Supplementary Material

The following material accompanies the article the facilitatory effects of adjuvant pharmaceutics to prolong the duration of local anesthetic for peripheral nerve bloke: A systematic review and network meta-analysis

**Table 1. Selected study information:**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Number | First Author | Year | Surgery | Block method | Intervention | Sample size | sex (Female %) | Outcome |
| 1 | Casati A | 2000 | Foot surgery | Sciatic-Femoral Nerve block | Pla(ropivacaine), Clo(ropivacaine) | 30 | 83.3 | MBT, FART |
| 2 | El Saied AH | 2000 | Hand or forearm surgery | Axillary brachial plexus | Clo(ropivacaine), Pla(ropivacaine) | 46 | 23.9 | SBT, MBT, FART |
| 3 | Erlacher W | 2000 | Hand or forearm surgery | Axillary perivascular brachial plexus block | Pla(ropivacaine), Clo(ropivacaine) | 40 | 40 | SBT |
| 4 | Erlacher W | 2001 | Forearm or hand surgery | Axillary perivascular brachial plexus block | Pla(ropivacaine), Clo(ropivacaine), Pla(bupivacaine), Clo(bupivacaine) | 80 |  | MBT |
| 5 | Karakaya D | 2001 | Hand, forearm, elbow surgery | Axillary brachial plexus | Pla(bupivacaine), Fen(bupivacaine) | 40 | 52.5 | SBT, MBT, FART |
| 6 | Kesimci E | 2007 | Hand or forearm surgery | Axillary brachial plexus block | Pla(ropivacaine), Tra(ropivacaine) | 40 | 45 | SBT, MBT, FART |
| 7 | Chakraborty S | 2010 | Upper limb orthopedic procedures | Supracalvicular brachial plexus block | Clo(bupivacaine), Pla(bupivacaine) | 63 | 31.7 | SBT, MBT, FART |
| 8 | Esmaoglu A | 2010 | Forearm and hand surgery | Axilary brachial plexus blockade | Pla(levobupivacaine), Dexm(levobupivacaine) | 60 | 25 | SBT, MBT, FART |
| 9 | Ammar AS | 2012 | upper limb surgery | Infraclavicular brachial plexus block | Pla(bupivacaine), Dexm(bupivacaine) | 60 | 48.3 | SBT, MBT, FART |
| 10 | Behr A | 2012 | Arthroscopic rotator cuff repair | Middle interscalene brachial plexus block | Pla(levobupivacaine), Bup(levobupivacaine) | 100 | 40 | SBT |
| 11 | Dogru K | 2012 | Arteriovenous fistule surgery | Axillary brachial plexus | Pla(Levobupivacaine), MgS(levobupivacaine) | 40 | NR | SBT, MBT |
| 12 | Geze S | 2012 | Orthopaedic upper extremity surgery | Axillary plexus block | Pla(levobupivacaine+lidocaine), Tra(levobupivacaine+lidocaine), Fen(levobupivacaine+lidocaine) | 60 | 36.7 | SBT, MBT, FART |
| 13 | Kaygusuz K | 2012 | Forearm and hand surgery | Axillary plexus block | Pla(levobupivacaine), Dexm(levobupivacaine) | 60 | 38.3 | SBT, MBT, FART |
| 14 | Swami SS | 2012 | Upper limb surgeries | Supraclavicular brachial plexus block | Clo(bupivacaine), Dexm(bupivacaine) | 60 | 31.7 | SBT, MBT, FART |
| 15 | Agarwal S | 2014 | Upper limb surgeries | Supraclavicular brachial plexus block | Pla(bupivacaine), Dexm(bupivacaine) | 50 | 28 | SBT, MBT, FART |
| 16 | Ali QE | 2014 | Surgeries on upper extremities | Supraclavicular brachial plexus block | Pla(ropivacaine), Clo(ropivacaine) | 40 | 47.5 | SBT, MBT |
| 17 | Biswas S | 2014 | Forearm and hand surgery | Brachial plexus block | Pla(levobupivacaine), Dexm(levobupivacaine) | 60 | NR | SBT, MBT, FART |
| 18 | Das A | 2014 | Orthopedic surgeries of elbow | Supraclavicular brachial plexus block | Dexm(ropivacaine), Pla(ropivacaine) | 80 | 81.3 | SBT, MBT |
| 19 | Gupta K | 2014 | Upper extremity surgery | Supracalvicular brachial plexus block | Pla(ropivacaine), Clo(ropivacaine) | 64 | 31.3 | SBT, MBT, FART |
| 20 | Kumar S | 2014 | Upper limb surgery | Supraclavicular brachial plexus block | Dexa(ropivacaine), Pla(ropivacaine) | 80 | 32.5 | SBT, MBT, FART |
| 21 | Mukherjee K | 2014 | Forearm and hand surgery | Supraclavicular brachial plexus block | MgS(ropivacaine), Pla(ropivacaine) | 100 | 42 | SBT, MBT, FART |
| 22 | Persec J | 2014 | Upper-extremity surgery | Supraclavicular brachial plexus block | Dexa(Levobupivacaine), Pla(levobupivacaine) | 60 | NR | SBT, MBT, FART |
| 23 | Rohan B | 2014 | Upper extremity surgery | Supraclavicular brachial plexus block | Pla(ropivacaine), Clo(ropivacaine) | 50 | 22 | SBT, MBT, FART |
| 24 | Faria-Silva R | 2014 | Shoulder arthroscopy | Brachial plexus block | Pla(ropivacaine), Clo(ropivacaine) | 50 | 56 | MBT |
| 25 | Zhang Y | 2014 | Forearm and hand surgery | Axillary brachial plexus block | Pla(ropivacaine), Dexm(ropivacaine) | 30 | 40 | SBT, MBT |
| 26 | Deshmukh R | 2015 | Orthopaedic upper limb surgery | Interscalene brachial plexus blockade | Pla(ropivacaine), Clo(ropivacaine) | 60 | NR | SBT, MBT, FART |
| 27 | Kathuria S | 2015 | Upper limb surgery | Supraclavicular brachial plexus block | Pla(ropivacaine), Dexm(ropivacaine) | 40 | 15 | SBT, MBT, FART |
| 28 | Kaur H | 2015 | Upper limb orthopedic surgeries | Brachial plexus block | Pla(levobupivacaine+lignocaine), Dexm(levobupivacaine+lignocaine) | 90 | 44.4 | SBT, MBT, FART |
| 29 | Liu J | 2015 | Shoulder arthroscopy | Supraclavicular brachial plexus block | Pla(bupivacaine), Dexa(bupivacaine) | 40 | NR | MBT, FART |
| 30 | Patil KN | 2015 | Upper limb surgeries | Supraclavicular brachial plexus block | Pla(ropivacaine), Clo(ropivacaine) | 60 | 38.3 | SBT, MBT, FART |
| 31 | Alarasan AK | 2016 | Upper limb surgery | Supraclavicular brachial plexus block | Pla(bupivacaine), Dexa(bupivacaine) | 60 | 23.3 | SBT, MBT |
| 32 | Baloda R | 2016 | Elbow, forearm and hand surgery | Supraclavicular brachial plexus block | Pla(levobupivacaine), Dexa(levobupivacaine) | 60 | 31.7 | SBT, MBT |
| 33 | Bangera A | 2016 | Forearm and hand surgery | Axillary brachial plexus | Pla(ropivacaine), Dexm(ropivacaine) | 80 | 35 | SBT, MBT, FART |
| 34 | Das B | 2016 | Upper limb orthopaedic surgery | Supraclavicular brachial plexus block | Pla(ropivacaine), Dexm(ropivacaine) | 80 | 46.3 | SBT, MBT, FART |
| 35 | Helal SM | 2016 | Below knee surgery | Femoral sciatic nerve block | Pla(bupivacaine), Dexm(bupivacaine) | 60 | 35 | SBT, MBT, FART |
| 36 | Lee MJ | 2016 | Forearm and hand surgery | Axillary brachial plexus block | Pla(ropivacaine), Dexa(ropivacaine), Dexm(ropivacaine) | 51 | 37.3 | SBT |
| 37 | Nazir N | 2016 | Upper limb | Supraclavicular brachial plexus block | Pla(bupivacaine), Dexm(bupivacaine) | 70 | 47.1 | SBT, MBT, FART |
| 38 | Tripathi A | 2016 | upper limb surgery | Supraclavicular brachial plexus block | Clo(bupivacaine), Dexm(bupivacaine) | 60 | 30 | SBT, MBT, FART |
| 39 | Wang C | 2016 | Lower extremity surgery | Lumbar plexus and sciatic nerve block | Pla(ropivacaine), Dexm(ropivacaine) | 60 | 48.3 | SBT, MBT, FART |
| 40 | Chinnappa J | 2017 | Upper limb Surgery | Supraclavicular brachial plexus block | Pla(ropivacaine), Dexm(ropivacaine) | 60 | 33.3 | SBT, MBT, FART |
| 41 | Nasir D | 2017 | Upper extremity surgery | Supraclavicular brachial plexus block | Pla(ropivacaine), Clo(ropivacaine), Dexa(ropivacaine), Clo+Dexa(ropivacaine) | 83 | 49.4 | SBT, MBT |
| 42 | Pani N | 2017 | Upper limb surgery | Supraclavicular brachial plexus block | Pla(levobupivacaine), Dexa(levobupivacaine) | 60 | 31.7 | SBT, MBT, FART |
| 43 | Koraki E | 2017 | forearm and hand surgery | Axillary brachial plexus block | Dexm(ropivacaine), Pla(ropivacaine) | 37 | NR | SBT, MBT, FART |
| 44 | Sakae TM | 2017 | Shoulder arthroscopy | Interscalene brachial plexus blocks | Pla(ropivacaine), Dexa(ropivacaine) | 40 | 42.5 | SBT, MBT |
| 45 | Wang X | 2017 | Distal arm or forearm surgery | Brachial plexus block | Pla(ropivacaine), Dexm(ropivacaine), Mor(ropivacaine) | 92 | 25 | SBT, MBT |
| 46 | Jung HS | 2018 | Arthroscopic shoulder surgery | Interscalene brachial plexus blockade | Pla(ropivacaine), Dexm(ropivacaine) | 47 | 53.2 | SBT, MBT, FART |
| 47 | Liu Z | 2018 | Upper limb surgery | Brachial plexus block | Pla(ropivacaine), Dexm(ropivacaine) | 114 | NR | SBT, MBT, FART |
| 48 | Mangal V | 2018 | Upper limb surgery | Subclavian perivascular brachial plexus block | Pla(ropivacaine), Dexm(ropivacaine) | 87 | 20.7 | SBT, MBT, FART |
| 49 | Nazir O | 2019 | Upper limb surgery | Supraclavicular brachial plexus block | Pla(ropivacaine), Clo(ropivacaine), Dexm(ropivacaine) | 75 | 26.7 | SBT, MBT, FART |
| 50 | Seering MS | 2019 | Shoulder surgery | Interscalene brachial plexus blocks | Pla(ropivacaine), Clo(ropivacaine), Dexa(ropivacaine), Bup(ropivacaine) | 158 | 24.7 | SBT, MBT, FART |
| 51 | Sharma A | 2019 | Upper extremity surgery | Interscalene brachial plexus block | MgS(bupivacaine), Pla(bupivacaine) | 60 | 30 | SBT, MBT, FART |
| 52 | Eletheria Soulioti | 2019 | Shoulder Surgery | Intersalene brachial plexus block | Tra(ropivacaine), Pla(ropivacaine) | 78 | NR | SBT, MBT |
| 53 | Soulioti E, | 2017 | Upper limb surgery | Infraclavicular block | Pla(ropivacaine), Pla(bupivacaine),  Dexa(ropivacaine),  Dexa(bupivacaine) | 218 | 38.1 | SBT, FART |

