**Appendix Table D57. Dose response in adverse effects with divalproex sodium in children (results from randomized controlled clinical trial)5, 6**

| **Compared doses** | **Type of outcome** | **Reference** | **Events/**  **randomized with smaller dose** | **Events/**  **randomized with larger dose** | **Relative risk**  **(95% CI)** | **Absolute risk difference**  **(95% CI)** | **Arcsine transformed**  **Risk difference**  **(95% CI)** |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 250mg vs. 500mg | Abdominal pain | Apostol, 20085 | 1/83 | 6/74 | 0.1  (0.0 to 1.2) | -0.07  (-0.14 to 0.00) | -0.18  (-0.34 to -0.02) |
| 250mg vs. 1000mg | Abdominal pain | Apostol, 20085 | 1/83 | 3/75 | 0.3  (0.0 to 2.8) | -0.03  (-0.08 to 0.02) | -0.09  (-0.25 to 0.06) |
| 500mg vs. 1000mg | Abdominal pain | Apostol, 20085 | 6/74 | 3/75 | 2.0  (0.5 to 7.8) | 0.04  (-0.04 to 0.12) | 0.09  (-0.07 to 0.25) |
| 250mg vs. 500mg | Ammonia increased | Apostol, 20085 | 2/83 | 1/74 | 1.8  (0.2 to 19.3) | 0.01  (-0.03 to 0.05) | 0.04  (-0.12 to 0.20) |
| 250mg vs. 500mg | Ammonia increased  (>90 micromol/L) | Apostol, 20085 | 4/83 | 2/74 | 1.8  (0.3 to 9.5) | 0.02  (-0.04 to 0.08) | 0.06  (-0.10 to 0.21) |
| 250mg vs. 1000mg | Ammonia increased | Apostol, 20085 | 2/83 | 4/75 | 0.5  (0.1 to 2.4) | -0.03  (-0.09 to 0.03) | -0.08  (-0.23 to 0.08) |
| 250mg vs. 1000mg | Ammonia increased  (>90 micromol/L) | Apostol, 20085 | 4/83 | 8/75 | 0.5  (0.1 to 1.4) | -0.06  (-0.14 to 0.03) | -0.11  (-0.27 to 0.04) |
| 500mg vs. 1000mg | Ammonia increased | Apostol, 20085 | 1/74 | 4/75 | 0.3  (0.0 to 2.2) | -0.04  (-0.10 to 0.02) | -0.12  (-0.28 to 0.04) |
| 500mg vs. 1000mg | Ammonia increased  (>90 micromol/L) | Apostol, 20085 | 2/74 | 8/75 | 0.3  (0.1 to 1.2) | -0.08  (-0.16 to 0.00) | -0.17  (-0.33 to -0.01) |
| 250mg vs. 500mg | Any adverse event | Apostol, 20085 | 53/83 | 53/74 | 0.9  (0.7 to 1.1) | -0.08  (-0.22 to 0.07) | -0.08  (-0.24 to 0.07) |
| 250mg vs. 1000mg | Any adverse event | Apostol, 20085 | 53/83 | 48/75 | 1.0  (0.8 to 1.3) | 0.00  (-0.15 to 0.15) | 0.00  (-0.16 to 0.15) |
| 500mg vs. 1000mg | Any adverse event | Apostol, 20085 | 53/74 | 48/75 | 1.1  (0.9 to 1.4) | 0.08  (-0.07 to 0.23) | 0.08  (-0.08 to 0.24) |
| 250mg vs. 500mg | Cough | Apostol, 20085 | 1/83 | 4/74 | 0.2  (0.0 to 1.9) | -0.04  (-0.10 to 0.01) | -0.12  (-0.28 to 0.03) |
| 250mg vs. 1000mg | Cough | Apostol, 20085 | 1/83 | 2/75 | 0.5  (0.0 to 4.9) | -0.01  (-0.06 to 0.03) | -0.05  (-0.21 to 0.10) |
| 500mg vs. 1000mg | Cough | Apostol, 20085 | 4/74 | 2/75 | 2.0  (0.4 to 10.7) | 0.03  (-0.04 to 0.09) | 0.07  (-0.09 to 0.23) |
