAS]
2.4.1 Low risk of bias			Total			Total	Weight	14, Randolli, 55% Of [4A5	
Brogly 2008	26	22	22	27	17	21	4.6%	-1.00 [-12.72, 10.72]	
Fassoulaki 2005	41	69	25	40.5	68	28	1.6%	0.50 [-36.46, 37.46]	
Grosen 2014	23.13	25.71	52	23.03	20.99	52	5.0%	0.10 [-8.92, 9.12]	+
Vonks 2015	40	6.7	100	47	8.15	97	5.8%	-7.00 [-9.09, -4.91]	•
Moore 2010	10	5.5	21	18	15	23	5.4%	-8.00 [-14.57, -1.43]	
Paul 2015	94.9	29.8	48	94.4	30.8	54	4.6%	0.50 [-11.27, 12.27]	<u> </u>
Short 2012	34.5	10.99	84	30	20	42	5.4%	4.50 [-1.99, 10.99]	
Srivastava 2010	30	2.5	60	46	2.5	60	5.8%	-16.00 [-16.89, -15.11]	•
Subtotal (95% CI)		2.0	412	10	2.0	377	38.0%	-4.52 [-10.64, 1.61]	•
Heterogeneity: Tau ² =	55.92: Chi ² = 1	17.37. df = 1	7 (P < ().00001): l² = 9	4%			• • •	
Test for overall effect:			. (,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	.,,,				
2.4.2 Unclear/High ris	sk of bias								
Al-Mujadi 2005	23	12	35	35	11	37	5.5%	-12.00 [-17.33, -6.67]	-
Clarke 2009b	36	3.97	76	29	4	39	5.8%	7.00 [5.46, 8.54]	
Dierking 2003	37.48	27.03	39	34.12	20.96	32	4.7%	3.36 [-7.81, 14.53]	
Durmus 2007	51	68	25	68	79	25	1.4%	-17.00 [-57.86, 23.86]	
assoulaki 2002	20	31	25	31	54	25	2.7%	-11.00 [-35.41, 13.41]	
Hout 2007	30	74.1	23	15	59.3	28	1.6%	15.00 [-22.41, 52.41]	
Kim 2004	46	26.8	21	34	16	20	4.3%	12.00 [-1.44, 25.44]	<u> </u>
Venda 2010	51	61	30	54	63	30	2.0%	-3.00 [-34.38, 28.38]	
Vetry 2008	23.99	12.46	67	35	11	34	5.6%	-11.01 [-15.76, -6.26]	-
Omran 2006	54	38.66	25	76	38.66	25	3.1%	-22.00 [-43.43, -0.57]	
Prabhakar 2007	54.5	10.1	10	66.5	16.3	10	4.6%	-12.00 [-23.88, -0.12]	
Rapchuk 2010	45	65	27	45	63	27	1.8%	0.00 [-34.14, 34.14]	<u> </u>
Sen 2009a	9	4	20	29	30	20	4.3%	-20.00 [-33.26, -6.74]	
Sen 2009b	2	3	30	15	15	29	5.5%	-13.00 [-18.56, -7.44]	+
Turan 2003a	15.4	7	25	16	7	25	5.6%	-0.60 [-4.48, 3.28]	+
Jcak 2011	37	25	20	51	66	20	2.0%	-14.00 [-44.93, 16.93]	
Yoon 2001	23	41	16	37	58	16	1.7%	-14.00 [-48.80, 20.80]	
Subtotal (95% CI)			514			442	62.0%	-6.22 [-12.54, 0.10]	\blacklozenge
Heterogeneity: Tau ² =	104.22; Chi ² =	152.63, df =	: 16 (P	< 0.00001); ² :	= 90%			-	
Test for overall effect:			`						
Γotal (95% CI)			926			819	100.0%	-5.43 [-10.88, 0.01]	•
Heterogeneity: Tau ² =	132.78: Chi ² =	720.36. df =		< 0.00001): l ² :	= 97%			• • •	
Test for overall effect:			(,	5.00001/11	31 /0				-100 -50 0 50 100 Favours Gabapentin Favours Control

Appendix 16: Forest plot of adverse events nausea

Study or Subgroup	Gabape Events		Contr Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio I M-H, Random, 95% CI
2.5.1 Low risk of bias	_						
Bartholdy 2006	3	38	4	38	0.6%	0.75 [0.18, 3.13]	
Grosen 2014	25	52	37	52	7.3%	0.68 [0.49, 0.94]	-
Misra 2013	4	36	13	37	1.1%	0.32 [0.11, 0.88]	
Moore 2010	12	21	8	23	2.3%	1.64 [0.84, 3.21]	
Paul 2013	33	52	40	49	10.5%	0.78 [0.61, 0.99]	-
Paul 2015	0	0	0	0		Not estimable	
Short 2012	44	84	21	42	6.4%	1.05 [0.73, 1.51]	
Subtotal (95% CI)		283		241	28.1%	0.83 [0.62, 1.11]	
Total events	121		123				
Heterogeneity: Tau ² = 0. Test for overall effect: Z			f = 5 (P =	: 0.06);	l² = 53%		
2.5.2 Unclear/High risk	of bias						
Ajori 2011	8	69	19	69	1.9%	0.42 [0.20, 0.90]	
Bang 2009	6	23	8	23	1.4%	0.75 [0.31, 1.82]	
Bashir 2009	1	50	1	50	0.2%	1.00 [0.06, 15.55]	
Behdad 2012	5	30	5	31	0.9%	1.03 [0.33, 3.21]	
Clarke 2009b	24	76	14	38	3.5%	0.86 [0.50, 1.46]	
Clarke 2014	26	88	26	77	4.6%	0.88 [0.56, 1.37]	-+
Deniz 2012	7	25	12	26	1.9%	0.61 [0.29, 1.29]	+
Dierking 2003	12	39	11	32	2.3%	0.90 [0.46, 1.75]	
Doha 2010	2	30	4	29	0.4%	0.48 [0.10, 2.44]	
Durmus 2007	7	25	9	25	1.6%	0.78 [0.34, 1.76]	
Erten 2010	0	39	0	20		Not estimable	
Fassoulaki 2006	1	27	5	24	0.3%	0.18 [0.02, 1.42]	
Ghafari 2009	5	33	7	33	1.0%	0.71 [0.25, 2.02]	
Gilron 2004	4	20	12	22	1.2%	0.37 [0.14, 0.95]	
Grover 2009	12	15	6	21	2.1%	2.80 [1.36, 5.76]	
Jajeda 2014	0	25	3	25	0.1%	0.14 [0.01, 2.63]	· · · · · · · · · · · · · · · · · · ·
Kavitha 2013	3	28	4	28	0.6%	0.75 [0.18, 3.05]	
Khan 2010	12	150	2	25	0.6%	1.00 [0.24, 4.20]	
Khurana 2013	2	30	0	30	0.1%	5.00 [0.25, 99.95]	
Kim 2004	8	21	8	20	1.8%	0.95 [0.44, 2.05]	<u> </u>
Koc 2007	1	20	1	20	0.2%	1.00 [0.07, 14.90]	
Kosucu 2013	2	29	4	31	0.4%	0.53 [0.11, 2.70]	
Menda 2010	9	30	18	30	2.7%	0.50 [0.27, 0.93]	
Mikkelsen 2006	3	20	3	20	0.5%	1.00 [0.23, 4.37]	
Ménigaux 2004	3	20	3	20	0.5%	1.00 [0.23, 4.37]	
Omran 2006	5	50	7	50	1.0%	0.71 [0.24, 2.10]	
Pakravan 2012	3	50	0	50	0.1%	7.00 [0.37, 132.10]	
Panday 2004a	4	80	1	20	0.1%	1.00 [0.12, 8.46]	
Panday 2004a Panday 2004c		28	4	28	0.8%	1.25 [0.37, 4.17]	
Panday 20040 Panday 2005	6	40	4	20			
		40	4		0.7%	1.00 [0.28, 3.59]	
Pathak 2013	1			40	0.3%	0.25 [0.03, 2.14]	
Radhakrishnan 2005	6	30	6	30	1.1%	1.00 [0.36, 2.75]	
Rajendran 2014	4	30	4	30	0.7%	1.00 [0.28, 3.63]	
Said-Ahmed 2007	16	60	5	20	1.5%	1.07 [0.45, 2.54]	
Sava 2009	7	25	11	25	1.8%	0.64 [0.30, 1.37]	
Sekhavet 2009	32	49	37	49	9.9%	0.86 [0.67, 1.12]	
Sen 2009a	9	20	8	20	2.0%	1.13 [0.55, 2.32]	
Siddiqui 2013	17	36	17	36	4.1%	1.00 [0.61, 1.63]	
Takmaz 2007	9	30	9	15	2.3%	0.50 [0.25, 0.99]	
Tuncer 2005	9	30	4	15	1.1%	1.13 [0.41, 3.06]	
Turan 2003a	5	25	7	25	1.1%	0.71 [0.26, 1.95]	
Turan 2003b	5	25	7	25	1.1%	0.71 [0.26, 1.95]	
Turan 2004	4	25	4	25	0.7%	1.00 [0.28, 3.56]	
Turan 2005	10	20	14	20	3.6%	0.71 [0.42, 1.21]	+
Turan 2006	6	25	2	25	0.5%	3.00 [0.67, 13.46]	+
Ucak 2011	4	20	2	20	0.5%	2.00 [0.41, 9.71]	
Verma 2008	5	25	4	25	0.8%	1.25 [0.38, 4.12]	— —
Yoon 2001	7	16	9	15	2.2%	0.73 [0.36, 1.46]	+-
Zaldivar Ramirez 2011	4	18	15	16	1.4%	0.24 [0.10, 0.57]	
Özgencil 2011	8	30	7	30	1.4%	1.14 [0.47, 2.75]	
Subtotal (95% CI)	-	1789		1443	71.9%	0.82 [0.73, 0.92]	•
Total events	354		376				
Heterogeneity: Tau ² = 0. Test for overall effect: Z	00; Chi² =			= 0.45); I² = 1%		
Total (95% CI)		2072		1684	100.0%	0.82 [0.73, 0.91]	•
Total events	475		499				
Heterogeneity: Tau ² = 0.	01; Chi² =	59.34, d	f = 54 (P	= 0.29); I² = 9%		0.01 0.1 1 10 100
Test for overall effect: Z							0.01 0.1 1 10 100 Favours Gabapentin Favours Controls

Appendix 17: Forest plot of adverse events vomiting

Study or Subgroup	Gabape Events		Conti Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
2.6.1 Low risk of bias	Lvento	Total	Lvento	Total	Weight		
Bartholdy 2006	3	38	3	38	0.9%	1.00 [0.22, 4.65]	
Grosen 2014	23	52	22	52	10.5%	1.05 [0.67, 1.62]	<u> </u>
Moore 2010	5	21	3	25	1.2%	1.98 [0.54, 7.34]	
Short 2012	17	84	10	42	4.3%	0.85 [0.43, 1.69]	
Subtotal (95% CI)	17	195	10	157	4.3 <i>%</i> 16.8%	1.04 [0.73, 1.47]	▲
	40	155	20	157	10.070	1.04 [0.75, 1.47]	Ť
Total events	48	4 07 46	38	0 7 4). 13	2 - 00/		
Heterogeneity: Tau ² = 0. Test for overall effect: Z			- 3 (P -	0.74), P	- 0%		
2.6.2 Unclear/High risk	of bias						
Abdelmageed 2010	2	30	9	30	1.0%	0.22 [0.05, 0.94]	
Ajori 2011	5	69	16	69	2.3%	0.31 [0.12, 0.81]	
Bang 2009	1	23	3	23	0.4%	0.33 [0.04, 2.97]	
Behdad 2012	5	30	7	31	1.9%	0.74 [0.26, 2.07]	
Bharti 2012	6	40	9	40	2.3%	0.67 [0.26, 1.70]	
Clarke 2009b	9	40 76	9 7	38	2.5%	0.64 [0.26, 1.59]	
	9	25	0		2.070		
Deniz 2012 Dierking 2003	18	25 39		26 32	0 10/	Not estimable	<u> </u>
Dierking 2003			15	32	8.1%	0.98 [0.60, 1.62]	
Doha 2010	3	30	5	29	1.1%	0.58 [0.15, 2.21]	
Durmus 2007	3	25	6	25	1.3%	0.50 [0.14, 1.78]	
Ghafari 2009	4	33	9	33	1.8%	0.44 [0.15, 1.30]	
Grover 2009	7	25	7	21	2.7%	0.84 [0.35, 2.01]	
Jajeda 2014	3	25	5	25	1.2%	0.60 [0.16, 2.25]	
Kavitha 2013	0	28	0	28		Not estimable	
Khan 2010	8	150	1	25	0.5%	1.33 [0.17, 10.21]	
Khurana 2013	1	30	2	30	0.4%	0.50 [0.05, 5.22]	
Kim 2004	4	21	2	20	0.8%	1.90 [0.39, 9.28]	
Koc 2007	7	20	14	20	4.6%	0.50 [0.26, 0.97]	
Kosucu 2013	7	29	4	31	1.6%	1.87 [0.61, 5.73]	
Menda 2010	0	30	0	30		Not estimable	
Metry 2008	2	77	1	34	0.4%	0.88 [0.08, 9.41]	
Mikkelsen 2006	6	22	2	27	0.9%	3.68 [0.82, 16.47]	+
Mohammadi 2008	0	35	0	35		Not estimable	
Omran 2006	1	50	7	50	0.5%	0.14 [0.02, 1.12]	
Panday 2004a	7	80	2	20	0.9%	0.88 [0.20, 3.89]	
Panday 2004a Panday 2004c	3	28	4	28	1.0%	0.75 [0.18, 3.05]	
Panday 20040 Panday 2005	2	40	2	20	0.6%	0.50 [0.08, 3.29]	
Pathak 2013	0	40	1	40	0.0%		
Radhakrishnan 2005	2	40 30	3	30		0.33 [0.01, 7.95]	
	19	60	4	30	0.7%	0.67 [0.12, 3.71]	
Raghove 2010					2.1%	2.38 [0.89, 6.36]	
Said-Ahmed 2007	10	60 25	5	20	2.3%	0.67 [0.26, 1.72]	
Sava 2009	5	25	7	25	2.0%	0.71 [0.26, 1.95]	
Sekhavet 2009	18	49	19	49	7.8%	0.95 [0.57, 1.58]	
Sen 2009a	8	20	8	20	3.5%	1.00 [0.47, 2.14]	
Sen 2009b	1	30	1	29	0.3%	0.97 [0.06, 14.74]	
Siddiqui 2013	5	36	6	36	1.7%	0.83 [0.28, 2.49]	
Takmaz 2007	7	30	7	15	2.8%	0.50 [0.21, 1.16]	
Tuncer 2005	3	30	2	15	0.7%	0.75 [0.14, 4.02]	
Turan 2003a	6	25	9	25	2.7%	0.67 [0.28, 1.59]	+-
Turan 2003b	1	25	6	25	0.5%	0.17 [0.02, 1.29]	
Turan 2005	9	20	10	20	4.8%	0.90 [0.47, 1.73]	
Turan 2006	12	25	18	25	9.0%	0.67 [0.41, 1.07]	
Ucak 2011	4	20	2	20	0.8%	2.00 [0.41, 9.71]	
Verma 2008	3	25	4	25	1.0%	0.75 [0.19, 3.01]	
Yoon 2001	4	16	1	15	0.5%	3.75 [0.47, 29.87]	
Zaldivar Ramirez 2011	0	18	7	16	0.3%	0.06 [0.00, 0.97]	<
Özgencil 2011	3	50	5	50	1.1%	0.60 [0.15, 2.38]	
Subtotal (95% CI)	5	1744	5	1350	83.2%	0.76 [0.65, 0.88]	♦
Total events	234		264			1	. [
Heterogeneity: Tau ² = 0.	00; Chi² =		f = 42 (P	= 0.55)	; I² = 0%		
Test for overall effect: Z	= 3.52 (P =	= 0.0004)				
Total (95% CI)	000	1939	000	1507	100.0%	0.80 [0.69, 0.92]	•
Total events Heterogeneity: Tau ² = 0.	282 00: Chi ² =	44 02 4	302 f = 46 (P	= 0.56	· 12 = 00/		
Test for overall effect: Z			- 40 (P	- 0.00	,1 - 0%		0.01 0.1 1 10 100
Lesi for overall effect. Z	- 3.13 (P =	- U.UUZ)					Favours Gabapentin Favours Control

Appendix 18: Forest plot of adverse events sedation

Study or Subgroup	Gabape Events		Conti Events		Weight	Risk Ratio M-H, Random, 95% Cl	Risk Ratio M-H, Random, 95% Cl
2.12.1 Low risk of bias							
Bartholdy 2006	21	38	13	38	4.5%	1.62 [0.96, 2.73]	⊢
Ghai 2011	10	30	12	30	3.7%	0.83 [0.43, 1.63]	
Grosen 2014	10	52	7	52	2.8%	1.43 [0.59, 3.47]	_ _
Kinney 2011	10	57	10	63	3.2%	1.11 [0.50, 2.46]	_ _
Moore 2010	17	21	17	23	5.6%	1.10 [0.80, 1.51]	
Paul 2013	35	52	35	49	5.9%	0.94 [0.73, 1.22]	
Short 2012	47	84	24	42	5.6%	0.98 [0.71, 1.35]	Ť
Spence 2011	20	26	21	31	5.6%	1.14 [0.82, 1.57]	†
Srivastava 2010	14	60	8	60	3.2%	1.75 [0.79, 3.86]	+
Waikakul 2011	1	26	0	24	0.4%	2.78 [0.12, 65.08]	
Subtotal (95% CI)		446		412	40.5%	1.08 [0.94, 1.23]	♦
Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z				P = 0.6	5); $I^2 = 0$ %	%	
2.12.2 Unclear/High ris	k of bias	trials					
Abdelmageed 2010	2	30	1	30	0.6%	2.00 [0.19, 20.90]	—— —
Ajori 2011	0	69	0	69		Not estimable	
Al-Mujadi 2005	0	37	0	35		Not estimable	
Bang 2009	1	23	1	23	0.5%	1.00 [0.07, 15.04]	
Clarke 2009b	18	76	7	38	3.2%		_ _
						1.29 [0.59, 2.81]	
Dirks 2002	21	31	22	34	5.5%	1.05 [0.74, 1.48]	Ť
Erten 2010	0	39	0	20		Not estimable	
Ghafari 2009	2	33	3	33	1.1%	0.67 [0.12, 3.73]	
Ghai 2012	8	30	0	30	0.5%	17.00 [1.03, 281.91]	· · · ·
Jajeda 2014	8	25	3	25	1.9%	2.67 [0.80, 8.90]	+
Kavitha 2013	3	28	9	28	1.9%	0.33 [0.10, 1.10]	— — —
Kazak 2009	0	30	0	30		Not estimable	
Khan 2010	8	125	1	25	0.8%	1.60 [0.21, 12.23]	_
Khurana 2013	4	30	0	30	0.4%	9.00 [0.51, 160.17]	
Kim 2004	5	21	5	20			
					2.2%	0.95 [0.32, 2.80]	
Kosucu 2013	2	29	1	31	0.6%	2.14 [0.20, 22.34]	
Mishra 2016	12	30	4	30	2.4%	3.00 [1.09, 8.25]	· · · · ·
Neogi 2012	1	30	0	30	0.4%	3.00 [0.13, 70.83]	
Omran 2006	2	50	1	50	0.6%	2.00 [0.19, 21.36]	— •
Panday 2004a	0	80	0	20		Not estimable	
Panday 2004b	52	153	5	153	2.8%	10.40 [4.27, 25.32]	
Panday 2005	3	40	1	20	0.7%	1.50 [0.17, 13.52]	.
Panday 2006	4	125	2	125	1.1%	2.00 [0.37, 10.72]	— • ——
Radhakrishnan 2005	1	30	1	30	0.5%	1.00 [0.07, 15.26]	
Raghove 2010	0	60	0	30	5.570	Not estimable	
Ray 2015	0	30	0	30			
,					4 00/	Not estimable	
Rorarius 2004	14	38	12	37	4.0%	1.14 [0.61, 2.12]	
Said-Ahmed 2007	8	60	2	20	1.4%	1.33 [0.31, 5.77]	
Sava 2009	2	25	1	25	0.6%	2.00 [0.19, 20.67]	— <u> </u>
Sekhavet 2009	26	49	22	49	5.1%	1.18 [0.79, 1.78]	+
Sen 2009a	3	20	3	20	1.4%	1.00 [0.23, 4.37]	
Siddiqui 2013	28	36	36	36	6.2%	0.78 [0.65, 0.93]	→
Takmaz 2007	5	30	1	15	0.8%	2.50 [0.32, 19.53]	
Turan 2003a	1	25	0	25	0.4%	3.00 [0.13, 70.30]	
	2						
Turan 2003b		25	1	25	0.6%	2.00 [0.19, 20.67]	
Turan 2005	5	20	2	20	1.3%	2.50 [0.55, 11.41]	
Ucak 2011	2	20	1	20	0.7%	2.00 [0.20, 20.33]	
Vahedi 2011	16	36	0	40	0.5%	36.57 [2.27, 588.35]	· · · · · · · · · · · · · · · · · · ·
Yoon 2001	13	16	13	16	5.5%	1.00 [0.72, 1.39]	+
Zaldivar Ramirez 2011	2	18	0	16	0.4%	4.47 [0.23, 86.77]	
Özgencil 2011	8	30	5	30	2.5%	1.60 [0.59, 4.33]	-
Subtotal (95% CI)	5	1732	2	1413	59.5%	1.61 [1.14, 2.25]	 ◆
Total events	292		166				▼
Heterogeneity: $Tau^2 = 0$. Test for overall effect: Z	43; Chi ²		5, df = 3	33 (P <	0.00001)); $I^2 = 72\%$	
Total (95% CI)		2178		1825	100.0%	1.33 [1.09, 1.61]	
Total events	477		313		20010/0	1.00 [1.00, 1.01]	▼
		107 0		12 (0 -	0.00001	$1^{2} - 60^{9}$	
Heterogeneity: $Tau^2 = 0$.				+3 (P <	0.00001)	1, 1 = 00%	0.01 0.1 1 10 10
Test for overall effect: Z	= 2.80 (P	= 0.00	5)				Favours Gabapentin Favours Control
Test for subgroup differe	ences. Ch	$i^2 = 4.6$	$\frac{1}{4}$ df = 1	$(\mathbf{P} = 0)$	(03) $I^2 =$	78 4%	ravours Gapapentin Favours Control

Appendix 19: Forest plot of adverse events dizziness

Study or Subgroup 2.13.1 Low risk of bia Bartholdy 2006		iotai					
Bartholdy 2006					neight	M-H, Random, 95% CI	M-H, Random, 95% Cl
		20	10	20	2 40/	1 20 [0 50 2 44]	
	12	38	10	38	2.4%	1.20 [0.59, 2.44]	
Fassoulaki 2005	1	29	0	30	0.1%	3.10 [0.13, 73.14]	
Ghai 2011	8	30	1	30	0.3%	8.00 [1.07, 60.09]	
Grosen 2014	41	52	40	52	29.0%	1.02 [0.84, 1.26]	Ť
Kinney 2011	9	57	10	63	1.8%	0.99 [0.44, 2.27]	
Paul 2013	29	52	28	49	10.4%	0.98 [0.69, 1.37]	+
Spence 2011	10	26	9	31	2.3%	1.32 [0.64, 2.76]	- -
Srivastava 2010	5	60	7	60	1.0%	0.71 [0.24, 2.13]	
Waikakul 2011	0	26	1	24	0.1%	0.31 [0.01, 7.23]	
Subtotal (95% CI)	-	370	-	377	47.4%	1.04 [0.88, 1.22]	•
Total events	115		106				Ĭ
Heterogeneity: Tau ² = Test for overall effect:	0.00; Ch		4, $df = 3$	8 (P = 0).59); I ² =	0%	
2.13.2 Unclear/High I	risk of bi	as					
Abdelmageed 2010	6	30	5	30	1.1%	1.20 [0.41, 3.51]	
Ajori 2011	0	69	0	69	1.1/0	Not estimable	
5	0	37	0				
Al-Mujadi 2005				35	3 101	Not estimable	
Azemati 2013	14	50	14	50	3.1%	1.00 [0.53, 1.87]	
Bang 2009	3	23	3	23	0.5%	1.00 [0.22, 4.45]	
Behdad 2012	0	30	0	31		Not estimable	
Bekawi 2014	17	30	25	30	9.9%	0.68 [0.48, 0.97]	
Chowdhury 2010	4	100	5	100	0.7%	0.80 [0.22, 2.89]	
Clarke 2009b	19	76	8	38	2.3%	1.19 [0.57, 2.46]	_ _
Clarke 2013	9	22	0	0	2.370	Not estimable	
Clarke 2013 Clarke 2014		88	12	77	0.6%		
	2				0.6%	0.15 [0.03, 0.63]	-
Deniz 2012	0	25	0	26	C 001	Not estimable	
Dierking 2003	23	39	15	32	6.0%	1.26 [0.80, 1.98]	
Dirks 2002	11	31	14	34	3.1%	0.86 [0.46, 1.60]	
Doha 2010	8	30	2	29	0.6%	3.87 [0.90, 16.70]	
Ghafari 2009	2	33	2	33	0.3%	1.00 [0.15, 6.68]	
Ghai 2012	10	30	1	30	0.3%	10.00 [1.36, 73.33]	
Grover 2009	10	25	7	21	2.0%	1.20 [0.55, 2.60]	
Kavitha 2013	2	28	4	28	0.5%	0.50 [0.10, 2.51]	
Kazak 2009	0	30	0	30	0.5%		
					0.20/	Not estimable	
Khan 2010	5	125	1	25	0.3%	1.00 [0.12, 8.20]	
Kim 2004	8	21	9	20	2.3%	0.85 [0.41, 1.76]	
Leung 2006	0	12	0	9		Not estimable	
Mardani-Kivi 2013	3	55	6	53	0.7%	0.48 [0.13, 1.83]	
Mishra 2016	3	30	6	30	0.7%	0.50 [0.14, 1.82]	
Mohammadi 2009	2	40	0	40	0.1%	5.00 [0.25, 100.97]	
Neogi 2012	1	30	1	30	0.2%	1.00 [0.07, 15.26]	
Omran 2006	6	50	4	50	0.8%	1.50 [0.45, 4.99]	
Panday 2004a	Ő	80	0	20	0.0/0	Not estimable	
Panday 2004a Panday 2004b	0						
		153	0	153	0.10/	Not estimable	
Panday 2004c	1	28	0	28	0.1%	3.00 [0.13, 70.64]	
Pathak 2013	0	40	1	40	0.1%	0.33 [0.01, 7.95]	
Raghove 2010	0	60	0	30		Not estimable	
Rajendran 2014	3	30	3	30	0.5%	1.00 [0.22, 4.56]	
Ray 2015	2	30	2	30	0.3%	1.00 [0.15, 6.64]	
Rorarius 2004	6	38	4	37	0.9%	1.46 [0.45, 4.76]	
Said-Ahmed 2007	12	60	3	20	0.9%	1.33 [0.42, 4.25]	
	5	49		20 49			
Sekhavet 2009			7		1.0%	0.71 [0.24, 2.10]	
Sen 2009a	2	20	2	20	0.4%	1.00 [0.16, 6.42]	
Takmaz 2007	12	30	7	15	2.5%	0.86 [0.43, 1.72]	
Tirault 2010	2	69	0	66	0.1%	4.79 [0.23, 97.85]	
Tuncer 2005	7	30	4	15	1.1%	0.88 [0.30, 2.53]	
Turan 2003a	2	25	1	25	0.2%	2.00 [0.19, 20.67]	
Turan 2003b	6	25	4	25	0.9%	1.50 [0.48, 4.68]	_
Turan 2004	4	25	4	25	0.8%	1.00 [0.28, 3.56]	
Turan 2005	7	20	1	20	0.3%	7.00 [0.95, 51.80]	
Turan 2006	6	25	2	25	0.5%	3.00 [0.67, 13.46]	
Ucak 2011	2	20	1	20	0.2%	2.00 [0.20, 20.33]	
Verma 2008	1	25	0	25	0.1%	3.00 [0.13, 70.30]	
Yoon 2001	10	16	9	15	3.9%	1.04 [0.59, 1.83]	+-
Özgencil 2011	9	30	6	30	1.5%	1.50 [0.61, 3.69]	-+
Subtotal (95% CI)		2117		1766	52.6%	1.00 [0.86, 1.16]	♦
Total events	267		205]
Heterogeneity: $Tau^2 =$ Test for overall effect:	0.00; Ch		48, df =	40 (P =	= 0.54); I ²	$^{2} = 0\%$	
Total (95% CI)		2487		2143	100.0%	1.02 [0.91, 1.13]	
Total events	382		311				
Heterogeneity: Tau ² =				49 (P =	= 0.64); I ²	$^{2} = 0\%$	0.01 0.1 1 10 100
	Z = 0.29						0.01 0.1 1 10 100

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

	Gal	bapenti	n	C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
4.1.1 Trials = 50</td <td>patients</td> <td>in each</td> <td>n group</td> <td>p</td> <td></td> <td></td> <td></td> <td></td> <td></td>	patients	in each	n group	p					
Brogly 2008	0	1.48	22	0	4.4	21	10.3%	0.00 [-1.98, 1.98]	+
Fassoulaki 2005	20.3	7.9	29	25.7	11.2	30	7.8%	-5.40 [-10.33, -0.47]	-
Ghai 2011	5.44	1.56	30	4.28	1.87	30	10.9%	1.16 [0.29, 2.03]	•
Misra 2013	24.6	19.6	37	29.15	25.2	36	3.9%	-4.55 [-14.93, 5.83]	
Moore 2010	3	3	21	4	5	23	10.0%	-1.00 [-3.41, 1.41]	1
Paul 2013	27.94	22.99	52	26.77	18.96	49	5.1%	1.17 [-7.03, 9.37]	+
Paul 2015	19.7	16.39	48	25.1	14.5	54	6.8%	-5.40 [-11.44, 0.64]	-
Short 2012	6.2	4.53	84	7.9	3.8	42	10.6%	-1.70 [-3.20, -0.20]	-
Waikakul 2011	15.5	9.25	24	18	15.5	24	5.8%	-2.50 [-9.72, 4.72]	-
Subtotal (95% CI)			347			309	71.3%	-1.06 [-2.61, 0.49]	(
4.1.2 Trials > 50 pa	tients in	each g	roup						
Grosen 2014	11.2	21.62	52	17.92	23.55	52	4.8%	-6.72 [-15.41, 1.97]	
Lunn 2015	42.8	38.4	186	50.5	41.4	99	4.1%	-7.70 [-17.55, 2.15]	
Monks 2015	10	11.9	100	10	7.4	97	9.8%	0.00 [-2.76, 2.76]	+
Srivastava 2010	25.39	4.48	60	37.58	8.35	60	10.0%	-12.19 [-14.59, -9.79]	-
Subtotal (95% CI)			398			308	28.7%	-6.58 [-14.59, 1.44]	•
Heterogeneity: Tau ²	= 56.38;	Chi ² =	42.76,	df = 3 (P < 0.0	0001);	$ ^2 = 93\%$		
Test for overall effec	t: Z = 1.6	51 (P = 0)	0.11)						
Total (95% CI)			745			617	100.0%	-3.07 [-5.60, -0.54]	•
Heterogeneity: Tau ²	= 15.11;	$Chi^2 =$	118.65	, df = 1	2 (P < 0	0.00001); $I^2 = 90$	%	
T	t: Z = 2.3	87 (P = 0)	0.02)						Favours [Gabapentin] Favours [Control]
Test for overall effec									

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

	Gabape		Contro			Risk Ratio	Risk Ratio
Study or Subgroup						M-H, Random, 95% CI	M-H, Random, 95% Cl
4.2.1 Small trials wi	th = 50</td <td>patien</td> <td>ts in each</td> <td>grou</td> <td>р</td> <td></td> <td></td>	patien	ts in each	grou	р		
Bartholdy 2006	7	38	3	38	20.1%	2.33 [0.65, 8.36]	
Brogly 2008	0	22	0	21		Not estimable	
Paul 2013	0	52	0	49		Not estimable	
Short 2012	0	84	0	42		Not estimable	
Waikakul 2011	0	26	0	24		Not estimable	
Subtotal (95% CI)		222		174	20.1%	2.33 [0.65, 8.36]	
Total events	7		3				
Heterogeneity: Not a	pplicable						
Test for overall effec	t: Z = 1.30	(P = 0.	19)				
4.2.2 Trials with > !	50 patients	s in eac	h group				
Grosen 2014	13	52	8	52	52.1%	1.63 [0.74, 3.59]	+∎
Kinney 2011	4	57	5	63	20.4%	0.88 [0.25, 3.13]	
Lunn 2015	6	183	1	91	7.4%	2.98 [0.36, 24.41]	
Srivastava 2010	0	60	0	60		Not estimable	
Subtotal (95% CI)		352		266	79.9%	1.47 [0.78, 2.79]	◆
Total events	23		14				
Heterogeneity: Tau ²	= 0.00; Ch	$i^2 = 1.1$	2, df = 2 ((P = 0)	57); I ² =	0%	
Test for overall effec	t: Z = 1.18	(P = 0.1)	24)				
rest for overall clice							
		574		440	100.0%	1.61 [0.91, 2.86]	•
Total (95% CI)							
	30		17				
Total (95% CI)				(P = 0)	.68); I ² =	0%	
Total (95% CI) Total events	= 0.00; Ch	i ² = 1.5	2, df = 3 ((P = 0.	.68); I ² =	0%	0.01 0.1 1 10 100 Favours [Gabapentin] Favours [Control]

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 generelated 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

<u>Analyses</u>

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 l², which quantifies inconsistencies. If the l² 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.

Strengths and limitations of the subgroup analyses

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 al¹⁰⁴ 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 | TRIAL CHARACTERISTICS

Reference	Surgical procedure	Ν	Intervention		Postoperative analgesia	Anesthetic	Bias
(Author and year)		Gabapentin	Dose (mg)	Single/		technique	assessmen
		/Control		Continuous		·	
Cholecystectom	y 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 tr	ials						
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	30/3 I	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	High
			-	•		anesthesia	-
Ray 2015	Abdominal hysterectomy	30/30	300 mg	Single	NSAID	Spinal	High
						anesthesia	
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	Continuous	Acetaminophen/Codeine	GA	High
			mg/d)		-		-
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 trialsClarke 2009aTotal knee arthroplasty

Clarke 2009a	Tota

29/7

600 mg(300/600 Single Morphine/NSAID

Spinal

High

Clarke 2009b Total hip arthroplasty 76/39 600 mg Single Morphine/NSAID/Ace Clarke 2014 Total knee arthroplasty 95/84 600 mg Single Morphine/NSAID/Reg Lunn 2015 Total knee arthroplasty 186/99 900/600mg (1300/900mg/d) Continuous Sufentanil /Oxycodone /Acetaminophen/LIA Paul 2013 Total hip arthroplasty 52/49 600 mg (600 mg) Continuous Morphine/NSAID/Ace	gional anesthesia gional anesthesia Spinal High anesthesia and sedation he/NSAID Spinal Low anesthesia and sedation
Lunn 2015 Total knee arthroplasty 186/99 900/600mg Continuous Sufentanil /Oxycodone (1300/900mg/d) /Acetaminophen/LIA Paul 2013 Total hip arthroplasty 52/49 600 mg (600 mg) Continuous Morphine/NSAID/Ace	gional anesthesia Spinal High anesthesia and sedation he/NSAID Spinal Low anesthesia and sedation
(1300/900mg/d) /Acetaminophen/LIA Paul 2013 Total hip arthroplasty 52/49 600 mg (600 mg) Continuous Morphine/NSAID/Ace	anesthesia and sedation
	etaminophen Spinal Low
	anesthesia and sedation
Paul 2015 Total hip arthroplasty 48/54 600 mg/(600 mg) Continuous Morphine/NSAID/Ace	etaminophen Spinal Low anesthesia and sedation
Spinal surgery trials	
Erten 2010 Laminectomy 39/20 900/1200 mg Single Tramadol/Pethidine/N	VSAID GA High
Khan 2010 Laminectomy 150/25 600/900/1200mg Continuous Morphine (600/900/1200 mg) (600/900/1200 mg)<	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 (900 mg/d) Continuous Hydromorphine	GA Unclear
Özgencil 2011 Laminectomy or 30/30 1800 mg (1200 Continuous Morphine discoidectomy mg/d)	GA Unclear
Panday 2004a Discoidectomy 80/20 300/600/900/1200 Single Fentanyl mg	GA High
Panday 2004c Discoidectomy 28/28 300 mg Single Fentanyl	GA Unclear
Radhakrishnan Laminectomy or 30/30 800 mg (800 mg/d) Continuous Morphine 2005 discoidectomy	GA High
Turan 2003b Discoidectomy or spinal 25/25 I 200 mg Single Morphine fusion	GA High
Vahedi 2011 Laminectomy or 36/40 300 mg Single Morphine discoidectomy	GA High
Vasigh 2015Laminectomy38/38600 mg (900 mg/d)ContinuousMorphine	GA High
Thoracic surgery trials	
Grosen 2014 Thoracotomy for 52/52 1200 mg (1200mg/d) Continuous Morphine/NSAID/Ace malignancies Epidural analgesia	
Hout 2007 Exploratory thoracotomy, 23/28 I 200 mg Single Hydromorphine/Epidu	ural analgesia GA High

Kinney 2011	pneumonectomy, lobectomy, segmentectomy, biopsy 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 201	II 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	Cholecystecto		Hysterectomy		Mastectomy		Orthopedic art		Spinal Surgery		Thoracic surgery		
procedure		•			•		surgery	. ,	,				
Outcomes	Reduction (mg) /RR Estimate (95% Cl; p-value; trials)	Test for subgroup difference <i>P-valu</i> e	Reduction (mg) /RR Estimate (95% CI; p-value; trials)	Test for subgroup difference <i>P-valu</i> e	Reduction (mg) /RR Estimate (95% CI; p-value; trials)	Test for subgroup difference P-value	Reduction (mg) /RR Estimate (95% Cl; p-value; trials)	Test for subgroup difference <i>P-valu</i> e	Reduction (mg) /RR Estimate (95% Cl; p-value; trials)	Test for subgroup difference <i>P-valu</i> e	Reduction (mg) /RR Estimate (95% Cl; p-value; trials)	Test for subgroup difference <i>P-valu</i> e	
BENEFICIAL	DUTCOMES												
24-hour morphine consumption Low risk of bias	12.2 mg (95% Cl: 9.8, 14.6; p = -; 1 trial; TSA adj. Cl: -)	-	1.6 mg (95% Cl: -4.8, 8.0; 2 trials; p = 0.62; TSA adj. Cl: -11.2, 17.1; 20.6%)	P = 0.21	-	-	4.0 mg (95% Cl: -0.8, 8.7; p = 0.1; 3 trials; TSA adj. Cl: -4.1, 12.0; 41.0%)	P = 0.75	-	-	6.7 mg (95% Cl: -2.0, 15.4; p = -; 1 trial; TSA adj. Cl: -)	-	
24-hour morphine consumption All trials	7.3 mg (95% Cl: 4.6, 9.9; p < 0.00001; 10 trials; TSA adj. Cl: 4.6, 9.9; 124.9%)	P= 0.9	10.5 mg (95% Cl: 6.7, 14.4; p < 0.00001; 14 trials; TSA adj. Cl: 6.7; 14.4 67.8%)	P=0.16	5.2 mg (95% Cl: 0.9, 9.5; p= 0.02; 6 trials; TSA adj. Cl: -1.6, 12.0; 26.7%)	P=0.15	6.1 mg (95% Cl: 0.2, 12.1; p = 0.04; 6 trials; TSA adj. Cl: -7.1, 19.4; 24.6%)	P=0.47	10.6 mg (95% Cl: 2.1, 19.0; p = 0.01; 8 trials; TSA adj. Cl: -24.1, 45.2; 11.6 %)	P=0.52	6.3 mg (95% Cl: 2.9, 9.8; p = 0.0003; 7 trials; TSA adj. Cl: 2.9, 9.8; 7.39%)	P=0.25	
HARMFUL OU	JTCOMES												
Serious adverse events Low risk of bias	Not estimable	-	-	-	-	-	2.98 (95% Cl: 0.36, 24.41; 2 trials; TSA adj. Cl: -)	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% Cl: 0.36, 24.41; p = 0.31; 2 trials; TSA adj. Cl: - ; 2.1%)	P=0.3	Not estimable	-	1.0 (95% Cl: 0.57, 1.74; p= 0.81; 4 trials; TSA adj.Cl: 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. Cl: Trial Sequential Analysis adjusted Confidence Interval

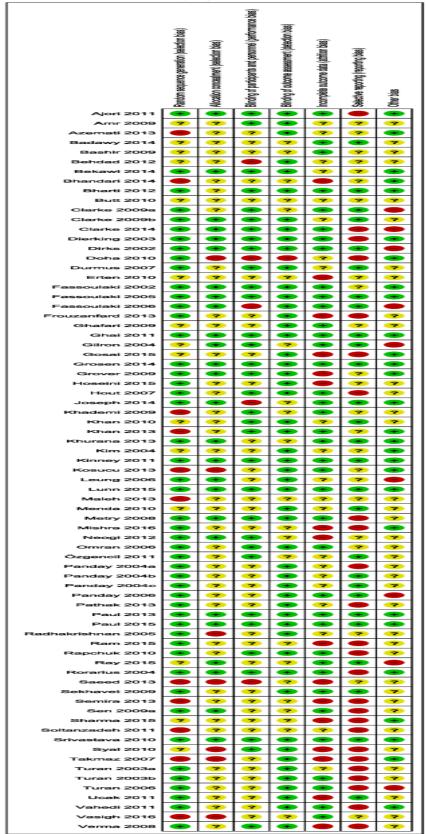
TABLE 3 SECONDARY OUTCOMES FROM TRIALS WITH LOW RISK OF BIAS AND ALL

Surgical procedure	Cholecystector	ny	Hysterectomy		Mastectomy		Orthopedic art surgery	hroplasty	Spinal Surgery		Thoracic surg	gery
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% Cl; p-value; trials)	Test for subgroup difference <i>P-valu</i> e	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 <i>P-valu</i> e	Reduction (mm) / RR Estimate (95% Cl; p-value; trials)	Test for subgroup difference P-value
BENEFICIAL	OUTCOMES											
6-hour VAS at rest Low risk of bias	26.0 mm (95% Cl: 24.8, 27.2; p = -; l trial; TSA adj. Cl: -)	-	3.0 mm (95% Cl: -12.9, 18.9; p = -; 1 trial; TSA adj. Cl: -)	-	-	-	-	-	-	-	5.0 mm (95% Cl: -0.7, 10.7; p = 0.08; 2 trials; TSA adj. Cl: -2.6, 12.6; 112.8%)	P = 0.36
6-hour VAS at rest All trials	13.6 mm (95% Cl: -6.2, 33.4; p = 0.18; 3 trials; TSA adj. Cl: -21.8, 94.3; 8.7%)	P=0.87	16.4 mm (95% Cl: 11.9, 21.0; p < 0.00001; 16 trials; TSA adj. Cl: 11.9, 21.0; 208.5%)	P=0.05	7.8 mm (95% Cl: 1.9, 13.7; p = 0.01; 7 trials; TSA adj. Cl: 1.9, 13.7; 103.3%)	P=0.15	Not estimable	-	10.2 mm (95% Cl: 2.3, 18.0; p = 0.01; 7 trials; TSA adj. Cl: -0.9, 21.2; 58.8%)	P=0.59	4.6 mm (95% Cl: 0.9, 10.2; p = 0.1; 6 trials; TSA adj. Cl: -1.5, 10.8; 118.5%)	P=0.02
6-hour VAS at mobilization Low risk of bias	11.5 mm (95% Cl: 10.3, 12.7; p = -; 1 trial; TSA adj. Cl: -)	-	13.0 mm (95% Cl: -26.0, 52.0; p = -; 1 trial; TSA adj. Cl: -)	-		-	-	-	-	-	8.9 mm (95% Cl: 1.6, 16.1; p = -; 1 trial; TSA adj. Cl: -)	-
6-hour VAS at mobilization All trials	II.5 mm (95%Cl: 10.3, 12.7; p = -; 1 trial; TSA adj. Cl: -)	P=0.04	8.5 mm (95%Cl: 2.8, 14.2; p = 0.004; 6 trials; TSA adj.Cl: 2.8, 14.2; 112.1%)	P=0.97	5.2 mm (95%Cl: -1.6, 12.0; p = 0.14; 6 trials; TSA adj. Cl: -9.5, 20.1; 22.4%)	P=0.07	Not estimable	-	10.0 mm (95%Cl: 1.1, 19.0; p = 0.03; 1 trial; TSA adj. Cl: -)	P=0.73	10.9 mm (95%Cl: 4.4, 17.4; p = 0.001; 4 trials; TSA adj. Cl: 4.4, 17.4; 85.5%)	P=0.41
24-hour VAS at rest Low risk of bias	7.0 mm (95% Cl: 5.8, 8.2; I trial; TSA adj. Cl: -)	-	9.0 mm (95% Cl: -2.8, 20.8; I trial; TSA adj. Cl: -)	-	-	-	0.9 mm (95% Cl: -6.3, 8.1; 1 trial; TSA adj. Cl: -)	-	-	-	4.2 mm (95% Cl: -0.2, 8.5; 2 trials; TSA adj. Cl: -)	P = 0.06

24-hour VAS at rest All trials	3.2 mm (95% Cl: -1.9, 8.4; p = 0.22; 3 trials; TSA adj. Cl: -3.2, 9.7; 138.3%)	P=0.1	10.5 mm (95% Cl: 6.9, 14.2; p < 0.00001; 15 trials; TSA adj. Cl: 6.9, 14.2; 266.9%)	P=0.02	2.6 mm (95% Cl: -3.2, 8.5; p = 0.2; 3 trials; TSA adj. Cl: -2.9, 8.2; 225.9%)	P=0.02	1.0 mm (95% Cl: -1.7, 3.7; p = 0.45; 3 trials; TSA adj. Cl: -2.3, 4.4; 496.1%)	P=0.001	6.2 mm (95% Cl: 0.9, 11.6; p = 0.02; 6 trials; TSA adj. Cl: 0.0, 12.4; 77.9%)	P=0.61	9.7 mm (95% Cl: 2.4, 17.1; p = 0.01; 8 trials; TSA adj. Cl: 2.4, 17.1; 66.9%)	P=0.51
24-hour VAS at mobilization Low risk of bias	16.0 mm (95% Cl: 15.1, 16.9; 1 trial; TSA adj. Cl: -)	-	0.5 mm (95% Cl: -36.5, 37.5; 1 trial; TSA adj. Cl: -)	-	-	-	0.5 mm (95% Cl: -11.4, 12.3; 1 trial; TSA adj. Cl: -)	-	-	-	0.1 mm (95% Cl: -8.9, 9.1; 1 trial; TSA adj. Cl: -)	-
24-hour VAS at mobilization All trials	16.0 mm (95% Cl: 15.1, 16.9; _P < 0.0001; 1 trial; TSA adj. Cl: -)	P <0.00001	4.5 mm (95% Cl: -4.5, 13.5; p = 0.34; 5 trials; TSA adj. Cl: -1.0, 19.1; 45.0%)	P=0.91	3.1 mm (95% Cl: -13.6, 19.8; p = 0.72; 3 trials; -65.1, 71.3; 13.1%)	P=0.87	- 6.5 mm (95% Cl: 3.0, 9.9; p = 0.0002; 2 trials; TSA adj.Cl: 2.5, 10.5; 150.7%)	P=0.0008	Not estimable	-	3.0 mm (95% Cl: -4.5, 10.4; p = 0.43; 6 trials; TSA adj. Cl: - 6.7,12.6; 66.1%)	P=0.86
HARMFUL O	UTCOMES											
Nausea Low risk of bias	-	-	-	-	-	-	0.8 (95% CI: 0.6,1.0; 2 trials)	P = 0.5	-	-	0.7 (95% Cl: 0.5, 0.9; 1 trial)	-
Nausea All trials	0.5 (95% CI: 0.25, 0.99; p = 0.05; I 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% Cl: 0.85, 2.23; p = 0.19; 3 trials; TSA adj. Cl: -; 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% Cl: 0.5, 0.88; p = 0.005; 5 trials; TSA adj. Cl: 0.4, 1.0; 49.9%)	P=0.1
	(95% CI: 0.25, 0.99; _P = 0.05; I trial; TSA adj.	P=0.16 -	(95% Cl: 0.63, 0.95; p = 0.01; 11 trials; TSA adj. Cl: 0.6, 1.1;	P=0.73 -	(95% CI: 0.85, 2.23; p = 0.19; 3 trials; TSA adj.	P=0.33	0.83 (95% CI: 0.66, 1.03; p = 0.08; 4 trials; TSA adj.	P=0.91	(95% CI: 0.68, I.68; p = 0.78; 8 trials; TSA adj. CI: 0.4, 3.2;	P=0.29 -	0.66 (95% Cl: 0.5, 0.88; p = 0.005; 5 trials; TSA adj. Cl: 0.4, 1.0;	P=0.1

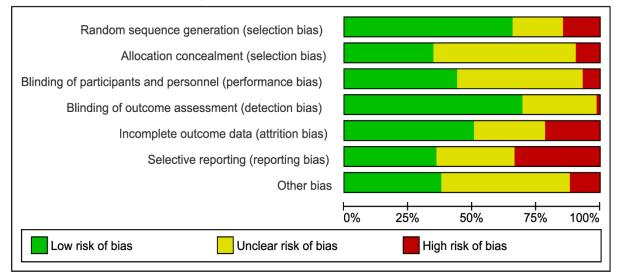
Sedation Low risk of bias	I.8 (95% Cl: 0.8, 3.9; I trial; TSA adj. Cl)	-	0.8 (95% CI: 0.4, I.6; I trial; TSA adj. CI)	-	-	-	0.9 (95% CI: 0.7, 1.2; 1 trial; TSA adj. CI)	-	-	-	1.2 (95% CI: 0.7, 2.3; 2 trials; TSA adj. CI)	P = 0.55
Sedation All trials	3.28 (95% Cl: 1.55, 6.94; p = 0.002; 5 trials; TSA adj. Cl: -; 3.9%)	P=0.009	1.08 (95% Cl: 0.81, 1.45; p = 0.61; 7 trials; TSA adj. Cl: 0.5, 2.2; 23.2%)	P=0.06	I.04 (95% Cl: 0.75, I.44; p = 0.83; 2 trials; TSA adj. Cl: - ; 4.8%)	P=0.06	0.97 (95% Cl: 0.76, 1.24; p = 0.82; 2 trials; TSA adj. Cl: 0.7, 1.6; 44.3%)	P=0.01	2.65 (95% Cl: 0.94, 7.52; p = 0.07; 7 trials; TSA adj. Cl: - ; 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	I.0 (95% Cl: 0.7, I.4; I trial; TSA adj. Cl)	-	6.2 (95% Cl: 1.1, 34.0; 1 trial; TSA adj. Cl)	-	-	-	0.7 (95% CI: 0.2, 2.1; 1 trial; TSA adj. CI)	-	-	-	I.0 (95% CI: 0.8, I.3; 2 trials; TSA adj. CI)	P = 0.64
Dizziness All trials	0.7 (95% Cl: 0.52, 0.94; p = 0.02; 6 trials; TSA adj. Cl: 0.2, 2.6; 27.1%)	P=0.01	I.34 (95% Cl: 0.95, I.89; p = 0.1; I I trials; TSA adj. Cl: 0.3, 5.6; I6.8%)	P=0.2	1.03 (95% Cl: 0.74, 1.43; p = 0.88; 5 trials; TSA adj. Cl: 0.6, 2.1; 31.4%)	P=0.84	0.72 (95% Cl: 0.32, 1.66; p = 0.45; 3 trials; TSA adj. Cl: 0.0, 18.1; 5.6%)	P=0.44	1.03 (95% Cl: 0.74, 1.43; p = 0.88; 5 trials; TSA adj. Cl: 0.6, 2.1; 31.4%)	P=0.22	1.04 (95% Cl: 0.85, 1.26; p = 0.7; 4 trials; TSA adj. Cl: 0.7, 1.5; 36.4%)	P=0.66