Pla=placebo, Clo=clonidine, Tra=tramadol, Bup=buprenorphine, Dexa=dexamethasone, Dexm=dexmedetomidine, Fen=fentanyl, MgS=MgSO4, SB=sensory block, MB=motor block, FAR=first analgesia request.

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**Table 2. Summary table of relevant counts.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total included trials | SB time | MB time | Time of FAR |
| Number of studies | 53 | 49 | 49 | 38 |
| Number of Studies of each local anesthetic | | | | |
| Bupivacaine | 11 | 10 | 12 | 10 |
| Ropivacaine | 30 | 28 | 28 | 20 |
| Levobupivacaine | 8 | 8 | 7 | 5 |
| Ropivacaine/  Bupivacaine | 2 | 1 | 1 | 1 |
| Levobupivacaine +  lidocaine | 1 | 1 | 1 | 1 |
| Levobupivacaine +  lignocaine | 1 | 1 | 1 | 1 |
| Number of studies of each adjuvant/adjuvant combination | | | | |
| Clonidine | 16 | 13 | 15 | 11 |
| Fentanyl | 2 | 2 | 2 | 2 |
| Tramadol | 3 | 3 | 3 | 2 |
| MgSO4 | 3 | 3 | 3 | 2 |
| Dexamethasone | 11 | 10 | 9 | 6 |
| Dexmedetomidine | 24 | 24 | 23 | 20 |
| Buprenorphine | 2 | 2 | 0 | 0 |
| Number of studies of surgery | | | | |
| Upper extremity | 51 | 48 | 47 | 35 |
| Lower extremity | 2 | 1 | 2 | 2 |

SB=sensory block, MB=motor block, FAR=first analgesia request.

