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Explaining heterogeneity and efficacy of analgesics for postoperative pain: a systematic review and meta-regression analysis adjusted for baseline risk

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	heterogeneity in reviews of analgesic adjuncts. Moreover, we have utilized these findings to present a novel method of reporting effect estimates, which both reduces confounding from variable baseline risk in included trials and is able to adjust for other clinical and methodological confounding variables. We recommend use of these methods in future reviews of analgesics for postoperative pain. Other implications for clinical practice, primary and secondary research studies are discussed.
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Explaining heterogeneity and efficacy of analgesics for postoperative pain: a systematic review and meta-regression analysis adjusted for baseline risk

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Abstract

Introduction: Statistical heterogeneity can increase the uncertainty of results and reduce the quality of evidence derived from systematic reviews. At present, it is uncertain what are the major factors that account for heterogeneity in meta-analyses of analgesic adjuncts. Therefore, the aim of this review was to identify whether various covariates could explain statistical heterogeneity and use this to improve accuracy when reporting the efficacy of analgesics.

Methods: We searched for reviews using MEDLINE, EMBASE, CINAHL, AMED and *Cochrane Database of Systematic Reviews*. Firstly, we identified the existence of considerable statistical heterogeneity. Secondly, we conducted meta-regression analysis for the outcome of 24-hour morphine consumption using baseline risk and other covariates. Finally, we constructed a league table of analgesic adjuncts assuming a fixed consumption of postoperative morphine.

Results: We included 344 randomized controlled trials with 28,130 participants. 91% of analyses showed considerable statistical heterogeneity. Baseline risk was a significant cause of between-study heterogeneity for acetaminophen, NSAIDS/COX-2 inhibitors, tramadol, ketamine, alpha-2 agonists, gabapentin, pregabalin, lidocaine, magnesium and dexamethasone (R^2 15-100%; $p<0.05$). There was some evidence that methodological limitations of the trials explained some of the residual heterogeneity. Type of surgery was not independently associated with analgesic efficacy. Assuming

a fixed baseline risk, gabapentin, acetaminophen, alpha-2 agonists and NSAIDS/COX-2 inhibitors were the most effective analgesics.

Discussion: This is the first review to identify a major source of between-study heterogeneity in reviews of analgesic adjuncts. Moreover, we have utilized these findings to present a novel method of reporting effect estimates, which both reduces confounding from variable baseline risk in included trials and is able to adjust for other clinical and methodological confounding variables. We recommend use of these methods in future reviews of analgesics for postoperative pain. Other implications for clinical practice, primary and secondary research studies are discussed.

Introduction

Meta-analyses have emerged as a useful method to summarize research findings and increase the statistical power of primary research studies. However, one of the major limitations of this form of analysis is the aggregation of trials conducted in both different populations and in different clinical circumstances. This is termed clinical heterogeneity. Such clinical heterogeneity, along with other methodological limitations, may give rise to statistical heterogeneity,[1] which can be quantified using measures such as the I^2 statistic.

Unexplained statistical heterogeneity can increase the uncertainty surrounding effect estimates derived from meta-analyses and reduce the quality of evidence used to inform healthcare decisions.[2] In addition, in the presence of statistical heterogeneity, effect estimates may be inaccurate and lead to erroneous conclusions on the clinical significance of a particular agent. Therefore, investigating causes for heterogeneity is essential using techniques such as meta-regression analysis.[3] Baseline risk is a particular covariate that can help predict between-study heterogeneity in meta-analyses. However, conventional meta-regression analyses may be biased due to measurement error in the covariate and regression to the mean.[4,5] Therefore, alternative analyses such as Bayesian meta-regression are recommended.[6]

Heterogeneity is a particular problem in meta-analyses of analgesics used to prevent postoperative pain.[7] Indeed, a previous review has suggested that type of surgery should be explored in these review.[7] However, even within the same type of surgical

procedure, pain levels can be heterogeneous. In addition, differing analgesic protocols can further confound the association between type of surgery and the efficacy of the analgesic. Previous primary research has shown that the pain level experienced by a participant determines analgesic efficacy, with higher pain levels resulting in higher absolute pain score reductions following analgesic administration.[8,9] We have previously demonstrated that using control group morphine consumption (baseline risk), we were able to explain a large degree of between-study heterogeneity.[10,11]

This finding may have important clinical implications as meta-analyses are often used to inform clinical decision-making. However, any one finding from a meta-analysis of an analgesic may be confounded by the variable baseline risk in the included trials. If control group morphine consumption is found to be a significant predictor of between-study heterogeneity, quoting regression parameter estimates from a fixed value of morphine consumption would allow more accurate comparisons between analgesic adjuncts and help better inform clinical decision-making. In addition, explaining heterogeneity could improve the quality of systematic review evidence as per the Grades of Recommendation, Assessment, Development and Evaluation Group (GRADE).[2] With regards to clinical practice and trial conduct, more intensive use of analgesic adjuncts in situations where expected postoperative morphine consumption is high would help improve their clinical significance and may help reduce opioid adverse effects.

Therefore, the aims of this review were as follows: 1) due to the large number of previously published reviews on the subject, we searched for existing systematic reviews and performed a meta-epidemiological study of their methods for investigating heterogeneity and the methodological conduct in the included randomized controlled trials 2) we identified the existence of considerable statistical heterogeneity 3) we investigated heterogeneity using baseline risk and other clinical and methodological covariates 4) we utilized these principles to construct a league table of analgesic adjuncts assuming a fixed consumption of postoperative morphine to more accurately report efficacy and reduce confounding.

Methods

We reported this review in accordance with the PRISMA checklist.[12] We prospectively registered this review on the PROSPERO website using the registration number CRD42016039109. Due to the numerous previous systematic reviews published on the subject, the aim of this study was to search for previous reviews of postoperative analgesic agents and perform a meta-epidemiological study of these and a secondary analysis of the individual randomized controlled trials. We searched all databases from inception to May 2016: MEDLINE, EMBASE, CINAHL, AMED and the *Cochrane Database of Systematic Reviews*. We used the following search terms: 'postoperative AND pain', 'surgery', 'analgesi*', 'morphine AND consumption', 'opioid AND consumption' and we exploded the MeSH term 'ACUTE PAIN'. We combined these terms with the specific generic term for the analgesic agent. We then limited our search to reviews and meta-analyses.

We extracted the data onto an electronic database. We extracted the following data: study author, year of publication, type of agent, methods for investigating heterogeneity, postoperative opioid used and data used to calculate effect estimates. If results were not reported in the original meta-analysis, we extracted data from the original publications. In order to reduce selective reporting bias, if standard deviations were not reported, we estimated these from other studies in the analysis.[13] We did not attempt to estimate means and standard deviations from medians or inter-quartile ranges due to the high likelihood of non-normal data.[13] If results were not reported in the text, these were estimated from published graphs.

