

APPENDIX D. CHARACTERISTICS OF INCLUDED STUDIES

We characterized type of migraine based on review of full text articles as follows:

- **Episodic:** < 15 migraines or headaches/month, or provided a mean with standard deviations (SD) where the mean + 2 SDs < 15
- **Chronic:** ≥ 15 migraines or headaches/month
- **Episodic + Chronic:** Studies only reporting baseline as a range of headaches which crossed > 15 headaches/month
- **Not reported:** If studies only reported migraines > 2/month and no other data OR studies that provided no description of baseline migraines/headaches per month
- **Other:** Studies not meeting any of these prior criteria

Table D-1. Characteristics of Included Studies for Map 1 (Benefits and Harms)

Study Details	Patients	Interventions
Amitriptyline		
Reference: Couch 2011 ²⁴ Country: USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 391 Mean Age (Years): 34.9 Gender (% female): 81% History of migraine: NR Type of migraine: Episodic + Chronic	Amitriptyline-25 mg daily
Reference: Goncalves 2016 ²⁵ Country: Brazil Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 196 Mean Age (Years): 37 Gender (% female): 75 History of migraine: 22 years Type of migraine: Episodic	Amitriptyline-25 mg daily Melatonin-3 mg Placebo
Atogepant		
Reference: Goadsby 2020 ²⁶ Country: USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 834 Mean Age (Years): 40 Gender (% female): 87 History of migraine: 19 years Type of migraine: Episodic	Atogepant-10 mg once daily Atogepant-30 mg once daily Atogepant-60 mg once daily Atogepant-30 mg twice daily Atogepant-60 mg twice daily Placebo

Study Details	Patients	Interventions
Candesartan		
Reference: Stovner 2014 ²⁷ Country: Norway Study Design: Crossover Overall RoB: High	Number of Randomized Patients: 72 Mean Age (Years): 37 Gender (% female): 87 History of migraine: 19 years Type of migraine: Episodic + Chronic	Candesartan-16 mg Placebo Propranolol-160 mg slow-release
Reference: Trovnik 2003 ²⁸ Country: Norway Study Design: Crossover Overall RoB: Unclear	Number of Randomized Patients: 60 Mean Age (Years): NR Gender (% female): NR History of migraine: NR Type of migraine: Episodic + Chronic	Candesartan-16 mg Placebo
Eptinezumab		
Reference: Ashina 2020 ²⁹ Country: Georgia, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 898 Mean Age (Years): 39.8 Gender (% female): 84.3 History of migraine: 17.4 years Type of migraine: Episodic	Eptinezumab-30 mg/day, up to 4 doses Eptinezumab-100 mg/day, up to 4 doses Eptinezumab-300 mg/day, up to 4 doses Placebo
Reference: Dodick 2019 ³⁰ Country: Australia, Georgia, New Zealand, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 665 Mean Age (Years): 37 Gender (% female): 87 History of migraine: 17.9 Type of migraine: Chronic + Medication Overuse	Eptinezumab-10 mg, single dose Eptinezumab-30 mg, single dose Eptinezumab-100 mg, single dose Eptinezumab-300 mg, single dose Placebo
Reference: Lipton 2020 ³¹ Country: Belgium, Czech Republic, Denmark, Georgia, Germany, Hungary, Italy, Russia, Slovakia, Spain, Ukraine, UK, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 1121 Mean Age (Years): 40.5 Gender (% female): 88.2 History of migraine: 18.1 years Type of migraine: Chronic	Eptinezumab-100 mg, up to 2 doses Eptinezumab-300 mg, up to 2 doses Placebo

Study Details	Patients	Interventions
Erenumab		
Reference: Dodick 2018 ³² Country: Denmark, France, Greece, Portugal, Russia, Spain, Switzerland, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 577 Mean Age (Years): 42 Gender (% female): 85 History of migraine: 21 years Type of migraine: Episodic	Erenumab-70 mg monthly injection Placebo
Reference: Goadsby 2017 ³³ Country: Austria, Belgium, Canada, Czech Republic, Finland, Germany, Netherlands, Poland, Slovakia, Sweden, Turkey, UK, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 955 Mean Age (Years): 41 Gender (% female): 85 History of migraine: NR Type of migraine: Episodic	Erenumab-70 mg subcutaneous Erenumab-140 mg subcutaneous Placebo
Reference: Reuter 2018 ³⁴ Country: Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 246 Mean Age (Years): 44 Gender (% female): 81 History of migraine: NR Type of migraine: Episodic	Erenumab-140 mg every 4 weeks Placebo
Reference: Sakai 2019 ³⁵ Country: Japan Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 475 Mean Age (Years): 44.4 Gender (% female): 84.4 History of migraine: NR Type of migraine: Episodic	Erenumab-28 mg Erenumab-70 mg Erenumab-140 mg Placebo
Reference: Sun 2016 ³⁶ Country: Canada, Denmark, Finland, Germany, Norway, Portugal, Sweden, USA Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 483 Mean Age (Years): 41.1 Gender (% female): 81 History of migraine: 21.3 years Type of migraine: Episodic	Erenumab-7 mg/month Erenumab-21 mg/month Erenumab-70 mg/month Placebo