**Figure 1**





Risk of bias summary

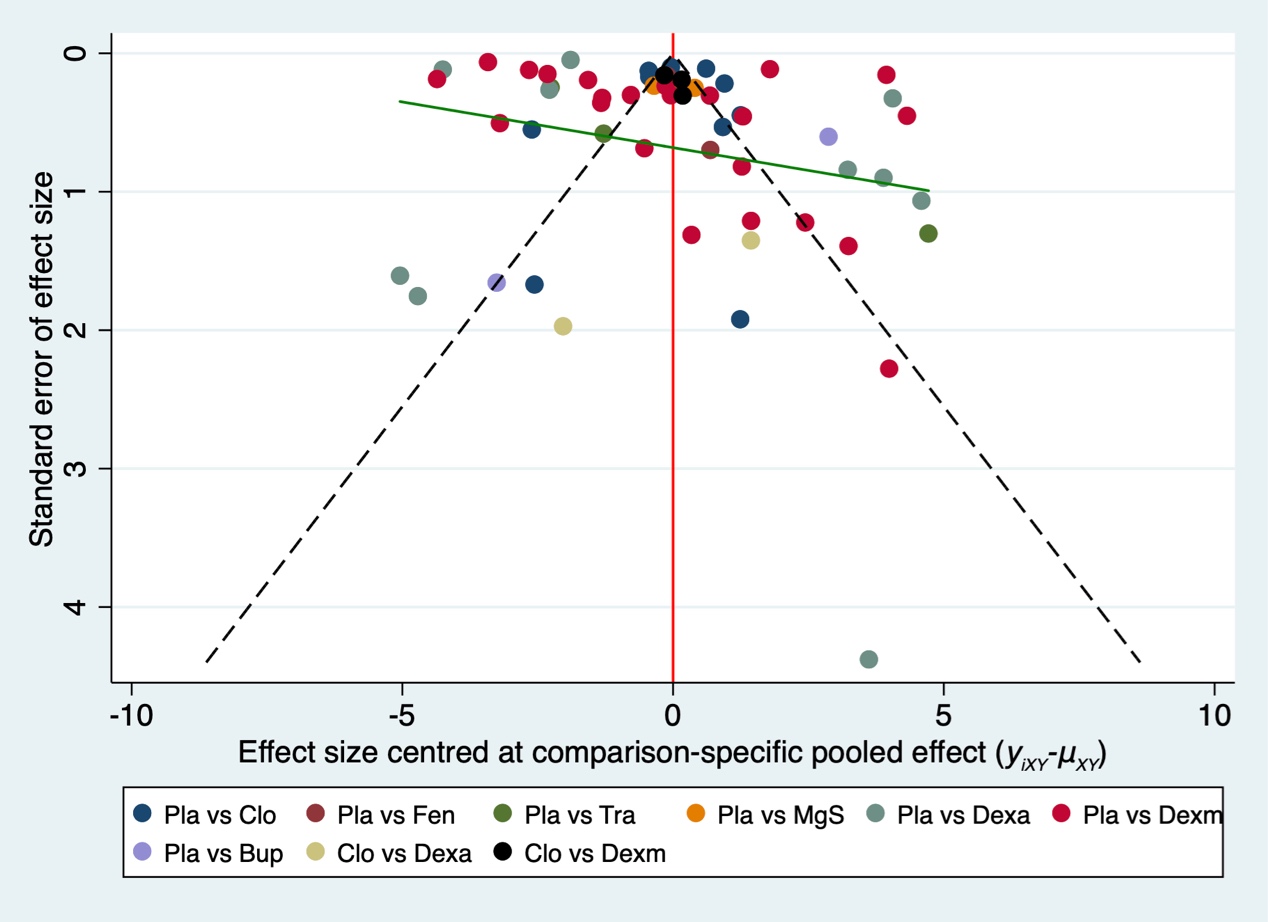
**Figure 2**



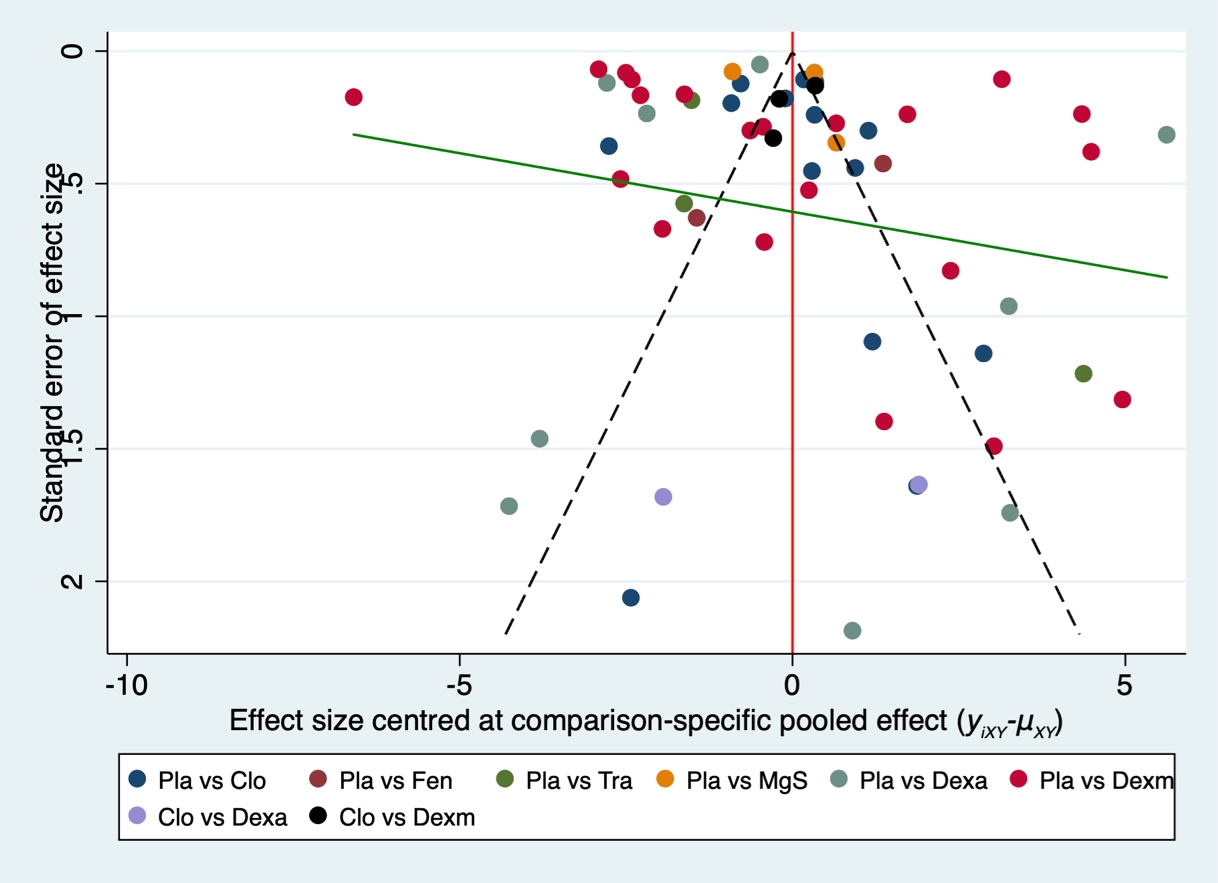
Risk of Bias graph

**Figure 3**

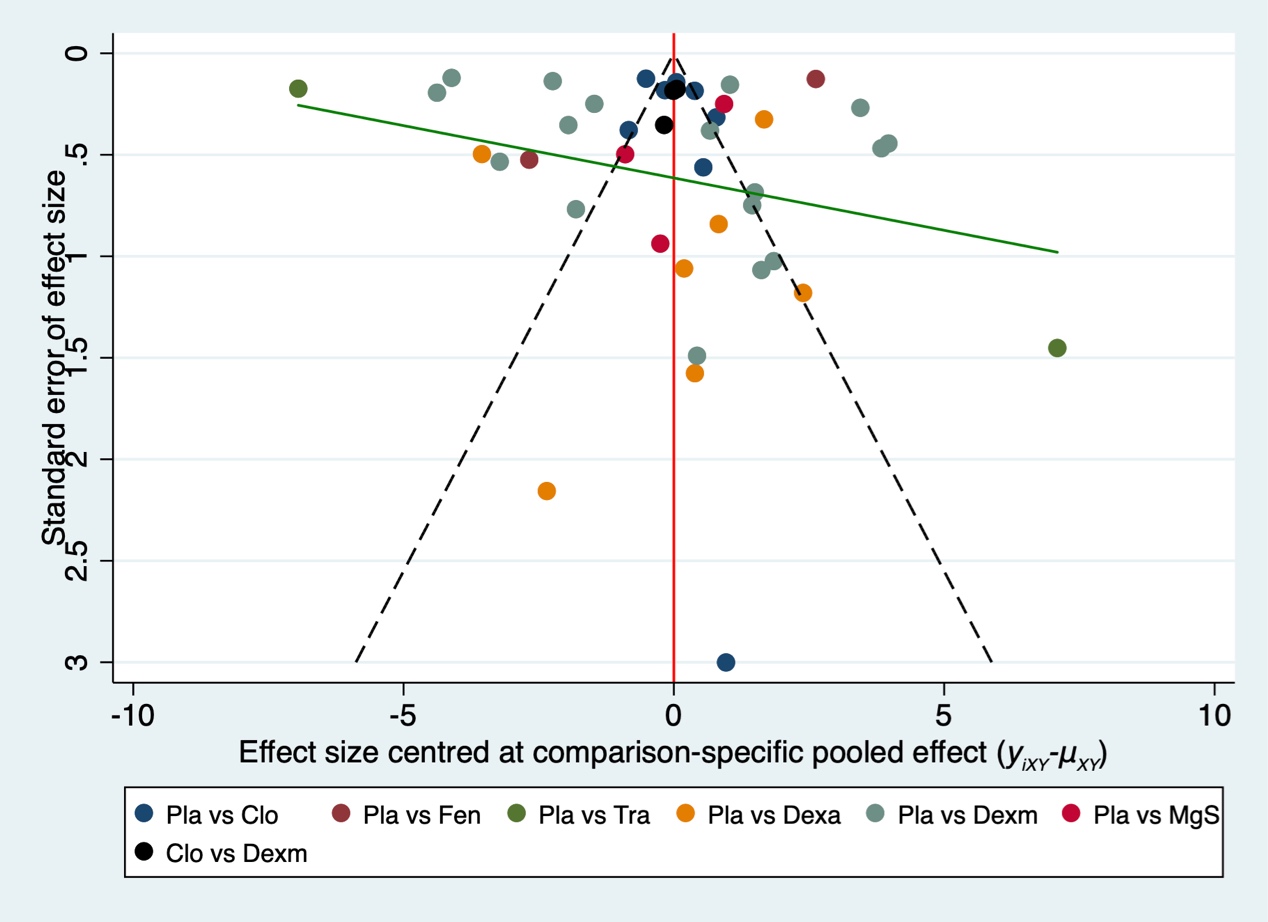
**A**



**B**



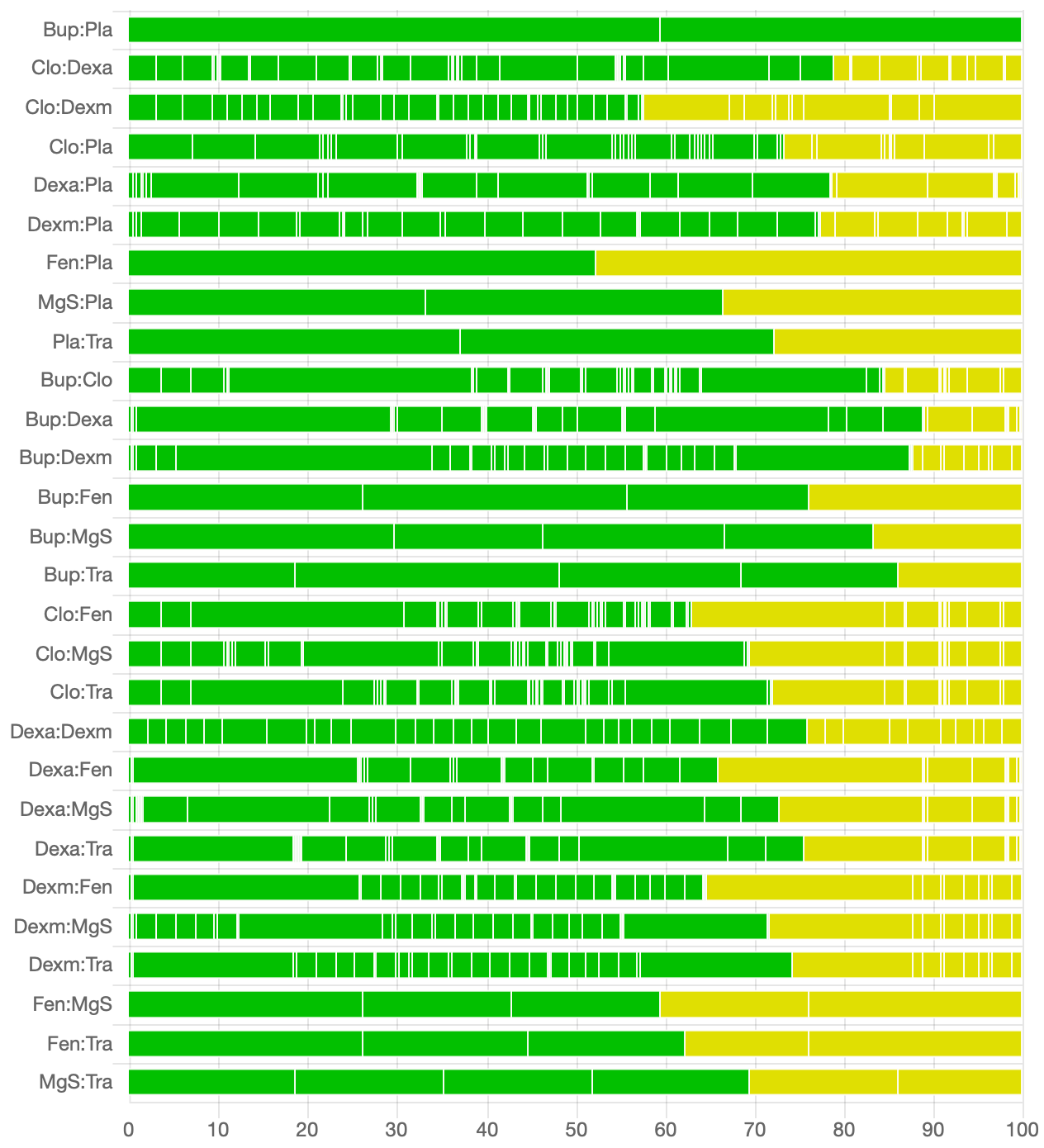
**C**



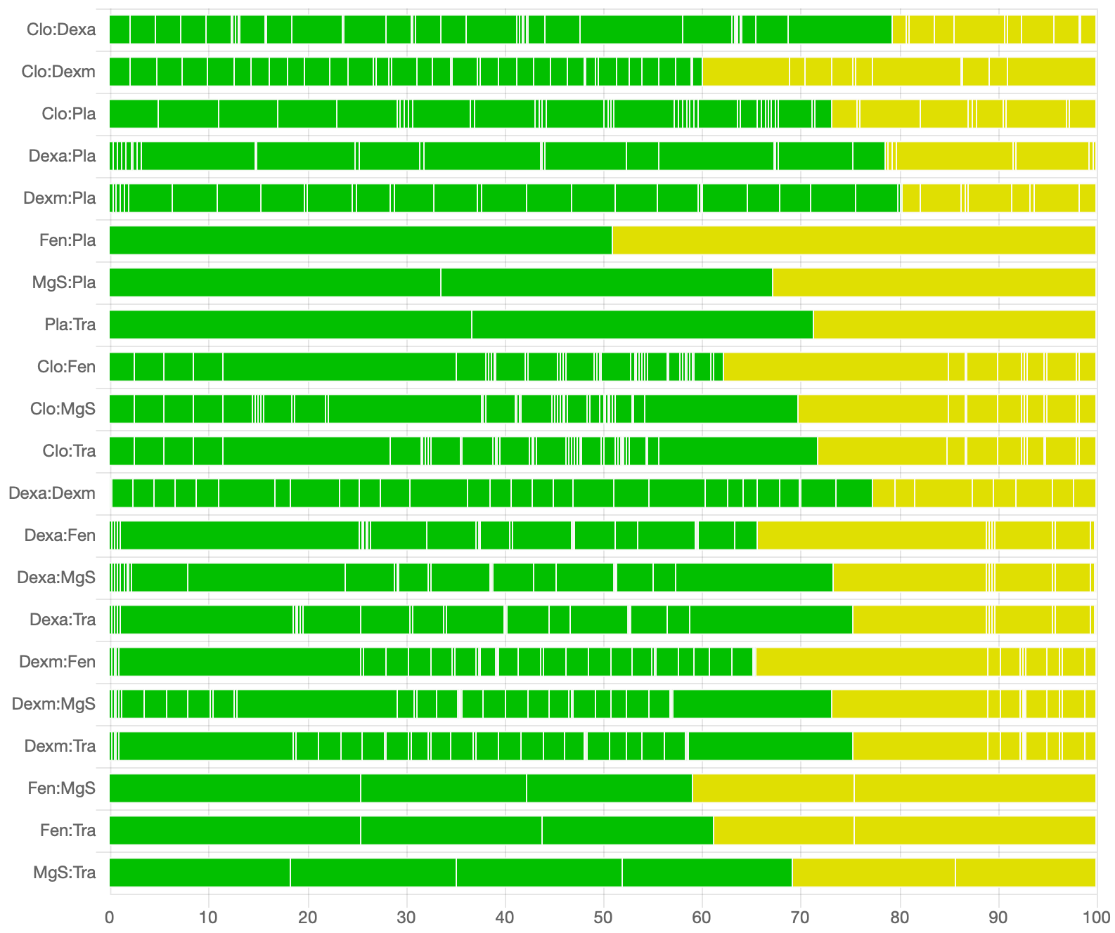
Comparison-adjust funnel plot for the analgesia network. A is funnel plot of sensory block time, B is funnel plot of motor block time, and C is funnel plot of time of first analgesia request. The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The green line is the regression line. Different colors correspond to different comparisons. (Pla=placebo, Clo=clonidine, Tra=tramadol, Bup=buprenorphine, Dexa=dexamethasone, Dexm=dexmedetomidine, Fen=fentanyl, MgS=MgSO4)