We had no language restrictions for inclusion in our review and we translated non-English language papers. We included reviews that included the following analgesic agents versus placebo for postoperative pain: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDS) and cyclooxygenase (COX) 2 inhibitors, tramadol, intravenous ketamine, alpha-2 agonists (clonidine and dexmedetomidine), gabapentin, pregabalin, nefopam, lidocaine, magnesium and dexamethasone. We aimed to identify reviews of prophylactic administration (defined as first dose given before the onset of pain or agents added to postoperative analgesic regimens, such as patient-controlled analgesia). We did not include reviews evaluating single dose analgesics for established postoperative pain or reviews in dental surgery, as these are unlikely to report 24-hour morphine consumption.

The outcome of interest was 24-hour opioid consumption. We chose opioid consumption as this serves as a surrogate measure for both how painful the procedure was and any concurrent analgesia used. In addition, as participants within these trials can use variable amounts of morphine to achieve a desired level of comfort, it may be more appropriate than pain score data, which may be confounded by variable morphine use between the groups. Moreover, one of the main goals of multimodal analgesia is to reduce opioid consumption. We only included primary studies where we could extract morphine consumption data. If studies reported dosage per kilogram, we converted this to a 70-kilogram weight. We also used data from the day of surgery or postoperative day one and analysed this as 24-hour data. If alternative opioids were

reported, these were converted to morphine equivalents using the following conversion factors: oral to intravenous morphine (3:1),[14] pethidine/meperidine (10:1),[15] ketobemidone (1:1),[16] tramadol (20:1),[17] fentanyl (1:100),[18] remifentanil (1:100),[19] piritramide (1:0.75),[20] hydromorphone (1:3),[21] oral hydrocodone (2:1), intravenous oxycodone (1:1.5),[22] oral oxycodone (2.5:1), papaveretum (1.5:1),[23] meptazinol (5:1),[24] nalbuphine (1:1),[25] propoxyphene (10:1),[26] sublingual buprenorphine (1:25)[27] and trimeperidine (2:1).

We undertook assessment of randomized controlled trials from included reviews using the Cochrane risk of bias tool. For blinding to receive low risk, studies had to describe in enough detail study drugs and placebos that were identical or similar in appearance rather than simply describe the study as 'double-blind'.[28] Outcome assessment also needed to be blinded. Attrition bias would receive high risk if patients were excluded from the analysis for reasons that may influence opioid consumption, such as those with uncontrolled pain or potential opioid adverse effects. Studies only received low risk for selective outcome reporting if outcomes were pre-stated in a published protocol or trial registration referenced in the included study. Other bias included baseline characteristic imbalances which have been associated with influencing pain (for example gender and pre-operative pain)[29] or industry sponsorship.[30]

Statistical Analysis

To quantify the degree of statistical heterogeneity we used the I^2 statistic, with values exceeding 75% as evidence of considerable heterogeneity and those exceeding 50% as evidence of moderate statistical heterogeneity.[1] For the available data, we calculated the mean difference (MD) in morphine consumption (mg) with 95% confidence intervals (CI) using a random-effects model. In order to identify whether control group morphine consumption could explain the between-study heterogeneity we undertook meta-regression analysis.[3] This analysis is similar to conventional regression analysis, although it involves using study-level covariates, such as the dose of the analgesic used in the trial as the predictor variable and the effect estimate (MD) as the outcome variable, with each study weighted for the precision of the results (lower standard errors having more weight).

We performed meta-regression initially using control group morphine consumption (baseline risk) as a covariate based on previous findings.[10] We also used the following clinical covariates: dose or route of drug administration, type of agent (NSAIDS versus COX-2 inhibitor for example), type of surgery and type of anesthesia. For type of surgery, where possible, we aimed to include procedure-specific evidence, if this was not possible we grouped procedures by specialty or anatomical location. In addition, we assessed whether measures of internal validity were responsible for statistical heterogeneity including: randomization, allocation concealment, blinding and attrition bias. Except for attrition bias, these covariates were only included in models if they exaggerated effect estimates. Control group morphine consumption

was initially added to the model, we then added other covariates to a multivariate model to adjust regression estimates for these confounding variables if they significantly improved the model, in a stepwise approach ($p<0.1$ for retention in the model). Due to the problems with analyzing baseline risk using conventional meta-regression, we additionally undertook Bayesian meta-regression using Markov Chain Monte Carlo (MCMC) with Gibbs sampling following recently developed methodology that incorporates the uncertainty of the covariate estimates, which avoids the problems of regression to the mean.[6] We present the results of regression parameters as the median with the associated 95% credible intervals (CrIs) of the estimated predictive distributions. Further details on these analyses are available from the authors on request.

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

If we identified baseline risk as a significant cause of between-study heterogeneity, we produced a league table of analgesic adjuncts based on a fixed control group consumption of 50mg using Bayesian parameter estimates. We regarded a difference of >20mg as a large clinically significant difference, >10mg a moderate clinically significant difference and >5mg of small clinical significance. This analysis allows comparison of analgesic adjuncts when adjusted for the variable control group morphine consumption from the included randomized controlled trials in order to reduce confounding. However, we ranked agents based on the point estimate and did not incorporate the uncertainty around these into these ranks and therefore these should be interpreted with caution. Where dose or route of administration was found to be a significant predictor, we included results from the most effective clinical situation and specified this where appropriate (for adjusted conventional estimates). We present both Bayesian parameter estimates (median) and adjusted conventional estimates with 95% CIs/CrIs. We conducted all analyses using Comprehensive Meta-analysis Version 3,[31] STATA Version 14[32] and WinBUGS Version 1.4.[33]

Results

We included 344 randomized controlled trials with 28,130 participants (Table 1). We identified these studies from 8 narrative reviews ,[34-41] 25 systematic reviews[42-66] and 72 meta-analyses[10-11, 67-136] (Figure 1). Of the included reviews that conducted a meta-analysis, 78% investigated heterogeneity. In 75%, investigation of heterogeneity was conducted using subgroup or sensitivity analysis and only 18% conducted meta-regression. In 32% of meta-analyses, investigation of heterogeneity was based on type of surgery, 35% used dose and 11% used type of anesthesia. In 31% of meta-analyses, heterogeneity was investigated using methodological covariates. On risk of bias assessment of the individual randomized controlled trials, adequate randomization was described in 58% of studies, adequate allocation concealment in 29%, adequate blinding in 50% and lack of attrition bias in 71% (Figure S1-10).[10]

From the included randomized controlled trials, there was evidence of considerable statistical heterogeneity (I^2 >75%) in most analyses (91%). On meta-regression analysis (Table 1), control group morphine consumption (baseline risk) explained between-study heterogeneity for acetaminophen, NSAIDS/COX-2 inhibitors, tramadol, ketamine, alpha-2 agonists, gabapentin, pregabalin, lidocaine, magnesium and dexamethasone (Figure 2). We could not analyze nefopam as we only identified five studies. When re-analysed using Bayesian meta-regression, control group morphine consumption remained a significant cause of heterogeneity and parameter estimates were very similar (Table 1). Mean control group consumption in each meta-analysis varied between 26.76mg to 47.24mg (Table 1).

