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Efficacy and safety of pharmacological treatments for patent ductus arteriosus closure: A systematic review and network meta-analysis of clinical trials and observational studies

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1 **Title:**

2 Efficacy and safety of pharmacological treatments for Patent Ductus Arteriosus closure: a
3 systematic review and network meta-analysis of clinical trials and observational studies

4

5 **Authors:**

6 Ettore Marconi^{1*}, PharmD, Alessandra Bettiol^{1*}, PhD, Giuseppe Ambrosio², MD, PhD, Vittorio
7 Perduca³, PhD, Alfredo Vannacci¹, MD, Stefania Troiani⁴, MD, Carlo Dani^{1,5}, MD, Alessandro
8 Mugelli¹, MD, Ersilia Lucenteforte⁶, PhD.

9

10 **Affiliations:**

11 ¹ Department of Neurosciences, Psychology, Drug Research and Child Health (NEUROFARBA),
12 University of Florence, 50139, Florence, Italy.

13 ² Division of Cardiology, University Hospital, Perugia, Italy

14 ³ Laboratoire de Mathématiques Appliquées - MAP5 (UMR CNRS 8145), Université Paris
15 Descartes, Paris, France

16 ⁴ Division Neonatology, University Hospital, Perugia, Italy

17 ⁵ Division of Neonatology, Careggi University Hospital of Florence, Florence, Italy

18 ⁶ Department of Clinical and Experimental Medicine University of Pisa, Pisa, Italy

19 * contributed equally

20

21 **Corresponding author:**

22 Ersilia Lucenteforte, ScD, PhD, Assistant Professor

23 ersilia.lucenteforte@unipi.it

24 Department of Clinical and Experimental Medicine University of Pisa

25 Via Savi, 10 – 56126 Pisa, Italy

26

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28

29 **ABSTRACT**

30 Efficacy and safety profiles of different pharmacological interventions used to treat patent ductus
31 arteriosus (PDA) are relatively unexplored. Integrating the findings of randomized clinical trials
32 (RCTs) with those from observational studies may provide key evidence on this important issue.

33 We aimed at estimating the relative likelihood of failure to close the PDA, need for surgical closure,
34 and occurrence of adverse events among preterm and full-term infants treated with indomethacin,
35 ibuprofen, or acetaminophen, placebo, or no treatment including both RCTs and observational
36 studies.

37 We searched PubMed, Embase, and the Register of Controlled Trials from inception to October 30,
38 2018. We first estimated proportions of subjects with failure to close the PDA, subjects in whom
39 surgical closure was performed after pharmacological treatment, death, and subjects with selected
40 adverse events (AEs). These estimates were obtained using frequentist random-effect meta-analysis
41 of arm-specific proportions. We then compared active drugs with each other and with control
42 (either placebo or no treatment) by summarizing results at the end of treatment reported in the
43 papers, regardless of number of administration(s), dose, route and type of administration, and study
44 design and quality. We also summarized primary outcome results separately at first, second and
45 third cycles of treatment. These estimates were obtained using Bayesian random-effects network
46 meta-analysis for mixed comparisons, and frequentist random-effect pairwise meta-analysis for
47 direct comparisons.

48 We included 64 RCTs and 24 observational studies including 14,568 subjects (5339 in RCTs and
49 9229 in observational studies, 8292 subjects received indomethacin, 4761 ibuprofen, 574
50 acetaminophen, and 941 control (including placebo or no intervention).The proportion of subjects
51 with failure to close the PDA was 0.24 (95% Confidence Interval, CI: 0.20, 0.29) for indomethacin,
52 0.18 (0.14, 0.22) for ibuprofen, 0.19 (0.09, 0.30) for acetaminophen, and 0.59 (0.48, 0.69) for

53 control . At end of treatment, compared to control, we found inverse associations between all active
54 drugs and failure to close PDA (for indomethacin Odds Ratio, OR, was 0.17 [95% Credible
55 Interval, CrI: 0.11-0.24], ibuprofen 0.19 [0.12-0.28], and acetaminophen 0.15 [0.09-0.26]), without
56 differences among active drugs. We showed inverse associations between effective drugs and need
57 for surgical closure, as compared to control (for indomethacin OR was 0.28 [0.15-0.50], ibuprofen
58 0.30 [0.16-0.54], and acetaminophen 0.19 [0.07-0.46]), without differences among drugs.
59 Indomethacin was directly associated with intraventricular hemorrhage (IVH) (1.27; 1.00, 1.62)
60 compared to ibuprofen, and to oliguria as compared to ibuprofen (3.92; 1.69, 9.82) or
61 acetaminophen (10.8; 1.86, 93.1).
62 In conclusion, active pharmacological treatment, with indomethacin, ibuprofen, or acetaminophen,
63 is inversely associated with failure to close the PDA compared to non-treatment. Quality of
64 evidence was moderate, high and low, respectively. Ibuprofen should be preferred to indomethacin
65 to avoid occurrence of IVH or oliguria, acetaminophen should be preferred to indomethacin to
66 avoid oliguria.

67

68 **Keywords**

69 adverse events; intraventricular hemorrhage; network meta-analysis; observational studies; oliguria;
70 patent ductus arteriosus.

71

72 **Chemical compounds**

73 Chemical compounds studied in this article were: Indomethacin (PubChem CID: 3715); Ibuprofen
74 (PubChem CID: 1983); Paracetamol/Acetaminophen (PubChem CID: 1983)

75

76 **Abbreviations**

77 AEs: adverse events

78 BPD: bronchopulmonary dysplasia

- 79 CI: confidence interval
- 80 CrI: credible interval
- 81 ECHO: echocardiographic
- 82 IV: intravenous
- 83 IVH: intraventricular hemorrhage
- 84 NMA: network meta-analysis
- 85 NSAIDs : non-steroidal anti-inflammatory drugs
- 86 OR: odds ratio
- 87 PDA: patent ductus arteriosus
- 88 RCTs: randomized clinical trials
- 89

90 1. BACKGROUND

91 In fetal life, the ductus arteriosus connects the pulmonary artery to the aorta, playing a central role
92 in the regulation of fetal circulation. At birth, when breathing begins, ductus arteriosus starts
93 closing. However, failure to close or reopening can occur. This condition, defined as patent ductus
94 arteriosus (PDA), has been associated in preterm infants with increased mortality and with major
95 complications, including metabolic acidosis, renal failure, intraventricular hemorrhage (IVH),
96 pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC),
97 prolonged ventilator dependence, and heart failure[1]. PDA is one of the most common
98 cardiovascular diseases in premature infants. It occurs in up to 33% and 65% in very low birth-
99 weight infants and extremely low birth-weight infants, respectively [2, 3].