FIGURE I 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

Study or Subgroup Me	Experie an (mol of		Total		stroi SD Imai	Total	Wainht	Mean Difference IV, Random, 95% Ci (mg)	Mean Difference IV, Random, 95% Ci [mg]
.1.1 Cholecystectomy	en fundi e	20 (0930)	12602	wess troll	an findi	10121	280GUL	in, managin, as a si jingg	iv, remain, so is or [mg]
Bekawi 2014	0	2.2	30	7.5	0.7	32	2.6%	-7.50 [-8.32, -6.68]	~
loseini 2015	65.11	11.81	22	78.41	13.3	22	1.7%		
			44			43		-13.30 [-20.73, -5.87]	
(hademi 2009	2.83	1.29		3.51	1.51		2.6%	-0.68 [-1.27, -0.09]	1
Jaleh 2013	2.5	2.6	40	2.7	2.7	40	2.5%	-0.20 [-1.36, 0.96]	
/ishra 2016	8.1	1	30	11.9	1.4	30	2.6%	-3.80 [-4.42, -3.18]	
Panday 2004b	40.42	31.26	153	53.03	27.48	153	1.8%	-12.61 [-19.21, -6.01]	
Panday 2006	39.19	26.31	125	67.66	25.27	125	1.9%	-28.47 [-34.87, -22.07]	
Srivastava 2010	25.39	4.48	60	37.58	8.35	60	2.4%	-12.19 [-14.59, -9.79]	~
Syal 2010	40.2	35.2	30	46,7	35.8	30	0.6%	-6.50 [-24.47, 11.47]	
akmaz 2007	5.47	3.43	30	6.25	3.44	15	2.5%	-0.78 [-2.91, 1.35]	.1
Subtotal (95% CI)			564			550	21.1%	-7.25 [-9.94, -4.55]	•
leterogeneity: Tau ² = 14.30 est for overall effect: Z = 5			= 9 (P <	< 0.00001); l ² :	= 97%				
.1.2 Hysterectomy									
Badawy 2014	11.5	2.3	19	13	2.9	19	2.5%	-1.50 [-3.16, 0.16]	1
Dierking 2003	43	23.7	39	63	25.9	32	1.1%	-20.00 [-31.66, -8.34]	
Jurmus 2007	40	10	25	66	10	25	2.0%	-26.00 [-31.54, -20.46]	I
assoulakl 2005	20.3	7.9	25	25.7	11.2	28	2.1%	-5.40 [-10.58, -0.22]	
assoulaki 2006	22	2.9	27	35	4.8	24	2.5%	-13.00 [-15.21, -10.79]	~
rouzanfard 2013	1.2	0.29	25	5.2	2.8	25	2.5%	-4.00 [-5.10, -2.90]	~
Shafari 2009	15.78	1.15	33	26.94	2.28	33	2.6%	-11.16 [-12.03, -10.29]	e
Shai 2011	5.44	1.56	30	4.28	1.87	30	2.6%	1.16 [0.29, 2.03]	ŕ
Silron 2004	56.78	32.41	23	82.11	48.2	24	0.4%	-25.33 [-48.72, -1.94]	
oseph 2014	38.65	18.04	25	44,29	16.02	25	1.4%	-5.64 [-15.10, 3.82]	
(han 2013	13.21	4.71	34	24.31	9.28	35	2.3%	-11.10 [-14.56, -7.64]	
Sekhavet 2009	40.1	14.5	49	52.7	21.1	49	1.7%	-12.60 [-19.77, -5.43]	
en 2009a	31	12	20	48	17	20	1.4%	-17.00 [-26.12, -7.88]	<u> </u>
uran 2003a	27.04	14.44	25	41.96	8.36	25	1.8%	-14.92 [-21.46, -8.38]	
lubtots! (95% CI)			399			384	28.9%	-10.53 [-14.38, -6.69]	◆
leterogeneity: Tau ² = 43.11 est for overall effect: Z = 5			= 13 (P	< 0.00001); l ^a	^t = 98%			*	
.1.3 Mastectomy									
Amr 2009	13.5	0.5	50	22	2.1	50	2.6%	-8.50 [-9.10, -7.90]	*
Sharti 2012	2.1	2.2	20	4.9	3.4	20	2.5%	-2.80 [-4.57, -1.03]	4
Joha 2010	39.9	33	30	42,7	36.1	29	0.6%	-2.80 [-20.47, 14.87]	
assoulaki 2002	23.8	5	25	23.2	5.8	25	2.4%	0.60 [-2.40, 3.60]	÷
(im 2004	35.8	20.8	21	33.5	26,1	20	0.9%	2.30 [-12.19, 16.79]	
Aetry 2008	16.1	7.7	67	29.2	9.6	34	2.3%	-13.10 [-16.82, -9.38]	
Subiotal (95% CI)			213			178	11.2%	-5.19 [-9.52, -0.86]	•
leterogeneity: Tau ² = 20.39 est for overall effect: Z = 2			5 (P <	0.00001); l ² =	93%				
.1.4 Orthopeadic surgery	,								
.1.4 Orthopeadic surgery Clarke 2009a	33.2	20.73	29	63.8	36.5	7	0.3%	-30.60 [-58.67, -2.53]	
		20.73 4	29 76	63.8 35	36.5 4	7 39	0.3% 2.5%	-30.60 [-58.67, -2.53] -1.90 [-3.44, -0.36]	
Clarke 2009a	33.2								
Clarke 2009a Clarke 2009b	33.2 33.1	4	76	35	4	39	2.5%	-1.90 [-3.44, -0.36]	
Clarke 2009a Clarke 2009b Clarke 2014 Junn 2015	33.2 33.1 37	4 1.5	76 95	35 48	4 1.33	39 84	2.5% 2.6%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15]	
Clarke 2009a Clarke 2009b Clarke 2014	33.2 33.1 37 42.8 27.94	4 1.5 38.4 22.99	76 95 186	35 48 50.5	4 1.33 41.4 18.96	39 84 99	2.5% 2.6% 1.3%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59]	· · · · · · · · · · · · · · · · · · ·
Clarke 2009a Clarke 2009b Clarke 2014 Junn 2015 Paul 2013	33.2 33.1 37 42.8	4 1.5 38.4	76 95 186 52	35 48 50.5 26.77	4 1.33 41.4	39 84 99 49	2.5% 2.6% 1.3% 1.6%	-1.90 [-3.44, -0.38] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37]	· · · · · · · · · · · · · · · · · · ·
Clarke 2009a Clarke 2009b Clarke 2014 Junn 2015 Paul 2013 Paul 2015	33.2 33.1 37 42.8 27.94 19.7 0; Chl ^z = 13	4 1.5 38.4 22.99 16.39 36.90, df	76 95 186 52 48 486	35 48 50.5 26.77 25.1	4 1.33 41.4 18.96 14.5	39 84 99 49 54	2.5% 2.6% 1.3% 1.6% 1.9%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Jarke 2014 Paul 2015 Paul 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 38.90 Fest for overall effect: Z = 2	33.2 33.1 37 42.8 27.94 19.7 0; Chl ^z = 13	4 1.5 38.4 22.99 16.39 36.90, df	76 95 186 52 48 486	35 48 50.5 26.77 25.1	4 1.33 41.4 18.96 14.5	39 84 99 49 54	2.5% 2.6% 1.3% 1.6% 1.9%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64]	· · · · · · · · · · · · · · · · · · ·
Clarke 2009a Clarke 2009b Clarke 2014 Janke 2014 Paul 2015 Paul 2015 Paul 2015 Subhotai (95% CI) Heterogeneity: Tau ² = 38.90 rest for overall effect: Z = 2 (1.5 Spinal Surgery	33.2 33.1 37 42.8 27.94 19.7 0; Chl ^z = 1: 2.02 (P = 0.	4 1.5 38.4 22.99 16.39 36.90, df .04)	76 95 186 52 48 48 *85 = 5 (P •	35 48 50.5 26.77 25.1 < 0.00001); I ^a	4 1.33 41.4 18.96 14.5 = 96%	39 84 99 49 54 332	2.5% 2.6% 1.3% 1.6% 1.9% 10.2%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.08, -0.18]	· · · · · · · · · · · · · · · · · · ·
Xarke 2009a Xarke 2009b Xarke 2014 Junn 2015 Yaul 2013 Yaul 2015 Heterogenetity: Tau ² = 38.90 Test for overall effect: Z = 2 .1.5 Spinal Surgery inten 2010	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 1; 2.02 (P = 0. 3.31	4 1.5 38.4 22.99 16.39 36.90, df .04)	76 95 186 52 48 48 *85 = 5 (P •	35 48 50.5 26.77 25.1 < 0.00001); ² 3.56	4 1.33 41.4 18.96 14.5 = 96% 0.64	39 84 99 54 332 20	2.5% 2.6% 1.3% 1.6% 1.9% 10.2%	-1.90 [-3.44, -0.38] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.95, -0.18]	
Xarke 2009a Xarke 2009b Xarke 2014 um 2015 Vall 2013 Vall 2013 Vall 2013 Vall 2015 Vall 2015 Vall 2015 Vall 2015 Vall 2015 Vall 2016 Vall 2016 Vall 2010 Vall 2017 Vall 201	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 13 2.02 (P = 0. 3.31 20.8	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72	76 95 186 52 48 48 48 5 (P 39 150	35 48 50.5 26.77 25.1 <0.00001); I ^a 3.56 31.5	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6	39 84 99 54 332 20 25	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3%	-1.90 [-3.44, -0.38] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.98, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83]	
Xarke 2009a Xarke 2009b Xarke 2014 unn 2015 Paul 2015 Paul 2015 Eval 2015 Eval 2015 Eval 2015 Eval 2016 Eval 2010 Chan 2010 Anday 2004a	33.2 33.1 37 42.8 27.94 19.7 0; Chl ^z = 1: 0.02 (P = 0. 3.31 20.8 39.18	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31	78 95 186 52 48 48 485 = 5 (P - 39 150 80	35 48 50.5 26.77 25.1 <0.00001); I ² 3.56 31.5 52.65	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27	39 84 99 54 332 20 25 20	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 1.3%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.08, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94]	
Clarke 2009a Clarke 2009b Clarke 2014 Jarke 2014 Jarke 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2016 Paul 2010 Panday 2004a Panday 2004a	33.2 33.1 37 42.8 27.94 19.7 0; ChI ^z = 1: 0.02 (P = 0. 3.31 20.8 39.18 90.85	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1	76 95 186 52 48 486 ≈ 5 (P ≺ 39 150 80 28	35 48 50.5 26.77 25.1 <0.00001); I ⁹ 3.56 31.5 52.65 92.49	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27 41.77	39 84 99 54 332 20 25 20 28	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 1.3% 0.5%	-1.90 [-3.44, -0.38] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.08, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.81, 18.33]	· · · · · · · · · · · · · · · · · · ·
Xarke 2009e Jarke 2009b Jarke 2009b Jarke 2014 unn 2015 Paul 2015 Subtotal (85% CF) Heterogeneity: Tau ² = 38.9f Test for overall effect: Z = 2 .1.5 Spinal Surgery riten 2010 chan 2010 chan 2010 anday 2004c 'anday 2004c	33.2 33.1 37 42.8 27.94 19.7 0; Chl ^z = 1: .02 (P = 0. 3.31 20.8 39.18 90.85 16.3	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9	76 95 186 52 48 48 52 52 48 52 48 52 48 52 52 5 7 7 7 7 7 7 7 7 7 7 7 7 7 7 80 80 28 25	35 48 50.5 26.77 25.1 * 0.00001); I ² * 0.00001]; I ² * 0.00000]; I ² * 0.000000]; I ² * 0.000000]; I ² * 0.000000]; I ²	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9	39 84 99 54 332 20 25 20 28 25	2.5% 2.6% 1.3% 1.6% 1.9% ₩.2% 2.6% 2.3% 1.3% 0.5% 2.0%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.95, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.81, 18.33] -26.50 [-32.02, -20.98]	
Xarke 2009a Xarke 2009b Xarke 2009b Xarke 2014 unn 2015 Paul 2015 Vaul 2015 Vaul 2015 Vaul 2015 Vaul 2015 Vaul 2015 Vaul 2018 Vaul 2010 Vanday 2004a Vanday 2004c Vanan 2003b Vahedi 2011	33.2 33.1 37 42.8 27.94 19.7 0; Chl ^z = 1: 2.02 (P = 0. 3.31 20.8 90.85 16.3 18.61	4 1.5 38.4 22.99 16.39 36.90, df : .04) 0.98 5.72 22.31 34.1 34.1 8.9 9.03	76 95 186 52 48 485 = 5 (P - 39 150 80 28 25 36	35 48 50.5 26.77 25.1 <0.000001); P 3.56 31.5 52.65 92.49 42.8 21.53	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.66 21.27 41.77 10.9 11.3	39 84 99 54 332 20 25 20 28	2.5% 2.6% 1.3% 1.6% 10.2% 2.6% 2.3% 1.3% 0.5% 2.0% 2.1%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.98, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.81, 18.33] -26.50 [-32.02, -20.98] -2.82 [-7.50, 1.66]	
Xarke 2009a Xarke 2009b Xarke 2014 Jarke 2014 Jarke 2015 Paul 2015 Paul 2015 Vaul 2015 Spinal Surgery Heterogeneity: Tau ² = 38,90 est for overall effect: Z = 2 .1.5 Spinal Surgery riten 2010 Khan 2010 Yanday 2004a Panday 200	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 1; .02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9	76 95 186 52 48 485 = 5 (P - 39 150 80 28 25 36 38	35 48 50.5 26.77 25.1 <0.00001); I ⁹ 3.56 31.5 52.65 92.49 42.8 21.53 30.1	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6	39 84 99 54 332 20 25 20 28 25 40 38	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.8% 2.3% 1.3% 2.5%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.04] -1.64 [-21.81, 18.33] -26.50 [-32.02, -20.98] -2.82 [-7.50, 1.66] -18.20 [-19.61, -16.79]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Jarke 2014 Jarke 2014 Jarke 2014 Jarke 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2016 Paul 2016 Paul 2016 Paul 2016 Paul 2016 Paul 2011 Paul 2016 Paul 2011	33.2 33.1 37 42.8 27.94 19.7 0; Chl ^z = 1: 2.02 (P = 0. 3.31 20.8 90.85 16.3 18.61	4 1.5 38.4 22.99 16.39 36.90, df : .04) 0.98 5.72 22.31 34.1 34.1 8.9 9.03	76 95 186 52 48 48 52 52 48 52 48 52 48 52 53 50 150 80 28 25 36 38 30	35 48 50.5 26.77 25.1 <0.000001); P 3.56 31.5 52.65 92.49 42.8 21.53	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.66 21.27 41.77 10.9 11.3	39 84 99 54 332 20 25 20 28 25 20 28 25 40 38 30	2.5% 2.6% 1.3% 1.9% 10.2% 10.2% 2.6% 2.3% 1.3% 0.5% 2.0% 2.1%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.95, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.61, 18.33] -26.50 [-32.02, -20.98] -2.92 [-7.50, 1.6.79] -7.86 [-12.70, -3.02]	
Xarke 2009a Xarke 2009b Xarke 2014 um 2015 Vaul 2013 Vaul 2013 Vaul 2013 Vaul 2013 Vaul 2015 Vaul 2013 Vaul 2015 Vaul 2016 Vaul 2016 Vaul 2011 Vaul 2016 Vaul 2011 Vaul 2016 Vaul 2011	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 1; .02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4	76 95 186 52 48 485 = 5 (P - 39 150 80 28 25 36 38	35 48 50.5 26.77 25.1 <0.00001); I ⁹ 3.56 31.5 52.65 92.49 42.8 21.53 30.1	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6	39 84 99 54 332 20 25 20 28 25 40 38	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.8% 2.3% 1.3% 2.5%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.04] -1.64 [-21.81, 18.33] -26.50 [-32.02, -20.98] -2.82 [-7.50, 1.66] -18.20 [-19.61, -16.79]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Janke 2014 Janke 2015 Paul 2015 Paul 2015 Substats (85% CI) Heterogeneity: Tau ² = 38,90 rest for overall effect: Z = 2 .1.5 Spinal Surgery riten 2010 Chan 2010 Panday 2004a Panday 2004a	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 1; .02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = 1	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df	76 95 186 52 48 48 52 52 48 52 48 52 52 53 50 50 80 28 25 36 38 30 428	35 48 50.5 26.77 25.1 <0.00001); P 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5	39 84 99 54 332 20 25 20 28 25 20 28 25 40 38 30	2.5% 2.6% 1.3% 1.9% 10.2% 10.2% 2.6% 2.3% 1.3% 0.5% 2.0% 2.1%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.95, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.61, 18.33] -26.50 [-32.02, -20.98] -2.92 [-7.50, 1.6.79] -7.86 [-12.70, -3.02]	
Xarke 2009a Xarke 2009b Xarke 2014 Jarke 2015 Vaul 2010 Vanday 2004a Vanday 2004a Vanday 2004a Vanday 2004a Vanday 2004a Vanday 2004b Vanday 2004b Va	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 1; .02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = 1 .43 (P = 0.	4 1.5 38.4 22.99 16.39 36.90, df 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df 0.01	76 95 186 52 48 48 48 5 7 7 9 150 80 28 25 36 38 30 428 5 7 (P	35 48 50.5 26.77 25.1 <0.00001); P 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 <0.00001); P	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99%	39 84 99 49 54 332 20 25 20 28 25 20 28 25 30 38 30 228	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 2.6% 2.3% 2.1% 2.5% 2.1% 15.4%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.98, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.81, 18.33] -26.50 [-32.02, -20.98] -2.82 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -49.55 [-18.04, -2.95]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Jarke 2014 Jarke 2014 Jarke 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 38.9f Test for overall effect: Z = 2 .1.5 Spinal Surgery Tene 2010 Chan	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 11 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = (43 (P = 0.) 11.2	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df .01) 21.62	76 95 186 52 48 48 48 48 5 5 5 7 7 80 28 25 36 80 28 25 36 38 30 42% 5 7 7 7 7 7 7 7 7 7 80 28 25 5 25 52	35 48 50.5 26.77 25.1 <0.00001); ² 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); ²	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 = 99% 23.55	39 84 99 49 53 332 20 25 20 28 25 20 28 25 20 28 25 20 28 30 225 52	2.5% 2.6% 1.3% 1.9% 1.9% 10.2% 2.6% 2.3% 1.3% 0.5% 2.0% 2.1% 15.4%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.61, 16.33] -28.50 [-32.02, -20.98] -2.92 [-7.50, 1.66] -18.20 [-9.61, -16.79] -7.86 [-12.70, -3.02] -19.55 [-19.04, -2.95]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Jarke 2014 Jarke 2014 Jarke 2015 Subtotal (95% CI) Heterogeneity: Tau ² = 38.9f Test for overall effect: Z = 2 .1.5 Spinal Surgery Tene 2010 Chan	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 1; .02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = 1 .43 (P = 0.	4 1.5 38.4 22.99 16.39 36.90, df 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df 0.01	76 95 186 52 48 48 48 5 7 7 9 150 80 28 25 36 38 30 428 5 7 (P	35 48 50.5 26.77 25.1 <0.00001); P 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 <0.00001); P	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99%	39 84 99 49 54 332 20 25 20 28 25 20 28 25 30 38 30 228	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 2.6% 2.3% 2.1% 2.5% 2.1% 15.4%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.98, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.81, 18.33] -26.50 [-32.02, -20.98] -2.82 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -49.55 [-18.04, -2.95]	
Xarke 2009a Xarke 2009b Xarke 2009b Xarke 2014 umn 2015 Vaul 2013 Vaul 2013 Vaul 2013 Vaul 2015 Vaul 2015 Vaul 2015 Vaul 2016 Vaul 2010 Vaul 2011 Vaul 2011 Vaul 2016 Vaul 2016 Vaul 2011 Vaul 2016 Vaul 2011 Vaul 2011 Vaul 2011 Vaul 2011 Vaul 2014 Vaul 2017 Vaul	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 11 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = (43 (P = 0.) 11.2	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df .01) 21.62	76 95 186 52 48 48 48 48 5 5 5 7 7 80 28 25 36 80 28 25 36 38 30 42% 5 7 7 7 7 7 7 7 7 7 80 28 25 5 25 52	35 48 50.5 26.77 25.1 <0.00001); ² 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); ²	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 = 99% 23.55	39 84 99 49 53 332 20 25 20 28 25 20 28 25 20 28 25 20 28 30 225 52	2.5% 2.6% 1.3% 1.9% 1.9% 10.2% 2.6% 2.3% 1.3% 0.5% 2.0% 2.1% 15.4%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.61, 16.33] -28.50 [-32.02, -20.98] -2.92 [-7.50, 1.66] -18.20 [-9.61, -16.79] -7.86 [-12.70, -3.02] -19.55 [-19.04, -2.95]	
Xarke 2009a Xarke 2009b Xarke 2009b Xarke 2014 unn 2015 Paul 2015 Vaul 2015 Vaul 2015 Vaul 2015 Vaul 2015 Vaul 2015 Vaul 2015 Vaul 2016 Vanday 2004a Vanday 2004a Vanday 2004a Vanday 2004a Vana 2003b Vahedi 2011 Vaubtaki (85% GI) Heterogeneity: Tau ² = 135.] Vast for overall effect: Z = 2 V.8. Thoracic surgery Srosen 2014 Vort 2007 Kosucu 2013	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 1: 2.02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = 0. 11.2 2.36	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 34.1 34.1 34.9 9.03 4.4 9.64 679.10, df .01) 21.62 2.5	76 95 186 52 48 48 488 = 5 (P < 39 150 28 25 36 38 30 25 36 38 30 428 57 (P	35 48 50.5 26.77 25.1 <0.00001); P 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); P	4 1.33 41.4 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.56 3.2	39 84 99 49 54 332 20 25 20 28 30 32 25 40 38 30 225 40 38 30 226 52 28	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.3% 1.3% 0.5% 2.1% 2.5% 15.4%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.14 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.64 [-21.61, 18.33] -26.50 [-28.20, -2.0.88] -2.92 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-19.70, -3.02] -7.85 [-19.04, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Lunn 2015 Paul 2015 Paul 2015 Paul 2015 Subhotal (BS% CI) Heterogeneity: Tau ² = 38.9(rest for overall effect: Z = 2 1.5 Spinal Surgery riten 2010 Chan 2010 Panday 2004a Panday 2004a Panday 2004a Panday 2004b Panday 2004b Pa	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 11 0.02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = 1 (.43 (P = 0. 11.2 2.36 25.9	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df .01) 21.62 2.5 8.3	76 95 186 52 48 48 486 = 5 (P < 39 150 28 30 25 36 38 30 25 36 38 30 25 25 25 26 27 (P 52 23 29	35 48 50.5 26.77 25.1 <0.00001); P 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); P	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.55 3.2 11	39 84 99 54 332 20 25 20 28 25 20 28 30 225 40 38 30 226 52 28 31	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 2.6% 2.1% 2.5% 2.1% 15.4%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.98, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.64 [-21.61, 18.33] -26.50 [-32.02, -20.98] -2.52 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -19.55 [-18.04, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27] -18.10 [-23.01, -13.19]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Jarke 2014 Jarke 2014 Jarke 2014 Jarke 2014 Jarke 2015 Subtotal (95% CF) Heterogeneity: Tau ² = 38.9(Test for overall effect: Z = 2 .1.5 Spinal Surgery Erten 2010 Chan 2010 Panday 2004c Turan 2003b /ahedi 2011 Subtotal (95% CF) Heterogeneity: Tau ² = 135.1 Test for overall effect: Z = 2 .1.6 Thoracic surgery Srosen 2014 Hout 2007 Cosucu 2013 Alenda 2010 Dirran 2006	$\begin{array}{c} 33.2\\ 33.1\\ 37\\ 42.8\\ 27.94\\ 19.7\\ 0; Ch ^{2}=1;\\ 0.02 \ (P=0,0)\\ 3.31\\ 20.8\\ 39.18\\ 90.85\\ 16.3\\ 18.61\\ 11.9\\ 29.47\\ 70; Ch ^{2}=0,0\\ 11.2\\ 2.36\\ 25.9\\ 6\\ 23.9\end{array}$	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df .01) 21.62 2.5 8.3 8.5	76 95 52 48 488 = 5 (P - 39 150 80 28 25 36 38 30 28 25 27 (P 52 23 29 30 25	35 48 50.5 26.77 25.1 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); P 17.92 2.65 44 15.1 31.5	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.55 3.2 11 20 2.78	39 84 99 54 332 20 25 20 28 25 20 28 25 20 28 30 228 30 228 52 28 30 228 30 228 25 20 28 25 20 28 25 20 20 25 20 20 25 20 20 25 20 20 25 20 20 20 20 20 25 20 20 20 20 20 20 20 20 20 20 20 20 20	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.3% 1.3% 0.5% 2.1% 2.5% 2.1% 15.4% 1.5% 2.5% 2.1% 2.5%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.14 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.64 [-21.61, 18.33] -26.50 [-23.02, -20.86] -2.92 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -7.85 [-19.64, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27] -18.10 [-23.01, -13.19] -9.10 [-16.88, -1.32] -7.06 [-8.09, -6.11]	
Clarke 2009a Jarke 2009b Jarke 2009b Jarke 2014 unn 2015 Paul 2013 Paul 2015 Paul 2015 Seat for overall effect: Z = 2 .1.5 Spinal Surgery Firten 2010 Panday 2004a Panday 2	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 11 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = 1 29.47 70; Chi ^z = 2 .43 (P = 0.	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df .01) 21.62 8.3 8.5 2.6 0.9	76 95 52 48 48¢ = 5 (P - 39 150 28 25 36 38 30 28 25 36 32 36 32 36 32 32 9 30 25 30	35 48 50.5 26.77 25.1 <0.00001); P 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 <0.00001); P 17.92 2.65 44 15.1 31.5 31.5 345 44	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.55 3.2 11 20 2.78 1.5	39 84 99 49 54 332 20 25 20 28 25 20 28 25 40 38 30 226 52 28 31 30 25 53 30	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 2.6% 2.3% 2.1% 1.5% 2.1% 1.5% 2.1% 1.6% 2.5% 2.1%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.98, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.61, 18.33] -26.50 [-32.02, -20.98] -2.52 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -18.55 [-18.04, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27] -18.10 [-2.30, 1, -13.19] -9.10 [-18.08, -1.32] -7.60 [-9.09, -6.11] -1.50 [-2.13, -0.87]	
Xarke 2009a Jarke 2009b Jarke 2009b Jarke 2009b Jarke 2009b Jarke 2014 unn 2015 Vall 2013 Vall 2015 Vall 2013 Vall 2013 Vall 2013 Vall 2014 Vall 2014 Vall 2010 Vana 2004b Vana 2004b Va	$\begin{array}{c} 33.2\\ 33.1\\ 37\\ 42.8\\ 27.94\\ 19.7\\ 0; Ch ^{2}=1;\\ 0.02 \ (P=0,0)\\ 3.31\\ 20.8\\ 39.18\\ 90.85\\ 16.3\\ 18.61\\ 11.9\\ 29.47\\ 70; Ch ^{2}=0,0\\ 11.2\\ 2.36\\ 25.9\\ 6\\ 23.9\end{array}$	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df .01) 21.62 2.5 8.3 8.5	76 95 52 48 488 = 5 (P - 39 150 80 28 25 36 38 30 28 25 27 (P 52 23 29 30 25	35 48 50.5 26.77 25.1 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); P 17.92 2.65 44 15.1 31.5	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.55 3.2 11 20 2.78	39 84 99 54 332 20 25 20 28 25 20 28 25 20 28 30 228 30 228 52 28 30 228 30 228 25 20 28 25 20 28 25 20 20 25 20 20 25 20 20 25 20 20 25 20 20 20 20 20 25 20 20 20 20 20 20 20 20 20 20 20 20 20	2.5% 2.6% 1.3% 1.9% 1.9% 10.2% 10.2% 2.5% 2.1% 15.4% 2.5% 2.1% 1.5% 2.5% 2.1% 1.6% 2.5% 2.5% 2.5% 2.5%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.64 [-21.81, 18.33] -26.50 [-32.02, -20.98] -2.92 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -18.55 [-19.04, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27] -18.10 [-23.01, -13.19] -9.10 [-16.88, -1.32] -7.60 [-9.09, -6.11] -1.50 [-2.13, 0.87] -5.04 [-9.00, -1.08]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2009b Clarke 2009b Clarke 2014 Lunn 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2016 Paul 2010 Paul 2010 Paul 2010 Paul 2010 Paul 2010 Paul 2010 Paul 2011 Subtobal (95% Cl) Heterogeneity: Tau ² = 135.7 Fest for overall effect: Z = 2 H.8 Thoracle surgery Strosen 2014 Hout 2007 Kosucu 2013 Aenda 2010 Durran 2006 Soltanzadeh 2011 Loak 2011 Subtobal (95% Cl) Heterogeneity: Tau ² = 16.3	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 11 20.2 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = (29.47 70; Chi ^z = (2.43) (P = 0. 11.2 2.36 25.9 6 23.9 1; Ch ^z = 10 (Ch ^z = 10) (Ch ^z = 10)	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df 0.01) 21.62 2.5 8.3 8.5 2.66 0.9 5.38 0.9 0.9 0.9 0.9 0.9 0.9 0.9 0.9	76 95 52 48 488 488 488 488 488 52 5 5 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	35 48 50.5 26.77 25.1 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); P 17.92 2.65 44 15.1 31.5 15.1 31.5	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.55 3.2 11 20 2.78 1.5 7.25	39 84 99 54 332 20 25 20 28 52 28 540 38 38 32 228 52 28 52 28 31 30 25 53 00 25 52 28 52 28 52 28 52 28 53 20 20 20 20 20 20 20 20 20 20 20 20 20	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 2.6% 2.3% 2.1% 1.5% 2.1% 1.5% 2.1% 1.6% 2.5% 2.1%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -8.11 [-12.98, -0.18] -0.25 [-0.87, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.61, 18.33] -26.50 [-32.02, -20.98] -2.52 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -18.55 [-18.04, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27] -18.10 [-2.30, 1, -13.19] -9.10 [-18.08, -1.32] -7.60 [-9.09, -6.11] -1.50 [-2.13, -0.87]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Jarke 2014 Jarke 2014 Jarke 2014 Jarke 2014 Jarke 2015 Bubtotal (95% CI) Heterogeneity: Tau ² = 38.9(Test for overall effect: Z = 2 .1.5 Spinal Surgery Erten 2010 Chan 2010 Panday 2004c Turan 2003b /ahedi 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 13.3 Tosen 2014 Hout 2007 Cosucu 2013 Arenda 2010 Dmran 2006 Soltanzadeh 2011 Jubtotal (95% CI) Heterogeneity: Tau ² = 16.3 Test for overall effect: Z = 3 .1.8 Thoracic	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 11 20.2 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = (29.47 70; Chi ^z = (2.43) (P = 0. 11.2 2.36 25.9 6 23.9 1; Ch ^z = 10 (Ch ^z = 10) (Ch ^z = 10)	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df 0.01) 21.62 2.5 8.3 8.5 2.66 0.9 5.38 0.9 0.9 0.9 0.9 0.9 0.9 0.9 0.9	76 95 52 48 485 = 5 (P < 39 150 80 28 25 36 36 38 30 428 = 7 (P 52 23 29 30 25 30 25 30 20 25 30 20 25 20 9 = 6 (P <	35 48 50.5 26.77 25.1 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); P 17.92 2.65 44 15.1 31.5 15.1 31.5	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.55 3.2 11 20 2.78 1.5 7.25	39 84 99 949 54 332 20 225 20 28 825 20 28 830 38 80 2228 52 28 311 300 225 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 228 229 229	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 1.3% 0.5% 2.1% 2.5% 2.1% 15.4% 2.5% 2.1% 1.5% 2.5% 2.1% 1.6% 2.5% 2.5% 2.5% 2.5% 1.5%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.14 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.61, 18.33] -26.50 [-23.02, -20.88] -2.92 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -7.85 [-19.04, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27] -18.10 [-23.01, -13.19] -9.10 [-16.88, -1.32] -7.60 [-9.09, -6.11] -1.50 [-2.13, -0.87] -5.04 [-9.00, -1.08] -6.37 [-9.57, -2.86]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2009b Clarke 2014 Lunn 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2015 Paul 2016 Paul 2010 Paul 2010 Paul 2010 Paul 2004c Paul 2004	33.2 33.1 37 42.8 27.94 19.7 0; Chi ^z = 11 2.02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; Chi ^z = (1) 29.47 70; Chi ^z = (2) 29.47 11.2 2.36 25.9 6 23.9 11.2 2.36 25.9 9.9 1; ChP = 10 .61 (P = 0.	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df 0.01) 21.62 2.5 8.3 8.5 2.66 0.9 5.38 00.9 0.38 0.9 0.38 0.9 0.03 0.9 0.9 0.03 0.9 0.04 0.9 0.9 0.9 0.9 0.9 0.9 0.9 0.9	76 95 52 48 485 = 5 (P < 39 150 28 25 36 30 20 20 20 20 20 20 20 20 20 20 20 20 20	35 48 50.5 26.77 25.1 < 0.00001); P 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); P 17.92 2.65 44 15.1 31.5 31.5 44 15.1 31.5 4 4.94 < 0.00001); P	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.55 3.2 11 20 2.78 1.5 7.25 = 94%	39 84 99 949 54 332 20 225 20 28 825 20 28 830 38 80 2228 52 28 311 300 225 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 228 229 229	2.5% 2.6% 1.3% 1.9% 1.9% 10.2% 10.2% 2.5% 2.1% 15.4% 2.5% 2.1% 1.5% 2.5% 2.1% 1.6% 2.5% 2.5% 2.5% 2.5%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.11 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.64 [-21.81, 18.33] -26.50 [-32.02, -20.98] -2.92 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -18.55 [-19.04, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27] -18.10 [-23.01, -13.19] -9.10 [-16.88, -1.32] -7.60 [-9.09, -6.11] -1.50 [-2.13, 0.87] -5.04 [-9.00, -1.08]	
Clarke 2009a Clarke 2009b Clarke 2009b Clarke 2014 Jarke 2014 Jarke 2014 Jarke 2014 Jarke 2014 Jarke 2015 Bubtotal (95% CI) Heterogeneity: Tau ² = 38.9(Test for overall effect: Z = 2 .1.5 Spinal Surgery Erten 2010 Chan 2010 Panday 2004c Turan 2003b /ahedi 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 13.3 Tosen 2014 Hout 2007 Cosucu 2013 Arenda 2010 Dmran 2006 Soltanzadeh 2011 Jubtotal (95% CI) Heterogeneity: Tau ² = 16.3 Test for overall effect: Z = 3 .1.8 Thoracic	33.2 33.1 37 42.8 27.94 19.7 0; ChI [≠] = 11 1.02 (P = 0. 3.31 20.8 39.18 90.85 16.3 18.61 11.9 29.47 70; ChI [≠] = 4 2.36 25.9 6 23.9 2.5 9.9 1; ChI [≠] = 11 1.2 2.36 25.9 9.9 1; ChI [≠] = 11 1.2 2.36 2.39 2.35 9.9 1; ChI [≠] = 12 2.36 2.39 2.35 9.9 1; ChI [≠] = 12 2.36 2.39 2.5 9.9 1; ChI [≠] = 12 3.31 3.31 2.36 2.39 2.5 9.9 1; ChI [≠] = 12 2.36 2.39 2.5 9.9 1; ChI [≠] = 12 3.31 2.36 2.39 2.5 9.9 1; ChI [≠] = 12 3.31 2.36 2.39 2.5 9.9 1; ChI [≠] = 12 2.36 2.39 2.5 9.9 1; ChI [≠] = 13 3.5 1; ChI [‡] = 14 3.5 1; ChI [‡] = 34 3.5 1; CHI [‡]	4 1.5 38.4 22.99 16.39 36.90, df .04) 0.98 5.72 22.31 34.1 8.9 9.03 4.4 9.64 679.10, df .01) 21.62 2.5 8.3 8.5 2.6 0.9 5.38 0.9 5.38 0.9 0.38 0.9 0.38 0.9 0.9 0.9 0.9 0.9 0.9 0.9 0.9	76 95 52 48 485 = 5 (P < 39 150 28 25 36 30 20 20 20 20 20 20 20 20 20 20 20 20 20	35 48 50.5 26.77 25.1 < 0.00001); P 3.56 31.5 52.65 92.49 42.8 21.53 30.1 37.33 < 0.00001); P 17.92 2.65 44 15.1 31.5 31.5 44 15.1 31.5 4 4.94 < 0.00001); P	4 1.33 4.14 18.96 14.5 = 96% 0.64 9.6 21.27 41.77 10.9 11.3 0.6 9.5 * = 99% 23.55 3.2 11 20 2.78 1.5 7.25 = 94%	39 84 99 949 54 332 20 225 20 28 825 20 28 830 38 80 2228 52 28 311 300 225 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 222 228 228 229 229	2.5% 2.6% 1.3% 1.6% 1.9% 10.2% 2.6% 2.3% 1.3% 0.5% 2.1% 2.5% 2.1% 15.4% 2.5% 2.1% 1.5% 2.5% 2.1% 1.6% 2.5% 2.5% 2.5% 2.5% 1.5%	-1.90 [-3.44, -0.36] -11.00 [-11.41, -10.59] -7.70 [-17.55, 2.15] 1.17 [-7.03, 9.37] -5.40 [-11.44, 0.64] -6.14 [-12.98, -0.18] -0.25 [-0.67, 0.17] -10.70 [-14.57, -6.83] -13.47 [-24.00, -2.94] -1.84 [-21.61, 18.33] -26.50 [-23.02, -20.88] -2.92 [-7.50, 1.66] -18.20 [-19.61, -16.79] -7.86 [-12.70, -3.02] -7.85 [-19.04, -2.95] -6.72 [-15.41, 1.97] -0.29 [-1.85, 1.27] -18.10 [-23.01, -13.19] -9.10 [-16.88, -1.32] -7.60 [-9.09, -6.11] -1.50 [-2.13, -0.87] -5.04 [-9.00, -1.08] -6.37 [-9.57, -2.86]	

Forest plot of 24-hour morphine consumption

FIGURE 4 Forest plot of Serious Adverse Events

	Gabape		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	I M-H, Fixed, 95% CI
1.14.1 Cholecystector	e						
Srivastava 2010 Subtotal (95% CI)	0	60 60	0	60 60		Not estimable Not estimable	
Total events	0		0				
leterogeneity: Not app	licable		-				
Test for overall effect: N		able					
1.14.2 Hysterectomy							
Ajori 2011	0	69	0	69		Not estimable	
Dierking 2003	0	39	0	32		Not estimable	
Fassoulaki 2006	0	27	0	24		Not estimable	
Gilron 2004	1	20	2	22	6.9%	0.55 [0.05, 5.61]	
Khan 2013	0	34	0	35		Not estimable	
Subtotal (95% CI)		189		182	6.9%	0.55 [0.05, 5.61]	
Total events	1		2				
Heterogeneity: Not app							
Test for overall effect: 2		P = 0.61)				
1.14.3 Mastectomy							
Dirks 2002	0	31	0	34		Not estimable	
Fassoulaki 2002	0	25	0	25		Not estimable	
Subtotal (95% Cl)		58		59		Not estimable	
Total events	0		0				
Heterogeneity: Not app	licable		-				
Test for overall effect: I		able					
1.14.4 Orthopaedic su	irgery						
Lunn 2015	6	183	1	91	4.9%	2.98 [0.36, 24.41]	
Paul 2013	0	52	0	49		Not estimable	
Subtotal (95% CI)		235		140	4.9%	2.98 [0.36, 24.41]	
Total events	6		1				
Heterogeneity: Not app	licable						
Test for overall effect: 2	z = 1.02 (F	P = 0.31)				
1.14.5 Spinal surgery							
Vahedi 2011	0	36	0	40		Not estimable	*****
Subtotal (95% CI)		36		40		Not estimable	
lotal events	0		0				
Heterogeneity: Not app	licable						
Test for overall effect: I		able					
1.14.6 Thoracic surge	•						
Grosen 2014	13	52	8	52	29.1%	1.63 [0.74, 3.59]	
Hout 2007	1	28	0	28	1.8%	3.00 [0.13, 70.64]	
Kinney 2011	4	57	5	63	17.3%	0.88 [0.25, 3.13]	
Jcak 2011	7	20	11	20	40.0%	0.64 [0.31, 1.30]	
Subtotal (95% CI)		157		163	88.2%	1.06 [0.66, 1.71]	•
Fotal events	25		24			-	
Heterogeneity: Chi ² = 3		B(P=0)		16%			
Test for overall effect: 2							
Total (95% Ci)		733		644	100.0%	1.12 [0.71, 1.77]	
Total events	32		27				
Heterogeneity: Chi ² = 4		5 (P = 0.		0%			
							0.01 0.1 1 10 1
Test for overall effect: 2	Z == 0,48 /F	° = 0.63)				Favours Gabapentin Favours Control

Forest plot of Serious Adverse Events

APPENDIX PAPER II

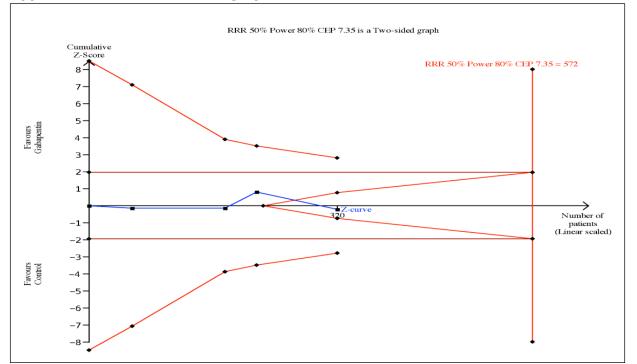
Appendix 1: Search strategies Appendix from PAPER I.

Appendix 2: Opioid conversion table Appendix from PAPER 1.

Appendix 3: Forest plot SAE low risk of bias

	Gabape		Contr			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Fixed, 95% C	I M-H, Fixed, 95% Cl
1.3.1 Cholecystectom							
Srivastava 2010 Subtotal (95% CI)	0	60 60	0	60 60		Not estimable Not estimable	
Total events Heterogeneity: Not app Test for overall effect:		able	0				
1.3.2 Hysterectomy Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not app Test for overall effect:		able					
1.3.3 Mastectomy Subtotal (95% Cl)		0		0		Not estimable	
Total events Heterogeneity: Not app Test for overall effect: I		ible	0				
1.3.4 Orthopaedic su	aerv						
Lunn 2015	6	183	1	91	9.5%	2.98 [0.36, 24.41]	
Paul 2013	ō	52	Ó	49	0.070	Not estimable	
Subtotal (95% CI)		235		140	9.5%	2.98 [0.36, 24.41]	
Total events Heterogeneity: Not app Test for overall effect: 2		° = 0.31	1				
1.3.5 Spinal surgery							
Subtotal (95% CI)		Ő		0		Not estimable	
Total events	0		0				
Heterogeneity: Not app Test for overall effect:		able					
1.3.6 Thoracic surger	v						
Grosen 2014	, 13	52	8	52	56.8%	1.63 [0.74, 3.59]	
Kinney 2011	4	57	5	63	33.7%	0.88 [0.25, 3.13]	
Subtotal (95% CI)		109		115	90.5%	1.35 [0.69, 2.63]	*
Total events Heterogeneity: Chi ² = (17).64, df = 1	(P = 0.	13 42); l² = ()%			
Test for overall effect:	Z = 0.88 (F	e = 0.38)				
Total (95% Cl)		404		315	100.0%	1.50 [0.80, 2.84]	
Total events	23		14				-
Heterogeneity: Chi ² = 1	l.12, df = 2	(P = 0.)%			
Test for overall effect:		•					0.01 0.1 1 10 100 Favours Gabapentin Favours Control
Test for subgroup diffe	rences Cł	$h^2 = 0.5$	0 df = 1	D - 0 /	19) 12 - 00	/	LANDER CONSTRUCT CANOUS COMMON

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 β 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

	Gaber			Con				Maan Difference	Mean Difference
	Mean [VAS] S	[8AV] 01	Total	Mean [VAS]	id [vas]	Total	Weight	IV, Random, \$5% CI [VAS]	IV, Random, 95% CI [VAS]
1.1 Cholecystectomy									
loseini 2015	16.4	10.2	22	30.9	10.1	22	2.8%	-14.50 [-20.50, -8.50]	. uuqua.
Aishra 2016	30.7	4.4	30	31	2.1	30	3.0%	-0.30 [-2.04, 1.44]	ę.
Frivastava 2010	23	3.17	60	49	3.33	60	3.0%	-26.00 [-27.16, -24.84]	2
lubtotal (85% Ci)			11Z			112	8.7%	-13.60 [-33.36, 6.17]	
leterogeneity: Tau ² = 30	1.60; Chi ² = 57	8.37, df =	2 (P <	0.00001); l ² = 10	0%				
fest for overall effect: Z	= 1.35 (P = 0.18	3)	-						
1.1.2 Hysterectomy									
Vori 2011	40	30	69	63	28	69	2.5%	-23.00 [-32.68, -13.32]	
adawy 2014	40	5	19	45	5	19	2.9%	-5.00 [-8.18, -1.82]	~
Sehdad 2012	38	9.6	30	66.2	13.7	31	2.8%	-28.20 [-34.12, -22.28]	
Dierking 2003	14.12	15.23	40	21.53	18.59	40	2.7%	-7.41 [-14.86, 0.04]	
Durmus 2007	45	51	25	52	61	25	0.9%	-7.00 [-38.17, 24.17]	
assoulaki 2005	17	28	25	20	31	28	1.9%	-3.00 [-18.88, 12.88]	
Fassoulaki 2006	25.7	16.1	27	26.8	19.6	24	2.4%	-1.10 [-11.02, 8.82]	
rouzanfard 2013	35.6	15	25	65.6	18	25	2.5%		
								-30.00 [-39.18, -20.82]	
Shafari 2009	42.5	3.5	33	58.1	4	33	3.0%	-15.60 [-17.41, -13.79]	-
Silron 2004	29	4	23	39	3	24	3.0%	-10.00 [-12.03, -7.97]	
Chan 2013	36.17	13.4	34	52	10.51	35	2.8%	-15.83 [-21.52, -10.14]	
Ray 2015	56.16	14.24	30	77	12.9	30	2.7%	-20.84 [-27.72, -13.96]	
Sekhavet 2009	37.9	20.8	49	76.6	22.4	49	2.6%	-38.70 [-47.26, -30.14]	
Sen 2009a	28	24	20	41	47	20	1.4%	-13.00 [-36.13, 10.13]	
Furan 2003a	18	16	25	42	10	25	2.7%	-24.00 [-31.40, -16.60]	
/erma 2008	23	14	25	32	16	25	2.6%	-9.00 [-17.33, -0.67]	
Subtotal (95% CI)			499			502	39.2%	-16.43 [-20.62, -12.24]	•
teterogeneity: Tau ² = 52	2.07; Chi² = 141	.40, df = 1	5 (P <	0.00001); I ² = 89	9%				
Test for overall effect: Z	= 7.69 (P < 0.00	0001)		-					
2.1.3 Mastectomy									
Dirks 2002	14	18	31	18	15	34	2.6%	-4.00 [-12.10, 4.10]	
Joha 2010	18	17	30	33	11	29	2.7%	-15.00 [-22.28, -7.72]	
assoulaki 2002	7	20	25	9	19	25	2.4%	-2.00 [-12.81, 8.81]	
		<u>∠</u> 0 5			8				
Bosal 2015	36		30	52		30	2.9%	-16.00 [-19.38, -12.62]	
Grover 2009	10	8.15	27	10	8.15	23	2.9%	0.00 [-4.53, 4.53]	
(im 2004	27	22.2	21	29	17.6	20	2.2%	-2.00 [-14.23, 10.23]	
Metry 2008	12.52	9,5	67	24.1	13	34	2.8%	-11.58 [-16.51, -6.65]	
Subtotal (95% CI)			231			195	18.5%	-7.80 [-13.73, -1.87]	▼
leterogeneity: Tau ² = 49			(P < 0.0	00001); i² = 85%					
Test for overall effect: Z	= 2.58 (P = 0.0	10)							
+ + A Mathemanata auro	~~·								
1.1.4 Orthopaedic surg	101 Y					0		Mai antimakla	
Subtotal (95% CI)			Û			v		Not estimable	
leterogeneity: Not appli									
fest for overall effect: No	ot applicable								
1.1.5 Spinal surgery									
Erten 2010	25.89	7.11	39	30.5	8.8	20	2.9%	-4.61 [-9.07, -0.15]	
Chan 2010	44.4	14.55	150	68	11	25	2.8%	-23.60 [-28.50, -18.70]	
anday 2004a	36.5	12.97	80	61.5	13	20	2.7%	-25.00 [-31.37, -18.63]	
Radhakrishnan 2005	10	12.5	30	10	12.5	30	2.7%	0.00 [-6.33, 6.33]	
furan 2003b	13	15	25	24	18	25	2.5%	-11.00 [-20.18, -1.82]	
/ahedi 2011	61.1	20.9	36	56.8	24.4	40	2.4%	4.30 [-5.89, 14.49]	
Özgencil 2011	24	6.7	30	33.3	10.9	30	2.9%	-9.30 [-13.88, -4.72]	
Subtotal (95% CI)	£.7		390	00.0	10.0	190	19.0%	-10.17 [-18.02, -2.32]	•
leterogeneity: Tau ² = 10	0.36: Chi² = 77	64. df = F		00001): 12 = 0.20	6			, twowing working	-
Test for overall effect: Z			0		-				
energiane and and the second of the		••							
1.1.6 Thoracic surgery									
	6.84	12.97	52	13.95	17.94	52	2.8%	71111242 4003	[
	6.84 0							-7.11 [-13.13, -1.09] 0.00 [-2.78, 2.78]	L .
Grosen 2014		5.93	23	0	3.7	28	2.9%		<u>Ĺ</u>
Grosen 2014 Hout 2007		25.2	57	28	26.2	68	2.5%	-1.00 [-10.03, 8.03]	
Grosen 2014 Hout 2007 Kinney 2011	27		29	42	21	31	2.6%	-13.00 [-21.59, -4.41]	
Grosen 2014 Hout 2007 Kinney 2011 Kosucu 2013	27 29	12		30	48	30	1.5%	-10.00 [-30.45, 10.45]	
Grosen 2014 Hout 2007 Kinney 2011 Kosucu 2013 Menda 2010	27 29 20	31	30			25	1.2%	-26.00 [-51.30, -0.70]	
Grosen 2014 Hout 2007 Kinney 2011 Kosucu 2013	27 29		30 25	61	45.69				Ē
Grosen 2014 Hout 2007 Kinney 2011 Kosucu 2013 Menda 2010 Omran 2006 Jeak 2011	27 29 20	31	25 20		45.69 65	20	1.1%	-20.10 [-48.60, 8.40]	
Grosen 2014 Hout 2007 Kinney 2011 Kosucu 2013 Menda 2010 Omran 2006	27 29 20 35	31 45.59	25	61					•
Grosen 2014 Hout 2007 Kinney 2011 Kosucu 2013 Menda 2010 Dmran 2006 Jeak 2011 Subtotal (95% CI)	27 29 20 35 29.9	31 45.59 2	25 20 236	61 50		20	1.1%	-20.10 [-48.60, 8.40]	•
Grosen 2014 tout 2007 (inney 2011 (sosucu 2013 Menda 2010 Omran 2006 Joak 2011 Subitotal (98% Ci) teterogeneity: Tau ² = 25	27 29 20 35 29.9 9.37; Chi ^z = 16.5	31 45.59 2 50, df = 6	25 20 236	61 50		20	1.1%	-20.10 [-48.60, 8.40]	•
Grosen 2014 tout 2007 (inney 2011 (sosucu 2013 Menda 2010 Omran 2006 Joak 2011 Subitotal (98% Ci) teterogeneity: Tau ² = 25	27 29 20 35 29.9 9.37; Chi ^z = 16.5	31 45.59 2 50, df = 6	25 20 236	61 50		20	1.1%	-20.10 [-48.60, 8.40]	•
Grosen 2014 Gout 2007 Ginney 2011 Gosucu 2013 Aenda 2010 Jornan 2006 Jock 2011 Subtotal (95% CI) leterogeneity: Tau ² = 25 Test for overall effect: Z	27 29 20 35 29.9 9.37; Chi ^z = 16.5	31 45.59 2 50, df = 6	25 20 236	61 50		20 254	1.1%	-20.10 [-48.60, 8.40] -6.63 [-12.42, -0.84]	•
Grosen 2014 tout 2007 Kinney 2011 Kosucu 2013 Menda 2010 Jmran 2006 Jock 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 25 (est for overall effect: Z Fotal (95% CI)	27 29 20 35 29.9 9.37; Chi ² = 16.4 = 2.24 (P = 0.0)	31 45.59 2 50, df = 6	25 20 236 (P = 0.0	61 50 01); I² = 64%	65	20 254	1.1% 14.8%	-20.10 [-48.60, 8.40]	• •
Grosen 2014 Gout 2007 Ginney 2011 Gosucu 2013 Aenda 2010 Jornan 2006 Jock 2011 Subtotal (95% CI) leterogeneity: Tau ² = 25 Test for overall effect: Z	27 29 20 35 29.9 3.37; Chi ² = 16.4 = 2.24 (P = 0.0) 6.58; Chi ² = 10	31 45.59 2 50, df = 6 2) 30.96, df	25 20 236 (P = 0.0	61 50 01); I² = 64%	65	20 254	1.1% 14.8%	-20.10 [-48.60, 8.40] -6.63 [-12.42, -0.84]	-100 -50 0 50 100 Favours Gabapentin Favours Control

Appendix 6: Forest plot 6 hour VAS mobilization

		pentin			iontrol			Mean Difference	Mean Difference
Study or Subgroup		sd [vas]	Total	Mean [VAS]	SD [VAS]	Total	Weight	IV, Random, 95% CI [VAS]	IV, Random, 95% CI [VAS]
2.2.1 Cholecystectom									
Srivastava 2010 Subtotal (95% Ci)	59	3.33	60 60	70.5	3.5	60 50	22.5% 22.5%	-11.50 [-12.72, -10.28] -11.50 [-12.72, -10.28]	≈
Heterogeneity: Not app	licable								
Test for overall effect: 2	2 = 18.44 (P < 0	.00001)							
2.2.2 Hysterectomy									
Dierking 2003	42.53	25.9	40	51.09	28.27	40	5.1%	-8.56 [-20.44, 3.32]	
Durmus 2007	67	77	25	76	83	25	0.5%	-9.00 [-53.38, 35.38]	
Fassoulaki 2005	40	67	25	53	78	28	0.6%	-13.00 [-52.04, 26.04]	
Fassoulaki 2006	47.8	19.7	27	45.1	24.6	24	4.8%	2.70 [-9.63, 15.03]	-+
Sen 2009a	32	34	20	56	54	20	1.1%	-24.00 [-51.97, 3.97]	······
Turan 2003a	31.2	17	25	43	12	25	8.7%	-11.80 [-19.96, -3.64]	
Subtotal (95% CI)			162			162	20.7%	-8.47 [-14.18, -2.78]	◆
Heterogeneity: Tau ² = 0 Test for overall effect: 2			= 0.41); i² = 1%					
2.2.3 Mastectomy									
Dirks 2002	19	21	31	31	23	34	6.0%	-12.00 [-22.70, -1.30]	
Fassoulaki 2002	21	35	25	29	2.5 52	25	1.4%		
		-						-8.00 [-32.57, 16.57]	
Grover 2009	30	14.81	27	30	7.41	23	11.5%	0.00 [-6.35, 6.35]	1
Kim 2004	42	25.2	21	37	15.8	20	4.5%	5.00 [-7.81, 17.81]	
Metry 2008	20.52	14.48	67	31.3	15	34	11.9%	-10.78 [-16.90, -4.66]	
Subtotal (95% Ci) Heterogeneity: Tau ² = 3	22 48• Chi2 = 9 7	78 df = 4 (171 P=00	A)- 12 = 50%		136	35.4%	-5.20 (-12.04, 1.65)	•
Heterogeneity: Tau ² = 3 Test for overall effect: 2	Z = 1.49 (P = 0.1			4); i² = 59%		136	35.4%	-5.20 (-12.04, 1.63)	•
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopsedic sur	Z = 1.49 (P = 0.1		P = 0.0	4);			35.4%		•
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopsedic surr Subtotal (85% Cl)	Z = 1.49 (P = 0.1 gery			4); I² = 59%		136 0	35.4%	-5.20 [-12.04, 1.65] Not sstimable	•
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopsedic sur	Z = 1.49 (P = 0.1 gery licable		P = 0.0	4); i² = 59%			35.4%		•
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopsedic sun Subtots! (95% CI) Heterogeneity: Not app	Z = 1.49 (P = 0.1 gery licable		P = 0.0	4); i² = 59%			35.4%		•
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopaedic sun Subtatal (85% C1) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005	Z = 1.49 (P = 0.1 gery licable		P = 0.0 8 30	4}; * = 59% 30	20	ş 30	7.7%	Not ssiimable -10.00 [-18.95, -1.05]	
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopaedic sun Subtotal (85% CI) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005 Subtotal (95% Ci)	Z = 1.49 (P = 0.1 gary licable Not applicable 20	14)	9 = 0.0 8		20	ø		Not estimable	◆
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopaedic sun Subtatal (85% C1) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable	14) 15	P = 0.0 8 30		20	ş 30	7.7%	Not ssiimable -10.00 [-18.95, -1.05]	•
Heterogeneity: Tau ² = 3 Test for overall effect: Z 2.2.4 Orthopsedic sum Subtotal (85% Cl) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005 Subtotal (95% Cl) Heterogeneity: Not app	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable Z = 2.19 (P = 0.0	14) 15	P = 0.0 8 30		20	ş 30	7.7%	Not ssiimable -10.00 [-18.95, -1.05]	•
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopaedic autor Subtotal (85% C1) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005 Sustotal (95% C1) Heterogeneity: Not app Test for overall effect: 2	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable Z = 2.19 (P = 0.0	14) 15	P = 0.0 8 30		20	ş 30	7.7%	Not ssiimable -10.00 [-18.95, -1.05]	•
Heterogeneity: Tau ² = 3 Test for overall effect: Z 2.2.4 Orthopsedic sum Subtotal (85% Cl) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005 Subtotal (95% Cl) Heterogeneity: Not app Test for overall effect: Z 2.2.6 Thorsoic surgery	Z = 1.49 (P = 0.1 gery licable vot applicable 20 licable Z = 2.19 (P = 0.0	14) 15)3)	P = 0.0 8 30 39	30		9 30 39	7.7% 7.7%	Not ssiimable -10.00 [-18.95, -1.05] -10.90 [-18.95, -1.05] -8.87 [-16.14, -1.60]	
Heterogeneity: Tau ² = 3 Test for overall effect: Z 2.2.4 Orthopaedic sur- Subtotal (85% Cl) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005 Sustotal (95% Cl) Heterogeneity: Not app Test for overall effect: Z 2.2.6 Thorseic surgery Grosen 2014 Menda 2010	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable Z = 2.19 (P = 0.0 y 12.42 43.5	14) 15 18.55 57	P = 0.0 8 30 39 52 30	30 21.29 65	19.28 78	8 30 38 52 30	7.7% 7.7% 9.9% 0.7%	Not sstimable -10.00 [-18.95, -1.05] -10.90 [-18.95, -1.05] -8.87 [-16.14, -1.60] -21.50 [-56.07, 13.07]	
Heterogeneity: Tau ² = 3 Test for overall effect: Z 2.2.4 Orthopsedic sum Subtotal (85% C1) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakristnan 2005 Subtotal (95% C1) Heterogeneity: Not app Test for overall effect: Z 2.2.6 Thorsoic surgery Grosen 2014 Menda 2010 Omran 2006	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable Z = 2.19 (P = 0.0 y 12.42 43.5 60	14) 15 18.55 57 35.16	P = 0.0 8 30 39 52 30 25	30 21.29 65 80	19.28 78 35.16	8 30 38 52 30 25	7.7% 7.7% 9.9% 0.7% 2.2%	Nof estimable -10.00 [-18.95, -1.05] -10.90 [-18.95, -1.05] -8.87 [-16.14, -1.60] -21.50 [-56.07, 13.07] -20.00 [-39.49, -0.51]	
Heterogeneity: Tau ² = 3 Test for overall effect: Z 2.2.4 Orthopaedic sur- Subtotal (85% Cl) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005 Sustotal (95% Cl) Heterogeneity: Not app Test for overall effect: Z 2.2.6 Thorseic surgery Grosen 2014 Menda 2010	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable Z = 2.19 (P = 0.0 y 12.42 43.5	14) 15 18.55 57	P = 0.0 8 30 39 52 30	30 21.29 65	19.28 78	8 30 38 52 30	7.7% 7.7% 9.9% 0.7%	Not sstimable -10.00 [-18.95, -1.05] -10.90 [-18.95, -1.05] -8.87 [-16.14, -1.60] -21.50 [-56.07, 13.07]	
Heterogeneity: Tau ² = 3 Test for overall effect: 2 2.2.4 Orthopaedic sun Subtatal (85% CI) Heterogeneity: Not app Test for overall effect: A 2.2.5 Spinal surgery Radhakristnan 2005 Subtotal (95% CI) Heterogeneity: Not app Test for overall effect: 2 2.2.6 Thoracic surgery Grosen 2014 Menda 2010 Omran 2006 Ucak 2011	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable Z = 2.19 (P = 0.0 y 12.42 43.5 60 39 0.00; Chi ² = 1.60	14) 15 18.55 57 35.16 20), df = 3 (P	P = 0.0 0 30 39 52 30 25 20 127	30 21.29 65 80 55	19.28 78 35.16	9 30 39 52 30 25 20	7.7% 7.7% 9.9% 0.7% 2.2% 0.9%	Not sstimable -10.00 [-18.95, -1.05] -10.90 [-18.95, -1.05] -8.87 [-16.14, -1.60] -21.50 [-56.07, 13.07] -20.00 [-39.49, -0.51] -16.00 [-47.06, 15.06]	• • •
Heterogeneity: Tau ² = 3 Test for overall effect: Z 2.2.4 Orthopaedic sum Subtotal (85% Cl) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005 Subtotal (85% Cl) Heterogeneity: Not app Test for overall effect: Z 2.2.6 Thoracic surgery Grosen 2014 Menda 2010 Omran 2006 Ucak 2011 Subtotal (85% Cl) Heterogeneity: Tau ² = C	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable Z = 2.19 (P = 0.0 y 12.42 43.5 60 39 0.00; Chi ² = 1.60	14) 15 18.55 57 35.16 20), df = 3 (P	P = 0.0 0 30 39 52 30 25 20 127	30 21.29 65 80 55	19.28 78 35.16	8 30 38 52 30 25 20 127	7.7% 7.7% 9.9% 0.7% 2.2% 0.9%	Not sstimable -10.00 [-18.95, -1.05] -10.90 [-18.95, -1.05] -8.87 [-16.14, -1.60] -21.50 [-56.07, 13.07] -20.00 [-39.49, -0.51] -16.00 [-47.06, 15.06]	
Heterogeneity: Tau ² = 3 Test for overall effect: Z 2.2.4 Orthopaedic sum Subtotal (85% Ci) Heterogeneity: Not app Test for overall effect: N 2.2.5 Spinal surgery Radhakrishnan 2005 Subtotal (95% Ci) Heterogeneity: Not app Test for overall effect: Z 2.2.6 Thoracic surgery Grosen 2014 Menda 2010 Omran 2006 Ucak 2011 Subtotal (85% Ci) Heterogeneity: Tau ² = 0 Test for overall effect: 2	Z = 1.49 (P = 0.1 gery licable Not applicable 20 licable Z = 2.19 (P = 0.0 y 12.42 43.5 60 39 0.00; Chi ² = 1.60 Z = 3.27 (P = 0.0	14) 15 18.55 57 35.16 20), df = 3 (P)01)	8 30 39 52 30 25 20 127 = 0.66 550	30 21.29 65 80 55); I ² = 0%	19.28 78 35.16	8 30 38 52 30 25 20 127	7.7% 7.7% 9.9% 0.7% 2.2% 0.9% 13.8%	Nof sstimable -10.00 [-18.95, -1.05] -10.90 [-18.95, -1.05] -8.87 [-16.14, -1.60] -21.50 [-56.07, 13.07] -20.00 [-39.49, -0.51] -16.00 [-47.06, 15.06] -19.89 [-17.42, -4.35]	

Appendix 7: Forest plot 24 hour VAS rest

Storester was Sector was	Gaba		Tain)	Control	water	Total	18101-24	Mean Difference	Mean Difference
Study or Subgroup 2.3.1 Cholecystector		en (avel	10131	Mean [VAS] SU [vasj	i otai	weight	IV, Random, 95% CI [VAS]	IV, Random, 95% CI [VAS]
Bekawi 2014	9 .7	5.6	30	6	6.2	32	3.7%	3.70 [0.76, 6.64]	~
Mishra 2016	20.1	3.4	30	26	4.1	30	3.9%	-5.90 [-7.81, -3.99]	~
Srivastava 2010	21	3.25	60	28	3.33	60	4.0%	-7.00 [-8.18, -5.82]	*
Subtotal (95% CI)			120			122	11.6%	-3.24 [-8.37, 1.88]	4
Heterogeneity: Tau ² = Test for overall effect: 2	,		(P < 0.)	00001); I ² = 95%					
2.3.2 Hysterectomy									
Ajori 2011	2	8	69	9	13	69	3.6%	-7.00 [-10.60, -3.40]	~-
Badawy 2014	20	2.5	19	25	2.5	19	3.9%	-5.00 [-6.59, -3.41]	*
Behdad 2012	25.3	5	30	42.7	14.2	31	3.3%	-17.40 [-22.71, -12.09]	- And
Dierking 2003	13.64	19.19	40	15.21 1	8.93	40	2.6%	-1.57 [-9.92, 6.78]	
Durmus 2007	27	40	25	39	49	25	0.7%	-12.00 [-36.79, 12.79]	
Fassoulaki 2005	16	27	25	7	14	28	1.9%	9.00 [-2.79, 20.79]	
Frouzanfard 2013	5.6	5.8	25	17.2	12.7	25	3.2%	-11.60 [-17.07, -6.13]	
Ghafari 2009	18.1	3	33	34.8	4	33	3.9%	-16.70 [-18.41, -14.99]	(m
Gilron 2004	13.82	12.5	23	23.63 1	6.52	24	2.6%	-9.81 [-18.16, -1.46]	
Khan 2013	8.52	7.43	34	24.28 1	1.18	35	3.4%	-15.76 [-20.23, -11.29]	**,***
Ray 2015	37	12.56	30	54.66	15.5	30	2.8%	-17.66 [-24.80, -10.52]	
Sekhavet 2009	40.1	14.5	49	52.7	21.1	49	2.8%	-12.60 [-19.77, -5.43]	
Sen 2009a	2	5	20	16	28	20	1.8%	-14.00 [-26.47, -1.53]	
Turan 2003a	5	7	25	16	12	25	3.2%	-11.00 [-16.45, -5.55]	
Verma 2008	12	13	25	21	12	25	2.9%	-9.00 [-15.94, -2.06]	
Subtotal (95% Ci) Heterogeneity: Tau ² = 1 Test for overall effect: 1			472 14 (P <	0.00001); I² = 89%		478	42.5%	-10.54 [-14.18, -6.89]	•
	(,							
2.3.3 Mastectomy				-		~~			
Fassoulaki 2002	4	12	25	7	14	25	2.8%	-3.00 [-10.23, 4.23]	
Kim 2004	23	19	21	20	10.3	20	2.3%	3.00 [-6.30, 12.30]	
Metry 2008 Subtotal (95% CI)	18.49	14.94	67 113	23	13	34 79	3.2% 8.3%	-4.51 [-10.16, 1.14] -2.64 [-6.66, 1.37]	
Heterogeneity: Tau ² = 1 Test for overall effect: 2	Z = 1.29 (P = 0.2		= 0.40)	k; I² = 0%					
2.3.4 Orthopaedic su Clarke 2009a	gery 36.53	25.97	29	51	21.8	7	1.0%	14 47 1 99 40 4 941	
Clarke 2009a Clarke 2009b	30.53	25.97	29 76	51 14	21.0 4	39	3.9%	-14.47 [-33.18, 4.24]	
Paul 2015	24.5	16.1	48	23.6	20.8	54	2.8%	-1.00 [-2.54, 0.54] 0.90 [-6.28, 8.08]	4
Subtotal (95% CI)	24.0	10.1	153	20.0	20.0	100	7.8%	-1.04 [-3.73, 1.66]	4
Heterogeneity: Tau ² = Test for overall effect: 2			= 0.32	; l² = 11%					
2.3.5 Spinal surgery									
Erten 2010	9.22	8.04	39	13	9.7	20	3.3%	-3.78 [-8.72, 1.16]	
Leung 2006	60	20	9	50	20	12	1.2%	10.00 [-7.29, 27.29]	
Panday 2004a	25.73	15.07	80	45	14	20	2.9%	-19.27 [-26.24, -12.30]	
Turan 2003b	7	8	25	11	14	25	3.0%	-4.00 [-10.32, 2.32]	
Vahedi 2011	25.8	19.5	36	34	27.2	40	2.1%	-8.20 [-18.77, 2.37]	
Özgencil 2011	11	4.8	30	15	7.7	30	3.7%	-4.00 [-7.25, -0.75]	7
Subtotal (95% CI)	00 44: 01 M - 17	ou .e -	218	AA. 18		147	16.2%	-8.22 [-11.55, -0.89]	•
Heterogeneity: Tau ² = : Test for overall effect: 2			(+ = 0.1	JUT); F = 75%					
2.3.6 Thoracic surger	У								
Grosen 2014	6.58	13.61	52	12.43	16.4	52	3.1%	-5.85 [-11.64, -0.06]	
Hout 2007	5	59.3	23	0	14.8	28	0.7%	5.00 [-19.85, 29.85]	
Kinney 2011	29	18.2	57	31	18.9	68	3.0%	-2.00 [-8.52, 4.52]	-
Kosucu 2013	13	8	29	32	11	31	3.4%	-19.00 [-23.84, -14.16]	
Menda 2010	23	35	30	38	60	30	0.7%	-15.00 [-39.86, 9.86]	
Omran 2006	32	38.66	25		8.66	25	0.8%	-22.00 [-43.43, -0.57]	
Rapchuk 2010	18	33	27	21	34	27	1.1%	-3.00 [-20.87, 14.87]	
Ucak 2011	12	0.1	20	30	48	20	0.9%	-18.00 [-39.04, 3.04]	
Subtotal (95% CI) Heterogeneity: Tau ² = 1 Test for overall effect; 2	•		263 (P = 0.)	0009); l² = 72%		281	13.8%	-9.74 [-17.12, -2.36]	•
	с – «.oə (Р = 0.0)							
Total (95% Ci)			1340			1207	100.0%	-7.51 [-9.73, -5.30]	•
Heterogeneity: Tau ² =			37 (P <	0.00001); l ² = 90%					-100 -50 0 50 100
Test for overall effect:									Favours Gabapentin Favours Control
	ronces: Chiž – 29	13 '861 - AF F	× (₽ ≃ C	.001), l ² = 75.4%					

Appendix 8: Forest plot 24 hour VAS mobilization

	Gab	apantin		Co	antroi			Mean Difference	Mean Difference
Study or Subgroup		SD [VAS]	Total	Mean (VAS)	80 [VAS]	Total	Weight	IV, Random, 95% CI (VAS)	IV, Random, 95% CI (VAS)
2.4.1 Cholecystecton	ny								
Srivastava 2010	30	2.5	60	46	2.5	60	8.5%	-16.00 [-16.89, -15.11]	°
Subtotal (95% CI)			80			60	8.5%	-16.00 [-16.89, -15.11]	
Heterogeneity: Not ap Test for overall effect:		0.00001)							
2.4.2 Hysterectomy									
Dierking 2003	37.48	27.03	40	34.12	20.96	40	7.5%	3.36 [-7.24, 13.96]	
Durmus 2007	51	68	25	68	79	25	2.7%	-17.00 [-57.86, 23.86]	
Fassoulaki 2005	41	69	25	40.5	68	28	3.1%	0.50 [-36.46, 37.46]	
Sen 2009a Subtotsi (95% Ci)	9	4	20 110	29	30	20 113	7.0% 20.2%	-20.00 [-33.26, -6.74] -7.73 [-23.80, 8.15]	
Heterogeneity: Tau ² =	137.37; Chi ² =	7.67. df = 3	(P = 0)	.05); l² = 61%					
Test for overall effect:	-		C	,					
2.4.3 Mastectomy									
Fassoulaki 2002	20	31	25	31	54	25	4.8%	-11.00 [-35.41, 13.41]	
Kim 2004	46	26.8	21	34	16	20	6,9%	12.00 [-1.44, 25.44]	
Metry 2008	23.99	12.46	67	35	11	34	8.3%	-11.01 [-15.76, -6.26]	~~
Subtotal (95% CI)			113			79	26.9%	-3.08 [-19.80, 13.63]	•
Heterogeneity: Tau ² = Test for overall effect:	Z = 0.36 (P = 0		2 (P = 1	0.007); i* = 601	70				
2.4.4 Orthopaedic su	• •		-				0.50	* 00 /F 40 0 F 41	
Clarke 2009b	36	3.97	76	29	4	39	8.5%	7.00 [5.46, 8.54]	
Paul 2015 Subtotal (95% Ci)	94.9	29.8	48 124	94.4	30,8	54 93	7.2% 15.8%	0.50 [-11.27, 12.27] 6.48 [3.01, 9.94]	
Heterogeneity: Tau ² = Test for overall effect:			9 = 0.28	i); l² = 13%				···· 1	
2.4.5 Spinal surgery									
Turan 2003a	15.4	7	25	16	7	25	8.4%	-0.60 [-4.48, 3.28]	
Subtotal (95% CI)			25			25	8.4%	-0.60 [-4.48, 3.28]	•
Heterogeneity: Not ap Test for overall effect:		.76)							
2.4.6 Thoracic surge	ny .								
Grosen 2014	23.13	25.71	52	23.03	20.99	52	7.7%	0.10 [-8.92, 9.12]	<u> </u>
Hout 2007	30	74.1	23	15	59.3	28	3.0%	15.00 [-22.41, 52.41]	
Menda 2010	51	61	30	54	63	30	3.8%	-3.00 [-34.38, 28.38]	
Omran 2006	54	38.66	25	76	38.66	25	5.4%	-22.00 [-43.43, -0.57]	
Rapchuk 2010	45	65	27	45	63	27	3.4%	0.00 [-34.14, 34.14]	
Ucak 2011 Subtotal (95% CI)	37	25	20 177	51	66	20 182	3.8% 27.1%	-14.00 [-44.93, 16.93] -2.96 [-10.40, 4.47]	
Heterogeneity: Tau ² = Test for overall effect:			9 = 0.43	l); l² = 0%				•	
Fotal (95% Ci)			609			552	100.6%	-4.34 [-12.47, 3.78]	•
									+
Heterogeneity: Tau ² =	201.10: Chi2 =	692.97, df :	= 16 (P	< 0.00001)* P	= 98%				-100 -50 0 50 100

Appendix 9: Forest plot Nausea

	Gabape Events		Contre Events		Weight	Risk Ratio M-H, Fixed, 95% C	Risk Ratio M-H, Finnd, 95% Cl
2.5.1 Cholecystectomy			_				
Takmaz 2007	9	30	9	15	3.5%	0.50 [0.25, 0.99]	
Subtotal (95% CI)	_	30	_	15	3.5%	0.50 [0.25, 0.99]	
Total events	9		9				
Heterogeneity: Not appli Test for overall effect: Z		= 0.05)					
2.5.2 Hysterectomy							
Ajori 2011	8	69	19	69	5.6%	0.42 [0.20, 0.90]	
Behdad 2012	5	30	5	31	1.4%	1.03 [0.33, 3.21]	
Dierking 2003	12	39	11	32	3.5%	0.90 [0.46, 1.75]	
Durmus 2007	7	25	9	25	2.6%	0.78 [0.34, 1.76]	
Fassoulaki 2006	1	27	5	24	1.6%	0.18 [0.02, 1.42]	
Ghafari 2009	5	33	7	33	2.1%	0.71 [0.25, 2.02]	
Gilron 2004	4	20	12	22	3.4%	0.37 [0.14, 0.95]	
Sekhavet 2009	32	49	37	49	10.9%	0.86 [0.67, 1.12]	
Sen 2009a	9	20	8	20	2.3%		
Turan 2003a	5	25	7	25	2.3%	1.13 [0.55, 2.32]	
Turan 2005a Turan 2006	6	25	2	25	0.6%	0.71 [0.26, 1.95]	
/erma 2008	5	25	4	25	1.2%	3.00 [0.67, 13.46]	
Subtotal (95% CI)	5	387	4	380	37.2%	1.25 [0.38, 4.12] 0.77 [0.63, 0.95]	
· ·	99		126	~~~	84 - 364 - Coge	are faradi kigal	•
Total events Heterogeneity: Chi ² = 12		11/0-7		- 1 40/			
Test for overall effect: Z			.31); ==	- 1470			
2.5.3 Mastectomy							
Doha 2010	2	30	4	29	1.2%	0.48 [0.10, 2.44]	
Grover 2009	12	15	6	21	1.5%	2.80 [1.36, 5.76]	
Kim 2004	8	21	8	20	2.4%	0.95 [0.44, 2.05]	
Subtotal (95% Ci)	-	86	-	70	5.1%	1.38 [0.85, 2.23]	★
Total events	22		18				-
Heterogeneity: Chi ² = 6.7 Test for overall effect: Z			4); ² = 6	8%			
2.5.4 Orthopaedic surg		-					
Clarke 2009b	24	76	14	38	5.5%	0.86 [0.50, 1.46]	
Clarke 2014	26	88	26	77	8.1%	0.88 [0.56, 1.37]	*
Paul 2013	33	52	40	49	12.1%	0.78 [0.61, 0.99]	
Paul 2015	0	0 216	0	0 164	25.7%	Not estimable	
Subtotal (95% CI) Total events	83	A 10	80	104	6.4 .9 79	0.83 (0.66, 1.03)	
Heterogeneity: Chi ² = 0.3 Test for overall effect: Z	31, df = 2			%			
2.5.5 Spinal surgery							
Erten 2010	0	39	0	20		Not estimable	
Khan 2010	12	150	2	25	1.0%	1.00 [0.24, 4.20]	
Khurana 2013	2	30	0	30	0.1%	5.00 [0.25, 99.95]	
Panday 2004a	4	80	1	20	0.5%	1.00 [0.12, 8.46]	
Panday 2004c	5	28	4	28	1.2%	1.25 [0.37, 4.17]	
Radhakrishnan 2005	6	30	6	30	1.8%	1.00 [0.36, 2.75]	
Turan 2003b	5	25	7	25	2.1%	0.71 [0.26, 1.95]	
Özgencil 2011	8	30	7	30	2.1%	1.14 [0.47, 2.75]	
Subtotal (95% CI)		412		208	8.7%	1.07 [0.68, 1.68]	—
Total events Heterogeneity: Chi ² = 1.3 Test for overall effect: Z			27 4); l² = 0	%			
2.5.6 Thoracic surgery							
Grosen 2014	25	52	37	52	10.9%	0.68 [0.49, 0.94]	——————————————————————————————————————
Kosucu 2013	2	29	4	31	1.1%	0.53 [0.11, 2.70]	
Menda 2010	9	30	18	30	5.3%	0.50 [0.27, 0.93]	
Omran 2006	5	50	7	50	2.1%	0.71 [0.24, 2.10]	
Ucak 2011	4	20	2	20	0.6%	2.00 [0.41, 9.71]	
Subtotal (95% CI)	-	181		183	19.9%	0.66 [0.50, 0.88]	\bullet
Total events	45		68				-
Heterogeneity: Chi ^z = 2.3 Test for overall effect: Z	77, df = 4		0); l² = 0	%			
Total (95% CI)		1292		1020	100.0%	0.81 [0.72, 0.92]	♦
Total events	300		328				, , , , , , , , , , , , , , , , , , , ,
Heterogeneity: Chi ² = 34		30 (P = 0 = 0.0008		= 13%			0.01 0.1 1 10 100 Favours Gabapentin Favours Controis