Other significant causes of between-study heterogeneity when added to the model (Table 2 and 3) included route of administration and allocation concealment for acetaminophen (R^2=94%; p<0.001). Intravenous acetaminophen was more effective than other routes. For ketamine, the final model included blinding and allocation concealment, which explained the majority of the between-study heterogeneity (R^2=56%; p<0.001). For alpha-2 agonists, the addition of attrition bias and route of administration significantly improved the model, with intravenous and epidural/spinal administration the most effective (R^2=75%; p<0.001). The gabapentin model was improved by the addition of peri-operative dose (R^2=93%; p<0.001). For pregabalin, the final model included allocation concealment, which significantly improved the model (R^2=78%; p<0.001). For lidocaine, the final model included route of administration and attrition bias (R^2=87%; p<0.001). Intravenous administration was more effective than subcutaneous patch. For magnesium, the addition of allocation concealment significantly improved the final model (R^2=32%; p=0.006). We did not include dose, as this did not exaggerate effect estimates. Dexamethasone was the only analysis where type of surgery was a significant predictor. The final model included type of surgery and blinding (R^2=100%; p<0.001), with larger morphine reductions in spinal and ENT surgery (although only based on single studies). However, analysis could not performed with type of surgery and allocation due to multicollinearity.

When assuming a fixed consumption of 50mg of postoperative morphine (Figure 3), we observed moderate clinically significant reductions (in order of efficacy) with

gabapentin, acetaminophen, alpha-2 agonists, NSAIDS/COX-2 inhibitors, pregabalin, tramadol, magnesium and lidocaine. We observed small clinically significant reductions with ketamine and dexamethasone. When adjusting conventional estimates for confounders, gabapentin (1200mg) demonstrated a large clinically significant reduction and the results for magnesium adjusted for allocation concealment resulted in a small clinical effect (Table 3).

Discussion

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

Recent meta-analyses have attempted to explore heterogeneity using clinical covariates such as dose and type of surgery.[115] However, these often report a low proportion of variation explained when compared to our results using baseline risk. We derived this covariate from previous empirical studies suggesting larger reductions in pain scores following analgesic treatment with higher baseline pain scores. One study examined around 500 participants following dental extraction and found those with severe pain (3/3) had greater reductions in pain scores following treatment with ibuprofen compared to those with moderate pain (2/3).[8] Another study found acetaminophen and codeine treatment following Caesarean section was only effective in those participants with severe pain (>6/10).[9] Although it should be noted

other factors in addition to degree of pain may also influence postoperative opioid consumption such as access to patient-controlled analgesia, concurrent analgesic protocols, patient characteristics and the prescribing practices of attending medical professionals (which may be region dependent).

A previous study of postoperative pain reviews has found widespread statistical heterogeneity and suggested that this should be explored based on type of surgery or pain scores.[7] This review recommended future meta-analyses should include only trials from the same surgical procedures or those with close acute postoperative pain levels and explore this using subgroup analysis. We would argue that baseline risk is a more appropriate covariate than type of surgery and meta-regression a more useful analysis than subgroup analysis as it allows reporting of the proportion of heterogeneity explained by the model (R^2) as well as the ability to adjust for other confounding variables. In our previous meta-analysis with gabapentin, morphine consumption varied even within procedure-specific subgroups and type of surgery was a small determinant of heterogeneity between studies in relation to morphine consumption and pain scores.[10] Our results suggest that expected postoperative morphine consumption (as a surrogate for pain and concurrent analgesia) is a large determinant of heterogeneity between studies.

Our results demonstrate that with baseline risk held constant, type of surgery was not a significant predictor of between-study heterogeneity for nearly all analyses. Previous groups have argued that procedure-specific evidence is necessary when

evaluating evidence derived from trials of analgesic agents.[137] Our results suggest that the efficacy of analgesic agents is determined more by the degree of morphine consumption during the postoperative period rather than the type of surgery. Indeed, procedure-specific meta-analyses still suffer from considerable statistical heterogeneity.[108] Therefore, we could find little empirical basis for conducting such procedure-specific reviews for analgesic adjuncts. However, we could not exclude an effect of type of surgery mediated via differences in baseline risk (some procedures having higher morphine consumption). Furthermore, we acknowledge that other interventions such as regional anaesthesia may have more relevance to procedure-specific evidence.

When reporting the results from analgesics using a fixed consumption of postoperative morphine, we found the most effective analgesics were gabapentin, acetaminophen, alpha-2 agonists, NSAIDS/COX-2 inhibitors, pregabalin, tramadol, magnesium and lidocaine, all with moderate clinically significant effects. Ketamine and dexamethasone had small clinically significant effects. However, these rankings should be interpreted with caution due to the uncertainties surrounding the point estimates, which may mean analgesics lower down the table are statistically equivalent. Furthermore, efficacy is not the only consideration when considering use of these agents. Adverse effects should also be considered when selecting an analgesic agent. Agents such acetaminophen, which have a low incidence of adverse events may be preferable to agents that induce peri-operative adverse effects such as

sedation with gabapentin, especially as the differences between these agents is negligible.

In terms of the implications of our work for clinical practice, as meta-analyses are often used to inform clinical practice, reviews should present opioid reductions using a fixed consumption of morphine to more accurately reflect efficacy, as quoting the mean difference will be heavily influenced by the mean control morphine consumption from the included trials. In addition, indiscriminate use of analgesic adjuncts around the peri-operative period should be avoided. Instead, clinicians can use information from small audits of mean opioid consumption and the regression parameters in our analysis to estimate the likely mean reduction in morphine consumption for samples of patients in that particular clinical situation. As all agents are associated with adverse effects, this more targeted use of analgesic adjuncts may help improve clinical significance and avoid inappropriate use of multiple agents when expected opioid reductions are small.

In terms of randomized controlled trial design, when studying analgesic agents for postoperative pain, trials should be conducted in surgeries where expected postoperative morphine consumption is anticipated to be high. For example, for intravenous acetaminophen, where the expected postoperative morphine consumption is either 70mg or 20mg in the first 24-hours postoperatively, the anticipated reduction in morphine would be 26mg and 6mg respectively. Relying solely on the mean difference (8mg) may underestimate clinical significance in the context where

postoperative morphine consumption is high. Furthermore, such larger reductions in morphine consumption may have a more pronounced effect on opioid adverse effects, which have additional clinical relevance. In terms of trial conduct, as with previous studies, we have found evidence that methodological limitations, in particular allocation concealment, were associated with larger reductions in morphine for many adjuncts.[138] Given that only 29% of the included studies reported adequate allocation concealment, this is a particular area of internal validity future studies should aim to address.

In terms of secondary research studies, future meta-analyses of postoperative analgesic agents should aim to explore heterogeneity using control group morphine consumption, in addition to other sources of clinical heterogeneity such as dose or route of administration. Such explanation of statistical heterogeneity would lead to higher quality evidence derived from these reviews as per GRADE.[2] Estimates from these reviews should be reported using a fixed consumption of morphine to avoid confounding by the variable consumption of opioid in the included primary studies (using Bayesian analysis). As an extension to this, incorporating other clinical and methodological covariates into these regression models to adjust estimates can reduce further confounding. As systematic reviews are inherently observational (despite deriving data from randomized studies),[139] more advanced and appropriate statistical methods are required (regression) that allows more accurate prediction than using mean differences, while having the additional advantage of controlling for known confounders. For these reasons, future reviews of postoperative analgesics should

avoid univariate subgroup analyses (due to confounding) and move towards multivariate regression models, which include control group morphine consumption (as is common practice in observational primary research studies).