**Figure 4**

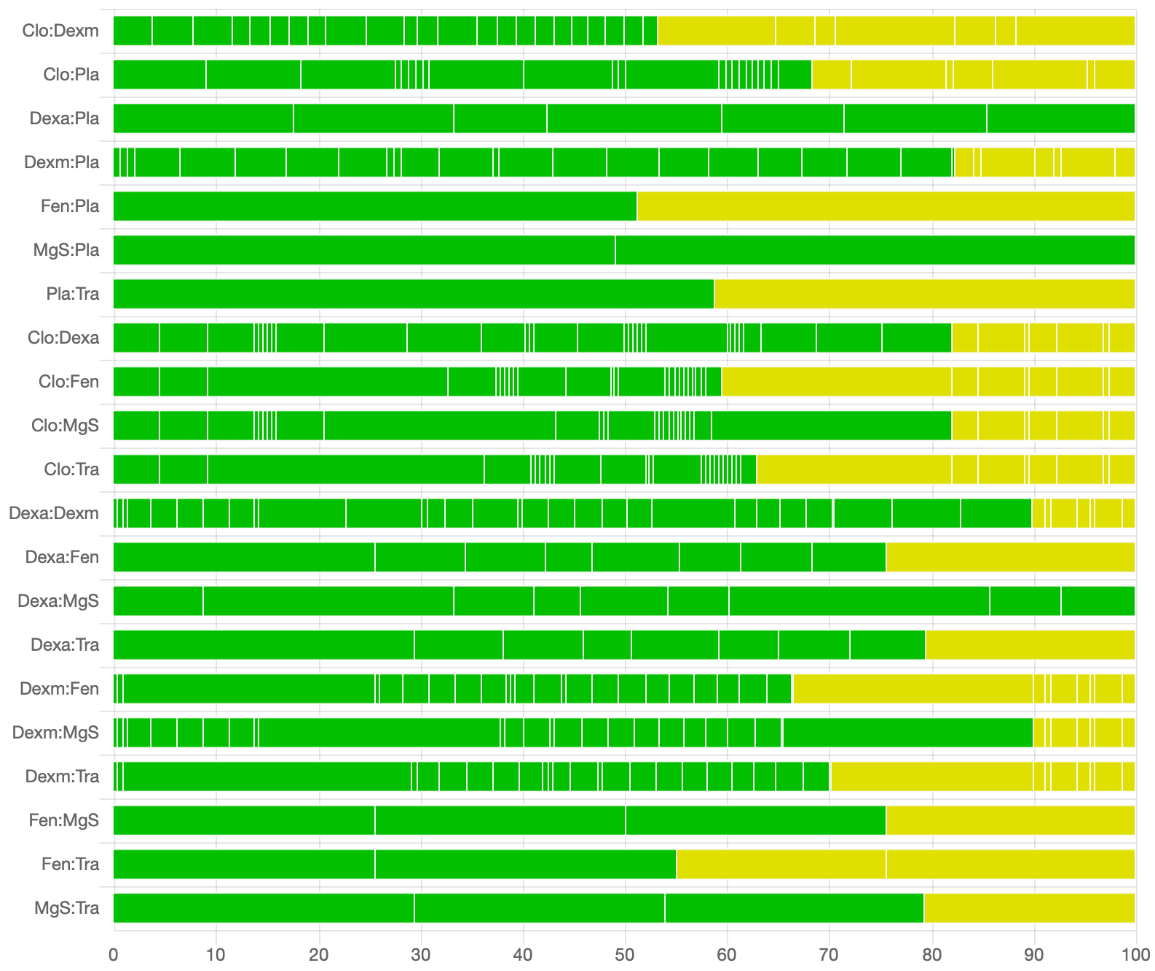
**A**



B

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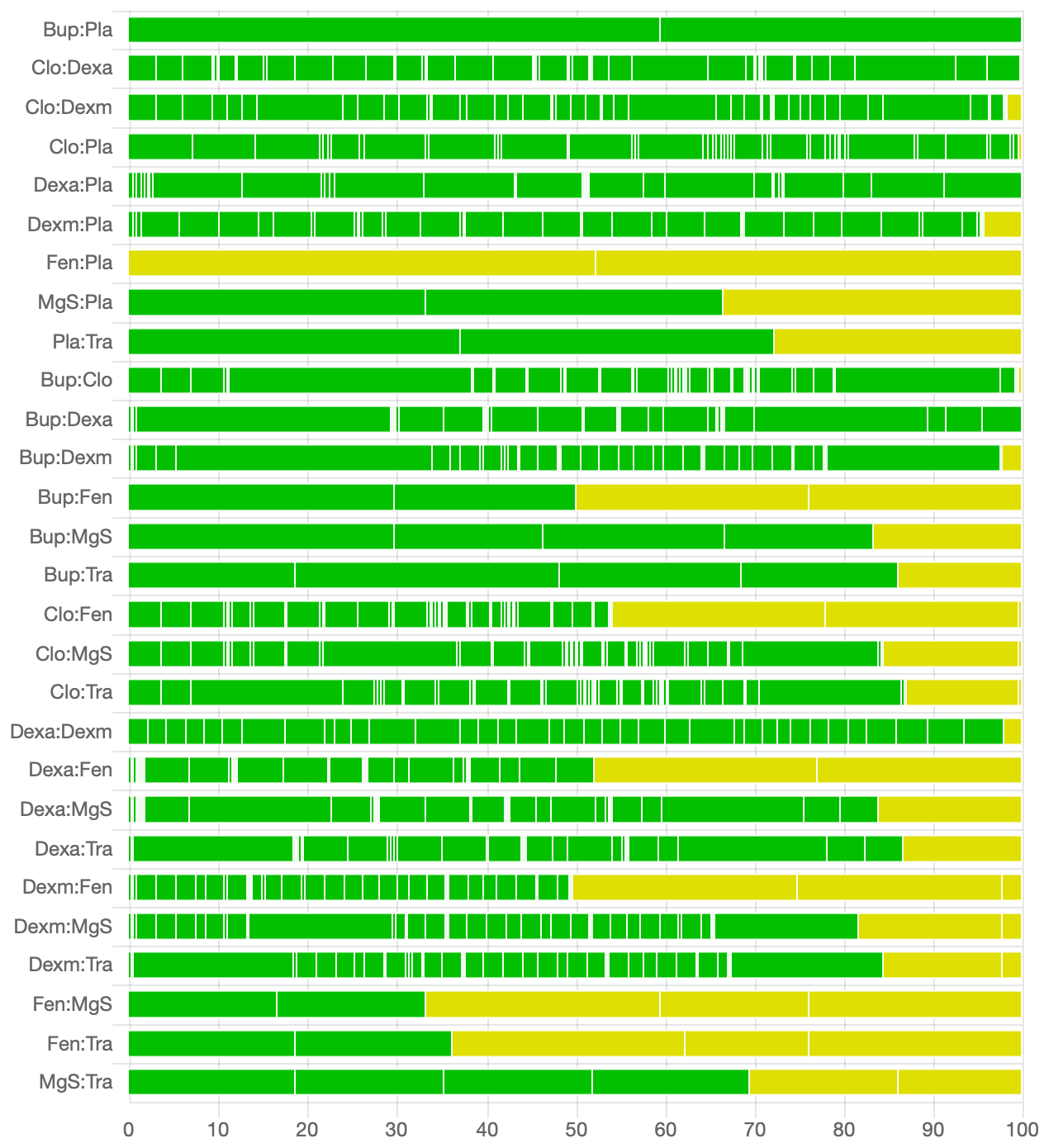
C