Study Details	Patients	Interventions
Reference: Teppers 2017 ³⁷ Country: Canada, Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, UK, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 667 Mean Age (Years): 42 Gender (% female): 82.8 History of migraine: 21 years Type of migraine: Chronic	Erenumab-70 mg Erenumab-140 mg Placebo
Fremanezumab		
Reference: Bigal 2015 ³⁸ Country: USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 297 Mean Age (Years): 41 Gender (% female): 88 History of migraine: 19 years Type of migraine: Episodic	Fremanezumab-225 mg one injection Fremanezumab-675 mg total over 3 injections Placebo
Reference: Bigal 2015 ³⁹ Country: USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 264 Mean Age (Years): 40.7 Gender (% female): 86 History of migraine: 18.3 years Type of migraine: Chronic	Fremanezumab-900 mg/month Fremanezumab-225 to 675 mg/month Placebo
Reference: Dodick 2018 ⁴⁰ Country: Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 875 Mean Age (Years): 41.8 Gender (% female): 85 History of migraine: 20 years Type of migraine: Episodic	Fremanezumab-monthly Fremanezumab-single higher dose Placebo
Reference: Ferrari 2019 ⁴¹ Country: Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 838 Mean Age (Years): 46.2 Gender (% female): 83.6 History of migraine: 24.2 years Type of migraine: Episodic + Chronic	Fremanezumab-675 mg, administered quarterly Fremanezumab-225 to 675 mg, administered monthly Placebo

Study Details	Patients	Interventions
Reference: Silberstein 2017 ⁴² Country: USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 1,130 Mean Age (Years): 41 Gender (% female): 88 History of migraine: 20 years Type of migraine: Chronic	Fremanezumab-675 mg single injection at baseline Fremanezumab-3 injections, one per month, at doses of 675 mg, 225 mg and 225 mg. Placebo
Galcanezumab		
Reference: Detke 2018 ⁴³ Country: Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, Netherlands, Spain, Taiwan, UK, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 1,117 Mean Age (Years): 41 Gender (% female): 85 History of migraine: 21 years Type of migraine: Chronic	Galcanezumab-120 mg injection once a month Galcanezumab-240 mg injection once a month Placebo
Reference: Dodick 2014 ⁴⁴ Country: USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 218 Mean Age (Years): 41.3 Gender (% female): 85 History of migraine: NR Type of migraine: Episodic	Galcanezumab-150 mg subcutaneous every 2 weeks Placebo
Reference: Mulleners 2020 ⁴⁵ Country: Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, Netherlands, South Korea, Spain, UK, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 463 Mean Age (Years): 46 Gender (% female): 86 History of migraine: 23 years Type of migraine: Episodic + Chronic	Galcanezumab-120 mg injection once a month Placebo
Reference: Sakai 2020 ⁴⁶ Country: Japan Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 459 Mean Age (Years): 44 Gender (% female): 84 History of migraine: 21 years Type of migraine: Episodic	Galcanezumab-120 mg per month (one injection a month) Galcanezumab-240 mg a month (one injection a month) Placebo