There are several limitations with this review. Firstly, meta-regression analysis should be regarded as observational despite deriving data from randomized studies. Such analyses are prone to both residual confounding and aggregation bias (as results are based on aggregated study estimates rather than from individual patients). For this reason, our implications for clinical practice focus on aggregated patient outcomes (from audits) rather than applying these to individual patients. Secondly, we cannot rule out type I errors in our analyses. Although conventional to set a lower level of significance to covariate adjustment in regression models ($p<0.1$), this may also increase false positive results. Thirdly, although our models can adjust for confounding variables, our analyses are limited to published primary studies and are therefore still susceptible to publication bias. Although identification of imprecise study effects is possible in systematic reviews, it is impossible to know if this is secondary to true publication bias and therefore this limits our findings. Finally, as we generally derived our studies from reviews of active versus placebo groups, we were unable to perform network meta-analysis, which may be a more appropriate method to directly compare analgesics in future reviews.

In conclusion, we have identified widespread, considerable statistical heterogeneity in meta-analyses of analgesic adjuncts. Moreover, we have demonstrated for the first

time, an empirically-derived, consistent covariate responsible for a large proportion of between-study heterogeneity in meta-analyses of analgesics for postoperative pain. Extending this principle, we have presented methods for more accurate reporting of the efficacy of analgesics that can adjust for other clinical and methodological covariates. Despite the limitations of our analysis, we recommend use of these principles in clinical practice, primary and secondary research studies.

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Figure Legends

Figure 1: PRISMA flowchart of included reviews and randomized controlled trials.

Figure 2: Meta-regression plot for included analgesics. Plots are from top left to bottom right: acetaminophen, NSAIDS/COX-2 inhibitors, ketamine, alpha-2 agonists, gabapentin, pregabalin, lidocaine, magnesium and dexamthasone. X axis is baseline risk (mg of control group morphine consumption) and Y axis is mean difference in morphine consumption (mg).

Figure 3: Bar chart of reductions in 24-hour morphine consumption (y axis) for each analgesic agent (in order of efficacy). Figures are derived from Bayesian parameter estimates (medians).

Figure S1: Risk of bias for acetaminophen.

Figure S2: Risk of bias for NSAIDS/COX-2 inhibitors.

Figure S3: Risk of bias for tramadol.

Figure S4: Risk of bias for ketamine.

Figure S5: Risk of bias for alpha-2 agonists.

Figure S6: Risk of bias for pregabalin.

Figure S7: Risk of bias for nefopam.

Figure S8: Risk of bias for lidocaine.

Figure S9: Risk of bias for magnesium.

Figure S10: Risk of bias for dexamethasone.

Table 1

Analgesic	**Studies (participants)**	**I^2**	**R^2 control morphine (p value)**	**Intercept**	**Beta coefficient and (95% CIs)**	**Bayesian Intercept**	**Bayesian beta coefficient (median) and (95% CrIs)**	**Mean control group morphine consumption in included trials**
Acetaminophen	25 (1812)	99%	**R^2=79%; p<0.001**	0.84	-0.39 (-0.49 to -0.29)	0.77	-0.38 (-0.48 to -0.28)	27.97mg
NSAIDS/COX-2 inhibitors	86 (6937)	92%	**R^2=81%; p<0.001**	2.42	-0.35 (-0.41 to -0.30)	2.56	-0.36 (-0.41 to -0.30)	42.71mg
Tramadol	11 (889)	90%	**R^2=48%; p=0.03**	2.93	-0.30 (-0.56 to -0.05)	2.96	-0.30 (-0.55 to -0.03)	41.58mg
Ketamine	62 (4309)	95%	**R^2=29%; p<0.001**	-1.05	-0.18 (-0.25 to -0.10)	-1.01	-0.18 (-0.24 to -0.10)	47.24mg
Alpha-2 agonists	33 (1930)	96%	**R^2=66%;**	-0.52	-0.34 (-0.47 to -	-0.95	-0.32 (-0.44 to -	

			p<0.001		0.21)		0.19)	38.2mg
Gabapentin	67 (5082)	97%	**R^2=92%; p<0.001**	1.12	-0.39 (-0.44 to -0.34)	1.11	-0.39 (-0.43 to -0.35)	32.75mg
Pregabalin	34 (3201)	94%	**R^2=58%; p<0.001**	-2.62	-0.21 (-0.30 to -0.12)	-2.91	-0.20 (-0.28 to -0.11)	31.97mg
Nefopam	5 (394)	38%	N/A	N/A	N/A	N/A	N/A	N/A
Lidocaine	22 (1319)	80%	**R^2=62%; p<0.001**	-0.25	-0.20 (-0.31 to -0.09)	-0.29	-0.20 (-0.30 to -0.08)	31.35mg
Magnesium	22 (1194)	90%	**R^2=15%; p=0.02**	-1.74	-0.17 (-0.31 to -0.03)	-1.35	-0.19 (-0.34 to -0.04)	30.72mg
Dexamethasone	16 (2163)	88%	**R^2=100%; p<0.001**	0.69	-0.19 (-0.23 to -0.14)	0.86	-0.18 (-0.24 to -0.12)	26.76mg

Table 1: Meta-regression estimates for each analgesic adjunct. Asterisk denotes statistical significance ($p<0.1$). *CI=confidence interval; CrIs=credible intervals; I^2=measure of variability in results due to between-study differences compared to sampling variance; N/A=not applicable; R^2=proportion of between-study variance explained by model.*

Table 2

Analgesic	**Type of surgery**	**Type of anesthesia**	**Type of regimen, dose or route**	**Random**	**Allocation**	**Blinding**	**Attrition**
Acetaminophen	R^2=4%; p=0.22 (CABG, ENT, cholecystectomy, C-section, orthopedic, hysterectomy and spinal surgery)	R^2=0%; p=0.95 (GA, SA and mixed)	**R^2=6%; p=0.05** (IV, PO and PR)	R^2=0%; p=0.80	**R^2=4%; p=0.09** (low and unclear risk)	R^2=2%; p=0.21	R^2=0%; p=0.97
NSAIDS/COX-2 inhibitors	R^2=4%; p=0.31 (abdominal, mixed arthroplasty, C-section, CABG, cholecystectomy, hip arthroplasty,	R^2=3%; p=0.18 (NR, GA, GA/LA, GA/SA and GA/SA/EA)	R^2 =2%; p=0.83 (NSAID and COX-2) and R^2=1%; p=0.89 (IM, IN, IV, PO and PR)	R^2=2%; p=0.47	R^2=2%; p=0.31		R^2=1%; p=0.84