100 Management of PDA is based on conservative treatments (i.e. fluid restriction, diuretics, etc.) while
101 waiting for spontaneous closure [4], pharmacological therapy with cyclooxygenase inhibitors, and
102 surgical closure [5].

103 A major issue in the management of patients with PDA is the choice of treatment, both in terms of
104 timing and type of treatment. The most common options for pharmacological closure of PDA are
105 indomethacin and ibuprofen. Indomethacin has been historically used as the main first-line therapy,
106 but it has been associated with several adverse events (AEs) (i.e. renal insufficiency, NEC) [6]. As
107 for ibuprofen, a recent meta-analysis demonstrated that it is as effective as indomethacin in closing
108 PDA, with significantly lower gastrointestinal and renal AEs, and recommended it as first-line
109 treatment [7].

110 More recently, acetaminophen has also been introduced in clinical practice for the management of
111 PDA, mainly in infants with contraindications to cyclooxygenase inhibitors. According to a recent
112 Cochrane systematic review, acetaminophen resulted comparable to ibuprofen in terms of efficacy,
113 with a better safety profile [8]. However, this approach still awaits definitive validation due to a
114 lack of data on long-term follow-up of acetaminophen-treated infants.

115 In 2018, a network meta-analysis (NMA) comparing the efficacy and safety of these three active
116 principles was published [9] and concluded that high-dose oral ibuprofen represented the most
117 effective pharmacotherapeutic option for PDA closure. However, that NMA included only RCTs.
118 As randomized allocation protects against bias and confounding effects that can undermine the
119 validity of the study, RCTs are the gold standard to evaluate drug efficacy. However, RCT design
120 may have limitations. In particular, due to strict inclusion criteria, RCTs may not provide a
121 representative picture of “real world” management of the disease. Moreover, RCTs, generally with
122 short follow-up and small sample size, are often inadequate to evaluate drug safety because only
123 frequent and acute AEs are usually assessed in these studies, whereas unknown, rare, and/or long-
124 term latency AEs are difficult to detect due to insufficient length of follow up. Thus, observational
125 studies may provide additional information also regarding safety. Another advantage of including
126 non-randomized studies is that network meta-analysis including studies with both designs allow to
127 improve density network and to connect disconnected drugs [10]. All these advantages may offer
128 opportunities to provide more comprehensive evidence about the comparative safety and
129 effectiveness of treatments.

130 We conducted a systematic review and NMA of both RCTs and observational studies, using a
131 Bayesian approach, for the comparison of the efficacy and safety profiles of the
132 pharmacotherapeutic options available for PDA treatment, namely indomethacin, ibuprofen, and
133 acetaminophen, with the aim of complementing current knowledge on this issue and contributing to
134 evidence-based drug selection.

135

136 2. METHODS

137 The protocol for this systemic review and network meta-analysis has been registered in the
138 PROSPERO database (CRD42016053487).

139

140 **2.1. Criteria for considering studies**

141 Types of studies: We considered RCTs and observational studies. We considered full-text
142 publications written in English, irrespective of date of publication.

143 Types of participants: We included studies performed on preterm infants (<37 weeks' gestational
144 age), full term (≥ 37 weeks' gestational age), low-birth-weight (<2500 g), and normal-weight infants
145 (≥ 2500 g), with PDA diagnosed either clinically or by echocardiographic (ECHO) criteria in the
146 neonatal period (<28 days).

147 Types of interventions: We considered studies employing any of the following pharmacological
148 treatments: ibuprofen; indomethacin; acetaminophen; no active intervention. For each intervention,
149 we considered:

150 i) the active principle;

151 ii) the route of administration: oral, intravenous (IV), or rectal;

152 iii) the type of IV infusion: rapid infusion (bolus over 1 min), standard infusion (over 5-30 min),
153 slow infusion (over 30-60 min), continuous infusion (CI, over 4-36 h);

154 iv) the type of administration: ECHO-guided administration (i.e. PDA status was verified after each
155 administration; if PDA closure occurred, no further dose was administered) vs non-ECHO-guided
156 administration (i.e. the whole course was administered independently of occurrence of PDA closure
157 before the end of the course).

158 v) cycle of treatment: number of times therapy was repeated, if any.

159 vi) the following treatment dosage scheme:

160 • For indomethacin:

161 - Low dose (total intake ≤ 0.30 mg/kg; max duration of treatment: 3 days): 0.1 mg/kg x 3
162 doses, every 12 or 24 h; 0.15 mg/kg x 2 doses at 12-h interval; 1 dose of 0.2 mg/kg.

163 - Intermediate dose (total intake between 0.40 and 0.70 mg/kg; max duration of

164 treatment: 3 days): 0.2 mg/kg x 3 doses every 12 or 24 h; 0.2 mg/kg x 1 dose + 0.1

- 165 mg/kg x 2 doses every 12 or 24 h; 0.2 mg/kg x 1 dose + 0.25 mg/kg x 2 doses every 12
166 or 24 h; 0.2 mg/kg x 2 doses at 24- h interval; 0.25 mg/kg x 2 doses at 24-h interval.
- 167 - High dose (total intake >0.70 mg/kg): 0.30 mg/kg x 3 doses at 24-h interval (schedule
168 intervals not further specified).
- 169 - Prolonged treatment (total intake of 0.60-0.80 mg/kg; duration of treatment: 6-7 days):
170 0.1 mg/kg x 6 doses at 24-h interval; 0.1 mg/kg x 7 doses at 24-h interval; 0.15 mg/kg x
171 2 doses at 12-h interval + 0.1 mg/kg x 5 doses at 24-h interval).
- 172 • For ibuprofen:
- 173 - Low dose: 1 dose of ibuprofen 10 mg/kg.
- 174 - Intermediate dose (total intake of 20 mg/kg): 10 mg/kg x 1 dose + 5 mg/kg x 2 doses,
175 every 12 or 24 h.
- 176 - High dose (total intake between 30-40 mg/kg): 20 mg/kg x 1 dose + 10 mg/kg x 2
177 doses, every 12 or 24 h; 10 mg/kg x 3 doses, at 24-h interval.
- 178 • For acetaminophen:
- 179 - Intermediate dose (total intake <200 mg/kg; duration 3-4 days): 15 mg/kg every 6 h for
180 3 days (tot: 195 mg/kg); 20 mg/kg x 1 dose + maintaining doses of 7.5 mg/kg every 6 h
181 for 4 days (145 mg/kg); 10 mg/kg every 6 h for 3 days (tot: 130 mg/kg).
- 182 - Prolonged treatment (total intake >400 mg/kg; duration 7 days): 15 mg/kg every 6 h for
183 7 days (tot: 435 mg/kg).