Study Details	Patients	Interventions
Reference: Skljarevski 2018 ⁴⁷ Country: USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 410 Mean Age (Years): 40.2 Gender (% female): 83 History of migraine: NR Type of migraine: Episodic	Galcanezumab-5 mg Galcanezumab-50 mg Galcanezumab-120 mg Galcanezumab-300 mg Placebo
Reference: Skljarevski 2018 ⁴⁸ Country: Argentina, Czech Republic, Germany, Israel, Mexico, Netherlands, South Korea, Spain, Taiwan, UK, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 922 Mean Age (Years): 42 Gender (% female): 85 History of migraine: 20 years Type of migraine: Episodic	Galcanezumab-120 mg/month Galcanezumab-240 mg/month Placebo
Reference: Stauffer 2018 ⁴⁹ Country: USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 862 Mean Age (Years): 40.7 Gender (% female): 84 History of migraine: 20.1 years Type of migraine: Episodic	Galcanezumab-120 mg per month Galcanezumab-240 mg per month Placebo
Lisinopril		
Reference: Schrader 2001 ⁵⁰ Country: Norway Study Design: Crossover Overall RoB: High	Number of Randomized Patients: 60 Mean Age (Years): 41 Gender (% female): 81 History of migraine: NR Type of migraine: Episodic	Lisinopril-10 mg/day Placebo
Metoprolol		
Reference: Andersson 1983 ⁵¹ Country: Denmark, Sweden Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 71 Mean Age (Years): NR Gender (% female): 84.5 History of migraine: NR Type of migraine: Episodic	Metoprolol-200 mg Placebo
Reference: Bayer 2019 ⁵² Country: Germany Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 130 Mean Age (Years): 43.6 Gender (% female): 60.8 History of migraine: NR Type of migraine: NR	Metoprolol-47.5 to 95 mg/day Placebo

Study Details	Patients	Interventions
Reference: Steiner 1988 ⁵³ Country: UK Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 59 Mean Age (Years): 37 Gender (% female): 23.8 History of migraine: NR Type of migraine: Episodic	Metoprolol-50 mg - twice daily Placebo
Non-Invasive Vagal Nerve Stimulation		
Reference: Diener 2019 ⁵⁴ Country: Belgium, Denmark, Germany, Greece, Netherlands, Norway, Spain, UK Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 341 Mean Age (Years): 42 Gender (% female): 84 History of migraine: NR Type of migraine: Episodic	Non-invasive vagal nerve stimulation (gammaCore) Sham
OnabotulinumtoxinA		
Reference: Anand 2006 ⁵⁵ Country: India Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 32 Mean Age (Years): NR Gender (% female): 75 History of migraine: NR Type of migraine: Episodic	OnabotulinumtoxinA-50 U Placebo
Reference: Aurora 2010 ⁵⁶ Country: Canada, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 679 Mean Age (Years): 42 Gender (% female): 87 History of migraine: NR Type of migraine: Chronic	OnabotulinumtoxinA-155-195 U injected twice Placebo
Reference: Aurora 2007 ⁵⁷ Country: Canada, USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 369 Mean Age (Years): 45 Gender (% female): 89.2 History of migraine: 22.7 years Type of migraine: Episodic	OnabotulinumtoxinA-100 Units Placebo
Reference: Barrientos 2003 ⁵⁸ Country: Chile Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 30 Mean Age (Years): 41.1 Gender (% female): 80 History of migraine: 15.6 years Type of migraine: Episodic	OnabotulinumtoxinA-50 U Placebo

Study Details	Patients	Interventions
Reference: Cady 2008 ⁵⁹ Country: USA Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 61 Mean Age (Years): 42 Gender (% female): 85 History of migraine: NR Type of migraine: Episodic + Chronic	OnabotulinumtoxinA-139 U in one set of injections Placebo
Reference: Diener 2010 ⁶⁰ Country: Germany, Sweden, USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 705 Mean Age (Years): 41 Gender (% female): 85.4 History of migraine: 18 years Type of migraine: Chronic	OnabotulinumtoxinA-155 Units Placebo
Reference: Elkind 2006 ⁴ Country: USA Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 418 Mean Age (Years): 44 Gender (% female): 85 History of migraine: 21 years Type of migraine: Episodic	OnabotulinumtoxinA-7.5 U single set of injections OnabotulinumtoxinA-25 U OnabotulinumtoxinA-50 U Placebo
Reference: Evers 2004 ⁶¹ Country: Germany Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 60 Mean Age (Years): 38 Gender (% female): 83 History of migraine: 22 years Type of migraine: Episodic migraine + Tension type headache	OnabotulinumtoxinA-100 units (frontal + neck) OnabotulinumtoxinA-16 Units (frontal), placebo for neck Placebo
Reference: Freitag 2008 ⁶² Country: USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 60 Mean Age (Years): 42 Gender (% female): 73 History of migraine: NR Type of migraine: Chronic	OnabotulinumtoxinA-100 U one set of injections Placebo
Reference: Hou 2015 ⁶³ Country: China Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 102 Mean Age (Years): 41 Gender (% female): 75 History of migraine: 6 years Type of migraine: Episodic + Chronic	OnabotulinumtoxinA-Fixed sites 25 U OnabotulinumtoxinA-Acupoints 25 U Placebo