| 250mg vs. 500mg | Fatigue | Apostol, 20085 | 1/83 | 1/74 | 0.9  (0.1 to 14.0) | 0.00  (-0.04 to 0.03) | -0.01  (-0.16 to 0.15) |
| 250mg vs. 1000mg | Fatigue | Apostol, 20085 | 1/83 | 6/75 | 0.2  (0.0 to 1.2) | -0.07  (-0.13 to 0.00) | -0.18  (-0.33 to -0.02) |
| 500mg vs. 1000mg | Fatigue | Apostol, 20085 | 1/74 | 6/75 | 0.2  (0.0 to 1.4) | -0.07  (-0.13 to 0.00) | -0.17  (-0.33 to -0.01) |
| 250mg vs. 500mg | Gastroenteritis viral | Apostol, 20085 | 4/83 | 1/74 | 3.6  (0.4 to 31.2) | 0.03  (-0.02 to 0.09) | 0.10  (-0.05 to 0.26) |
| 250mg vs. 1000mg | Gastroenteritis viral | Apostol, 20085 | 4/83 | 4/75 | 0.9  (0.2 to 3.5) | -0.01  (-0.07 to 0.06) | -0.01  (-0.17 to 0.14) |
| 500mg vs. 1000mg | Gastroenteritis viral | Apostol, 20085 | 1/74 | 4/75 | 0.3  (0.0 to 2.2) | -0.04  (-0.10 to 0.02) | -0.12  (-0.28 to 0.04) |
| 250mg vs. 500mg | Infection, viral | Apostol, 20085 | 3/83 | 4/74 | 0.7  (0.2 to 2.9) | -0.02  (-0.08 to 0.05) | -0.04  (-0.20 to 0.11) |
| 250mg vs. 1000mg | Infection, viral | Apostol, 20085 | 3/83 | 0/75 | 6.3  (0.3 to 120.6) | 0.04  (-0.01 to 0.08) | 0.19  (0.04 to 0.35) |
| 500mg vs. 1000mg | Infection, viral | Apostol, 20085 | 4/74 | 0/75 | 9.1  (0.5 to 166.5) | 0.05  (0.00 to 0.11) | 0.23  (0.07 to 0.40) |
| 250mg vs. 500mg | Influenza | Apostol, 20085 | 1/83 | 5/74 | 0.2  (0.0 to 1.5) | -0.06  (-0.12 to 0.01) | -0.15  (-0.31 to 0.00) |
| 250mg vs. 1000mg | Influenza | Apostol, 20085 | 1/83 | 3/75 | 0.3  (0.0 to 2.8) | -0.03  (-0.08 to 0.02) | -0.09  (-0.25 to 0.06) |
| 500mg vs. 1000mg | Influenza | Apostol, 20085 | 5/74 | 3/75 | 1.7  (0.4 to 6.8) | 0.03  (-0.04 to 0.10) | 0.06  (-0.10 to 0.22) |
| 250mg vs. 500mg | Nasopharyngitis | Apostol, 20085 | 5/83 | 5/74 | 0.9  (0.3 to 3.0) | -0.01  (-0.08 to 0.07) | -0.01  (-0.17 to 0.14) |
| 250mg vs. 1000mg | Nasopharyngitis | Apostol, 20085 | 5/83 | 3/75 | 1.5  (0.4 to 6.1) | 0.02  (-0.05 to 0.09) | 0.05  (-0.11 to 0.20) |
| 500mg vs. 1000mg | Nasopharyngitis | Apostol, 20085 | 5/74 | 3/75 | 1.7  (0.4 to 6.8) | 0.03  (-0.04 to 0.10) | 0.06  (-0.10 to 0.22) |
| 250mg vs. 500mg | Nausea | Apostol, 20085 | 5/83 | 6/74 | 0.7  (0.2 to 2.3) | -0.02  (-0.10 to 0.06) | -0.04  (-0.20 to 0.12) |
| 250mg vs. 1000mg | Nausea | Apostol, 20085 | 5/83 | 7/75 | 0.6  (0.2 to 1.9) | -0.03  (-0.12 to 0.05) | -0.06  (-0.22 to 0.09) |
| 500mg vs. 1000mg | Nausea | Apostol, 20085 | 6/74 | 7/75 | 0.9  (0.3 to 2.5) | -0.01  (-0.10 to 0.08) | -0.02  (-0.18 to 0.14) |
| 250mg vs. 500mg | Pharyngolaryngeal pain | Apostol, 20085 | 1/83 | 5/74 | 0.2  (0.0 to 1.5) | -0.06  (-0.12 to 0.01) | -0.15  (-0.31 to 0.00) |