184 All these parameters were analyzed separately in subgroup analysis.

185 Types of outcome measures: We assessed benefits and harm of pharmacological interventions by
186 evaluating the following outcomes: failure to close PDA (according to ECHO criteria and/or
187 clinical evaluation) as primary outcome; need for surgical PDA closure, death, and occurrence of
188 selected AEs, as secondary outcomes. AEs were defined as any untoward medical occurrence, or
189 death, not necessarily having a causal relationship with treatment. Based on biological plausibility

190 and expert clinical consensus, we considered the following AEs: NEC, Intestinal perforation,
191 Gastrointestinal bleeding, BPD, IVH, Periventricular leukomalacia, and Oliguria.

192

193

194 **2.2. Search methods for identification of studies**

195 Electronic searches: We searched PubMed and Embase from inception to October 30, 2018 for
196 studies comparing two or more of the above interventions on infants with PDA. To identify
197 additional trials, we also searched ClinicalTrials.gov. Full search strategies are available in
198 *Appendix 1*. Briefly, two search themes were combined using the Boolean operator “AND”: the
199 first theme about drugs (i.e. Non-Steroidal Anti-Inflammatory Drugs - NSAIDs, acetaminophen,
200 ibuprofen, indomethacin), and the second theme about condition (i.e. patent ductus arteriosus).

201 Papers selection: EndNote Basic software was used to manage the records retrieved from the
202 searches. Two authors (EM, AB) independently identified studies for inclusion by screening titles
203 and abstracts yielded from the search. We retrieved the full-text of all articles that at least one of the
204 review authors had identified for potential inclusion. We selected studies for inclusion on the basis
205 of review of full-text articles. Discrepancies were resolved through consensus.

206

207 **2.3. Data extraction and management**

208 Two authors (EM, AB) independently extracted the following data:

- 209 1. Treatment data: active principle; route of administration; type of IV infusion (when
210 appropriate); ECHO- or non-ECHO-guided administration; cycles of treatment; dosage.
- 211 2. Outcome data: number of randomized participants and number of participants included in the
212 analysis (for RCTs); number of participants with events for binary outcomes; definition of
213 outcomes, if appropriate.
- 214 3. Data on potential effect modifiers: participants’ characteristics, such as age, gender; assessment
215 of bias risk.

216 4. Other data: study design; year of publication; country in which participants were recruited;
217 follow-up time; funding sources.

218 Assessment of risk of bias: To assess the risk of bias of RCTs, we followed the *Cochrane*
219 *Handbook for Systematic Reviews of Interventions* [11]. Specifically, we assessed risk of bias for
220 the following domains: selection (random sequence generation; allocation concealment);
221 performance (blinding of participants and personnel); detection (blinding of outcome); attrition
222 (incomplete outcome data); reporting (selective reporting); other unclear bias. To assess the risk of
223 bias of observational studies, we followed the *Newcastle-Ottawa Quality Assessment Scale* [12].
224 Specifically, for cohort studies, we assessed risk of bias for the following domains: selection
225 (representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of
226 exposure; lack of definition of pre-defined end-point); comparability; outcome (assessment of
227 outcome; appropriate length of follow-up; adequacy of follow-up of cohorts).

228

229 **2.4. Data analysis**

230 We first estimated proportions of subjects with failure to close the PDA, subjects in whom surgical
231 closure was performed after pharmacological treatment, deaths, and subjects with selected AEs.

232 We defined proportion as number of subjects reporting the selected events divided by total number
233 of subjects. We considered studies comparing two active drugs or one drug with control (placebo or
234 no treatment), and studies comparing the same drugs at different doses, routes or types of
235 administration, and types of infusion.

236 We conducted a random effect frequentist meta-analysis of arm-specific proportions using the
237 arcsine transformation for arm-specific proportions, the 95% Clopper-Pearson Confidence Interval,
238 CI, for arm-specific CI, the inverse variance method for pooling the overall proportion, and the
239 DerSimonian-Laird method for estimation of the between-study variance. We used the “metaprop”
240 routine within the META R package [13]. Results are presented as pooled proportions with 95%
241 Confidence Interval (CI).

242 We then compared drugs with each other and with control by meta-analyzing studies that
243 comparing two active drugs or one drug with control (placebo or no treatment) and by considering
244 results reported at the end of the treatment (i.e. last cycle of treatment) regardless of route and type
245 of administration, type of infusion, dose, and study design and quality. Thus, we did not consider
246 studies comparing the same drugs at different doses, routes or types of administration, and types of
247 infusion).

248 We also considered separately the first, second, and third cycle of treatment for failure to close
249 PDA, and compared route and type of administration, type of infusion, and dose within active
250 principle for failure to close PDA and need of surgical closure. We performed a network meta-
251 analysis with the aim of simultaneously analyzing direct comparisons of interventions within
252 studies (subject of conventional pairwise meta-analysis), and indirect comparisons across studies. If
253 the efficacy of two interventions (A and B) is to be compared but no studies comparing them are
254 available, indirect evidence can be obtained by studying either A or B versus a common
255 comparator. When both direct and indirect evidence were available (mixed comparison), the
256 information was combined. The network maps show which interventions are directly compared
257 with each other and depict how much information is available for each drug and for each
258 comparison. For mixed-treatment comparison, we performed a random-effect NMA within a
259 Bayesian framework using the GeMTC (Generate Mixed Treatment Comparisons) R package
260 (<https://CRAN.R-project.org/package=gemtc>) [14]. We simultaneously ran four chains with
261 different arbitrarily-chosen initial values, with a variance scaling factor of 2.5. Convergence and
262 lack of autocorrelation were checked and confirmed after 20,000 iterations with thinning interval
263 equal to 1, followed by 50,000 iterations to estimate parameters. We used default noninformative
264 values for priors, and default values for the likelihood and link functions (suitable for the data).
265 Results are presented as Odds Ratios (ORs) and their 95% Credible Intervals (CrIs), the Bayesian
266 equivalent to Confidence Intervals (CIs). For direct comparisons, we performed a random-effects
267 pairwise meta-analysis within the frequentist approach using the Mantel-Haenszel method for

268 pooling, continuity correction of 0.5 in studies with zero cell frequencies, and the DerSimonian-
269 Laird method for estimation of the between-study variance. We used the routine “metabin” within
270 the META R package ([https://CRAN.R- project.org/package=meta](https://CRAN.R-project.org/package=meta)) [13]. Results are presented as
271 ORs and their 95% CIs.