Appendix 10: Forest plot Vomiting

	Events	ntin Total	Contr Events		Weight	Risk Ratio M-H, Fixed, 95% C	Risk Ratio M-H, Fixed, 95% Cl
2.6.1 Cholecystectom	У						
Takmaz 2007	7	30	7	15	4.3%	0.50 [0.21, 1.16]	
Subtotal (95% CI)		30		15	4.3%	0.50 [0.21, 1.16]	
Total events	7		7				
Heterogeneity: Not app	licable						
Test for overall effect: 2	Z = 1.61 (F	° = 0.11					
2.6.2 Hysterectomy							
Ajori 2011	5	69	16	69	7.4%	0.31 [0.12, 0.81]	
Behdad 2012	5	30	7	31	3.2%	0.74 [0.26, 2.07]	
Dierking 2003	18	39	15	32	7.6%	0.98 [0.60, 1.62]	
Durmus 2007	3	25	6	25	2.8%	0.50 [0.14, 1.78]	
Ghafari 2009	4	33	9	33	4.2%	0.44 [0.15, 1.30]	
Sekhavet 2009	18	49	19	49	8.8%	0.95 [0.57, 1.58]	
Sen 2009a	8	20	8	20	3.7%	1.00 [0.47, 2.14]	
Turan 2003a	6	25	9	25	4.2%	0.67 [0.28, 1.59]	
Turan 2006	12	25	18	25	8.3%	0.67 [0.41, 1.07]	
Verma 2008	3	25	4	25	1.9%	0.75 [0.19, 3.01]	
Subtotal (95% CI)		340		334	52.0%	0.71 [0.57, 0.90]	◆
Total events	82		111				
Heterogeneity: Chi ² = 7				1%			
Test for overall effect: 2	z = 2.84 (F	? = 0.00	5)				
2.6.3 Mastectomy							Y AND A STATE OF A STA
Bharti 2012	6	40	9	40	4.2%	0.67 [0.26, 1.70]	
Doha 2010	3	30	5	29	2.4%	0.58 [0.15, 2.21]	
Grover 2009	7	25	7	21	3.5%	0.84 [0.35, 2.01]	
Kim 2004	4	21	2	20	0.9%	1.90 [0.39, 9.28]	***********************************
Metry 2008	2	77	1	34	0.6%	0.88 [0.08, 9.41]	
Subtotal (95% CI)		193		144	11.6%	0.81 [0.48, 1.37]	
Total events Heterogeneity: Chi ^z = 1	22		24				
Test for overall effect: 2 2.6.4 Orthopaedic sur	gery						
Clarke 2009b	9	76 76	7	38 38	4.3%	0.64 [0.26, 1.59]	
Subtotal (95% Cl)		£85					
Total avanta	0		7	90	4.3%	0.64 (0.26, 1.59)	
	9 licable		7	90	4.3%	0.64 (0.26, 1.59)	
Heterogeneity: Not app	licable			30	4.3%	0.64 (0.26, 1.59)	
Heterogeneity: Not app Test for overall effect: 2	licable			36	4.3%	0.64 (0.26, 1.59)	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery	licable Z = 0.95 (F	P = 0.34					
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010	licable)	25 30	4.3% 0.8% 0.9%	0.64 [0.28, 1.59] 1.33 [0.17, 10.21] 0.50 [0.05, 5.22]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013	licable Z = 0.95 (F 8	9 = 0.34 150	1	25	0.8%	1.33 [0.17, 10.21]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a	licable Z = 0.95 (F 8 1	• = 0.34 150 30	1 2 2 4	25 30	0.8% 0.9%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c	licable 2 = 0.95 (F 8 1 7 3 2	9 = 0.34 150 30 80	1 2 2 4 3	25 30 20	0.8% 0.9% 1.5%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b	licable Z = 0.95 (F 8 1 7 3 2 1	9 = 0.34 150 30 28 30 25	1 2 2 4 3 6	25 30 20 30 30 25	0.8% 0.9% 1.5% 1.9% 1.4% 2.8%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencil 2011	licable 2 = 0.95 (F 8 1 7 3 2	2 = 0.34 150 30 80 28 30 25 50	1 2 2 4 3	25 30 20 28 30 25 50	0.8% 0.9% 1.5% 1.9% 1.4% 2.8% 2.3%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI)	licable 2 = 0.95 (F 8 1 7 3 2 1 3	9 = 0.34 150 30 28 30 25	1 2 2 4 3 6 5	25 30 20 30 30 25	0.8% 0.9% 1.5% 1.9% 1.4% 2.8%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004a Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events	licable 2 = 0.95 (F 8 1 7 3 2 1 3 3 2 5	9 = 0.34 150 30 80 28 30 25 50 393	1 2 2 4 3 6 5 23	25 30 20 28 30 25 50 208	0.8% 0.9% 1.5% 1.9% 1.4% 2.8% 2.3%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2	licable 2 = 0.95 (F 8 1 7 3 2 1 3 2 1 3 2 5 2.47, df = 6	2 = 0.34 150 30 80 28 30 25 50 393 6 (P = 0.	1 2 2 4 3 6 5 23 87); ² = (25 30 20 28 30 25 50 208	0.8% 0.9% 1.5% 1.9% 1.4% 2.8% 2.3%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 Test for overall effect: 2	licable Z = 0.95 (F 8 1 7 3 2 1 3 25 2.47, df = 6 Z = 1.60 (F	2 = 0.34 150 30 80 28 30 25 50 393 6 (P = 0.	1 2 2 4 3 6 5 23 87); ² = (25 30 20 28 30 25 50 208	0.8% 0.9% 1.5% 1.9% 1.4% 2.8% 2.3%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004a Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 Test for overall effect: 2 2.6.6 Thoracic surger	licable Z = 0.95 (F 8 1 7 3 2 1 3 25 2.47, df = 6 Z = 1.60 (F	2 = 0.34 150 30 80 28 30 25 50 393 6 (P = 0.	1 2 2 4 3 6 5 23 87); ² = (25 30 20 28 30 25 50 208	0.8% 0.9% 1.5% 1.9% 1.4% 2.8% 2.3%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencii 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 Test for overall effect: 2 2.6.6 Thoracic surger; Grosen 2014	licable Z = 0.95 (F 8 1 7 3 2 1 3 25 2.47, df = € Z = 1.60 (F	150 30 80 28 30 25 50 393 6 (P = 0. 11)	1 2 4 3 6 5 23 87); ² = (25 30 20 28 30 25 50 208	0.8% 0.9% 1.5% 1.9% 1.4% 2.8% 2.3%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 0.61 [0.33, 1.12]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 Test for overall effect: 2 2.6.6 Thoracic surger; Grosen 2014 Kosucu 2013	licable Z = 0.95 (F 8 1 7 3 2 1 3 25 2.47, df = 6 Z = 1.60 (F ¥ 23	2 = 0.34 150 30 80 28 30 25 50 393 6 (P = 0. 2 = 0.11 52	1 2 2 4 3 6 5 23 87); ² = (25 30 28 30 25 50 208 0%	0.8% 0.9% 1.5% 1.4% 2.8% 2.3% 11.5%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 0.61 [0.33, 1.12]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 Test for overall effect: 2 2.6.6 Thoracic surger Grosen 2014 Kosucu 2013 Menda 2010	licable Z = 0.95 (F 8 1 7 3 2 1 3 25 2.47, df = 6 Z = 1.60 (F Y 23 7	2 = 0.34 150 30 80 28 30 25 50 393 6 (P = 0. 2 = 0.11 52 29	1 2 2 4 3 6 5 23 87); ² = () 22 4	25 30 28 30 25 50 208 0% 52 31	0.8% 0.9% 1.5% 1.4% 2.8% 2.3% 11.5%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 0.61 [0.33, 1.12] 1.05 [0.67, 1.62] 1.87 [0.61, 5.73]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004a Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 Test for overall effect: 2 2.6.6 Thoracic surger; Grosen 2014 Kosucu 2013 Menda 2010 Omran 2006 Ucak 2011	licable Z = 0.95 (F 8 1 7 3 25 2.47, df = 6 Z = 1.60 (F Y 23 7 0	150 30 80 28 30 25 50 393 (P = 0. 11) 52 29 30 50 20	1 2 2 4 3 6 5 23 87); ² = () 22 4 0	25 30 20 28 30 25 50 268 30 8 52 31 30 50 20 20 20	0.8% 0.9% 1.9% 1.4% 2.8% 2.3% 11.5% 10.2% 1.8% 3.2% 0.9%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 6.81 [0.33, 1.12] 1.05 [0.67, 1.62] 1.87 [0.61, 5.73] Not estimable 0.14 [0.02, 1.12] 2.00 [0.41, 9.71]	
Total events Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004a Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 Test for overall effect: 2 2.6.6 Thoracic surger; Grosen 2014 Kosucu 2013 Menda 2010 Omran 2006 Ucak 2011 Subtotal (95% CI)	licable Z = 0.95 (F 8 1 7 3 25 247, df = 6 Z = 1.60 (F ¥ 2 2 1 7 0 1 4	2 = 0.34 150 30 80 28 30 25 50 393 (P = 0. 11 52 29 30 50	1 2 2 4 3 6 5 23 87); ² = () 22 4 0 7 2	25 30 20 28 30 25 50 208 0% 52 31 30 50	0.8% 0.9% 1.5% 1.4% 2.3% 14.5% 14.5%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 0.61 [0.33, 1.12] 1.05 [0.67, 1.62] 1.87 [0.61, 5.73] Not estimable 0.14 [0.02, 1.12]	
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Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 2.6.6 Thoracic surger Grosen 2014 Kosucu 2013 Menda 2010 Omran 2006 Ucak 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5	licable Z = 0.95 (F 8 1 7 3 2 2 4 2 2 1 3 2 2 5 2 4 7 0 1 2 2 3 2 2 5 2 4 7 7 3 2 2 2 5 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 4 7 4 7 5 5 7 7 4 7 4 7 4 7 4 7 7 7 7 7 7 7 7 7 7 7 7 7	2 = 0.34 150 30 80 28 30 25 50 393 6 (P = 0. 29 30 50 20 181 6 (P = 0.	1 2 4 3 6 5 23 87); ² = () 22 4 0 7 2 15); ² = 2	25 30 20 28 30 25 50 208 30% 50 208 31 30 50 208 31 30 50 208 31 30 50 208 31 30 50 208 31 30 208 31 208 25 50 208 25 50 200 25 50 25 200 25 25 200 25 25 25 200 25 25 25 25 25 25 25 25 25 25 25 25 25	0.8% 0.9% 1.9% 1.4% 2.8% 2.3% 11.5% 10.2% 1.8% 3.2% 0.9%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 6.81 [0.33, 1.12] 1.05 [0.67, 1.62] 1.87 [0.61, 5.73] Not estimable 0.14 [0.02, 1.12] 2.00 [0.41, 9.71]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004a Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 Test for overall effect: 2 2.6.6 Thoracic surger; Grosen 2014 Kosucu 2013 Menda 2010 Omran 2006 Ucak 2011	licable Z = 0.95 (F 8 1 7 3 2 2 4 2 2 1 3 2 2 5 2 4 7 0 1 2 2 3 2 2 5 2 4 7 7 3 2 2 2 5 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 4 7 4 7 5 5 7 7 4 7 4 7 4 7 4 7 7 7 7 7 7 7 7 7 7 7 7 7	2 = 0.34 150 30 80 28 30 25 50 393 6 (P = 0. 29 30 50 20 181 6 (P = 0.	1 2 4 3 6 5 23 87); ² = () 22 4 0 7 2 15); ² = 2	25 30 20 28 30 25 50 268 31 30 50 208 31 30 50 203 44%	0.8% 0.9% 1.9% 1.4% 2.8% 2.3% 11.5% 10.2% 1.8% 3.2% 0.9%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.05] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 6.81 [0.33, 1.12] 1.05 [0.67, 1.62] 1.87 [0.61, 5.73] Not estimable 0.14 [0.02, 1.12] 2.00 [0.41, 9.71]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 2.6.6 Thoracic surger) Grosen 2014 Kosucu 2013 Menda 2010 Omran 2006 Ucak 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5 Test for overall effect: 2	licable Z = 0.95 (F 8 1 7 3 2 2 4 2 2 1 3 2 2 5 2 4 7 0 1 2 2 3 2 2 5 2 4 7 7 3 2 2 2 5 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 3 2 2 5 5 7 4 7 4 7 5 5 7 7 4 7 4 7 4 7 4 7 7 7 7 7 7 7 7 7 7 7 7 7	150 30 80 28 30 25 50 393 6 (P = 0. 2 = 0.11) 52 29 30 50 20 181 6 (P = 0. 20	1 2 4 3 6 5 23 87); ² = () 22 4 0 7 2 15); ² = 2	25 30 20 28 30 25 50 268 31 30 50 208 31 30 50 203 44%	0.8% 0.9% 1.9% 2.8% 2.3% 11.5% 10.2% 1.8% 3.2% 0.9% 16.1%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.06] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 0.61 [0.33, 1.12] 1.05 [0.67, 1.62] 1.87 [0.61, 5.73] Not estimable 0.14 [0.02, 1.71] 1.01 [0.69, 1.49]	
Heterogeneity: Not app Test for overall effect: 2 2.6.5 Spinal surgery Khan 2010 Khurana 2013 Panday 2004a Panday 2004c Radhakrishnan 2005 Turan 2003b Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 2 2.6.6 Thoracic surgery Grosen 2014 Kosucu 2013 Menda 2010 Omran 2006 Ucak 2011 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 5 Test for overall effect: 2 Total (95% CI)	licable Z = 0.95 (F 8 1 7 3 25 247, df = 6 Z = 1.60 (F 23 7 0 1 4 35 5.37, df = 3 Z = 0.05 (F 180 11.40, df =	2 = 0.34 150 30 80 25 50 393 6 (P = 0. 29 30 20 181 6 (P = 0. 20 1213 27 (P =	1 2 4 3 6 5 23 87); $ ^2 = 0$ 22 4 0 7 2 35 15); $ ^2 = 4$ 207 0.77); $ ^2$	25 30 28 30 25 208 30 208 30 20 183 30 50 20 183 44% \$22	0.8% 0.9% 1.9% 2.8% 2.3% 11.5% 10.2% 1.8% 3.2% 0.9% 16.1%	1.33 [0.17, 10.21] 0.50 [0.05, 5.22] 0.88 [0.20, 3.89] 0.75 [0.18, 3.06] 0.67 [0.12, 3.71] 0.17 [0.02, 1.29] 0.60 [0.15, 2.38] 0.61 [0.33, 1.12] 1.05 [0.67, 1.62] 1.87 [0.61, 5.73] Not estimable 0.14 [0.02, 1.71] 1.01 [0.69, 1.49]	

Appendix II: Forest plot Sedation

	Events	ntin Total	Contr Evente		Weight	Risk Ratio M-H, Random, 95% C	Risk Ratio M-H, Random, 95% Cl
2.12.1 Cholecystecton	~						
Mishra 2016	12	30	4	30	4.4%	3.00 [1.09, 8.25]	
Neogi 2012	1	30	0	30	0.7%	3.00 [0.13, 70.83]	v
Panday 2004b	52	153	5	153	5.1%	10.40 [4.27, 25.32]	
Panday 2006	4	125	2	125	2,2%	2.00 [0.37, 10.72]	
Srivastava 2010	14	60	8	60	5.7%	1.75 [0.79, 3.86]	
Takmaz 2007	5	30	1	15	1.6%	2.50 [0.32, 19.53]	
Subtotal (95% Cl)		428		413	19.8%	3.28 [1.55, 6.94]	
Total events	88		20				
Heterogeneity: Tau ² = 0 Test for overall effect: Z				= 0.07); l² = 50%	, D	
2.12.2 Hysterectomy							
Ajori 2011	0	69	0	69		Not estimable	
Ghafari 2009	2	33	3	33	2.1%	0.67 [0.12, 3.73]	
Ghai 2011	10	30	12	30	6.5%	0.83 [0.43, 1.63]	
Ray 2015	0	30	0	30		Not estimable	
Rorarius 2004	14	38	12	37	6.8%	1.14 [0.61, 2.12]	
Sekhavet 2009	26	49	22	49	8.4%	1.18 [0.79, 1.78]	
Sen 2009a	- 3	20	3	20	2.7%	1.00 [0.23, 4.37]	
Turan 2003a	1	25	0	25	0.8%	3.00 [0.13, 70.30]	·····
Subtotal (95% CI)		294	v	293	27.3%	1.08 [0.81, 1.45]	•
Total events	56		52			form of second	ſ
Heterogeneity: Tau ² = 0		-151 +		-0.94	l² = ∩%		
Test for overall effect: Z				0.01),	. — 4 74		
2.12.3 Mastectomy							
Dirks 2002	21	31	22	34	8.8%	1.05 [0.74, 1.48]	
Kim 2004	5	21	5	20	4.1%	0.95 [0.32, 2.80]	
Subtotal (95% CI)		52		54	12.9%	1.04 [0.75, 1.44]	◆
Total events	26		27				
Heterogeneity: Tau ² = 0		= 0.03. d		= 0,86)-	$l^2 = 0\%$		
Clarke 2009b Paul 2013	18 35	76 52	7 35	38 49	5.7% 9.4%	1.29 [0.59, 2.81] 0.94 [0.73, 1.22]	
Subtatal (85% CB							
		128		87	15.1%	0.97 [0.76, 1.24]	†
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2	53).00; Chi² =	128 = 0.66, d	42	87	15.1%		•
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery	53 0.00; Chi² = 2 = 0.23 (P	128 = 0.66, d = 0.82)	42 f = 1 (P =	87 = 0.42);	15.1%	0.97 [0.76, 1,24]	•
Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2 2.12.5 Spinal surgery Erten 2010	53 0.00; Chi² = 2 = 0.23 (P 0	128 = 0.66, d = 0.82) 39	42 f = 1 (P = 0	87 = 0.42); 20	15.1% I² = 0%		•
Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2 2.12.5 Spinal surgery Erten 2010	53 0.00; Chi² = 2 = 0.23 (P	128 = 0.66, d = 0.82)	42 f = 1 (P =	87 = 0.42);	15.1%	0.97 [0.76, 1,24]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010	53 0.00; Chi ^x = 2 = 0.23 (P 0 8 4	128 = 0.66, d = 0.82) 39	42 F = 1 (P = 0 1 0	\$7 = 0.42); 20 25 30	15.1% I² = 0%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.17]	•
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khurana 2013	53 0.00; Chi ^z = 2 = 0.23 (P 0 8 4 0	128 = 0.66, d = 0.82) 39 125 30 80	42 f = 1 {P = 0 1 0 0	87 = 0.42); 20 25 30 20	15.1% ² = 0% 1.6%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23]	•
Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2 2.12.5 Spinal surgery Erten 2010 Khar 2010 Khurana 2013 Panday 2004a	53 0.00; Chi ^x = 2 = 0.23 (P 0 8 4	128 = 0.66, d = 0.82) 39 125 30	42 F = 1 (P = 0 1 0	\$7 = 0.42); 20 25 30	15.1% ² = 0% 1.6%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.17]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005	53 0.00; Chi ^z = 2 = 0.23 (P 0 8 4 0	128 = 0.66, d = 0.82) 39 125 30 80	42 f = 1 {P = 0 1 0 0	87 = 0.42); 20 25 30 20	15.1% ² = 0% 1.6% 0.9%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.17] Not estimable	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b	53 0.00; Chi ^z = 2 = 0.23 (P 0 8 4 0 1	128 = 0.66, d = 0.82) 39 125 30 80 30	42 f = 1 {P = 0 1 0 0 1	\$7 = 0.42); 20 25 30 20 30	\$5.\$% ² = 0% 1.6% 0.9% 1.0%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.7] Not estimable 1.00 [0.07, 15.26]	······································
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011	53 0.00; Chi [*] = 2 = 0.23 (P 0 8 4 0 1 2	128 = 0.66, d = 0.82) 39 125 30 80 30 25	42 f = 1 (P = 0 1 0 1 1 1	\$7 = 0.42); 20 25 30 20 30 25 40 30	\$5.\$% ² = 0% 1.6% 0.9% 1.0% 1.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.17] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khara 2010 Khara 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencii 2011	53 0.00; Chi [*] = 2 = 0.23 (P 0 8 4 0 1 2 16	128 = 0.86, d = 0.82) 39 125 30 80 30 25 36	42 f = 1 (P = 0 1 0 0 1 1 0	\$7 20 25 30 20 30 25 40	\$5.\$% ² = 0% 1.6% 0.9% 1.0% 1.3% 0.9%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.17] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khara 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Subtotal (95% CI)	53 0.00; Chi [*] = 2 = 0.23 (P 0 8 4 0 1 2 16	128 = 0.66, d = 0.82) 39 125 30 80 30 25 36 30	42 f = 1 (P = 0 1 0 0 1 1 0	\$7 = 0.42); 20 25 30 20 30 25 40 30	\$5.\$% ² = 0% 1.6% 0.9% 1.0% 1.3% 0.9% 4.5%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.77] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0	53 0.00; Chi ^z = 2 = 0.23 (P 0 8 4 0 1 2 16 8 39 0.54; Chi ² =	128 = 0.66, d = 0.82) 39 125 30 80 30 25 36 30 39% = 7.47, d	42 f == 1 (P = 0 1 0 0 1 1 0 5 8	87 20 25 30 20 30 25 40 30 25	\$5.\$% ² = 0% 1.6% 0.9% 1.0% 1.3% 0.9% 4.5% \$8.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.77] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khan 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Substata (§5% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z	53 0.00; Chi ^z = 0.23 (P 0 8 4 0 1 2 16 8 39 0.54; Chi ^z = 1.83 (P	128 = 0.66, d = 0.82) 39 125 30 80 30 25 36 30 39% = 7.47, d	42 f == 1 (P = 0 1 0 0 1 1 0 5 8	87 20 25 30 20 30 25 40 30 25	\$5.\$% ² = 0% 1.6% 0.9% 1.0% 1.3% 0.9% 4.5% \$8.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.77] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Özgencil 2011 Özgencil 2011 Subtotal (§ő% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.6 Thoracic surger	53 0.00; Chi ^z = 0.23 (P 0 8 4 0 1 2 16 8 39 0.54; Chi ^z = 1.83 (P	128 = 0.66, d = 0.82) 39 125 30 80 30 25 36 30 39% = 7.47, d	42 f == 1 (P = 0 1 0 0 1 1 0 5 8	87 20 25 30 20 30 25 40 30 25	\$5.\$% ² = 0% 1.6% 0.9% 1.0% 1.3% 0.9% 4.5% \$8.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.17] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33] 2.85 [0.94, 7.52]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.6 Thoracic surger Grosen 2014	53 .00; Chi ² = 0.23 (P 0 8 4 0 1 2 16 8 39 .54; Chi ² = 1.83 (P ^{ry} 10	128 = 0.66, d = 0.82) 39 125 30 80 30 25 36 30 39% = 7.47, d = 0.07) 52	42 f = 1 (P = 0 1 0 0 1 1 5 5 f = 5 (P =	87 20 25 30 20 30 20 30 25 40 30 228 = 0.19);	\$5.\$% ² = 0% 1.6% 0.9% 1.0% 1.3% 0.9% 4.5% \$8.3% ² = 33% 5.1%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.77] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33] 2.85 [0.94, 7.52]	
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Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Özgencil 2011 Subtotal (\$5% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.6 Thoracic surger Grosen 2014 Kinney 2011 Kosucu 2013 Omran 2006 Ucak 2011	53 0.00; Chi2 = 0.23 (P 0 8 4 0 1 2 16 8 39 0.54; Chi2 = 1.83 (P ry 10 10 2	128 = 0.66, d = 0.82) 39 125 30 30 25 36 30 398 = 7.47, d = 0.07) 52 57 29 50 20	42 f = 1 (P = 0 1 0 0 1 1 0 5 f = 5 (P = 7 10 1	\$7 200 25 30 20 20 25 40 30 229 = 0.19); 52 63 31 50 20 20 20 22 229 229 229 229 229 229 22	\$5.1% ² = 0% 1.6% 0.9% 1.0% 1.3% 0.9% 4.5% \$0.3% ² = 33% 5.1% 5.6% 1.3% 1.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.7] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33] 2.65 [0.94, 7.52] 1.43 [0.59, 3.47] 1.11 [0.50, 2.46] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 2.00 [0.20, 20.33]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.6 Thoracic surger Grosen 2014 Kinney 2011 Kosucu 2013 Omran 2006 Ucak 2011 Subtotal (95% CI)	53 0.00; Chi [#] = 2 = 0.23 (P 0 8 4 0 1 2 16 8 39 0.54; Chi ² = 2 = 1.83 (P Fy 10 10 2 2 2	128 = 0.66, d = 0.82) 39 125 30 80 30 25 36 30 395 = 7,47, d = 0.07) 52 57 29 50	42 f = 1 (P = 0 1 0 0 1 1 0 5 5 f = 5 (P = 7 10 1 1 1 1	87 200 25 30 200 20 300 20 300 25 400 300 25 400 30 25 400 30 30 25 400 30 30 30 30 30 30 30 30 30 30 30 30 3	\$5.\$% ² = 0% 1.6% 0.9% 1.0% 1.3% 4.5% \$0.3% ² = 33% 5.1% 5.6% 1.3% 1.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.77] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33] 2.65 [0.94, 7.52] 1.43 [0.59, 3.47] 1.11 [0.50, 2.46] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.6 Thoracic surger Grosen 2014 Kinney 2011 Kosucu 2013 Omran 2006 Ucak 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0	53 .00; Chi [#] = 2 = 0.23 (P 0 8 4 0 1 2 16 8 39 .54; Chi [#] = 10 10 2 2 2 2 26 .00; Chi [#] =	128 = 0.66, d = 0.82) 39 125 30 30 25 36 30 395 = 7.47, d = 0.07) 52 57 29 50 20 208 = 0.62, d	42 f = 1 (P = 0 1 0 0 1 1 1 5 f = 5 (P = 7 10 1 1 1 1 1 20	\$7 20 25 30 20 20 30 20 30 25 40 30 228 = 0.19); 52 52 33 31 50 20 218	\$5.1% $ ^2 = 0\%$ 1.6% 0.9% 1.0% 1.3% 0.9% 4.5% 10.3% 1.3% 1.2% 1.3% 1.3% 1.3% 1.3% 1.3% 1.3% 1.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.7] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33] 2.65 [0.94, 7.52] 1.43 [0.59, 3.47] 1.11 [0.50, 2.46] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 2.00 [0.20, 20.33]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencil 2011 Özgencil 2011 Subtotal (\$5% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.6 Thoracic surger Grosen 2014 Kinney 2011 Kosucu 2013 Omran 2006 Ucak 2011	53 .00; Chi [#] = 2 = 0.23 (P 0 8 4 0 1 2 16 8 39 .54; Chi [#] = 10 10 2 2 2 2 26 .00; Chi [#] =	128 = 0.66, d = 0.82) 39 125 30 30 25 36 30 395 = 7.47, d = 0.07) 52 57 29 50 20 208 = 0.62, d	42 f = 1 (P = 0 1 0 0 1 1 1 5 f = 5 (P = 7 10 1 1 1 1 1 20	\$7 20 25 30 20 25 40 30 25 40 30 25 40 30 25 40 30 25 40 30 25 25 26 33 31 50 20 21 52 63 31 50 21 52 63 52 52 52 53 52 53 52 53 52 55 53 53 53 53 53 53 53 53 53 53 53 53	\$5.1% $ ^2 = 0\%$ 1.6% 0.9% 1.0% 1.3% 0.9% 4.5% 10.3% 1.3% 1.2% 1.3% 1.3% 1.3% 1.3% 1.3% 1.3% 1.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.7] Not estimable 1.00 [0.07, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33] 2.65 [0.94, 7.52] 1.43 [0.59, 3.47] 1.11 [0.50, 2.46] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 2.00 [0.20, 20.33]	
Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.5 Spinal surgery Erten 2010 Khan 2010 Khurana 2013 Panday 2004a Radhakrishnan 2005 Turan 2003b Vahedi 2011 Özgencii 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z 2.12.6 Thoracic surger Grosen 2014 Kinney 2011 Kosucu 2013 Omran 2006 Ucak 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: Z	53 .00; Chi [#] = 2 = 0.23 (P 0 8 4 0 1 2 16 8 39 .54; Chi [#] = 10 10 2 2 2 2 26 .00; Chi [#] =	128 = 0.66, d = 0.82) 39 125 30 80 30 25 36 30 398 = 7.47, d = 0.07) 52 57 29 50 20 208 = 0.62, d = 0.29)	42 f = 1 (P = 0 1 0 0 1 1 1 0 5 f = 5 (P = 7 10 1 1 1 1 1 20	\$7 20 25 30 20 25 40 30 25 40 30 25 40 30 25 40 30 25 40 30 25 25 26 33 31 50 20 21 52 63 31 50 21 52 63 52 52 52 53 52 53 52 53 52 55 53 53 53 53 53 53 53 53 53 53 53 53	\$5.1% $ ^2 = 0\%$ 1.6% 0.9% 1.0% 1.3% 0.9% 4.5% 10.3% 1.3%	0.97 [0.76, 1.24] Not estimable 1.60 [0.21, 12.23] 9.00 [0.51, 160.17] Not estimable 1.00 [0.77, 15.26] 2.00 [0.19, 20.67] 36.57 [2.27, 588.35] 1.60 [0.59, 4.33] 2.65 [0.94, 7.52] 1.43 [0.59, 3.47] 1.11 [0.50, 2.46] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 2.00 [0.29, 20.33] 1.34 [0.78, 2.32]	

Appendix 12: Forest plot Dizziness

Study or Subgroup	- 1	ntin	Contr			Risk Ratio	Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% C	i M-H, Random, 95% Cl
2.13.1 Cholecystectom	У						***
Bekawi 2014	17	30	25	30	11.8%	0.68 [0.48, 0.97]	
Mishra 2016	3	30	6	30	0.9%	0.50 [0.14, 1.82]	
Neogi 2012	1	30	1	30	0.2%	1.00 [0.07, 15.26]	
Panday 2004b	Ó	153	Ó	153	*-= **	Not estimable	
Srivastava 2010	5	60	7	60	1.2%	0.71 [0.24, 2.13]	
Takmaz 2007	12	30	7	15	3.0%	0.86 [0.43, 1.72]	······
Subtotal (95% CI)	12	333	'	318	17.1%	0.70 [0.52, 0.94]	
		where a	40	414	15.14.20	or o forma moved	•
Total events	38		46				
Heterogeneity: Tau ² = 0.				= 0.95)	; F = 0%		
Test for overall effect: Z	= 2.37 (P	= 0.02)					
2.13.2 Hysterectomy							
Ajori 2011	0	69	0	69		Not estimable	
Behdad 2012	0	30	0	31		Not estimable	
Dierking 2003	23	39	15	32	7.1%	1.26 [0.80, 1.98]	
Fassoulaki 2005	1	25	0	28	0.1%	3.35 [0.14, 78.60]	
Ghafari 2009	2	33	2	33	0,4%	1.00 [0.15, 6.68]	
Ghai 2011	8	30	1	30	0.4%	8.00 [1.07, 60.09]	
Ray 2015	2	30	2	30	0.4%	1.00 [0.15, 6.64]	·····
Rorarius 2004	6	38	4	37	1.0%	1.46 [0.45, 4.76]	
Sekhavet 2009	5	49	7	49	1.3%	0.71 [0.24, 2.10]	
							<u> </u>
Sen 2009a	2	20	2	20	0.4%	1.00 [0.16, 6.42]	3
Turan 2003a	2	25	1	25	0.3%	2.00 [0.19, 20.67]	
Turan 2006	6	25	2	25	0.6%	3.00 [0.67, 13.46]	
Verma 2008	1	25	0	25	0.1%	3.00 [0.13, 70.30]	
Subtotal (95% CI)		438		434	12.2%	1.34 [0.95, 1.89]	•
Total events	58		36				sa na sa
Heterogeneity: Tau ² = 0.	00; Chi² =	= 6.78, d	lf = 10 (F	° = 0.75	5); l² = 0%		2444
Test for overall effect: Z	= 1.67 (P	= 0.10}	•				
	•	,					v.awaa
2.13.3 Mastectomy							
Azemati 2013	14	50	14	50	3.7%	1.00 [0.53, 1.87]	
Dirks 2002	11	31	14	34	3.8%	0.86 [0.46, 1.60]	
Doha 2010	8	30	2	29	0.7%	3.87 [0.90, 16.70]	
Grover 2009	10	25	7	21	2.4%	1.20 [0.55, 2.60]	
Kim 2004	8	21	, 9	20	2.7%	0.85 [0.41, 1.76]	
Subtotal (95% CI)	0	157	3	154	13.3%	1.03 [0.74, 1.43]	📥
	54	e or n	40	1.00	1000000	the farmer track	T
Total events	51	- 4 04 -	46	- 0 400	12 - 09/		
Heterogeneity: Tau ² = 0.			n = 4 (r*	- 0.40)	i, i= − 07α		¥
Test for overall effect: Z	- U. ID (P	~ U.CO)					
2.13.4 Orthansedia our	ante						
2.13.4 Orthopsedic sur			5	20	0.79/	4 40 10 27 0 403	
Clarke 2009b	19	76	8	38	2.7%	1.19 [0.57, 2.46]	
Clarke 2009b Clarke 2014	19 2	88	12	77	0.7%	0.15 [0.03, 0.63]	
Clarke 2009b Clarke 2014 Paul 2013	19	88 52		77 49	0.7% 12.4%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (95% CI)	19 2 29	88	12 28	77	0.7%	0.15 [0.03, 0.63]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (95% Cl) Total events	19 2 29 50	88 52 216	12 28 48	77 49 164	0.7% 12.4% 15.8%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (85% Cl) Total events Heterogeneity: Tau ² = 0.	19 2 29 50 36; Chl ² :	88 52 216 = 7.37, d	12 28 48 If = 2 (P	77 49 164	0.7% 12.4% 15.8%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (95% Cl) Total events	19 2 29 50 36; Chl ² :	88 52 216 = 7.37, d	12 28 48 If = 2 (P	77 49 164	0.7% 12.4% 15.8%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (85% Cl) Total events Heterogeneity: Tau ² = 0.	19 2 29 50 36; Chl ² :	88 52 216 = 7.37, d	12 28 48 If = 2 (P	77 49 164	0.7% 12.4% 15.8%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (85% Cl) Total events Heterogeneity: Tau ² = 0.	19 2 29 50 36; Chl ² :	88 52 216 = 7.37, d	12 28 48 If = 2 (P	77 49 164	0.7% 12.4% 15.8%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (85% Cl) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z 2.13.5 Spinal surgery	19 2 29 50 36; Chl ² ± ≈ 0.76 (P	88 52 218 = 7.37, d = 0.45)	12 28 48 If = 2 (P	77 49 164 = 0.03)	0.7% 12.4% 15.8% ; i² = 73%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37] 8.72 [0.32, 1.66]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (85% Cl) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z 2.13.5 Spinal surgery Khan 2010	19 2 29 50 36; Chl ² = = 0.76 (P	88 52 218 = 7.37, d = 0.45) 125	12 28 48 If = 2 (P	77 49 164 = 0.03) 25	0.7% 12.4% 15.8%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37] 0.72 [0.32, 1.86] 1.00 [0.12, 8.20]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (95% Ci) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z 2.13.5 Spinal surgery Khan 2010 Leung 2006	19 2 29 50 36; Chl ² : = 0.76 (P 5 0	88 52 218 = 7.37, d = 0.45) 125 12	12 28 48 If = 2 (P 1 0	77 49 164 = 0.03) 25 9	0.7% 12.4% 15.8% ; i² = 73%	0.15 (0.03, 0.63) 0.98 (0.69, 1.37) 0.72 [0.32, 1.46] 1.00 [0.12, 8.20] Not estimable	
Clarke 2009b Clarke 2014 Paul 2013 Substrati (95% Cl) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z 2.13.5 Spinal surgery Khan 2010 Leung 2006 Panday 2004a	19 2 29 50 36; Chi² ≠ ≈ 0.76 (P 5 0 0	88 52 21\$ = 7.37, d = 0.45) 125 12 80	12 28 48 If = 2 (P 1 0 0	77 49 164 = 0.03) 25 9 20	0.7% 12.4% 15.\$% ; ² = 73% 0.3%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37] 0.72 [0.32, 1.46] 1.00 [0.12, 8.20] Not estimable Not estimable	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (85% Cl) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z 2.13.5 Spinal surgery Khan 2010 Leung 2006 Panday 2004a Panday 2004c	19 2 29 36; Chi ^a : = 0.76 (P 5 0 0 1	88 52 218 = 7.37, d = 0.45) 125 12 80 28	12 28 48 If = 2 (P 1 0 0 0	77 49 164 = 0.03) 25 9 20 28	0.7% 12.4% 15.8% ; I ² = 73% 0.3% 0.1%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37] 0.72 [0.32, 1.46] 1.00 [0.12, 8.20] Not estimable 3.00 [0.13, 70.64]	
Clarke 2009b Clarke 2014 Paul 2013 Subtotal (95% Ci) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z 2.13.5 Spinal surgery Khan 2010 Leung 2006 Panday 2004a Panday 2004c Turan 2003b	19 2 29 36; Chi ² = = 0.76 (P 5 0 0 1 6	88 52 218 = 7.37, d = 0.45) 125 12 80 28 25	12 28 48 ff = 2 (P 1 0 0 0 4	77 49 164 = 0.03) 25 9 20 28 25	0.7% 12.4% 15.8%); l ² = 73% 0.3% 0.1% 1.1%	0.15 [0.03, 0.63] 0.98 [0.69, 1.37] 0.72 [0.32, 1.46] 1.00 [0.12, 8.20] Not estimable Not estimable 3.00 [0.13, 70.64] 1.50 [0.48, 4.68]	
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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. CRD4201300653812.²⁰

Literature search

Our comprehensive search strategy was planned by a trial search coordinator and reported in the published systematic review²¹ 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.

<u>Data</u>

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.

<u>Analyses</u>

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.

<u>Outcomes</u>

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 morphinesparing 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 followup 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 I: The estimates on primary outcomes from trials with low risk of bias and from all trials despite risk of bias

011								
Surgical	Dose 0-350 mg		Dose 351-700 m	g	701-1050 mg		>1050 mg	
procedure								
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 <i>P-value</i>	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 OUT	COMES							
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. Cl: .0.1, 4.6; 191%)	P = 0.69	3.4 mg (0.9, 7.7; p=0.12; 7 trials; 700 participants; TSA adj. Cl: -3.3, 11.6; 44%)	P = 0.33	- 1.1 mg (-0.3, -2.0; p=0.01; 2 trials; 181 participants; TSA adj. Cl: 0.3, 2.0; 329%)	P = 0.002	2.9 mg (1.1, 6.9; p=0.2; 4 trials; 326 participants; TSA adj. Cl: -1.4, 5.6; 89.6%)	P = 0.9
24-hour morphine consumption <i>All trials</i>	8.0 mg (6.2, 9.8; p<0.00001; 11 trials; 1070 participants; TSA adj. Cl: 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. Cl: 3.1, 6.1; 389%)	P = 0.004	2.6 mg (-1.4, 6.6; p=0.2; 7 trials; 375 participants; TSA adj. Cl: - 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. Cl: 7.2, 11; 245.6%)	P = 0.02
HARMFUL OUTCO Serious adverse	OMES Not estimable		0.9	P = 0.44	0.6	P = 0.52	2.0	P = 0.29
events Trials with low risk of bias	(2 trials, 113 participants)	-	(0.2, 3.4; P= 0.85; 4 trials; 404 participants; TSA adj. Cl: 0.0, 220.8; 18.1%)		(0.04, 8.6; p = 0.70; 1 trial; 121 patients; TSA adj)		2.0 (0.9, 4.5; p=0.1; 3 trials; 287 participants; TSA adj. Cl: 0.1, 40.0; 17.8%)	
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. Cl: 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	I.3 (0.8, 2.4; p=0.33; I3 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. Cl: Trial Sequential Analysis adjusted Confidence Interval

BENEFICIAL	0-350 mg		351-700 mg		701-1050 mg		> 1050 mg	
OUTCOMES								
	Reduction (mm) MD Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference <i>P-valu</i> e	Reduction (mm) MD Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference <i>P-value</i>	Reduction (mm) MD Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference <i>P-valu</i> e	Reduction (mm) MD Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference <i>P-valu</i> e
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. Cl: -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. Cl: -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. Cl: 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. Cl: 10.7, 20.0; 175%)	P = 0.05	6.0 mm (2.7, 9.3; p = 0.0003; 7 trials; 294 participants; TSA adj. Cl: 0.9, 11.1; 330%)	P = 0.006	9.4 mm (5.6, 13.3; p < 0.00001; 27 trials; 1519 participants; TSA adj. Cl: 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. Cl -)	-	12.4 mm (8.0; 16.8 p <0.0001; 3 trials; 227 participants; TSA adj. Cl: 8.0, 16.1; 258%)	P = 0.16	-	-	3.8 mm (-7.9, 15.4; p=0.53; 3 trials; 206 participants; TSA adj. Cl: -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. Cl: -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. Cl: 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. Cl: -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. Cl: 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. Cl: -)	P = 0.02	3.9 mm (-0.1, 7.9; p = 0.05; 5 trials; 526 participants; TSA adj. Cl: -0.1, 7.9; 268%)	P = 0.005	-	-	I.8 mm (-3.4, 7.0; p = 0.51; 4 trials; 331 participants; TSA adj. Cl: -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. Cl: 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. Cl: -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. Cl: 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
			108					

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

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

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

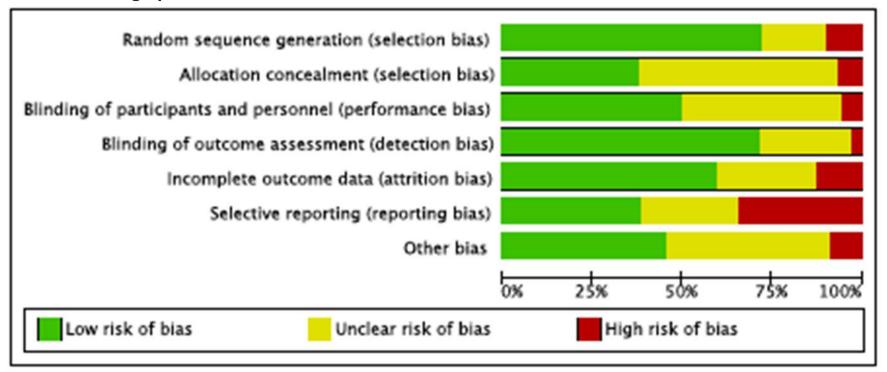
HARMFULL OUTCOMES	0-350 mg		351-700 mg		701-1050 mg		> 1050 mg	
	RR Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference <i>P-value</i>	RR Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference <i>P-valu</i> e	RR Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference <i>P-valu</i> e	RR Estimate (95% Cl; p-value; trials; participants; TSA adj. Cl; accrued percentage of required information size)	Test for subgroup difference <i>P-value</i>
Nausea Low risk of bias	-	-	0.8 (0.4, 1.6; p = 0.54; 3 trials; 218 participants; TSA adj. Cl: 1.9, 15.6; 72.9%)	P = 0.66	-	-	0.7 (0.5, 0.9; p =0.02; 2 trials; 180 participants; TSA adj. Cl: 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. Cl: 0.7, 1.1; 70.6%)	P = 0.42	0.8 (0.6, 1.1; p = 0.10; 15 trials; 1019 participants; TSA adj. Cl: 0.5, 1.3; 40.0%)	P = 0.82	0.8 (0.5, 1.4; p = 0.51; 4 trials; 271 participants; TSA adj. Cl: 0.1, 7.2; 12.8%)	P = 0.91	0.8 (0.6, 0.9; p = 0.003; 21 trials; 1203 participants; TSA adj. Cl: 0.3, 1.8; 50.4%)	P = 0.47
Vomiting Low risk of bias	-	-	2.0 (0.5, 7.3; p = 0.3; I trial; 46 participants; TSA adj. Cl: -)	-	-	-	1.0 (0.7, 1.6; p = 0.85; 2 trials, 180 participants; TSA adj. Cl: 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. Cl: 04, 1.7; 29.2%)	P = 0.82	0.7 (0.5, 0.9; p = 0.007; 14 trials; 948 participants; TSA adj. Cl: 0.4, 1.1; 54.8%)	P = 0.17	0.7 (0.1, 3.7; p = 0.64; 2 trials; 111 participants; TSA adj. Cl: 0.1. 7.2; 12.8%)	P = 0.85	0.8 (0.7, 1.1; p = 0.002; 19 trials; 1188 participants; TSA adj. Cl: 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. Cl: 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. Cl: 0.4, 1.1; 54.8%)	P = 0.35	0.8 (0.4, 1.6; p = 0.59; 1 trial; 60 participants; TSA adj. Cl: -)	-	1.6 (1.0, 2.5; p = 0.05; 2 trials; 180 participants; TSA adj. Cl: 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. Cl: < 5%)	P = 0.13	I.0 (0.8, I.2; p = 0.97; I5 trials; I317 participants; TSA adj. Cl: 0.8, I.2; 98.7%)	P = 0.009	I.9 (0.4, 8.7; p = 0.43; 4 trials; 240 participants; TSA adj. Cl: < 5%)	P = 0.67	1.3 (1.0, 1.6; p = 0.02; 15 trials; 942 participants; TSA adj. Cl: 0.9, 1.9; 41.7%)	P = 0.94
Dizziness Low risk of bias	I.2 (0.6, 2.5; p = 0.57; 2 trials; 107 participants; TSA adj. Cl: 0.1, 26.5; 5.8%)	P = 0.64	1.0 (0.7, 1.3; p = 0.77; 3 trials; 341 participants; TSA adj. Cl: 0.5, 1.8; 28.9%)	P = 0.37	8.0 (1.1, 60.1; p = 0.04; 1 trial; 60 participants; TSA adj. Cl: -)	-	1.0 (0.9, 1.3; p = 0.68; 3 trials; 239 participants; TSA adj. Cl: 0.7, 1.7; 21.9%)	P = 0.95

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

Dizziness All trials	0.8 (0.5, 1.3; p = 0.45; 12 trials; 1209 participants; TSA adj. Cl: 0.2, 4.4; 14.6%)	P = 0.34	1.0 (0.8, 1.2; p = 0.89; 13 trials; 1101 participants; TSA adj. Cl: 0.7, 1.3; 64.8%)	P = 0.36	3.0 (0.8, 11.2; p = 0.10; 6 trials; 312 participants; TSA adj. Cl: <5%)	P = 0.11	1.2 (1.0, 1.5; p = 0.11; 21 trials; 1400 participants; TSA adj. Cl: 0.9, 1.2; 87.2%)	P = 0.20
	CI: 0.2, 4.4; 14.6%)		CI: 0.7, 1.3; 64.8%)		CI: <5%)		CI: 0.9, 1.2; 87.2%)	
							1	

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

FIGURE | Bias graph



Study or Subgroup M 3.1.1 0-350 mg Short 2012	ean [mg]				ntrol			Mean Difference	Mean Difference
*		SD [mg]	Total	Mean [mg]	SD [mg]	Total	Weight	IV, Random, 95% CI [mg]	IV, Random, 95% CI [mg]
Short 2012									
011011 2012	5.7	5.3	42	7.9	3.8	21	9.3%	-2.20 [-4.48, 0.08]	-
Waikakul 2011	15.5	9.25	24	18	15.5	24	5.2%	-2.50 [-9.72, 4.72]	.
Subtotal (95% CI)			66			45	14.6%	-2.23 [-4.40, -0.05]	•
Heterogeneity: Tau ² = 0.0			(P = 0.	94); l² = 0%					
Test for overall effect: Z =	2.01 (P = ().04)							
3.1.3 351-700 mg									
Misra 2013	24.6	19.6	37	29.15	25.2	36	3.5%	-4.55 [-14.93, 5.83]	
Monks 2015	10	11.9	100	10	7.4	97	9.0%	0.00 [-2.76, 2.76]	+
Moore 2010	3	3	21	4	5	23	9.2%	-1.00 [-3.41, 1.41]	+
Paul 2013	27.94	22.99	52	26.77	18.96	49	4.6%	1.17 [-7.03, 9.37]	+
Paul 2015	19.7	16.39	48	25.1	14.5	54	6.1%	-5.40 [-11.44, 0.64]	-
Short 2012a	6.7	3.6	42	7.9	3.8	21	9.5%	-1.20 [-3.16, 0.76]	1
Srivastava 2010	25.39	4.48	60	37.58	8.35	60	9.2%	-12.19 [-14.59, -9.79]	-
Subtotal (95% CI)			360			340	51.2%	-3.41 [-7.67, 0.86]	•
3.1.5 701-1050 mg									
Ghai 2011	5.44	1.56	30	4.28	1.87	30	10.1%	1.16 [0.29, 2.03]	•
Lunn 2015 Subtotal (95% CI)	45.4	35.7	92 122	50.2	41.4	29 59	1.7% 11.7%	-4.80 [-21.54, 11.94] 1.14 [0.27, 2.01]	
Heterogeneity: Tau ² = 0.0			(P = 0.	49); l² = 0%					
Test for overall effect: Z =	2.58 (P = 0	0.010)							
3.1.6 > 1050 mg									
Brogly 2008	0	1.48	22	0	4.4	21	9.5%	0.00 [-1.98, 1.98]	†
Fassoulaki 2005	20.3	7.9	29	25.7	11.2	30	7.1%	-5.40 [-10.33, -0.47]	-
Grosen 2014	11.2	21.62	52	17.92	23.55	52	4.3%	-6.72 [-15.41, 1.97]	+
Lunn 2015a	46.2	41.1	91	50.5	41.4	29	1.6%	-4.30 [-21.57, 12.97]	
Subtotal (95% CI)			194			132	22.5%	-2.89 [-6.90, 1.12]	•
Heterogeneity: Tau ² = 7.4			(P = 0.	12); l² = 49%					
Test for overall effect: Z =	1.41 (P = ().16)							
Total (95% CI)			742			576	100.0%	-2.81 [-5.18, -0.44]	•
Heterogeneity: Tau ² = 14.	31; Chi ² = '	17.37, df	= 14 (F	? < 0.00001);	l ² = 88%			-	-50 -25 0 25 50