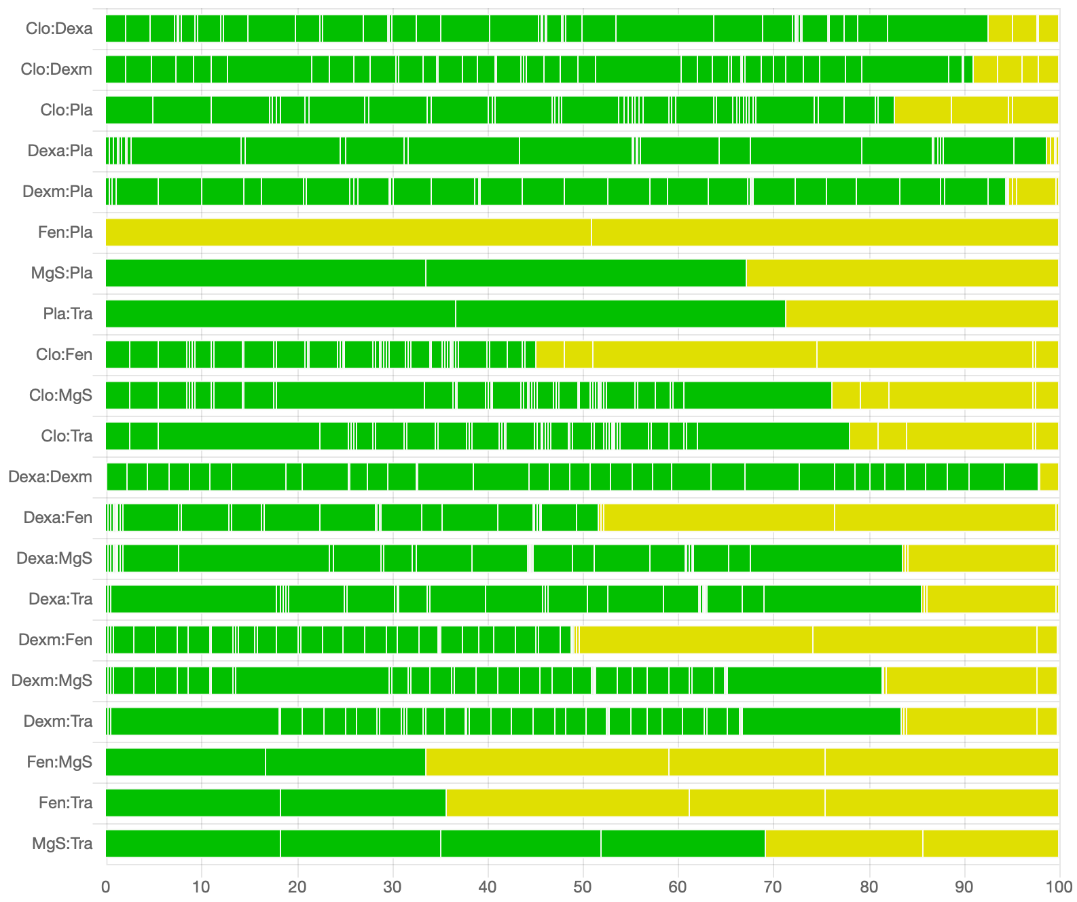
Risk of bias bar chart for the comparison of effects of adjuvants to prolong the duration of local anesthetics. A is risk of bias bar chart of sensory block time, B is risk of bias bar chart of motor block time, and C is risk of bias bar chart of time of first analgesia request. The bar chart shows the contributions of each piece of study to the network estimate. While vertical lines separate the percentage contribution of different studies. Each bar shows the percentage contribution from studies judged to be at low (green), moderate (yellow), and high (red) risk of bias. We do not have high risk of bias in this network. (Pla=placebo, Clo=clonidine, Tra=tramadol, Bup=buprenorphine, Dexa=dexamethasone, Dexm=dexmedetomidine, Fen=fentanyl, MgS=MgSO4)

**Figure 5**

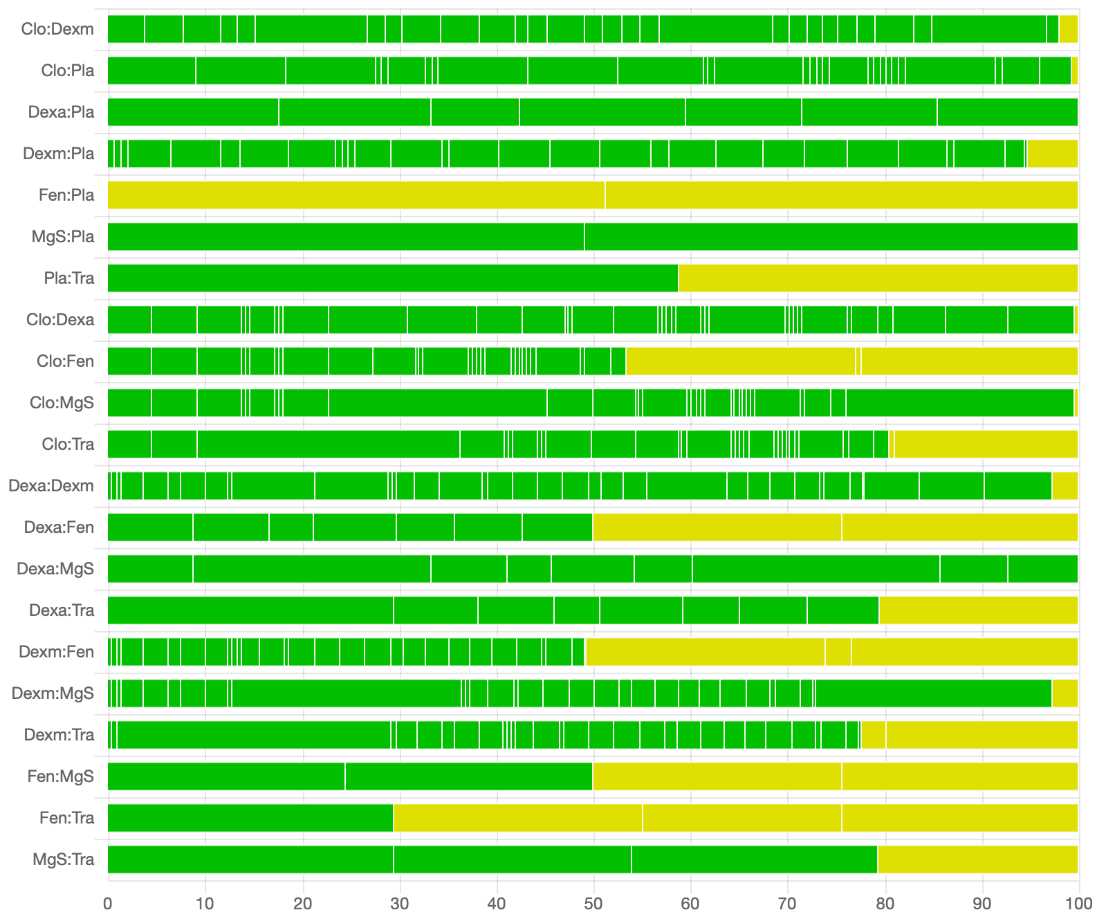
**A**



B



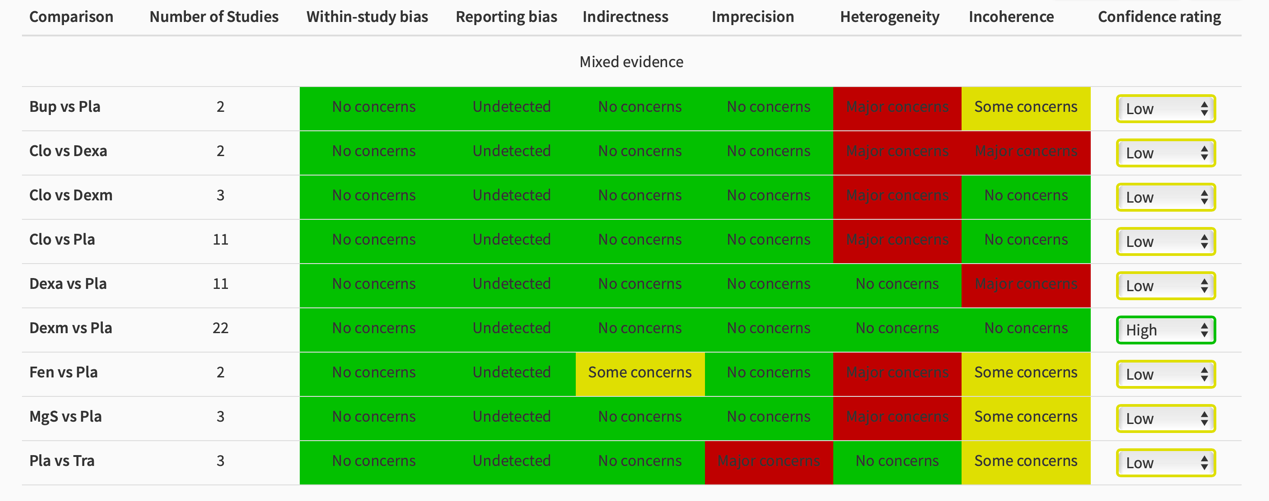
C



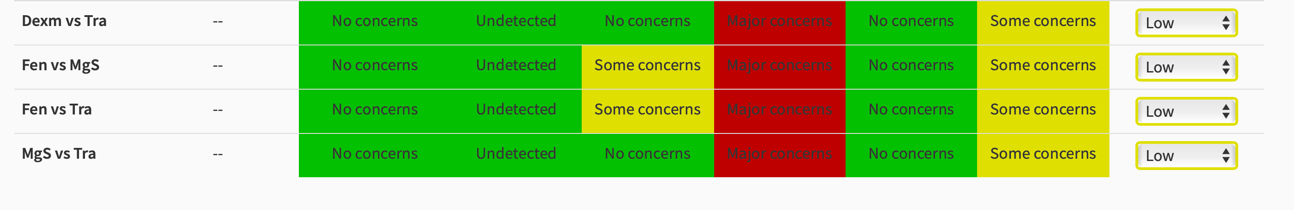
Indirectness contributions bar chart for the comparison of effects of adjuvants to prolong the duration of local anesthetics. A is risk of bias bar chart of sensory block time, B is risk of bias bar chart of motor block time, and C is risk of bias bar chart of time of first analgesia request. The bar chart shows the contributions of each study to the network estimate. While vertical lines separate the percentage contribution of different studies. Each bar shows the percentage contribution from studies judged to be at low (green), moderate (yellow), and high (red) risk of indirectness contribution. We do not have high risk of indirectness contribution in this network. (Pla=placebo, Clo=clonidine, Tra=tramadol, Bup=buprenorphine, Dexa=dexamethasone, Dexm=dexmedetomidine, Fen=fentanyl, MgS=MgSO4)