272 We assessed heterogeneity in meta-analyses of arm-specific proportions and in pairwise meta-
273 analyses of direct comparisons with the Cochrane Q test.

274 We assessed inconsistency in network meta-analysis with node-splitting analysis.

275 We assessed robustness of results by performing subgroup analysis by study design (RCTs versus
276 observational studies).

277 We assessed similarity between RCTs and observational studies by comparing pairwise meta-
278 analyses of direct comparisons limited to RCTs with those limited to observational studies.

279 A p-value < 0.05 was considered statistically significant.

280

281 3. RESULTS

282 The reference flow is summarized in the study flow diagram (*Fig. 1*). We identified 5,395
283 references through electronic searches of PubMed (n=1760), Embase (n=3590) and
284 ClinicalTrials.gov (n=45). After removing 1592 duplicates, 3803 references were screened. We
285 excluded 3275 irrelevant references by reading titles and abstracts. We retrieved 528 full-text
286 references, of which 437 were excluded as detailed in Figure 1. In total, 88 references met inclusion
287 criteria, 64 were RCTs [15-78] and 24 observational studies [79-102]. All observational studies
288 included had a cohort design. The intervention strategies of the 88 included studies are reported in
289 *Appendix 2*.

290 Data on efficacy outcome, defined as failure to close PDA, were available for 83 studies (63 RCTs,
291 20 observational studies), and 59 studies (46 RCTs, 13 observational studies) compared two or
292 more interventions (*Appendix 3*). Data about the need for PDA surgical closure were available for
293 54 studies (36 RCTs, 18 observational studies), and 34 studies (22 RCTs, 12 observational studies)

294 compared two or more interventions. Data on safety were reported in 71 studies (51 RCTs, 20
295 observational studies); 42 studies (30 RCTs, 12 observational studies) compared two or more
296 interventions in terms of death; 39 studies (28 RCTs, 11 observational studies) compared two or
297 more interventions in terms of NEC; 14 studies (7 RCTs, 7 observational studies) compared two or
298 more interventions in terms of intestinal perforation; 17 studies (14 RCTs, 3 observational studies)
299 compared two or more interventions in terms of gastrointestinal bleeding; 29 studies (21 RCTs, 8
300 observational studies) compared two or more interventions in terms of BPD; 34 studies (26 RCTs, 8
301 observational studies) compared two or more interventions in terms of IVH; 14 studies (11 RCTs, 3
302 observational studies) compared two or more interventions in terms of periventricular leukomalacia;
303 and 12 studies (9 RCTs, 3 observational studies) compared two or more interventions in terms of
304 oliguria.

305 Overall, 14,568 subjects were investigated (5339 in RCTs and 9229 in observational studies).
306 Median follow-up was 18 (range 0.5-70) months for RCTs, and 53 (11-120) months for
307 observational studies. With respect to intervention, 8292 subjects received indomethacin, 4761
308 ibuprofen, 574 acetaminophen, and 941 control, including placebo or no intervention.

309

310 **3.1. Risk of bias**

311 30 RCTs were judged at high risk of performance bias [15-18, 20, 21, 25-28, 30, 31, 35, 39, 42, 44,
312 45, 47, 48, 53, 57, 59-62, 64, 70, 73, 74, 77], 11 at high risk of attrition bias [15, 22, 23, 31, 35, 44,
313 54, 56, 60, 62, 69], 12 at high risk of detection bias [18, 21, 26-28, 48, 53, 57, 61, 70, 73, 74], and
314 three at high risk of selection bias (either considering randomization or allocation) [52, 54, 55]
315 (*Appendix 4 and Appendix 5*). Nineteen studies were at high risk of bias in at least two items, 27
316 were at low/unclear risk of bias in all items, and two studies had low risk of bias in all items.
317 Selective reporting bias was the least reported domain, with no studies judged at high risk.
318 Considering observational studies, all 24 studies had a cohort design. Based on the *Newcastle-*
319 *Ottawa Quality Assessment Scale* for this type of study design, 12 studies obtained a score of 9 out

320 of 9 [79-81, 84, 89, 91, 93-95, 97, 99, 101], nine had a score of 8 [83, 85, 86, 88, 92, 96, 98, 100,
321 102], two studies a score of 7 [82, 87], and one a score of 6 [90] (*Appendix 6*).

322

323 **3.2. Efficacy - failure to close PDA**

324 The proportion of subjects with failure to close the PDA was 0.24 (95% CI: 0.20, 0.29) for
325 indomethacin, 0.18 (0.14, 0.22) for ibuprofen, 0.19 (0.09, 0.30) for acetaminophen, and 0.59 (0.48,
326 0.69) for control (*Table 1*).

327 Fifty-nine studies compared the efficacy of different active principles to treat PDA (*Fig. 2a*). At last
328 cycle of treatment, we found an inverse association between active principles and failure to close
329 PDA as compared to control (OR was 0.17 [95% CI: 0.11, 0.24] for indomethacin, 0.19 [0.12, 0.28]
330 for ibuprofen, and 0.15 [0.09, 0.26] for acetaminophen), with no differences among them (*Table 2*).

331 All direct evidences contributing to the meta-analyses that showed the above significant ORs came
332 from RCTs: 2 studies for acetaminophen versus control, 6 studies for ibuprofen versus control, and
333 10 studies for indomethacin versus control (*Appendix 2*). The overall quality of these RCTs was
334 moderate for acetaminophen versus control (1 out of 2 studies was judged at high risk of
335 performance and detection bias, *Appendix 5*) and indomethacin versus control (6 out of 10 studies
336 were judged at high risk of selection or attrition or performance bias), and high for ibuprofen
337 versus control (1 out of 6 studies was judged at high risk of performance and detection bias).

338 Regarding cycle of treatment, we observed similar effectiveness of studied drugs for both the first
339 and second pharmacological course (*Table 2*). Data for the third cycle were scanty and the control
340 arm was missing, thus, it was not possible to compare results of this cycle with those of the last
341 cycle of treatment. Direct comparisons confirmed the results of mixed comparisons.

342 When we limited analysis to RCTs (*Appendix 7*) these results were confirmed, as we found no
343 association between failure to close PDA and different routes of administration, dosages or
344 procedures for indomethacin (*Appendix 8*) and ibuprofen (*Appendix 9*). No study tested different
345 routes of administrations, dosages or procedures for acetaminophen. When we compared results of

346 direct comparisons from RCTs and observational studies (*Appendix 7*), similarity between study
347 designs was observed.