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

FIGURE 3 Forest plot of 24-hour morphine consumption

Study or Subgroup		mental SD [mg]	Total Me	Cont an [mg] S		Total	Weight	Mean Difference IV, Random, 95% CI [mg]	Mean Difference IV, Random, 95% CI [mg]
3.3.1 0-350 mg	12.5		FC	22	2.1	50	2.1~	9 50 1 0 10 7 001	.
Amr 2009 Bang 2009	13.5 32.07	0.5 29.07	50 23	22 30.07	2.1 28.57	50 23	2.1% 0.5%	-8.50 [-9.10, -7.90] 2.00 [-14.66, 18.66]	<u> </u>
Clarke 2014	32.07	29.07	23 95	48	1.33	84	2.1%	-11.00 [-11.41, -10.59]	. [
Ghafari 2009	15.78	1.15	33	26.94	2.28	33	2.1%	-11.16 [-12.03, -10.29]	
Panday 2004b	40.42	31.26	153	53.03	27.48	153	1.4%	-12.61 [-19.21, -6.01]	
Panday 2004c	90.85	34.1	28	92.49	41.77	28	0.4%	-1.64 [-21.61, 18.33]	-+
Sekhavet 2009	40.1	14.5	49	52.7	21.1	49	1.4%	-12.60 [-19.77, -5.43]	
Short 2012	5.7	5.3	42	7.9	3.8	21	2.0%	-2.20 [-4.48, 0.08]	-
Vahedi 2011	18.61	9.03	36	21.53	11.3	40	1.7%	-2.92 [-7.50, 1.66]	-+
Waikakul 2011	15.5	9.25	24	18	15.5	24	1.4%	-2.50 [-9.72, 4.72]	+
Yoon 2001	24.1	9.9	16	32.7	14.6	16	1.2%	-8.60 [-17.24, 0.04]	
Subtotal (95% CI)			549			521	16.4%	-8.02 [-9.84, -6.19]	•
Heterogeneity: Tau ² Test for overall effect				< 0.00001);	$I^2 = 91\%$	5			
3.3.2 351-700 mg									
Bharti 2012	2.1	2.2	20	4.9	3.4	20	2.1%	-2.80 [-4.57, -1.03]	-
Clarke 2009b	33.1	4	76	35	4	39	2.1%	-1.90 [-3.44, -0.36]	4
Khademi 2009	2.83	1.29	44	3.51	1.51	43	2.1%	-0.68 [-1.27, -0.09]	1
Maleh 2013	2.5	2.6	40	2.7	2.7	40	2.1%	-0.20 [-1.36, 0.96]	t
Mardani-Kivi 2013	2.5	2.3	55	3.7	2.5	53	2.1%	-1.20 [-2.11, -0.29]	1
Menda 2010	6	8.5	30	15.1	20	30	1.3%	-9.10 [-16.88, -1.32]	
Metry 2008 Micro 2012	16.1	7.7	67	29.2	9.6	34	1.9%	-13.10 [-16.82, -9.38]	-
Misra 2013 Monks 2015	24.6	19.6	37	29.15	25.2	36	1.0%	-4.55 [-14.93, 5.83]	-T
Monks 2015 Moore 2010	10	11.9 3	100 21	10	7.4	97 23	2.0% 2.0%	0.00 [-2.76, 2.76]	1
Panday 2005	59.37	23.17	40	4 92.47	5 41.75	23	2.0%	-1.00 [-3.41, 1.41] -33.10 [-52.76, -13.44]	[
Panday 2005 Panday 2006	39.19	26.31	125	92.47 67.66	41.75	125	0.4%	-33.10 [-52.76, -13.44] -28.47 [-34.87, -22.07]	· · · · · · · · · · · · · · · · · · ·
Parikh 2010	31.7	20.31	30	31.9	19.84	30	1.0%	-28.47 [-34.87, -22.07] -0.20 [-10.36, 9.96]	
Paul 2013	27.94	22.99	52	26.77	19.84	49	1.2%	1.17 [-7.03, 9.37]	+
Paul 2015	19.7	16.39	48	25.1	14.5	54	1.5%	-5.40 [-11.44, 0.64]	
Sava 2009	35.6	14.14	25	54.7	13.02	25	1.3%	-19.10 [-26.63, -11.57]	
Short 2012a	6.7	3.6	42	7.9	3.8	21	2.0%	-1.20 [-3.16, 0.76]	4
Soltanzadeh 2011	2.5	0.9	30	4	1.5	30	2.1%	-1.50 [-2.13, -0.87]	4
Srivastava 2010	25.39	4.48	60	37.58	8.35	60	2.0%	-12.19 [-14.59, -9.79]	-
Özcan 2012	15.3	5	20	19	4.2	20	2.0%	-3.70 [-6.56, -0.84]	
Subtotal (95% CI)			962			849	33.7%	-4.56 [-6.08, -3.03]	+
Heterogeneity: Tau ² : Test for overall effect				< 0.00001);	I ² = 92%	5			
3.3.3 701-1050 mg									
Badawy 2014	11.5	2.3	19	13	2.9	19	2.1%	-1.50 [-3.16, 0.16]	4
Deniz 2012	22.2	11.9	25	25.6	10.5	26	1.5%	-3.40 [-9.57, 2.77]	-+
Ghai 2011	5.44	1.56	30	4.28	1.87	30	2.1%	1.16 [0.29, 2.03]	ł
Kim 2004	35.8	20.8	21	33.5	26.1	20	0.6%	2.30 [-12.19, 16.79]	-
Lunn 2015	45.4	35.7	92	50.2	41.4	29	0.5%	-4.80 [-21.54, 11.94]	-+-
Marashi 2012	18.3	15.6	22	65.7	31	22	0.6%	-47.40 [-61.90, -32.90]	—— I
Prabhakar 2007	23.8	5	10	20.04	2.09	10	1.9%	3.76 [0.40, 7.12]	▲ [™]
Subtotal (95% CI) Heterogeneity: Tau ² :	= 16.68; Chi ² =	55.24, d	219 f = 6 (P <	0.00001); I	² = 89%	156	9.4%	-2.61 [-6.58, 1.35]	•
Test for overall effect	:: Z = 1.29 (P =	0.20)							
3.3.4 > 1050 mg			20	12.2		20	3 100		
Abdelmageed 2010	6.6	1.3 7.6	30 35	12.2 29.5	1.1	30 37	2.1%	-5.60 [-6.21, -4.99]	
Al-Muiadi 2005			20	29.5	9	37	1.8%	-14.30 [-18.14, -10.46]	-
Al-Mujadi 2005 Rekowi 2014	15.2		20		0.7	2.2		-750[-833 669]	
Bekawi 2014	0	2.2	30	7.5	0.7	32	2.1%	-7.50 [-8.32, -6.68]	·
Bekawi 2014 Brogly 2008	0 0	2.2 1.48	22	7.5 0	4.4	21	2.1% 2.0%	0.00 [-1.98, 1.98]	[
Bekawi 2014 Brogly 2008 Dierking 2003	0 0 43	2.2 1.48 23.7	22 40	7.5 0 63	4.4 25.9	21 40	2.1% 2.0% 0.9%	0.00 [-1.98, 1.98] -20.00 [-30.88, -9.12]	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010	0 43 39.9	2.2 1.48 23.7 33	22 40 30	7.5 0	4.4 25.9 36.1	21 40 29	2.1% 2.0% 0.9% 0.5%	0.00 [-1.98, 1.98] -20.00 [-30.88, -9.12] -2.80 [-20.47, 14.87]	
Bekawi 2014 Brogly 2008 Dierking 2003	0 43 39.9 40	2.2 1.48 23.7	22 40 30 25	7.5 0 63 42.7 66	4.4 25.9 36.1 10	21 40 29 25	2.1% 2.0% 0.9% 0.5% 1.6%	0.00 [-1.98, 1.98] -20.00 [-30.88, -9.12] -2.80 [-20.47, 14.87] -26.00 [-31.54, -20.46]	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007	0 43 39.9	2.2 1.48 23.7 33 10	22 40 30	7.5 0 63 42.7	4.4 25.9 36.1	21 40 29	2.1% 2.0% 0.9% 0.5%	0.00 [-1.98, 1.98] -20.00 [-30.88, -9.12] -2.80 [-20.47, 14.87]	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002	0 43 39.9 40 23.8	2.2 1.48 23.7 33 10 5	22 40 30 25 25	7.5 0 63 42.7 66 23.2	4.4 25.9 36.1 10 5.8	21 40 29 25 25	2.1% 2.0% 0.9% 0.5% 1.6% 1.9%	0.00 [-1.98, 1.98] -20.00 [-30.88, -9.12] -2.80 [-20.47, 14.87] -26.00 [-31.54, -20.46] 0.60 [-2.40, 3.60]	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005	0 43 39.9 40 23.8 20.3 22 1.2	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29	22 40 30 25 25 29	7.5 0 63 42.7 66 23.2 25.7	4.4 25.9 36.1 10 5.8 11.2	21 40 29 25 25 30	2.1% 2.0% 0.9% 0.5% 1.6% 1.9% 1.7%	0.00 [-1.98, 1.98] -20.00 [-30.88, -9.12] -2.80 [-20.47, 14.87] -26.00 [-31.54, -20.46] 0.60 [-2.40, 3.60] -5.40 [-10.33, -0.47]	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2006	0 43 39.9 40 23.8 20.3 22	2.2 1.48 23.7 33 10 5 7.9 2.9	22 40 25 25 29 30	7.5 0 42.7 66 23.2 25.7 35	4.4 25.9 36.1 10 5.8 11.2 4.8	21 40 29 25 25 30 30	2.1% 2.0% 0.9% 1.6% 1.9% 1.7% 2.0%	0.00 [-1.98, 1.98] -20.00 [-30.88, -9.12] -2.80 [-20.47, 14.87] -26.00 [-31.54, -20.46] 0.60 [-2.40, 3.60] -5.40 [-10.33, -0.47] -13.00 [-15.01, -10.99]	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2005 Frouzanfard 2013	0 43 39.9 40 23.8 20.3 22 1.2	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29	22 40 25 25 29 30 25 23 52	7.5 0 63 42.7 66 23.2 25.7 35 5.2	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8	21 40 29 25 30 30 25	2.1% 2.0% 0.9% 1.6% 1.9% 1.7% 2.0% 2.1%	$\begin{array}{c} 0.00 \left[-1.98, 1.98\right] \\ -20.00 \left[-30.88, -9.12\right] \\ -2.60 \left[-30.88, -9.12\right] \\ -2.60 \left[-31.54, -20.46\right] \\ 0.60 \left[-2.40, 3.60\right] \\ -5.40 \left[-10.33, -0.47\right] \\ -13.00 \left[-15.01, -10.99\right] \\ -4.00 \left[-5.10, -2.90\right] \\ -6.72 \left[-15.41, 1.97\right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007	0 43 39,9 40 23,8 20,3 22 1,2 56,78 11,2 2,36	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 32.41 21.62 2.5	22 40 25 25 29 30 25 23 52 23	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2	21 40 29 25 25 30 30 25 24 52 28	2.1% 2.0% 0.9% 0.5% 1.6% 1.7% 2.0% 2.1% 0.3% 1.2% 2.1%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -0.29 \left[-1.85, 1.27 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014	0 43 39.9 40 23.8 20.3 22 1.2 56.78 11.2 2.36 38.65	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 0.29 32.41 21.62 2.5 18.04	22 40 30 25 29 30 25 23 52 23 52 23 25	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02	21 40 29 25 30 30 25 24 52 28 25	2.1% 2.0% 0.9% 0.5% 1.6% 1.7% 2.0% 2.1% 0.3% 1.2% 2.1% 1.1%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -0.29 \left[-1.85, 1.27 \right] \\ -5.64 \left[-15.10, 3.82 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013	0 0 43 39.9 40 23.8 20.3 22 1.2 55.78 11.2 2.36 38.65 38.65 13.21	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 32.41 21.62 2.5 18.04 4.71	22 40 25 25 29 30 25 23 52 23 23 25 23 25 34	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02 9.28	21 40 29 25 30 30 25 24 52 28 25 35	2.1% 2.0% 0.5% 1.6% 1.9% 2.0% 2.1% 0.3% 2.1% 1.2% 2.1% 1.1%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -5.264 \left[-15.10, 3.82 \right] \\ -11.10 \left[-14.56, -7.64 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013	0 0 43 39.9 40 23.8 20.3 22 1.2 56.78 11.2 2.36 38.65 13.21 25.9	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 32.41 21.62 2.5 18.04 4.71 8.3	22 40 25 25 29 30 25 23 52 23 52 23 25 34 29	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31 44	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02 9.28 11	21 40 29 25 30 30 25 24 52 28 25 35 31	2.1% 2.0% 0.5% 1.6% 1.7% 2.0% 2.1% 0.3% 1.2% 2.1% 1.1% 1.9% 1.7%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -5.64 \left[-15.10, 3.82 \right] \\ -1.10 \left[-14.56, -7.64 \right] \\ -18.10 \left[-23.01, -13.19 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013	0 43 39.9 40 23.8 20.3 22 1.2 56.78 11.2 2.36 38.65 13.21 25.9 46.2	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 32.41 21.62 2.5 18.04 4.71 8.3 41.1	22 40 30 25 29 30 25 23 52 23 25 34 29 91	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31 44 50.5	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02 9.28 11 41.4	21 40 29 25 30 30 25 24 52 28 25 35 31 29	2.1% 2.0% 0.9% 1.6% 1.9% 2.1% 0.3% 1.2% 2.1% 1.2% 2.1% 1.9% 1.7% 0.5%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.60 \left[-30.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -5.29 \left[-15.41, 1.97 \right] \\ -5.64 \left[-15.10, 3.82 \right] \\ -11.10 \left[-14.56, -7.64 \right] \\ -18.10 \left[-23.07, 12.97 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013 Lunn 2015a Ménigaux 2004	0 0 43 39.9 40 23.8 20.3 22 1.2 56.78 11.2 2.36 38.65 13.21 25.9 46.2 21	2.2 1.48 23.7 33 10 5 7.9 0.29 32.41 21.62 2.5 18.04 4.71 8.3 41.1 12	22 40 30 25 25 29 30 25 23 52 23 25 34 29 91 20	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31 44 50.5 20	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02 9.28 11 41.4 19	21 40 29 25 30 30 25 24 52 28 25 35 31 29 20	2.1% 2.0% 0.9% 1.6% 1.9% 2.0% 2.1% 0.3% 1.2% 1.1% 1.9% 1.9% 1.7% 0.5%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -25.33 \left[-48.72, -1.94 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -0.29 \left[-1.85, 1.27 \right] \\ -5.64 \left[-15.10, 3.82 \right] \\ -11.10 \left[-14.56, -7.64 \right] \\ -118.10 \left[-23.01, -13.19 \right] \\ -4.30 \left[-21.57, 12.97 \right] \\ 1.00 \left[-8.85, 10.85 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013 Lunn 2015a Ménigaux 2004 Omran 2006	0 0 43 39.9 40 23.8 20.3 22 1.2 2.36 38.65 13.21 25.9 46.2 21 23.9	2.2 1.48 23.7 33 10 5 5 7.9 0.29 0.29 0.29 0.29 12.62 2.5 18.04 4.71 8.3 41.1 12 2.6	22 40 30 25 25 29 30 25 23 52 23 25 34 29 91 20 25	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31 44 50.5 20 31.5	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02 9.28 11 41.4 19 2.78	21 40 29 25 30 30 25 24 52 28 25 35 31 29 20 25	2.1% 2.0% 0.5% 1.6% 1.7% 2.0% 2.1% 1.2% 2.1% 1.2% 1.9% 1.7% 0.5% 1.0% 2.1%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -2.90 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.51, 0.3.82 \right] \\ -11.10 \left[-14.56, -7.64 \right] \\ -18.10 \left[-23.01, -13.19 \right] \\ -4.30 \left[-21.57, 12.97 \right] \\ 1.00 \left[-8.85, 10.85 \right] \\ -7.60 \left[-9.09, -6.11 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Purmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009a	0 0 43 39.9 40 23.8 20.3 22 56.78 11.2 2.36 38.65 13.21 25.9 46.2 21 23.9 31	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 32.41 21.62 2.5 18.04 4.71 8.3 41.1 12 2.6 2.6 12	22 40 30 25 29 30 25 23 25 23 25 23 25 23 25 34 29 91 20 25 20	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31 44 50.5 20 31.5 48	4.4 25.9 36.1 10 5.8 11.2 4.8 4.8 23.55 3.2 23.55 3.2 16.02 9.28 11 41.4 19 2.78 2.79 17	21 40 29 25 30 30 25 24 52 28 25 35 31 29 20 25 20	2.1% 2.0% 0.5% 1.6% 1.7% 2.0% 2.1% 1.2% 2.1% 1.1% 1.9% 0.5% 1.0% 2.1% 1.1%	$\begin{array}{c} 0.00 \left[-1.98, 1.98\right] \\ -20.00 \left[-30.88, -9.12\right] \\ -2.80 \left[-20.47, 14.87\right] \\ -26.00 \left[-31.54, -20.46\right] \\ 0.60 \left[-2.40, 3.60\right] \\ -5.40 \left[-10.33, -0.47\right] \\ -13.00 \left[-15.10, -10.99\right] \\ -4.00 \left[-5.10, -2.90\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -0.29 \left[-1.85, 1.27\right] \\ -5.64 \left[-15.10, 3.82\right] \\ -11.10 \left[-23.01, -13.19\right] \\ -4.30 \left[-21.57, 12.97\right] \\ 1.00 \left[-8.85, 10.85\right] \\ -7.60 \left[-9.09, -6.11\right] \\ -17.00 \left[-26.12, -7.88\right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009b	0 43 39.9 40 23.8 20.3 22 1.2 2.56.78 11.2 2.36 38.65 13.21 25.9 46.2 21 23.9 31 20	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 32.41 21.62 2.5 18.04 4.71 8.3 41.1 12 2.6 (12) 2.15	22 40 30 25 25 29 30 25 23 25 23 25 34 29 91 20 25 20 30	7.5 0 42.7 6 6 23.2 25.7 35 5.2 82.11 17.92 2.65 24.21 24.31 44 50.5 20 31.5 48 28	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02 9.28 11 41.4 19 2.78 17 11.5	21 40 29 25 30 30 25 24 52 28 25 35 31 29 20 25 20 29	2.1% 2.0% 0.5% 1.6% 1.7% 2.0% 2.1% 1.2% 2.1% 1.1% 1.9% 1.7% 0.5% 1.0% 2.1% 1.6%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -25.33 \left[-48.72, -1.94 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -0.29 \left[-1.85, 1.27 \right] \\ -5.64 \left[-15.10, 3.82 \right] \\ -11.10 \left[-14.56, -7.64 \right] \\ -118.10 \left[-23.01, -13.19 \right] \\ -4.30 \left[-21.57, 12.97 \right] \\ 1.00 \left[-8.85, 10.85 \right] \\ -7.60 \left[-9.09, -6.11 \right] \\ -17.00 \left[-26.12, -7.88 \right] \\ -8.00 \left[-1.387, -2.13 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Frassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009a Sen 2009b Syal 2010	0 0 43 39.9 40 23.8 20.3 22 1.2 2.56.78 11.2 2.36 38.65 13.21 25.9 46.2 21 23.9 31 20 40.2	2.2 1.48 23.7 33 10 5 7.9 2.9 32.41 21.62 2.5 18.04 4.71 8.3 41.1 12 2.66 12 1.65 35.2	22 40 25 25 29 30 25 23 25 23 25 23 25 23 25 23 25 24 29 91 20 25 20 30 30	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 24.52 44.29 24.31 44.29 24.31 44.29 24.31 44.2 20.5 20.5 20.5 20.5 48 28 48 28 28 28 28 28 28 28 28 28 2	4.4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02 9.28 11 41.4 19 2.78 17 11.5 35.8	21 40 29 25 30 25 24 52 28 25 35 31 29 20 25 20 29 30	2.1% 2.0% 0.9% 0.5% 1.6% 2.0% 2.1% 1.7% 2.1% 1.1% 1.7% 0.5% 1.0% 1.1% 1.1% 1.1%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.60 \left[-30.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -5.64 \left[-15.10, 3.82 \right] \\ -11.10 \left[-14.56, -7.64 \right] \\ -18.10 \left[-23.01, -13.19 \right] \\ -4.30 \left[-21.57, 12.97 \right] \\ 1.00 \left[-8.85, 10.85 \right] \\ -7.60 \left[-9.99, -6.11 \right] \\ -17.00 \left[-26.12, -7.88 \right] \\ -8.00 \left[-13.87, -2.13 \right] \\ -6.50 \left[-24.47, 11.47 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009a Sen 2009b Syal 2010 Turan 2003a	0 43 39.9 40 23.8 20.3 22 1.2 56.78 11.2 2.36 38.65 13.21 25.9 46.2 21 23.9 31 20 40.2 27.04	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 32.41 21.62 2.5 18.04 4.71 8.04 4.71 12 2.6 18.04 4.71 12 2.6 12 12 12 12 12 12 12 12 12 12 12 12 12	22 40 30 25 25 30 25 23 25 23 25 34 20 25 20 20 20 30 30 30 25	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31 44 50.5 20 31.5 20 31.5 20 31.5 20 34.8 24.8 48 48 48 48 48.7	4.4 25.9 36.1 10 5.8 11.2 4.8 23.55 3.2 16.02 9.28 11 41.4 19 2.78 17 11.5 35.8 8.36	21 40 29 25 30 30 25 24 52 28 25 35 31 29 20 25 20 25 20 25 20 25	2.1% 2.0% 0.5% 1.6% 2.0% 2.1% 2.1% 2.1% 1.2% 1.2% 2.1% 1.2% 1.2	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -5.73 \left[-48.72, -1.94 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -0.29 \left[-1.85, 1.27 \right] \\ -5.64 \left[-15.10, 3.82 \right] \\ -11.10 \left[-14.56, -7.64 \right] \\ -11.10 \left[-14.56, -7.64 \right] \\ -11.10 \left[-23.01, -13.19 \right] \\ -4.30 \left[-21.57, 12.97 \right] \\ 1.00 \left[-8.85, 10.85 \right] \\ -7.60 \left[-9.09, -6.11 \right] \\ -17.00 \left[-26.12, -7.88 \right] \\ -8.00 \left[-13.87, -2.13 \right] \\ -6.50 \left[-24.47, 11.47 \right] \\ -14.92 \left[-21.46, -8.38 \right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009b Syal 2010 Turan 2003a Turan 2003b	0 0 43 39.9 40 23.8 20.3 22 1.2 2.36 38.65 13.21 25.9 46.2 21 23.9 31 20 40.2 21 23.9 31 20 40.2 27.04 40.2 27.04 1.2 27.04 1.2 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2	2.2 1.48 23.7 33 10 5 7.9 0.29 32.41 21.62 2.5 18.04 4.71 8.3 41.1 12 2.6 12 11.5 35.2 14.44 8.9	22 40 25 25 29 30 25 23 52 23 25 23 25 23 25 24 29 91 20 25 20 30 30 25 25	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 24.31 44.29 24.31 44 50.5 20 31.5 48 28 46.7 41.96 42.8	4.4 25.9 36.1 10 5.8 2.8 2.8 2.8 2.5 3.2 23.55 3.2 9.28 11 41.4 19 2.78 11.5 35.8 8.36 10.9	21 40 29 25 30 30 25 24 52 28 25 35 31 29 20 25 20 29 30 25 25	2.1% 2.0% 0.9% 0.5% 1.9% 1.7% 2.0% 2.1% 1.2% 2.1% 1.2% 2.1% 1.2% 2.1% 1.2% 0.5% 1.6%	$\begin{array}{c} 0.00 \left[-1.98, 1.98\right] \\ -20.00 \left[-30.88, -9.12\right] \\ -2.60 \left[-30.88, -9.12\right] \\ -2.60 \left[-31.54, -20.46\right] \\ 0.60 \left[-2.40, 3.60\right] \\ -5.40 \left[-10.33, -0.47\right] \\ -13.00 \left[-15.01, -10.99\right] \\ -4.00 \left[-5.10, -2.90\right] \\ -5.33 \left[-48.72, -1.94\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -0.29 \left[-1.85, 1.27\right] \\ -5.64 \left[-15.10, 3.82\right] \\ -11.10 \left[-14.56, -7.64\right] \\ -18.10 \left[-23.01, -13.19\right] \\ -4.30 \left[-21.57, 12.97\right] \\ 1.00 \left[-8.85, 10.85\right] \\ -7.60 \left[-9.09, -6.11\right] \\ -17.00 \left[-26.12, -7.81\right] \\ -8.00 \left[-21.47, 11.47\right] \\ -14.92 \left[-21.46, -8.38\right] \\ -80.01 \left[-21.24.02, -2.098\right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Frassoulaki 2006 Frouzanfard 2013 Gilron 2004 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009a Sen 2009a Sen 2009b Syal 2010 Turan 2003a Turan 2003b Ucak 2011	0 0 43 39.9 40 23.8 20.3 1.2 56.78 11.2 2.36 38.65 13.21 25.9 46.2 21 23.9 31 20 40.2 27.04 16.3 9.9	2.2 1.48 23.7 33 5 7.9 0.29 32.62 2.5 18.04 4.71 8.3 41.1 12 12 12 12 12 12 12 12 12 35.2 14.44 8.3	22 40 30 25 29 30 25 23 25 23 25 23 25 34 20 20 30 20 30 25 20 30 25 25 20	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 24.31 44.29 24.31 450.5 20 31.5 48 28 46.7 41.96 42.8	4.4 25.9 36.1 10 5.8 2.8 2.8 2.5 3.2 16.02 9.28 11 41.4 19 2.78 17 11.5 35.8 8.36 10.9 7.25	21 40 29 25 30 30 25 24 52 28 25 31 29 20 29 30 29 30 25 20 29 30 25 20	2.1% 2.0% 0.5% 1.6% 2.0% 2.1% 0.3% 2.1% 1.2% 2.1% 1.2% 2.1% 1.9% 1.2% 2.1% 1.9% 1.6% 0.5% 1.6% 0.5% 1.5% 1.6%	$\begin{array}{c} 0.00 \left[-1.98, 1.98\right] \\ -20.00 \left[-30.88, -9.12\right] \\ -2.80 \left[-20.47, 14.87\right] \\ -26.00 \left[-31.54, -20.46\right] \\ 0.60 \left[-2.40, 3.60\right] \\ -5.40 \left[-10.33, -0.47\right] \\ -13.00 \left[-15.10, -10.99\right] \\ -4.00 \left[-5.10, -2.90\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -0.29 \left[-1.85, 1.27\right] \\ -5.64 \left[-15.10, 3.82\right] \\ -11.10 \left[-23.01, -13.19\right] \\ -4.30 \left[-21.57, 12.97\right] \\ 1.00 \left[-8.85, 10.85\right] \\ -7.60 \left[-9.09, -6.11\right] \\ -17.00 \left[-26.12, -7.88\right] \\ -8.00 \left[-13.87, -2.13\right] \\ -6.50 \left[-32.02, -20.88\right] \\ -5.06 \left[-30.02, -20.98\right] \\ -5.06 \left[-30.02, -20.98\right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009b Syal 2010 Turan 2003a Turan 2003b Ucak 2011	0 0 43 39.9 40 23.8 20.3 22 1.2 2.36 38.65 13.21 25.9 46.2 21 23.9 31 20 40.2 21 23.9 31 20 40.2 27.04 40.2 27.04 1.2 27.04 1.2 2.5 2.5 2.5 2.5 2.5 2.5 2.5 2	2.2 1.48 23.7 33 10 5 7.9 0.29 32.41 21.62 2.5 18.04 4.71 8.3 41.1 12 2.6 12 11.5 35.2 14.44 8.9	22 40 25 25 29 30 25 23 52 23 25 23 25 23 25 24 29 91 20 25 20 30 30 25 25	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 24.31 44.29 24.31 44 50.5 20 31.5 48 28 46.7 41.96 42.8	4.4 25.9 36.1 10 5.8 2.8 2.8 2.8 2.5 3.2 23.55 3.2 9.28 11 41.4 19 2.78 11.5 35.8 8.36 10.9	21 40 29 25 30 30 25 24 52 28 25 35 31 29 20 25 20 29 30 25 25	2.1% 2.0% 0.9% 0.5% 1.9% 1.7% 2.0% 2.1% 1.2% 2.1% 1.2% 2.1% 1.2% 2.1% 1.2% 0.5% 1.6%	$\begin{array}{c} 0.00 \left[-1.98, 1.98\right] \\ -20.00 \left[-30.88, -9.12\right] \\ -2.80 \left[-30.88, -9.12\right] \\ -2.80 \left[-2.40, 37, 14.87\right] \\ -26.00 \left[-31.54, -20.46\right] \\ 0.60 \left[-2.40, 3.60\right] \\ -5.40 \left[-10.33, -0.47\right] \\ -13.00 \left[-15.01, -10.99\right] \\ -4.00 \left[-5.10, -2.90\right] \\ -25.33 \left[-48.72, -1.94\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -0.29 \left[-1.85, 1.27\right] \\ -5.64 \left[-15.10, 3.82\right] \\ -11.10 \left[-14.56, -7.64\right] \\ -18.10 \left[-23.01, -13.19\right] \\ -4.30 \left[-21.57, 12.97\right] \\ 1.00 \left[-8.85, 10.85\right] \\ -7.60 \left[-9.99, -6.11\right] \\ -17.00 \left[-26.12, -7.88\right] \\ -8.00 \left[-13.87, -2.13\right] \\ -6.50 \left[-24.47, 11.47\right] \\ -14.92 \left[-21.46, -8.38\right] \\ -26.50 \left[-32.02, -20.98\right] \\ -5.04 \left[-9.20, -1.08\right] \\ -8.80 \left[-12.70, -3.02\right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009a Sen 2009b Syal 2010 Turan 2003a Turan 2003b Ucak 2011 Ozgencil 2011 Subtotal (95% CI)	0 43 39.9 40 23.8 20.3 22 1.2 2.36 38.65 13.21 25.9 46.2 2.39 31 20 40.2 2.7.04 16.3 9.9 29.47 = 15.95; Chi ² =	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 2.41 21.62 2.5 18.04 4.71 8.3 41.1 12 2.66 12 11.5 35.2 14.44 8.9 5.38 9.64 360.74	22 40 30 25 29 30 25 23 23 23 23 23 23 23 23 23 23	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 24.5 24.29 24.31 44.29 24.31 44.29 24.31 44.29 24.31 44.29 24.31 44.29 24.31 44.29 24.31 48 46.7 41.96 42.8 14.94 37.33	4,4 25.9 36.1 10 5.8 11.2 4.8 2.8 48.2 23.55 3.2 16.02 9.28 11 41.4 19 2.78 17 11.5 35.8 8.36 10.9 7.25 9.5	21 40 29 25 25 30 30 25 24 4 52 28 8 25 35 31 29 20 25 20 25 20 25 20 30 30 25 772	2.1% 2.0% 0.9% 0.5% 1.9% 1.7% 2.0% 2.1% 1.2% 2.1% 1.2% 2.1% 1.9% 1.7% 0.5% 1.6% 1.6% 1.6% 1.6%	$\begin{array}{c} 0.00 \left[-1.98, 1.98\right] \\ -20.00 \left[-30.88, -9.12\right] \\ -2.80 \left[-20.47, 14.87\right] \\ -26.00 \left[-31.54, -20.46\right] \\ 0.60 \left[-2.40, 3.60\right] \\ -5.40 \left[-10.33, -0.47\right] \\ -13.00 \left[-15.10, -10.99\right] \\ -4.00 \left[-5.10, -2.90\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -0.29 \left[-1.85, 1.27\right] \\ -5.64 \left[-15.10, 3.82\right] \\ -11.10 \left[-23.01, -13.19\right] \\ -4.30 \left[-21.57, 12.97\right] \\ 1.00 \left[-8.85, 10.85\right] \\ -7.60 \left[-9.09, -6.11\right] \\ -17.00 \left[-26.12, -7.88\right] \\ -8.00 \left[-13.87, -2.13\right] \\ -6.50 \left[-32.02, -20.88\right] \\ -5.06 \left[-30.02, -20.98\right] \\ -5.06 \left[-30.02, -20.98\right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009a Sen 2009b Syal 2010 Turan 2003a Turan 2003b Ucak 2011 Ozgencil 2011 Subtotal (95% CI)	0 43 39.9 40 23.8 20.3 22 1.2 2.36 38.65 13.21 25.9 46.2 2.39 31 20 40.2 2.7.04 16.3 9.9 29.47 = 15.95; Chi ² =	2.2 1.48 23.7 33 10 5 7.9 2.9 0.24 2.5 18.04 4.71 8.3 41.1 12 2.6 6 12 2.5 18.04 4.71 8.3 41.1 12 2.6 12 11.5 35.2 14.44 8.9 9.64 360.74,1 0.00001	22 40 30 25 29 30 25 23 23 25 23 34 29 1 20 20 30 25 20 30 25 25 20 30 25 25 20 30 4 4 29 20 30 25 20 30 4 25 20 34 20 25 20 25 23 24 25 23 25 23 24 25 25 23 25 23 25 25 23 25 25 23 25 25 23 25 25 23 25 25 23 25 25 23 25 25 23 25 25 23 25 25 23 25 25 23 25 25 23 25 25 25 25 25 25 25 25 25 25 25 25 25	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 24.5 24.29 24.31 44.29 24.31 44.29 24.31 44.29 24.31 44.29 24.31 44.29 24.31 44.29 24.31 48 46.7 41.96 42.8 14.94 37.33	4.4 25.99 36.1 10 5.8 11.2 4.8 2.8 23.55 3.2 16.02 9.28 11 41.4 19 2.78 35.8 8.36 10.9 7.25 9.5 9; ² = 93	21 40 29 25 25 30 25 24 25 35 31 29 20 25 20 29 30 25 20 29 30 25 25 20 29 30 30 25 5 35	2.1% 2.0% 0.5% 1.6% 1.7% 2.0% 2.1% 1.7% 2.0% 2.1% 1.1% 1.2% 2.1% 1.1% 1.7% 0.5% 1.6% 1.6% 1.6% 1.5% 1.6% 1.7% 40.5%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -5.764 \left[-15.10, 3.82 \right] \\ -11.10 \left[-23.01, -13.19 \right] \\ -4.30 \left[-21.57, 12.97 \right] \\ 1.00 \left[-8.85, 10.85 \right] \\ -7.60 \left[-9.09, -6.11 \right] \\ -17.00 \left[-26.12, -7.88 \right] \\ -8.00 \left[-13.87, -2.13 \right] \\ -5.50 \left[-32.02, -20.98 \right] \\ -5.04 \left[-12.02, -20.98 \right] \\ -5.04 \left[-10.85, -7.10 \right] \\ \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009b Syal 2010 Turan 2003a Turan 2003b Ucak 2011 Subtotal (95% CI) Heterogenetity: Tau ² , Test for overall effect	0 43 39.9 40 23.8 20.3 22 1.2 2.36 38.65 13.21 25.9 46.2 23.9 31 20 40.2 27.04 16.3 9.9 29.47 = 15.95; Chi ² = : Z = 9.38 (P <	2.2 1.48 23.7 33 10 5 7.9 2.9 0.29 32.41 21.62 2.5 5 18.04 4.71 8.3 41.1 12 2.6 12 12 2.6 12 11.5 35.2 14.44 8.9 5.38 9.64 360.74, 0.00001)	22 40 30 25 29 30 25 23 23 25 23 25 23 25 23 25 23 25 20 30 25 20 30 25 25 23 25 23 25 23 25 23 25 23 25 23 25 23 25 23 25 23 25 23 25 25 23 25 25 25 25 23 25 25 25 25 25 25 25 25 25 25	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31 44 50.5 20 31.5 48 28 46.7 41.96 42.8 14.94 37.33 < 0.00001	4.4 25.9 36.1 10 5.8 11.2 4.8 23.55 3.2 16.02 9.28 11 41.4 19 2.78 8.36 10.9 7.25 9.5 9.5 1 ² = 93	21 40 29 25 25 30 30 25 24 52 28 25 31 29 20 25 20 30 25 20 30 25 20 30 25 20 30 25 20 30 25 25 31 29 20 25 25 35 35 31 29 20 25 24 25 25 25 25 25 25 25 25 25 25 25 25 25	2.1% 2.0% 0.9% 0.5% 1.9% 1.7% 2.0% 2.1% 1.2% 2.1% 1.2% 2.1% 1.9% 1.7% 0.5% 1.6% 1.6% 1.6% 1.6%	$\begin{array}{c} 0.00 \left[-1.98, 1.98\right] \\ -20.00 \left[-30.88, -9.12\right] \\ -2.80 \left[-30.88, -9.12\right] \\ -2.80 \left[-2.40, 37, 14.87\right] \\ -26.00 \left[-31.54, -20.46\right] \\ 0.60 \left[-2.40, 3.60\right] \\ -5.40 \left[-10.33, -0.47\right] \\ -13.00 \left[-15.01, -10.99\right] \\ -4.00 \left[-5.10, -2.90\right] \\ -25.33 \left[-48.72, -1.94\right] \\ -6.72 \left[-15.41, 1.97\right] \\ -0.29 \left[-1.85, 1.27\right] \\ -5.64 \left[-15.10, 3.82\right] \\ -11.10 \left[-14.56, -7.64\right] \\ -18.10 \left[-23.01, -13.19\right] \\ -4.30 \left[-21.57, 12.97\right] \\ 1.00 \left[-8.85, 10.85\right] \\ -7.60 \left[-9.99, -6.11\right] \\ -17.00 \left[-26.12, -7.88\right] \\ -8.00 \left[-13.87, -2.13\right] \\ -6.50 \left[-24.47, 11.47\right] \\ -14.92 \left[-21.46, -8.38\right] \\ -26.50 \left[-32.02, -20.98\right] \\ -5.04 \left[-9.20, -1.08\right] \\ -8.80 \left[-12.70, -3.02\right] \end{array}$	
Bekawi 2014 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Joseph 2014 Khan 2013 Kosucu 2013 Lunn 2015a Ménigaux 2004 Omran 2006 Sen 2009a Sen 2009b Syal 2010 Turan 2003a Turan 2003b Ucak 2011 Ozgencil 2011 Subtotal (95% CI)	0 0 43 39.9 40 23.8 20.3 22 1.2 2.56.78 11.2 2.36 38.65 13.21 25.9 46.2 21 23.9 46.2 21 23.9 31 31 21 25.9 46.2 21 23.9 31 31 21 25.9 46.2 21 23.9 31 31 21 25.9 46.2 21 23.9 31 31 21 25.9 46.2 21 23.9 31 31 21 25.9 46.2 27.04 16.3 9.9 29.47 15.55; Chi ² = 29.47 20.3 20.4 20.4 20.5 20.4 20.5 2	2.2 1.48 23.7 33 10 0.29 0.29 0.29 0.29 2.41 21.62 2.5 18.04 4.71 8.3 8 3 41.1 12 2.6 12 11.5 5.2 14.44 8.9 5.38 9.64 360.74, 0.00001) 2408.40	22 40 25 29 30 25 23 32 23 25 23 25 23 24 29 91 20 25 20 30 25 23 34 29 91 20 25 20 30 25 23 34 29 25 23 34 29 25 25 23 34 29 25 25 23 34 25 25 25 25 23 25 23 25 25 23 25 23 25 25 23 25 25 23 25 25 23 25 25 25 25 25 25 25 25 25 25	7.5 0 63 42.7 66 23.2 25.7 35 5.2 82.11 17.92 2.65 44.29 24.31 44 50.5 20 31.5 48 28 46.7 41.96 42.8 14.94 37.33 < 0.00001	4.4 25.9 36.1 10 5.8 11.2 4.8 23.55 3.2 16.02 9.28 11 41.4 19 2.78 8.36 10.9 7.25 9.5 9.5 1 ² = 93	21 40 29 25 25 30 30 25 24 52 28 25 31 29 20 25 20 30 25 20 30 25 20 30 25 20 30 25 20 30 25 25 31 29 20 25 25 35 35 31 29 20 25 24 25 25 25 25 25 25 25 25 25 25 25 25 25	2.1% 2.0% 0.5% 1.6% 1.7% 2.0% 2.1% 1.7% 2.0% 2.1% 1.1% 1.2% 2.1% 1.1% 1.7% 0.5% 1.6% 1.6% 1.6% 1.5% 1.6% 1.7% 40.5%	$\begin{array}{c} 0.00 \left[-1.98, 1.98 \right] \\ -20.00 \left[-30.88, -9.12 \right] \\ -2.80 \left[-20.47, 14.87 \right] \\ -26.00 \left[-31.54, -20.46 \right] \\ 0.60 \left[-2.40, 3.60 \right] \\ -5.40 \left[-10.33, -0.47 \right] \\ -13.00 \left[-15.01, -10.99 \right] \\ -4.00 \left[-5.10, -2.90 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -6.72 \left[-15.41, 1.97 \right] \\ -5.764 \left[-15.10, 3.82 \right] \\ -11.10 \left[-23.01, -13.19 \right] \\ -4.30 \left[-21.57, 12.97 \right] \\ 1.00 \left[-8.85, 10.85 \right] \\ -7.60 \left[-9.09, -6.11 \right] \\ -17.00 \left[-26.12, -7.88 \right] \\ -8.00 \left[-13.87, -2.13 \right] \\ -5.50 \left[-32.02, -20.98 \right] \\ -5.04 \left[-12.02, -20.98 \right] \\ -5.04 \left[-10.85, -7.10 \right] \\ \end{array}$	

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

FIGURE 4 Forest plot of SAE

	Gabape	entin	Conti	ol		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
3.4.1 0-350 mg							
Short 2012	0	42	0	21		Not estimable	
Waikakul 2011	0	26	0	24		Not estimable	
Subtotal (95% CI)		68		45		Not estimable	
Total events	0		0				
Heterogeneity: Not ap							
Test for overall effect	Not app	licable					
3.4.2 351-700 mg							
Kinney 2011	4	57	5	63	25.0%	0.88 [0.23, 3.40]	
Paul 2013	0	52	0	49		Not estimable	
Short 2012a	0	42	0	21		Not estimable	
Srivastava 2010	0	60	0	60		Not estimable	
Subtotal (95% CI)		211		193	25.0%	0.88 [0.23, 3.40]	
Total events	4		5				
Heterogeneity: Not ap	plicable						
Test for overall effect	Z = 0.19	$\Theta(P=0)$.85)				
3.4.4 701-1050 mg							
Lunn 2015	2	92	1	29	6.4%	0.59 [0.04, 8.59]	
Subtotal (95% CI)		92		29	6.4%	0.59 [0.04, 8.59]	
Total events	2		1				
Heterogeneity: Not ap							
Test for overall effect	Z = 0.38	B (P = 0)	.70)				
3.4.5 > 1050 mg							
Brogly 2008	0	22	0	21		Not estimable	
Grosen 2014	13	52	8	52	50.5%	1.81 [0.70, 4.68]	+=-
Lunn 2015a	6	91	1	49	18.2%	2.59 [0.53, 12.67]	
Subtotal (95% CI)		165		122	68.6%	1.99 [0.88, 4.50]	
Total events	19		9	_			
Heterogeneity: Chi ² =	,	•	, ,	$^{2} = 0\%$			
Test for overall effect	Z = 1.65	5 (P = 0)	.10)				
Total (95% CI)		536		389	100.0%	1.50 [0.76, 2.95]	•
Total events	25		15	_			
Heterogeneity: $Chi^2 =$				$^{2} = 0\%$			0.01 0.1 1 10 100
Test for overall effect	Z = 1.17	7 (P = 0	.24)				Favours Gabapentin Favours Control
Test for subgroup dif					-		ravours Gabapentin ravours Control

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

FIGURE 5 Forest plot of SAE

	Gabape	num	Conti	01		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
3.6.1 0-350 mg							
Lichtinger 2011	0	20	0	20		Not estimable	
Short 2012	0	42	0	21		Not estimable	
Vahedi 2011	0	36	0	40		Not estimable	
Subtotal (95% CI)	0	98	0	81		Not estimable	
Total events	0		0				
Heterogeneity: Not appli			0				
Test for overall effect: N		ble					
rest for overall effect. Iv	or applica	bie					
3.6.2 351-700 mg							
Ajori 2011	0	69	0	69		Not estimable	
Kavitha 2013	0	28	0	28		Not estimable	
	4		5		15 20/		
Kinney 2011		57		63	15.2%	0.88 [0.23, 3.40]	-
Paul 2013	0	52	0	49		Not estimable	
Short 2012a	0	42	0	21		Not estimable	
Srivastava 2010	0	60	0	60		Not estimable	
Waikakul 2011	0	26	0	24		Not estimable	
Zaldivar Ramirez 2011	0	18	0	16		Not estimable	
Subtotal (95% CI)		352		330	15.2%	0.88 [0.23, 3.40]	
Total events	4		5				
Heterogeneity: Not appli	icable						
Test for overall effect: Z	= 0.19 (P	= 0.85)				
3.6.3 701-1050 mg							
Lunn 2015	2	92	1	29	3.9%	0.59 [0.04, 8.59]	
Prabhakar 2007	0	20	0	20		Not estimable	
Rajendran 2014	0	30	0	30		Not estimable	
Subtotal (95% CI)	-	142	-	79	3.9%	0.59 [0.04, 8.59]	
Total events	2		1				
Heterogeneity: Not appli			_				
Test for overall effect: Z		= 0.70	0				
			/				
3.6.4 > 1050 mg							
Bartholdy 2006	7	38	3	38	16.0%	2.48 [0.66, 9.30]	
Brogly 2008	0	22	0	21	2010/0	Not estimable	
Dierking 2003	õ	39	Ő	32		Not estimable	
Dirks 2002	õ	31	Ő	34		Not estimable	
Fassoulaki 2002	0	25	0	25		Not estimable	
	0		0				
Fassoulaki 2006	-	30	-	30	E 20/	Not estimable	
Gilron 2004	1	20	2	22	5.2%	0.55 [0.05, 5.59]	
Grosen 2014	13	52	8	52	30.7%	1.81 [0.70, 4.68]	, , , , , , , , , , , , , , , , , , ,
Hout 2007	1	28	0	28	1.8%	7.39 [0.15, 372.38]	
Khan 2013	0	34	0	35		Not estimable	
Lunn 2015a	6	91	1	29	8.8%	1.76 [0.30, 10.42]	
Pathak 2013	0	40	0	40		Not estimable	
Ucak 2011	7	20	11	20	18.4%	0.45 [0.13, 1.56]	
Subtotal (95% CI)		470		406	80.9%	1.34 [0.75, 2.41]	•
Total events	35		25				
Heterogeneity: Chi ² = 5.	57, df = 5	5 (P = 0)	.35); I ² =	10%			
Test for overall effect: Z	= 0.98 (P	= 0.33)				
Total (95% CI)		1062		896	100.0%	1.22 [0.72, 2.06]	*
Total events	41		31				
Heterogeneity: Chi ² = 6.	17, df = 7	7 (P = 0)	.52); I ² =	0%			0.01 0.1 1 10 100

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

APPENDIX PAPER III

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Appendix I Search strategies See search strategy from paper I

Appendix 2 Opioid conversion See opioid conversion from paper I.

Total 24-hour morphine consumption Intra venous morphine (mg)

	No* of		Dose mg/day	Treatment Single /	Intervention (mg)	Control (mg)
Trial	patients	Surgical Procedures	(bolus mg)	Multiple dose	(Mean SD)	(Mean SD)
	•	0	300 mg/day	Multiple dose		(/
Amr 2009 ³²	100	Radical or partial mastectomy	(300 mg)		13.5 (0.5)	22.0 (2.1)
Bang 2009 ³⁶	46	Arthroscopic shoulder surgery	300 mg/day 300 mg/day	Single dose	32.1 (29.1)	30.1 (28.67)
Behdad 2012 ³⁹	61	Hysterectomy	(100 mg)	Multiple dose	-	-
Chowdhury 2010 ⁴⁶	200	Gynecological surgery	300 mg/day 200 mg /day	Single dose	-	-
Clarke 2014 ⁴⁸	179	Total knee arthroplasty	(600 mg) 300 mg/day	Multiple dose	37 (1.5)	48 (1.3)
Ghafari 2009 ⁶⁰	66	Abdominal hysterectomy and salphingooophrectomy	(300 mg)	Multiple dose	15.8 (1.2)	26.9 (2.3)
Hassani 2014 ⁶⁷	60	Laparoscopic gastric by-pass	100 mg/day 300 mg/day	Single dose	-	-
Khurana 2013 ⁷⁷	60	Lumbar discectomy	(300 mg)	Multiple dose	-	-
Mohammadi 2008 ⁹⁵	70	Assisted reproductive techniques	300 mg/day	Single dose	-	-
Mohammadi 2009 [%]	80	Abdominal surgery/gynecological surgery	300 mg/day 300 mg/day	Single dose	-	-
Lichtinger 2011 ⁸⁴	40	Bilateral photorefractive keratectomy	(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 300 mg /day	Single dose	-	-
Sekhavet 2009 ¹²³	98	Abdominal hysterectomy	(600 mg) 300mg/day	Multiple dose	40.1 (14.5)	52.7 (21.1)
Spence 2011 ¹³¹	57	Shoulder arthroscopy	(300 mg)	Multiple dose	-	-
Vahedi 2011 ¹⁴⁰	76	Lumbar laminectomy and discectomy	300 mg/day 300 mg/day	Single dose	18.6 (9.0)	21.5 (11.3)
Vasigh 2016 ¹⁴¹	76	Laminectomy	(600 mg)	Multiple dose	-	-
Verma 2008 ¹⁴²	50	Abdominal hysterectomy	300 mg/day 300 mg/day	Single dose Multiple dose	-	- 18 (15.5)
Waikakul 2011 ¹⁴⁴	48	Spine, major joint, tumor and major limb surgery	(400 mg) 300 mg/day		15.5 (9.3)	
Yoon 2001 145	32	Hysterectomy	(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	-	-
Basilii 2007	100		600 mg/day	Single dose	-	-
Bhandari 2014 ⁴¹	40	Laparoscopic cholecystectomy	(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	2.1 (2.2)	ч. 7 (э.т)
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	57.0 (1.5)	(1.5)
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	-	-
		Cholecystectomy	600 mg/day	Silligie dose	-	-
Joseph 201471	50	Abdominal hysterectomy	(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	-	-
		Thoratectomy; lobectomy; pneumonectomy; chest wall		Shiple dose		
Kinney 2011 ⁷⁹	125	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)
			000 116, 447	onigie dobe	2.0 (2.0)	3.7 (2.5)
Mardani-Kivi 2013 ⁸⁸	108	Anterior Collateral Ligament reconstruction	600 mg/day	Single dose	2.5 (2.3)	0 (2)
Menda 2010 ⁸⁹	60	Coronary Artery Bypass Graft	600 mg/day	Single dose	6.0 (8.5)	15.1 (20)
			600 mg/day	0		()
Metry 2008 ⁹¹	68	Unilateral radical mastectomy and axillary dissection	(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)
			600 mg/day		()	10.0 (7.4)
Monks 2015 ⁹⁸	197	Cesarean section	(600 mg)	Multiple dose	10.0 (11.9)	
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)
		U ,	600 mg/day	0	· /	()
Paul 2013 ¹¹¹	101	Total knee arthroplasty	(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)	· · /
			5 /		· · /	

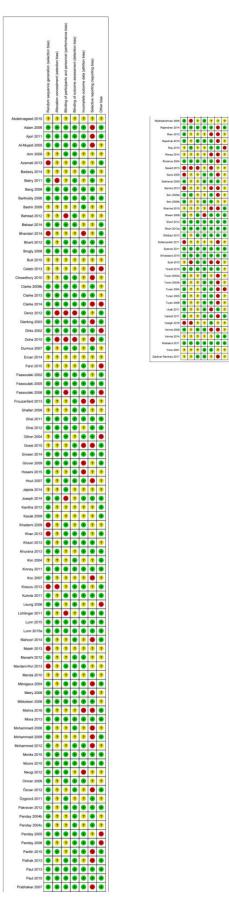
			(600 mg)	Multiple dose		25.1 (14.5)
Saeed 2013 ¹²¹	100	Laparoscopic cholecystectomy	600 mg/day	Single dose	-	-
Sava 2009 ¹²²	50	Colorectal surgery	600 mg/day	Single dose	35.6 (14.1)	54.7 (13.0)
Semira 2013 ¹²⁴	60	Laparoscopic cholecystectomy	600 mg/day	Single dose	-	-
			600 mg/day	Ū		
Sharma 2015 ¹²⁷	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 <u>-</u> 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 201249	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 2015⁵	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	l 200 mg/day l 200 mg/day	Single dose	-	-
Bekawi 2014 ⁴⁰	60	Laparoscopic cholecystectomy	(1200 mg)	Multiple dose	0 (2.2)	7.5 (0.7)
Brogly 200843	43	Total or partial thyroidectomy	1200 mg/day	Single dose	0 (1.48)	0 (4.4)
Butt 201044	100	Mastectomy	1200 mg/day	Single dose	-	-
Clarke 201347	44	General-, gynecological-, plastic and ENT surgery	1200 mg/day	Single dose	-	-
			2400 mg/day	-		
Dierking 2003 ⁵⁰	80	Abdominal hysterectomy and salphingooophrectomy	(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)
		Radical mastectomy or lobectomy with axillary node	1200 mg/day	•		
Fassoulaki 2002 ⁵⁷	50	dissection	(1200 mg) 1600 mg/day 400	Multiple dose	23.8 (5.0)	23.2 (5.8)
Fassoulaki 2005 ⁵⁸	59	Abdominal hysterectomy	mg ,	Multiple dose	20.3 (7.9)	25.7 (11.2)
			1600 mg/day 800			
Fassoulaki 2006 ⁵⁶	60	Abdominal hysterectomy	mg	Multiple dose	22.0 (2.9)	35.0 (4.8)
Frouzanfard 2013 ⁵⁹	50	Abdominal hysterectomy	1200 mg/day 1800 mg/day	Single dose	1.2 (0.2)	5.2 (2.8)
Gilron 200463	47	Abdominal hysterectomy	600 mg 🥤	Multiple dose	56.8 (32.4)	82.1 (48.2)
			1200 mg/day			
Grosen 2014 ⁶⁵	104	Thoracotomy for malignancy	(1200 mg)	Multiple dose	11.2 (21.6)	17.9 (23.69)
		Exploratory thoracotomy, pneumonectomy, lobectomy,				
Hout 2007 ⁶⁹	51	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 201375	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)
			1800 mg/day			
Mikkelsen 2006 ⁹²	51	Tonsillectomy	(1200 mg)	Multiple dose	-	-
Mohammed 2012 ⁹⁷	80	Functional endoscopic sinus surgery	l 200 mg/day l 200 mg/day	Single dose	-	-
Omran 2005 ¹⁰¹	50	Posterolateral thoracotomy for lobectomy	(1200 mg) 1800 mg/day 600	Multiple dose	23.9 (2.6)	31.5 (2.8)
Özgenzil 2011 ¹⁰³	60	Decompressive lumbar laminectomy and discectomy	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)
		Ear-nose and throat-, general-, orthopedic-, and gynecologic	• •	•	· · ·	
Tirault 2010 ¹³⁴	135	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	-	-
126	10		1200 mg/day			
Turan 2005 ¹³⁶	40	Lower limb surgery	(1200 mg)	Multiple dose	-	-
			1200 mg/day			-
Turan 2006 ¹³⁸	50	Abdominal hysterectomy and salphingooophrectomy	(1200 mg)	Multiple dose	-	
			1200 mg/day			
Ucak 2011 ¹³⁹	40	Coronary Artery Bypass Graft	(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

		pentin			itrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [VAS]	SD [VAS]	Total	Mean [VAS]	SD [VAS]	Total	Weight	IV, Random, 95% CI [VAS]	IV, Random, 95% CI [VAS]
3.7.1 0-350 mg									
Short 2012	14	7.4	42	20	10	21	12.1%	-6.00 [-10.83, -1.17]	· -
Waikakul 2011	50	25	24	60	25	24	9.7%	-10.00 [-24.14, 4.14]	
Subtotal (95% CI)			66			45	21.8%	-6.42 [-10.99, -1.85]	•
leterogeneity: Tau ² =			1 (P =	0.60 ; $I^2 = 0\%$					
fest for overall effect:	: Z = 2.75 (P =	0.006)							
.7.2 351-700 mg									
Cinney 2011	27	25.2	57	28	26.2	68	11.2%	-1.00 [-10.03, 8.03]	ı ↓
loore 2010	19.5	15.5	21	40	20	23	10.8%	-20.50 [-31.02, -9.98]	·
hort 2012a	15	6.7	42	20	10	21	12.1%	-5.00 [-9.73, -0.27]	-
rivastava 2010	23	3.17	60	49	3.33	60	12.5%	-26.00 [-27.16, -24.84]	
Subtotal (95% CI)			180			172	46.5%	-13.24 [-27.57, 1.08]	◆
Subtotal (95% CI)			0			0		Not estimable	
ubtotal (95% CI) leterogeneity: Not ap		e	0			0		Not estimable	
ubtotal (95% CI) leterogeneity: Not ap est for overall effect:		e	0			0		Not estimable	
iubtotal (95% CI) leterogeneity: Not ap est for overall effect: 3.7.5 > 1050 mg		e 19.1	-	23.5	21.3	0 21	10.3%		
Gubtotal (95% CI) Heterogeneity: Not ap Fest for overall effect: 3.7.5 > 1050 mg Brogly 2008	Not applicabl		0 22 29	23.5 20	21.3 31	-	10.3% 9.4%	Not estimable -1.00 [-13.11, 11.11] -3.00 [-18.06, 12.06]	
iubtotal (95% Cl) Heterogeneity: Not ap est for overall effect: 5.7.5 > 1050 mg irogly 2008 fassoulaki 2005	Not applicabl	19.1	22 29 52			21 30 52	9.4% 11.9%	-1.00 [-13.11, 11.11]	
Aubtotal (95% CI) Heterogeneity: Not ap Test for overall effect: 1.7.5 > 1050 mg Horogly 2008 Assoulaki 2005 Grosen 2014	Not applicabl 22.5 17	19.1 28	22 29	20	31	21 30	9.4%	-1.00 [-13.11, 11.11] -3.00 [-18.06, 12.06]	
Aubtotal (95% CI) Heterogeneity: Not ap rest for overall effect: A.7.5 > 1050 mg Hrogly 2008 Aassoulaki 2005 Grosen 2014 Jubtotal (95% CI) Heterogeneity: Tau ² =	22.5 17 6.84 = 0.00; Chi ² =	19.1 28 12.97 0.91, df =	22 29 52 103	20 13.95	31	21 30 52	9.4% 11.9%	-1.00 [-13.11, 11.11] -3.00 [-18.06, 12.06] -7.11 [-13.13, -1.09]	
3.7.4 701–1050 mg Subtotal (95% CI) Heterogeneity: Not ap Fest for overall effect: 3.7.5 > 1050 mg Srogly 2008 Fassoulaki 2005 Grosen 2014 Subtotal (95% CI) Feterogeneity: Tau ² = Fest for overall effect: Fotal (95% CI)	22.5 17 6.84 = 0.00; Chi ² =	19.1 28 12.97 0.91, df =	22 29 52 103	20 13.95	31	21 30 52 103	9.4% 11.9%	-1.00 [-13.11, 11.11] -3.00 [-18.06, 12.06] -7.11 [-13.13, -1.09]	•
Subtotal (95% CI) Heterogeneity: Not ap Fest for overall effect: 3.7.5 > 1050 mg Brogly 2008 Fassoulaki 2005 Grosen 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect:	22.5 17 6.84 = 0.00; Chi ² = 1 : Z = 2.15 (P =	19.1 28 12.97 0.91, df = 0.03)	22 29 52 103 2 (P = 9 349	20 13.95 0.63); I ² = 0%	31 17.94	21 30 52 103 320	9.4% 11.9% 31.7%	-1.00 [-13.11, 11.11] -3.00 [-18.06, 12.06] -7.11 [-13.13, -1.09] -5.57 [-10.65, -0.50]	
Subtotal (95% CI) Heterogeneity: Not ap Fest for overall effect: 3.7.5 > 1050 mg Brogly 2008 Frassoulaki 2005 Grosen 2014 Subtotal (95% CI) Heterogeneity: Tau ² = Fest for overall effect: Fotal (95% CI)	: Not applicabl 22.5 17 6.84 = 0.00; Chi ² = (: Z = 2.15 (P = = 183.29; Chi ²	19.1 28 12.97 0.91, df = 0.03) = 200.72,	22 29 52 103 2 (P = 9 349	20 13.95 0.63); I ² = 0%	31 17.94	21 30 52 103 320	9.4% 11.9% 31.7%	-1.00 [-13.11, 11.11] -3.00 [-18.06, 12.06] -7.11 [-13.13, -1.09] -5.57 [-10.65, -0.50]	•

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

Study or Subgroup	Gabap Mean [VAS]		Total	Con Mean [VAS]		Total	Weight	Mean Difference IV, Random, 95% CI [VAS]	Mean Difference IV, Random, 95% CI [VAS]
3.8.1 0-350 mg									
Bang 2009	45	20	23	60	20	23	1.5%	-15.00 [-26.56, -3.44]	
Behdad 2012	38	9.6	30	66.2	13.7	31	1.9%	-28.20 [-34.12, -22.28]	-
Chowdhury 2010	40.8	5.26	100	45	3.37	100	2.0%	-4.20 [-5.42, -2.98]	•
Ghafari 2009	42.5	3.5	33	58.1	4	33	2.0%	-15.60 [-17.41, -13.79]	•
Sekhavet 2009	37.9	20.8	49	76.6	22.4	49	1.7%	-38.70 [-47.26, -30.14]	
Short 2012	14	7.4	42	20	10	21	1.9%	-6.00 [-10.83, -1.17]	-
Vahedi 2011	61.1	20.9	36	56.8	24.4	40	1.6%	4.30 [-5.89, 14.49]	+
Verma 2008	23	14	25	32	16	25	1.7%	-9.00 [-17.33, -0.67]	-
Waikakul 2011	50	25	24	60	25	24	1.4%	-10.00 [-24.14, 4.14]	
Yoon 2001	29	72	16	41	59	16	0.3%	-12.00 [-57.61, 33.61]	
Subtotal (95% CI)	25	12	378	41	35	362	16.0%	-13.65 [-20.17, -7.13]	
Heterogeneity: $Tau^2 = 8$	$25 \ 21 \cdot Chi^2 = 20$	4 97 df -		$0.00001) \cdot 1^2 -$	96%				•
Test for overall effect: Z			9 (r <	0.00001), 1 =	50%				
3.8.2 351-700 mg Ajori 2011	40	30	69	63	28	69	1.6%	-23.00 [-32.68, -13.32]	_
Dirks 2002	14		31		15	34		-4.00 [-12.10, 4.10]	
Grover 2002	14	18 8.15	27	18 10	8.15	34 23	1.7% 1.9%	-4.00 [-12.10, 4.10] 0.00 [-4.53, 4.53]	1
									I
Kazak 2009	15	22.5	30	22	29.5	30	1.4%	-7.00 [-20.28, 6.28]	
Khezri 2013	0	8	30	0	19	30	1.8%	0.00 [-7.38, 7.38]	I
Kinney 2011	27	25.2	57	28	26.2	68	1.7%	-1.00 [-10.03, 8.03]	_ T
Mahoori 2014	30	15.8	25	56.8	11.4	25	1.8%	-26.80 [-34.44, -19.16]	
Mardani-Kivi 2013	50	8	55	70	7	30	2.0%	-20.00 [-23.28, -16.72]	-
Menda 2010	20	31	30	30	48	30	1.0%	-10.00 [-30.45, 10.45]	
Metry 2008	12.52	9.5	67	24.1	13	34	1.9%	-11.58 [-16.51, -6.65]	
Moore 2010	19.5	15.5	21	40	20	23	1.6%	-20.50 [-31.02, -9.98]	
Panday 2005	29.5	12.36	40	50	10	20	1.9%	-20.50 [-26.32, -14.68]	-
Parikh 2010	29	7	30	55	6	30	2.0%	-26.00 [-29.30, -22.70]	-
Rajendran 2014	42.7	5.2	30	65	7.3	30	2.0%	-22.30 [-25.51, -19.09]	-
Short 2012a	15	6.7	42	20	10	21	1.9%	-5.00 [-9.73, -0.27]	7
Srivastava 2010	23	3.17	60	49	3.33	60	2.0%	-26.00 [-27.16, -24.84]	·
Zaldivar Ramirez 2011	30	13	18	55	9.8	16	1.8%	-25.00 [-32.69, -17.31]	-
Özcan 2012	12	23	20	34	13	20	1.5%	-22.00 [-33.58, -10.42]	
Subtotal (95% CI)			682			593	31.4%	-15.33 [-19.96, -10.71]	♦
Heterogeneity: Tau² = 8 Test for overall effect: Z			17 (P ·	< 0.00001); I ²	= 94%				
	. = 0.50 (1 < 0.0								
3.8.4 701-1050 mg	40	-	10	45	-	10	2.00/	F 00 [0 10 1 02]	_
Badawy 2014	40	5	19	45	5	19	2.0%	-5.00 [-8.18, -1.82]	
Deniz 2012 Kim 2004	23	28	25	31	27	26	1.3%	-8.00 [-23.11, 7.11]	<u> </u>
Kim 2004	27	22.2	21	29	17.6	20	1.5%	-2.00 [-14.23, 10.23]	
Koc 2007	2.3	9	20	12.5	27	20	1.5%	-10.20 [-22.67, 2.27]	
Marashi 2012	48	10	22	59	9				
						22	1.9%	-11.00 [-16.62, -5.38]	-
	37.5	11.1	10	47.5	14.4	10	1.5%	-10.00 [-21.27, 1.27]	
Radhakrishnan 2005	37.5 10		10 30			10 30	1.5% 1.8%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33]	
Prabhakar 2007 Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4	10	11.1 12.5	10 30 147	47.5 10	14.4	10	1.5%	-10.00 [-21.27, 1.27]	•
Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4	10 4.94; Chi ² = 8.22	11.1 12.5 2, df = 6 (F	10 30 147	47.5 10	14.4	10 30	1.5% 1.8%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33]	
Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4 Test for overall effect: Z	10 4.94; Chi ² = 8.22	11.1 12.5 2, df = 6 (F	10 30 147	47.5 10	14.4	10 30	1.5% 1.8%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33]	•
Radhakrishnan 2005 Subtotal (95% Cl) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg	10 4.94; Chi ² = 8.22 2 = 3.59 (P = 0.0	11.1 12.5 2, df = 6 (F 0003)	$10 \\ 30 \\ 147 \\ P = 0.2$	47.5 10 2); I ² = 27%	14.4 12.5	10 30 147	1.5% 1.8% 11.5%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] - 5.99 [-9.25, -2.72]	•
Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010	10 4.94; Chi ² = 8.22	11.1 12.5 2, df = 6 (F	10 30 147	47.5 10	14.4 12.5	10 30	1.5% 1.8%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58]	
Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005	10 4.94; Chi ² = 8.22 2 = 3.59 (P = 0.0 32	11.1 12.5 2, df = 6 (F 0003) 8	$10 \\ 30 \\ 147 \\ P = 0.2 \\ 30$	47.5 10 2); I ² = 27% 21	14.4 12.5	10 30 147 30	1.5% 1.8% 11.5% 1.9%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58] -10.10 [-14.89, -5.31]	
Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006	10 4.94; Chi ² = 8.22 2 = 3.59 (P = 0.0 32 14 4	$\begin{array}{c} 11.1 \\ 12.5 \\ 2, df = 6 \\ 0003 \\ 8 \\ 7 \\ 7.4 \end{array}$	$ \begin{array}{r} 10 \\ 30 \\ 147 \\ P = 0.2 \\ 30 \\ 35 \\ 38 \\ \end{array} $	47.5 10 2); I ² = 27% 21 24.1 6	14.4 12.5 6 13 6.6	10 30 147 30 37 38	1.5% 1.8% 11.5% 1.9% 1.9% 2.0%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58] -10.10 [-14.89, -5.31] -2.00 [-5.15, 1.15]	
Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008	10 4.94; Chi ² = 8.22 = 3.59 (P = 0.0 32 14 4 22.5	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 19.1	10 30 147 9 = 0.2 30 35 38 22	47.5 10 2); $I^2 = 27\%$ 21 24.1 6 23.5	14.4 12.5 6 13 6.6 21.3	10 30 147 30 37 38 21	1.5% 1.8% 11.5% 1.9% 2.0% 1.5%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58] -10.10 [-14.89, -5.31] -2.00 [-5.15, 1.15] -1.00 [-13.11, 11.11]	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003	10 4.94; Chi ² = 8.22 = 3.59 (P = 0.0) 32 14 4 22.5 14.12	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 19.1 15.23	$ \begin{array}{c} 10 \\ 30 \\ 147 \\ 9 = 0.2 \\ 30 \\ 35 \\ 38 \\ 22 \\ 40 \\ \end{array} $	$47.5 \\ 10$ 2); $I^2 = 27\%$ 21 24.1 6 23.5 21.53	14.4 12.5 6 13 6.6 21.3 18.59	10 30 147 30 37 38 21 40	1.5% 1.8% 11.5% 1.9% 1.9% 2.0% 1.5% 1.8%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58] -10.10 [-14.89, -5.31] -2.00 [-5.15, 1.15] -1.00 [-13.11, 11.11] -7.41 [-14.86, 0.04]	
Radhakrishnan 2005 Subtotal (95% C)) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010	10 4.94; Chi ² = 8.22 = 3.59 (P = 0.0) 32 14 4 22.5 14.12 18	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 19.1 15.23 17	$ \begin{array}{c} 10 \\ 30 \\ 147 \\ 9 = 0.2 \\ \end{array} $ $ \begin{array}{c} 30 \\ 35 \\ 38 \\ 22 \\ 40 \\ 30 \\ \end{array} $	47.5 10 2); l ² = 27% 21 24.1 6 23.5 21.53 33	14.4 12.5 6 13 6.6 21.3 18.59 11	10 30 147 30 37 38 21 40 29	1.5% 1.8% 11.5% 1.9% 1.9% 2.0% 1.5% 1.8% 1.8%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007	10 4.94; Chi ² = 8.22 2 = 3.59 (P = 0.0 32 14 4 22.5 14.12 18 45	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 19.1 15.23 17 51	$ \begin{array}{r} 10 \\ 30 \\ 147 \\ 7 = 0.2 \\ \begin{array}{r} 30 \\ 35 \\ 38 \\ 22 \\ 40 \\ 30 \\ 25 \\ \end{array} $	$47.5 \\ 10$ 2); $I^2 = 27\%$ 21 24.1 6 23.5 21.53	14.4 12.5 6 13 6.6 21.3 18.59 11 61	10 30 147 30 37 38 21 40 29 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 0.6%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58] -10.10 [-14.89, -5.31] -2.00 [-5.15, 1.15] -1.00 [-13.11, 11.11] -7.41 [-14.86, 0.04] -15.00 [-22.28, -7.72] -7.00 [-38.17, 24.17]	
Radhakrishnan 2005 Subtotal (95% Cl) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002	10 4.94; Chi ² = 8.22 = 3.59 (P = 0.0) 32 14 4 22.5 14.12 18 45 7	11.1 12.5 2. df = 6 (F 003) 8 7 7.4 19.1 15.23 17 51 20	$ \begin{array}{r} 10 \\ 30 \\ 147 \\ 7 = 0.2 \\ \begin{array}{r} 30 \\ 35 \\ 38 \\ 22 \\ 40 \\ 30 \\ 25 \\ 25 \\ \end{array} $	47.5 10 2); I ² = 27% 21 24.1 6 23.5 21.53 33 52 9	14.4 12.5 6 13 6.6 21.3 18.59 11 61 9	10 30 147 30 37 38 21 40 29 25 25	1.5% $1.8%$ $11.5%$ $1.9%$ $1.9%$ $2.0%$ $1.5%$ $1.8%$ $0.6%$ $1.6%$	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58] -10.10 [-14.89, -5.31] -2.00 [-5.15, 1.15] -1.00 [-13.11, 11.11] -7.41 [-14.86, 0.04] -15.00 [-22.28, -7.72] -7.00 [-38.17, 24.17] -2.00 [-12.81, 8.81]	
Radhakrishnan 2005 Subtotal (95% C)) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005	10 1.94; Chi ² = 8.22 2 = 3.59 (P = 0.0 32 14 4 22.5 14.12 18 45 7 17	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 19.1 15.23 17 51 20 0 28	10 30 147 2 = 0.2 30 35 38 22 40 30 25 25 29	47.5 10 2); I ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19 31	10 30 147 30 37 38 21 40 29 25 25 30	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 0.6% 1.3%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: 2 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005	10 1.94; Chi ² = 8.22 = 3.59 (P = 0.0 32 14 4 22.5 14.12 18 45 7 17 25.7	11.1 12.5 2, df = 6 (F 003) 8 7 7.4 19.1 15.23 17 51 20 28 16.1	10 30 147 9 = 0.2 30 35 38 22 40 30 25 25 29 30	47.5 10 2); I ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19 31 19.6	10 30 147 30 37 38 21 40 29 25 25 30 30	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 0.6% 1.3% 1.3%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58] -10.10 [-14.89, -5.31] -2.00 [-5.15, 1.15] -1.00 [-13.11, 11.11] -7.41 [-14.86, 0.04] -15.00 [-22.28, -7.72] -7.00 [-3.8.17, 24.17] -2.00 [-12.81, 8.81] -3.00 [-18.06, 12.06] -1.10 [-10.18, 7.98]	
Radhakrishnan 2005 Subtotal (95% Cl) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2005 Frouzanfard 2013	10 1.94; Chi ² = 8.22 = 3.59 (P = 0.0 32 14 4 22.5 14.12 18 45 7 17 25.7 35.6	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 4 19.1 15.23 17 51 20 28 16.1 15	10 30 147 9 = 0.2 30 35 38 22 40 30 25 29 30 25	47.5 10 2); I ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19 31 19.6 18	10 30 147 30 37 38 21 40 29 25 25 30 30 25	1.5% 1.8% 11.5% 1.9% 1.9% 1.5% 1.8% 1.8% 1.6% 1.6% 1.7%	-10.00 [-21.27, 1.27] 0.00 [-6.33, 6.33] -5.99 [-9.25, -2.72] 11.00 [7.42, 14.58] -10.10 [-14.89, -5.31] -2.00 [-5.15, 1.15] -1.00 [-13.11, 11.11] -7.41 [-14.86, 0.04] -15.00 [-22.28, -7.72] -7.00 [-38.17, 24.17] -2.00 [-12.81, 8.81] -3.00 [-18.06, 12.06] -1.10 [-10.18, 7.98] -30.00 [-39.18, -20.82]	
Radhakrishnan 2005 Subtotal (95% CI) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004	10 1.94; Chi ² = 8.22 2 = 3.59 (P = 0.0 14 4 22.5 14.12 18 45 7 17 25.7 35.6 29	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 19.1 15.23 17 51 20 28 16.1 15 5 4	10 30 147 2 = 0.2 30 35 38 22 40 30 25 25 29 30 25 23	47.5 10 2); l ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19 31 19.6 18 3	10 30 147 30 37 38 21 40 29 25 25 30 30 25 25 30 25 24	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 1.6% 1.3% 1.7% 2.0%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014	10 1.94; Chl ² = 8.22 = 3.59 (P = 0.0 32 14 4 22.5 14.12 18 45 7 17 25.7 35.6 29 6.84	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 19.1 15.23 15.23 16.1 15 20 28 8 16.1 15 4 4 12.97	10 30 147 2 = 0.2 30 35 38 22 40 30 25 25 29 30 25 23 52	47.5 10 2); l ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39 13.95	14.4 12.5 6 3 3 6.6 21.3 18.59 11 61 19 31 19.6 18 3 17.94	10 30 147 30 37 38 21 40 29 25 25 30 30 25 25 30 30 25 24 52	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 0.6% 1.6% 1.3% 1.7% 1.7% 1.7% 2.0%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right] \\ 0.00 \left[-6.33, 6.33\right] \\ -5.99 \left[-9.25, -2.72\right] \\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C)) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2008 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Gilton 2014 Grosen 2014 Hout 2007	10 1.94; Chi ² = 8.22 = 3.59 (P = 0.0 32 14 4 22.5 14.12 18 45 7 17 25.7 35.6 29 6.84 0	11.1 12.5 2, df = 6 (F 003) 8 7 7.4 19.1 15.23 17 51 20 28 16.1 15 4 12.97 5.93	10 30 147 2 = 0.2 30 35 38 22 40 30 25 25 29 30 25 23 22 30 25 23	47.5 10 2); I ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39 13.95 0	14.4 12.5 6 13 6.6 21.3 18.59 11 61 199 31 19.6 18 3 17.94 3.7	10 30 147 30 37 38 21 40 29 25 25 30 30 25 25 25 25 25 22 8	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 1.8% 1.6% 1.3% 1.7% 2.0% 1.8% 2.0%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: 2 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Jajeda 2014	10 $1.94; Chi2 = 8.22$ $= 3.59 (P = 0.0$ 32 14 4 22.5 14.12 18 45 7 7 25.7 35.6 29 6.84 0 31.6	11.1 12.5 2, df = 6 (F 003) 8 7 7.4 19.1 15.23 17 51 20 28 16.1 15.5 4 12.97 5.93 4.7	10 30 147 9 = 0.2 30 35 38 22 40 30 25 25 29 30 25 23 25 23 25	47.5 10 2); l ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39 13.95 0 52.4	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19.6 19.6 31 19.6 3 17.94 3.7 10.5	10 30 147 30 37 38 21 40 29 25 25 30 25 24 528 22 28 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 0.6% 1.6% 1.3% 1.7% 1.7% 1.7% 1.8% 2.0% 1.8% 2.0%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% Cl) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Jajeda 2014 Khan 2013	10 1.94; Chi ² = 8.22 = 3.59 (P = 0.0 14 4 22.5 14.12 18 45 7 17 25.7 35.6 29 6.84 0 31.6 36.17	11.1 12.5 2, df = 6 (F 003) 8 7 7.4 19.1 15.23 17 51 20 28 16.1 15 20 28.1 6.1 15 4 20,26 28.1 15 4,207 5.93 4.7 13.4	10 30 147 2 = 0.2 30 35 38 22 40 25 25 29 30 25 23 52 23 52 23 52 23 52 23 52 23	47.5 10 2); l ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39 13.95 0 52.4 52	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19.6 19.3 19.6 18.3 3 17.94 3.7 10.5	10 30 147 30 37 38 21 40 25 25 30 25 25 30 25 24 52 28 5 35	1.5% 1.8% 11.5% 1.9% 1.9% 1.5% 1.8% 1.8% 1.6% 1.6% 1.7% 2.0% 1.7% 2.0% 1.8% 2.0% 1.9%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2008 Brogly 2008 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Griouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Jajeda 2014 Khan 2013 Kosucu 2013	10 1.94; Chi ² = 8.22 = 3.59 (P = 0.0 32 14 4 22.5 14.12 18 45 7 17 25.7 35.6 29 6.84 0 31.6 36.17 29	11.1 12.5 2, df = 6 (f 0003) 8 7 7.4 19.1 15.23 17 51 20 28 16.1 15 5 5 4 12.97 5.93 4.7 13.4 4 12	10 30 147 2 = 0.2 30 35 38 22 40 30 25 25 29 30 25 23 52 23 52 23 52 23 52 23 34 29	47.5 10 2); l ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39 13.95 0 52.4 52 42	14.4 12.5 6 13 6.6 21.3 18.59 11 19.6 18 3 17.94 3.7 10.5 10.51 21	10 30 147 30 37 38 21 40 29 25 30 30 25 25 30 30 25 24 52 28 25 35 31	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.6% 1.7% 1.3% 2.0% 1.8% 2.0% 1.8% 2.0% 1.9% 1.9%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
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Radhakrishnan 2005 Subtotal (95% C)) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2008 Diorking 2003 Diorking 2003 Diorking 2003 Diorking 2003 Diorking 2003 Diorking 2003 Comparison 2004 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2004 Grosen 2014 Hout 2007 Jajeda 2014 Khan 2013 Kosucu 2013 Ménigaux 2004 Omran 2005 Sen 2009a Sen 2009a Sen 2009a Turan 2003a Turan 2003 Turan 2005	10 1.94; Chi ² = 8.22 14 4 2.5 14.12 18 45 7 17 25.7 35.6 29 6.84 0 31.6 36.17 29 18 35 28 18 35 28 18 35 28 18 35 29 18 35 29 18 35 29 20 31.6 35.7 20 31.6 35.7 35.6 20 31.6 35.7 35.8 35.7 35.8 35.7 35.8 35.7 35.8 35.7 35.8 35.7 35.8 35.7 35.8 35.7 35.8 35.8 35.7 35.8 35.8 35.7 35.8 35.7 35.8 35.7 35.8 35.8 35.7 35.8 3	11.1 12.5 2, df = 6 (F 003) 8 7 7.4 19.1 15.23 17 51 20 20 20 20 20 20 20 20 4 4 12.97 5.9 4.7 13.4 12.97 5.9 24 12 25 24 15 15 31	10 30 147 2 = 0.2 30 35 38 22 40 0 25 23 30 25 23 34 25 20 20 25 20 20 25 20 20 25 20 20 25 20 20 20 20 20 20 20 20 20 20	$\begin{array}{c} 47.5\\ 10\\ \end{array}$	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19.6 19.3 17.94 31 19.6 18 31 7.94 45.69 47 25 10.51 21 34 45.69 47 25 10 10 8 35	100 300 1477 300 377 388 244 40 29 25 25 25 26 20 20 25 25 20 0 25 25 25 25 25 25 25 25 25 25 25 25 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 1.8% 1.6% 1.7% 1.7% 1.7% 1.7% 2.0% 1.9% 1.7% 1.8% 2.0% 1.9% 1.6% 1.8% 0.8% 0.8% 0.9%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Diorking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Jajeda 2014 Khan 2013 Kosucu 2013 Ménigaux 2004 Omran 2006 Sen 2009b Sura 2003b Turan 2003b Turan 2004 Turan 2005 Lucak 2011	10 1.94; Chi ² = 8.22 14 4 22.5 14.12 14.12 18 45 7 17 25.7 35.6 29 6.84 0 31.6 36.17 29 18 35 28 18 35 18 13 15 34	11.1 12.5 2, df = 6 (f 0003) 8 7 7.4 19.1 15.23 17 51 20 28 16.1 15 5.93 4.7 13.4 12.97 5.93 4.7 13.4 12 7 45.59 24 12 12 6 15 31 11	100 30 30 3147 2 = 0.2 30 35 38 8 22 23 33 8 25 25 23 34 25 25 20 20 30 30 30 25 25 25 20 20 30 30 30 25 25 25 20 20 30 30 30 30 30 30 30 30 30 30 30 30 30	$\begin{array}{c} 47.5\\ 10\\ \end{array}$	14.4 12.5 6 13 6.6 21.3 18.59 11 19,6 19,31 19,6 19,6 19,6 19,6 19,6 19,6 19,6 19,	10 30 147 30 37 38 21 40 29 25 30 30 25 24 25 28 825 31 20 29 25 20 29 25 20 25 25 20 25 25 20 25 25 20 25 25 20 25 20 25 20 25 20 25 20 25 25 20 25 25 20 25 25 25 25 25 25 25 25 25 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.6% 1.3% 2.0% 1.3% 2.0% 1.3% 2.0% 1.3% 2.0% 1.3% 1.6% 1.3% 1.6% 1.6% 1.6% 1.6%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C)) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Grosen 2014 Hout 2007 Grosen 2014 Hout 2007 Grosen 2014 Hout 2007 Grosen 2014 Hout 2007 Sen 2009a Sen 2009b Turan 2005 Sen 2009b Turan 2004 Turan 2005 Ucak 2011 Ozgencil 2011	10 1.94; Chi ² = 8.22 = 3.59 (P = 0.0 32 14 4 22.5 14.12 18 45 7 7 25.7 35.6 26 29 6.84 0 31.6 36.17 29 18 35 28 15 18 13 15 34 29.9	11.1 12.5 2, df = 6 (f 0003) 8 7,4 19.1 15.23 17 51 20 28 16.1 15 20 28 8 16.1 15 4 12.97 5.93 4.7 7 45.59 24 4 12 6 15 5 31 11 2	10 30 147 2 = 0.2 30 35 38 22 29 30 30 25 23 25 23 25 23 25 23 25 20 30 30 25 22 23 25 20 20 20 20 20 20 20 20 20 20	$\begin{array}{c} 47.5\\ 10\\ \end{array}$	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19 31 19.6 18 3 17.94 3.7 10.55 10.51 21 34 45.69 47 25 10 13 4 53 83 83	10 30 147 30 37 38 821 40 25 25 30 30 25 25 35 31 20 25 25 35 35 31 20 25 25 25 25 25 25 25 25 25 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 1.7% 1.7% 2.0% 1.6% 1.3% 0.6% 1.8% 2.0% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9% 1.9	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2006 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Jajeda 2014 Khan 2013 Kosucu 2013 Ménigaux 2004 Omran 2006 Sen 2009b Turan 2003b Turan 2003 Turan 2004 Turan 2005 Ucak 2011 Ozgencil 2011 Subtotal (95% C) Heterogeneity: Tau ² = 7	10 1.94; Chi ² = 8.22 14 4 22.5 14.12 18 45 7 7 75.7 35.6 29 6.84 0 31.6 36.17 29 18 35 28 15 34 29.9 24 23.68; Chi ² = 24	11.1 12.5 2, df = 6 (f 003) 8 7,4 19.1 15.23 17 51 20 28 16.1 15 28 16.1 15 4 4 12.97 5.93 4.7 13.4 12.97 5.93 4.7 13.4 12 26.7 7.48, df = 6 7.48, df = 6 7.4 19.1 19.1 19.1 19.1 19.1 19.1 19.1 19	100 30 30 3147 3 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5 5	$\begin{array}{c} 47.5\\ 10\\ \end{array}$	14.4 12.5 6 13 6.6 21.3 18.59 11 19,6 19 31 19,6 19,3 17.94 3,7 10.5 10.51 21 34 45.69 47 7 25 10.5 10.5 10.5 10.8 83 83 83 85 10.9	10 30 147 30 37 38 21 40 9 25 25 30 30 30 24 52 28 28 28 26 30 30 29 25 25 26 20 20 29 25 26 20 20 20 20 20 20 20 20 20 20	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.5% 1.8% 1.7% 1.3% 2.0% 1.3% 1.7% 1.3% 1.7% 1.3% 0.9% 1.9% 1.8% 1.7% 0.9%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2005 Fassoulaki 2005 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Jajeda 2014 Khan 2013 Kosucu 2013 Ménigaux 2004 Omran 2006 Sen 2009b Turan 2003b Turan 2003b Turan 2003b Turan 2005 Ucak 2011 Ozgencil 2011 Subtotal (95% C) Heterogeneity: Tau ² = 7 Test for overall effect: Z	10 1.94; Chi ² = 8.22 14 4 22.5 14.12 18 45 7 7 75.7 35.6 29 6.84 0 31.6 36.17 29 18 35 28 15 34 29.9 24 23.68; Chi ² = 24	11.1 12.5 2, df = 6 (f 0003) 8 7, 4 19.1 15.23 17 51 20 28 16.1 15 20 28 8 16.1 15 4 12.97 5.93 4,7 13.4 12.97 5.93 4,7 13.4 12. 6 6 5.59 24 4 6 5.59 24 6 6 5.59 24 6 6 7 7,4 12.1 6 7 7,4 13.4 12.97 5.3 7 7,4 12.97 5.3 7 7,4 12.97 5.3 7 7 7,4 12.97 5.3 7 7 7 7,4 12.97 5.3 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	100 30 30 3147 2 = 0.2 30 35 38 8 22 40 35 25 23 32 25 23 32 25 23 32 25 23 32 25 20 30 25 25 20 30 30 25 22 20 30 30 25 22 20 30 30 30 25 22 20 20 20 20 20 20 20 20 20 20 20 20	$\begin{array}{c} 47.5\\ 10\\ \end{array}$	14.4 12.5 6 13 6.6 21.3 18.59 11 19,6 19 31 19,6 19,3 17.94 3,7 10.5 10.51 21 34 45.69 47 7 25 10.5 10.5 10.5 10.8 83 83 83 85 10.9	10 30 147 30 37 38 821 40 25 25 30 30 25 24 45 22 28 35 31 20 25 25 35 31 20 25 25 25 25 25 25 25 25 25 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 1.7% 1.7% 1.3% 2.0% 1.8% 2.0% 1.3% 0.6% 1.3% 0.8% 0.9% 1.9% 1.6% 1.3% 0.9% 0.5% 1.9% 1.9% 1.9% 1.9% 1.1%	$\begin{array}{r} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C)) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Fassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Menigaux 2004 Omran 2005 Sen 2009b Turan 2004 Turan 2005 Sen 2009b Turan 2004 Turan 2005 Uran 2004 Turan 2005 Uran 2005 Turan 2004 Turan 2005 Luran 2005 Turan 20	10 $3.94; Chi2 = 8.22$ $3.59 (P = 0.0)$ 32 14 4 22.5 14.12 18 45 7 7 $7,7$ 35.6 29 6.84 0 31.6 36.17 29 8 35 28 18 35 28 15 18 35 28 15 18 35 28 15 34 29.9 24 $73.68; Chi2 = 24$ $24.78 (P < 0.0)$	11.1 12.5 2, df = 6 (F 0003) 8 7 7.4 4 19.1 15.23 16.1 15 5 1 20 28 16.1 15 5 4 12.97 4.7 13.4 12 7 45.59 24 12 16 15 31 1 11 2 2 6.7 7 .48, df = 6 5 31 11 2 7 7 .48, df = 6 24 25 24 24 26 55 15 20 24 26 27 7 7 .44 20 26 27 27 24 26 26 27 27 24 26 26 26 27 27 26 26 26 26 27 27 26 26 27 27 26 27 26 27 26 27 27 26 27 26 27 27 26 27 27 26 27 27 27 27 27 27 27 27 28 27 27 28 27 27 28 27 29 27 24 27 26 27 27 26 27 27 26 27 27 26 27 27 27 27 27 27 27 28 27 28 27 29 29 29 26 27 27 27 27 28 27 28 27 29 29 29 29 29 29 20 20 20 20 20 20 20 20 20 20 20 20 20	100 30 147 9 = 0.2 30 35 38 22 40 0 25 25 23 22 30 25 23 25 23 25 23 25 23 25 23 25 23 25 23 25 23 25 20 30 0 25 25 20 20 30 0 755 25 20 20 21 21 21 21 21 21 21 21 21 21 21 21 21	47.5 10 2); l ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39 13.95 0 52.4 42 21 61 41 20 42 24 33 52 42 21 6 52 42 21 6 53 52 9 20 20.8 52 42 21 53 52 9 20 20.8 52 9 20 20.8 52 42 21 53 33 52 9 20 20.8 52 42 21 53 52 9 20 20.8 52 13.95 0 52.4 42 21 53 33 52 9 20 20.8 52 42 21 53 33 52 21 53 33 52 20 20 20 20 20 20 20 20 20 2	14.4 12.5 6 13 6.6 21.3 18.59 11 19.6 19.3 17.94 3.7 10.5 10.51 21 34 45.69 47 25 10 0 18 83 65 10.9 = 89%	10 30 147 30 37 38 821 40 25 25 30 30 25 24 45 22 28 35 31 20 25 25 35 31 20 25 25 25 25 25 25 25 25 25 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.5% 1.8% 1.5% 1.8% 1.3% 1.7% 1.3% 1.7% 1.3% 1.9% 1.9% 1.9%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Jajeda 2014 Khan 2013 Ménigaux 2004 Omran 2006 Sen 2009b Turan 2003 Sen 2009b Turan 2004 Turan 2005 Ucak 2011 Özgencil 2011 Subtotal (95% CI) Heterogeneity: Tau ² = 7 Total (95% CI)	10 $1.94; Chi^{2} = 8.22$ 32 14 4 422.5 14.12 18 45 7 7 25.7 35.6 29 6.84 0 31.6 36.17 29 6.84 35 28 35 18 13 15 34 29.9 24 $23.68; Chi^{2} = 24$ $4.78 (P < 0.0$ $112.12; Chi^{2} = 1$	11.1 12.5 2, df = 6 (f 0003) 8 7 7.4 19.1 15.23 17 7 51 20 28 16.1 15 5.9 3 4.7 13.4 12 7 45.59 24 12 6 5.3 1 11 2 7 7.48, df = 6.7 7.48, df = 6.7 7.48, df = 12 6.7	100 30 147 9 = 0.2 30 35 38 22 40 0 25 25 23 22 30 25 23 25 23 25 23 25 23 25 23 25 23 25 23 25 23 25 20 30 0 25 25 20 20 30 0 755 25 20 20 21 21 21 21 21 21 21 21 21 21 21 21 21	47.5 10 2); l ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39 13.95 0 52.4 42 21 61 41 20 42 24 33 52 42 21 6 52 42 21 6 53 52 9 20 20.8 52 42 21 53 52 9 20 20.8 52 9 20 20.8 52 42 21 53 33 52 9 20 20.8 52 42 21 53 52 9 20 20.8 52 13.95 0 52.4 42 21 53 33 52 9 20 20.8 52 42 21 53 33 52 21 53 33 52 20 20 20 20 20 20 20 20 20 2	14.4 12.5 6 13 6.6 21.3 18.59 11 19.6 19.3 17.94 3.7 10.5 10.51 21 34 45.69 47 25 10 0 18 83 65 10.9 = 89%	10 30 147 30 37 38 821 40 25 25 30 30 25 24 45 22 28 35 31 20 25 25 35 31 20 25 25 25 25 25 25 25 25 25 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 1.7% 1.7% 1.3% 2.0% 1.8% 2.0% 1.3% 0.6% 1.3% 0.8% 0.9% 1.9% 1.6% 1.3% 0.9% 0.5% 1.9% 1.9% 1.9% 1.9% 1.1%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	
Radhakrishnan 2005 Subtotal (95% C) Heterogeneity: Tau ² = 4 Test for overall effect: Z 3.8.5 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Brogly 2008 Dierking 2003 Doha 2010 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007 Jajeda 2014 Khan 2013 Kosucu 2013 Ménigaux 2004 Omran 2006 Sen 2009a Sen 2009b Turan 2003b Turan 2005 Turan 2005 Tu	10 1,94; Chi ² = 8.22 1,359 (P = 0.0 1,22,59 (P = 0.0 1,122,12; Chi ² = 1 1,12 1,14 4,22,55 1,1,12 1,12	11.1 12.5 2, df = 6 (f 003) 8 7,4 19.1 15.23 17 51 20 28 16.1 15 20 28 16.1 15 4 12.97 5.93 4.7 13.4 12.97 5.93 4.7 13.4 12.97 5.93 24 4.7 25.59 24 12 16 15 5.31 11 27 5.33 4.7 7 45.59 24 6 6 5.59 24 6 6 7 7.48 12 6 7 7.48 12 12 7 7.48 12 12 7 7.48 12 12 7 7.48 12 12 7 7 7.48 12 12 7 7 7 7 4 12 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	100 30 147 9 = 0.2 30 35 38 8 22 40 25 25 23 30 25 23 32 25 23 34 29 20 25 23 34 25 23 34 25 25 20 30 30 25 25 22 23 32 25 22 20 20 25 25 22 20 20 25 22 20 20 25 22 20 20 25 22 20 20 25 22 20 20 20 25 22 20 20 20 20 20 20 20 20 20 20 20 20	47.5 10 2); ² = 27% 21 24.1 6 23.5 21.53 33 52 9 20 26.8 65.6 39 13.95 0 52.4 52 42 21 61 41 20 42 24 31 57 50 33.3 < 0.00001); ² (P < 0.00001);	14.4 12.5 6 13 6.6 21.3 18.59 11 61 19 31 19.6 18 3 17.94 3.7 10.55 10.51 21 34 45.69 47 25 10 10 83 33 65 10.9 83 83 65 10.9 83 83 65 10.9 1	10 30 147 30 37 38 821 40 25 25 30 30 25 24 45 22 28 35 31 20 25 25 35 31 20 25 25 25 25 25 25 25 25 25 25	1.5% 1.8% 11.5% 1.9% 2.0% 1.5% 1.8% 1.8% 1.7% 1.7% 1.3% 2.0% 1.8% 2.0% 1.3% 0.6% 1.3% 0.8% 0.9% 1.9% 1.6% 1.3% 0.9% 0.5% 1.9% 1.9% 1.9% 1.9% 1.1%	$\begin{array}{c} -10.00 \left[-21.27, 1.27\right]\\ 0.00 \left[-6.33, 6.33\right]\\ -5.99 \left[-9.25, -2.72\right]\\ \end{array}$	