| 250mg vs. 1000mg | Pharyngolaryngeal pain | Apostol, 20085 | 1/83 | 1/75 | 0.9  (0.1 to 14.2) | 0.00  (-0.04 to 0.03) | -0.01  (-0.16 to 0.15) |
| 500mg vs. 1000mg | Pharyngolaryngeal pain | Apostol, 20085 | 5/74 | 1/75 | 5.1  (0.6 to 42.3) | 0.05  (-0.01 to 0.12) | 0.15  (-0.01 to 0.31) |
| 250mg vs. 500mg | Somnolence | Apostol, 20085 | 2/83 | 4/74 | 0.4  (0.1 to 2.4) | -0.03  (-0.09 to 0.03) | -0.08  (-0.24 to 0.08) |
| 250mg vs. 1000mg | Somnolence | Apostol, 20085 | 2/83 | 4/75 | 0.5  (0.1 to 2.4) | -0.03  (-0.09 to 0.03) | -0.08  (-0.23 to 0.08) |
| 500mg vs. 1000mg | Somnolence | Apostol, 20085 | 4/74 | 4/75 | 1.0  (0.3 to 3.9) | 0.00  (-0.07 to 0.07) | 0.00  (-0.16 to 0.16) |
| 250mg vs. 500mg | Upper respiratory tract infection | Apostol, 20085 | 12/83 | 3/74 | 3.6  (1.0 to 12.1) | 0.10  (0.02 to 0.19) | 0.19  (0.03 to 0.34) |
| 250mg vs. 1000mg | Upper respiratory tract infection | Apostol, 20085 | 3/74 | 4/75 | 0.8  (0.2 to 3.3) | -0.01  (-0.08 to 0.06) | -0.03  (-0.19 to 0.13) |
| 250mg vs. 1000mg | Upper respiratory tract infection | Apostol, 20085 | 12/83 | 4/75 | 2.7  (0.9 to 8.0) | 0.09  (0.00 to 0.18) | 0.16  (0.00 to 0.31) |
| 250mg vs. 500mg | Vomiting | Apostol, 20085 | 2/83 | 4/74 | 0.4  (0.1 to 2.4) | -0.03  (-0.09 to 0.03) | -0.08  (-0.24 to 0.08) |
| 250mg vs. 1000mg | Vomiting | Apostol, 20085 | 2/83 | 3/75 | 0.6  (0.1 to 3.5) | -0.02  (-0.07 to 0.04) | -0.05  (-0.20 to 0.11) |
| 500mg vs. 1000mg | Vomiting | Apostol, 20085 | 4/74 | 3/75 | 1.4  (0.3 to 5.8) | 0.01  (-0.05 to 0.08) | 0.03  (-0.13 to 0.19) |
| 250mg vs. 500mg | Weight increased | Apostol, 20085 | 5/83 | 1/74 | 4.5  (0.5 to 37.3) | 0.05  (-0.01 to 0.10) | 0.13  (-0.03 to 0.29) |
| 250mg vs. 1000mg | Weight increased | Apostol, 20085 | 1/74 | 5/75 | 0.2  (0.0 to 1.7) | -0.05  (-0.12 to 0.01) | -0.14  (-0.31 to 0.02) |
| 250mg vs. 1000mg | Weight increased | Apostol, 20085 | 5/83 | 5/75 | 0.9  (0.3 to 3.0) | -0.01  (-0.08 to 0.07) | -0.01  (-0.17 to 0.14) |
| 250mg vs. 500mg | Any adverse event | U.S. Food and Drug Administration6 | 54/83 | 53/74 | 0.9  (0.7 to 1.1) | -0.07  (-0.21 to 0.08) | 0.00  (-0.23 to 0.08) |
| 250mg vs. 1000mg | Any adverse event | U.S. Food and Drug Administration6 | 54/83 | 48/75 | 1.0  (0.8 to 1.3) | 0.01  (-0.14 to 0.16) | 0.00  (-0.15 to 0.17) |
| 500mg vs. 1000mg | Any adverse event | U.S. Food and Drug Administration6 | 53/74 | 48/75 | 1.1  (0.9 to 1.4) | 0.08  (-0.07 to 0.23) | 0.00  (-0.07 to 0.25) |
| 250mg vs. 1000mg | Serious adverse effects | U.S. Food and Drug Administration6 | 1/83 | 1/75 | 0.9  (0.1 to 14.2) | 0.00  (-0.04 to 0.03) | -0.01  (-0.16 to 0.15) |