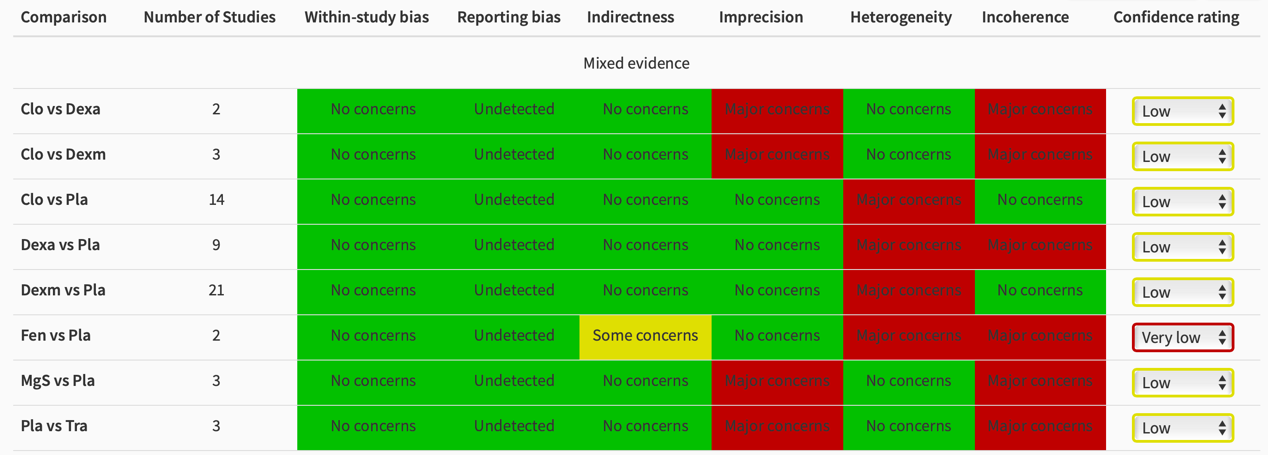
**Figure 6**

**A**

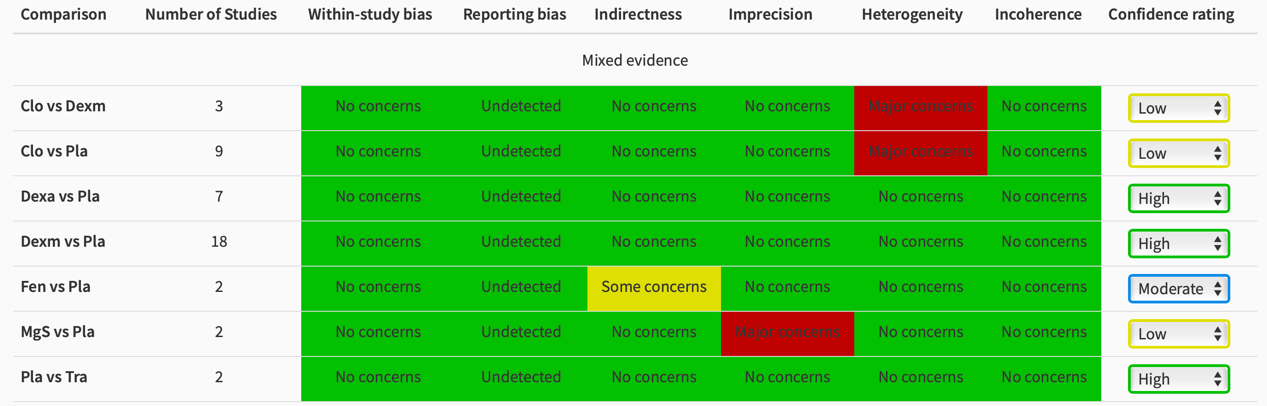






**B** 



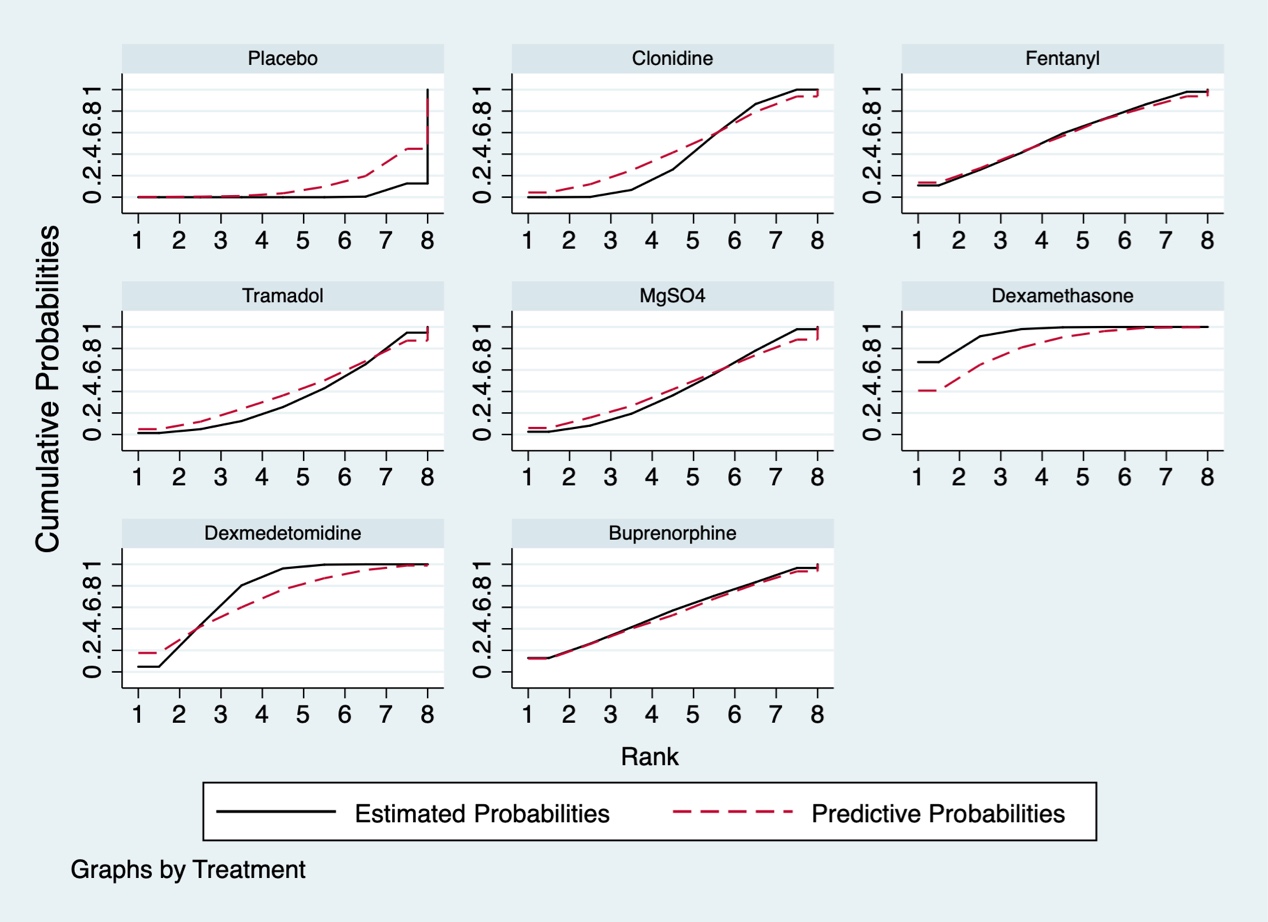
**C**  



Confidence rating report of the comparison of effects of adjuvants to prolong the duration of local anesthetics. A is confidence rating report of sensory block time, B is confidence rating report of motor block time, and C is confidence rating report of time of first analgesia request. The confidence rating report brings together all the judgments for the six domains (within study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence) across all evaluated treatment effects. The default judgment is “High” confidence; downgrading by one, two, or three levels will lead to a confidence rating of “Moderate,” “Low,” or “Very Low”, respectively.

**Figure 7**

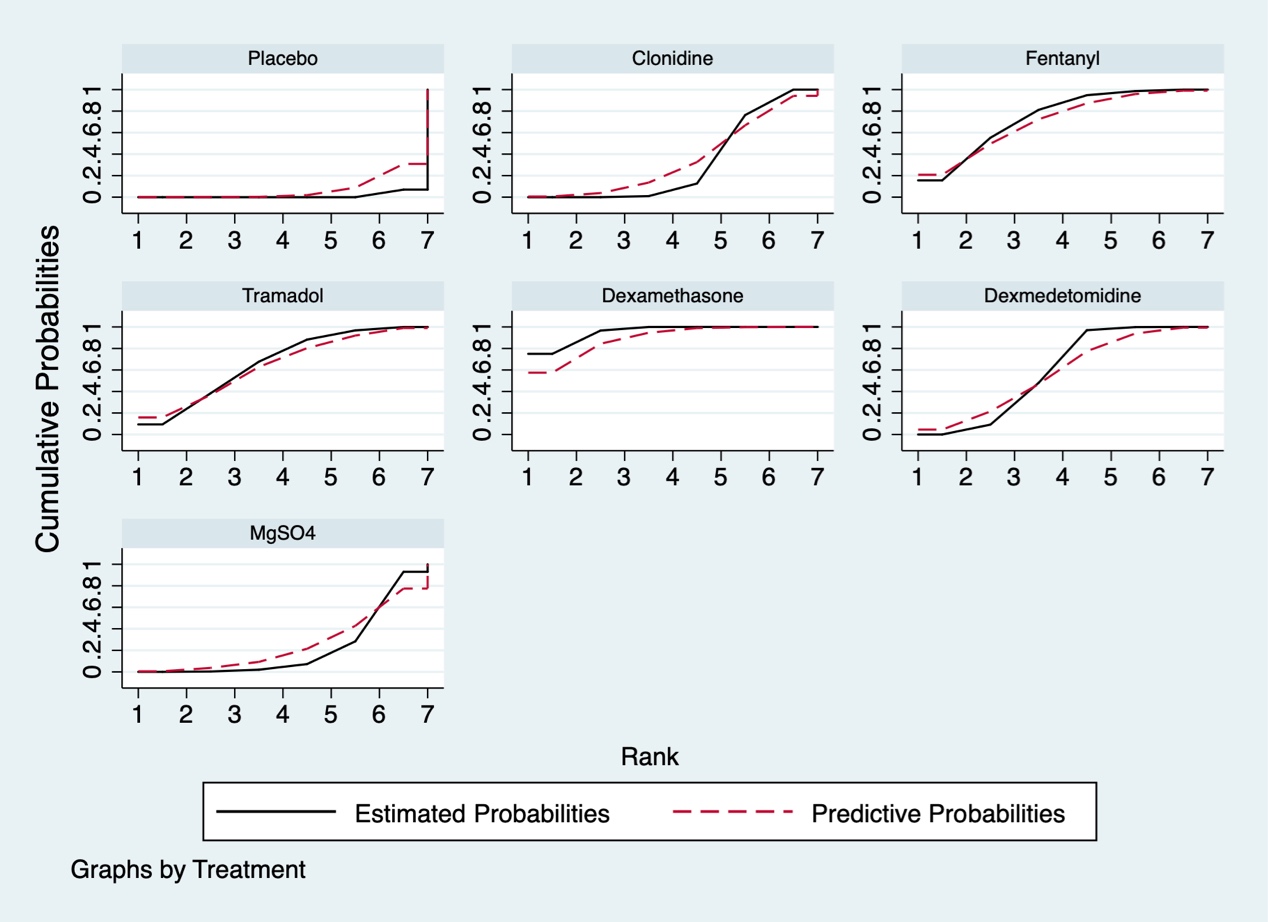
**A**

****

**B**

****

**C**

****

Plots of the surface under the cumulative ranking curves for all treatments in the network meta. A is a plot of sensory block time, B is plot of motor block time, and C is plot of s the time of first analgesia request. Black solid lines correspond to the estimated probabilities and red dashed lines to the predictive probabilities.