348

349 **3.3. Need for surgical closure**

350 The proportion of subjects in whom surgical closure was performed after pharmacological
351 treatment was 0.12 (95% CI: 0.10, 0.15) for indomethacin, 0.09 (0.06, 0.12) for ibuprofen, 0.03
352 (0.00, 0.15) for acetaminophen, and 0.18 (0.08, 0.31) for control (*Table 1*).

353 Thirty-four studies compared the proportion of surgical PDA closure for different drugs (*Fig. 2b*).
354 Mixed comparisons showed inverse associations between active principles and need for surgical
355 closure as compared to control (OR was 0.28 [95%CrI: 0.15, 0.50] for indomethacin, 0.30 [0.16,
356 0.54] for ibuprofen, and 0.19 [0.07, 0.46] for acetaminophen), without significant differences
357 among drugs (*Table 2*).

358 Direct comparisons confirmed the results of mixed comparisons.

359 These results were confirmed when we limited analysis to RCTs (*Appendix 7*), and we found no
360 association between surgical PDA closure and different routes of administrations, dosages or
361 procedures of indomethacin (*Appendix 8*) and ibuprofen (*Appendix 9*). No study tested different
362 routes of administration, dosages or procedures of acetaminophen.

363 When we compared results of direct comparisons from RCTs and observational studies (*Appendix*
364 *7*), similarity between study designs was observed.

365

366 **3.4. Safety**

367 The proportion of deaths ranged between 0.09 and 0.11 for acetaminophen, ibuprofen and
368 indomethacin, and it was 0.13 for control (*Table 1*). Many different AEs were reported in the
369 included studies (*Appendix 3*).

370 The proportions of subjects with NEC, intestinal perforation, gastrointestinal bleeding, and
371 periventricular leukomalacia were between 0.02 and 0.11 (*Table 1*). High proportions were

372 observed for BDP in subjects treated with indomethacin (0.39), ibuprofen (0.31), and control (0.29),
373 for IVH in subjects treated with indomethacin (0.17), ibuprofen or acetaminophen (0.12) or control
374 (0.18), and for oliguria in subjects treated with indomethacin (0.20) or control (0.28).

375 No significant association was found for the above AEs and active principles, with the exception of
376 IVH and oliguria (**Table 3**). Indomethacin was directly associated with IVH (OR=1.27; 95% CrI:
377 1.00, 1.62) as compared to ibuprofen, and with oliguria as compared to ibuprofen (3.92 [1.69, 9.82])
378 or acetaminophen (10.8 [1.86, 93.31]).

379 These results were confirmed when we limited analysis to RCTs (**Appendix 10**). When we
380 compared results of direct comparisons from RCTs and observational studies, similarity between
381 study designs was observed with exception of indomethacin vs ibuprofen (though p-values from
382 heterogeneity test for subgroup differences were not significant) regarding death, intestinal
383 perforation and oliguria where direct RCT evidence produces pooled OR of 1.05 (0.69, 1.59) while
384 observational evidence 0.74 (0.63, 0.86) for death, 1.16 (0.44, 3.04) and 0.47 (0.35, 0.63) for
385 intestinal perforation, 3.75 (1.74, 8.07) and 2.69 (0.79,9.10) for oliguria.

386

387 **4. DISCUSSION**

388 To the best of our knowledge, this is the first NMA that systematically assesses the efficacy and
389 safety of indomethacin, ibuprofen, and acetaminophen in closing PDA in preterm infants through
390 analysis of both RCTs and observational studies.

391 In our NMA, indomethacin, ibuprofen and acetaminophen had similar effect on failure to close the
392 PDA closure and decreasing the need for surgical closure, independent from the treatment cycle.

393 We can judge the superiority of ibuprofen over control with high quality of evidence (RCTs with
394 overall high quality), the superiority of indomethacin over control with moderate quality of
395 evidence (RCTs with overall moderate quality), and the superiority of acetaminophen over control
396 with low quality of evidence (only 2 RCTs with overall moderate).

397 All routes of administration, dosages, and ECHO- or non-ECHO-guided administrations were found
398 to have similar efficacy within the same medication. Occurrence of NEC, intestinal perforation,
399 gastrointestinal bleeding and periventricular leukomalacia was low (below 0.11) among the three
400 treatments. The most frequently reported AEs were BPD for indomethacin (0.39), ibuprofen (0.31),
401 and control (0.29), IVH for indomethacin (0.17), ibuprofen or acetaminophen (0.12) and control
402 (0.18), and oliguria (a proxy of acute renal failure) for indomethacin (0.20) and control (0.28). In
403 the comparison analysis, we found a direct association between indomethacin and IVH compared to
404 ibuprofen, and between indomethacin and oliguria compared to ibuprofen or acetaminophen,
405 confirming its poorest safety profile.

406 To date, only one NMA compared the efficacy and safety profiles of indomethacin, ibuprofen, and
407 acetaminophen in closing PDA [9]. That NMA was performed only on RCTs, including 4802
408 infants, and concluded that a high dose of oral ibuprofen was associated with higher rates of PDA
409 closure compared to standard dose of intravenous ibuprofen (OR 3.59; 95%CrI 1.64 -8.17) or
410 indomethacin (2.35; 1.08-5.31). Moreover, no significant differences in the odds of mortality, NEC,
411 IVH, and oliguria were found between pharmacological treatments and control groups. These
412 results seem partly at variance with our findings, but actually they cannot be directly compared as
413 our NMA was based on a much larger number of subjects, included observational studies as well,
414 and evaluated the possible effect of administration route within drug. Furthermore, in the cited
415 NMA, the superiority of a high dose of oral ibuprofen was mostly driven by the results of just three
416 RCTs [22, 62, 103] ; of note, those results cannot be easily translated into clinical practice due to
417 limited availability of oral ibuprofen and, mainly, of limited use of high ibuprofen doses.

418 On the other hand, our results are in partial agreement with a Cochrane review published in 2018
419 [7] concluding that ibuprofen is as effective as indomethacin in closing PDA while reducing the risk
420 of NEC and transient renal insufficiency, and with another Cochrane review published in 2018
421 [104] concluding that paracetamol is as effective as ibuprofen in closing a PDA, with a possibly
422 lower risk of gastrointestinal and renal AEs.

423 Pharmacological treatment of PDA has changed over recent decades with the introduction of
424 ibuprofen and quite recently of acetaminophen as alternatives to the traditional approach based on
425 indomethacin.

