**Appendix Table D6. Randomized controlled clinical trials that examined efficacy of preventive drugs in children with migraine**

| **Reference  Design**  **Sample**  **Number analyzed  % females** | **Age** | **Definition of migraine** | **Presence of aura** | **Baseline status** | **Overuse of drugs for acute migraine** | **Duration of migraine** | **Prior treatment** | **Subject compliance and suitability** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Ludvigsson, 19741  Design RCT Sample 32 Number analyzed 28 43.75% female | Eligible age 7 to16 years Mean age Not reported | Ad hoc Committee on classification of headache 1962, Classification of headache, J.Amer.med. Ass., Bille 1962 | 4/32 had visual aura | Mean 3.4 attacks of headache per month | Not reported | 4 years | Not reported | Not reported |
| Sillanpää, 19772 Design RCT Sample 57 Number analyzed 57 38.6% female | Eligible age 0-15 years Mean 11 years | Migraine was defined by the criteria of Vahlquist, i.e. paroxysmal headache separated by headache-free intervals and at least two of the following four: unilateral pain, nausea, visual aura and positive family history. | 12 patients in the clonidine group and 8 patients in the placebo group had classic migraine with visual aura. | Frequency of headache/month(n): 1-2: Clonidine: 8, Placebo: 7, 3-4: Clonidine: 12 and Placebo: 12 , 5-6: Clonidine: 3 and Placebo: 4, and >6: Clonidine: 5 and Placebo: 6; Intensity of headache: Mild: Clonidine: 2 and Placebo: 0; Moderate: Clonidine: 6 and Placebo: 8 and Severe: Clonidine: 20 and Placebo: 19; Duration of headache: < hours: Clonidine: 6 and Placebo: 6, 4-6 hours: Clonidine: 9 and Placebo: 11 and >6 hours: Clonidine: 13 and Placebo: 11 | Not reported | Not reported | Not reported | Not reported |
| Battistella, 19903  Design RCT Sample 37 Number analyzed Not reported 51.35% female | Eligible age 7 to 18 years Mean 12.2 years | Criteria of Ad Hoc Committee of the International Headache Society | 9 patients had migraine with aura and 28 had migraine without aura | Frequency of attacks/month: Placebo: 3.0±0.9 and in Nimodipine: 3.3 ±0.9; duration (number of hours/attack):Placebo: 6.9±2.0 and in Nimodipine: 7.5±2.0 | Not reported | Not reported | Prophylactic treatment was stopped for three months prior to the trial | Not reported |
| Battistella, 19934 Design RCT Sample 40 Number analyzed Not reported 45% female | Eligible age 7 to 18 years Mean 12.6 years | International Headache Society criteria for migraine | All patients had migraine without aura (inclusion criterion) | History of symptoms (yrs), mean (SD): 4.5 (1.3); mean frequency of attacks/month: Trazodone: 4.0±0.2 and Placebo: 3.5±0.1; Mean duration of attacks in hours: Trazodone: 20.2±1.3 and Placebo: 18.2±1.1 | Not reported | 4.5 years | Not reported | Not reported |
| Apostol, 20085  U.S. Food and Drug Administration, 20086 Design RCT Sample 305 Number analyzed 299 55% female | Eligible age 12 to 17 years Mean 14.2 years | International Headache Society criteria | Not reported | Migraine headaches within 3 months prior to screening: Mean (SD): Placebo: 16.7 (7.62), 250 mg DVPX ER: 16.6 (7.02), 500 mg DVPX ER: 18.0 (7.02), 1000 mg DVPX ER:17.3 (6.84) | Not reported | Not reported | Not reported | To document compliance with study medication, subjects were instructed to return all medication bottles and pill counts were performed. Site personnel were to counsel any subject with compliance <70%. |
| Lewis, 20097 Design RCT Sample 106 Number analyzed 103 61% female | Eligible age Between 12 and 17 years Mean 14.2 years | International Headache Society guidelines for pediatric migraine | Not reported | Mean migraine attacks, no/month: placebo: 4.1±1.48; 50mg topiramate: 4.1±1.74 and 100mg topiramate: 4.3±1.59 Mean migraine time: d/month: placebo: 6.1±3.02; 50mg topiramate: 6.4±2.86; and 100mg topiramate: 6.9±3.02 | Not reported | Not reported | Not reported | Subjects maintained medication records the accuracy of which was checked by their parents. |
| Winner, 20058 Design RCT Sample 162 Number analyzed 157 48.4% female | Eligible age 6 to 15 years Mean 11.1 years | According to International Headache Society classification of pediatric migraine with or without aura | Not reported | Mean (SD) monthly migraine days: topiramate: 5.4 (1.7) and placebo: 5.5 (2.0) | Not reported | Not reported | Not reported | Not reported |
| Olness, 19879 Design RCT Sample 33 Number analyzed 28 39.3% female | Eligible age 6 to 12 years Mean 9.2 years | Classic migraine, defined as paroxysmal headache associated with all of the following: 1) unilateral head pain, 2) nausea/ vomiting, 3) visual aura (scotomas, visual field defects) or other transitory neurologic disturbance (sensory or motor), and 4) a history of migraine on one of the parents or a sibling. | All children had classic migraine. | Not reported | Not reported | Not reported | Not reported | Compliance was monitored by pill counts and maintenance of diaries |

DVPX ER = Divalproex extended release; SD = standard deviation