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

		pentin		Cont				Mean Difference	Mean Difference
Study or Subgroup	Mean [VAS]	SD [VAS]	Total	Mean [VAS] S	D [VAS]	Total	Weight	IV, Random, 95% CI [VAS]	IV, Random, 95% CI [VAS]
3.9.1 0-350 mg									
Short 2012 Subtotal (95% CI)	29	10.4	42 42	40	10	21 21	18.8% 18.8%	-11.00 [-16.31, -5.69] - 11.00 [-16.31, -5.69]	
Heterogeneity: Not app Fest for overall effect:		0.0001)							
3.9.2 351-700 mg		,							
Moore 2010	20	13.25	21	10	14 5	22	11 20/		_
Short 2012a	20 31	13.25	42	40 40	14.5 10	23 21	11.3% 16.5%	-20.00 [-28.20, -11.80] -9.00 [-15.02, -2.98]	
Srivastava 2010	51	3.33	42 60	70.5	3.5	60	34.1%	-11.50 [-12.72, -10.28]	
Subtotal (95% CI)			123		5.5	104	61.9%	-12.43 [-16.81, -8.04]	
Heterogeneity: Tau ² = Test for overall effect:		,	2 (P =	0.09); I ² = 58%					
3.9.5 701-1050 mg									
Subtotal (95% CI)			0			0		Not estimable	
Heterogeneity: Not app Fest for overall effect:		2							
3.9.6 > 1050 mg									
Brogly 2008	45.6	24.8	22	39.4	20.1	21	5.3%	6.20 [-7.26, 19.66]	
assoulaki 2005	40	67	29	53	78	30	0.8%	-13.00 [-50.06, 24.06]	
Grosen 2014 Subtotal (95% CI)	12.42	18.55	52 103	21.29	19.28	52 103	13.3% 19.3%	-8.87 [-16.14, -1.60] -3.77 [-15.42, 7.89]	
Heterogeneity: Tau ² = Test for overall effect:			= 2 (P =	: 0.14); I ² = 489	5				
Fotal (95% CI)			268			228	100.0%	-10.69 [-14.03, -7.35]	•
Heterogeneity: Tau ² =	8.15; Chi ² = 1	L1.92, df =	= 6 (P =	$= 0.06$; $I^2 = 50\%$	5				
Fact for overall offect:	Z = 6.27 (P <	0.00001)							Favours Gabapentin Favours Control
lest for overall effect.				$= 0.39$), $I^2 = 0\%$					

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

		pentin			ntrol			Mean Difference	Mean Difference
udy or Subgroup	Mean [VAS]	SD [VAS]	Total	Mean [VAS]	SD [VAS]	Total	Weight	IV, Random, 95% CI [VAS]	IV, Random, 95% CI [VAS]
10.1 0-350 mg									
ort 2012	29	10.4	42	40	10	21	7.2%	-11.00 [-16.31, -5.69]	-
oon 2001 I btotal (95% CI)	41	60	16 58	58	74	16 37	0.3% 7.5%	-17.00 [-63.68, 29.68] - 11.08 [-16.35, -5.80]	•
eterogeneity: Tau ² =			(P = 0)	.80); $I^2 = 0\%$					
est for overall effect:	Z = 4.12 (P <	0.0001)							
10.2 351-700 mg									
over 2009	30	14.81	27	30	7.41	23	6.4%	0.00 [-6.35, 6.35]	+
enda 2010	43.5	57	30	65	78	30	0.5%	-21.50 [-56.07, 13.07]	
etry 2008	20.52	14.48	67	31.3	15	34	6.5%	-10.78 [-16.90, -4.66]	-
oore 2010	20	13.25	21	40	14.5	23	5.1%	-20.00 [-28.20, -11.80]	
ort 2012a	31	14	42	40	10	21	6.6%	-9.00 [-15.02, -2.98]	-
ivastava 2010	59	3.33	60 247	70.5	3.5	60	10.1%	-11.50 [-12.72, -10.28]	1
ibtotal (95% CI) eterogeneity: Tau ² =	18 56' Chi ² -	17.46 df		-0.004 · $1^2 -$	71%	191	35.2%	-10.21 [-14.72, -5.70]	•
est for overall effect:			-) (/ -	- 0.004), 1 =	/ 1/0				
10.5 701–1050 mg									
m 2004	42	25.2	21	37	15.8	20	2.9%	5.00 [-7.81, 17.81]	
abhakar 2007	52.5	10.9	10	65	19.6	10	2.6%	-12.50 [-26.40, 1.40]	
dhakrishnan 2005	20	15	30	30	20	30	4.6%	-10.00 [-18.95, -1.05]	
ibtotal (95% CI)			61			60	10.1%	-6.11 [-16.15, 3.94]	•
eterogeneity: Tau ² =			2 (P =	$(0.11); I^2 = 55$	%				
est for overall effect:	Z = 1.19 (P =	0.23)							
10.6 . 1050									
10.6 > 1050 mg									
-Mujadi 2005	23	12	35	31.3	15	37	6.4%	-8.30 [-14.56, -2.04]	-
	23 3	12 7.4	35 38	31.3 5	15 9.6	37 38	6.4% 8.4%	-8.30 [-14.56, -2.04] -2.00 [-5.85, 1.85]	-
-Mujadi 2005 rtholdy 2006									-
-Mujadi 2005	3	7.4	38	5	9.6	38	8.4%	-2.00 [-5.85, 1.85]	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003	3 45.6	7.4 24.8	38 22	5 39.4	9.6 20.1	38 21	8.4% 2.7%	-2.00 [-5.85, 1.85] 6.20 [-7.26, 19.66] -8.56 [-20.44, 3.32]	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002	3 45.6 42.53	7.4 24.8 25.9	38 22 40	5 39.4 51.09	9.6 20.1 28.27	38 21 40	8.4% 2.7% 3.2%	-2.00 [-5.85, 1.85] 6.20 [-7.26, 19.66]	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002 rmus 2007	3 45.6 42.53 19	7.4 24.8 25.9 21	38 22 40 31	5 39.4 51.09 31	9.6 20.1 28.27 23	38 21 40 34	8.4% 2.7% 3.2% 3.7%	-2.00 [-5.85, 1.85] 6.20 [-7.26, 19.66] -8.56 [-20.44, 3.32] -12.00 [-22.70, -1.30]	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002 irmus 2007 ssoulaki 2002	3 45.6 42.53 19 67	7.4 24.8 25.9 21 77	38 22 40 31 25	5 39.4 51.09 31 76	9.6 20.1 28.27 23 83	38 21 40 34 25	8.4% 2.7% 3.2% 3.7% 0.3% 1.0%	-2.00 [-5.85, 1.85] 6.20 [-7.26, 19.66] -8.56 [-20.44, 3.32] -12.00 [-22.70, -1.30] -9.00 [-53.38, 35.38] -8.00 [-32.57, 16.57]	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002 urmus 2007 ssoulaki 2002 ssoulaki 2005	3 45.6 42.53 19 67 21 40	7.4 24.8 25.9 21 77 35 67	38 22 40 31 25 25 29	5 39.4 51.09 31 76 29 53	9.6 20.1 28.27 23 83 52 78	38 21 40 34 25 25 30	8.4% 2.7% 3.2% 3.7% 0.3% 1.0% 0.5%	-2.00 [-5.85, 1.85] 6.20 [-7.26, 19.66] -8.56 [-20.44, 3.32] -12.00 [-22.70, -1.30] -9.00 [-52.338, 35.38] -8.00 [-32.57, 16.57] -13.00 [-50.06, 24.06]	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002 Jirmus 2007 ssoulaki 2002 ssoulaki 2005 ssoulaki 2005	3 45.6 42.53 19 67 21 40 47.8	7.4 24.8 25.9 21 77 35 67 19.7	38 22 40 31 25 25 29 30	5 39.4 51.09 31 76 29 53 45.1	9.6 20.1 28.27 23 83 52 78 24.6	38 21 40 34 25 25 30 30	8.4% 2.7% 3.2% 3.7% 0.3% 1.0% 0.5% 3.5%	-2.00 [-5.85, 1.85] 6.20 [-7.26, 19.66] -8.55 [-20.44, 3.32] -12.00 [-22.70, -1.30] -9.00 [-53.38, 35.38] -8.00 [-32.57, 16.57] -13.00 [-50.06, 24.06] 2.70 [-8.58, 13.98]	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002 urmus 2007 ssoulaki 2002 ssoulaki 2005 ssoulaki 2005 osen 2014	3 45.6 42.53 19 67 21 40 47.8 12.42	7.4 24.8 25.9 21 77 35 67 19.7 18.55	38 22 40 31 25 25 29 30 52	5 39.4 51.09 31 76 29 53 45.1 21.29	9.6 20.1 28.27 23 83 52 78 24.6 19.28	38 21 40 34 25 25 30 30 52	8.4% 2.7% 3.2% 0.3% 1.0% 0.5% 3.5% 5.7%	-2.00 [-5.85, 1.85] 6.20 [-7.26, 19.66] -8.56 [-20.44, 3.32] -12.00 [-22.70, -1.30] -9.00 [-53.38, 35.38] -8.00 [-53.35, 7, 16.57] -13.00 [-50.06, 24.06] 2.70 [-8.58, 13.98] -8.87 [-16.14, -1.60]	
-Mujadi 2005 irtholdy 2006 ogly 2008 erking 2003 rks 2002 urmus 2007 ssoulaki 2005 ssoulaki 2005 ssoulaki 2006 osen 2014 mran 2006	3 45.6 42.53 19 67 21 40 47.8 12.42 60	7.4 24.8 25.9 21 77 35 67 19.7 18.55 35.16	38 22 40 31 25 29 30 52 25	5 39.4 51.09 31 76 53 53 45.1 21.29 80	9.6 20.1 28.27 23 83 52 78 24.6 19.28 35.16	38 21 40 34 25 25 30 30 52 25	8.4% 2.7% 3.2% 3.7% 0.3% 1.0% 0.5% 3.5% 5.7% 1.5%	-2.00 [-5.85, 1.85] 6.20 [-7.26, 19.66] -8.56 [-20.44, 3.32] -12.00 [-22.70, -1.30] -9.00 [-53.38, 35.38] -8.00 [-32.57, 16.57] -13.00 [-50.06, 24.06] 2.70 [-8.58, 13.98] -8.87 [-16.14, -1.60] -20.00 [-39.49, -0.51]	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002 urmus 2007 ssoulaki 2002 ssoulaki 2005 ssoulaki 2005 ssoulaki 2006 osen 2014 mran 2006 n 2009a	3 45.6 42.53 19 67 21 40 47.8 12.42 60 32	7.4 24.8 25.9 21 77 35 67 19.7 18.55 35.16 34	38 22 40 31 25 29 30 52 25 20	5 39.4 51.09 31 76 29 53 45.1 21.29 80 56	9.6 20.1 28.27 23 83 52 78 24.6 19.28 35.16 54	38 21 40 34 25 25 30 30 52 25 20	8.4% 2.7% 3.2% 3.7% 0.3% 1.0% 0.5% 3.5% 5.7% 1.5% 0.8%	$\begin{array}{c} -2.00 \left[-5.85, 1.85\right]\\ 6.20 \left[-7.26, 19.66\right]\\ -8.56 \left[-20.44, 3.32\right]\\ -12.00 \left[-22.70, -1.30\right]\\ -9.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-50.06, 24.06\right]\\ 2.70 \left[-8.58, 13.98\right]\\ -8.87 \left[-16.14, -1.60\right]\\ -20.00 \left[-39.49, -0.51\right]\\ -24.00 \left[-51.97, 3.97\right]\end{array}$	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002 urmus 2007 ssoulaki 2002 ssoulaki 2005 ssoulaki 2006 osen 2014 mran 2006 n 2009a n 2009b	3 45.6 42.53 19 67 21 40 47.8 12.42 60 32 19	7.4 24.8 25.9 21 77 35 67 19.7 18.55 35.16 34 15	38 22 40 31 25 29 30 52 25 20 30	5 39.4 51.09 31 76 29 53 45.1 21.29 80 56 21	9.6 20.1 28.27 23 83 52 78 24.6 19.28 35.16 54 25	38 21 40 34 25 25 30 30 52 25 20 29	8.4% 2.7% 3.2% 3.7% 0.3% 1.0% 0.5% 5.5% 5.7% 1.5% 0.8% 3.8%	$\begin{array}{c} -2.00 \left[-5.85, 1.85\right]\\ 6.20 \left[-7.26, 19.66\right]\\ -8.56 \left[-20.44, 3.32\right]\\ -12.00 \left[-22.70, -1.30\right]\\ -9.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.257, 16.57\right]\\ -13.00 \left[-50.06, 24.06\right]\\ 2.70 \left[-8.58, 13.98\right]\\ -8.87 \left[-16.14, -1.60\right]\\ -20.00 \left[-39.49, -0.51\right]\\ -24.00 \left[-51.97, 3.97\right]\\ -2.00 \left[-12.56, 8.56\right]\end{array}$	
-Mujadi 2005 rtholdy 2006 ogly 2008 erking 2003 rks 2002 urmus 2007 ssoulaki 2005 ssoulaki 2005 ssoulaki 2006 osen 2014 nran 2006 n 2009a n 2009b ran 2003a	3 45.6 42.53 19 67 21 40 47.8 12.42 60 32 19 31.2	7.4 24.8 25.9 21 77 35 67 19.7 18.55 35.16 34 15 17	38 22 40 31 25 29 30 52 25 20 30 25	5 39,4 51.09 31 76 29 53 45.1 21.29 80 56 21 43	9.6 20.1 28.27 23 83 52 78 24.6 19.28 35.16 54 25 12	38 21 40 34 25 25 30 30 52 25 20 29 25	8.4% 2.7% 3.2% 3.7% 1.0% 0.5% 3.5% 5.7% 1.5% 0.8% 3.8% 5.1%	$\begin{array}{c} -2.00 [-5.85, 1.85] \\ 6.20 [-7.26, 19.66] \\ -8.55 [-20.44, 3.32] \\ -12.00 [-22.70, -1.30] \\ -9.00 [-53.38, 35.38] \\ -8.00 [-32.57, 16.57] \\ -13.00 [-50.06, 24.06] \\ 2.70 [-8.58, 13.98] \\ -8.87 [-16.14, -1.60] \\ -20.00 [-39.49, -0.51] \\ -24.00 [-51.97, 3.97] \\ -2.00 [-12.56, 8.57] \\ -11.80 [-19.96, -3.64] \end{array}$	
-Mujadi 2005 artholdy 2006 ogly 2008	3 45.6 42.53 19 67 21 40 47.8 12.42 60 32 19	7.4 24.8 25.9 21 77 35 67 19.7 18.55 35.16 34 15	38 22 40 31 25 29 30 52 25 20 30	5 39.4 51.09 31 76 29 53 45.1 21.29 80 56 21	9.6 20.1 28.27 23 83 52 78 24.6 19.28 35.16 54 25	38 21 40 34 25 25 30 30 52 25 20 29	8.4% 2.7% 3.2% 3.7% 0.3% 1.0% 0.5% 5.5% 5.7% 1.5% 0.8% 3.8%	$\begin{array}{c} -2.00 \left[-5.85, 1.85\right]\\ 6.20 \left[-7.26, 19.66\right]\\ -8.56 \left[-20.44, 3.32\right]\\ -12.00 \left[-22.70, -1.30\right]\\ -9.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.257, 16.57\right]\\ -13.00 \left[-50.06, 24.06\right]\\ 2.70 \left[-8.58, 13.98\right]\\ -8.87 \left[-16.14, -1.60\right]\\ -20.00 \left[-39.49, -0.51\right]\\ -24.00 \left[-51.97, 3.97\right]\\ -2.00 \left[-12.56, 8.56\right]\end{array}$	
-Mujadi 2005 irtholdy 2006 ogly 2008 erking 2003 rks 2002 irmus 2007 issoulaki 2002 issoulaki 2005 issoulaki 2005 issoulaki 2006 iosen 2014 mran 2006 in 2009b iran 2003a iak 2011	3 45.6 42.53 19 67 21 40 47.8 12.42 60 32 19 31.2 39 8.60; Chi ² = 1	7.4 24.8 25.9 21 77 35 67 19.7 18.55 35.16 34 15 17 20 8.55, df =	38 22 40 31 25 29 30 52 20 30 25 20 447	5 39.4 51.09 31 76 29 53 45.1 21.29 80 56 21 43 55	9.6 20.1 28.27 23 83 52 78 24.6 19.28 35.16 54 25 12 68	38 21 40 34 25 25 30 30 52 25 20 29 25 20	8.4% 2.7% 3.2% 3.7% 0.3% 1.0% 0.5% 3.5% 5.7% 1.5% 0.8% 3.8% 5.1% 0.6%	$\begin{array}{c} -2.00 \left[-5.85, 1.85\right]\\ 6.20 \left[-7.26, 19.66\right]\\ -8.56 \left[-20.44, 3.32\right]\\ -12.00 \left[-22.70, -1.30\right]\\ -9.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.35, 16.57\right]\\ -13.00 \left[-50.06, 24.06\right]\\ 2.70 \left[-8.58, 13.98\right]\\ -8.87 \left[-16.14, -1.60\right]\\ -20.00 \left[-39.49, -0.51\right]\\ -24.00 \left[-51.97, 3.97\right]\\ -2.00 \left[-12.56, 8.56\right]\\ -11.80 \left[-19.96, -3.64\right]\\ -16.00 \left[-47.06, 15.06\right]\end{array}$	
-Mujadi 2005 irtholdy 2006 ogly 2008 erking 2003 irks 2002 urmus 2007 issoulaki 2005 issoulaki 2005 issoulaki 2006 osen 2014 mran 2006 in 2009a in 2009b uran 2003a tak 2011 bibotal (95% CI) eterogeneity: Tau ² = ist for overall effect:	3 45.6 42.53 19 67 21 40 47.8 12.42 60 32 19 31.2 39 8.60; Chi ² = 1	7.4 24.8 25.9 21 77 35 67 19.7 18.55 35.16 34 15 17 20 8.55, df =	38 22 40 31 25 29 30 52 25 20 30 25 20 447 14 (P =	5 39.4 51.09 31 76 29 53 45.1 21.29 80 56 21 43 55	9.6 20.1 28.27 23 83 52 78 24.6 19.28 35.16 54 25 12 68	38 21 40 34 25 25 30 30 52 25 20 29 25 20 451	8.4% 2.7% 3.2% 0.3% 1.0% 0.5% 3.5% 5.7% 1.5% 0.8% 3.8% 5.1% 0.6% 47.2%	$\begin{array}{c} -2.00 \left[-5.85, 1.85\right]\\ 6.20 \left[-7.26, 19.66\right]\\ -8.55 \left[-20.44, 3.32\right]\\ -12.00 \left[-22.70, -1.30\right]\\ -9.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-32.57, 16.57\right]\\ -13.00 \left[-50.06, 24.06\right]\\ 2.70 \left[-8.58, 13.98\right]\\ -8.87 \left[-16.14, -1.60\right]\\ -20.00 \left[-39.49, -0.51\right]\\ -24.00 \left[-51.97, 3.97\right]\\ -2.00 \left[-12.56, 8.56\right]\\ -11.80 \left[-12.96, -3.64\right]\\ -16.00 \left[-47.06, 15.06\right]\\ -6.34 \left[-9.60, -3.08\right]\end{array}$	
-Mujadi 2005 irtholdy 2006 ogly 2008 erking 2003 rks 2002 irmus 2007 issoulaki 2002 issoulaki 2005 issoulaki 2006 issoulaki 2006 in 2009a in 2009b in 2009b ir 2009b iran 2003a iak 2011 ibtotal (95% CI) iterogeneity: Tau ² =	3 45.6 42.53 19 67 21 40 47.8 12.42 60 32 19 31.2 39 8.60; Chi ² = 1 Z = 3.81 (P =	7.4 24.8 25.9 21 77 35 67 19.7 18.55 35.16 34 15 17 20 8.55, df = 0.0001)	38 22 40 31 25 25 29 30 52 25 20 447 14 (P = 813	5 39.4 51.09 31 76 29 53 45.1 21.29 80 56 21 43 55 = 0.18); i ² = 2	9.6 20.1 28.27 83 52 78 24.6 19.28 35.16 54 25 12 68	38 21 40 34 25 25 30 30 52 25 20 29 25 20 451	8.4% 2.7% 3.2% 3.7% 0.3% 1.0% 0.5% 3.5% 5.7% 1.5% 0.8% 3.8% 5.1% 0.6%	$\begin{array}{c} -2.00 \left[-5.85, 1.85\right]\\ 6.20 \left[-7.26, 19.66\right]\\ -8.56 \left[-20.44, 3.32\right]\\ -12.00 \left[-22.70, -1.30\right]\\ -9.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.38, 35.38\right]\\ -8.00 \left[-53.35, 16.57\right]\\ -13.00 \left[-50.06, 24.06\right]\\ 2.70 \left[-8.58, 13.98\right]\\ -8.87 \left[-16.14, -1.60\right]\\ -20.00 \left[-39.49, -0.51\right]\\ -24.00 \left[-51.97, 3.97\right]\\ -2.00 \left[-12.56, 8.56\right]\\ -11.80 \left[-19.96, -3.64\right]\\ -16.00 \left[-47.06, 15.06\right]\end{array}$	

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

		pentin			ntrol			Mean Difference	Mean Difference
Study or Subgroup	Mean [VAS]	SD [VAS]	Total	Mean [VAS]	SD [VAS]	Total	Weight	IV, Random, 95% CI [VAS]	IV, Random, 95% CI [VAS]
3.11.1 0-350 mg									
Spence 2011	4	7	28	4	8	31	11.9%	0.00 [-3.83, 3.83]	
Waikakul 2011	30	20	24	35	17.5	24	5.1%	-5.00 [-15.63, 5.63]	
Subtotal (95% CI)			52			55	17.0%	-0.57 [-4.18, 3.03]	•
Heterogeneity: Tau ² =			1 (P =	0.39 ; $I^2 = 0\%$					
Test for overall effect:	: Z = 0.31 (P =	0.75)							
3.11.2 351-700 mg									
Monks 2015	11	4.4	100	19	5.9	97	14.2%	-8.00 [-9.46, -6.54]	•
Moore 2010	7	5.5	21	20	22.5	23	5.9%	-13.00 [-22.49, -3.51]	
Paul 2015	24.5	16.1	48	23.6	20.8	54	8.0%	0.90 [-6.28, 8.08]	+
Short 2012a	17	5.9	42	10	10	21	10.9%	7.00 [2.37, 11.63]	-
Srivastava 2010	21	3.25	60	28	3.33	60	14.4%	-7.00 [-8.18, -5.82]	•
Subtotal (95% CI)			271			255	53.5%	-3.92 [-7.91, 0.07]	◆
Test for overall effect:	: Z = 1.93 (P =		= 4 (P	< 0.00001); I ²	² = 91%				
Heterogeneity: Tau ² = Fest for overall effect: 3.11.4 701-1050 mg Subtotal (95% CI)	: Z = 1.93 (P =		= 4 (P 0	< 0.00001); l ²	? = 91%	0		Not estimable	
Test for overall effect: 3.11.4 701-1050 mg Subtotal (95% CI) Heterogeneity: Not ap	: Z = 1.93 (P = 9 pplicable	0.05)		< 0.00001); l ²	? = 91%	0		Not estimable	
Test for overall effect: 3.11.4 701–1050 mg Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect:	: Z = 1.93 (P = 9 pplicable	0.05)		< 0.00001); I ²	? = 91%	0		Not estimable	
Test for overall effect: 3.11.4 701–1050 mg Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect: 3.11.5 > 1050 mg	: Z = 1.93 (P = pplicable : Not applicabl	e 0.05)	0			-	6 5%		
Test for overall effect: 3.11.4 701–1050 mg Subtotal (95% Cl) Heterogeneity: Not ap Test for overall effect: 3.11.5 > 1050 mg Brogly 2008	: Z = 1.93 (P = pplicable : Not applicabl 12.4	e 10.4	0	15.5	17.9	21	6.5%	-3.10 [-11.90, 5.70]	_
Fest for overall effect: 3.11.4 701–1050 mg Subtotal (95% Cl) Heterogeneity: Not ap Fest for overall effect: 3.11.5 > 1050 mg Grogly 2008 Fassoulaki 2005	: Z = 1.93 (P = pplicable : Not applicabl 12.4 16	e 10.4 27	0 22 29	15.5 7	17.9 14	21 30	4.9%	-3.10 [-11.90, 5.70] 9.00 [-2.03, 20.03]	
Test for overall effect: 3.11.4 701–1050 mg Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect: 3.11.5 > 1050 mg 3rogly 2008 Tassoulaki 2005 Grosen 2014	: Z = 1.93 (P = pplicable : Not applicabl 12.4 16 6.58	e 10.4 27 13.61	0 22 29 52	15.5 7 12.43	17.9 14 16.4	21 30 52	4.9% 9.5%	-3.10 [-11.90, 5.70] 9.00 [-2.03, 20.03] -5.85 [-11.64, -0.06]	
Test for overall effect: 3.11.4 701-1050 mg Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect: 3.11.5 > 1050 mg Brogly 2008 Fassoulaki 2005 Grosen 2014 Kinney 2011	: Z = 1.93 (P = pplicable : Not applicabl 12.4 16	e 10.4 27	0 22 29	15.5 7	17.9 14	21 30	4.9% 9.5% 8.7%	-3.10 [-11.90, 5.70] 9.00 [-2.03, 20.03] -5.85 [-11.64, -0.06] -2.00 [-8.52, 4.52]	
Test for overall effect: 3.11.4 701-1050 mg Subtotal (95% Cl) Heterogeneity: Not ap Test for overall effect: 3.11.5 > 1050 mg Brogly 2008 Fassoulaki 2005 Grosen 2014 Subtotal (95% Cl)	: Z = 1.93 (P = pplicable : Not applicabl 12.4 16 6.58 29	e 10.4 27 13.61 18.2	0 22 29 52 57 160	15.5 7 12.43 31	17.9 14 16.4 18.9	21 30 52 68	4.9% 9.5% 8.7%	-3.10 [-11.90, 5.70] 9.00 [-2.03, 20.03] -5.85 [-11.64, -0.06]	
Test for overall effect: 3.11.4 701-1050 mg Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect: 3.11.5 > 1050 mg Brogly 2008 Fassoulaki 2005 Grosen 2014 Kinney 2011	: Z = 1.93 (P = pplicable : Not applicabl 12.4 16 6.58 29 = 12.53; Chi ² =	e 10.4 27 13.61 18.2 = 5.50, df =	0 22 29 52 57 160	15.5 7 12.43 31	17.9 14 16.4 18.9	21 30 52 68	4.9% 9.5% 8.7%	-3.10 [-11.90, 5.70] 9.00 [-2.03, 20.03] -5.85 [-11.64, -0.06] -2.00 [-8.52, 4.52]	
Test for overall effect: 3.11.4 701-1050 mg Subtotal (95% Cl) Heterogeneity: Not ap Test for overall effect: 3.11.5 > 1050 mg Brogly 2008 Fassoulaki 2005 Grosen 2014 Kinney 2011 Subtotal (95% Cl) Heterogeneity: Tau ² =	: Z = 1.93 (P = pplicable : Not applicabl 12.4 16 6.58 29 = 12.53; Chi ² =	e 10.4 27 13.61 18.2 = 5.50, df =	0 22 29 52 57 160	15.5 7 12.43 31	17.9 14 16.4 18.9	21 30 52 68 171	4.9% 9.5% 8.7%	-3.10 [-11.90, 5.70] 9.00 [-2.03, 20.03] -5.85 [-11.64, -0.06] -2.00 [-8.52, 4.52]	-+
Test for overall effect: 3.11.4 701-1050 mg Subtotal (95% CI) Heterogeneity: Not ap Test for overall effect: 3.11.5 > 1050 mg Brogly 2008 Brogly 2008 Brosen 2014 Kinney 2011 Subtotal (95% CI) Heterogeneity: Tau ² = Test for overall effect: Subtotal e	: Z = 1.93 (P = pplicable : Not applicable 12.4 16 6.58 29 = 12.53; Chi ² = : Z = 0.66 (P =	e 10.4 27 13.61 18.2 5.50, df = 0.51)	0 22 29 52 57 160 = 3 (P = 483	15.5 7 12.43 31 • 0.14); I ² = 45	17.9 14 16.4 18.9	21 30 52 68 171	4.9% 9.5% 8.7% 29.5%	-3.10 [-11.90, 5.70] 9.00 [-2.03, 20.03] -5.85 [-11.64, -0.06] -2.00 [-8.52, 4.52] -1.76 [-6.95, 3.43]	-+

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

Study or Subgroup		pentin SD [VAS]	Total	Con Mean [VAS]		Total	Weight	Mean Difference IV, Random, 95% CI [VAS]	Mean Difference IV, Random, 95% CI [VAS]
3.12.1 0-350 mg									
Bang 2009	32	20	23	38	20	23	1.3%	-6.00 [-17.56, 5.56]	-+
3ehdad 2012	25.3	5	30	42.7	14.2	31	1.9%	-17.40 [-22.71, -12.09]	-
Ghafari 2009	18.1	3	33	34.8	4	33	2.2%	-16.70 [-18.41, -14.99]	•
Kazak 2009	10.5	12.5	30	17.5	19	30	1.7%	-7.00 [-15.14, 1.14]	
ichtinger 2011	49	30	20	69.5	30	20	0.8%	-20.50 [-39.09, -1.91]	
Paul 2015	24.5	16.1	48	23.6	20.8	54	1.8%	0.90 [-6.28, 8.08]	+
Sekhavet 2009	40.1	14.5	49	52.7	21.1	49	1.8%	-12.60 [-19.77, -5.43]	-
Short 2012	13	2.7	42	10	10	21	2.0%	3.00 [-1.35, 7.35]	
Spence 2011	4	7	28	4	8	31	2.1%	0.00 [-3.83, 3.83]	Ť
/ahedi 2011	25.8	19.5	36	34	27.2	40	1.4%	-8.20 [-18.77, 2.37]	
/erma 2008	12	13	25	21	12	25	1.8%	-9.00 [-15.94, -2.06]	
Vaikakul 2011	30	20	24	35	17.5	24	1.4%	-5.00 [-15.63, 5.63]	-+
(oon 2001	17	32	16	11	30	16	0.6%	6.00 [-15.49, 27.49]	
Subtotal (95% CI)	17	52	404	11	50	397	20.7%	-7.26 [-12.82, -1.70]	
Heterogeneity: Tau ² = 8 Fest for overall effect: Z				< 0.00001); I ²	= 91%	557	20.770	-7.20 [-12.02, -1.70]	•
3.12.2 351-700 mg	- 2.50 (1 - 0.	.01)							
Ajori 2011	2	8	69	9	13	69	2.1%	-7.00 [10.60 3.40]	_
								-7.00 [-10.60, -3.40]	.]
Clarke 2009b	13	3.97	76	14	4	39	2.2%	-1.00 [-2.54, 0.54]	1
Kinney 2011	29	18.2	57	31	18.9	68	1.8%	-2.00 [-8.52, 4.52]	+
Mahoori 2014	4	7	25	11.2	12.3	25	1.9%	-7.20 [-12.75, -1.65]	-
Mardani–Kivi 2013	40	7	55	69	10	53	2.1%	-29.00 [-32.27, -25.73]	-
Menda 2010	23	35	30	38	60	30	0.5%	-15.00 [-39.86, 9.86]	
Metry 2008	18.49	14.94	67	23	13	34	1.9%	-4.51 [-10.16, 1.14]	-
Monks 2015	11	4.4	100	19	5.9	97	2.2%	-8.00 [-9.46, -6.54]	.
Moore 2010	7	5.5	21	20	22.5	23	1.5%	-13.00 [-22.49, -3.51]	
2005 Panday	32.5	18.11	40	30	20	20	1.4%	2.50 [-7.91, 12.91]	+-
Parikh 2010	37	7	30	46	6	30	2.1%	-9.00 [-12.30, -5.70]	-
Short 2012a	17	5.9	42	10	10	21	2.0%	7.00 [2.37, 11.63]	
Srivastava 2010	21	3.25	60	28	3.33	60	2.2%	-7.00 [-8.18, -5.82]	•
Zaldivar Ramirez 2011	10	10	18	37	5.55	16	1.9%	-27.00 [-32.48, -21.52]	-
					9			-27.00 [-32.48, -21.32] -18.00 [-29.64, -6.36]	
Özcan 2012 Subtotal (95% CI)	9	25	20	27	9	20	1.3%		· · · · · · · · · · · · · · · · · · ·
Subtotal (95% CI)			710			605	27.3%	-8.87 [-12.88, -4.85]	▼
Heterogeneity: Tau ² = 5 Fest for overall effect: Z			14 (P	< 0.00001); l²	= 96%				
3.12.4 701-1050 mg									
3adawy 2014	20	2.5	19	25	2.5	19	2.2%	-5.00 [-6.59, -3.41]	-
Deniz 2012	12	19	25	8	15	26	1.5%	4.00 [-5.42, 13.42]	+
Kim 2004	23	19	21	20	10.3	20	1.5%	3.00 [-6.30, 12.30]	<u> </u>
Koc 2007							2.1%		1
	2	4	20	3	6	20		-1.00 [-4.16, 2.16]	
Leung 2006	60	20	9	50	20	12	0.9%	10.00 [-7.29, 27.29]	+
_eung 2006 Marashi 2012	60 33	20 6	9 22	50 35	20 7	12 22	0.9% 2.1%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85]	+
∟eung 2006 Marashi 2012 Prabhakar 2007	60	20	9 22 10	50	20	12 22 10	0.9% 2.1% 1.4%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09]	
Leung 2006 Marashi 2012 Prabhakar 2007 Subtotal (95% CI)	60 33 38.5	20 6 10	9 22 10 126	50 35 54	20 7 13.5	12 22	0.9% 2.1%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85]	-
Leung 2006 Marashi 2012 Prabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 10 Fest for overall effect: Z	60 33 38.5 0.03; Chi ² = 1	20 6 10 8.02, df = 0	9 22 10 126	50 35 54	20 7 13.5	12 22 10	0.9% 2.1% 1.4%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09]	
Leung 2006 Marashi 2012 Prabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 1 Fest for overall effect: Z 3.12.5 > 1050 mg	60 33 38.5 0.03; Chi ² = 1	20 6 10 8.02, df = 0	9 22 10 126	50 35 54 0.006); I ² = 675	20 7 13.5 %	12 22 10	0.9% 2.1% 1.4%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09]	
Leung 2006 Marashi 2012 Prabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 1 Fest for overall effect: Z 3.12.5 > 1050 mg	60 33 38.5 0.03; Chi ² = 1	20 6 10 8.02, df = 0	9 22 10 126	50 35 54	20 7 13.5	12 22 10	0.9% 2.1% 1.4%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09]	
eung 2006 Marashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Fest for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010	60 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0.	20 6 10 8.02, df = 0 19)	9 22 10 126 5 (P = 0	50 35 54 0.006); I ² = 675	20 7 13.5 %	12 22 10 129	0.9% 2.1% 1.4% 11.7%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Fest for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006	60 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30	20 6 10 8.02, df = 9 19) 4 60	9 22 10 126 5 (P = 0 30 27	$50 \\ 35 \\ 54 \\ 0.006); I^2 = 675 \\ 10 \\ 30$	20 7 13.5 % 7 60	12 22 10 129 30 26	0.9% 2.1% 1.4% 11.7% 2.1% 0.3%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 11.00 [8.12, 13.88] 0.00 [-32.31, 32.31]	
eung 2006 Warashi 2012 Prabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Fest for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005	60 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30 18	20 6 10 8.02, df = 0 19) 4 60 16	9 22 10 126 5 (P = 0 30 27 35	$\begin{array}{r} 50\\ 35\\ 54\\ 0.006); \ \mathbf{l}^2 = 675\\ 10\\ 30\\ 23\\ \end{array}$	20 7 13.5 % 7 60 13	12 22 10 129 30 26 37	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 11.00 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Sekawi 2014	$\begin{array}{c} 60\\ 33\\ 38.5\\ 0.03; \ Chi^2 = 1\\ = 1.31 \ (P = 0.21\\ 30\\ 18\\ 9.7\\ \end{array}$	20 6 10 8.02, df = 0 19) 4 60 16 5.6	9 22 10 126 5 (P = 0 30 27 35 30	$\begin{array}{c} 50\\ 35\\ 54\\ 0.006); \ \mathbf{I}^2 = 679\\ 10\\ 30\\ 23\\ 6\end{array}$	20 7 13.5 % 7 60 13 6.2	12 22 10 129 30 26 37 32	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8% 2.1%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 11.00 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76] 3.70 [0.76, 6.64]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Fest for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Bekawi 2014 Brogly 2008	60 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30 18 9.7 12.4	$20 \\ 6 \\ 10 \\ 8.02, df = 6 \\ 19) \\ 4 \\ 60 \\ 16 \\ 5.6 \\ 10.4 \\ 10.4$	9 22 10 126 5 (P = 0 30 27 35 30 22	50 35 54 0.006); I ² = 679 10 30 23 6 15.5	20 7 13.5 % 7 60 13 6.2 17.9	12 22 10 129 30 26 37 32 21	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 11.00 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76] 3.70 [0.76, 6.64] -3.10 [-11.90, 5.70]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 1/ Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Sekawi 2014 Brogly 2008 Dierking 2003	$\begin{array}{c} 60\\ 33\\ 38.5\\ 0.03; Chi^2 = 1\\ = 1.31 \ (P=0.21)\\ 30\\ 18\\ 9.7\\ 12.4\\ 13.64 \end{array}$	20 6 10 8.02, df = 0 19) 4 60 16 5.6 10.4 19.19	9 22 10 126 5 (P = 0 30 27 35 30 22 40	50 35 54 0.006); l ² = 679 10 30 23 6 15.5 15.21	20 7 13.5 % 7 60 13 6.2 17.9 18.93	12 22 10 129 30 26 37 32 21 40	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 11.00 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76] 3.70 [0.76, 6.64] -3.10 [-11.90, 5.70] -1.57 [-9.92, 6.78]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Eest for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Sekawi 2014 Arogly 2008 Dierking 2003 Durmus 2007	600 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0, 130 18 9.7 12.4 13.64 13.64 27	$\begin{array}{c} 20\\ 6\\ 10\\ 8.02, df = 0\\ 19)\\ \end{array}$ $\begin{array}{c} 4\\ 60\\ 16\\ 5.6\\ 10.4\\ 19.19\\ 40\\ \end{array}$	9 22 10 126 5 (P = 0 30 27 35 30 22 40 25	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39	20 7 13.5 % 7 60 13 6.2 17.9 18.93 49	12 22 10 129 30 26 37 32 21 40 25	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6% 0.5%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Fest for overall effect: Z 3.12.5 > 1050 mg Modelmageed 2010 Adam 2006 Al-Mujadi 2005 Sekawi 2014 Brogly 2008 Dierking 2003 Dierking 2007 Tassoulaki 2002	$\begin{array}{c} 60\\ 33\\ 38.5\\ 0.03; Chi^2 = 1\\ = 1.31 (P = 0.\\ 130\\ 18\\ 9.7\\ 12.4\\ 13.64\\ 27\\ 4\end{array}$	$\begin{array}{c} 20\\ 6\\ 10\\ 8.02, df = 0\\ 19)\\ \begin{array}{c} 4\\ 60\\ 16\\ 5.6\\ 10.4\\ 19.19\\ 40\\ 12\end{array}$	9 22 10 126 5 (P = (30 27 35 30 22 40 25 25	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39 7	20 7 13.5 % 7 60 13 6.2 17.9 18.93 18.93 14	12 22 10 129 30 26 37 32 21 40 25 25	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.6% 1.6% 0.5% 0.5%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 11.00 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76] 3.70 [0.76, 6.64] -3.10 [-11.90, 5.70] -1.57 [-9.29, 6.78] -12.00 [-36.79, 12.79] -3.00 [-10.23, 4.23]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Fest for overall effect: Z 3.12.5 > 1050 mg Modelmageed 2010 Adam 2006 Al-Mujadi 2005 Sekawi 2014 Brogly 2008 Dierking 2003 Dierking 2007 Tassoulaki 2002	600 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0, 130 18 9.7 12.4 13.64 13.64 27	$\begin{array}{c} 20\\ 6\\ 10\\ 8.02, df = 0\\ 19)\\ \end{array}$ $\begin{array}{c} 4\\ 60\\ 16\\ 5.6\\ 10.4\\ 19.19\\ 40\\ \end{array}$	9 22 10 126 5 (P = 0 30 27 35 30 22 40 25	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39	20 7 13.5 % 7 60 13 6.2 17.9 18.93 49	12 22 10 129 30 26 37 32 21 40 25	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6% 0.5%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 1/ Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Sekawi 2014 Srogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2005	$\begin{array}{c} 60\\ 33\\ 38.5\\ 0.03; Chi^2 = 1\\ = 1.31 (P = 0.\\ 130\\ 18\\ 9.7\\ 12.4\\ 13.64\\ 27\\ 4\end{array}$	$\begin{array}{c} 20\\ 6\\ 10\\ 8.02, df = 0\\ 19)\\ \begin{array}{c} 4\\ 60\\ 16\\ 5.6\\ 10.4\\ 19.19\\ 40\\ 12\end{array}$	9 22 10 126 5 (P = (30 27 35 30 22 40 25 25	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39 7	20 7 13.5 % 7 60 13 6.2 17.9 18.93 18.93 14	12 22 10 129 30 26 37 32 21 40 25 25	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.6% 1.6% 0.5% 0.5%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 11.00 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76] 3.70 [0.76, 6.64] -3.10 [-11.90, 5.70] -1.57 [-9.29, 6.78] -12.00 [-36.79, 12.79] -3.00 [-10.23, 4.23]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Sekawi 2014 3rogly 2008 Dierking 2003 Dierking 2003 Diurmus 2007 Fassoulaki 2005 Forouzanfard 2013		20 6 10 8.02, df = 6 19) 4 60 16 5.6 10.4 19.19 40 12 27 5.8	9 22 10 126 5 (P = 0 30 27 35 30 22 40 25 25 29 25	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39 7 7 7 7 7	20 7 13.5 % 7 60 13 6.2 2 17.9 18.93 49 14 14 12.7	12 22 10 129 30 26 37 32 21 40 25 30 25	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6% 0.5% 1.6% 0.5% 1.4%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] -100 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76] 3.70 [0.76, 6.64] -3.10 [-11.90, 5.70] -1.57 [-9.92, 6.78] -12.00 [-36.79, 12.79] -3.00 [-10.23, 4.23] 9.00 [-2.03, 20.03] -11.60 [-1.70, -6.13]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Fest for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Jekawi 2014 Srogly 2008 Dierking 2003 Durmus 2007 Tassoulaki 2002 Frouzanfard 2013 Silron 2004	60 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30 18 9.7 12.4 13.64 27 4 13.64 27 4 13.64 27 6 5.66 5.66 13.82	20 6 10 8.02, df = (19) 4 60 16 5.66 10.4 19.19 40 0 12 27 5.88 12.5	9 22 10 126 5 (P = 0 30 27 35 30 22 40 25 29 25 29 25 23	$50 \\ 35 \\ 54 \\ 0.006); I^2 = 673 \\ 10 \\ 30 \\ 23 \\ 6 \\ 15.5 \\ 15.21 \\ 39 \\ 7 \\ 7 \\ 7 \\ 17.2 \\ 23.63 \\ $	20 7 13.5 % 7 60 13 6.2 17.9 18.93 49 14 14 12.7 7 16.52	12 22 10 129 30 26 37 32 21 40 25 25 30 0 25 24	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.6% 1.6% 1.6% 1.9% 1.4%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] 11.00 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76] 3.70 [0.76, 6.64] -3.10 [-11.90, 5.70] -1.57 [-9.92, 6.78] -12.00 [-36.79, 12.79] -3.00 [-10.23, 4.23] 9.00 [-2.03, 20.03] -11.60 [-17.07, -6.13] -9.81 [-18.16, -1.46]	
eung 2006 Marashi 2012 Yrabhakar 2007 Subtotal (95% Cl) Heterogeneity: Tau ² = 1/ Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Bekawi 2014 Brogly 2008 Dierking 2003 Dierking 2003		20 6 10 8.02, df = (19) 4 4 60 16 5.6 10.4 4 19.19 40 12 27 5.8 12.5 13.61	9 22 10 126 5 (P = 0 30 27 35 30 22 40 25 25 29 25 29 25 23 52	50 35 54 0.006); I ² = 675 10 23 6 15.5 15.21 39 7 7 7 7 7 7 7 23.63 22.43	20 7 13.5 % 7 60 13 6.2 17.9 18.93 49 14 4 12.7 16.52 16.4	12 22 10 129 30 26 37 32 21 40 25 25 30 25 30 25 24 52	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 2.1% 1.6% 0.5% 1.6% 1.6% 1.4% 1.9% 1.6%	10.00 [-7.29, 27.29] -2.00 [-5.85, 1.85] -15.50 [-25.91, -5.09] -2.24 [-5.59, 1.10] -10.00 [8.12, 13.88] 0.00 [-32.31, 32.31] -5.00 [-11.76, 1.76] 3.70 [0.76, 6.64] -3.10 [-11.90, 5.70] -1.57 [-9.92, 6.78] -12.00 [-36.79, 12.79] -3.00 [-10.23, 4.23] 9.00 [-2.03, 20.03] -11.60 [-17.07, -6.13] -9.81 [-18.16, -1.46] -5.85 [-11.64, -0.06]	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Sekawi 2014 Brogly 2008 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2007 Fassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Gilron 2004 Grosen 2014 Hout 2007	$\begin{array}{c} 60\\ 33\\ 38.5\\ 0.03; Chl^2 = 1\\ = 1.31 (P = 0.\\ 21\\ 30\\ 18\\ 9.7\\ 12.4\\ 13.64\\ 27\\ 4\\ 16\\ 6.6\\ 13.82\\ 6.58\\ 5\\ 5\end{array}$	20 6 10 8.02, df = 1 19) 4 60 16 5.6 10.4 19.19 40 12 27 7 5.8 12.5 13.61 59.3	9 22 10 10 5 (P = 0 30 27 35 30 22 40 25 25 29 25 23 23	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39 7 7 7 7 7 7 7 7 23.63 12.43 0	20 7 13.5 % 7 60 13 6.2 17.9 18.93 49 14 12.7 16.52 16.52 16.52 16.52	12 22 10 129 30 26 37 32 21 40 25 25 30 25 24 25 30 25 24 25 28	0.9% 2.1% 1.7% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6% 0.5% 1.7% 1.6% 1.9% 1.6% 1.9%	$\begin{array}{c} 10.00 \left[-7.29, 27.29\right]\\ -2.00 \left[-5.85, 1.85\right]\\ -15.50 \left[-25.91, -5.09\right]\\ -2.24 \left[-5.59, 1.10\right]\\ \end{array}$	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Jekawi 2014 Brogly 2008 Dierking 2003 Durmus 2007 Tassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Cilron 2004 Grosen 2014	600 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30 18 9.7 12.4 13.64 27 4 13.64 27 6.56 5.6 5.6 5.6 5.3 30	20 6 10 8.02, df = 1 19) 4 60 16 5.6 10.4 19.19 40 12 27 5.8 12.5 5 13.61 59.3 1	9 22 10 126 5 (P = 0 30 27 35 30 22 40 25 25 23 25 23 22 23 25	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39 7 7 7 17.2 23.63 12.43 39,2	20 7 13.5 % 7 60 13 6.2 17.9 18.93 49 14 14 12.7 16.52 16.4 14.8 8.81	12 22 10 129 30 26 37 32 21 40 25 25 24 52 25 24 52 28 8 25	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6% 1.6% 1.6% 1.7% 1.4% 1.9% 0.5% 2.1%	$\begin{array}{c} 10.00 \ [-7.29, 27.29]\\ -2.00 \ [-5.85, 1.85]\\ -5.50 \ [-25.91, -5.09]\\ -2.24 \ [-5.59, 1.10]\\ \end{array}$	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Jekawi 2014 Brogly 2008 Dierking 2003 Durmus 2007 Tassoulaki 2002 Fassoulaki 2005 Frouzanfard 2013 Cilron 2004 Grosen 2014	$\begin{array}{c} 60\\ 33\\ 38.5\\ 0.03; Chl^2 = 1\\ = 1.31 (P = 0.\\ 21\\ 30\\ 18\\ 9.7\\ 12.4\\ 13.64\\ 27\\ 4\\ 16\\ 6.6\\ 13.82\\ 6.58\\ 5\\ 5\end{array}$	20 6 10 8.02, df = 1 19) 4 60 16 5.6 10.4 19.19 40 12 27 7 5.8 12.5 13.61 59.3	9 22 10 126 5 (P = 0 30 27 35 30 22 40 25 25 25 23 52 23 52 23 52 23 34	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39 7 7 7 7 7 7 7 7 23.63 12.43 0	20 7 13.5 % 7 60 13 6.2 17.9 18.93 49 14 12.7 16.52 16.52 16.52 16.52	12 22 10 129 30 26 37 32 21 40 25 25 30 25 24 25 30 25 24 25 28	0.9% 2.1% 1.7% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6% 0.5% 1.7% 1.6% 1.9% 1.6% 1.9%	$\begin{array}{c} 10.00 \left[-7.29, 27.29\right]\\ -2.00 \left[-5.85, 1.85\right]\\ -15.50 \left[-25.91, -5.09\right]\\ -2.24 \left[-5.59, 1.10\right]\\ \end{array}$	
eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% Cl) Heterogeneity: Tau ² = 1/ Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Bekawi 2014 Brogly 2008 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Corrouz anfard 2013 Gilron 2004 Grosen 2014 Hout 2007 ajeda 2014 Khan 2013	600 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30 18 9.7 12.4 13.64 27 4 13.64 27 6.56 5.6 5.6 5.6 5.3 30	20 6 10 8.02, df = 1 19) 4 60 16 5.6 10.4 19.19 40 12 27 5.8 12.5 5 13.61 59.3 1	9 22 10 126 5 (P = 0 30 27 35 30 22 40 25 25 23 25 23 22 23 25	50 35 54 0.006); I ² = 675 10 30 23 6 15.5 15.21 39 7 7 7 17.2 23.63 12.43 39,2	20 7 13.5 % 7 60 13 6.2 17.9 18.93 49 14 14 12.7 16.52 16.4 14.8 8.81	12 22 10 129 30 26 37 32 21 40 25 25 24 52 25 24 52 28 8 25	0.9% 2.1% 1.4% 11.7% 2.1% 0.3% 1.8% 2.1% 1.6% 1.6% 1.6% 1.7% 1.4% 1.9% 0.5% 2.1%	$\begin{array}{c} 10.00 \ [-7.29, 27.29]\\ -2.00 \ [-5.85, 1.85]\\ -5.50 \ [-25.91, -5.09]\\ -2.24 \ [-5.59, 1.10]\\ \end{array}$	
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eung 2006 Warashi 2012 Yrabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 1/ Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Bekawi 2014 Strogly 2008 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Cassoulaki 2005 Frouzanfard 2013 Giron 2004 Grosen 2014 Grosen 2014 Grosen 2014 Grosen 2014 Genigaux 2004 Dimran 2005 Bapchuk 2010 Sien 2009a Sien 2009a Sien 2009a Furan 2003a Furan 2004 Furan 2003a Furan 2005 Juak 2011 Digenig 2011 Digenig 2011 Subtotal (95% CI)		20 6 10 8.02, df = 19) 4 60 16 5.6 10.4 19.19 40 12 27 5.8 12.5 13.61 59.3 1 7.43 8 17.5 38.66 333 5 4 7 7 8 8 10.5 1 0.1 0.1 4.8	9 9 222 10 126 5 (P = (30 27 5 30 225 25 33 23 24 29 25 25 23 24 29 25 25 23 34 29 20 25 25 23 34 29 20 25 25 25 25 25 25 25 25 25 25 25 25 25	$50 \\ 35 \\ 54 \\ 0.006); l^2 = 675 \\ 10 \\ 30 \\ 23 \\ 6 \\ 15.5 \\ 15.21 \\ 39 \\ 7 \\ 7 \\ 17.2 \\ 23.63 \\ 12.43 \\ 0 \\ 39.2 \\ 24.28 \\ 32 \\ 21 \\ 54 \\ 21 \\ 16 \\ 11 \\ 16 \\ 11 \\ 16 \\ 11 \\ 14 \\ 26 \\ 30 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 1$	20 7 13.5 % 7 60 13 18.93 18.93 49 14 12.7 16.52 16.4 14.8 8.1 11.18 8.1 11.18 8.1 11.18 23 38.66 34 428 22 12 21 22 14 23.5 46 48 7,7	12 22 10 129 30 26 37 32 21 4 25 25 24 25 25 24 25 228 25 235 31 25 27 20 20 29 25 25 25 26 20 20 20 20 20	0.9% 2.1% 1.4% 11.7% 2.1% 1.6% 1.6% 1.6% 1.6% 1.9% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0	$\begin{array}{c} 10.00 \ [-7.29, 27.29] \\ -2.00 \ [-5.85, 1.85] \\ 15.50 \ [-5.58, 1.85] \\ -2.24 \ [-5.59, 1.10] \\ \hline \\ \\ 11.00 \ [8.12, 13.88] \\ 0.00 \ [-32.31, 32.31] \\ -3.00 \ [-10.76, 1.76] \\ 3.70 \ [0.76, 6.64] \\ -3.10 \ [-11.70, 1.76] \\ 3.70 \ [0.76, 6.64] \\ -3.10 \ [-11.70, 7.61] \\ 3.70 \ [0.76, 6.64] \\ -3.10 \ [-11.00, 2, 4.23] \\ 9.00 \ [-2.03, 20.03] \\ -11.60 \ [-17.07, -6.13] \\ -9.00 \ [-2.03, 20.03] \\ -11.60 \ [-17.07, -6.13] \\ -9.85 \ [-11.64, -0.06] \\ 5.00 \ [-18.85, 29.85] \\ -9.20 \ [-12.40, -6.00] \\ -15.76 \ [-20.23, -11.29] \\ -9.00 \ [-12.44, -0.66] \\ 5.00 \ [-12.44, -0.66] \\ 5.00 \ [-12.44, -0.66] \\ 5.00 \ [-12.44, -0.66] \\ 5.00 \ [-12.44, -0.67] \\ -3.00 \ [-20.87, 14.87] \\ -3.00 \ [-20.87, 14.87] \\ -3.00 \ [-20.87, 14.87] \\ -3.00 \ [-20.87, 14.87] \\ -3.00 \ [-20.43, -57] \\ -3.00 \ [-20.43, -57] \\ -3.00 \ [-20.43, -57] \\ -3.00 \ [-20.43, -57] \\ -3.00 \ [-20.43, -57] \\ -1.100 \ [-20.47, 1.53] \\ -0.00 \ [-10.61, -7.39] \\ -11.00 \ [-26.47, -1.53] \\ -0.00 \ [-10.64, -3.23] \\ -11.00 \ [-20.9, -0.91] \\ -6.00 \ [-26.16, 14.16] \\ -18.00 \ [-39.04, 3.04] \end{array}$	
eung 2006 Warashi 2012 'rabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 11 Test for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Jekadi 2005 Jekadi 2005 Jekadi 2003 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2004 Grosen 2014 Hout 2007 ajeda 2014 Chan 2013 Kénigaux 2004 Dirran 2005 Eine 2009b Turan 2005 Turan 2004 Furan 2005 Jeka 2011 Diegencil 2011	600 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30 18 9.7 12.4 13.64 27 4 13.64 27 4 13.64 27 4 13.64 27 12.4 13.64 27 4 13.64 27 4 13.62 5 30 8.52 21 32 21 32 21 32 21 32 21 32 21 32 32 20 21 32 21 32 32 20 21 32 21 32 21 32 32 20 21 32 21 32 32 20 21 32 32 21 32 32 20 21 32 32 21 32 32 32 21 32 32 32 32 32 32 32 32 32 32 32 32 32	$\begin{array}{c} 20\\ 6\\ 10\\ 8.02, df = \\ 19\\ 19\\ \end{array}$ $\begin{array}{c} 4\\ 4\\ 00\\ 16\\ 5.6\\ 10.4\\ 19.19\\ 40\\ 12\\ 27\\ 5.8\\ 12.5\\ 13.61\\ 5.9\\ 13.61\\ 5.9\\ 13.61\\ 5.8\\ 12.5\\ 13.63\\ 5\\ 4\\ 7\\ 7\\ 8\\ 8\\ 10.5\\ 1\\ 0.1\\ 8\\ 10.5\\ 1\\ 0.1\\ 4.8\\ \end{array}$	9 9 222 10 126 5 (P = (30 27 5 30 225 25 33 23 24 29 25 25 23 24 29 25 25 23 34 29 20 25 25 23 34 29 20 25 25 25 25 25 25 25 25 25 25 25 25 25	$50 \\ 35 \\ 54 \\ 0.006); l^2 = 675 \\ 10 \\ 30 \\ 23 \\ 6 \\ 15.5 \\ 15.21 \\ 39 \\ 7 \\ 7 \\ 17.2 \\ 23.63 \\ 12.43 \\ 0 \\ 39.2 \\ 24.28 \\ 32 \\ 21 \\ 54 \\ 21 \\ 16 \\ 11 \\ 16 \\ 11 \\ 16 \\ 11 \\ 14 \\ 26 \\ 30 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 1$	20 7 13.5 % 7 60 13 18.93 18.93 49 14 12.7 16.52 16.4 14.8 8.1 11.18 8.1 11.18 8.1 11.18 23 38.66 34 428 22 12 21 22 14 23.5 46 48 7,7	12 22 10 12 29 30 26 37 32 21 40 25 23 30 25 24 40 25 22 8 35 31 20 25 22 8 25 25 25 25 25 25 25 25 20 20 20 20 20 20 20 20 20 20 20 20 20	0.9% 2.1% 1.4% 1.7% 2.1% 1.7% 2.1% 1.6% 0.5% 1.7% 1.6% 0.5% 1.7% 2.1% 2.0% 2.1% 2.0% 2.0% 2.1% 2.0% 2.0% 1.2% 1.2% 1.6% 0.5% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.2% 1.5%	$\begin{array}{c} 10.00 \ [-7.29, 27.29] \\ -2.00 \ [-5.85, 1.85] \\ -2.00 \ [-5.85, 1.85] \\ -2.24 \ [-5.59, 1.10] \\ \end{array} \\ \begin{array}{c} 11.00 \ [8.12, 13.88] \\ 0.00 \ [-32.31, 32.31] \\ -5.00 \ [-11.76, 1.76] \\ 3.70 \ [0.76, 6.64] \\ -3.10 \ [-11.90, 5.70] \\ -1.57 \ [-9.92, 6.78] \\ -12.00 \ [-36.79, 12.79] \\ -3.00 \ [-10.23, 4.23] \\ 9.00 \ [-2.03, 20.03] \\ -11.60 \ [-17.07, -6.13] \\ 9.00 \ [-2.03, 20.03] \\ -11.60 \ [-17.07, -6.13] \\ -9.81 \ [-18.16, -1.46] \\ -5.85 \ [-11.64, -0.06] \\ 5.00 \ [-19.85, 29.85] \\ -9.20 \ [-12.40, -6.00] \\ -15.76 \ [-20.23, -11.29] \\ -19.00 \ [-2.38, -14.16] \\ 0.00 \ [-2.38, -14.3] \\ -3.00 \ [-2.38, -14.3] \\ -3.00 \ [-2.64, -1.55] \\ -4.00 \ [-10.61, -7.39] \\ -9.00 \ [-10.61, -7.39] \\ -9.00 \ [-10.61, -7.39] \\ -11.00 \ [-21.09, -0.91] \\ -6.00 \ [-21.09, -0.91] \\ -6.00 \ [-20.65, -0.75] \\ -4.00 \ [-3.40, -3.04] \\ -4.00 \ [-3.25, -0.75] \end{array}$	
eung 2006 Warashi 2012 'rabhakar 2007 Subtotal (95% CI) Heterogeneity: Tau ² = 1/ Eest for overall effect: Z 3.12.5 > 1050 mg Abdelmageed 2010 Adam 2006 Al-Mujadi 2005 Bekawi 2014 Brogy 2008 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Dierking 2003 Cassoulaki 2005 Frouzanfard 2013 Girlon 2004 Grosen 2014 Hout 2007 ajeda 2014 Chan 2013 Gosucu 2013 Geing 2004 Dirran 2006 Rapchuk 2010 Dien 2009a Sien 2009b Furan 2003b Furan 2003b Furan 2003b Furan 2003b Furan 2003b Furan 2004 Dirran 2003b Furan 2005 Jocak 2011 Disubtotal (95% CI) Heterogeneity: Tau ² = 6: Fest for overall effect: Z	600 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30 18 9.7 12.4 13.64 27 4 13.64 27 4 13.64 27 4 13.64 27 12.4 13.64 27 4 13.64 27 4 13.62 5 30 8.52 21 32 21 32 21 32 21 32 21 32 21 32 32 20 21 32 21 32 32 20 21 32 21 32 21 32 32 20 21 32 21 32 32 20 21 32 32 21 32 32 20 21 32 32 21 32 32 32 21 32 32 32 32 32 32 32 32 32 32 32 32 32	$\begin{array}{c} 20\\ 6\\ 10\\ 8.02, df = \\ 19\\ 19\\ \end{array}$ $\begin{array}{c} 4\\ 4\\ 00\\ 16\\ 5.6\\ 10.4\\ 19.19\\ 40\\ 12\\ 27\\ 5.8\\ 12.5\\ 13.61\\ 5.9\\ 13.61\\ 5.9\\ 13.61\\ 5.8\\ 12.5\\ 13.63\\ 5\\ 4\\ 7\\ 7\\ 8\\ 8\\ 10.5\\ 1\\ 0.1\\ 8\\ 10.5\\ 1\\ 0.1\\ 4.8\\ \end{array}$	9 9 222 10 126 5 (P = (30 27 5 30 225 25 33 23 24 29 25 25 23 24 29 25 25 23 34 29 20 25 25 23 34 29 20 25 25 25 25 25 25 25 25 25 25 25 25 25	$50 \\ 35 \\ 54 \\ 0.006); l^2 = 675 \\ 10 \\ 30 \\ 23 \\ 6 \\ 15.5 \\ 15.21 \\ 39 \\ 7 \\ 7 \\ 17.2 \\ 23.63 \\ 12.43 \\ 0 \\ 39.2 \\ 24.28 \\ 32 \\ 21 \\ 54 \\ 21 \\ 16 \\ 11 \\ 16 \\ 11 \\ 16 \\ 11 \\ 14 \\ 26 \\ 30 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 15 \\ 1$	20 7 13.5 % 7 60 13 18.93 18.93 49 14 12.7 16.52 16.4 14.8 8.1 11.18 8.1 11.18 8.1 11.18 23 38.66 34 428 22 12 21 22 14 23.5 46 48 7,7	12 22 10 129 30 26 37 32 21 4 4 25 25 24 25 25 24 25 25 24 25 25 26 20 20 20 20 30 27 27 20 20 20 25 25 25 25 25 26 20 20 25 25 25 26 26 26 26 26 26 26 26 26 26 26 26 26	0.9% 2.1% 1.4% 11.7% 2.1% 1.6% 1.6% 1.6% 1.6% 1.6% 1.6% 2.1% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0% 2.0	$\begin{array}{c} 10.00 \ [-7.29, 27.29] \\ -2.00 \ [-5.85, 1.85] \\ -2.00 \ [-5.50] \ -2.5.91, -5.09] \\ -2.24 \ [-5.59, 1.10] \\ \hline \\ 11.00 \ [8.12, 13.88] \\ 0.00 \ [-32.31, 32.31] \\ -3.00 \ [-11.76, 1.76] \\ 3.70 \ [0.76, 6.64] \\ -3.10 \ [-11.90, 5.70] \\ -1.57 \ [-9.92, 6.78] \\ -12.00 \ [-36.79, 12.79] \\ -3.00 \ [-10.23, 4.23] \\ 9.00 \ [-2.03, 20.03] \\ -11.60 \ [-17.07, -6.13] \\ 9.00 \ [-2.03, 20.03] \\ -11.60 \ [-17.07, -6.13] \\ -9.81 \ [-18.16, -1.46] \\ -5.85 \ [-11.64, -0.06] \\ 5.00 \ [-12.40, -6.00] \\ -15.76 \ [-20.23, -11.29] \\ -9.00 \ [-12.40, -6.00] \\ -15.76 \ [-20.23, -11.29] \\ -9.00 \ [-12.44, -6.00] \\ -15.76 \ [-20.23, -11.29] \\ -9.00 \ [-12.44, -6.00] \\ -2.00 \ [-4.34, 3, -0.57] \\ -3.00 \ [-2.647, -1.53] \\ -9.00 \ [-10.645, -5.55] \\ -4.00 \ [-10.32, 2.32] \\ -11.00 \ [-26.16, 14.16] \\ -18.00 \ [-39.04, 3.04] \\ -4.00 \ [-7.25, -0.75] \\ -6.08 \ [-9.65, -2.51] \end{array}$	
eung 2006 warashi 2012 'rabhakar 2007 Subtotal (95% CI) leterogeneity: Tau ² = 11 rest for overall effect: Z 3.12.5 > 1050 mg bbdelmageed 2010 Adam 2006 July 2008 Dierking 2003 Dierking 2003 Jurans 2004 Gosucu 2013 dénigaux 2004 Diran 2005 Rapchuk 2010 Sein 2009a Sein 2009b Furan 2003a Furan 2003 Furan 2004 Furan 2005 Furan 2005 Fura	60 33 38.5 0.03; Chi ² = 1 = 1.31 (P = 0. 21 30 18 9.7 12.4 13.64 27 4 13.64 27 4 13.64 27 12.4 13.64 27 4 13.64 27 12.4 13.64 27 12.4 13.82 6.58 6.58 6.58 6.53 20 13 21 32 2 5 7 7 3 20 12 2 11 32.5; Chi ² = 2 = 3.33 (P = 0.	20 6 10 8.02, df = 1 19) 4 4 600 16 5.6 10.4 19.19 40 12 27 5.8 8 12.5 13.61 59.3 1 1 7.43 8 17 38.66 33 5 4 4 7 8 8 10.5 1 1 7.43 8.61 10 8.62 10 10 10 10 10 10 10 10 10 10 10 10 10	9 9 222 10 126 5 (P = (300 27 35 300 225 29 25 23 23 25 22 23 23 25 22 23 23 25 22 20 20 25 27 20 20 25 27 20 00 25 52 27 20 00 25 27 20 00 27 10 10 10 10 10 10 10 10 10 10 10 10 10	$50 \\ 35 \\ 54 \\ 0.006); I^2 = 673 \\ 10 \\ 30 \\ 23 \\ 6 \\ 15.5 \\ 15.21 \\ 39 \\ 7 \\ 7 \\ 7 \\ 17.2 \\ 23.63 \\ 12.43 \\ 0 \\ 39.2 \\ 24.28 \\ 21 \\ 54 \\ 21 \\ 54 \\ 21 \\ 16 \\ 11 \\ 14 \\ 26 \\ 30 \\ 15 \\ < 0.00001); I^2$	20 7 13.5 % 7 60 0 13 6.2 17.9 18.93 49 14 14 14.12 7 16.52 16.4 14.8 8.1 11.18 11.18 33.66 34 22 2 2 12 14 23.5 5 46 48 7,7 = 90%	12 22 10 129 30 26 37 32 21 4 4 25 25 24 25 25 24 25 25 24 25 25 26 20 20 20 20 30 27 27 20 20 20 25 25 25 25 25 26 20 20 25 25 25 26 26 26 26 26 26 26 26 26 26 26 26 26	0.9% 2.1% 1.4% 1.7% 2.1% 1.7% 2.1% 1.6% 0.5% 1.7% 1.6% 0.5% 1.7% 2.1% 2.0% 2.1% 2.0% 2.0% 2.1% 2.0% 2.0% 1.2% 1.2% 1.6% 0.5% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.6% 1.7% 1.2% 1.5%	$\begin{array}{c} 10.00 \ [-7.29, 27.29] \\ -2.00 \ [-5.85, 1.85] \\ -2.00 \ [-5.85, 1.85] \\ -2.24 \ [-5.59, 1.10] \\ \end{array} \\ \begin{array}{c} 11.00 \ [8.12, 13.88] \\ 0.00 \ [-32.31, 32.31] \\ -5.00 \ [-11.76, 1.76] \\ 3.70 \ [0.76, 6.64] \\ -3.10 \ [-11.90, 5.70] \\ -1.57 \ [-9.92, 6.78] \\ -12.00 \ [-36.79, 12.79] \\ -3.00 \ [-10.23, 4.23] \\ 9.00 \ [-2.03, 20.03] \\ -11.60 \ [-17.07, -6.13] \\ 9.00 \ [-2.03, 20.03] \\ -11.60 \ [-17.07, -6.13] \\ -9.81 \ [-18.16, -1.46] \\ -5.85 \ [-11.64, -0.06] \\ 5.00 \ [-19.85, 29.85] \\ -9.20 \ [-12.40, -6.00] \\ -15.76 \ [-20.23, -11.29] \\ -19.00 \ [-2.38, -14.16] \\ 0.00 \ [-2.38, -14.3] \\ -3.00 \ [-2.38, -14.3] \\ -3.00 \ [-2.64, -1.55] \\ -4.00 \ [-10.61, -7.39] \\ -9.00 \ [-10.61, -7.39] \\ -9.00 \ [-10.61, -7.39] \\ -11.00 \ [-21.09, -0.91] \\ -6.00 \ [-21.09, -0.91] \\ -6.00 \ [-20.65, -0.75] \\ -4.00 \ [-3.40, -3.04] \\ -4.00 \ [-3.25, -0.75] \end{array}$	