	hysterectomy, knee arthroplasty, mixed surgeries, orthopedic, spinal surgery, thoracotomy, thyroid and tonsillectomy)					R^2=3%; p=0.17	
Tramadol	R^2=0%; p=0.99 (abdominal, C-section, CABG, knee arthroplasty and TURP)	R^2=1%; p=0.47 (GA and SA)	R^2=0%; p=0.59 (IV and spinal) and R^2=6%; p=0.25 (dose)	R^2=0%; p=0.80	R^2=10%; p=0.22	R^2=0%; p=0.87	R^2=0%; p=0.63
Ketamine	R^2=0%; p=0.45 (abdominal, arthroplasty, arthroscopy, C-section, cholecystectomy, ENT,	R^2=0%; p=0.44 (GA, GA/EA, GA/RA, LA, mixed and SA)	R^2=0%; p=0.86 (total 24-hour dose in milligrams)	**R^2=4%; p=0.09** (low, unclear and high risk)	**R^2=4%; p=0.1** (low, unclear and high risk)	**R^2=17%;**	R^2=0%; p=0.45

	gynecology, hysterectomy, mixed surgeries, orthopedic, spinal surgery and thoracotomy)					**p<0.001** (low, unclear and high risk)	
Alpha-2 agonists	R^2=0%; p=0.87 (abdominal, arthroplasty, C-section, CABG, ENT, gynecology, hysterectomy, spinal surgery and cholecystectomy)	R^2=0%; p=0.53 (EA, GA, NR, GA/EA, GA/SA and SA)	R^2=1%; p=0.12 (dexmedetomidine and clonidine) and **R^2=34%; p=0.07** (IV, IV/SC, PO/SC, PO and spinal/epidural)	R^2=0%; p=0.87	R^2=0%; p=0.87	R^2=0%; p=0.60	R^2=0%; p=0.34
Gabapentin	R^2=0%; p=0.36 (abdominal,	**R^2=1%; p=0.08** (GA, SA, GA/RA	**R^2=1%; p=0.008** (peri-operative dose	R^2=0%; p=0.99	R^2=0%; p=0.84		R^2=1%; p=0.12

	hysterectomy, breast, CABG, cholecystectomy, C-section, arthroplasty, arthroscopy, nasal, neurosurgery, orthopedic, plastic surgery, spinal surgery, thoracotomy, thyroid and tonsillectomy)	and GA/EA)	in milligrams)			R^2=1%; p=0.15	

Pregabalin	R^2=0%; p=0.89 (abdominal, arthroscopy, breast, cardiac surgery, cholecystectomy, ENT, hysterectomy, laparoscopic abdominal, mixed surgeries, orthopedic, spinal surgery and arthroplasty)	R^2=0%; p=0.58 (RA, SA/RA, SA and GA)	R^2=0%; p=0.84 (peri-operative dose in milligrams)	R^2=5% p=0.11 (low and unclear risk)	**R^2=20%; p=0.004** (low and unclear risk)	**R^2=9%; p=0.01** (low, unclear and high risk)	R^2=0%; p=0.70
Nefopam	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Lidocaine	R^2=0%; p=0.33 (abdominal, breast, cholecystectomy, ENT and spinal surgery)	N/A (only GA subgroup)	R^2=8%; p=0.99 (24-hour dose in milligrams) and **R^2=18%; p=0.03** (intravenous versus patch)	R^2=21%; p=0.06 (did not exaggerate effect estimate)	R^2=0%; p=0.58	R^2=4% p=0.18	**R^2=13%; p=0.05** (low and unclear risk)
Magnesium	R^2=0%; p=0.69 (abdominal, cardiac surgery, cholecystectomy, hysterectomy, mixed surgeries, orthopedic and spinal surgeries)	R^2=0%; p=0.33 (GA and SA)	R^2=17%; p=0.02 (total 24-hour dose, did not exaggerate effect estimate)	R^2=10%; p=0.06 (low and unclear risk, did not exaggerate effect estimate)	**R^2=17%; p=0.02** (low and unclear risk)	R^2=0%; p=0.87	R^2=0%; p=0.97

Dexamethasone	**R^2=0%; p=0.06** (abdominal, cholecystectomy, ENT, hysterectomy, mixed surgeries, orthopaedic and spinal surgery)	R^2=0%; p=0.63 (GA and SA)	R^2=0%; p=0.12 (dose in milligrams)	**R^2=0%; p=0.1** (low, unclear and high risk)	R^2=0%; p=0.18	R^2=0%; p=0.84	R^2=0%; p=0.67

Table 2: Results from meta-regression analyses for the covariates below when added to the model with control group morphine consumption. Each covariate is reported with the R^2 analogue change (%) and the p value for the change in model. Categories for each covariate are presented in parentheses. Risk of bias elements are classified according to the Cochrane risk of bias tool. Statistically significant results (p<0.1) are highlighted in bold. *CABG= coronary artery bypass graft; ENT= ear, nose and throat; EA= epidural anesthesia; GA=general anesthesia; IM= intra-muscular; IN= intra-nasal; IV= intravenous; LA= local anesthesia; N/A= not applicable; NR=not reported; prostate; PO= oral; PR= rectal; RA= regional anesthesia; SA= spinal anesthesia; TURP= trans-urethral resection of prostate.*

Table 3

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

Pregabalin	-8.18mg (-9.6mg to -6.76mg)	-11.36mg (allocation)	-12.75mg (-15.23mg to -10.11mg)
Tramadol	-8.48mg (-11.88mg to -4.89mg)	-12.17mg (none)	-11.99mg (-16.21mg to -7.28mg)
Magnesium	-6.77mg (-8.39mg to -5.15mg)	-3.91mg (allocation)	-10.60mg (-14.19mg to -7.10mg)
Lidocaine	-5.04mg (-7.42mg to -2.66mg)	-9.15mg (administration; intravenous and attrition)	-10.09mg (-13.49mg to -6.36mg)
Ketamine	-8.13mg (-10.23mg to -6.03mg)	-7.75mg (allocation and blinding)	-9.76mg (-12.15mg to -7.33mg)
Dexamethasone	-4.23mg (-5.79mg to -2.67mg)	-5.18mg (type of surgery and blinding)	-8.07mg (-9.79mg to -6.04mg)

Nefopam	-14.75mg (-19.34mg to -10.17mg)	N/A	N/A

Table 3: League table of analgesic adjuncts assuming a 50mg consumption of morphine in the control group. Random-effects mean difference, adjusted and Bayesian meta-regression parameter estimates are presented. For adjusted models, covariates are listed in parentheses. We ranked analgesics according to point Bayesian estimates. *CIs=confidence intervals; CrIs=credible intervals; mg=milligrams; N/A=not applicable.*