**Table3. SUCRA values of ranking probabilities**

|  |  |  |  |
| --- | --- | --- | --- |
| LA adjuvant | SB time | MB time | Time of FAR |
| Dexamethasone | 93.7 | 79.1 | 95.0 |
| Dexmedetomidine | 75.3 | 77.6 | 59.0 |
| Fentanyl | 55.8 | 76.3 | 74.5 |
| Buprenorphine | 55.2 | NA | NA |
| MgSO4 | 43.0 | 31.9 | 21.5 |
| Clonidine | 39.5 | 48.6 | 32.1 |
| Tramadol | 35.6 | 32.1 | 66.6 |
| Placebo | 1.9 | 4.2 | 1.3 |

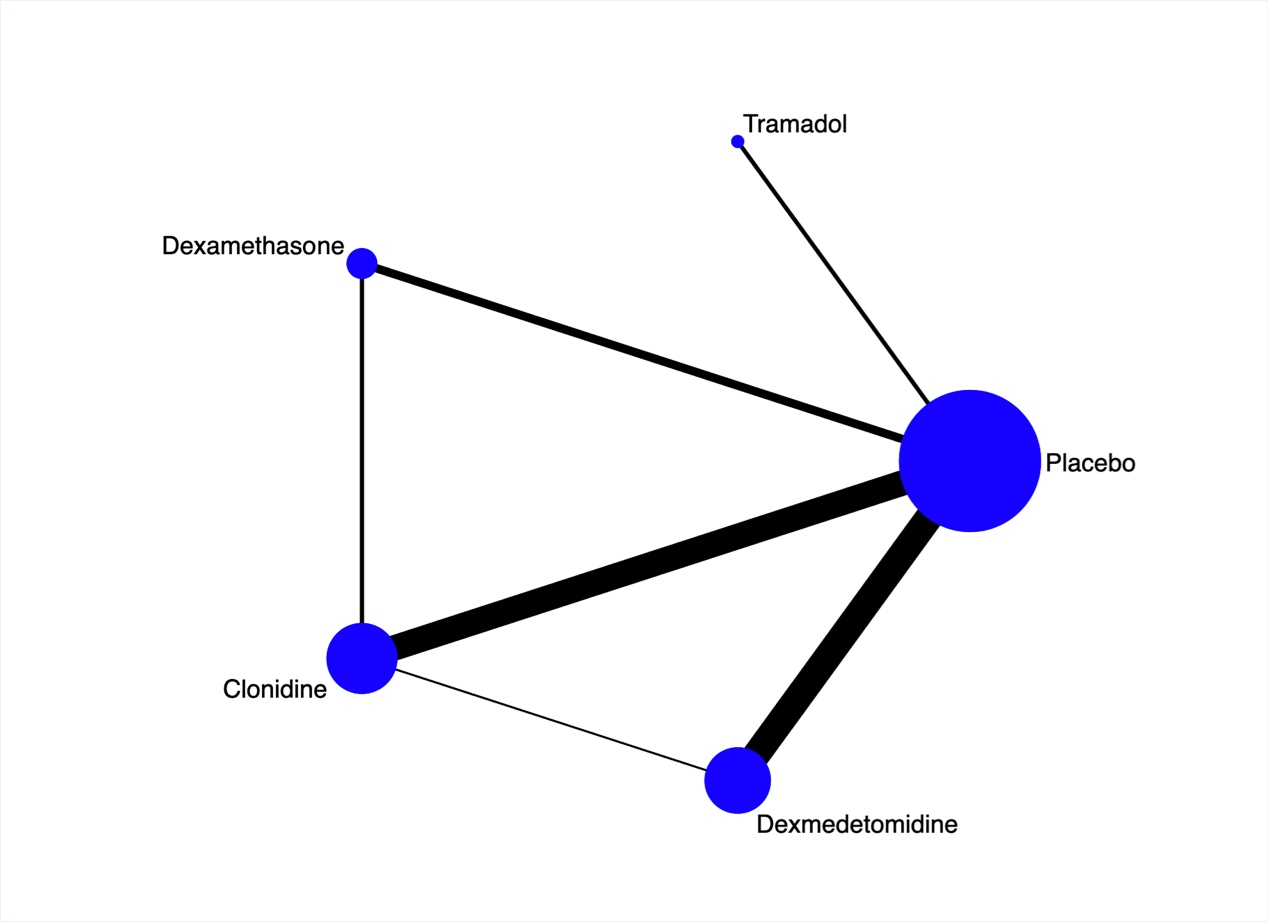
Surface under the cumulative ranking curve (SUCRA), a simple transformation of the mean rank, is used to provide the hierarchy for the all treatments. The larger the SUCRA value, the better the rank of the treatment.