Study Details	Patients	Interventions
Reference: Pijpers 2019 ⁶⁴ Country: Netherlands Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 179 Mean Age (Years): 45.2 Gender (% female): 76 History of migraine: 27 years Type of migraine: Chronic migraine + Medication Overuse Headache	OnabotulinumtoxinA-155 Units Placebo
Reference: Relja 2007 ³ Country: Belgium, Croatia, Denmark, Finland, France, Germany, Norway, Switzerland, UK Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 495 Mean Age (Years): 43 Gender (% female): 88 History of migraine: 23 years Type of migraine: Episodic	OnabotulinumtoxinA-225 U single set of injections OnabotulinumtoxinA-150 U single set of injections OnabotulinumtoxinA-75 U Placebo
Reference: Sandrini 2011 ⁶⁵ Country: Italy Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 68 Mean Age (Years): 48.8 Gender (% female): 80.4 History of migraine: 20 years Type of migraine: Chronic + medication overuse	OnabotulinumtoxinA-100 U Placebo
Reference: Saper 2007 ⁶⁶ Country: USA Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 232 Mean Age (Years): 43.6 Gender (% female): 85.8 History of migraine: 23.8 years Type of migraine: Episodic	OnabotulinumtoxinA-10 U, Frontal administration OnabotulinumtoxinA-6 U, Temporal administration OnabotulinumtoxinA-9 U, Glabellar administration OnabotulinumtoxinA-25 U, Frontal, Temporal, and Glabellar administration Placebo
Reference: Silberstein 2000 ⁶⁷ Country: USA Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 123 Mean Age (Years): 44 Gender (% female): 85 History of migraine: 23 years Type of migraine: Episodic	OnabotulinumtoxinA-25 U single set of injections OnabotulinumtoxinA-75 U single set of injections Placebo

Study Details	Patients	Interventions
Reference: Silberstein 2005 ¹⁹ Country: Canada, USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 702 Mean Age (Years): 43.4 Gender (% female): 82.9 History of migraine: 13.7 years Type of migraine: Chronic	OnabotulinumtoxinA-225 U OnabotulinumtoxinA-150 U OnabotulinumtoxinA-75 U Placebo
Reference: Vo 2007 ⁶⁸ Country: USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 49 Mean Age (Years): 43 Gender (% female): 85 History of migraine: 20 years Type of migraine: Episodic + Chronic	OnabotulinumtoxinA-135 - 205 U, single set of injections Placebo-single set of injections
Propranolol		
Reference: al-Qassab 1993 ⁶⁹ Country: UK Study Design: Crossover Overall RoB: High	Number of Randomized Patients: 45 Mean Age (Years): 36 Gender (% female): 80 History of migraine: 9 years Type of migraine: Episodic + Chronic	Propranolol-160 mg/day (Long-Acting) Propranolol-80 mg/day (Long-Acting) Placebo
Reference: Dahlof 1987 ⁷⁰ Country: Sweden Study Design: Crossover Overall RoB: Unclear	Number of Randomized Patients: 28 Mean Age (Years): NR Gender (% female): NR History of migraine: NR Type of migraine: Episodic	Propranolol-40 mg three times a day Placebo
Reference: Diener 1996 ⁷¹ Country: NR Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 214 Mean Age (Years): 39 Gender (% female): 78 History of migraine: 19 years Type of migraine: Episodic	Propranolol-120 mg/day Cyclandelate-Dose range not reported Placebo
Reference: Diener 2004 ⁷² Country: Australia, Denmark, Finland, Germany, Italy, Netherlands, South Africa, South Korea, Spain, Sweden, Taiwan, UK Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 575 Mean Age (Years): 40.9 Gender (% female): 79.8 History of migraine: NR Type of migraine: Episodic	Propranolol-160 mg/day Topiramate-100 mg/day Topiramate-200 mg/day Placebo