Figure 1

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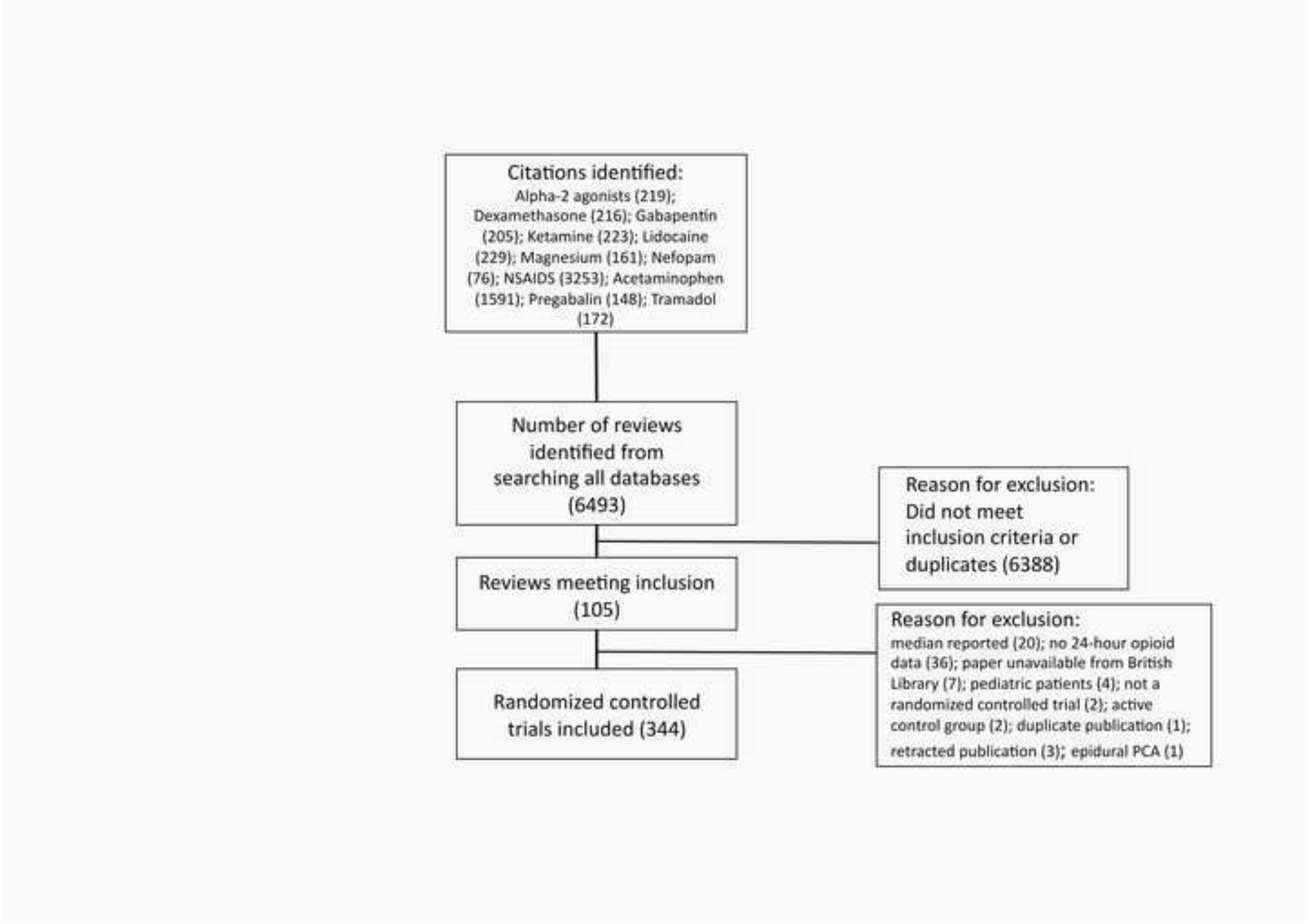

Figure 2

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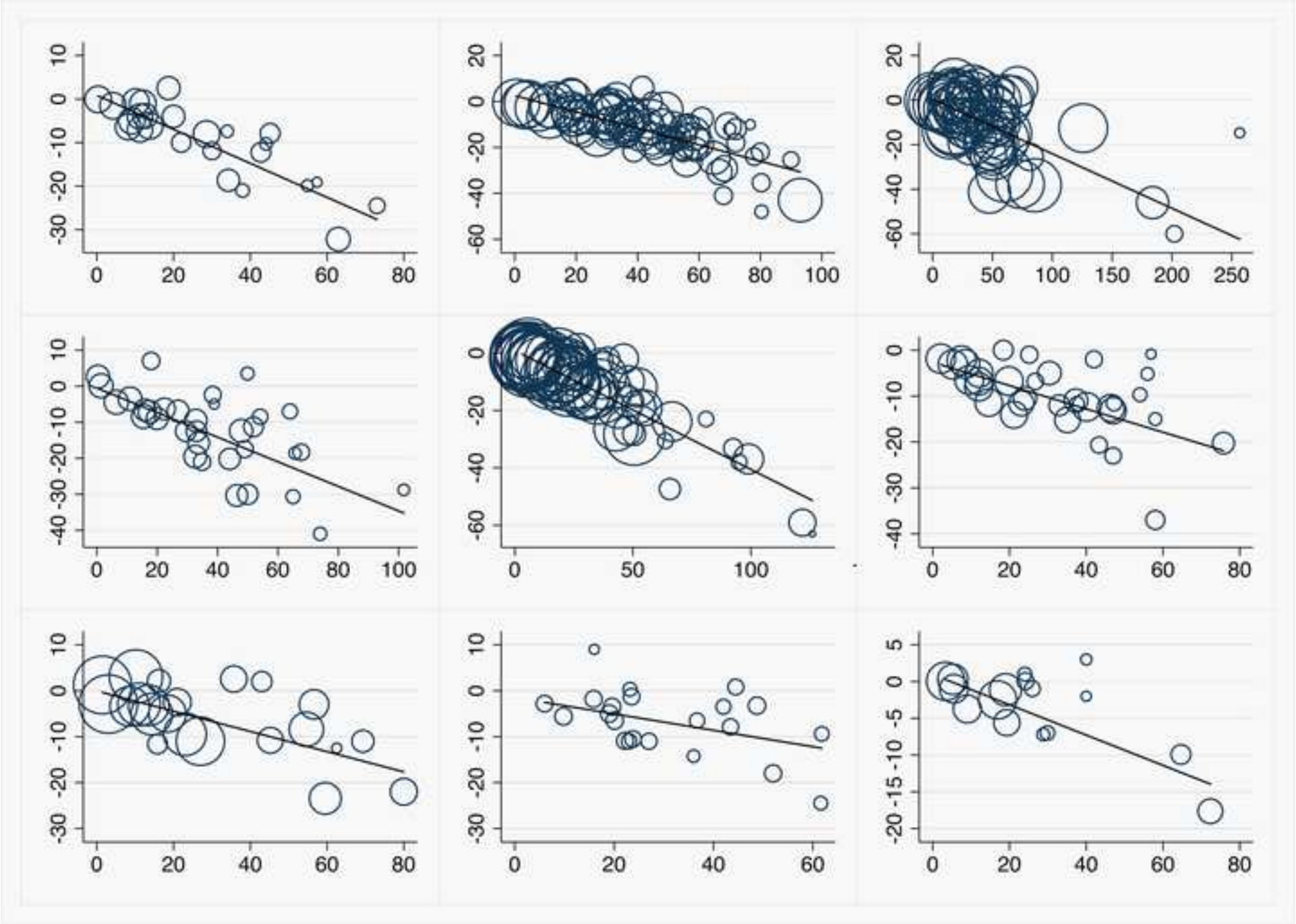