426 The favorable results of acetaminophen may have a pharmacological explanation as it is now clear
427 that, contrary to a long-held tenet, acetaminophen also inhibits cyclo-oxygenase, thus explaining its
428 efficacy in favoring PDA closure [105]. Our study reinforces the notion that active pharmacological
429 treatment is superior to non-treatment in decreasing the risks of unfavorable clinical conditions
430 associated with PDA, such as an increase of pulmonary blood flow and edema, and a decrease of
431 renal, mesenteric and cerebral perfusion. Similarly, by decreasing the need for surgical closure,
432 effective pharmacological therapy avoids surgical risks and postoperative complications [106].

433 However, despite the higher rates of failure to close PDA, we observed that controls had similar
434 mortality as well as similar risk of overall AEs in comparison with active treatments. On the other
435 hand, it has been previously reported that the lack of improvement in preterm infants' outcomes in
436 trials on PDA treatment may reflect several possible factors, such as the inaccurate assessment of
437 hemodynamic significance of PDA in studied infants, and the 50-70% cross-over of placebo-
438 assigned infants to the active treatment group [107]. Thus, the "treatment" versus "no treatment"
439 RCTs may not accurately capture the morbidity effects of PDA in preterm infants [108, 109].

440 The present study has some limitations. First, this NMA was based on the assumption that baseline
441 clinical characteristics were largely similar among different studies comparing different
442 medications. Variations in gestational age, birth weight, timing of treatment, comorbidities and co-
443 treatments may have influenced our results. More important, the inclusion of both preterm and term
444 infants in the review could substantially affect interpretation of results as the physiology, natural
445 history and management of PDA are different in the two populations. Second, the no risk-adjusted
446 estimates from the included observational studies may have influenced our results even if no
447 differences were observed between results from RCTs and those from observational studies. Third,

448 limited sample size of studies evaluating specific AEs or types of intervention may have resulted in
449 imprecision in estimating proportions, precluding the derivation of meaningful inferences.

450

451 **5. CONCLUSIONS**

452 In conclusion, our NMA confirms that pharmacological treatment with either indomethacin,
453 ibuprofen or acetaminophen is effective (with moderate, high and low quality of evidence,
454 respectively) in closing PDA and limiting PDA surgical closure in comparison with non-treatment.
455 Ibuprofen limits the risk of IVH and oliguria in comparison to indomethacin; acetaminophen pose
456 less risk of oliguria in comparison to indomethacin. We are confident that ongoing further RCTs,
457 comparing short-term effects on PDA closure and safety and long-term effects on
458 neurodevelopmental outcome, in preterm infants treated with ibuprofen or paracetamol will support
459 evidence-based neonatologists' prescription choices.

460

461 **Author Contributions**

462 EM and AB contributed equally to the study.

463 EL had full access to all data and took responsibility for its integrity and the accuracy of its
464 analysis.

465 Study concept and design: GA, CD, AM, and EL.

466 Administrative, technical, or material support and acquisition of data: EM and AB.

467 Statistical analysis: VP and EL.

468 Drafting of the manuscript: EM, AB, and EL.

469 Critical revision of the manuscript for important intellectual content: All authors.

470 Study supervision: EL.

471

472 **Conflict of Interest Disclosures**

473 EM, AB, VP, AV, ST, and EL have no conflict of interest to declare. GA has served as a consultant
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819

820 **Figure legends**

821 **Figure 1.** Study flow diagram, retrieved on October 30, 2018.

822 **Figure 2.** Direct comparisons of interventions among included studies evaluating a) failure to close PDA,
823 n=59 studies; and b) the need for surgical intervention, n=34 studies).

824 Node size is proportional to the number of direct treatment comparisons which include that node, edge size is
825 proportional to the number of direct treatment comparisons.

826 a) Failure to close the PDA (2 studies compared acetaminophen with indomethacin, 10 with ibuprofen,
827 and 2 with control; 31 studies compared indomethacin with ibuprofen, and 10 with control; 6 studies
828 compared ibuprofen with control).

829 b) Need for surgical closure (1 study compared acetaminophen with indomethacin, 3 with ibuprofen; 23
830 studies compared indomethacin with ibuprofen, and 6 with control; 3 studies compared ibuprofen
831 with control).

832

833

834 **Table 1.** Meta-analysis of proportions of failure to close PDA, need for surgical PDA closure and occurrence
 835 of selected adverse events stratified according to intervention.

	Number of study-arms	proportion ^a (95% CI)
Failure to close PDA		
Indomethacin	64	0.24 (0.20, 0.29)
Ibuprofen	76	0.18 (0.14, 0.22)
Acetaminophen	13	0.19 (0.09, 0.30)
Control	18	0.59 (0.48, 0.69)
Need of surgical closure		
Indomethacin	45	0.12 (0.10, 0.15)
Ibuprofen	52	0.09 (0.06, 0.12)
Acetaminophen	3	0.03 (0.00, 0.15)
Control	9	0.18 (0.08, 0.31)
Death		
Indomethacin	46	0.11 (0.10, 0.13)
Ibuprofen	50	0.10 (0.08, 0.12)
Acetaminophen	8	0.09 (0.04, 0.17)
Control	12	0.13 (0.09, 0.19)
Necrotizing enterocolitis (NEC)		
Indomethacin	42	0.08 (0.06, 0.11)
Ibuprofen	53	0.06 (0.05, 0.08)
Acetaminophen	10	0.05 (0.01, 0.11)
Control	8	0.03 (0.01, 0.05)
Intestinal perforation		
Indomethacin	16	0.02 (0.01, 0.04)
Ibuprofen	21	0.03 (0.01, 0.04)
Control	3	0.02 (0.00, 0.08)
Gastrointestinal bleeding		
Indomethacin	20	0.11 (0.06, 0.17)
Ibuprofen	27	0.04 (0.02, 0.07)
Acetaminophen	6	0.03 (0.00, 0.09)
Control	4	0.04 (0.00, 0.19)
Bronchopulmonary dysplasia (BPD)		
Indomethacin	23	0.39 (0.32, 0.46)
Ibuprofen	32	0.31 (0.24, 0.39)
Acetaminophen	7	0.08 (0.02, 0.17)
Control	8	0.29 (0.13, 0.48)
Intraventricular haemorrhage (IVH)		
Indomethacin	30	0.17 (0.14, 0.22)
Ibuprofen	40	0.12 (0.10, 0.15)
Acetaminophen	10	0.12 (0.06, 0.19)
Control	6	0.18 (0.07, 0.33)
Periventricular leukomalacia		
Indomethacin	15	0.06 (0.04, 0.09)

Ibuprofen	14	0.06 (0.04, 0.08)
Acetaminophen	4	0.05 (0.00, 0.17)
Control	3	0.04 (0.01, 0.08)
Oliguria		
Indomethacin	17	0.20 (0.14, 0.28)
Ibuprofen	27	0.03 (0.01, 0.06)
Acetaminophen	3	0.08 (0.02, 0.19)
Control	1	0.28 (0.13, 0.47)

836 ^a Estimates obtained by random effect meta-analysis of arm-specific proportions using the arcsine
837 transformation for arm-specific proportions, the 95% Clopper-Pearson Confidence Interval for arm-
838 specific Confidence Intervals, the inverse variance method for pooling, and the DerSimonian-Laird
839 method for between-study variance.
840 CI: Confidence Interval
841
842
843
844

Table 2. Comparison of active principles and controls on **failure to close PDA** and **need for surgical PDA closure**, overall and stratified according to cycle of treatment.