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

Study on Cubanous		apentin	Tetal		ntrol	Tatal	Wainht	Mean Difference	Mean Difference
Study or Subgroup 3.13.1 0-350 mg	Mean [VAS]	SD [VAS]	Total	Mean [VAS]	SD [VAS]	Total	weight	IV, Random, 95% CI [VAS]	IV, Random, 95% CI [VAS]
	22		12	20	20	21	0.00/	2 00 / 7 10 11 10	
Short 2012 Subtotal (95% CI)	32	11.1	42 42	30	20	21 21	8.9% 8.9%		
	a a Baada la		42			21	0.9%	2.00 [-7.19, 11.19]	—
Heterogeneity: Not a		0.07)							
Test for overall effect	Z = 0.43 (P = 0.43)	0.67)							
3.13.2 351-700 mg									
Monks 2015	40	6.7	100	47	8.15	97	11.7%	-7.00 [-9.09, -4.91]	•
Moore 2010	10	5.5	21	18	15	23	10.1%	-8.00 [-14.57, -1.43]	-
Paul 2015	94.9	29.8	48	94.4	30.8	54	7.7%	0.50 [-11.27, 12.27]	
Short 2012a	37	10.4	42	30	20	21	8.9%	7.00 [-2.11, 16.11]	-
Srivastava 2010	30	2.5	60	46	2.5	60			
Subtotal (95% CI) Heterogeneity: Tau ²			271			255	50.3%	-5.94 [-12.78, 0.90]	•
3.13.4 701-1050 m Lunn 2015 Subtotal (95% CI)	g 41	14.5	92 92	42	8.7	29 29	11.1% 11.1%		
Heterogeneity: Not a Test for overall effect		- 0.65)				-			
3.13.5 > 1050 mg									
Brogly 2008	26	22	22	27	17	21	7.7%	-1.00 [-12.72, 10.72]	-
Fassoulaki 2005	41	69	29	40.5	68	30	2.0%	0.50 [-34.47, 35.47]	
Grosen 2014	23.13	25.71	52	23.03	20.99	52	9.0%		
unn 2015a	41	14.5	91	42	8.7	29	11.1%		
Subtotal (95% CI)			194			132	29.8%	-0.80 [-4.49, 2.89]	•
			3 (P =	1.00); l ² = 0%					
Heterogeneity: Tau ² Test for overall effect						437	100.0%	-2.96 [-8.43, 2.51]	•
J /			599						
Test for overall effect	= 65.60; Chi ² =	= 182.25, c		(P < 0.00001); I ² = 95%				
Test for overall effect Total (95% CI)				(P < 0.00001); I ² = 95%				-100 -50 0 50 100 Favours Gabapentin Favours Control

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

Study or Subgroup		pentin			ntrol			Mean Difference	Mean Difference
	Mean [VAS]	SD [VAS]	Total	Mean [VAS]	SD [VAS]	Total	Weight	IV, Random, 95% CI [VAS]	IV, Random, 95% CI [VAS]
3.14.1 0-350 mg									
Short 2012	32	11.1	42	30	20	21	4.3%	2.00 [-7.19, 11.19]	+-
roon 2001 Subtotal (95% CI)	23	41	16 58	37	58	16 37	1.4% 5.7%	-14.00 [-48.80, 20.80] 0.96 [-7.93, 9.84]	•
Heterogeneity: Tau ² =	= 0.00; Chi ² =	0.76, df =	1 (P =	0.38 ; $I^2 = 0\%$					
Test for overall effect	:: Z = 0.21 (P =	0.83)							
3.14.2 351-700 mg									
Clarke 2009b	36	3.97	76	29	4	39	5.0%	7.00 [5.46, 8.54]	•
Kim 2004	46	26.8	21	34	16	20	3.7%	12.00 [-1.44, 25.44]	
Menda 2010	51	61	30	54	63	30	1.7%	-3.00 [-34.38, 28.38]	
Metry 2008	23.99	12.46	67	35	11	34	4.8%	-11.01 [-15.76, -6.26]	-
Monks 2015	40	6.7	100	47	8.15	97	5.0%	-7.00 [-9.09, -4.91]	•
Moore 2010	10	5.5	21	18	15	23	4.6%	-8.00 [-14.57, -1.43]	-
Paul 2015	94.9	29.8	48	94.4	30.8	54	3.9%	0.50 [-11.27, 12.27]	+-
Short 2012a	37	10.4	42	30	20	21	4.3%	7.00 [-2.11, 16.11]	<u>+</u>
Srivastava 2010	30	2.5	60	46	2.5	60	5.1%	-16.00 [-16.89, -15.11]	•
Subtotal (95% CI)	50	2.5	465	10	2.5	378	38.2%	-2.50 [-11.38, 6.37]	
Heterogeneity: Tau ² =	= 158.70; Chi ²	= 674.96,	df = 8	(P < 0.00001)); $I^2 = 99\%$				
Test for overall effect	:: Z = 0.55 (P =	0.58)							
3.14.4 701–1050 mg	-								
_unn 2015	41	14.5	92	42	8.7	29	4.9%	-1.00 [-5.34, 3.34]	1
Prabhakar 2007	54.5	10.1	10	66.5	16.3	10	3.9%	-12.00 [-23.88, -0.12]	
Subtotal (95% CI) Heterogeneity: Tau ² = Fact for overall offect			102 = 1 (P =	$= 0.09$; $I^2 = 6$	5%	39	8.8%	-5.05 [-15.45, 5.35]	•
Heterogeneity: Tau ² = Test for overall effect				$= 0.09$; $I^2 = 60$	5%	39	8.8%	-5.05 [-15.45, 5.35]	•
Heterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg	:: Z = 0.95 (P =	0.34)	= 1 (P =						-
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005	:: Z = 0.95 (P = 23	0.34)	= 1 (P =	35	11	37	4.8%	-12.00 [-17.33, -6.67]	-
Heterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008	:: Z = 0.95 (P = 23 26	0.34) 12 22	= 1 (P = 35 22	35 27	11 17	37 21	4.8% 3.9%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72]	●
Heterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003	: Z = 0.95 (P = 23 26 37.48	12 22 27.03	= 1 (P = 35 22 40	35 27 34.12	11 17 20.96	37 21 40	4.8% 3.9% 4.1%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96]	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007	: Z = 0.95 (P = 23 26 37.48 51	0.34) 12 22 27.03 68	= 1 (P = 35 22 40 25	35 27 34.12 68	11 17 20.96 79	37 21 40 25	4.8% 3.9% 4.1% 1.1%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86]	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 3rogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002	: Z = 0.95 (P = 23 26 37.48 51 20	12 22 27.03 68 31	= 1 (P = 35 22 40 25 25	35 27 34.12 68 31	11 17 20.96 79 54	37 21 40 25 25	4.8% 3.9% 4.1% 1.1% 2.3%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86] -11.00 [-55.41, 13.41]	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005	: Z = 0.95 (P = 23 26 37.48 51 20 41	12 22 27.03 68 31 69	= 1 (P = 35 22 40 25 25 29	35 27 34.12 68 31 40.5	11 17 20.96 79 54 68	37 21 40 25 25 30	4.8% 3.9% 4.1% 1.1% 2.3% 1.4%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86] -11.00 [-35.41, 13.41] 0.50 [-34.47, 35.47]	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Grosen 2014	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13	12 22 27.03 68 31 69 25.71	= 1 (P = 35 22 40 25 25 29 52	35 27 34.12 68 31 40.5 23.03	11 17 20.96 79 54 68 20.99	37 21 40 25 25 30 52	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86] -11.00 [-35.41, 13.41] 0.50 [-34.47, 35.47] 0.10 [-8.92, 9.12]	
-leterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Grosen 2014 Hout 2007	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30	12 22 27.03 68 31 69 25.71 74.1	= 1 (P = 35 22 40 25 25 29 52 23	35 27 34.12 68 31 40.5 23.03 15	11 17 20.96 79 54 68 20.99 59.3	37 21 40 25 25 30 52 28	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.3%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86] -11.00 [-35.41, 13.41] 0.50 [-34.47, 35.47] 0.10 [-8.92, 9.12] 15.00 [-22.41, 52.41]	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Grosen 2014 Hout 2007 Junn 2015a	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41	12 22 27.03 68 31 69 25.71 74.1 14.5	= 1 (P = 35 22 40 25 25 29 52 23 91	35 27 34.12 68 31 40.5 23.03 15 42	11 17 20.96 79 54 68 20.99 59.3 8.7	37 21 40 25 25 30 52 28 29	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.3% 4.9%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86] -11.00 [-55.4, 13.41] 0.50 [-34.47, 35.47] 0.10 [-8.92, 912] 15.00 [-22.41, 52.41] -1.00 [-5.35, 3.35]	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2007 Fassoulaki 2005 Grosen 2014 Hout 2007 Lunn 2015a Dmran 2006	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54	12 22 27.03 68 31 69 25.71 74.1 14.5 38.66	= 1 (P = 35 22 40 25 25 29 52 23 91 25	35 27 34.12 68 31 40.5 23.03 15 42 76	11 17 20.96 79 54 68 20.99 59.3 8.7 38.66	37 21 40 25 25 30 52 28 29 25	4.8% 3.9% 4.1% 2.3% 1.4% 4.3% 1.3% 4.9% 2.6%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86] -11.00 [-53.41, 13.41] 0.50 [-34.47, 35.47] 0.10 [-8.92, 9.12] 15.00 [-22.41, 52.41] -1.00 [-5.35, 3.35] -22.00 [-43.43, -0.57]	
-leterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Fassoulaki 2005 Grosen 2014 Hout 2007 Lunn 2015a Omran 2006 Rapchuk 2010	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54 41 54 45	20.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65	= 1 (P = 35 22 40 25 25 29 52 23 91 25 27	35 27 34.12 68 31 40.5 23.03 15 42 76 45	11 17 20.96 79 54 68 20.99 59.3 8.7 38.66 63	37 21 40 25 25 30 52 28 29 25 27	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.3% 4.9% 2.6% 1.5%	$\begin{array}{c} -12.00 \ [-17.33, -6.67] \\ -1.00 \ [-12.72, 10.72] \\ 3.36 \ [-7.24, 13.96] \\ -17.00 \ [-57.86, 23.86] \\ -11.00 \ [-53.41, 13.41] \\ 0.50 \ [-34.47, 35.47] \\ 0.10 \ [-8.92, 9.12] \\ 15.00 \ [-22.41, 52.41] \\ -1.00 \ [-5.35, 3.35] \\ -22.00 \ [-43.43, -0.57] \\ 0.00 \ [-34.14, 34.14] \end{array}$	
Heterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Groson 2014 Hout 2007 Lunn 2015a Dmran 2006 Rapchuk 2010 Sen 2009a	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54 45 9	0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4	= 1 (P = 35 22 40 25 29 52 29 52 29 52 29 52 29 52 27 20	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29	11 17 20.96 79 54 68 20.99 59.3 8.7 38.66 63 30	37 21 40 25 25 30 52 28 29 25 27 20	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 2.6% 1.5% 3.7%	$\begin{array}{c} -12.00 \ [-17.33, -6.67] \\ -1.00 \ [-12.72, 10.72] \\ 3.36 \ [-7.24, 13.96] \\ -17.00 \ [-57.86, 23.86] \\ -11.00 \ [-35.41, 13.41] \\ 0.50 \ [-34.47, 35.47] \\ 0.10 \ [-8.92, 9.12] \\ 15.00 \ [-2.41, 52.41] \\ -1.00 \ [-5.35, 3.35] \\ -22.00 \ [-3.43.4, -0.57] \\ 0.00 \ [-3.41.4, 34.14] \\ -20.00 \ [-3.326, -6.74] \end{array}$	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Fassoulaki 2005 Grosen 2014 Hout 2007 Junn 2015a Dmran 2006 Rapchuk 2010 Sen 2009a Sen 2009a	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54 45 9 2	2 0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4 3 4 3	= 1 (P = 35 22 40 25 25 29 52 23 91 25 27 20 30	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29 15	11 17 20.96 79 54 68 20.99 59.3 8.7 38.66 63 300 15	37 21 40 25 25 30 52 28 29 25 27 20 29	4.8% 3.9% 4.1% 1.1% 2.3% 1.3% 4.3% 1.3% 4.9% 2.6% 1.5% 3.7% 4.8%	$\begin{array}{c} -12.00 \ [-17.33, -6.67] \\ -1.00 \ [-12.72, 10.72] \\ 3.36 \ [-7.24, 13.96] \\ -17.00 \ [-57.86, 23.86] \\ -11.00 \ [-53.44, 13.41] \\ 0.50 \ [-34.47, 35.47] \\ 0.10 \ [-8.92, 9.12] \\ 15.00 \ [-22.41, 52.41] \\ -1.00 \ [-5.35, 3.35] \\ -22.00 \ [-43.43, -0.57] \\ 0.00 \ [-33.26, -6.74] \\ -30.00 \ [-18.56, -7.44] \end{array}$	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Frosen 2014 Hout 2007 Junn 2015a Dmran 2006 Rapchuk 2010 Sen 2009a Sen 2009b Furan 2003a	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54 45 9 2 215.4	0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4 3 7	= 1 (P = 35 22 40 25 25 29 52 23 91 25 27 20 30 25	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29 15 16	11 17 20.96 79 544 68 20.99 59.3 8.7 38.66 63 30 15 7	37 21 40 25 30 52 28 29 25 27 20 29 25	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.3% 4.9% 2.6% 1.5% 3.7% 4.8% 4.9%	$\begin{array}{c} -12.00 \ [-17.33, -6.67] \\ -1.00 \ [-12.72, 10.72] \\ 3.36 \ [-7.24, 13.96] \\ -17.00 \ [-57.86, 23.86] \\ -11.00 \ [-53.41, 13.41] \\ 0.50 \ [-34.47, 35.47] \\ 0.10 \ [-8.92, 9.12] \\ 15.00 \ [-22.41, 52.41] \\ -1.00 \ [-5.35, 3.35] \\ -22.00 \ [-43.43, -0.57] \\ 0.00 \ [-43.14, 34.14] \\ -20.00 \ [-33.26, -6.74] \\ -13.00 \ [-18.56, -7.44] \\ -0.60 \ [-4.48, 3.28] \\ \end{array}$	
-leterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Grosen 2014 Hout 2007 Lunn 2015a Dmran 2006 Kapchuk 2010 Sen 2009a Sen 2009a Sen 2009a Juan 2003a Juak 2011	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54 45 9 2	2 0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4 3 4 3	= 1 (P = 35 22 40 25 29 52 23 91 25 27 20 30 25 20	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29 15	11 17 20.96 79 54 68 20.99 59.3 8.7 38.66 63 300 15	37 21 40 25 30 52 28 29 25 27 20 29 25 20	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.3% 4.9% 2.6% 3.7% 4.8% 4.9% 1.7%	$\begin{array}{c} -12.00 \ [-17.33, -6.67] \\ -1.00 \ [-12.72, 10.72] \\ 3.36 \ [-7.24, 13.96] \\ -17.00 \ [-57.86, 23.86] \\ -11.00 \ [-35.41, 13.41] \\ 0.50 \ [-34.47, 35.47] \\ 0.10 \ [-8.92, 9.12] \\ 15.00 \ [-22.41, 52.41] \\ -1.00 \ [-5.35, 3.35] \\ -22.00 \ [-43.43, -0.57] \\ 0.00 \ [-34.14, 34.14] \\ -20.00 \ [-33.26, -6.74] \\ -13.00 \ [-18.56, -7.44] \\ -0.60 \ [-4.48, 3.28] \\ -14.00 \ [-44.43, 3, 16.3] \end{array}$	
Heterogeneity: Tau ² = Fest for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Fassoulaki 2005 Grosen 2014 Hout 2007 Lunn 2015a Dmran 2006 Rapchuk 2010 Sen 2009a Sen 2009a Sen 2009a Jcak 2011 Subtotal (95% CI)	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 0 41 54 45 9 2 15.4 37	2 0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4 3 7 25	= 1 (P = 35 22 40 25 25 29 52 29 52 29 52 29 52 29 91 25 27 20 30 25 20 489	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29 15 16 51	11 17 20.96 79 54 68 20.99 59.3 8.7 38.66 63 300 15 7 66	37 21 40 25 30 52 28 29 25 27 20 29 25	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.3% 4.9% 2.6% 1.5% 3.7% 4.8% 4.9%	$\begin{array}{c} -12.00 \ [-17.33, -6.67] \\ -1.00 \ [-12.72, 10.72] \\ 3.36 \ [-7.24, 13.96] \\ -17.00 \ [-57.86, 23.86] \\ -11.00 \ [-53.41, 13.41] \\ 0.50 \ [-34.47, 35.47] \\ 0.10 \ [-8.92, 9.12] \\ 15.00 \ [-22.41, 52.41] \\ -1.00 \ [-5.35, 3.35] \\ -22.00 \ [-43.43, -0.57] \\ 0.00 \ [-43.14, 34.14] \\ -20.00 \ [-33.26, -6.74] \\ -13.00 \ [-18.56, -7.44] \\ -0.60 \ [-4.48, 3.28] \\ \end{array}$	
-leterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Grosen 2014 Hout 2007 Lunn 2015a Dmran 2006 Kapchuk 2010 Sen 2009a Sen 2009a Sen 2009a Juan 2003a Juak 2011	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54 45 9 2 15.4 37 = 31.21; Chi ² =	• 0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4 3 7 25 = 36.30, df	= 1 (P = 35 22 40 25 25 29 52 29 52 29 52 29 52 29 91 25 27 20 30 25 20 489	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29 15 16 51	11 17 20.96 79 54 68 20.99 59.3 8.7 38.66 63 300 15 7 66	37 21 40 25 30 52 28 29 25 27 20 29 25 20	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.3% 4.9% 2.6% 3.7% 4.8% 4.9% 1.7%	$\begin{array}{c} -12.00 \ [-17.33, -6.67] \\ -1.00 \ [-12.72, 10.72] \\ 3.36 \ [-7.24, 13.96] \\ -17.00 \ [-57.86, 23.86] \\ -11.00 \ [-35.41, 13.41] \\ 0.50 \ [-34.47, 35.47] \\ 0.10 \ [-8.92, 9.12] \\ 15.00 \ [-22.41, 52.41] \\ -1.00 \ [-5.35, 3.35] \\ -22.00 \ [-43.43, -0.57] \\ 0.00 \ [-34.14, 34.14] \\ -20.00 \ [-33.26, -6.74] \\ -13.00 \ [-18.56, -7.44] \\ -0.60 \ [-4.48, 3.28] \\ -14.00 \ [-44.43, 3, 16.3] \end{array}$	
Heterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Grosen 2014 Hout 2007 Junn 2015a Dmran 2006 Kapchuk 2010 Sen 2009a Sen 2009a Sen 2009a Sen 2009a Joak 2011 Subtotal (95% Cl) Heterogeneity: Tau ² = Fest for overall effect	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54 45 9 2 15.4 37 = 31.21; Chi ² =	• 0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4 3 7 25 = 36.30, df	= 1 (P = 35 22 40 25 29 52 23 91 25 27 20 30 25 27 20 489 = 14 (I	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29 15 16 51	11 17 20.96 79 54 68 20.99 59.3 8.7 38.66 63 300 15 7 66	37 21 40 25 30 52 28 29 25 27 20 29 29 20 433	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.5% 2.6% 3.7% 4.8% 4.9% 1.7% 47.3%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86] -11.00 [-35.41, 13.41] 0.50 [-34.47, 35.47] 0.10 [-8.92, 9.12] 15.00 [-22.41, 52.41] -1.00 [-5.35, 3.35] -22.00 [-34.14, 34.14] -20.00 [-34.14, 34.14] -20.00 [-34.26, -6.74] -13.00 [-18.56, -7.44] -0.60 [-4.48, 3.28] -14.00 [-44.93, 16.93] -5.86 [-10.28, -1.45]	
Heterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2002 Fassoulaki 2005 Grosen 2014 Hout 2007 Lunn 2015a Dmran 2006 Rapchuk 2010 Sen 2009a Sen 2009b Sen 2007b Sen	: Z = 0.95 (P = 23 26 37.48 51 20 41 23.13 30 41 54 45 9 2 15.4 37 = 31.21; Chi ² = : Z = 2.60 (P =	2 0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4 3 7 25 38.630, df 0.009)	35 22 40 25 25 29 52 23 91 52 27 20 30 52 27 20 30 5 = 1 (P =	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29 15 16 51 P = 0.0009); I	$ \begin{array}{c} 11\\ 17\\ 20.96\\ 79\\ 54\\ 68\\ 20.99\\ 59.3\\ 8.7\\ 38.66\\ 63\\ 30\\ 15\\ 7\\ 66\\ \end{array} $	37 21 40 25 25 30 52 28 29 25 27 20 29 25 20 433	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.3% 4.9% 2.6% 3.7% 4.8% 4.9% 1.7%	$\begin{array}{c} -12.00 \ [-17.33, -6.67] \\ -1.00 \ [-12.72, 10.72] \\ 3.36 \ [-7.24, 13.96] \\ -17.00 \ [-57.86, 23.86] \\ -11.00 \ [-35.41, 13.41] \\ 0.50 \ [-34.47, 35.47] \\ 0.10 \ [-8.92, 9.12] \\ 15.00 \ [-22.41, 52.41] \\ -1.00 \ [-5.35, 3.35] \\ -22.00 \ [-43.43, -0.57] \\ 0.00 \ [-34.14, 34.14] \\ -20.00 \ [-33.26, -6.74] \\ -13.00 \ [-18.56, -7.44] \\ -0.60 \ [-4.48, 3.28] \\ -14.00 \ [-44.43, 3, 16.3] \end{array}$	
Heterogeneity: Tau ² = Test for overall effect 3.14.5 > 1050 mg Al-Mujadi 2005 Brogly 2008 Dierking 2003 Durmus 2007 Fassoulaki 2002 Fassoulaki 2005 Grosen 2014 Hout 2007 Junn 2015a Dmran 2006 Kapchuk 2010 Sen 2009a Sen 2009a Sen 2009a Sen 2009a Juna 2005 Furan	Z = 0.95 (P = 23) = 23 = 26 = 26 = 26 = 26 = 26 = 26 = 26	• 0.34) 12 22 27.03 68 31 69 25.71 74.1 14.5 38.66 65 4 3 7 25 = 36.30, df • 0.009) = 748.24,	35 22 40 25 25 29 52 23 91 52 27 20 30 52 27 20 30 5 = 1 (P =	35 27 34.12 68 31 40.5 23.03 15 42 76 45 29 15 16 51 P = 0.0009); I	$ \begin{array}{c} 11\\ 17\\ 20.96\\ 79\\ 54\\ 68\\ 20.99\\ 59.3\\ 8.7\\ 38.66\\ 63\\ 30\\ 15\\ 7\\ 66\\ \end{array} $	37 21 40 25 25 30 52 28 29 25 27 20 29 25 20 433	4.8% 3.9% 4.1% 1.1% 2.3% 1.4% 4.3% 1.5% 2.6% 3.7% 4.8% 4.9% 1.7% 47.3%	-12.00 [-17.33, -6.67] -1.00 [-12.72, 10.72] 3.36 [-7.24, 13.96] -17.00 [-57.86, 23.86] -11.00 [-35.41, 13.41] 0.50 [-34.47, 35.47] 0.10 [-8.92, 9.12] 15.00 [-22.41, 52.41] -1.00 [-5.35, 3.35] -22.00 [-34.14, 34.14] -20.00 [-34.14, 34.14] -20.00 [-34.26, -6.74] -13.00 [-18.56, -7.44] -0.60 [-4.48, 3.28] -14.00 [-44.93, 16.93] -5.86 [-10.28, -1.45]	

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

	Gabape		Control		Risk Ratio	Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
3.15.2 0-350 mg							
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not a							
Test for overall effect	:: Not appl	icable					
3.15.3 351-700 mg							
Misra 2013	4	36	13	37	9.1%	0.32 [0.11, 0.88]	
Moore 2010	12	21	8	23	16.7%	1.64 [0.84, 3.21]	+
Paul 2013	33	52	40	49	36.9%	0.78 [0.61, 0.99]	-
Subtotal (95% CI)		109		109	62.8%	0.81 [0.40, 1.61]	•
Total events	49		61				
Heterogeneity: Tau ² =	= 0.27; Ch	$i^2 = 7.6$	58, df = 2	2 (P = 0)).02); I ² =	74%	
Test for overall effect	Z = 0.61	(P = 0	.54)				
2 1 5 4 701 1050							
3.15.4 701-1050 mg	g	•		0		Net estimable	
Subtotal (95% CI)	-	0		0		Not estimable	
Subtotal (95% CI) Total events	0	0	0	0		Not estimable	
Subtotal (95% CI) Total events Heterogeneity: Not aj	0 oplicable	-	0	0		Not estimable	
Subtotal (95% CI) Total events	0 oplicable	-	0	0		Not estimable	
Subtotal (95% CI) Total events Heterogeneity: Not aj	0 oplicable	-	0	0		Not estimable	
Subtotal (95% Cl) Total events Heterogeneity: Not a Test for overall effect	0 oplicable	-	0	0 38	5.2%	Not estimable 0.75 [0.18, 3.13]	
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 3.15.5 > 1050 mg Bartholdy 2006 Grosen 2014	0 oplicable :: Not appl	icable 38 52	-	38 52	32.0%	0.75 [0.18, 3.13] 0.68 [0.49, 0.94]	
Subtotal (95% CI) Total events Heterogeneity: Not an Test for overall effect 3.15.5 > 1050 mg Bartholdy 2006	0 oplicable :: Not appl 3	icable 38	4	38		0.75 [0.18, 3.13]	•
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 3.15.5 > 1050 mg Bartholdy 2006 Grosen 2014 Subtotal (95% CI) Total events	0 oplicable :: Not appl 3 25 28	icable 38 52 90	4 37 41	38 52 90	32.0% 37.2%	0.75 [0.18, 3.13] 0.68 [0.49, 0.94] 0.68 [0.49, 0.94]	•
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 3.15.5 > 1050 mg Bartholdy 2006 Grosen 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ²	0 pplicable :: Not appl 3 25 28 = 0.00; Ch	icable 38 52 90 i ² = 0.0	4 37 41 D2, df = 1	38 52 90	32.0% 37.2%	0.75 [0.18, 3.13] 0.68 [0.49, 0.94] 0.68 [0.49, 0.94]	•
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 3.15.5 > 1050 mg Bartholdy 2006 Grosen 2014 Subtotal (95% CI) Total events	0 pplicable :: Not appl 3 25 28 = 0.00; Ch	icable 38 52 90 i ² = 0.0	4 37 41 D2, df = 1	38 52 90	32.0% 37.2%	0.75 [0.18, 3.13] 0.68 [0.49, 0.94] 0.68 [0.49, 0.94]	•
Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect 3.15.5 > 1050 mg Bartholdy 2006 Grosen 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ²	0 pplicable :: Not appl 3 25 28 = 0.00; Ch	icable 38 52 90 i ² = 0.0	4 37 41 D2, df = 1	38 52 90 1 (P = 0	32.0% 37.2%	0.75 [0.18, 3.13] 0.68 [0.49, 0.94] 0.68 [0.49, 0.94]	•
Subtotal (95% CI) Total events Heterogeneity: Not aj Test for overall effect 3.15.5 > 1050 mg Bartholdy 2006 Grosen 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect	0 pplicable :: Not appl 3 25 28 = 0.00; Ch	icable 38 52 90 $i^2 = 0.0$ (P = 0)	4 37 41 D2, df = 1	38 52 90 1 (P = 0	32.0% 37.2% 0.89); I ² =	0.75 [0.18, 3.13] 0.68 [0.49, 0.94] 0.68 [0.49, 0.94] 0%	•
Subtotal (95% CI) Total events Heterogeneity: Not aj Test for overall effect 3.15.5 > 1050 mg Bartholdy 2006 Grosen 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI)	0 oplicable :: Not appl 3 25 28 = 0.00; Ch :: Z = 2.35 77	icable 38 52 90 $i^2 = 0.0$ (P = 0 199	4 37 41 02, df = 1 .02) 102	38 52 90 1 (P = 0 199	32.0% 37.2% 0.89); l ² = 100.0%	0.75 [0.18, 3.13] 0.68 [0.49, 0.94] 0.68 [0.49, 0.94] 0% 0.77 [0.55, 1.09]	

Appendix 14	Forest pl	ot of nausea	from all	trials estimates
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Study or Subgroup	Gabaper Events		Contro Events		Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M–H, Random, 95% Cl
3.16.1 0-350 mg	Lycints	, otai	_vents	Jordi	neight		in ri, Kandoni, 55% Ci
이는 것은 것은 것이 있는 것이 있는 것이 같은 것이 가지 않는 것이 있다. 같은 것이 같은 것이 있는 것이 같은 것이 같은 것이 같은 것이 있다.	c	22	0	22	1 70/	0.75 (0.21, 1.82)	
Bang 2009	6	23	8	23	1.7%	0.75 [0.31, 1.82]	
Behdad 2012	5	30	5	31	1.1%	1.03 [0.33, 3.21]	
Clarke 2014	26	88	26	77	5.2%	0.88 [0.56, 1.37]	-
Ghafari 2009	5	33	7	33	1.2%	0.71 [0.25, 2.02]	
Khurana 2013	2	30	0	30	0.2%	5.00 [0.25, 99.95]	
Panday 2004c	5	28	4	28	0.9%	1.25 [0.37, 4.17]	
Sekhavet 2009	32	49	37	49	10.2%	0.86 [0.67, 1.12]	-
Verma 2008	5	25	4	25	1.0%	1.25 [0.38, 4.12]	
Yoon 2001	7	16	9	15	2.6%	0.73 [0.36, 1.46]	
Subtotal (95% CI)	'	322	9	311	24.1%	0.87 [0.72, 1.06]	
		322		511	24.1/0	0.87 [0.72, 1.00]	N
Total events Heterogeneity: $Tau^2 = 0$	93 00. Chi ² =	2 67	100 df = 8 (P	= 0.95	5) $I^2 = 0\%$		
Test for overall effect: Z				0.55	,,, = 0,0		
3.16.2 351-700 mg							
Ajori 2011	8	69	19	69	2.2%	0.42 [0.20, 0.90]	
Bashir 2009	1	50	1	50	0.2%	1.00 [0.06, 15.55]	
Clarke 2009b	24	76	14	38	4.0%	0.86 [0.50, 1.46]	
Grover 2009	12	15	6	21	2.4%	2.80 [1.36, 5.76]	· · · · ·
Kavitha 2013	3	28	4	28	0.7%	0.75 [0.18, 3.05]	
Kim 2004	8	21	8	20	2.2%	0.95 [0.44, 2.05]	
Koc 2007	1	20	1	20	0.2%	1.00 [0.07, 14.90]	
Menda 2010	9	30	18	30	3.2%	0.50 [0.27, 0.93]	
Misra 2013	4	36	13	37	1.3%	0.32 [0.11, 0.88]	
Moore 2010	12	21	8	23	2.8%	1.64 [0.84, 3.21]	—
Panday 2005	6	40	3	20	0.8%	1.00 [0.28, 3.59]	
Paul 2013	33	52	40	49	10.8%	0.78 [0.61, 0.99]	-
Sava 2009	7	25	11	25	2.2%	0.64 [0.30, 1.37]	
Siddiqui 2013	17	36	17	36	4.6%	1.00 [0.61, 1.63]	
Zaldivar Ramirez 2011	4	18	15	16	1.7%	0.24 [0.10, 0.57]	
Subtotal (95% CI)	4	537	12	482	39.3%	0.24 [0.10, 0.57] 0.78 [0.58, 1.05]	
Total events	149		178				•
Heterogeneity: Tau ² = 0 Test for overall effect: Z				(P = 0	.002); 1* =	= 58%	
3.16.3 701-1050 mg Deniz 2012	7	25	12	26	2.2%	0.61 [0.29, 1.29]	
Pakravan 2012	3	50	0	50	0.2%	7.00 [0.37, 132.10]	,
	6	30	6		1.3%		
Radhakrishnan 2005				30		1.00 [0.36, 2.75]	
Rajendran 2014 Subtotal (95% CI)	4	30 135	4	30 136	0.8% 4.6%	1.00 [0.28, 3.63] 0.83 [0.48, 1.44]	
	20	133	22	130	4.0%	0.83 [0.48, 1.44]	
Total events	20	2.07	22	0.30	12 20/		
Heterogeneity: $Tau^2 = 0$ Test for overall effect: Z				= 0.38	$(3); 1^{-} = 2\%$		
3.16.4 > 1050 mg							
Bartholdy 2006	3	38	4	38	0.7%	0.75 [0.18, 3.13]	
Dierking 2003	12	39	11	32	2.8%	0.90 [0.46, 1.75]	
Doha 2010	2	30	4	29	0.5%	0.48 [0.10, 2.44]	
Durmus 2007	7	25	9	25	1.9%	0.78 [0.34, 1.76]	
Fassoulaki 2006	1	27	5	24	0.3%	0.18 [0.02, 1.42]	
Gilron 2004	4	20	12	22	1.5%		
						0.37 [0.14, 0.95]	
Grosen 2014	25	52	37	52	7.9%	0.68 [0.49, 0.94]	
Jajeda 2014	0	25	3	25	0.2%	0.14 [0.01, 2.63]	
Kosucu 2013	2	29	4	31	0.5%	0.53 [0.11, 2.70]	
Mikkelsen 2006	3	20	3	20	0.6%	1.00 [0.23, 4.37]	
Ménigaux 2004	3	20	3	20	0.6%	1.00 [0.23, 4.37]	
Omran 2006	5	50	7	50	1.2%	0.71 [0.24, 2.10]	
Pathak 2013	1	40	4	40	0.3%	0.25 [0.03, 2.14]	
Sen 2009a	9	20	8	20	2.4%	1.13 [0.55, 2.32]	
	5		8				
Turan 2003a		25		25	1.3%	0.71 [0.26, 1.95]	
Turan 2003b	5	25	7	25	1.3%	0.71 [0.26, 1.95]	
Turan 2004	4	25	4	25	0.9%	1.00 [0.28, 3.56]	
Turan 2005	10	20	14	20	4.1%	0.71 [0.42, 1.21]	
Turan 2006	6	25	2	25	0.6%	3.00 [0.67, 13.46]	
Ucak 2011	4	20	2	20	0.6%	2.00 [0.41, 9.71]	
Özgencil 2011	8	30	7	30	1.7%	1.14 [0.47, 2.75]	
Subtotal (95% CI)	Ŭ	605		598	32.0%	0.75 [0.62, 0.91]	•
	110		157				•
Total events	119	14 75		(D C	701-12	0%	
Heterogeneity: $Tau^2 = 0$ Test for overall effect: Z				(P = 0)	.79); 1° =	0%	
		1599		1527	100.0%	0.81 [0.72, 0.91]	•
Total (95% CI)							
Total (95% CI) Total events	381		457				
Total events		54.67		(P = 0	.24); I ² =	12%	
Total events Heterogeneity: Tau² = 0	.02; Chi ² =		, df = 48	(P = 0	.24); I ² =	12%	
	.02; Chi ² = = 3.51 (P	= 0.00	, df = 48 04)				0.01 0.1 1 10 100 Favours Gabapentin Favours Controls

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

Study or Subgroup E 3.17.1 0-350 mg Subtotal (95% CI) Total events Heterogeneity: Not appl Test for overall effect: N			Events	Total	Woight M		
Subtotal (95% CI) Total events Heterogeneity: Not appl					weight M	-H, Random, 95% CI	M-H, Random, 95% Cl
Total events Heterogeneity: Not appl							
Heterogeneity: Not appl		0		0		Not estimable	
5 / 11	0		0				
rest for overall effect. It		cable					
3.17.2 351-700 mg							
Moore 2010	5	21	3	25	9.5%	1.98 [0.54, 7.34]	
Subtotal (95% CI)		21		25	9.5%	1.98 [0.54, 7.34]	
Total events	5		3				
Heterogeneity: Not appl							
Test for overall effect: Z	2 = 1.03	(P=0)	.30)				
3.17.3 701-1050 mg				-			
Subtotal (95% CI)		0		0		Not estimable	
Total events	0		0				
Heterogeneity: Not appl							
Test for overall effect: N	lot appli	cable					
3.17.4 > 1050 mg							
Bartholdy 2006	3	38	3	38	6.9%	1.00 [0.22, 4.65]	<u> </u>
Grosen 2014	23	52	22	52	83.7%	1.05 [0.67, 1.62]	
Subtotal (95% CI)		90		90	90.5%	1.04 [0.68, 1.59]	•
Total events	26		25				
Heterogeneity: $Tau^2 = 0$,		,	I (P = C)	$(.96); I^2 = 0$	%	
Test for overall effect: Z	. = 0.19	(P=0)	.85)				
Total (95% CI)		111		115	100.0%	1.11 [0.74, 1.66]	•
Total events	31		28				
Heterogeneity: $Tau^2 = 0$,		,	2 (P = 0)	$(.65); I^2 = 0$	%	0.01 0.1 1 10 100
Test for overall effect: Z							Favours Gabapentin Favours Control
Test for subgroup differ	rences: ($Chi^2 = 0$	0.84, df :	= 1 (P =	$= 0.36$), $ ^2 =$	0%	·

Appendix 16	Forest plot o	of vomiting fr	rom all trials	estimates
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	Gabape		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.18.1 0-350 mg							
lang 2009	1	23	3	23	0.5%	0.33 [0.04, 2.97]	
Tehdad 2012	5	30	7	31	2.2%	0.74 [0.26, 2.07]	
Chafari 2009	4	33	9	33	2.0%	0.44 [0.15, 1.30]	
Churana 2013	1	30	2	30	0.4%	0.50 [0.05, 5.22]	
Mohammadi 2008	0	35	0	35		Not estimable	
Panday 2004c	3	28	4	28	1.2%	0.75 [0.18, 3.05]	
Sekhavet 2009	18	49	19	49	9.1%	0.95 [0.57, 1.58]	-
Verma 2008	3	25	4	25	1.2%	0.75 [0.19, 3.01]	
Yeon 2001	- 4	16	1	15	0.5%	3.75 [0.47, 29.87]	-
Subtotal (95% CI)		269		269	17.2%	0.81 [0.56, 1.17]	•
Total events	39		49				
feterogeneity: Tau ² = 0			-	r = 0.7	$2); I^2 = 00$	6	
Fest for overall effect: Z	= 1.12 (P	= 0.26)				
3.18.2 351-700 mg							
Ajeri 2011	5	69	16	69	2.6%	0.31 [0.12, 0.81]	
Sharti 2012	6	40	9	40	2.7%	0.67 [0.26, 1.70]	
Clarke 2009b	9	76	7	38	2.8%	0.64 [0.26, 1.59]	+
Grever 2009	7	25	7	21	3.1%	0.84 [0.35, 2.01]	_ _ _
Cavitha 2013	0	28	0	28		Net estimable	
Gm 2004	4	21	2	20	0.9%	1.90 [0.39, 9.28]	
Kec 2007	7	20	14	20	5.3%	0.50 [0.26, 0.97]	
Menda 2010	0	30	0	30		Not estimable	
Metry 2008	2	77	1	34	0.4%	0.88 [0.08, 9.41]	
Moore 2010	5	21	3	25	1.4%	1.98 [0.54, 7.34]	
Panday 2005	2	40	2	20	0.7%	0.50 [0.08, 3.29]	
Sava 2009	5	25	7	25	2.3%	0.71 [0.26, 1.95]	
Siddiqui 2013	5	36	6	36	2.0%	0.83 [0.28, 2.49]	
Zaldivar Ramirez 2011	0	18	7	16	0.3%	0.06 [0.00, 0.97]	· •
Subtotal (95% CI)		526		422	24.6%	0.65 [0.48, 0.89]	•
Total events	57		81		A 20. 10		
the second se	- COL - 201-12				1.431: I* =		
Heterogeneity: Tau ² = 0 Test for overall effect: Z 8.18.3 701–1050 mg		= 0.00					
Test for overall effect: Z 8.18.3 701–1050 mg Deniz 2012 Radhakrishnan 2005		= 0.00 25 30		26 30	0.8%	Not estimable 0.67 [0.12, 3.71]	
Test for overall effect: Z 8.18.3 701–1050 mg Deniz 2012 Radhakrishnan 2005 Subtotal (95% CD	= 2.71 (P 0 2	= 0.00	77 0 3	26		Not estimable	-
Test for overall effect: Z 8.18.3 701–1050 mg Deniz 2012 Radhakrishnan 2005 Subtotal (95% Cl) Total events	= 2.71 (P 2 2	= 0.00 25 30	0	26 30	0.8%	Not estimable 0.67 [0.12, 3.71]	-
Test for overall effect: 2 8.18.3 701–1050 mg Deniz 2012 Radhakrishnan 2005 Rubtotal (95% CD	= 2.71 (P 2 icable	= 0.00 25 30 55	7) 0 3 3	26 30	0.8%	Not estimable 0.67 [0.12, 3.71]	-
Fest for overall effect: 2 k.18.3 701-1050 mg Deniz 2012 tadhakrishnan 2005 Kubtotal (95% C0 Fotal events feterogeneity: Not appl Fest for overall effect: 2	= 2.71 (P 2 icable	= 0.00 25 30 55	7) 0 3 3	26 30	0.8%	Not estimable 0.67 [0.12, 3.71]	-
Fest for overall effect: Z k.18.3 701–1050 mg Deniz 2012 tadhakrishnan 2005 fabtotal (95% C0 fotal events féterogeneity: Not appl fest for overall effect: Z k.18.4 > 1050 mg	= 2.71 (P 0 2 icable = 0.46 (P	= 0.00 25 30 55 = 0.64	7) 3 3	26 30 56	0.8% 0.8%	Not estimable 0.67 (0.12, 3.71) 0.67 [0.12, 3.71]	-
Fest for overall effect: Z k.18.3 701–1050 mg Deniz 2012 Kadhakrishnan 2005 Kabkotal (95% Cl) Fotal events feterogeneity: Not appl Fest for overall effect: Z k.18.4 > 1050 mg Abdelmageed 2010	= 2.71 (P 2 icable = 0.46 (P 2	= 0,00 25 30 55 = 0.64 30	7) 0 3 3 3 9	26 30 56 30	0.8% 0.8%	Not estimable 0.67 (0.12, 3.71) 0.67 [0.12, 3.71] 0.22 [0.05, 0.94]	_
Fast for overall effect: 2 k.18.3 701–1050 mg Deniz 2012 Kadhakrishnan 2005 Kubtotal (95% Cl) Fotal events feterogeneity: Not appl Fast for overall effect: 2 k.18.4 > 1050 mg Abdelmageed 2010 Fartholdy 2006	= 2.71 (P 2 icable = 0.46 (P 2 3	= 0,00 25 30 55 = 0.64 30 38	7) 0 3 3 9 3	26 30 56 30	0.8% 0.8% 1.1% 1.0%	Not estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.22 [0.05, 0.94] 1.00 [0.22, 4.65]	
Fest for overall effect: Z k.18.3 701–1050 mg Deniz 2012 Radhakrishnan 2005 Rubtotal (95% CD Fotal events feterogeneity: Not appl Fest for overall effect: Z k.18.4 > 1050 mg Abdelmageed 2010 Jantholdy 2006 Dierking 2003	= 2.71 (P 2 icable = 0.46 (P 2 3 18	= 0,00 25 30 55 = 0.64 30 38 39	7) 0 3 3 9 3 15	26 30 56 30 38 38	0.8% 0.8% 1.1% 1.0% 9.4%	Not estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.22 [0.05, 0.94] 1.00 [0.22, 4.65] 0.98 [0.60, 1.62]	
Fest for overall effect: Z k.18.3 701-1050 mg Deniz 2012 tadhakrishnan 2005 Kubtotal (95% C0 Fotal events feterogeneity: Not appl Fest for overall effect: Z k.18.4 > 1050 mg Nobelmageed 2010 Bartholdy 2006 Derking 2003 Doha 2010	= 2.71 (P 0 2 icable = 0.46 (P 2 3 18 3	= 0.00 25 30 55 = 0.64 30 38 39 30	7) 0 3 3 9 3 15 5	26 30 56 30 38 32 29	0.8% 0.8% 1.1% 1.0% 9.4% 1.3%	Net estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.22 [0.05, 0.94] 1.00 [0.22, 4.65] 0.98 [0.60, 1.62] 0.58 [0.15, 2.21]	
Fest for overall effect: 2 L18.3 701-1050 mg Deniz 2012 tadhakrishnan 2005 Jubtotal (95% CD) Fotal events feterogeneity: Not appl Fest for overall effect: 2 L18.4 > 1050 mg tadelmageed 2010 Jurtholdy 2006 Derking 2003 Data 2010 Durmus 2007	= 2.71 (P 2 icable = 0.46 (P 2 3 18 3 3	= 0.00 25 30 55 = 0.64 30 38 39 30 25	7) 0 3 3 3 5 5 6	26 30 56 30 38 32 29 25	0.8% 0.8% 1.1% 9.4% 1.3%	Not estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 1.00 [0.22, 4.65] 0.98 [0.60, 1.62] 0.58 [0.15, 2.21] 0.50 [0.14, 1.78]	
Fest for overall effect: 2 L18.3 701-1050 mg Deniz 2012 tadhakrishnan 2005 Jubtotal (95% Cl) Fotal events feterogeneity: Not appl fest for overall effect: 2 L18.4 > 1050 mg Abdelmageed 2010 Jartholdy 2006 Nerking 2003 Dena 2010 Jurmus 2007 Trosen 2014	= 2.71 (P 2 icable = 0.46 (P 2 3 18 3 23	= 0.00 25 30 55 = 0.64 30 38 39 30 25 52	7) 0 3 3 3 3 5 5 6 22	26 30 56 30 38 32 29 25 52	0.8% 0.8% 1.1% 1.0% 9.4% 1.5% 12.1%	Not estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 1.00 [0.22, 4.65] 0.98 [0.15, 2.21] 0.58 [0.15, 2.21] 0.50 [0.14, 1.78] 1.05 [0.67, 1.62]	
Fest for overall effect: Z k.18.3 701-1050 mg Deniz 2012 tadhakrishnan 2005 iabtotal (95% CD Fotal events feterogeneity: Not appl fest for overall effect: Z k.18.4 > 1050 mg Nodelmageed 2010 antholdy 2006 Derking 2003 Daha 2010 Durmus 2007 Fresen 2014 ajeda 2014	= 2.71 (P 2 icable = 0.46 (P 2 3 18 3 2 3 3 2 3 3	= 0.00 25 30 55 = 0.64 30 38 39 30 25 52 25	7) 3 3 3 3 3 5 5 6 22 5	26 30 56 30 38 32 29 25 52 25	0.8% 0.8% 1.1% 1.0% 9.4% 1.3% 12.1% 1.3%	Not estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 1.00 [0.22, 4.65] 0.98 [0.60, 1.62] 0.58 [0.15, 2.21] 0.59 [0.14, 1.78] 1.05 [0.67, 1.62] 0.69 [0.16, 2.25]	
Fest for overall effect: 2 L18.3 701-1050 mg Deniz 2012 tadhakrishnan 2005 Jabtotal (95% CD Fotal events feterogeneity: Not appl fest for overall effect: 2 L18.4 > 1050 mg Abdelmageed 2010 Jartholdy 2006 Derking 2003 Doha 2010 Dumus 2007 Grosen 2014 Jajeda 2014 Gesucu 2013	= 2.71 (P 2 icable = 0.46 (P 2 3 18 3 23 3 7	= 0.00 25 30 55 = 0.64 30 38 39 30 25 52 25 29	7) 0 3 3 15 5 6 22 5 4	26 30 56 30 38 32 29 25 25 25 31	0.8% 0.8% 1.1% 1.0% 9.4% 1.3% 1.5% 1.3% 1.3%	Net estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 1.00 [0.22, 4.65] 0.98 [0.60, 1.62] 0.58 [0.15, 2.21] 0.50 [0.14, 1.78] 1.05 [0.67, 1.62] 0.60 [0.16, 2.25] 1.87 [0.61, 5.73]	
Fest for overall effect: 2 k.18.3 701-1050 mg Deniz 2012 tadhakrishnan 2005 Kubtotal (95% CD Fotal events feterogeneity: Not appl fest for overall effect: 2 k.18.4 > 1050 mg Nobelmageed 2010 Bartholdy 2006 Denking 2003 Denka 2010 Dumus 2007 Grosen 2014 Agieda 2014 Gesucu 2013 Mikkelsen 2006	= 2.71 (P 2 icable = 0.46 (P 2 3 8 3 3 2 3 3 7 6	= 0.00 25 30 55 = 0.64 30 38 39 30 25 55 52 29 22	7) 0 3 3 5 5 6 22 5 4 2 2 2 5 4 2	26 30 56 30 38 32 29 25 25 25 25 25 25 25 25 25 25 25 25 25	0.8% 0.8% 1.1% 1.0% 1.3% 1.5% 1.3% 1.3% 1.9%	Net estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 1.00 [0.22, 4.65] 0.98 [0.60, 1.62] 0.58 [0.15, 2.21] 0.50 [0.14, 1.78] 1.05 [0.67, 1.62] 0.60 [0.16, 2.75] 1.87 [0.61, 5.73]	
Fest for overall effect: 2 k.18.3 701-1050 mg Deniz 2012 tadhakrishnan 2005 fablototal (95% CD) fotal events feterogeneity: Not appl fest for overall effect: 2 k.18.4 > 1050 mg bbdelmageed 2010 fartholdy 2006 Denking 2003 Denking 2003 Daha 2010 Dumus 2007 Grosen 2014 ajeda 2014 Gesucu 2013 Alikkelsen 2006 Dmran 2006	= 2.71 (P 2 icable = 0.46 (P 2 3 18 3 23 3 7 6 1	= 0.00 25 30 55 = 0.64 30 38 39 30 25 52 25 29 22 50	7) 0 3 3 9 3 15 5 6 22 5 4 2 7	26 30 56 30 30 30 30 32 29 25 52 25 25 31 27 50	0.8% 0.8% 1.0% 9.4% 1.3% 1.5% 1.3% 1.3% 1.9%	Not estimable 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 0.67 [0.12, 3.71] 1.00 [0.22, 4.65] 0.98 [0.60, 1.62] 0.58 [0.15, 2.21] 0.50 [0.14, 1.78] 1.05 [0.67, 1.62] 0.60 [0.16, 2.25] 1.87 [0.61, 5.73] 3.68 [0.82, 16.47] 0.14 [0.02, 1.12]	
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teterogeneity: $Tau^2 = 0.00$; $Chi^2 = 6.57$, $df = 8$ (P = 0.58); $I^2 = 0\%$ Test for overall effect: Z = 1.22 (P = 0.22)	otal (95% CI)		362		370	100.0%	1.10 [0.95, 1.27]	•	
Test for overall effect: Z = 1.22 (P = 0.22)	otal events	138		123					
est for overall effect: Z = 1.22 (P = 0.22) Eavours Gabapentin Eavours Control	5 /	,		,	8 (P = 0)	.58); I ² =	0%		
	ost for overall effect:	7 = 1.22	(P = 0)	22)					