Figure 3

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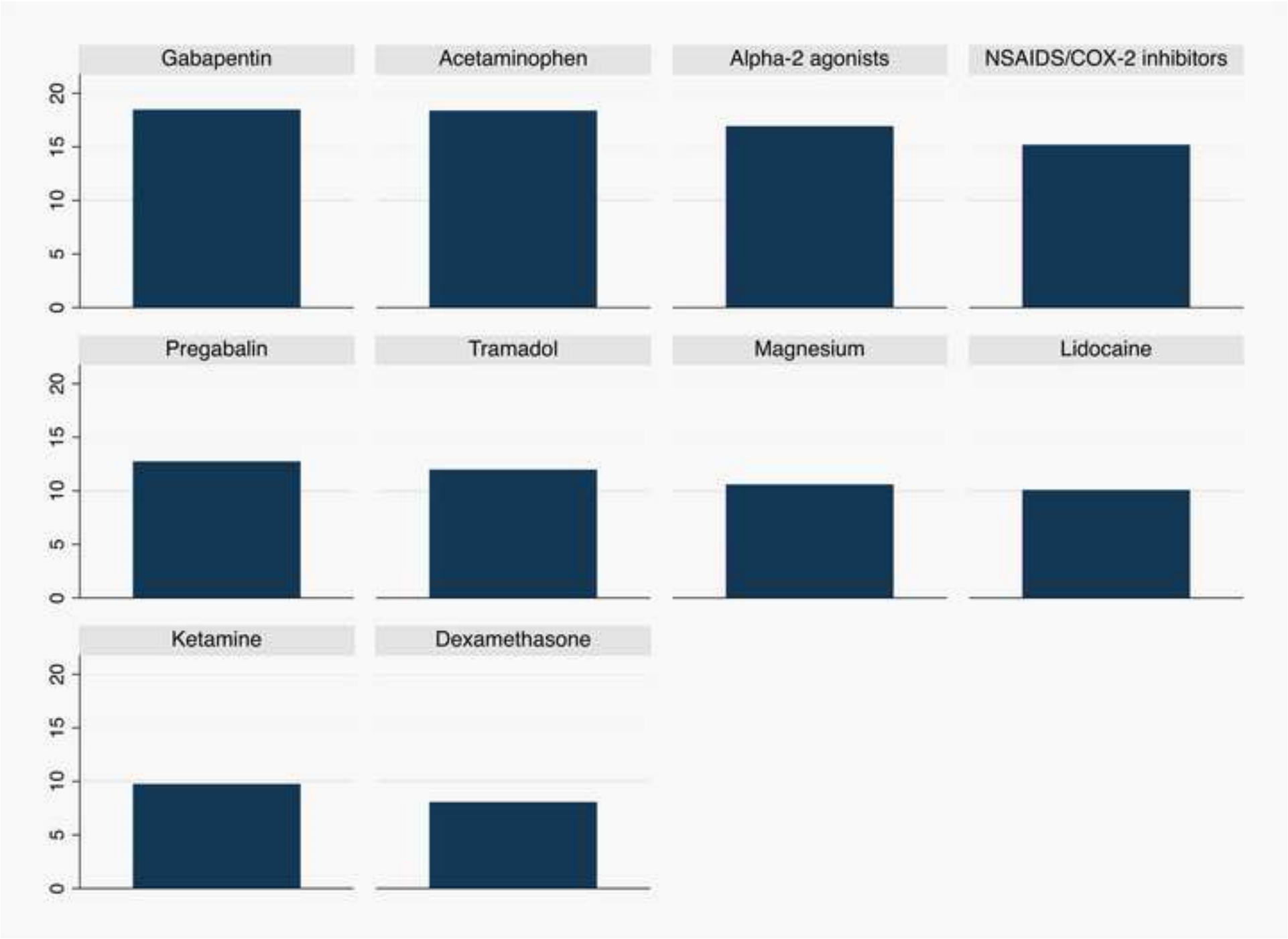

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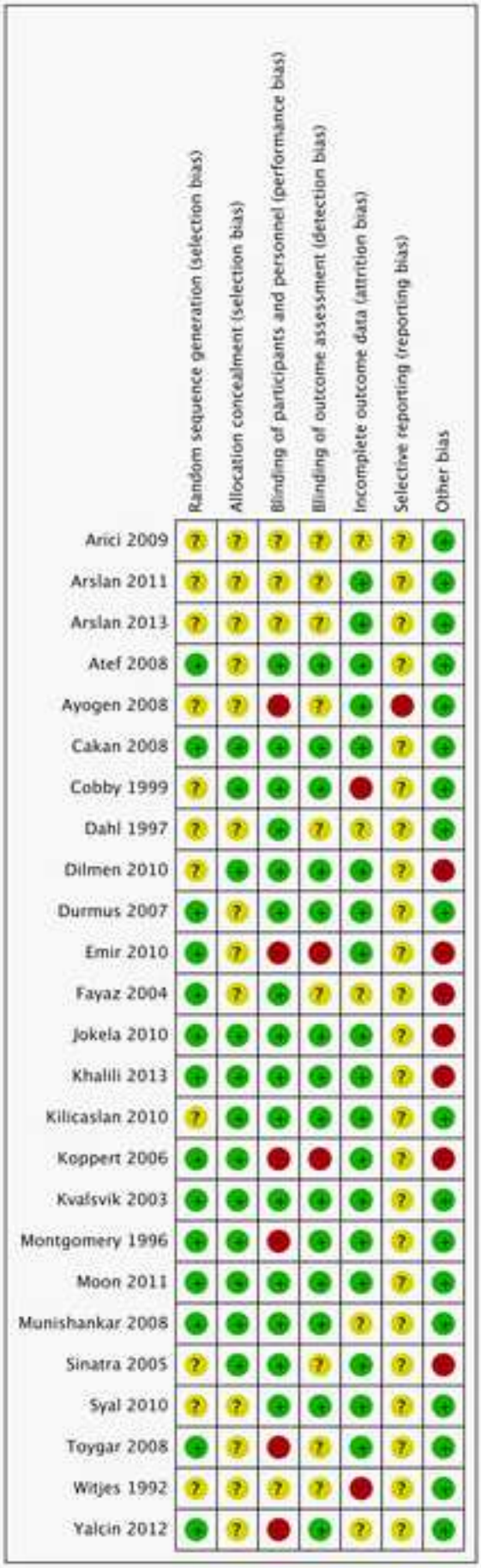