**Figure 8**

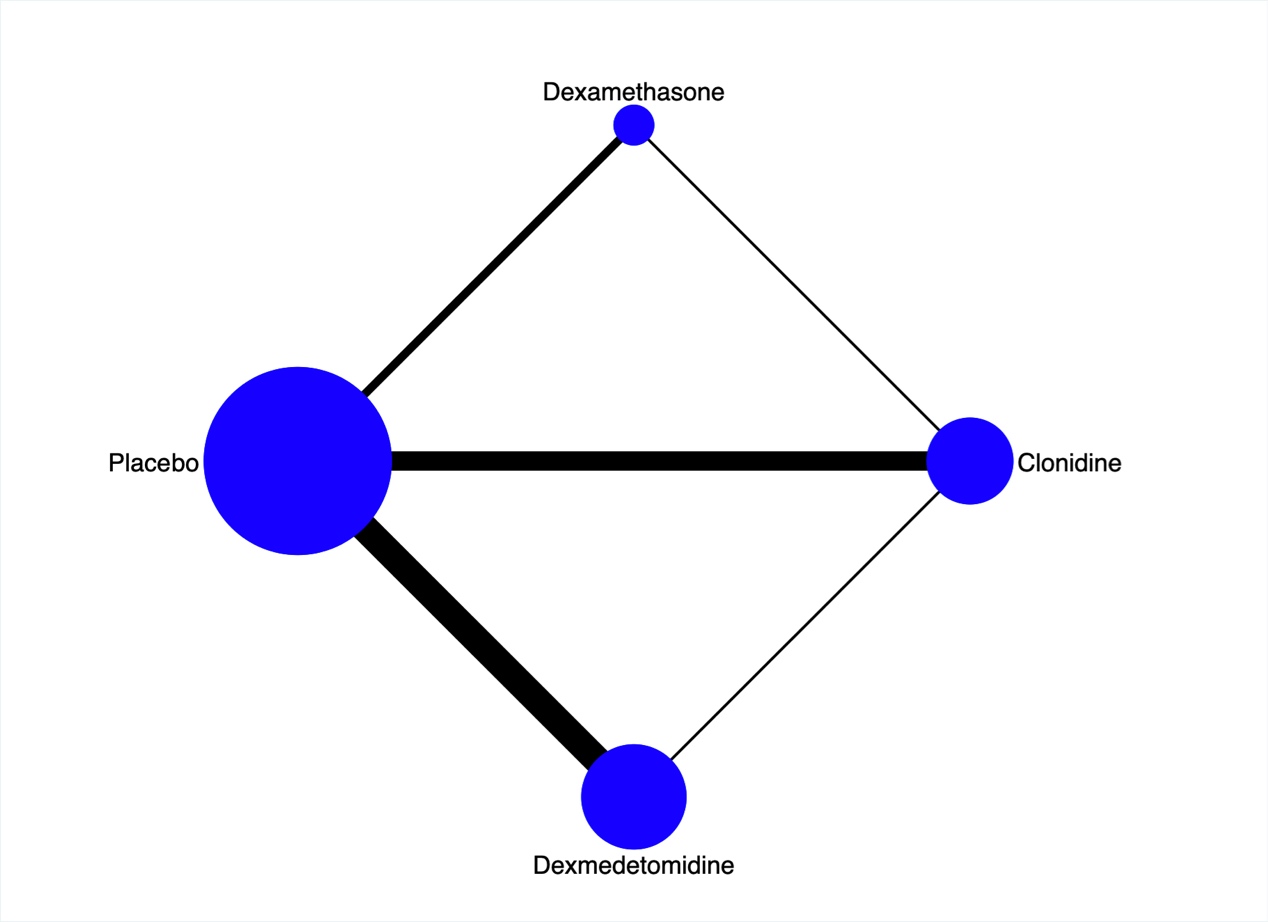
**A**



**B**



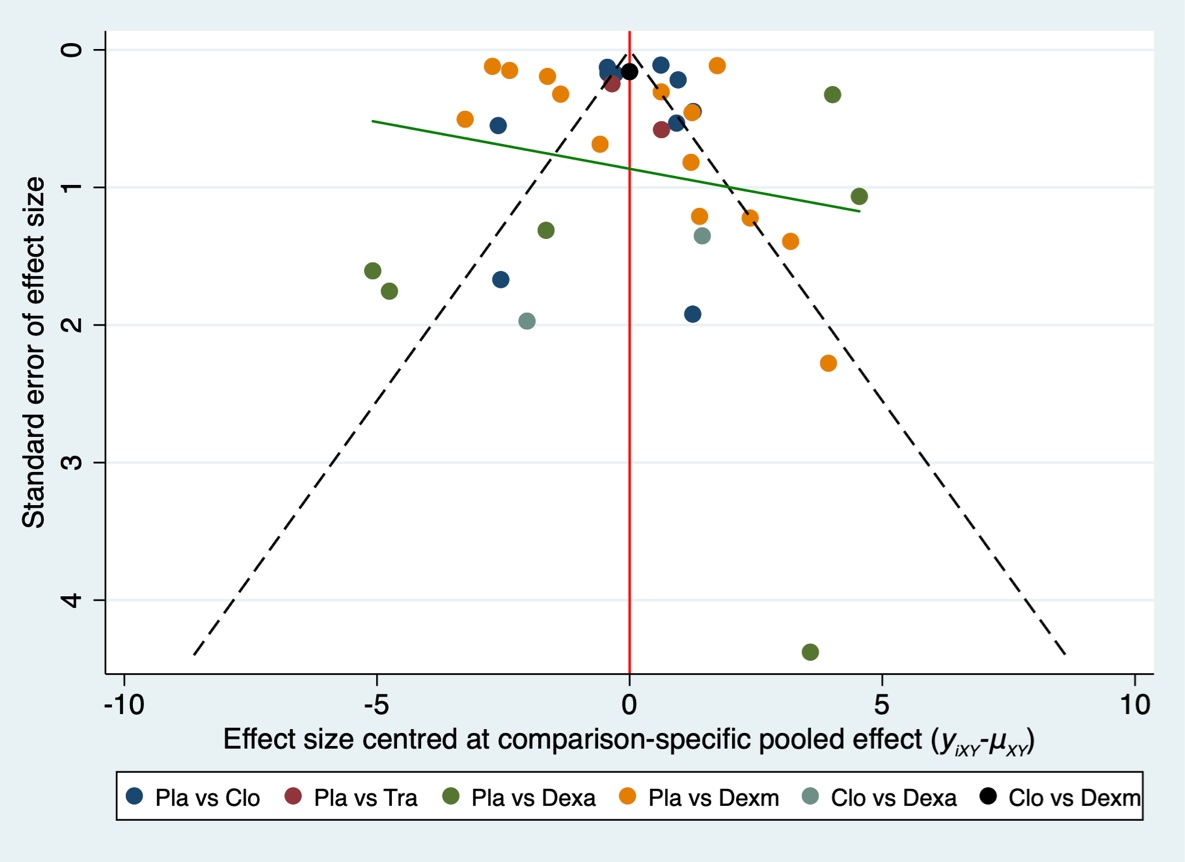
**C**



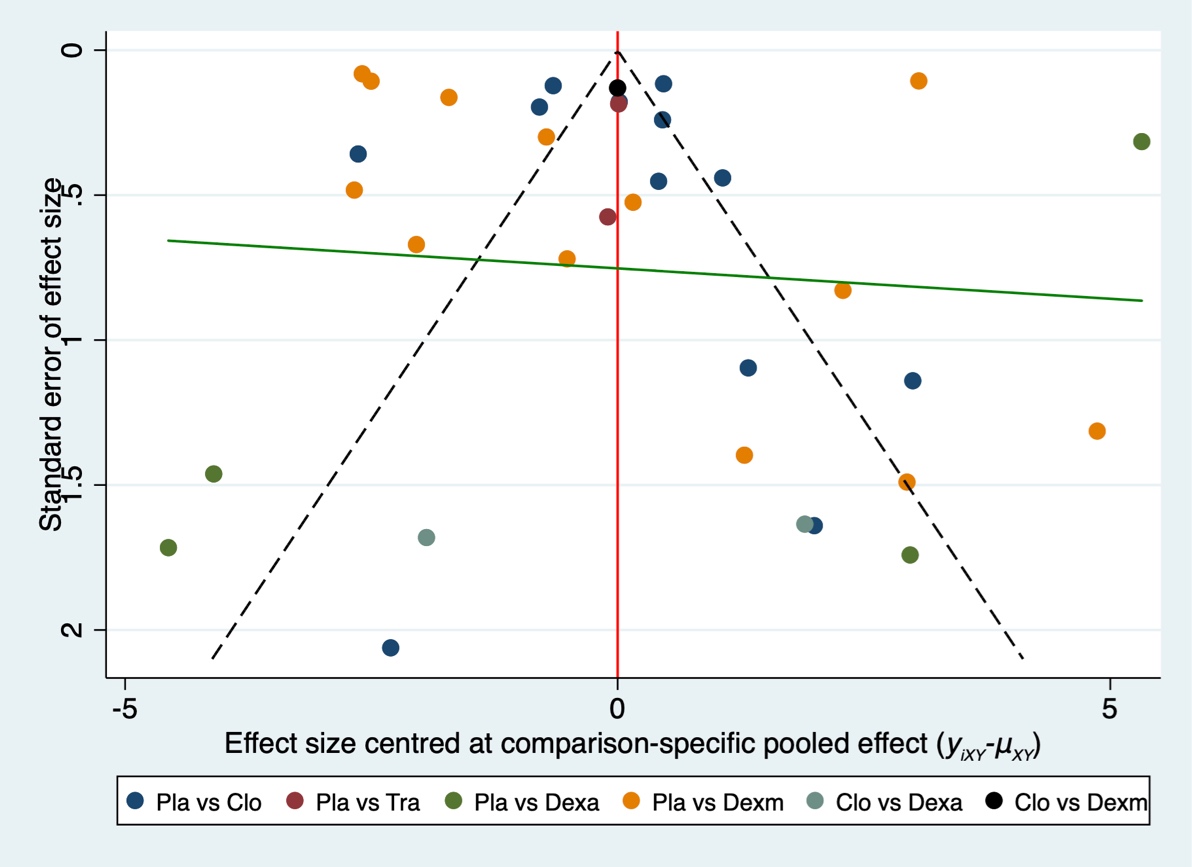
Network Plot for subgroup network meta-analysis of ropivacaine. A is a network plot of a subgroup analysis of sensory block time, B is a network plot of a subgroup analysis of motor block time, and C is a network plot of a subgroup analysis of the time of first analgesia request. Nodes are weighted according to the number of studies including the respective treatments. The widths of edges are weighted according to the number of studies in each comparison.

**Figure 9**

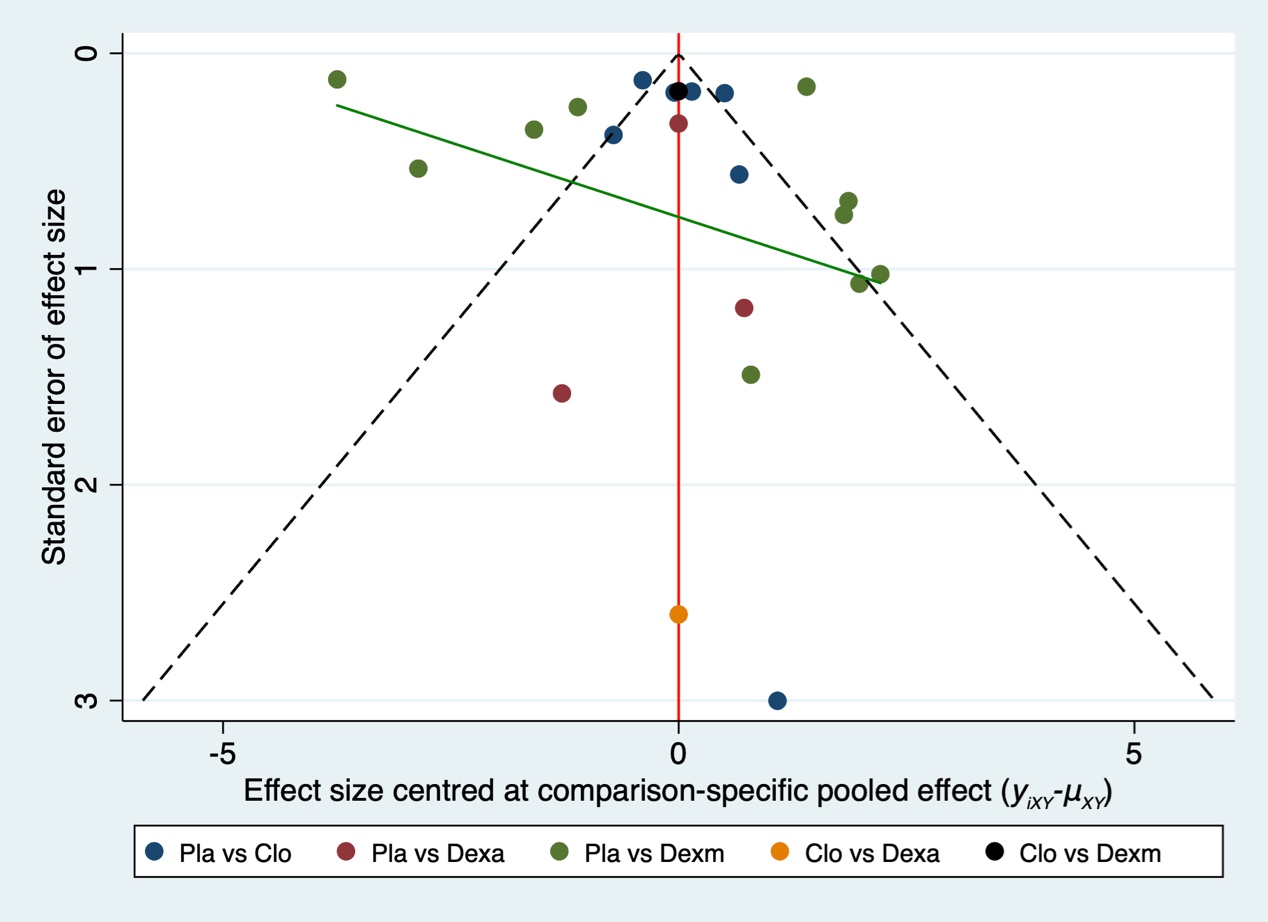
**A**



**B**



**C**



Comparison-adjust funnel plot for subgroup analysis of the analgesia network. A is a funnel plot of a subgroup analysis of sensory block time, B is a funnel plot of a subgroup analysis of motor block time, and C is a funnel plot of a subgroup analysis of the time of first analgesia request. The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The green line is the regression line. Different colors correspond to different comparisons. (Pla=placebo, Clo=clonidine, Tra=tramadol, Dexa=dexamethasone, Dexm=dexmedetomidine)