Study or Subgroup	Gabape		Contr			Risk Ratio	Risk Ratio
, ,	Events	Total	Events	Total	Weight N	A-H, Random, 95% CI	M-H, Random, 95% Cl
3.20.1 0-350 mg							
Bang 2009	1	23	1	23	0.6%	1.00 [0.07, 15.04]	
Ghafari 2009	2	33	3	33	1.3%	0.67 [0.12, 3.73]	
Khurana 2013	4	30	0	30	0.5%	9.00 [0.51, 160.17]	
Panday 2004b	52	153	5	153	3.2%	10.40 [4.27, 25.32]	
Sekhavet 2009	26	49	22	49	5.6%	1.18 [0.79, 1.78]	+-
Vahedi 2011	16	36	0	40	0.6%	36.57 [2.27, 588.35]	————
Waikakul 2011	1	26	0	24	0.4%	2.78 [0.12, 65.08]	
Yoon 2001	13	16	13	16	6.0%	1.00 [0.72, 1.39]	+
Subtotal (95% CI)		366		368	18.3%	2.51 [0.89, 7.05]	
Total events	115		44				
Heterogeneity: $Tau^2 = 1$ Test for overall effect: Z	1.40; Chi ² =		, df = 7	(P < 0.0	00001); I ²	= 89%	
3.20.2 351-700 mg							
Ajori 2011	0	69	0	69		Not estimable	
Clarke 2009b	18	76	7	38	3.7%	1.29 [0.59, 2.81]	- -
Kavitha 2013	3	28	9	28	2.2%	0.33 [0.10, 1.10]	
Kazak 2009	0	30	0	30		Not estimable	
Kim 2004	5	21	5	20	2.6%	0.95 [0.32, 2.80]	_
Kinney 2011	10	57	10	63	3.6%	1.11 [0.50, 2.46]	_
Moore 2010	17	21	17	23	6.1%	1.10 [0.80, 1.51]	+
Panday 2005	3	40	1	20	0.9%	1.50 [0.17, 13.52]	
Panday 2005 Panday 2006	4	125	2	125	1.4%	2.00 [0.37, 10.72]	
Paul 2013	35	52	35	49	6.4%	0.94 [0.73, 1.22]	1
Sava 2009	2	25	35 1	49 25	0.4% 0.8%	2.00 [0.19, 20.67]	
	28	25 36	36	25 36			_
Siddiqui 2013	28	26	36 21	36 31	6.7% 6.1%	0.78 [0.65, 0.93]	1
Spence 2011 Srivastava 2010						1.14 [0.82, 1.57]	<u> </u>
	14	60	8	60 16	3.6%	1.75 [0.79, 3.86]	
Zaldivar Ramirez 2011 Subtotal (95% CI)	2	18 684	0	16 633	0.5% 44.6%	4.47 [0.23, 86.77] 1.00 [0.83, 1.19]	
	1.01	004	150	033	44.0%	1.00 [0.05, 1.19]	Ţ
Total events Heterogeneity: $Tau^2 = 0$	161		152				
Test for overall effect: Z	= 0.01 (i	0.57	/				
3.20.3 701-1050 mg				_	_		
Ghai 2011	10	30	12	30	4.2%	0.83 [0.43, 1.63]	
Ghai 2011 Ghai 2012	8	30	0	30	0.6%	17.00 [1.03, 281.91]	
Ghai 2011 Ghai 2012 Neogi 2012	8 1	30 30	0 0	30 30	0.6% 0.4%	17.00 [1.03, 281.91] 3.00 [0.13, 70.83]	
Ghai 2011 Ghai 2012	8	30	0	30	0.6%	17.00 [1.03, 281.91]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events	8 1 1 20	30 30 30 120	0 0 1 13	30 30 30 120	0.6% 0.4% 0.6% 5.8%	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% Cl)	8 1 1 20 1.23; Chi ² =	30 30 30 120 = 6.10,	0 0 1 df = 3 (F	30 30 30 120	0.6% 0.4% 0.6% 5.8%	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg	8 1 1 20 1.23; Chi ² = Z = 0.80 (P	30 30 120 = 6.10, = 0.43	0 0 1 df = 3 (F	30 30 30 120 P = 0.12	$\begin{array}{l} 0.6\% \\ 0.4\% \\ 0.6\% \\ \textbf{5.8\%} \end{array}$ 1); $I^2 = 519$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010	8 1 1 1.23; Chi ² = Z = 0.80 (P	30 30 120 = 6.10, = 0.43	0 0 1 df = 3 (F)	30 30 30 120 P = 0.12 30	0.6% 0.4% 0.6% 5.8%	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 2.00 [0.19, 20.90]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005	$ \begin{array}{r} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ Z = 0.80 (P) \\ 2 \\ 0 \\ 2 \\ 0 \end{array} $	30 30 120 = 6.10, = 0.43 30 37	$ \begin{array}{c} 0 \\ 0 \\ 1 \\ df = 3 (F) \end{array} $	$ \begin{array}{r} 30 \\ 30 \\ 30 \\ 120 \\ 2 = 0.12 \\ 30 \\ 35 \\ \end{array} $	$\begin{array}{l} 0.6\% \\ 0.4\% \\ 0.6\% \\ \textbf{5.8\%} \end{array}$ 1); $I^2 = 519$ 0.8%	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 2.00 [0.19, 20.90] Not estimable	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: Z 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006	$ \begin{array}{r} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ z = 0.80 (P) \\ 2 \\ 0 \\ 21 \\ \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38	0 0 1 df = 3 (F) 1 1 3	$ \begin{array}{r} 30 \\ 30 \\ 30 \\ 120 \\ 2 = 0.12 \\ 30 \\ 35 \\ 38 \\ \end{array} $	$\begin{array}{l} 0.6\% \\ 0.4\% \\ 0.6\% \\ \textbf{5.8\%} \end{array}$ $1); \ \textbf{I}^2 = 519 \\ 0.8\% \\ \textbf{5.0\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ z = 0.80 (P \\ 2 \\ 0 \\ 21 \\ 21 \\ 21 \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31	0 0 1 df = 3 (F) 1 0 13 22	$ \begin{array}{r} 30 \\ 30 \\ 30 \\ 120 \\ 2 = 0.12 \\ 30 \\ 35 \\ 38 \\ 34 \\ \end{array} $	$\begin{array}{c} 0.6\% \\ 0.4\% \\ 0.6\% \\ \textbf{5.8\%} \end{array}$ 1); I ² = 519 $\begin{array}{c} 0.8\% \\ \textbf{5.0\%} \\ \textbf{6.0\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P \\ 2 \\ 0 \\ 21 \\ 21 \\ 10 \\ \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52	0 0 1 df = 3 (F) 1 0 13 22 7	$ \begin{array}{r} 30 \\ 30 \\ 30 \\ 120 \\ 2 = 0.12 \\ 30 \\ 35 \\ 38 \\ 34 \\ 52 \\ \end{array} $	$\begin{array}{c} 0.6\% \\ 0.4\% \\ 0.6\% \\ \textbf{5.8\%} \end{array}$ 1); $I^2 = 519$ $\begin{array}{c} 0.8\% \\ \textbf{5.0\%} \\ \textbf{6.0\%} \\ \textbf{3.2\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014	8 1 1 20 1.23; Chi ² = 2 = 0.80 (P 2 2 2 2 1 21 10 8	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25	0 0 1 df = 3 (F) 1 0 13 22 7 3	30 30 120	$\begin{array}{c} 0.6\% \\ 0.4\% \\ 0.6\% \\ \textbf{5.8\%} \end{array}$ 1); $I^2 = 519$ $\begin{array}{c} 0.8\% \\ \textbf{5.0\%} \\ \textbf{6.0\%} \\ \textbf{3.2\%} \\ \textbf{2.2\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P) \\ 2 \\ 0 \\ 21 \\ 21 \\ 10 \\ 8 \\ 2 \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29	0 0 1 df = 3 (F) 1 0 13 22 7 7 3 1	30 30 120 2 = 0.1 30 35 38 34 52 25 31	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ \textbf{5.8\%}\\ \end{array}$ 1); $ ^2=519$ $\begin{array}{c} 0.8\%\\ \textbf{5.0\%}\\ \textbf{6.0\%}\\ \textbf{3.2\%}\\ \textbf{2.2\%}\\ \textbf{0.8\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013	8 1 1 20 1.23; Chi ² = 2 = 0.80 (P 2 2 2 2 1 21 10 8	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25	0 0 1 df = 3 (F) 1 0 13 22 7 3	30 30 120	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ 5.8\%\\ \end{array}$ 1); $I^2=519$ $\begin{array}{c} 0.8\%\\ 5.0\%\\ 6.0\%\\ 3.2\%\\ 2.2\%\\ 0.8\%\\ 0.8\%\end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P) \\ 2 \\ 0 \\ 21 \\ 21 \\ 10 \\ 8 \\ 2 \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29	0 0 1 df = 3 (F) 1 0 13 22 7 7 3 1	30 30 120 2 = 0.1 30 35 38 34 52 25 31	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ \textbf{5.8\%}\\ \end{array}$ 1); $ ^2=519$ $\begin{array}{c} 0.8\%\\ \textbf{5.0\%}\\ \textbf{6.0\%}\\ \textbf{3.2\%}\\ \textbf{2.2\%}\\ \textbf{0.8\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: Z 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P) \\ 2 \\ 2 \\ 10 \\ 8 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2 \\ 2$	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29 50	0 0 1 df = 3 (F) 1 0 13 22 7 3 1 1	30 30 120	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ 5.8\%\\ \end{array}$ 1); $I^2=519$ $\begin{array}{c} 0.8\%\\ 5.0\%\\ 6.0\%\\ 3.2\%\\ 2.2\%\\ 0.8\%\\ 0.8\%\end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004 Sen 2009a	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P \\ 2 \\ 2 \\ 10 \\ 8 \\ 2 \\ 2 \\ 10 \\ 8 \\ 2 \\ 2 \\ 14 \\ \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29 50 38	0 0 1 df = 3 (F) 1 0 13 22 7 3 1 1 12	30 30 120	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ \textbf{5.8\%} \end{array}$ 1); $I^2 = 519$ $\begin{array}{c} 0.8\%\\ \textbf{5.0\%}\\ \textbf{6.0\%}\\ \textbf{3.2\%}\\ \textbf{2.2\%}\\ \textbf{0.8\%}\\ \textbf{0.8\%}\\ \textbf{4.5\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.000 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004 Sen 2009a Turan 2003a	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P \\ 2 \\ 2 \\ 10 \\ 8 \\ 2 \\ 10 \\ 8 \\ 2 \\ 14 \\ 3 \\ \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29 50 38 20	0 0 1 df = 3 (F) 1 0 13 22 7 3 1 1 12 3	30 30 120 9 = 0.1 30 35 38 34 52 251 50 37 20	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ \textbf{5.8\%} \end{array}$ 1); $l^2 = 519$ $\begin{array}{c} 0.8\%\\ \textbf{5.0\%}\\ 6.0\%\\ \textbf{3.2\%}\\ \textbf{2.2\%}\\ \textbf{0.8\%}\\ \textbf{0.8\%}\\ \textbf{4.5\%}\\ \textbf{1.7\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.000 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12] 1.00 [0.23, 4.37]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: Z 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P \\ 2 \\ 2 \\ 10 \\ 8 \\ 2 \\ 21 \\ 10 \\ 8 \\ 2 \\ 14 \\ 3 \\ 1 \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29 50 38 20 25	0 0 1 df = 3 (F) 1 0 13 22 7 3 1 1 12 3 0	30 30 120 9 = 0.11 30 35 38 34 52 25 31 50 37 20 25	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ \textbf{5.8\%} \end{array}$ 1); $I^2 = 519$ $\begin{array}{c} 0.8\%\\ \textbf{5.0\%}\\ \textbf{6.0\%}\\ \textbf{3.2\%}\\ \textbf{2.2\%}\\ \textbf{0.8\%}\\ \textbf{4.5\%}\\ \textbf{1.7\%}\\ \textbf{0.4\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12] 1.00 [0.23, 4.37] 3.00 [0.13, 70.30]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: Z 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004 Sen 2009a Turan 2003b Turan 2003b Turan 2005	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P) \\ 2 \\ 0 \\ 21 \\ 21 \\ 10 \\ 8 \\ 2 \\ 24 \\ 3 \\ 1 \\ 2 \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29 50 38 20 25 25	$df = \frac{13}{3} (F)$ $\frac{1}{10} = \frac{1}{10} (F)$ $\frac{1}{10} = \frac{1}{10} (F)$ $\frac{1}{10} = \frac{1}{10} (F)$ $\frac{1}{10} = \frac{1}{10} (F)$ $\frac{1}{10} (F)$ $$	30 30 120 ? = 0.1 30 35 38 34 52 25 31 50 37 20 25 25	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ \textbf{5.8\%} \end{array}$ 1); $ ^2 = 519$ $\begin{array}{c} 0.8\%\\ \textbf{5.0\%}\\ \textbf{6.0\%}\\ \textbf{3.2\%}\\ \textbf{2.2\%}\\ \textbf{0.8\%}\\ \textbf{0.8\%}\\ \textbf{4.5\%}\\ \textbf{1.7\%}\\ \textbf{0.4\%}\\ \textbf{0.8\%} \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12] 1.00 [0.23, 4.37] 3.00 [0.13, 70.30] 2.00 [0.19, 20.67]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004 Sen 2009a Turan 2003a Turan 2003a Turan 2003b Turan 2005 Ucak 2011 Özgencil 2011	$ \begin{array}{c} 8 \\ 1 \\ 20 \\ 1.23; Chi^2 = \\ 2 = 0.80 (P \\ 2 \\ 2 \\ 10 \\ 8 \\ 2 \\ 2 \\ 14 \\ 3 \\ 1 \\ 2 \\ 5 \\ \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29 50 38 20 25 25 20 30	$df = \frac{13}{3} (F)$ $\frac{1}{10} = \frac{13}{3} (F)$ $\frac{1}{10} = \frac{13}{3} (F)$ $\frac{13}{22} = \frac{13}{3} (F)$ $\frac{11}{12} = \frac{13}{3} = \frac{13}{3} (F)$ $\frac{13}{12} = \frac{13}{3} (F)$	30 30 120 2 = 0.1 30 35 38 34 52 25 31 31 37 20 25 25 20 00 30	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ 5.8\%\\ \end{array}$ 1); $l^2 = 519$ $\begin{array}{c} 0.8\%\\ 5.0\%\\ 6.0\%\\ 3.2\%\\ 2.2\%\\ 0.8\%\\ 0.8\%\\ 4.5\%\\ 1.7\%\\ 0.4\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ 2.8\%\\ \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.000 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12] 1.00 [0.23, 4.37] 3.00 [0.13, 70.30] 2.00 [0.19, 20.67] 2.50 [0.55, 11.41] 2.00 [0.20, 20.33] 1.60 [0.59, 4.33]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004 Sen 2009a Turan 2003a Turan 2003a Turan 2003b Turan 2005 Ucak 2011 Ozgencil 2011 Subtotal (95% Cl)	8 1 20 1.23; Chi ² = 2 = 0.80 (P 2 2 1 21 10 8 2 2 1 10 8 2 2 14 3 1 2 5 2 8	30 30 120 = 6.10, = 0.43 30 37 38 31 52 25 29 50 38 20 25 25 20 20	0 0 1 df = 3 (F) 1 0 13 22 7 3 1 1 12 3 0 1 2 1 5	30 30 120 2 = 0.1 30 35 38 34 52 25 31 50 37 20 25 25 20 20	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ 5.8\%\\ \end{array}$ 1); $I^2=519$ $\begin{array}{c} 0.8\%\\ 5.0\%\\ 6.0\%\\ 3.2\%\\ 2.2\%\\ 0.8\%\\ 4.5\%\\ 1.7\%\\ 0.4\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 6 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12] 1.00 [0.23, 4.37] 3.00 [0.13, 70.30] 2.00 [0.19, 20.67] 2.50 [0.55, 11.41] 2.00 [0.20, 20.33]	
Ghai 2011 Ghai 2012 Neogi 2012 Radhakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: Z 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004 Sen 2009a Turan 2003a Turan 2003a Turan 2003b Turan 2003b Turan 2005 Ucak 2011 Özgencil 2011 Subtotal (95% CI) Total events	$ \begin{array}{c} 8\\ 1\\ 20\\ 1.23; Chi^2 = \\ 2 = 0.80 (P) \end{array} $ $ \begin{array}{c} 2\\ 2\\ 2\\ 1\\ 21\\ 10\\ 8\\ 2\\ 2\\ 14\\ 3\\ 1\\ 2\\ 5\\ 2\\ 8\\ 101\\ 0.00; Chi^2 = \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 29 50 38 20 25 20 20 30 470 = 6.28,	$df = \frac{13}{3} (F)$ $\frac{1}{10}$ $\frac{1}{12}$ $\frac{1}{12}$ $\frac{1}{12}$ $\frac{3}{11}$ $\frac{1}{12}$	30 30 120 9 = 0.1 30 35 38 34 52 53 31 50 37 20 25 525 20 20 30 472	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ 5.8\%\\ \end{array}$ 1); $I^2 = 519$ $\begin{array}{c} 0.8\%\\ 5.0\%\\ 6.0\%\\ 3.2\%\\ 2.2\%\\ 0.8\%\\ 0.8\%\\ 4.5\%\\ 1.7\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ 31.3\%\\ \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 8 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12] 1.00 [0.23, 4.37] 3.00 [0.13, 70.30] 2.00 [0.19, 20.67] 2.50 [0.55, 11.41] 2.00 [0.20, 20.33] 1.60 [0.59, 4.33] 1.31 [1.04, 1.64]	
Ghai 2011 Ghai 2012 Redpakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004 Sen 2009a Turan 2003a Turan 2003a Turan 2003b Turan 2005 Ucak 2011 Ozgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0 Test for overall effect: 2	$ \begin{array}{c} 8\\ 1\\ 20\\ 1.23; Chi^{2} =\\ 2 = 0.80 (P)\\ 2\\ 2\\ 0\\ 21\\ 21\\ 10\\ 8\\ 2\\ 2\\ 14\\ 3\\ 1\\ 2\\ 5\\ 2\\ 8\\ 101\\ 0.00; Chi^{2} =\\ 2 = 2.32 (P) \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 29 50 38 20 25 20 20 30 470 = 6.28,	$df = \frac{13}{3} (F)$ $\frac{1}{10} (F)$	30 30 120 120 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ 5.8\%\\ \end{array}$ 1); $I^2 = 519$ $\begin{array}{c} 0.8\%\\ 5.0\%\\ 6.0\%\\ 3.2\%\\ 2.2\%\\ 0.8\%\\ 0.8\%\\ 4.5\%\\ 1.7\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ 31.3\%\\ \end{array}$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 8 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12] 1.00 [0.23, 4.37] 3.00 [0.13, 70.30] 2.00 [0.19, 20.67] 2.50 [0.55, 11.41] 2.00 [0.20, 20.33] 1.60 [0.59, 4.33] 1.31 [1.04, 1.64]	
Ghai 2011 Ghai 2012 Redpakrishnan 2005 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 1 Test for overall effect: 2 3.20.4 > 1050 mg Abdelmageed 2010 Al-Mujadi 2005 Bartholdy 2006 Dirks 2002 Grosen 2014 Jajeda 2014 Kosucu 2013 Omran 2006 Rorarius 2004 Sen 2009a Turan 2003a Turan 2003a Turan 2003b Turan 2005 Ucak 2011 Ozgencil 2011 Subtotal (95% CI) Total events Heterogeneity: Tau ² = C	$ \begin{array}{c} 8\\ 1\\ 20\\ 1.23; Chi^2 = \\ 2 = 0.80 (P) \end{array} $ $ \begin{array}{c} 2\\ 0\\ 21\\ 21\\ 10\\ 8\\ 2\\ 2\\ 14\\ 3\\ 1\\ 2\\ 5\\ 2\\ 8\\ 101\\ .00; Chi^2 = \\ 2 = 2.32 (P) \end{array} $	30 30 120 = 6.10, = 0.43 30 37 38 31 52 529 50 38 20 25 25 20 20 25 25 20 20 20 25 25 20 20 25 25 20 20 25 25 20 20 25 25 20 20 30 470	df = 3 (F) 13 $df = 3 (F)$ 1 0 13 22 7 3 1 12 3 0 1 2 $df = 13$ 281	30 30 120 9 = 0.1: 30 35 38 34 52 25 31 50 37 20 25 25 20 20 20 472 472 472 1593	$\begin{array}{c} 0.6\%\\ 0.4\%\\ 0.6\%\\ 5.8\%\\ \end{array}$ 1); $ ^2 = 519$ $\begin{array}{c} 0.8\%\\ 5.0\%\\ 6.0\%\\ 3.2\%\\ 2.2\%\\ 0.8\%\\ 4.5\%\\ 1.7\%\\ 0.4\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ 0.8\%\\ 1.6\%\\ 0.8\%\\ 0.8\%\\ 0.8\%\\ 1.6\%\\ 0.8\%$	17.00 [1.03, 281.91] 3.00 [0.13, 70.83] 1.00 [0.07, 15.26] 1.87 [0.40, 8.70] 8 2.00 [0.19, 20.90] Not estimable 1.62 [0.96, 2.73] 1.05 [0.74, 1.48] 1.43 [0.59, 3.47] 2.67 [0.80, 8.90] 2.14 [0.20, 22.34] 2.00 [0.19, 21.36] 1.14 [0.61, 2.12] 1.00 [0.23, 4.37] 3.00 [0.13, 70.30] 2.00 [0.19, 20.67] 2.50 [0.55, 11.41] 2.00 [0.20, 20.33] 1.60 [0.59, 4.33] 1.31 [1.04, 1.64] 6	

Appendix 18 Forest plot of sedation from all trials estimates

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

	Gabape		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
3.21.1 0-350 mg							
Spence 2011	10	26	9	31	4.8%	1.32 [0.64, 2.76]	
Waikakul 2011	0	26	1	24	0.3%	0.31 [0.01, 7.23]	
Subtotal (95% CI)		52		55	5.0%	1.23 [0.60, 2.51]	-
Total events	10		10				
Heterogeneity: Tau ²				(P = 0)	.37); l ² =	0%	
Test for overall effec	t: Z = 0.57	(P = 0.	57)				
3.21.2 351-700 mg							
Kinney 2011	9	57	10	63	3.8%	0.99 [0.44, 2.27]	_
Paul 2013	29	52	28	49	21.9%	0.98 [0.69, 1.37]	
Srivastava 2010	5	60	7	60	2.2%	0.71 [0.24, 2.13]	
Subtotal (95% CI)		169		172	27.8%	0.96 [0.70, 1.29]	+
Total events	43		45				
Heterogeneity: Tau ²				P = 0	.86); I ² =	0%	
Test for overall effec	t: $Z = 0.30$	(P=0.	.77)				
3.21.3 701–1050 m	g						
Ghai 2011 Subtotal (95% CI)	8	30 30	1	30 30	0.6% 0.6%	8.00 [1.07, 60.09] 8.00 [1.07, 60.09]	
Total events	8		1				
Heterogeneity: Not a							
Test for overall effec	t: $Z = 2.02$	(P=0.	.04)				
3.21.4 > 1050 mg							
-	12	38	10	38	5.1%	1.20 [0.59, 2.44]	
3.21.4 > 1050 mg Bartholdy 2006 Fassoulaki 2005	12 1	38 29	10 0	38 30	5.1% 0.3%	1.20 [0.59, 2.44] 3.10 [0.13, 73.14]	
Bartholdy 2006							
Bartholdy 2006 Fassoulaki 2005	1	29	0	30	0.3%	3.10 [0.13, 73.14]	•
Bartholdy 2006 Fassoulaki 2005 Grosen 2014 Subtotal (95% CI) Total events	1 41 54	29 52 119	0 40 50	30 52 120	0.3% 61.2% 66.5%	3.10 [0.13, 73.14] 1.02 [0.84, 1.26] 1.04 [0.86, 1.27]	•
Bartholdy 2006 Fassoulaki 2005 Grosen 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ²	1 41 54 = 0.00; Ch	29 52 119 $i^2 = 0.7$	0 40 50 76, df = 2	30 52 120	0.3% 61.2% 66.5%	3.10 [0.13, 73.14] 1.02 [0.84, 1.26] 1.04 [0.86, 1.27]	•
Bartholdy 2006 Fassoulaki 2005 Grosen 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ²	1 41 54 = 0.00; Ch	29 52 119 $i^2 = 0.7$	0 40 50 76, df = 2	30 52 120	0.3% 61.2% 66.5%	3.10 [0.13, 73.14] 1.02 [0.84, 1.26] 1.04 [0.86, 1.27]	•
Bartholdy 2006 Fassoulaki 2005 Grosen 2014 Subtotal (95% CI) Total events	1 41 54 = 0.00; Ch	29 52 119 $i^2 = 0.7$	0 40 50 76, df = 2	$30 \\ 52 \\ 120 \\ 2 (P = 0)$	0.3% 61.2% 66.5%	3.10 [0.13, 73.14] 1.02 [0.84, 1.26] 1.04 [0.86, 1.27]	
Bartholdy 2006 Fassoulaki 2005 Grosen 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effec Total (95% CI) Total events	1 41 54 = 0.00; Ch t: Z = 0.41 115	$29 \\ 52 \\ 119 \\ i^2 = 0.7 \\ (P = 0.370) \\ 370 \\ 370$	0 40 50 76, df = 2 .68) 106	$30 \\ 52 \\ 120 \\ 2 (P = 0) \\ 377 $	0.3% 61.2% 66.5% 0.68); I ² = 100.0%	3.10 [0.13, 73.14] 1.02 [0.84, 1.26] 1.04 [0.86, 1.27] 0%	
Bartholdy 2006 Fassoulaki 2005 Grosen 2014 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI)	$1 \\ 41 \\ 54 \\ = 0.00; Ch \\ t: Z = 0.41 \\ 115 \\ = 0.00; Ch \\ $	$29 \\ 52 \\ 119 \\ i^2 = 0.7 \\ (P = 0. \\ 370 \\ i^2 = 6.5 \\ 0.$	0 40 50 76, df = 2 68) 106 54, df = 8	$30 \\ 52 \\ 120 \\ 2 (P = 0) \\ 377 $	0.3% 61.2% 66.5% 0.68); I ² = 100.0%	3.10 [0.13, 73.14] 1.02 [0.84, 1.26] 1.04 [0.86, 1.27] 0%	

Appendix 20 Forest plot of dizziness from all trials estimates

Study or Subgroup 3.22.1 0-350 mg	Gabape Events		Contr Events		Weight M	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% Cl
3.22.1 0-350 mg Bang 2009	3	23	3	23	0.7%	1.00 [0.22, 4.45]	
Behdad 2012	0	30	0	31	0.7%	Not estimable	
Chowdhury 2010	4	100	5	100	1.0%	0.80 [0.22, 2.89]	
Clarke 2014	2	88	12	77	0.7%	0.15 [0.03, 0.63]	
Ghafari 2009	2	33	2	33	0.4%	1.00 [0.15, 6.68]	
Mohammadi 2009	2	40	0	40	0.2%	5.00 [0.25, 100.97]	
Panday 2004b	0	153	0	153	0.270	Not estimable	
Panday 2004c	1	28	0	28	0.2%	3.00 [0.13, 70.64]	
Sekhavet 2009	5	49	7	49	1.4%	0.71 [0.24, 2.10]	
Verma 2008	1	25	0	25	0.2%	3.00 [0.13, 70.30]	
Waikakul 2011	0	26	1	24	0.2%	0.31 [0.01, 7.23]	
Yoon 2001	10	16	9	15	4.6%	1.04 [0.59, 1.83]	
Subtotal (95% CI)	10	611	9	598	9.5%	0.84 [0.54, 1.32]	A
Total events	30		39				-
Heterogeneity: Tau ² = Test for overall effect	= 0.04; Chi		0, df = 9	(P = 0	.38); I ² = 7	7%	
3.22.2 351-700 mg							
Ajori 2011	0	69	0	69		Not estimable	
Azemati 2013	14	50	14	50	3.7%	1.00 [0.53, 1.87]	_ _
Clarke 2009b	19	76	8	38	2.9%	1.19 [0.57, 2.46]	-
Grover 2009	10	25	7	21	2.6%	1.20 [0.55, 2.60]	-
Kavitha 2013	2	28	4	28	0.6%	0.50 [0.10, 2.51]	
Kazak 2009	0	30	0	30		Not estimable	
Kim 2004	8	21	9	20	2.9%	0.85 [0.41, 1.76]	_
Kinney 2011	9	57	10	63	2.3%	0.99 [0.44, 2.27]	_ + _
Mardani-Kivi 2013	3	55	6	53	0.9%	0.48 [0.13, 1.83]	
Paul 2013	29	52	28	49	10.3%	0.98 [0.69, 1.37]	+
Sen 2009a	2	20	2	20	0.5%	1.00 [0.16, 6.42]	
Spence 2011	10	26	9	31	2.8%	1.32 [0.64, 2.76]	- -
Srivastava 2010	5	60	7	60	1.3%	0.71 [0.24, 2.13]	
Subtotal (95% CI)		569		532	30.7%	0.98 [0.80, 1.22]	•
Total events	111		104				
Heterogeneity: Tau ² = Test for overall effect				.0 (P =	0.97); I ² =	• 0%	
3.22.3 701-1050 mg	9						
Deniz 2012	0	25	0	26		Not estimable	
Ghai 2011	8	30	1	30	0.4%	8.00 [1.07, 60.09]	
Ghai 2012	10	30	1	30	0.4%	10.00 [1.36, 73.33]	
Leung 2006	0	12	0	9		Not estimable	
Neogi 2012	1	30	1	30	0.2%	1.00 [0.07, 15.26]	
Rajendran 2014	3	30	3	30	0.7%	1.00 [0.22, 4.56]	
Subtotal (95% CI) Total events	22	157	6	155	1.7%	2.99 [0.80, 11.22]	
Heterogeneity: Tau ² = Test for overall effect	= 0.77; Chi			(P = 0	.16); I ² = 4	43%	
3.22.4 > 1050 mg							
Abdelmageed 2010	6	30	5	30	1.4%	1.20 [0.41, 3.51]	_
Al-Mujadi 2005	0	37	0	35	_,	Not estimable	
Bartholdy 2006	12	38	10	38	3.0%	1.20 [0.59, 2.44]	- -
Bekawi 2014	17	30	25	30	9.9%	0.68 [0.48, 0.97]	
Clarke 2013	16	22	9	22	4.6%	1.78 [1.01, 3.12]	⊢ ⊷
Dierking 2003	23	39	15	32	6.6%	1.26 [0.80, 1.98]	+
Dirks 2002	11	31	14	34	3.8%	0.86 [0.46, 1.60]	_ + _
Doha 2010	8	30	2	29	0.8%	3.87 [0.90, 16.70]	+
Fassoulaki 2005	1	29	0	30	0.2%	3.10 [0.13, 73.14]	
Grosen 2014	41	52	40	52	19.4%	1.02 [0.84, 1.26]	+
Omran 2006	6	50	4	50	1.1%	1.50 [0.45, 4.99]	
Pathak 2013	0	40	1	40	0.2%	0.33 [0.01, 7.95]	
Rorarius 2004	6	38	4	37	1.1%	1.46 [0.45, 4.76]	_
Tirault 2010	2	69	0	66	0.2%	4.79 [0.23, 97.85]	
Turan 2003a	2	25	1	25	0.3%	2.00 [0.19, 20.67]	— ·
Turan 2003b	6	25	4	25	1.2%	1.50 [0.48, 4.68]	- -
Turan 2004	4	25	4	25	1.0%	1.00 [0.28, 3.56]	
Turan 2005	7	20	1	20	0.4%	7.00 [0.95, 51.80]	
Turan 2006	6	25	2	25	0.7%	3.00 [0.67, 13.46]	+
Ucak 2011	2	20	1	20	0.3%	2.00 [0.20, 20.33]	— · · · · ·
Özgencil 2011	9	30	6	30	1.9%	1.50 [0.61, 3.69]	- • -
Subtotal (95% CI)	-	705	-	695	58.1%	1.20 [0.96, 1.48]	
Total events	185		148				ľ
Heterogeneity: Tau ² =	= 0.05; Chi		03, df =	19 (P =	= 0.13); I ²	= 27%	
Test for overall effect				1980	100.0%	1.06 [0.94, 1.21]	L
		2042					
Total (95% CI)	348	2042	297	1500	100.070	1.00 [0.0 ., 1.1.1]	ľ
Total (95% CI) Total events	348 = 0.01 · Chi		297 99. df =			- 6%	
Total (95% CI)	= 0.01; Chi	² = 46.9	99, df =			= 6%	0.01 0.1 1 10 10 Favours Gabapentin Favours Control

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. Cl: 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. Cl: 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 α_2 - 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 I: 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 (\geq 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 Chisquared test to examine the heterogeneity between trials. The heterogeneity was assessed by l^2 that quantifies the observed differences and D^2 for information size adjustments in the trial sequential analyses.

Whenever I² 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 metaanalyses.

Trial Sequential Analyses (TSA) was used, with the risks of type-I 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: \leq 50 patients in each group, > 50 to 100 patients in each group, and \geq 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).

Add-on effect

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).

No add-on effect

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, COX2inhibitors, 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 | Subgroup analyses

Outcome	Estimates				Estimates			
Subgroup analyses	Trials with overall low risk of bias				All trials			
	Estimate MD/RR (REM/FEM/RR/Peto's OR) (95% CI; p-value; TSA adj. 95% CI)		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)	l 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%	/ 705 /553 /127.5%	P = 0.00 I	10.8 mg reduction (REM 95% Cl: 8.5, 13.2; p<0.00001; TSA adj. Cl: 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% Cl: 11.1, 34.0; p = 0.0001; TSA adj. Cl: -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)	9 2%	6/ 399 / 2644 /15.1%	P = 0.93	9.8 mg reduction (REM 95% Cl: 6.9, 12.6; p<0.00001; TSA adj. Cl 6.9, 12.6)	93%	22 / 1331 / 1189/ 111.9%	
24-hour morphine consumption - Multiple administration	2.4 mg (REM 95%Cl: 0.6, 4.2; p= 0.01; TSA adj. Cl: 0.5, 4.9)	41%	5 / 306 / 459 / 66.7%	P < 0.00001	12.7 mg reduction (REM 95% Cl: 8.2, 17.1; p<0.00001; TSA adj. Cl: 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% Cl: 5.5, 13.1; p < 0.00001; TSA adj. Cl: 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%	9 / 323 / 988/ 33.9 %	
24-hour VAS pain at rest	I.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% Cl: 1.6, 9.1; _P = 0.005; TSA adj. Cl: 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% Cl: 1.2, 6.8; p=0.02; TSA adj. Cl: 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% Cl: 0.3, 9.5; _P = 0.63;	0%	4 / 243 / 7323 / <5%	P = 0.47	RR 2.8 (Peto's OR 95% CI: 1.1, 6.9; p=0.03;	0%	10 / 766 / 6911 / 11.1%
Serious adverse events - Multiple administration	TSA adj. 95% Cl: -) RR 3.4 (Peto's OR 95% Cl: 1.3, 9.2; _P = 0.01; TSA adj. Cl: 0.1, 190.7)	0%	6 / 487 / 8912 / 5.8%	P = 0.20	TSA adj. Cl: 0.1, 109.5) RR 2.2 (Peto's OR 95% Cl: 1.1, 4.4; p= 0.03; TSA adj. Cl: 0.3, 13.5)	0%	/ 834 / 4576 / 8.2%
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 I.I (REM 95% CI: 0.9, I.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%	/ 66 / 5439 / 2.1%	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 / I 3.3%	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. Cl: Trial Sequential Analysis adjusted Confidence Interval

	Pregabalin	Gabapentin	Paracetamol	NSAIDs	Cox2-inhibitors	Steroids
	Estimate MD/RR (REM/Peto's OR) (95% Cl; p-value; TSA adj. 95% Cl)	Estimate MD/RR (REM/Peto's OR) (95% Cl; p-value; TSA adj. 95% Cl)	Estimate MD (95% Cl; p-value)	Estimate MD (95% Cl; p-value)	Estimate MD (95% Cl; p-value)	Estimate MD (95% Cl; p-value)
TRIALS WITH OVERAL	L LOW RISK OF BIAS					
24-hour morphine consumption	5.8 mg reduction (REM 95% Cl: 3.2, 8.5; p < 0.0001; TSA adj. Cl: 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% Cl: 2.1, 8.5; p = 0.0002; TSA adj. Cl: 2.1, 8.5) (8 trials)	(12 mg reduction (REM 95% Cl: -0.3, 2.6; p = 0.12; TSA adj. Cl: -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	3.7 mg reduction (REM 95% Cl: 9.6, 7.8; p < 0.00001; TSA adj. Cl: 9.6. 7.8) (2 trials)	8.0 mg reduction (REM 95% Cl: -1.5, 17.4; p = 0.10; TSA adj. Cl: -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% Cl: 8.5, 13.2; p < 0.00001; TSA adj. Cl: 8.5, 13.2) (37 trials)	7.3 mg reduction (REM 95% Cl: 5.9, 8.8; p < 0.00001; TSA adj. Cl: 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% Cl: 6.7, 11.0; p < 0.0001; TSA adj. Cl: 6.7, 11.0) (21 trials)	4.4 mg reduction (REM 95% Cl: 2.4, 6.5; p < 0.00001; TSA adj. Cl: 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% Cl: 11.1, 34.0; p = 0.0001; TSA adj. Cl: -16.6,	10.6 mg reduction (REM 95% Cl: 8.4 to 12.8; p < 0.00001;	6.3 mg reduction (95% Cl: 3.7, 9.0); p < 0.05; ** ¹²⁵	10.2 mg reduction (95% Cl: 8.7, 11.7);	10.9 mg reduction (95% Cl: 9.1, 12.8);	No available data*

TABLE 2 Comparative data from meta-analyses of pregabalin, gabapentin, paracetamol, NSAIDs, cox2inhibitors and steroids in postoperative pain management

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	56.6) (9 trials)	TSA adj. Cl: 8.4, 12.8) (37 trials)		p < 0.05; ** ¹²⁵	p < 0.05; ** ¹²⁵	
TRIALS WITH OVERALL L	OW 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% Cl: 0.9, 2.9; p = 0.10 TSA adj. Cl: 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 I PRISMA diagram

Figure 1: PRISMA 2009 Flow Diagram

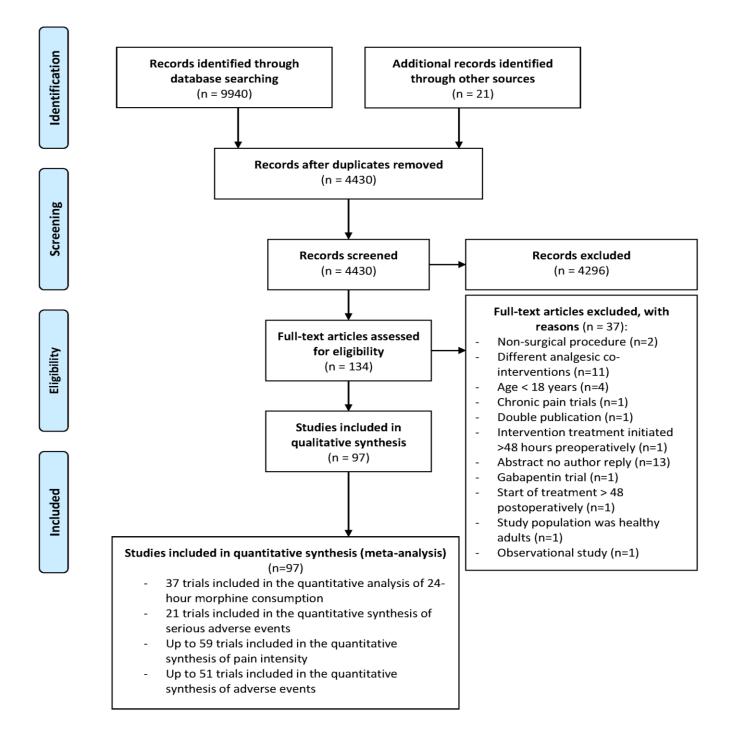
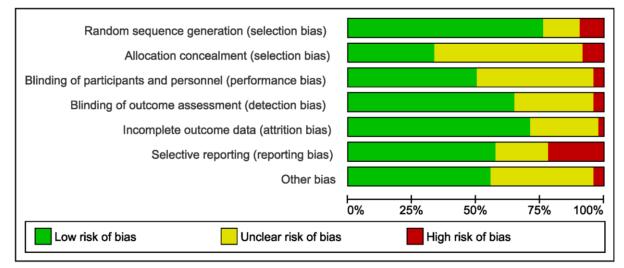


FIGURE 2 Bias graph



Risk of bias summary

FIGURE 3	Forest	plot of 24-hou	ur morphine	consumption
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	Pre	gabalir	ı	С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
.1.1 Low risk of bias									
Ahn 2016	40.7	20.7	30	50.7	26.3	30	1.8%	-10.00 [-21.98, 1.98]	
Jokela 2008a	25.6	14.6	56	31.8	15.6	29	2.6%	-6.20 [-13.05, 0.65]	-
Mahran 2015	20.23	6.8	30	34.43	10.14	30	3.0%	-14.20 [-18.57, -9.83]	-
Mathiesen 2008	24	14	30	47	28	38		-23.00 [-33.22, -12.78]	
Mathiesen 2009	40	22	39	42	20	40	2.2%	-2.00 [-11.28, 7.28]	+
Nutthachote 2014	0.13	0.48	27	1.04	3.5	27	3.3%	-0.91 [-2.24, 0.42]	•
Paech 2007	9	3	41	10	1.5	45	3.4%	-1.00 [-2.02, 0.02]	
Pesonen 2011	15	33.33	35	28.5		35	0.8%	-13.50 [-36.56, 9.56]	
Sarakatsianou 2013	1.8	2.1	20	5.2	4.1	20	3.3%	-3.40 [-5.42, -1.38]	-
Spreng 2011		13.33	22		12.59	24	2.5%	-12.50 [-20.01, -4.99]	
Yadeau 2012	10.9	8.6	30	13.2	6	27	3.1%	-2.30 [-6.12, 1.52]	4
Subtotal (95% CI)	10.0	0.0	360	10.2	Ũ	345	28.2%		•
Heterogeneity: Tau ² = 11.27	· Chi ² = 6	597 df	= 10 (F	< 0.000	01): l² =	85%			
Test for overall effect: Z = 4.			10 (1	0.000		0070			
3.1.2 Unclear or High risk of	of bias								
Ahiskalioglu 2015	26.06	24.7	20	50.99	26.21	20	1.3%	-24.93 [-40.71, -9.15]	
Akarsu 2012	17.03	3.36	30	25.78	3.95	30	3.3%	-8.75 [-10.61, -6.89]	•
Aydogan 2014	7.07	2.7	30	12.1	5.4	30	3.3%	-5.03 [-7.19, -2.87]	-
Bekawi 2014	0	24	30	75	7	30		-75.00 [-83.95, -66.05]	-
Cabrera Schulmeyer 2010	11.51	7.93	39	23.07	9.57	41	3.1%	-11.56 [-15.40, -7.72]	-
Chaparro 2012	7.5	9.8	50	23.07	8.9	49	3.1%	1.50 [-2.19, 5.19]	Ļ
Clarke 2015	40	14.6	83	55	14.2	79		-15.00 [-19.44, -10.56]	+
Demirhan 2013	3.5	8.3	20	7.7	9.33	20	2.9%	-4.20 [-9.67, 1.27]	-
Eman 2014	19	6.5	20	35.1	5.5	20		-16.10 [-19.83, -12.37]	-
Eskandar 2013	33.8	6.89	40	46.4	5.72	30	3.2%	-12.60 [-15.56, -9.64]	
Fassoulaki 2012	21	12	39	33	16	41	2.7%	-12.00 [-18.18, -5.82]	-
George 2014	48.9	22.1	59	54	26.2	30	2.0%	• • •	
-	40.9	11	30	58	20.2 19	30		-5.10 [-16.04, 5.84] -37.00 [-44.86, -29.14]	-
Ghoneim 2013 Ghoch 2016		3.4							-
Ghosh 2016 Cianagalla 2012	19.2	3.4 2	21 16	28.4	6.8	22	3.2%	-9.20 [-12.39, -6.01]	
Gianesello 2012	3			9.5	2.5	30	3.3%	-6.50 [-7.83, -5.17]	1
Hegarty 2011	5	1.19	14	9.9	7.4	18	3.1%	-4.90 [-8.37, -1.43]	Ţ
Hetta 2016	11	8.4	81	21	5.9	30	3.2%	-10.00 [-12.79, -7.21]	
Ittichaikulthol 2009	7.5	6	38	24	6.1	40		-16.50 [-19.19, -13.81]	<u> </u>
Lee 2015	43.67	7.57	24	57.81		24	2.2%	-14.14 [-23.65, -4.63]	
Mathiesen 2011	4.6	4.1	45	6.1	3.6	43	3.3%	-1.50 [-3.11, 0.11]	1
Niruthisard 2013	18.4	9.9	25	18.4	15.8	27	2.6%	0.00 [-7.11, 7.11]	I
Przesmycki 2011	31.5	23	20	32.1	9	20	2.0%	-0.60 [-11.42, 10.22]	_ T
Rimaz 2014		13.58	30	48.5	17	30		-29.34 [-37.13, -21.55]	
Sidiropoulou 2016	5.8	3.8	15	13	4.9	15	3.2%	• • •	
Sundar 2012	131.22			139.55		30	1.0%		
Yucel 2011	37.3	10.71	60	46.97	6.67	30	3.1%		λ.
Subtotal (95% CI)			909			809	/1.8%	-12.47 [-15.50, -9.43]	•
Heterogeneity: Tau ² = 52.47				P < 0.00	001); l²	= 95%			
Test for overall effect: Z = 8.	04 (P < 0	.00001)							
Fotal (95% CI)			1269			1154	100.0%	-10.83 [-13.19, -8.46]	•
Heterogeneity: Tau ² = 43.15	: Chi² = 7	23.16. c	f = 36 (P < 0.00	001): l²				
Test for overall effect: Z = 8.									-100 -50 0 50 100
correction of orbital filleon, $L = 0$.	•		if = 1 (F						Favours [Pregabalin] Favours [Control]

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

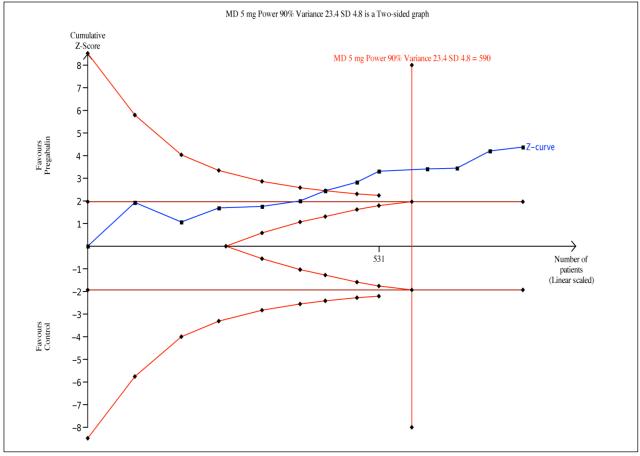


Figure 4: Trial sequential analysis of 24-hour morphine consumption from trials with low risk of bias. The minimal clinical difference was 5 mg with an α of 5% and β of 10% the z-curve crosses the monitoring boundary for benefit after six trials and the required information size is met. In conclusion 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. Cl is 3.2 to 8.5 mg.

FIGURE 5 Forest plot of SAE

	Pregaba		Contr			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
3.17.1 Low risk of bias							
Bornemann-Cimenti 2012	0	13	0	13		Not estimable	
Brulotte 2015	3	58	2	56	9.7%	1.46 [0.24, 8.70]	
Konstantatos 2016	2	52	1	46	5.9%	1.75 [0.18, 17.27]	
Mahran 2015	0	30	0	30		Not estimable	
Mathiesen 2008	0	40	0	38		Not estimable	
Mathiesen 2009	3	39	2	40	9.5%	1.57 [0.26, 9.47]	
Pesonen 2011	6	35	0	35	11.2%	8.64 [1.64, 45.51]	
Sarakatsianou 2013	0	20	0	20		Not estimable	
Yadeau 2012	1	28	0	26	2.0%	6.88 [0.14, 347.65]	
YaDeau 2015	2	83	0	28	3.0%	3.86 [0.16, 95.14]	
Subtotal (95% CI)		398		332	41.2%	2.85 [1.20, 6.77]	
Total events	17		5				
Heterogeneity: Chi ² = 3.08, Test for overall effect: Z = 2	2.37 (P = 0.						
3.17.2 Unclear or High risl	k of bias						
Burke 2010	1	20	0	20	2.0%	7.39 [0.15, 372.38]	
El Kenany 2016	0	90	0	45		Not estimable	
Fassoulaki 2012	3	39	2	37	9.5%	1.44 [0.24, 8.75]	
Freedman 2008	0	40	1	40	2.0%	0.14 [0.00, 6.82]	• • • • • • • • • • • • • • • • • • • •
Ghosh 2016	1	21	0	22	2.0%	7.75 [0.15, 390.96]	
Mathiesen 2011	12	45	4	43	26.5%	3.17 [1.08, 9.31]	
Park 2015	0	23	0	25		Not estimable	
Sagit 2013	0	96	0	47		Not estimable	
Shimony 2016	4	45	4	50	14.8%	1.12 [0.26, 4.74]	
Sidiropoulou 2016	1	15	0	15	2.0%	7.39 [0.15, 372.38]	
Wang 2011 Subtotal (95% CI)	0	36 470	0	30 374	58.8%	Not estimable 2.11 [1.02, 4.35]	•
Total events	22		11				
Heterogeneity: $Chi^2 = 4.55$, Test for overall effect: Z = 2	•		I ² = 0%				
Total (95% CI)		868		706	100.0%	2.39 [1.37, 4.16]	◆
Total events	39		16				
Total events			12 00/				
Heterogeneity: Chi ² = 7.91,	df = 12 (P	= 0.79)	; * = 0%				0.01 0.1 1 10 10

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 I: Search strategies

Searches performed 18 August 2015

Total number of references identified:	4389 references
Number of duplicates removed:	I 148 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)

#I 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)

I. 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)

I. 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: Number of duplicates removed:

5551 references 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)

#I 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)

I. 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)

I. 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. I 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*

#I TS=(pregabalin or lyrica)

Google scholar search

After the 1st search, 18th August 2015 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
I mg Fentanyl	i.v.	100 mg morphine
I mg Hydromorphone	i.v.	5 mg morphine
I mg Morphine oral	oral	0.33 mg morphine
I mg Nalbuphine	i.v.	I mg morphine
I mg Pethidine/Meperidine	i.v.	0.13 mg morphine
I mg Propoxyphene	i.v.	5 mg morphine
I mg Tramadol oral	oral	0.07 mg morphine

Frial N* Surgical procedure haracteristics		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.				
Akarsu 2012	N=60	Laparoscopic cholecystectomy	300 mg Single dose	GA	Pethidine (0.35mg/kg i.v.); NSAID (Diclofenac 75 mg i.m.)				
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.)				
Aydogan	N=60	Nephrelisthomia	75 mg Single dose	GA	Morphine (PCA); NSAID (Tenoxicam 20 mg i.v.)				
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	I 50mg/300 mg Single dose	GA	Fentanyl (25 ug i.v. p.n.)	24 hour			
Bekawi 2014	N=60	Laparoscopic cholecystectomy	150 mg Continuous dose	GA	Pethidine (1 mg/kg l.m.) Tramadol (1 mg/kg); NSAID (Diclofenac 75 mg i.m. p.n.)	24 hour			
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 × 4)	3 month			
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 month			
Buvanendran 2010	N=22 8	Total knee arthroplasty	300 mg Continuous dose	Spinal-epidural anesthesia	Opioids (morphine, Oxycodone, Hydromorphone); Epidural analgesia (PCIA Bupivacain 0.75% Img/ml + Fentanyl 25 ug) ******; NSAID (Celecoxib 200 mg x 3)	6 month			
Buvanendran 2012	N=44	Total knee arthroplasty	I 50 mg Single/continuous dose	Spinal-epidural anesthesia	Epidural analgesia (PCIA Bupivacain 0.75% 4 ml/h)	32 hour			
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 hour			
Cegin 2016	N=80	Upper extremity bone	75 mg/ 150 mg /300	LA	Infraclavicular blok (Levobupicavaine 75 mg)	24 hour			

Appendix 3: Trial characteristics

		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=10 6	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	l 50 mg Single dose	GA	NSAID (Keterolac); Paracetamol (1000 mg)	24 hours
Clarke 2016	N=18 4	Total hip arthroplasty	150 mg Single dose	Spinal anesthesia	Morphine (PCA I 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	I 50 mg Single dose	GA	Morphine (PCA)	24 hours
El Kenany 2016	N=13 5	Caesarean section	I 50 mg /300 mg Single dose	Spinal	Morphine (PCA I 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)	l 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=12 0	Laparoscopic cholecystectomy	I 50 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=11 1	Mastectomy	75 mg /150 mg /300 mg Single dose	GA	Morphine (0.1 mg/kg i.v.); Paracetamol (1000 mg i.v.)	24 hours
lttichaikulthol 2009	N=78	Abdominal hysterectomy	300 mg Single dose	GA	Morphine (PCA I 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	l 50 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	l 50mg/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 (I 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 (I-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)	I 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 I 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	I 50 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 I 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=13 5	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 I 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=14 3	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 (Img/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=10 0	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 Img 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	I 50 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	I 50 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=10 8	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	Spinal and epidural	Hydromorphone (PCA); Oxycodone- Paracetamol (5/325 mg); Regional analgesia	7 days
			(100 mg/d)	anesthesia	(Bupivacaine 0.375%, Clonidine 100 ug and epinephrine 5 ug/ml); LIA (Bupivacaine 0.5%)	
YaDeau 2015	N=11	Total knee arthroplasty	50mg/100mg	Spinal and epidural	Oxycodone-paracetamol (5 mg/325mg p.n.); Epidural analgesia (Bupivacaine 0.006% and	16 days
	I.		/150mg	anesthesia	Hydromorphone 10 ug/ml); Regional Analgesia (Bupivacaine 0.25% 30 ml with	
					adrenaline); NSAID (Meloxicam);	
Yucel 2011	N=90	Abdominal hysterectomy	150mg/300mg	GA	Morphine (PCA)	24 hours
			(300mg/d and 600			
			mg/d)			
Ziyaeifard 2015	N=60	Coronary Artery Bypass	150 mg	GA	Morphine (Img/kg i.v. p.n.)	24 hours
		surgery	Single dose			

*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 predefined cut-off; p.o: oral administration

Appendix 4: Bias assessments



Appendix 5: SoF and GRADE of trials with low risk of b	ias
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Quality	assessment						№ of patients		Effect		- Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Controls	Relative (95% Cl)	Absolute (95% CI)	Quanty
24-hour	opioid consumptio	on: Bias - Lov	w 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	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 consumptio	on: 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)	
24-hour	opioid consumptio	n: Single vs	Multiple dose B	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
S erious	Adverse Events: Bi	as - Low risl	k 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: Si	ngle vs Mult	iple dose - Sing	le 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 patier	nts	Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Controls	Relative (95% CI)	Absolute (95% Cl)	– Quality
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	e event: Vomiting: I	Bias - Low ri	sk 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)	9I fewer per 1.000 (from 11 more to 168 fewer)	⊕⊕⊕⊖ MODERATE
Adverse	e event: Sedation: E	Bias - Low ris	sk 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 risl	k 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 ris	k 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	e event: Dizziness:	Bias - Low ri	sk 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 patien	its	Effect		Quality
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pregabalin	Controls	Relative (95% Cl)	Absolute (95% Cl)	- Quality
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 24	h mob: Bias - Low r	isk 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	e event: Headache:	Bias - Low r	isk 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

Mathiesen 2008 Mathiesen 2009 Nutthachote 2014 0.	<u>an S</u> 5.6 14. 24 1	<u>D Total</u> 6 56	Mean	SD	Total	Weight	N/ Developed APR/ OI	IV, Random, 95% CI
Jokela 2008a 29 Mathiesen 2008 Mathiesen 2009 Nutthachote 2014 0.		6 56				Weight	IV, Random, 95% CI	IV, Random, 95% CI
Mathiesen 2008 Mathiesen 2009 Nutthachote 2014 0.		6 56						
Mathiesen 2009 Nutthachote 2014 0.	24 1	0 00	31.8	15.6	29	3.2%	-6.20 [-13.05, 0.65]	-
Nutthachote 2014 0.		4 30	47	28	38	2.3%	-23.00 [-33.22, -12.78]	
	40 2	2 39	42	20	40	2.5%	-2.00 [-11.28, 7.28]	+
Pesonen 2011	13 0.4	8 27	1.04	3.5	27	4.8%	-0.91 [-2.24, 0.42]	1
	15 33.3			61.11	35	0.7%	-13.50 [-36.56, 9.56]	+
Sarakatsianou 2013	1.8 2	1 20	5.2	4.1	20	4.7%	-3.40 [-5.42, -1.38]	1
	4.5 13.3			12.59	24	3.0%	-12.50 [-20.01, -4.99]	
	0.9 8			6	27	4.2%	-2.30 [-6.12, 1.52]	
Subtotal (95% Cl)		259			240	25.5%	-5.33 [-8.54, -2.12]	•
Heterogeneity: Tau ² = 11.43; Chi Test for overall effect: Z = 3.25 (F 3.8.2 Unclear or High risk of bia	P = 0.001			// .				
Ahiskalioglu 2015 26.	06 24	7 20	50.99	26.21	20	1.3%	-24.93 [-40.71, -9.15]	
Akarsu 2012 17.				3.95	30	4.7%	-8.75 [-10.61, -6.89]	•
Avdogan 2014 7.	07 2	7 30	12.1	5.4	30	4.6%	-5.03 [-7.19, -2.87]	-
Cabrera Schulmeyer 2010 11.	51 7.9	3 39	23.07	9.57	41	4.2%	-11.56 [-15.40, -7.72]	+
	7.5 9	8 50	6	8.9	49	4.3%	1.50 [-2.19, 5.19]	ł
Clarke 2015	40 14	6 83	55	14.2	79	4.0%	-15.00 [-19.44, -10.56]	-
Demirhan 2013	3.5 8	3 20	7.7	9.33	20	3.7%	-4.20 [-9.67, 1.27]	-4
Eskandar 2013 33	3.8 6.8	9 40	46.4	5.72	30	4.5%	-12.60 [-15.56, -9.64]	+
Fassoulaki 2012	21 1	2 39	33	16	41	3.5%	-12.00 [-18.18, -5.82]	-
George 2014 44	8.9 22	1 59	54	26.2	30	2.1%	-5.10 [-16.04, 5.84]	-+
Ghoneim 2013	21 1	1 30	58	19	30	2.9%	-37.00 [-44.86, -29.14]	
Ghosh 2016 19	9.2 3.	4 21	28.4	6.8	22	4.4%	-9.20 [-12.39, -6.01]	-
Gianesello 2012	3	2 16	9.5	2.5	30	4.8%	-6.50 [-7.83, -5.17]	•
Hegarty 2011	5 1.1	9 14	9.9	7.4	18	4.3%	-4.90 [-8.37, -1.43]	۳
Hetta 2016	11 8	4 81	21	5.9	30	4.5%	-10.00 [-12.79, -7.21]	*
Lee 2015 43.	67 7.5	7 24	57.81	22.53	24	2.5%	-14.14 [-23.65, -4.63]	
Mathiesen 2011	4.6 4.	1 45	6.1	3.6	43	4.7%	-1.50 [-3.11, 0.11]	1
Przesmycki 2011 3 [°]	1.5 2	3 20	32.1	9	20	2.2%	-0.60 [-11.42, 10.22]	+
Rimaz 2014 19.	16 13.5	8 30	48.5	17	30	2.9%	-29.34 [-37.13, -21.55]	-
Subtotal (95% CI)	5.8 3.	706		4.9	15 632	4.4% 7 4.5 %	-7.20 [-10.34, -4.06] -9.84 [-12.34, -7.34]	•
Heterogeneity: Tau² = 24.96; Chi Test for overall effect: Z = 7.72 (F			9 (P < 0.	00001);	l² = 91	%		
Total (95% CI)		965				100.0%	-8.87 [-11.00, -6.74]	•
Heterogeneity: Tau² = 24.17; Chi Test for overall effect: Z = 8.17 (F			7 (P < 0.	00001);	l² = 91	%	_	-100 -50 0 50 100

Appendix 7: Forest plot 24-hour morphine consumption –	add-on
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	Pre	gabalin		С	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
3.9.1 Low risk of bia	5								
Ahn 2016	40.7	20.7	30	50.7	26.3	30	10.1%	-10.00 [-21.98, 1.98]	
Mahran 2015	20.23	6.8	30	34.43	10.14	30	12.0%	-14.20 [-18.57, -9.83]	
Subtotal (95% CI)			60			60	22.1%	-13.71 [-17.81, -9.60]	♦
Heterogeneity: Tau ² =	0.00; Chi	² = 0.42	, df = 1	(P = 0.5	2); l² = (0%			
Test for overall effect:	Z = 6.55	(P < 0.0	0001)						
3.9.2 Unclear or High					_				
Bekawi 2014	0	24	30	75	7	30	11.0%	• • •	-
Eman 2014	19	6.5	20	35.1	5.5	20	12.1%	-16.10 [-19.83, -12.37]	•
Ittichaikulthol 2009	7.5	6	38	24	6.1	40	12.2%	-16.50 [-19.19, -13.81]	•
Niruthisard 2013	18.4	9.9	25	18.4	15.8	27	11.4%	0.00 [-7.11, 7.11]	+
Rimaz 2014	19.16	13.58	30	48.5	17	30	11.3%	-29.34 [-37.13, -21.55]	-
Sundar 2012	131.22	39.27	30	139.55	37.62	30	7.8%	-8.33 [-27.79, 11.13]	
Yucel 2011	37.3	10.71	60	46.97	6.67	30	12.1%	-9.67 [-13.28, -6.06]	. *
Subtotal (95% CI)			233			207	77.9%	-22.26 [-33.59, -10.92]	\bullet
Heterogeneity: Tau ² =	215.07; 0	Chi² = 20)9.84, c	if = 6 (P	< 0.000	01); l² =	= 97%		
Test for overall effect:	Z = 3.85	(P = 0.0	001)						
Total (95% CI)			293			267	100.0%	-20.04 [-29.01, -11.08]	•
Heterogeneity: Tau ² =	169.71; 0	Chi² = 21	11.91, c	f = 8 (P	< 0.000	01); l² =	= 96%	-	
Test for overall effect:									-100 -50 0 50 100
Test for subgroup diffe		•		= 1 (P = 0)) 16) I ²	= 48 39	%		Favours [Pregabalin] Favours [Control]