Failure to close PDA			
Last cycle			
Indomethacin	0.88 (0.71, 1.11), 31 studies ¹	1.22 (0.54, 2.74), 2 studies ²	0.17 (0.13, 0.24) , 10 studies ³
0.89 (0.68, 1.17)	Ibuprofen	1.02 (0.72, 1.44), 10 studies ⁴	0.27 (0.11, 0.64)^a , 6 studies ⁵
1.09 (0.66, 1.79)	1.22 (0.77, 1.91) ^b	Acetaminophen	0.07 (0.00, 2.18) ^c , 2 studies ⁶
0.17 (0.11, 0.24)	0.19 (0.12, 0.28)	0.15 (0.09, 0.26)	Control
1st cycle			
Indomethacin	0.77 (0.64, 0.93) , 26 studies ⁷	1.11 (0.41, 3.06), 2 studies ⁸	0.16 (0.12, 0.22) , 8 studies ⁹
0.78 (0.63, 0.98)	Ibuprofen	1.19 (0.88, 1.60), 10 studies ¹⁰	0.18 (0.04, 0.72)^d , 4 studies ¹¹
0.97 (0.66, 1.41)	1.25 (0.89, 1.73)	Acetaminophen	1.15 (0.02, 0.88) , 2 studies ¹²
0.15 (0.11, 0.21)	0.19 (0.13, 0.28)	0.15 (0.10, 0.25)	Control
2nd cycle			
Indomethacin	1.15 (0.79, 1.69), 12 studies ¹³	1.10 (0.47, 2.53), 1 study ¹⁴	1.14 (0.09, 0.22), 2 studies ¹⁵
1.26 (0.84, 1.99) ^d	Ibuprofen	1.24 (0.81, 1.89), 6 studies ¹⁶	-
1.82 (0.94, 3.81)	1.45 (0.79, 2.72) ^e	Acetaminophen	0.01 (0.00, 0.06) , 1 study ¹⁷
0.08 (0.03, 0.20)^f	0.07 (0.02, 0.17)	0.04 (0.01, 0.12)^g	Control
3rd cycle			
Indomethacin	1.87 (0.55, 6.36), 3 studies ¹⁸	-	
2.52 (0.51, 25.61)	Ibuprofen	0.44 (0.02, 12.01), 1 study ¹⁹	
1.854e-06 (1.376e-21, 5.77)	6.921e-07 (5.88e-22, 1.71)	Acetaminophen	
Need for surgical PDA ligation			
Indomethacin	0.90 (0.80, 1.00), 23 studies ²⁰	1.10 (0.47, 2.53), 1 study ²¹	0.35 (0.15, 0.79) , 6 studies ²²
0.92 (0.79, 1.12)	Ibuprofen	1.66 (0.80, 3.47), 3 studies ²³	0.32 (0.04, 2.26), 3 studies ²⁴
1.48 (0.76, 3.30)	1.59 (0.81, 3.50)	Acetaminophen	-
0.28 (0.15, 0.50)	0.30 (0.16, 0.54)	0.19 (0.07, 0.46)	Control

846 Data are reported as odds ratios (ORs) and 95% credible intervals for mixed comparisons and 95% confidence intervals for direct ones. Mixed ORs are shown in the triangle
847 below the diagonal and direct ORs are shown in the triangle above the diagonal. Significant results are in bold.

848 ^a p-value for heterogeneity =0.01; ^b p-value for inconsistency=0.02; ^c p-value for heterogeneity =0.001; ^d p-value for inconsistency=0.04; ^e p-value for inconsistency=0.04; ^f p-
849 value for inconsistency=0.03

850 1[18, 27, 34, 36, 42, 45, 48, 51, 53, 58, 59, 61, 68, 70, 71, 73, 74, 76, 78-81, 84, 86, 88, 91, 93-96, 101]; 2[30, 34]; 3[37, 40, 44, 47, 52, 54-56, 65, 75]; 4[17, 20, 22, 23, 28,
851 33, 34, 57, 76, 82]; 5[16, 19, 32, 38, 66, 67]; 6[21, 43]; 7[18, 27, 34, 36, 42, 45, 48, 51, 53, 58, 59, 61, 68, 70, 71, 73, 74, 76, 79, 81, 84, 86, 88, 91, 94-96, 101]; 8[30, 34];
852 9[37, 47, 52, 54-56, 65, 75]; 10[17, 20, 22, 23, 28, 33, 34, 57, 76, 82]; 11[16, 19, 32, 38, 66]; 12[21, 43]; 13[34, 36, 42, 48, 68, 76, 81, 91, 95, 96, 101]; 14[34]; 15[37, 40];
853 16[17, 22, 23, 28, 33, 34]; 17[21]; 18[36, 81, 91]; 19[17]; 20[34, 42, 45, 48, 51, 68, 70, 73, 74, 76, 78, 80, 81, 84, 86-90, 92, 93, 96, 101]; 21[34]; 22[40, 46, 54, 55, 65, 75];
854 23[33, 34, 57]; 24[38, 66, 67].