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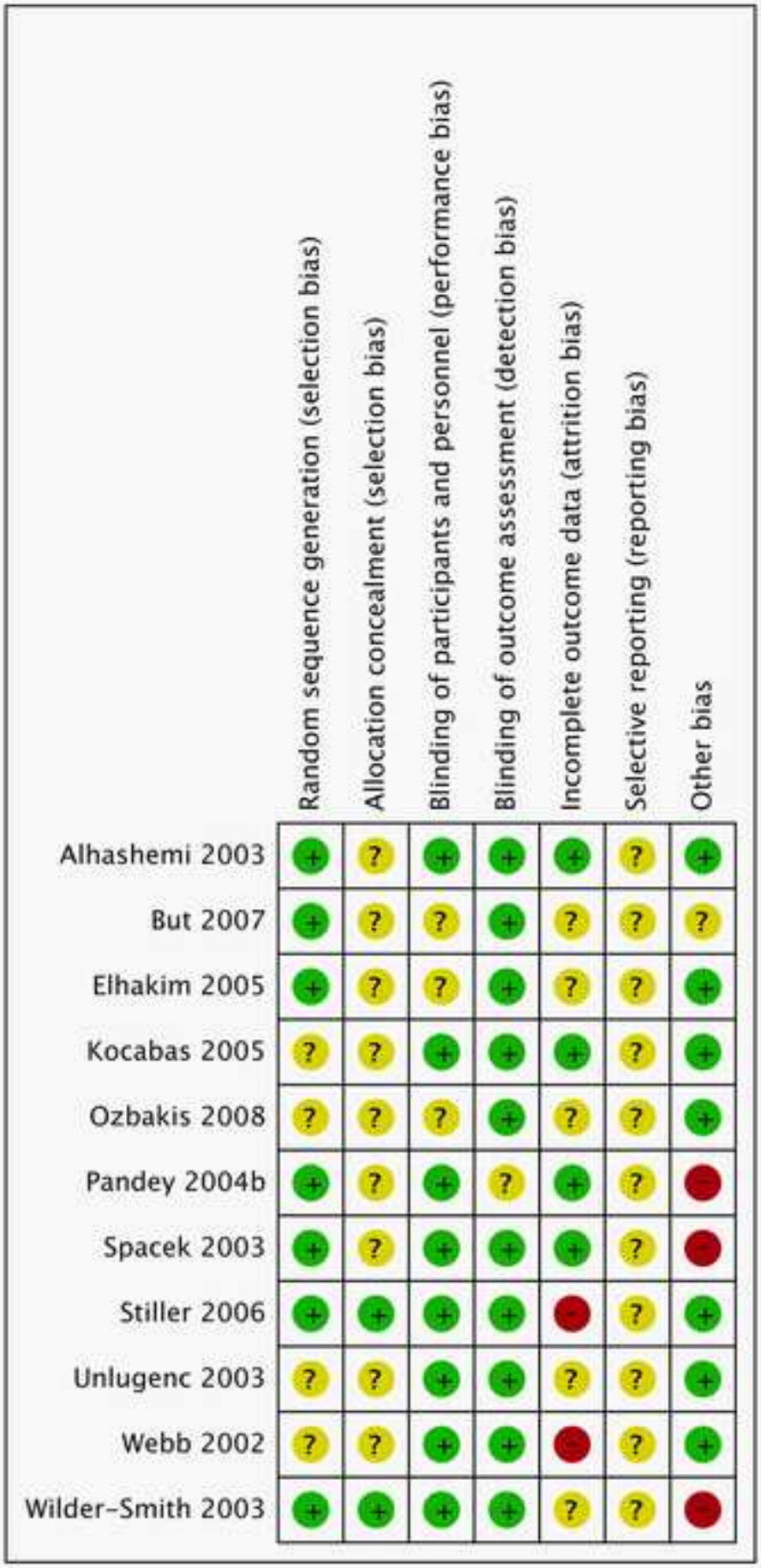

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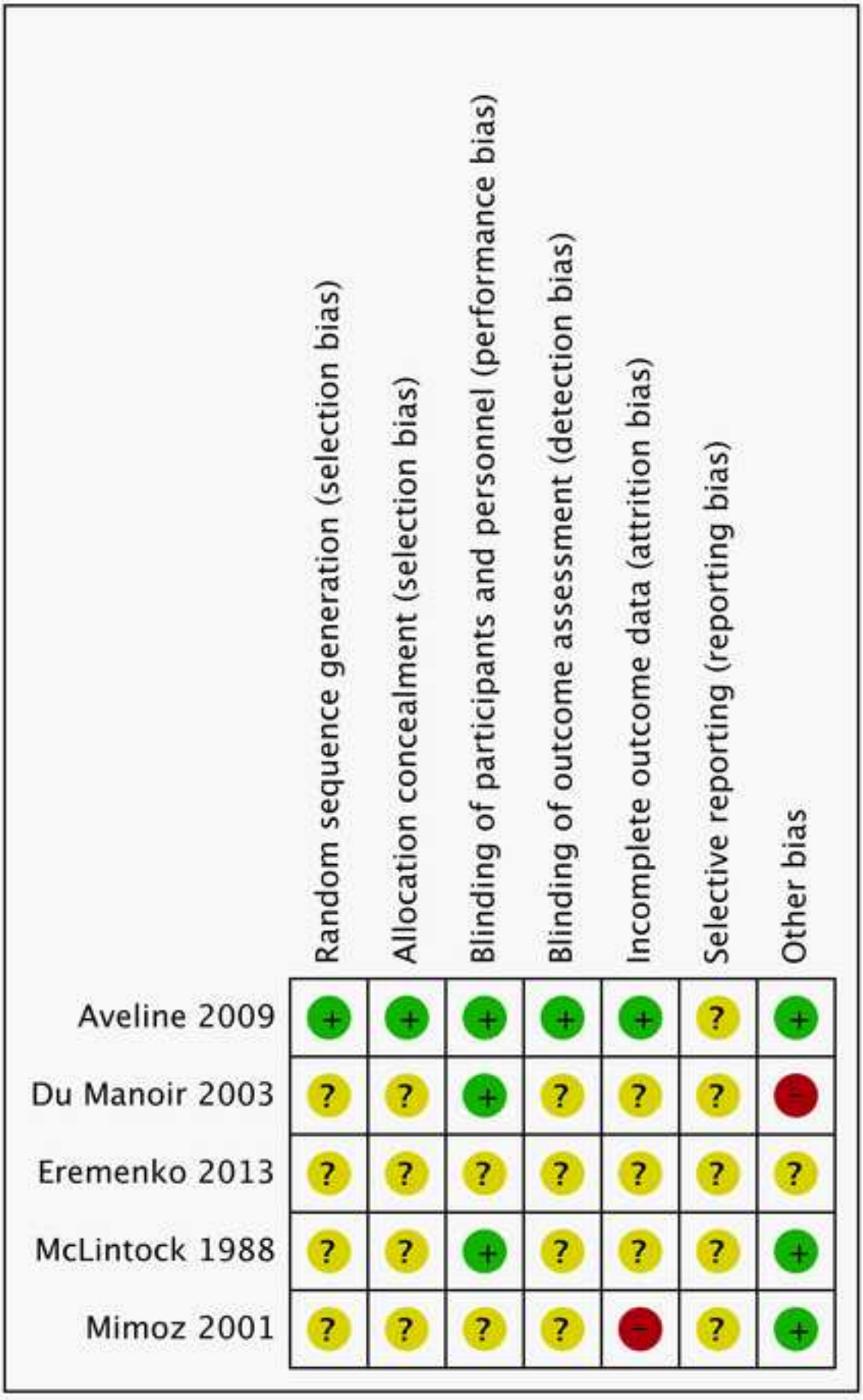

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