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

	Pre	egabalir	n	0	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
3.12.1 Single dose									
Ahn 2016	40.7	20.7	30	50.7	26.3	30	3.8%	-10.00 [-21.98, 1.98]	
Mahran 2015	20.23	6.8	30	34.43	10.14	30	11.3%	-14.20 [-18.57, -9.83]	-
Mathiesen 2008	24	14	30	47	28	38	4.8%	-23.00 [-33.22, -12.78]	
Mathiesen 2009	40	22	39	42	20	40	5.4%	-2.00 [-11.28, 7.28]	-+
Paech 2007	9	3	41	10	1.5	45	15.9%	-1.00 [-2.02, 0.02]	•
Spreng 2011 Subtotal (95% CI)	24.5	13.33	22 192	37	12.59	24 207	7.1% 48.3%	-12.50 [-20.01, -4.99] -10.10 [-17.79, -2.40]	
Heterogeneity: Tau ² =	76.35: 0	chi² = 59	0.07. df	= 5 (P	< 0.000)); ² =	92%		
Test for overall effect:	,			- (,,.			
		v	,						
3.12.2 Multiple dose									
Jokela 2008a	25.6	14.6	56	31.8	15.6	29	7.8%	-6.20 [-13.05, 0.65]	~
Nutthachote 2014	0.13	0.48	27	1.04	3.5	27	15.6%	-0.91 [-2.24, 0.42]	•
Pesonen 2011	15	33.33	35	28.5	61.11	35	1.2%	-13.50 [-36.56, 9.56]	
Sarakatsianou 2013	1.8	2.1	20	5.2	4.1	20	14.9%	-3.40 [-5.42, -1.38]	-
Yadeau 2012	10.9	8.6	30	13.2	6	27	12.2%	-2.30 [-6.12, 1.52]	+
Subtotal (95% CI)			168			138	51.7%	-2.38 [-4.19, -0.56]	
	1.51; Cł	ni² = 6.70	6, df =	4 (P = 0	.15); l ²	= 41%			
Heterogeneity: Tau ² =		$(\mathbf{D} - \mathbf{O})$	01)						
Heterogeneity: Tau ² = Test for overall effect:	Z = 2.56	(P = 0.0)	.,						I
	Z = 2.56	(P = 0.1	360			345	100.0%	-5.81 [-8.46, -3.15]	♦
Test for overall effect:			360	= 10 (P	< 0.000			-5.81 [-8.46, -3.15]	-100 -50 0 50 100

Appendix 9: Single vs. multiple dose SAE

	Pregab	alin	Contr	ol		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
3.24.1 Single dose							
Bornemann-Cimenti 2012	0	13	0	13		Not estimable	
Mahran 2015	0	30	0	30		Not estimable	
Mathiesen 2008	0	40	0	38		Not estimable	
Mathiesen 2009	3	39	2	40	23.1%	1.57 [0.26, 9.47]	
Subtotal (95% CI)		122		121	23.1%	1.57 [0.26, 9.47]	
Total events	3		2				
Heterogeneity: Not applicat	ole						
Test for overall effect: Z = 0	.49 (P = 0.	.63)					
3.24.2 Multiple dose							
Brulotte 2015	3	58	2	56	23.5%	1.46 [0.24, 8.70]	
Konstantatos 2016	2	52	1	46	14.2%	1.75 [0.18, 17.27]	
Pesonen 2011	6	35	0	35	27.1%	8.64 [1.64, 45.51]	· · · · · · · · · · · · · · · · · · ·
Sarakatsianou 2013	0	20	0	20		Not estimable	
Yadeau 2012	1	28	0	26	4.9%	6.88 [0.14, 347.65]	
YaDeau 2015	2	83	0	28	7.3%	3.86 [0.16, 95.14]	
Subtotal (95% CI)		276		211	76.9%	3.41 [1.27, 9.15]	
Total events	14		3				
Heterogeneity: Chi ² = 2.53,	df = 4 (P =	= 0.64);	l² = 0%				
Test for overall effect: Z = 2	.44 (P = 0.	.01)					
Total (95% CI)		398		332	100.0%	2.85 [1.20, 6.77]	-
Total events	17		5				
Heterogeneity: Chi ² = 3.08,	df = 5 (P =	= 0.69);	l² = 0%				0.01 0.1 1 10 100
Test for overall effect: Z = 2							0.01 0.1 1 10 100 Favours [Pregabalin] Favours [Control]

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

		egabalin			ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	IV, Random, 95% Cl
3.40.1 Low risk of bias									
Ahn 2016	47	27	30	75	15	30	1.8%	-28.00 [-39.05, -16.95]	
Jokela 2008a		15.15	56	20	14.81	28	2.0%	-4.64 [-11.41, 2.13]	
	10.41	9.35							\downarrow
Jokela 2008b			56	11	8.15	29	2.1%	-0.59 [-4.44, 3.26]	
Mahran 2015		10.66	30	42	16.64	30	2.0%	-2.30 [-9.37, 4.77]	T
Mathiesen 2008	16.5	33.5	40	20	37	38	1.6%	-3.50 [-19.19, 12.19]	
Mathiesen 2009	18	31	39	24	46.5	40	1.5%	-6.00 [-23.39, 11.39]	
Sarakatsianou 2013	18	17	20	45	22	20	1.8%	-27.00 [-39.18, -14.82]	
Spreng 2011	12	9.26	22	17	5.19	24	2.1%	-5.00 [-9.39, -0.61]	-
Yadeau 2012	5.5	24.5	29	5.5	18	27	1.8%		
	5.5	24.5	322	5.5	10	266		0.00 [-11.21, 11.21]	
Subtotal (95% CI)							16.6%	-7.73 [-13.30, -2.16]	\bullet
Heterogeneity: Tau ² = 48.38 Test for overall effect: Z = 2			= 8 (P	o < 0.00	01); 1² =	77%			
3.40.2 Unclear or high risk	of bias								
-			40	44 7	47.0	00	1 09/	2 00 1 40 40 4 501	
Abbasabadi 2015	37.9	14	46	41.7	17.8	23	1.9%	-3.80 [-12.12, 4.52]	
Ahiskalioglu 2015	7.5	15	20	18	35	20	1.5%	-10.50 [-27.19, 6.19]	— <u>+</u>
Akarsu 2012	18	4.8	30	43.4	7.6	30	2.1%	-25.40 [-28.62, -22.18]	-
Akhavanakbari 2013	60.6	2.1	30	91.3	1.1	30	2.1%	-30.70 [-31.55, -29.85]	·
Alimian 2012	25	15	40	51	17	40	2.0%	-26.00 [-33.03, -18.97]	
Aydogan 2014	12.5	8.5	30	12.5	7.1	30	2.1%	0.00 [-3.96, 3.96]	+
Cabrera Schulmeyer 2010	30	21	39	47	59	41	1.4%	-17.00 [-36.22, 2.22]	
Chang 2009	33	1.6	39	37	20	38	2.0%	-4.00 [-10.38, 2.38]	7
Choi 2013	20	7.41	36	30	14.8	36	2.1%	-10.00 [-15.41, -4.59]	-
Clendenen 2010	10	21	22	7	19	26	1.8%	3.00 [-8.42, 14.42]	+
Demirhan 2013	0	22.22	20	10	37.04	20	1.4%	-10.00 [-28.93, 8.93]	
Demirhan 2014	0	21	30	10	37.04	30	1.6%	-10.00 [-25.24, 5.24]	
		10.2							
Eskandar 2013	31		30	45	15.4	30	2.0%	-14.00 [-20.61, -7.39]	
Fassoulaki 2012	35	16.1	39	44	21.9	41	1.9%	-9.00 [-17.39, -0.61]	
Fujati 2016	44	23.8	60	50	41	32	1.6%	-6.00 [-21.43, 9.43]	
George 2014	26.1	18	59	40	19	30	1.9%	-13.90 [-22.10, -5.70]	
Ghoneim 2013	25	20	30	30	40	30	1.6%	-5.00 [-21.00, 11.00]	
Gianesello 2012	18	21	30	22	31	30	1.7%	-4.00 [-17.40, 9.40]	_ _
Hegarty 2011	15	8.15	14	20	14.07	18	2.0%	-5.00 [-12.78, 2.78]	
Hetta 2016	13.6	11.3	81	20	7.4	30	2.1%	-6.40 [-10.01, -2.79]	
Ittichaikulthol 2009	35	20	38	60	24	40	1.9%	-25.00 [-34.79, -15.21]	
Jajeda 2014	33.6	5.4	30	38.6	4.6	30	2.1%	-5.00 [-7.54, -2.46]	-
Joshi 2013	14	22	20	21	34	20	1.5%	-7.00 [-24.75, 10.75]	
Khurana 2014	2.5	0	30	5	0	30		Not estimable	
Kim 2010	20	14.81	47	30	16.3	47	2.0%	-10.00 [-16.30, -3.70]	
Kim 2011b	30	14.81	42	40	14.81	42	2.0%	-10.00 [-16.33, -3.67]	
Kim 2014	20	22.22	24	50	22.22	22	1.7%	-30.00 [-42.85, -17.15]	
Kumar 2013	41	52	25	58	64	25	0.8%	-17.00 [-49.32, 15.32]	
Lee 2013	41.3	7.2	31	48.6	7.9	29	2.1%	-7.30 [-11.13, -3.47]	-
Lee 2015	26.7	7.3	21	35.5	15	20	2.0%	-8.80 [-16.08, -1.52]	
Mansor 2015	5	1.25	25	12	1.25	24	2.1%		
								-7.00 [-7.70, -6.30]	
Mathiesen 2011	35	58	45	46	71	43	1.0%	-11.00 [-38.16, 16.16]	-
Niruthisard 2013	21	14	25	24	22	27	1.9%	-3.00 [-12.95, 6.95]	- <u>+</u>
Ozgencil 2011	11	11.8	30	15	7.7	30	2.1%	-4.00 [-9.04, 1.04]	
Park 2015	34	27	23	37	4.2	25	1.8%	-3.00 [-14.16, 8.16]	_ _
Prasad 2014	41.4	8.5	30	35.8	9.6	30	2.1%	5.60 [1.01, 10.19]	~
Przesmycki 2011	16	6	60	10	3	20	2.1%	6.00 [3.99, 8.01]	· · · · · · · · · · · · · · · · · · ·
Rajappa 2016	23.4	5.8	90	28	11	45	2.1%	-4.60 [-8.03, -1.17]	_ 1
Rajendran 2014	35	5	30	65	7.3	30		-30.00 [-33.17, -26.83]	- I
Rimaz 2014	22	4.2	30	33.8	3.8	30	2.1%	-11.80 [-13.83, -9.77]	*
Sagit 2013	24.4	17.12	35	36.8	18.1	35	1.9%	-12.40 [-20.65, -4.15]	
Sidiropoulou 2016	33	6.3	15	39	6.3	15	2.1%	-6.00 [-10.51, -1.49]	
									1
Sundar 2012	20.3	6.1	30	22	6.1	30	2.1%	-1.70 [-4.79, 1.39]	1
Wei 2015	14	18.25	26	25.6	19	23	1.8%	-11.60 [-22.06, -1.14]	
Yucel 2011	28.65	7.29	60	33.3	10	30	2.1%	-4.65 [-8.68, -0.62]	ㅋ
Ziyaeifard 2015	59.7	61	30	66.7	68	30	0.8%	-7.00 [-39.69, 25.69]	
Subtotal (95% CI)	5011		1617			1377	83.4%	-9.53 [-13.75, -5.32]	▲
Heterogeneity: $Tau^2 = 180.3$ Test for overall effect: $Z = 4$		2805.94	, df =	44 (P <	0.0000				
	,⊣o (F ≤ (,							
Total (95% CI)			1939			1643	100.0%	-9.33 [-13.13, -5.53]	♥
Heterogeneity: Tau ² = 175.4	4; Chi ² =	2896.62	. df =	53 (P <	0.0000	1); ² = 1	98%		
			-	v		<i>,</i> , .			-100 -50 0 50 10
Test for overall effect: Z = 4	81 (P - 1								Favours [Pregabalin] Favours [Control]

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

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
3.50.1 Low risk of bi	as								
Jokela 2008a	24.62	15.15	56	30	22.22	28	5.9%	-5.38 [-14.52, 3.76]	
Mahran 2015	5.57	9.35	30	59	10.29	30	6.8%	-53.43 [-58.41, -48.45]	-
Mathiesen 2008	19.5	40	30	23	13	30	4.5%	-3.50 [-18.55, 11.55]	
Mathiesen 2009	48	75	39	40	67	40	1.9%	8.00 [-23.39, 39.39]	
Sarakatsianou 2013 Subtotal (95% CI)	34	17	20 175	55	20	20 148	5.3% 24.5%	-21.00 [-32.50, -9.50] -16.34 [-42.62, 9.94]	
Heterogeneity: Tau ² =	= 831.40:	Chi ² = 1	22.21.	df = 4 (P < 0.00	0001): I	² = 97%		
Test for overall effect									
		,	-,						
3.50.2 Unclear or hig	gh risk of	f bias							
Fassoulaki 2012	60	26.5	39	67	22.8	41	5.5%	-7.00 [-17.86, 3.86]	
Ghoneim 2013	38	27	30	51	59	30	2.9%	-13.00 [-36.22, 10.22]	
Gianesello 2012	25	36	30	40	50	30	3.1%	-15.00 [-37.05, 7.05]	
Hetta 2016	20	7.3	81	20	7.4	30	7.1%	0.00 [-3.09, 3.09]	+
Joshi 2013	30	40	20	40	45	20	2.5%	-10.00 [-36.39, 16.39]	
Kim 2011b	50	22.22	42	50	22.22	42	5.8%	0.00 [-9.50, 9.50]	
Lee 2015	32.9	8.5	21	44.5	13.2	20	6.5%	-11.60 [-18.43, -4.77]	
Mansor 2015	8	1.63	25	13.5	1.25	24	7.3%	-5.50 [-6.31, -4.69]	•
Mathiesen 2011	42	71	45	63	86	43	1.8%	-21.00 [-54.03, 12.03]	
Niruthisard 2013	32	21	25	36	28	27	4.9%	-4.00 [-17.39, 9.39]	
Przesmycki 2011	20	2.7	60	20	4	20	7.2%	0.00 [-1.88, 1.88]	†
Rajappa 2016	32.9	6.2	90	38	12.4	45	7.0%	-5.10 [-8.94, -1.26]	-
Sidiropoulou 2016	53	5	15	65	5.4	15	7.0%	-12.00 [-15.72, -8.28]	-
Yucel 2011	39	6.82	60	44	10	30	7.0%	-5.00 [-8.97, -1.03]	T
Subtotal (95% CI)			583			417	75.5%	-5.22 [-7.81, -2.62]	•
Heterogeneity: Tau ² =				= 13 (P	< 0.000	001); l²	= 78%		
Test for overall effect	: Z = 3.94	(P < 0.	0001)						
Total (95% Cl)			758			565	100.0%	-9.83 [-14.94, -4.72]	◆
Heterogeneity: Tau ² =	= 93.15; C	chi² = 42	27.30, c	f = 18 (P < 0.00	0001); I	² = 96%		-100 -50 0 50 100
Test for overall effect	: Z = 3.77	(P = 0.)	0002)						-100 -50 0 50 100 Favours [Pregabalin] Favours [Control]

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

••							-		
	-								
		egabalii			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% C	I IV, Random, 95% CI
3.68.1 Low risk of bias									
Ahn 2016	33	22	30	61	15	30	1.7%	-28.00 [-37.53, -18.47]	
Brulotte 2015	0	2	58	0	3	56	1.9%	0.00 [-0.94, 0.94]	
Jokela 2008a	10	11.11	56	10	11.11	28	1.8%	0.00 [-5.04, 5.04]	+
Jokela 2008b	12.52	9.19	56	13	4	29	1.9%	-0.48 [-3.29, 2.33]	+
Konstantatos 2016	30	22.2	52	38	24.4	46	1.7%	-8.00 [-17.28, 1.28]	
Mahran 2015	29	11.5	30	30	11.14	30	1.8%	-1.00 [-6.73, 4.73]	
Martinez 2014	30	29.6	35	20	22.22	38	1.6%	10.00 [-2.09, 22.09]	
Mathiesen 2008	13	25	30	13	28	38	1.6%	0.00 [-12.62, 12.62]	
Mathiesen 2009	16	30	39	10.5	38	40	1.5%	5.50 [-9.58, 20.58]	
Nutthachote 2014	31.66	12.09	27	28.37	12.09	27	1.8%	3.29 [-3.16, 9.74]	<u>+−</u>
Paech 2007	30	14.81	41	10	5.56	45	1.8%	20.00 [15.18, 24.82]	
Sarakatsianou 2013	10	11	20	33	20	20	1.7%	-23.00 [-33.00, -13.00]	
Spreng 2011	23	10.37	22	26	8.89	24	1.8%	-3.00 [-8.61, 2.61]	
Yadeau 2012	32.5	37	29	30	49	27	1.1%	2.50 [-20.37, 25.37]	
YaDeau 2015	48.33	17.57	90	50	15.56	30	1.8%	-1.67 [-8.32, 4.98]	
Subtotal (95% CI)			615			508	25.4%	-1.39 [-5.48, 2.69]	T
Heterogeneity: Tau ² = 46.9	95; Chi² =	128.27,	df = 14	(P < 0.	00001);	l² = 89	%		
Test for overall effect: Z =	0.67 (P =	0.50)							
	-	-							
3.68.2 Unclear and high	risk of bia	S							
Abbasabadi 2015	2.23	1.43	46	21.7	5.8	23	1.9%	-19.47 [-21.88, -17.06]	+
Ahiskalioglu 2015	15	7.5	20	5	7.5	20	1.8%	10.00 [5.35, 14.65]	
-									
Akarsu 2012	16	5	30	21.3	7.8	30	1.9%	-5.30 [-8.62, -1.98]	
Akhavanakbari 2013	25.6	1.4	30	57.3	1.5	30	1.9%	-31.70 [-32.43, -30.97]	
Alimian 2012	6	8	40	16	15	40	1.8%	-10.00 [-15.27, -4.73]	
Aydogan 2014	10	7.9	30	8	4.1	30	1.9%	2.00 [-1.18, 5.18]	r
Bekawi 2014	6	6.2	30	11.3	6.3	30	1.9%	-5.30 [-8.46, -2.14]	-
Burke 2010	17.3	20.2	18	23.8	17.7	20	1.6%	-6.50 [-18.63, 5.63]	
Cabrera Schulmeyer 2010		23	39	49	59	41	1.3%	-19.00 [-38.45, 0.45]	
-									
Chang 2009	21	18	39	18	14	38	1.8%	3.00 [-4.19, 10.19]	
Chaparro 2012	53	26.8	50	54	23.4	49	1.7%	-1.00 [-10.90, 8.90]	
Choi 2013	30	22.22	36	50	25.39	36	1.6%	-20.00 [-31.02, -8.98]	
Clendenen 2010	31	24	23	39	27	24	1.5%	-8.00 [-22.59, 6.59]	
Demirhan 2013	0	14.81	30	5	14.81	30	1.8%	-5.00 [-12.49, 2.49]	
Eskandar 2013	21	7.9	40	19.5	8.3	30	1.9%	1.50 [-2.35, 5.35]	
Fassoulaki 2012	25	19.2	39	31	17.9	41	1.7%	-6.00 [-14.14, 2.14]	
	12.6	13.1	59	19	16	30	1.8%		
George 2014								-6.40 [-13.03, 0.23]	
Ghoneim 2013	22.5	11	30	24.5	31	30	1.6%	-2.00 [-13.77, 9.77]	
Gianesello 2012	5	12	30	7	10	30	1.8%	-2.00 [-7.59, 3.59]	T
Hegarty 2011	20	5.93	14	21	5.93	18	1.9%	-1.00 [-5.14, 3.14]	
Hetta 2016	11.7	10.43	81	20	7.4	30	1.9%	-8.30 [-11.79, -4.81]	
Ittichaikulthol 2009	24	30	38	35	25	40	1.6%	-11.00 [-23.29, 1.29]	
Jajeda 2014	27.8	3.9	30	34.6	4.8	30	1.9%	-6.80 [-9.01, -4.59]	
Joshi 2013	11	18	20	18	25	20	1.5%	-7.00 [-20.50, 6.50]	
Kim 2010	15	3.7	47	20	11.11	47	1.9%	-5.00 [-8.35, -1.65]	
Kim 2011b	20	14.81	42	30	14.81	42	1.8%	-10.00 [-16.33, -3.67]	
Kim 2014	20	37.03	24	50	29.63	23	1.3%	-30.00 [-49.13, -10.87]	
Lee 2013	14.19	5	31	23.8	6.8	29	1.9%	-9.61 [-12.65, -6.57]	~
Lee 2015	27.6	11.4	21	34	13.9	20	1.8%	-6.40 [-14.20, 1.40]	
Mansor 2015	2.5	1	25	5.5	1	24	1.9%	-3.00 [-3.56, -2.44]	
Mathiesen 2011	38	63	45	48	77	43	0.9%	-10.00 [-39.47, 19.47]	
Niruthisard 2013	33	21	25	27	22	27	1.6%	6.00 [-5.69, 17.69]	
Park 2015	31	40	23	37	43	25	1.1%	-6.00 [-29.48, 17.48]	
Prasad 2014	35.8	9.6	30	60	11.8	30	1.8%	-24.20 [-29.64, -18.76]	
Przesmycki 2011	10	3	60	10	4	20	1.9%	0.00 [-1.91, 1.91]	t t
Rajappa 2016	32.3	7.1	90	34.4	7.2	45	1.9%	-2.10 [-4.66, 0.46]	1
Rajendran 2014	67.7	0.93	30	60.3	8	30	1.9%	7.40 [4.52, 10.28]	
Sagit 2013	8.78	10.71	96	20.9	14.5	47	1.8%	-12.12 [-16.79, -7.45]	
Sahu 2010	19.7	17.5	35	39.3	22.4	35	1.7%	-19.60 [-29.02, -10.18]	
Sidiropoulou 2016	31	6.3	15	39	63	15	0.8%	-8.00 [-40.04, 24.04]	
Sundar 2012	20.7	7.4	30	20	6.4	30	1.9%	0.70 [-2.80, 4.20]	
Wei 2015	11.3	20	26	9.7	17.25	23	1.7%	1.60 [-8.83, 12.03]	-+
Yucel 2011	15.2	5.5	60	17.3	9	30	1.9%	-2.10 [-5.61, 1.41]	
Ziyaeifard 2015	18.3	18.9	30	24	25	30	1.6%	-5.70 [-16.91, 5.51]	
Subtotal (95% CI)		. 0.0	1627		20	1355	74.6%	-6.63 [-11.28, -1.97]	
Heterogeneity: Tau ² = 224	.75: Chi² =	4626 9		43 (P <	0.0000				•
			o, ui −		5.0000	1012	00/0		
Test for overall effect: Z =	2.19 (P =	0.005)							
						40.5			▲
Total (95% CI)			2242			1863	100.0%	-5.33 [-9.11, -1.55]	
Heterogeneity: Tau ² = 196	.21; Chi ² =	5329.0	4, df =	58 (P <	0.0000	1); ² =	99%		-100 -50 0 50 100
Test for overall effect: Z =						· ·			
Test for subgroup difference			f = 1 (P	= 0.10), ² = 6 ²	3.5%			Favours [Pregabalin] Favours [Control]
				50					

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

		gabali		-	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	I IV, Random, 95% CI
3.76.1 Low risk of bia									
Jokela 2008a		14.81	56		14.81	28	5.6%	0.00 [-6.72, 6.72]	+
Konstantatos 2016	49	27.4	52	49	27.4	46	3.7%	0.00 [-10.87, 10.87]	
Mahran 2015	40	10.83	30		10.93	30	6.2%	-3.30 [-8.81, 2.21]	
Martinez 2014	50	14.81	35			38	4.7%	0.00 [-8.60, 8.60]	
Mathiesen 2008	32	51	30	33	50	38	1.2%	-1.00 [-25.20, 23.20]	
Mathiesen 2009	36	58	39	36	55	40	1.1%	0.00 [-24.94, 24.94]	
Sarakatsianou 2013	23	14	20	42	18	20	4.1%	-19.00 [-28.99, -9.01]	
Subtotal (95% CI)			262			240	26.5%	-3.69 [-8.86, 1.48]	•
Heterogeneity: Tau ² =	20.48; C	chi² = 11	I.43, df	= 6 (P =	= 0.08);	l² = 47°	%		
Test for overall effect:	Z = 1.40	(P = 0.	16)						
3.76.2 Unclear or Hig	h risk o	f bias							
Burke 2010	35.2	31.3	18	37	23.1	20	2.0%	-1.80 [-19.45, 15.85]	
Fassoulaki 2012	45	26.2	39	56	26.6	41	3.5%	-11.00 [-22.57, 0.57]	
George 2014	37	18.4	59	43	28	30	3.6%	-6.00 [-17.06, 5.06]	
Ghoneim 2013	35	21	30	35	45	30	2.0%	0.00 [-17.77, 17.77]	
Gianesello 2012	10	20	30	15	20	30	4.0%	-5.00 [-15.12, 5.12]	+
Hetta 2016	20	10.2	81	20	7.4	30	7.2%	0.00 [-3.46, 3.46]	+
Joshi 2013	25	37	20	40	49	20	1.0%	-15.00 [-41.91, 11.91]	
Kim 2011b	30	14.81	42	50	22.22	42	4.9%	-20.00 [-28.08, -11.92]	
Lee 2015	34.3	10.8	21	43	14.2	20	5.1%	-8.70 [-16.45, -0.95]	
Mansor 2015	6	1.5	25	6	1.5	24	8.0%	0.00 [-0.84, 0.84]	•
Mathiesen 2011	55	76	45	60	81	43	0.7%	-5.00 [-37.85, 27.85]	
Niruthisard 2013	51	24	25	49	28	27	2.7%	2.00 [-12.14, 16.14]	
Przesmycki 2011	16.7	4	60	10	4	20	7.7%	6.70 [4.68, 8.72]	· · · · · · · · · · · · · · · · · · ·
Rajappa 2016	42.2	8	90	44.2	9.2	45	7.3%	-2.00 [-5.16, 1.16]	-
Sidiropoulou 2016	52	6.6	15	67	6	15	6.7%	-15.00 [-19.51, -10.49]	-
Yucel 2011	25	7.62	60	27.3	9	30	7.1%	-2.30 [-6.05, 1.45]	-
Subtotal (95% CI)			660			467	73.5%	-4.36 [-7.76, -0.97]	•
Heterogeneity: Tau ² =	27.83; C	chi² = 12	22.80, c	f = 15 (P < 0.0	0001); I	² = 88%		
Test for overall effect:	Z = 2.52	(P = 0.	01)						
Total (95% Cl)			922			707	100.0%	-4.17 [-7.03, -1.31]	•
Heterogeneity: Tau ² =	26.40; 0	chi² = 13	37.78, c	f = 22 (P < 0.0	0001): I	² = 84%		
Test for overall effect:				(-100 -50 0 50 100 Favours [Pregabalin] Favours [Control]

Appendix	 4:	Forest	plots	of	adverse	events:	nausea
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Mathlesen 2008 7 40 6 38 Mathlesen 2009 12 39 23 40 Paech 2007 9 41 9 45 Yadeau 2012 10 28 13 26 YaDeau 2015 34 87 10 29 Subtotal (95% CI) 356 275 Total events 96 79 Heterogeneity: Tau ² = 0.10; Chl ² = 11.57, df = 7 (P = 0.1) Test for overall effect: Z = 0.95 (P = 0.34) 3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Alimian 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 Chang 2009 17 39 23 6 24 Demirhan 2014 4 30 4 30 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Jain 2012 5<		Risk Ratio	Risk Ratio
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Jokela 2008a 15 56 1 29 Martinez 2014 2 35 6 38 Mathiesen 2008 7 40 6 38 Mathiesen 2009 12 39 23 40 Paech 2007 9 41 9 45 Yadeau 2012 10 28 13 26 Yabeau 2015 34 87 10 29 Subtotal (95% CI) 356 275 Total events 96 79 Heterogeneity: Tau ² = 0.10; Chi ² = 11.57, df = 7 (P = 0.17) Test for overall effect: Z = 0.95 (P = 0.34) 30 3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Alimian 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 24 40 <t< td=""><td></td><td></td><td></td></t<>			
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Mathiesen 2008 7 40 6 38 Mathiesen 2009 12 39 23 40 Paech 2007 9 41 9 45 Yadeau 2012 10 28 13 26 YaDeau 2015 34 87 10 29 Subtotal (95% CI) 356 275 Total events 96 79 Heterogeneity: Tau ² = 0.10; Chi ² = 11.57, df = 7 (P = 0.1) Test for overall effect: Z = 0.95 (P = 0.34) 3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Alimian 2012 5 40 17 40 Balaban 2012 6 60 5 30 Charg 2009 17 39 22 38 Charge 2011 18 50 14 49 Charge 2012 18 50 14 40 Demirhan 2014 4 30 4 30 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 <td< td=""><td>0.8%</td><td>7.77 [1.08, 55.92]</td><td></td></td<>	0.8%	7.77 [1.08, 55.92]	
Mathiesen 2009 12 39 23 40 Paech 2007 9 41 9 45 Yadeau 2012 10 28 13 26 YaDeau 2015 34 87 10 29 Subtotal (95% CI) 356 275 Total events 96 79 Heterogeneity: Tau ² = 0.10; Chi ² = 11.57, df = 7 (P = 0.1 Test for overall effect: Z = 0.95 (P = 0.34) 3.8.3.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Akarsu 2012 0 30 9 30	1.3%	0.36 [0.08, 1.68]	
Paech 2007 9 41 9 45 Yadeau 2012 10 28 13 26 Yadeau 2015 34 87 10 29 Subtotal (95% CI) 356 275 Total events 96 79 Heterogeneity: Tau ² = 0.10; Chi ² = 11.57, df = 7 (P = 0.17) Test for overall effect: Z = 0.95 (P = 0.34) 3.8.3.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Alimian 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Jain 2012 5 20 11 20 Jain 2011 3 30 23	2.6%	1.11 [0.41, 3.00]	· · · · ·
Yadeau 2012 10 28 13 26 YaDeau 2015 34 87 10 29 Subtotal (95% CI) 356 275 Total events 96 79 Heterogeneity: Tau ² = 0.10; Chi ² = 11.57, df = 7 (P = 0.47) Test for overall effect: Z = 0.95 (P = 0.34) 3.8.3.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Akarsu 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Jaja 2012 5 20 11 20 Jajada 2014 0 30 2 30 Kohli 2011 48 100 <td< td=""><td>5.2%</td><td>0.54 [0.31, 0.92]</td><td></td></td<>	5.2%	0.54 [0.31, 0.92]	
YaDeau 2015 34 87 10 29 Subtotal (95% CI) 356 275 Total events 96 79 Heterogeneity: Tau ² = 0.10; Chi ² = 11.57, df = 7 (P = 0.17) Test for overall effect: Z = 0.95 (P = 0.34) 3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Alimian 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Gianesello 2012 1 30 4 30 Jajeda 2014 0 30 2 30 Kohli 2011 3 14 20 1 20 Jajeda 2014 0 30 2 30 30 2 30	3.4%	1.10 [0.48, 2.50]	
Subtotal (95% CI) 356 275 Total events 96 79 Heterogeneity: Tau ² = 0.10; Chi ² = 11.57, df = 7 (P = 0.17) Test for overall effect: Z = 0.95 (P = 0.34) 3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Alkarsu 2012 0 30 9 30 Alimian 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 Chaparro 2012 18 50 14 49 20 4 20 Clendenen 2010 9 23 6 24 20 2 38 Chaparro 2012 18 50 14 49 20 4 20 Eskandar 2013 10 40 12 40 30 4 30 Gianesello 2012 1 30 4 30 4 30 30 30 Jajeda 2014 0 30	4.6%	0.71 [0.38, 1.34]	
Total events 96 79 Heterogeneity: Tau ² = 0.10; Chi ² = 11.57, df = 7 (P = 0.17) Test for overall effect: Z = 0.95 (P = 0.34) 3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Akarsu 2012 0 30 9 30 Akarsu 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chapgro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Legarty 2011 5 20 11 20 Jajeda 2014 0		1.13 [0.64, 2.00] 0.83 [0.58, 1.21]	
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 11.57$, $df = 7$ (P = 0.1) Test for overall effect: Z = 0.95 (P = 0.34) 3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Akarsu 2012 0 30 9 30 Akarsu 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Jajeda 2014 0 30 2 30 Kurana 2014 4 30 1 30 Kohli 2011 48 100 23 50	20.470	0.00 [0.00, 1.21]	•
Test for overall effect: Z = 0.95 (P = 0.34) 3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Akarsu 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20	10) 12 - 400	,	
3.83.2 Unclear or High risk of bias Akarsu 2012 0 30 9 30 Akarsu 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 Chaparro 2012 18 50 14 49 Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Jain 2012 5 20 11 20 Jain 2012 5 20 11 20 Jain 2011 48 100 23 50 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 30	12); 1- = 40%	0	
Akarsu 2012 0 30 9 30 Alimian 2012 5 40 17 40 Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hetta 2016 4 81 5 30 Jain 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012			
Alimian 20125401740Balaban 2012660530Chang 200917392238Chaparro 201218501449Clendenen 2010923624Demirhan 2014430430Eskandar 201310401240Ghoneim 2013630730Gianesello 2012130430Hegarty 2011314218Hetta 2016481530Jajeda 2014030230Khurana 2014430130Lee 2015321420Dageda 2014030230Kohli 2011481002350Lee 2015321420Ozgencil 2011530730Pakravan 2012030030Pakravan 20120303030Pakravan 2015126226Subtotal (95% CI)970788Total events281245Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0Test for overall effect: Z = 1.74 (P = 0.08)Ta26Total (95% CI)13261063			
Balaban 2012 6 60 5 30 Chang 2009 17 39 22 38 Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hetta 2016 4 81 5 30 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Lee 2015 3 21 4 20 Dagiapa 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 1 26 2 26 <tr< td=""><td>0.4%</td><td>0.05 [0.00, 0.87]</td><td>·</td></tr<>	0.4%	0.05 [0.00, 0.87]	·
Chang 2009 17 39 22 38 Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Hetta 2016 4 81 5 30 Jajeda 2014 0 30 2 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Dzgencil 2011 5 30 30 30 Pakravan 2012 0 30 30 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Subtotal (95%	3.0%	0.29 [0.12, 0.72]	
Chaparro 2012 18 50 14 49 Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Hetta 2016 4 81 5 30 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Dzgencii 2011 5 30 7 30 Pakravan 2012 0 30 30 30 Rajappa 2016 83 90 38 45	2.2%	0.60 [0.20, 1.81]	
Clendenen 2010 9 23 6 24 Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Hetta 2016 4 81 5 30 Jaicold 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Dzgencii 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Sidiropoulou 2016 6 15 0 15	6.1%	0.75 [0.48, 1.18]	
Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Hetta 2016 4 81 5 30 Jain 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Rajapap 2016 83 90 38 45 Rimaz 2014 4 30 12 30	4.9%	1.26 [0.71, 2.24]	
Demirhan 2014 4 30 4 30 Eman 2014 3 20 4 20 Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Hetta 2016 4 81 5 30 Jain 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Rajapap 2016 83 90 38 45 Rimaz 2014 4 30 12 30	3.2%	1.57 [0.66, 3.70]	
Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Hetta 2016 4 81 5 30 Jain 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Cogencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wei 2015 1 26 2 26		1.00 [0.28, 3.63]	
Eskandar 2013 10 40 12 40 Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Hetta 2016 4 81 5 30 Jain 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Cogencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wei 2015 1 26 2 26		0.75 [0.19, 2.93]	
Ghoneim 2013 6 30 7 30 Gianesello 2012 1 30 4 30 Hegarty 2011 3 14 2 18 Hetta 2016 4 81 5 30 Jain 2012 5 20 11 20 Jain 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 <tr< td=""><td></td><td>0.83 [0.41, 1.70]</td><td></td></tr<>		0.83 [0.41, 1.70]	
Gianesello 2012130430Hegarty 2011314218Hetta 2016481530Jain 20125201120Jajeda 2014030230Khurana 2014430130Lee 2015321420Dzgencil 2011530730Pakravan 2012030030Pakravan 201520251323Rajappa 201683903845Rimaz 20144301230Sidiropoulou 2016615015Wang 201116362130Veitotal (95% CI)970788788Total events281245245Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0Test for overall effect: Z = 1.74 (P = 0.08)Total (95% CI)13261063		0.86 [0.33, 2.25]	
Hegarty 2011314218Hetta 2016481530Jain 20125201120Jajeda 2014030230Khurana 2014430130Lee 2015321420Dzgencil 2011530730Pakravan 2012030030Pakravan 201520251323Rajappa 201683903845Rimaz 20144301230Sidiropoulou 2016615015Wang 201116362130Veit 2015126226Subtotal (95% CI)970788788Total events281245245Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0Test for overall effect: Z = 1.74 (P = 0.08)Total (95% CI)13261063		0.25 [0.03, 2.11]	
Hetta 2016 4 81 5 30 Jain 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Dzgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Subtotal (95% CI) 970 788 788 Total events 281 245 245 Heterogeneity: Tau ² = 0.12; Chi ² = 5		1.93 [0.37, 10.01]	
Jain 2012 5 20 11 20 Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Subtotal (95% CI) 970 788 70 Total events 281 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Test for overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326 1063		0.30 [0.09, 1.03]	
Jajeda 2014 0 30 2 30 Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Park 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 788 Total events 281 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Test for overall effect: Z = 1.74 (P = 0.08) 1326 1063		0.45 [0.19, 1.07]	
Khurana 2014 4 30 1 30 Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 788 Total events 281 245 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Test for overall effect: Z = 1.74 (P = 0.08) 1063		0.20 [0.01, 4.00]	
Kohli 2011 48 100 23 50 Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 788 Total events 281 245 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 788 763 Total (95% CI) 1326 1063 1063		4.00 [0.47, 33.73]	
Lee 2015 3 21 4 20 Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 788 Total events 281 245 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 788 788 Total events 281 245 745 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 788 788 Total (95% CI) 1326 1063 788		1.04 [0.73, 1.50]	_
Ozgencil 2011 5 30 7 30 Pakravan 2012 0 30 0 30 Pakravan 2012 0 30 0 30 Park 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 78 Total events 281 245 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 78 78 Tost for overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326 1063		0.71 [0.18, 2.80]	
Pakravan 2012 0 30 0 30 Pakravan 2012 0 30 0 30 Park 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 788 Total events 281 245 44 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 788 Tost for overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326			
Park 2015 20 25 13 23 Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 788 Total events 281 245 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 788 788 Total events 281 245 788 Total (95% CI) 1326 1063		0.71 [0.25, 2.00]	-
Rajappa 2016 83 90 38 45 Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 788 Total events 281 245 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Test for overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326 1063		Not estimable	
Rimaz 2014 4 30 12 30 Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 788 Total events 281 245 245 Heterogeneity: Tau² = 0.12; Chi² = 52.19, df = 24 (P = 0 Test for overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326 1063		1.42 [0.94, 2.13]	L
Sidiropoulou 2016 6 15 0 15 Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 Total events 281 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Total overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326 1063		1.09 [0.95, 1.25]	
Wang 2011 16 36 21 30 Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 Total events 281 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Total overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326 1063		0.33 [0.12, 0.92]	
Wei 2015 1 26 2 26 Subtotal (95% CI) 970 788 Total events 281 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Test for overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326 1063		13.00 [0.80, 212.02]	
Subtotal (95% CI) 970 788 Total events 281 245 Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0) Total (P = 0.08) Total (95% CI) 1326 1063		0.63 [0.41, 0.98]	
Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Test for overall effect: Z = 1.74 (P = 0.08) Total (95% CI) 1326 1063		0.50 [0.05, 5.18] 0.82 [0.65, 1.03]	•
Heterogeneity: Tau ² = 0.12; Chi ² = 52.19, df = 24 (P = 0 Test for overall effect: Z = 1.74 (P = 0.08) Total (95% Cl) 1326 1063			-
Test for overall effect: Z = 1.74 (P = 0.08) Total (95% Cl) 1326 1063	.0007): l ² =	54%	
	<i>"</i> .		
	100.0%	0.83 [0.68, 1.00]	•
Total events 377 324			
Heterogeneity: Tau ² = 0.10; Chi ² = 62.62, df = 32 (P = 0	.0010): l ² =	49%	
Test for overall effect: $Z = 1.99$ (P = 0.05)	<i>"</i>		0.01 0.1 1 10 100 Favours [Pregabalin] Favours [Control]

Appendix 15: Forest plots of adverse events: vomiting

Ofurther an Orch market	Pregab		Contr		Walcht	Risk Ratio	Risk Ratio
Study or Subgroup 3.28.1 Low risk of bia		lotal	Events	lotal	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
					4 504		
Jokela 2008a	5	56	1	29	1.5%	2.59 [0.32, 21.14]	
Martinez 2014	5	35	2	38	2.4%	2.71 [0.56, 13.10]	
Mathiesen 2008	10	40	6	38	4.8%	1.58 [0.64, 3.93]	
Mathiesen 2009	20	39	31	40	8.7%	0.66 [0.47, 0.94]	
Paech 2007	5	45	1	45	1.5%	5.00 [0.61, 41.11]	
Yadeau 2012 Subtotal (95% CI)	6	28 243	6	28 218	4.3% 23.1%	1.00 [0.37, 2.73] 1.34 [0.68, 2.65]	
Total events	51		47				
Heterogeneity: Tau ² =	0.35; Chi ²	= 11.85	ō, df = 5 (P = 0.0	4); l² = 58%		
Test for overall effect:	Z = 0.84 (I	P = 0.40))				
3.28.2 Unclear or Hig	h risk of t	oias					
Akarsu 2012	30	0	30	0		Not estimable	
Alimian 2012	1	40	5	40	1.5%	0.20 [0.02, 1.64]	
Balaban 2012	6	60	9	30	4.7%	0.33 [0.13, 0.85]	
Chang 2009	5	39	3 7	38	4.1%	0.70 [0.24, 2.00]	
Chaparro 2012	12	50	12	49	6.1%	0.98 [0.49, 1.97]	
Demirhan 2014	12	30	7	30	5.9%	2.29 [1.10, 4.74]	
Eskandar 2013	6	30 40	10	40	5.9% 4.8%	0.60 [0.24, 1.49]	
Ghoneim 2013	0	30	10	30	4.8% 0.7%		
Gianesello 2012	0	30	6	30	0.7%	0.33 [0.01, 7.87]	
	3		5			0.08 [0.00, 1.31]	
Hetta 2016	-	81	-	30	2.9%	0.22 [0.06, 0.87]	
Jain 2012	2	20	10	20	2.8%	0.20 [0.05, 0.80]	
Jajeda 2014	2	30	5	30	2.4%	0.40 [0.08, 1.90]	
Joshi 2013	1	20	3	20	1.4%	0.33 [0.04, 2.94]	
Khurana 2014	0	30	2	30	0.8%	0.20 [0.01, 4.00]	
Kohli 2011	41	100	18	50	8.1%	1.14 [0.73, 1.76]	
Mathiesen 2011	9	45	12	43	5.7%	0.72 [0.34, 1.53]	
Ozgencil 2011	3	30	5	30	3.0%	0.60 [0.16, 2.29]	
Rajappa 2016	36	90	16	45	7.8%	1.13 [0.70, 1.80]	7-
Rimaz 2014	3	30	8	30	3.4%	0.38 [0.11, 1.28]	
Shimony 2016	4	45	10	50	3.9%	0.44 [0.15, 1.32]	
Sidiropoulou 2016	0	15	0	15		Not estimable	
Sundar 2012	0	30	0	30		Not estimable	
Wang 2011 Subtotal (95% CI)	7	36 921	18	30 740	5.9% 76.9%	0.32 [0.16, 0.67] 0.59 [0.42, 0.83]	•
Total events	187		199				
Heterogeneity: Tau ² =	0.25; Chi ²	= 40.06	6, df = 19	(P = 0.	003); l² = 53	3%	
Test for overall effect:	-				•		
Total (95% CI)		1164		958	100.0%	0.72 [0.54, 0.94]	•
Total events	238		246				
Heterogeneity: Tau ² =	0.20; Chi ²	= 49.42	2, df = 25	(P = 0.	003); l² = 49	9%	0.01 0.1 1 10 100
		P = 0.02			-		0.01 0.1 1 10 100

	Pregab		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
3.32.1 Low risk of bias							
Bornemann-Cimenti 2012	4	13	6	13	2.3%	0.67 [0.24, 1.82]	
Ghai 2011	11	30	29	30	6.3%	0.38 [0.24, 0.61]	
Jokela 2008a	18	56	9	29	4.3%	1.04 [0.53, 2.01]	
Konstantatos 2016	14	52	14	48	4.6%	0.92 [0.49, 1.73]	
Mahran 2015	5	30	6	30	2.1%	0.83 [0.28, 2.44]	
Martinez 2014	6	35	6	38	2.2%	1.09 [0.39, 3.05]	
Nutthachote 2014	9	27	12	27	4.2%	0.75 [0.38, 1.48]	
Spreng 2011	2	22	5	24	1.1%	0.44 [0.09, 2.02]	
Yadeau 2012	7	28	6	26	2.5%	1.08 [0.42, 2.80]	
Subtotal (95% CI)		293		265	29.7%	0.73 [0.53, 0.98]	\bullet
Total events	76		93				
Heterogeneity: Tau ² = 0.05;	Chi ² = 10.	62, df =	8 (P = 0.	22); l² =	= 25%		
Test for overall effect: Z = 2.	06 (P = 0.	04)					
3.32.2 Unclear or High risk							
Abbasabadi 2015	22	46	10	23	5.4%	1.10 [0.63, 1.92]	
Ahiskalioglu 2015	2	20	8	20	1.3%	0.25 [0.06, 1.03]	· · · · · · · · · · · · · · · · · · ·
Aydogan 2014	1	30	0	30	0.3%	3.00 [0.13, 70.83]	
Bekawi 2014	9	30	26	30	5.3%	0.35 [0.20, 0.61]	
Burke 2010	3	20	0	18	0.3%	6.33 [0.35, 114.81]	
Cabrera Schulmeyer 2010	10	39	19	41	4.6%	0.55 [0.30, 1.04]	
Chotton 2015	1	45	0	45	0.3%	3.00 [0.13, 71.74]	
El Kenany 2016	24	90	22	45	6.6%	0.55 [0.35, 0.86]	
Kim 2010	7	47	10	47	2.9%	0.70 [0.29, 1.68]	
Kim 2011b	7	42	3	42	1.5%	2.33 [0.65, 8.42]	
Kim 2014	2	24	3	23	0.9%	0.64 [0.12, 3.48]	
Lee 2013	4	31	9	29	2.1%	0.42 [0.14, 1.20]	
Mansor 2015	19	25	17	24	8.4%	1.07 [0.77, 1.50]	+
Nimmaanrat 2012	10	27	14	29	4.7%	0.77 [0.41, 1.43]	
Niruthisard 2013	14	25	15	27	6.2%	1.01 [0.62, 1.64]	
Park 2015	14	23	23	26	8.1%	0.69 [0.48, 0.98]	
Prasad 2014	9	30	8	30	3.3%	1.13 [0.50, 2.52]	_ _
Sagit 2013	24	96	15	47	5.5%	0.78 [0.46, 1.35]	+-
Yucel 2011	7	60	7	30	2.5%	0.50 [0.19, 1.29]	
Subtotal (95% CI)		750		606	70.3%	0.74 [0.60, 0.92]	◆
Total events	189		209				
Heterogeneity: Tau ² = 0.07;	Chi ² = 29.	79, df =	18 (P = 0).04); l²	= 40%		
Test for overall effect: Z = 2.		- , -	- ,				
Total (95% CI)		1043		871	100.0%	0.74 [0.62, 0.88]	•
Total events	265		302			,	.
Heterogeneity: $Tau^2 = 0.06$;		50. df =).05): I ²	= 33%		· · · · · · · · · · · · · · · · · · ·
Test for overall effect: $Z = 3$.			-/ () - (0070		0.01 0.1 1 10 100
Test for subgroup difference		,	- 4 (D - 6	000 17			Favours [Pregabalin] Favours [Control]

	Pregab		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
3.36.1 Low risk of bias							
Ahn 2016	2	30	14	30	2.1%	0.14 [0.04, 0.57]	
Bornemann-Cimenti 2012	6	13	7	13	4.2%	0.86 [0.40, 1.86]	
Jokela 2008a	56	56	29	29	7.5%	1.00 [0.95, 1.05]	•
Martinez 2014	5	35	2	38	1.7%	2.71 [0.56, 13.10]	
Mathiesen 2008	32	40	18	38	6.4%	1.69 [1.17, 2.44]	
Mathiesen 2009	39	39	37	40	7.5%	1.08 [0.98, 1.19]	
Nutthachote 2014	0	27	0	27		Not estimable	
Spreng 2011	3	22	2	24	1.5%	1.64 [0.30, 8.90]	
Yadeau 2012	21	28	23	26	7.0%	0.85 [0.66, 1.09]	
YaDeau 2015	43	87	10	29	5.4%	1.43 [0.83, 2.47]	+
Subtotal (95% CI)		377		294	43.3%	1.06 [0.91, 1.25]	•
Total events	207		142				ſ
Heterogeneity: Tau ² = 0.02;		48 df =		001\- 12	= 69%		
Test for overall effect: Z = 0.	75 (P = 0.						
3.36.2 Unclear or High risk					4.00/	0.00 10.04 00 15	
Ahiskalioglu 2015	3	20	1	20	1.0%	3.00 [0.34, 26.45]	
Alimian 2012	0	40	0	40		Not estimable	
Aydogan 2014	0	30	0	30		Not estimable	
Balaban 2012	0	60	1	30	0.5%	0.17 [0.01, 4.04]	• • • • • • • • • • • • • • • • • • • •
Burke 2010	1	20	1	18	0.7%	0.90 [0.06, 13.36]	
Cabrera Schulmeyer 2010	0	39	0	41		Not estimable	
Chaparro 2012	9	50	6	49	3.4%	1.47 [0.57, 3.82]	
Choi 2013	6	36	3	36	2.3%	2.00 [0.54, 7.39]	
Clendenen 2010	12	23	12	24	5.3%	1.04 [0.60, 1.83]	_
Eskandar 2013	12	40	8	40	4.1%	1.50 [0.69, 3.27]	
Ghai 2012	8	30	0	30	0.6%	17.00 [1.03, 281.91]	
Gianesello 2012	3	30	5	30	2.2%	0.60 [0.16, 2.29]	
Gonano 2011	0	20	0	20		Not estimable	
Hegarty 2011	8	14	7	18	4.4%	1.47 [0.70, 3.07]	
Jajeda 2014	12	30	3	30	2.7%	4.00 [1.25, 12.75]	
Khurana 2014	3	30	0	30	0.6%	7.00 [0.38, 129.93]	
Kim 2011a	2	56	1	28	0.9%	1.00 [0.09, 10.56]	
Kim 2014	0	24	5	23	0.6%	0.09 [0.01, 1.49]	← · · · · · · · · · · · · · · · · · · ·
Kohli 2011	50	100	6	50	4.2%	4.17 [1.92, 9.05]	
Lee 2013	6	31	2	29	1.8%	2.81 [0.61, 12.81]	
Mansor 2015	0	25	ō	24	1.070	Not estimable	
Niruthisard 2013	10	25	7	27	4.1%	1.54 [0.69, 3.43]	
	7	30	5	30	4.1% 3.1%		
Ozgencil 2011 Park 2015	20	30 23	5 20	30 25		1.40 [0.50, 3.92]	
Park 2015 Bimor 2014					7.0%	1.09 [0.84, 1.40]	
Rimaz 2014	0	30	0	30	0.5%	Not estimable	
Sagit 2013	13	96	3	47	2.5%	2.12 [0.64, 7.09]	
Sebastian 2016	14	45	1	45	1.2%	14.00 [1.92, 102.03]	
Shimony 2016	1	45	2	50	0.9%	0.56 [0.05, 5.92]	
Wei 2015	4	26	0	23	0.6%	8.00 [0.45, 141.03]	
White 2009	12	81	2	27	2.0%	2.00 [0.48, 8.38]	
Subtotal (95% CI)		1149		944	56.7%	1.69 [1.21, 2.36]	\blacksquare
Total events Heterogeneity: Tau ² = 0.25; Test for overall effect: Z = 3.			101 23 (P = ().003);	² = 50%		
Total (95% CI)		1526		1238	100.0%	1.37 [1.08, 1.74]	♠
Total events	423		243				l ·
Heterogeneity: Tau ² = 0.19;	Chi ² = 218	8.26, df 009)		0.0000	1); l² = 85%	6	0.01 0.1 1 10 100

Appendix 18: Forest plots of adverse events: dizziness

	Pregaba		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% C	M-H, Random, 95% Cl
3.57.1 Low risk of bias							
Ahn 2016	14	30	1	30	1.0%	14.00 [1.96, 99.85]	
Bornemann-Cimenti 2012	0	13	0	13	1.070	Not estimable	
Ghai 2011	6	30	1	30	1.0%		
						6.00 [0.77, 46.87]	
Jokela 2008a	32	56	9	29	4.0%	1.84 [1.02, 3.32]	-
Mahran 2015	0	30	0	30		Not estimable	
Martinez 2014	6	35	2	38	1.5%	3.26 [0.70, 15.09]	
Mathiesen 2008	13	40	7	38	3.2%	1.76 [0.79, 3.94]	+
Mathiesen 2009	26	39	27	40	5.0%	0.99 [0.73, 1.35]	+
Nutthachote 2014	10	27	8	27	3.4%	1.25 [0.58, 2.68]	
Sarakatsianou 2013	13	20	0	20	0.6%	27.00 [1.71, 425.36]	
Spreng 2011	0	22	1	24	0.5%	0.36 [0.02, 8.46]	
Subtotal (95% CI)	Ŭ	342		319	20.3%	2.10 [1.12, 3.91]	
	120	• • • •	56	0.0	2010/0		\mathbf{I}
Total events					740/		
Heterogeneity: Tau ² = 0.48; Test for overall effect: Z = 2.3			8 (P = 0.0	JUU5); I	1 = 71%		
3.57.2 Unclear or high risk	of bais						
Abbasabadi 2015	9	46	0	23	0.6%	9.70 [0.59, 159.70]	
Ahiskalioglu 2015	0	20	1	20	0.5%	0.33 [0.01, 7.72]	
Akarsu 2012	1	30	2	30	0.8%	0.50 [0.05, 5.22]	
Alimian 2012	0	40	0	40		Not estimable	
Bekawi 2014	16	30	25	30	4.8%	0.64 [0.44, 0.93]	
Burke 2010	2	20	3	18	1.3%	0.60 [0.11, 3.19]	
Cabrera Schulmeyer 2010	0	39	0	41		Not estimable	
Choi 2013	13	36	8	36	3.4%	1.63 [0.77, 3.44]	+
Clendenen 2010	19	23	18	24	5.1%	1.10 [0.82, 1.48]	
Demirhan 2014	6	30	8	30	2.8%		
						0.75 [0.30, 1.90]	
Eskandar 2013	10	40	8	40	3.2%	1.25 [0.55, 2.84]	-
Fassoulaki 2012	19	33	11	38	4.1%	1.99 [1.12, 3.54]	
Ghai 2012	10	30	1	30	1.0%	10.00 [1.36, 73.33]	
Ghoneim 2013	2	30	1	30	0.8%	2.00 [0.19, 20.90]	
Gianesello 2012	2	30	3	30	1.3%	0.67 [0.12, 3.71]	
Gonano 2011	0	20	0	20		Not estimable	
Hegarty 2011	5	14	5	18	2.6%	1.29 [0.46, 3.58]	
Hetta 2016	5	81	4	30	2.0%	0.46 [0.13, 1.61]	
Jain 2012	2	20	0	20	0.5%	5.00 [0.26, 98.00]	
Jajeda 2014	2	30	õ	30	0.5%	5.00 [0.25, 99.95]	
Khetarpal 2016	5	30	4	30	2.1%	1.25 [0.37, 4.21]	
Khurana 2014	2	30	0	30	0.5%		
			-			5.00 [0.25, 99.95]	
Kim 2010	14	47	6	47	3.0%	2.33 [0.98, 5.55]	
Kim 2011b	22	42	15	42	4.4%	1.47 [0.89, 2.41]	
Kohli 2011	58	100	14	50	4.5%	2.07 [1.29, 3.33]	
Lee 2013	5	31	2	29	1.5%	2.34 [0.49, 11.13]	
Lee 2015	0	21	1	20	0.5%	0.32 [0.01, 7.38]	
Mansor 2015	16	25	9	24	4.0%	1.71 [0.94, 3.09]	⊢
Nimmaanrat 2012	7	27	14	29	3.5%	0.54 [0.26, 1.13]	—————
Ozgencil 2011	. 8	30	6	30	2.8%	1.33 [0.53, 3.38]	_
Rajappa 2016	70	90	2	45	1.8%	17.50 [4.49, 68.13]	· · · · · · · · · · · · · · · · · · ·
	4		2	45 30		2.00 [0.40, 10.11]	
Rajendran 2014		30			1.4%	• • •	
Rimaz 2014	5	30	2	30	1.5%	2.50 [0.53, 11.89]	
Sagit 2013	25	96	15	47	4.2%	0.82 [0.48, 1.40]	_ - _
Shimony 2016	2	50	2	45	1.1%	0.90 [0.13, 6.13]	
Sundar 2012	0	30	0	30		Not estimable	
Wang 2011	6	36	3	30	1.9%	1.67 [0.45, 6.11]	
Wei 2015	2	26	2	23	1.1%	0.88 [0.14, 5.79]	
White 2009	17	81	1	27	1.0%	5.67 [0.79, 40.60]	+
Yucel 2011	21	60	. 8	30	3.7%	1.31 [0.66, 2.61]	- -
Subtotal (95% CI)		1554		1246	79.7%	1.38 [1.08, 1.76]	
	440		200		/0	The Fund much	▼
Total events Heterogeneity: Tau ² = 0.22; Test for overall effect: Z = 2.8			206 35 (P < 0	.0001);	; I² = 54%		
		4000		4505	100 001	4 47 14 40 4 0 17	
Total (95% CI)		1896		1565	100.0%	1.47 [1.18, 1.84]	
Total events	532		262				
Heterogeneity: Tau ² = 0.23;	Chi ² = 103	. 42, d f :	= 44 (P <	0.0000	1); l² = 57%	6	0.01 0.1 1 10 10
Test for overall effect: Z = 3.4	40 (P = 0.0	007)	-				Favours [Pregabalin] Favours [Control]
Test for overall effect. $Z = 3.4$							ravous regapatini Favous Controll

Appendix 19: Forest plots of adverse events: headache

	Pregab		Contr			Risk Ratio	Risk Ratio
Study or Subgroup		Total	Events	Total	Weight	M-H, Random, 95% C	I M-H, Random, 95% Cl
3.88.1 Low risk of bi							
Ahn 2016	6	30	5	30	4.6%	1.20 [0.41, 3.51]	
Jokela 2008a	26	56	13	29	16.6%	1.04 [0.63, 1.69]	
Sarakatsianou 2013	2	20	2	20	1.6%	1.00 [0.16, 6.42]	
Spreng 2011	1	22	6	24	1.3%	0.18 [0.02, 1.39]	
Yadeau 2012 Subtotal (95% CI)	5	28 156	12	26 129	6.3% 30.4%	0.39 [0.16, 0.95] 0.74 [0.41, 1.33]	
Total events	40		38				
Heterogeneity: Tau ² =	= 0.16; Chi ²	= 6.46,	df = 4 (P	= 0.17); I² = 38%		
Test for overall effect	Z = 1.02 (P = 0.31	1)				
3.88.2 Unclear or hig	gh risk of b	ias					
Akarsu 2012	0	30	0	30		Not estimable	
Alimian 2012	0	40	0	40		Not estimable	
Chang 2009	11	39	5	38	5.6%	2.14 [0.82, 5.59]	
Choi 2013	5	36	5	36	4.0%	1.00 [0.32, 3.16]	
Eskandar 2013	4	40	2	40	2.0%	2.00 [0.39, 10.31]	
Ghai 2012	1	30	0	30	0.6%	3.00 [0.13, 70.83]	
Gianesello 2012	0	30	0	30		Not estimable	
Hegarty 2011	8	14	5	18	6.6%	2.06 [0.86, 4.92]	—
Khurana 2014	0	30	0	30		Not estimable	
Kim 2010	8	47	11	47	7.4%	0.73 [0.32, 1.64]	
Kim 2011b	6	42	12	42	6.5%	0.50 [0.21, 1.21]	
Mansor 2015	7	25	8	24	7.0%	0.84 [0.36, 1.96]	
Nimmaanrat 2012	6	27	7	29	5.6%	0.92 [0.35, 2.40]	
Park 2015	13	23	16	25	18.0%	0.88 [0.56, 1.40]	
Rajendran 2014	0	30	1	30	0.6%	0.33 [0.01, 7.87]	
Rimaz 2014	0	30	0	30		Not estimable	
Sidiropoulou 2016	0	15	2	15	0.6%	0.20 [0.01, 3.85]	· · · · · · · · · · · · · · · · · · ·
Wang 2011	8	36	4	30	4.4%	1.67 [0.56, 5.00]	
Wei 2015	2	26	0	23	0.6%	4.44 [0.22, 88.04]	
Subtotal (95% CI)		590		587	69.6%	1.01 [0.78, 1.31]	•
Total events	79		78				
Heterogeneity: Tau ² = Test for overall effect				(P = 0.	44); l² = 0%	5	
Total (95% CI)		746		716	100.0%	0.95 [0.75, 1.21]	+
Total events	119		116				
Heterogeneity: Tau ² =	= 0.03; Chi ²	= 19.96	6, df = 18	(P = 0.	34); l² = 10	%	0.01 0.1 1 10 100
Test for overall effect							Favours [Pregabalin] Favours [Control]
Test for subgroup diff	erences: C	$hi^2 = 0.0$	A3 df = 1	$(\mathbf{P} = 0)$	33) I ² = 0%		rates in regulating in avoirs [control]

	Pregab	alin	Cont	ol		Risk Ratio	Risk Ratio
Study or Subgroup	-		Events	Total	Weight	M-H, Random, 95% Cl	I M-H, Random, 95% CI
3.62.1 Low risk of bia						· · · · ·	
Ahn 2016	1	30	0	30	3.0%	3.00 [0.13, 70.83]	
Jokela 2008a	25	56	3	29	16.7%	4.32 [1.42, 13.10]	
Mahran 2015	0	30	0	30		Not estimable	
Nutthachote 2014	0	27	1	27	3.0%	0.33 [0.01, 7.84]	
Sarakatsianou 2013	1	20	0	20	3.0%	3.00 [0.13, 69.52]	
Subtotal (95% CI)		163		136	25.6%	3.21 [1.24, 8.28]	
Total events	27		4				
Heterogeneity: Tau ² = Test for overall effect:				9 = 0.52); l² = 0%		
3.62.2 Unclear or hig	h risk of b	oias					
Abbasabadi 2015	2	46	0	23	3.3%	2.55 [0.13, 51.09]	
Akarsu 2012	3	40	4	30	11.8%	0.56 [0.14, 2.33]	
Alimian 2012	0	40	0	40		Not estimable	
Chang 2009	4	39	0	38	3.5%	8.78 [0.49, 157.62]	
Choi 2013	0	36	0	36		Not estimable	
El Kenany 2016	16	90	0	45	3.7%	16.68 [1.02, 271.88]	· · · · · · · · · · · · · · · · · · ·
Eskandar 2013	4	40	0	40	3.5%	9.00 [0.50, 161.86]	
Fassoulaki 2012	9	35	2	33	11.4%	4.24 [0.99, 18.21]	
Fujati 2016	0	60	0	32		Not estimable	
Ghai 2012	0	30	0	30		Not estimable	
Ghoneim 2013	0	30	1	30	3.0%	0.33 [0.01, 7.87]	
Gianesello 2012	0	30	0	30		Not estimable	
Gonano 2011	0	20	0	20		Not estimable	
Hegarty 2011	3	14	2	18	9.4%	1.93 [0.37, 10.01]	
Jajeda 2014	0	30	0	30		Not estimable	
Khurana 2014	0	30	0	30		Not estimable	
Kim 2010	4	47	0	47	3.5%	9.00 [0.50, 162.62]	· · · · · · · · · · · · · · · · · · ·
Kim 2011a	0	56	1	28	3.0%	0.17 [0.01, 4.03]	
Kim 2011b	1	42	0	42	3.0%	3.00 [0.13, 71.61]	
Lee 2013	2	13	0	29	3.3%	10.71 [0.55, 208.71]	
Mansor 2015	0	25	0	24	0.00/	Not estimable	
Nimmaanrat 2012	2 2	27 30	3	29	8.8%	0.72 [0.13, 3.96]	
Ozgencil 2011 Rimaz 2014	2	30 30	0	30 30	3.3%	5.00 [0.25, 99.95] Not estimable	
Sidiropoulou 2016	0	30 15	0	30 15		Not estimable	
Subtotal (95% CI)	U	895	U	779	74.4%	2.24 [1.10, 4.57]	
Total events Heterogeneity: Tau ² = Test for overall effect:				(P = 0.			
Total (95% CI)		1058		915	100.0%	2.34 [1.33, 4.11]	
Total events	79		17			,,,,	
Heterogeneity: Tau ² =		= 19 34		(P = 0	31)· l ² = 1 ⁴	2%	· · · · · · · · · · · · · · · · · · ·
Test for overall effect:	Z = 2.96 (P = 0.00)3)				0.01 0.1 1 10 100 Favours [Pregabalin] Favours [Control]

Appendix 20: Forest plots of adverse events: visual disturbance

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Title of PhD thesis:

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3.	Involvement in the experimental work	C
4.	Presentation, interpretation and discussion in a journal article format of obtained data	В

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

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