Table 3. Comparison of different active principles on **occurrence of selected adverse events.**

Death			
Indomethacin	0.77 (0.67, 0.89) , 23 studies ¹	0.97 (0.32, 2.91), 1 study ²	0.55 (0.29, 1.07), 8 studies ³
0.85 (0.70, 1.10)	Ibuprofen	1.07 (0.62, 1.86), 6 studies ⁴	0.62 (0.26, 1.44), 3 studies ⁵
0.94 (0.55, 1.68)	1.11 (0.65, 1.88)	Acetaminophen	6.40 (0.75, 54.78), 1 study ⁶
0.51 (0.29, 0.85)	0.60 (0.34, 0.99)	0.54 (0.25, 1.10)	Control
Necrotizing enterocolitis (NEC)			
Indomethacin	1.08 (0.85, 1.38), 23 studies ⁷	2.72 (0.94, 7.89), 2 study ⁸	1.43 (0.41, 4.93), 4 studies ⁹
1.16 (0.88, 1.62)	Ibuprofen	0.99 (0.57, 1.71), 8 studies ¹⁰	1.45 (0.39, 5.45), 3 studies ¹¹
1.40 (0.77, 2.76)	1.20 (0.68, 2.22)	Acetaminophen	0.35 (0.01, 8.96), 1 study ¹²
1.39 (0.55, 3.55)	1.19 (0.45, 3.05)	1.00 (0.34, 2.93) ^a	Control
Intestinal perforation			
Indomethacin	0.51 (0.38, 0.68) , 11 studies ¹³		0.98 (0.06, 16.09), 1 study ¹⁴
0.58 (0.36, 1.11)	Ibuprofen		0.51 (0.10, 2.53), 2 studies ¹⁵
0.37 (0.06, 2.26)	0.63 (0.10, 3.61)		Control
Gastrointestinal bleeding			
Indomethacin	1.03 (0.61, 1.76), 8 studies ¹⁶	2.28 (0.12, 43.14) ^a , 2 studies ¹⁷	0.77 (0.11, 5.41), 3 studies ¹⁸
0.87 (0.39, 2.07)	Ibuprofen	3.51 (1.36, 9.08) , 5 studies ¹⁹	3.01 (0.96, 9.42), 1 study ²⁰
2.56 (0.79, 11.29)	2.94 (0.94, 11.81)	Acetaminophen	-
1.58 (0.22, 9.79)	1.82 (0.25, 10.48)	0.61 (0.05, 4.62)	Control
Bronchopulmonary dysplasia (BPD)			
Indomethacin	0.89 (0.81, 0.99) , 15 studies ²¹	-	0.67 (0.40, 1.11), 4 studies ²²
0.86 (0.71, 1.02)	Ibuprofen	1.20 (0.56, 2.54), 6 studies ²³	1.05 (0.18, 6.25), 3 studies ²⁴
1.21 (0.62, 2.46)	1.40 (0.74, 2.82)	Acetaminophen	0.47 (0.15, 1.55), 1 study ²⁵
0.70 (0.44, 1.08)	0.81 (0.51, 1.28)	0.58 (0.27, 1.17)	Control
Intraventricular haemorrhage (IVH)			
Indomethacin	1.25 (1.01, 1.56) , 19 studies ²⁶	1.32 (0.52, 3.34), 2 studies ²⁷	0.92 (0.05, 18.05), 2 studies ²⁸
1.27 (1.00, 1.62)	Ibuprofen	0.98 (0.58, 1.64), 8 studies ²⁹	0.92 (0.47, 1.82), 3 studies ³⁰
1.27 (0.78, 2.08)	0.99 (0.63, 1.60)	Acetaminophen	0.53 (0.16, 1.81), 1 study ³¹
1.00 (0.54, 1.83)	0.79 (0.44, 1.39)	0.80 (0.40, 1.53)	Control
Periventricular leukomalacia			
Indomethacin	0.83 (0.53, 1.30), 7 studies ³²	0.82 (0.27, 2.54), 1 studies ³³	2.58 (0.48, 13.85), 1 study ³⁴
0.90 (0.53, 1.61)	Ibuprofen	0.88 (0.28, 2.71), 3 studies ³⁵	1.91 (0.53, 6.82), 2 studies ³⁶
0.79 (0.27, 2.35)	0.88 (0.29, 2.60)	Acetaminophen	-
2.24 (0.70, 7.99)	2.48 (0.80, 8.53)	2.85 (0.63, 14.18)	Control
Oliguria			

Indomethacin	3.29 (1.80, 6.00) , 9 studies ³⁷	-	-
3.92 (1.69, 9.82)	Ibuprofen	2.45 (0.63, 9.54), 2 studies ³⁸	-
10.81 (1.86, 93.31)	2.75 (0.57, 18.38)	Acetaminophen	0.71 (0.19, 2.68), 1 study ³⁹
7.62 (0.42, 188.2)	1.94 (0.12, 40.50)	0.69 (0.07, 7.24)	Control

856 Data are reported as odds ratios (ORs) and 95% credible intervals for mixed comparisons and 95% confidence intervals for direct ones. Mixed ORs are shown in the columns
857 (i.e. in the triangle below the diagonal with the treatments) and direct ORs are shown in the rows (i.e. in the triangle above the diagonal).

858 Significant results are in bold.

859 ^a p-value for heterogeneity=0.01

860 1[27, 36, 42, 45, 48, 51, 68, 70, 71, 73, 74, 76, 81, 84, 87-90, 92, 93, 95, 96, 101]; 2[30]; 3[40, 44, 46, 47, 54, 55, 65, 75]; 4[17, 23, 28, 33, 57, 82]; 5[38, 66, 67]; 6[43]; 7[27,
861 34, 36, 42, 45, 48, 51, 68, 70, 71, 73, 74, 76, 81, 84, 87, 89, 91-94, 96, 101]; 8[30, 34]; 9[40, 46, 54, 75]; 10[17, 23, 28, 33, 34, 57, 77, 82]; 11[38, 66, 67]; 12[43]; 13[48, 68,
862 73, 74, 81, 87, 89, 90, 92, 93, 101]; 14[75]; 15[38, 67]; 16[34, 45, 68, 70, 73, 81, 94, 101]; 17[30, 34]; 18[46, 54, 65]; 19[28, 33, 34, 57, 76]; 20[66]; 21[27, 45, 48, 51, 68, 71,
863 74, 78, 81, 87, 89, 90, 93, 96, 101]; 22[40, 44, 46, 75]; 23[17, 23, 28, 33, 77, 82]; 24[38, 66, 67]; 25[43]; 26[27, 34, 36, 45, 51, 53, 68, 70, 71, 74, 76, 78, 81, 87, 89, 92, 93,
864 96, 101]; 27[30, 34]; 28[40, 75]; 29[17, 23, 28, 33, 34, 57, 77, 82]; 30[38, 66, 67]; 31[43]; 32[45, 48, 68, 70, 74, 87, 93]; 33[30]; 34[75]; 35[17, 28, 82]; 36[38, 67]; 37[45, 48,
865 53, 68, 73, 74, 88, 91, 94]; 38[28, 77]; 39[43].

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