Study Details	Patients	Interventions
Reference: Forssman 1976 ⁷³ Country: Sweden Study Design: Crossover Overall RoB: Unclear	Number of Randomized Patients: 32 Mean Age (Years): 37.4 Gender (% female): 87.5 History of migraine: 18.9 years Type of migraine: Episodic	Propranolol-40 mg Placebo
Reference: Pradalier 1989 ⁷⁴ Country: France Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 74 Mean Age (Years): 37.4 Gender (% female): 75.7 History of migraine: NR Type of migraine: Episodic	Propranolol-160 mg/day Placebo
Reference: Sargent 1985 ⁷⁵ Country: USA Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 161 Mean Age (Years): 30 Gender (% female): 79 History of migraine: 20 years Type of migraine: Episodic	Propranolol-40 mg three times a day Naproxen-550 mg twice daily Placebo
Reference: Stovner 2014 ²⁷ Country: Norway Study Design: Crossover Overall RoB: High	Number of Randomized Patients: 72 Mean Age (Years): 37 Gender (% female): 82 History of migraine: 19 years Type of migraine: Episodic + Chronic	Propranolol-160 mg slow-release Candesartan-16 mg Placebo
Reference: Tfelt 1984 ⁷⁶ Country: Denmark, Finland, Norway Study Design: Crossover Overall RoB: Unclear	Number of Randomized Patients: 96 Mean Age (Years): 39.5 Gender (% female): 74 History of migraine: 20.9 years Type of migraine: Episodic	Propranolol-80 mg twice daily Timolol-10 mg twice daily Placebo
Reference: Wideroe 1974 ⁷⁷ Country: Norway Study Design: Crossover Overall RoB:	Number of Randomized Patients: 30 Mean Age (Years): 38 Gender (% female): 86.7 History of migraine: NR Type of migraine: Episodic	Propranolol-160 mg/day Placebo
Topiramate		
Reference: Brandes 2004 ⁷⁸ Country: Canada, USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 483 Mean Age (Years): 39 Gender (% female): 87 History of migraine: NR Type of migraine: Episodic	Topiramate-50 mg daily Topiramate-100 mg daily Topiramate-200 mg daily Placebo

Study Details	Patients	Interventions
Reference: de Tommaso 2007 ⁷⁹ Country: Italy Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 45 Mean Age (Years): 37.9 Gender (% female): 77.8 History of migraine: NR Type of migraine: NR	Topiramate-100 mg daily Placebo Levitaracetam-1000 mg daily
Reference: Diener 2007 ⁸⁰ Country: Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Norway, Poland, Portugal, Russia, Saudi Arabia, Slovenia, Spain, Switzerland, Turkey, UK Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 514 Mean Age (Years): 39.8 Gender (% female): 87 History of migraine: NR Type of migraine: Episodic	Topiramate-50 - 200 mg daily Placebo
Reference: Diener 2004 ⁷² Country: Australia, Denmark, Finland, Germany, Italy, Netherlands, South Africa, South Korea, Spain, Sweden, Taiwan, UK Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 575 Mean Age (Years): 40.9 Gender (% female): 79.8 History of migraine: NR Type of migraine: Episodic	Topiramate-100 mg/day Topiramate-200 mg/day Propranolol-160 mg/day Placebo
Reference: Diener 2007 ⁸¹ Country: NR Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 59 Mean Age (Years): 46 Gender (% female): 75 History of migraine: NR Type of migraine: Chronic	Topiramate-50-200 mg/day Placebo
Reference: Gupta 2007 ⁸² Country: India Study Design: Crossover Overall RoB: Unclear	Number of Randomized Patients: 60 Mean Age (Years): 29.4 Gender (% female): 78.3 History of migraine: 5.1 years Type of migraine: Episodic + Chronic	Topiramate-50 mg Lamotrigine-50 mg Placebo

Study Details	Patients	Interventions
Reference: Lipton 2011 ⁸³ Country: USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 385 Mean Age (Years): 40 Gender (% female): 89 History of migraine: 20 years Type of migraine: Episodic	Topiramate-100 mg daily Placebo
Reference: Mei 2004 ⁸⁴ Country: Italy Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 115 Mean Age (Years): 39 Gender (% female): 54 History of migraine: NR Type of migraine: Episodic	Topiramate-100 mg Placebo
Reference: Mei 2006 ⁸⁵ Country: Italy Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 50 Mean Age (Years): 45.9 Gender (% female): 68.6 History of migraine: 5.0 years Type of migraine: Chronic + Medication Overuse	Topiramate-Titrated from 25 mg/day to 100 mg/day Placebo
Reference: Silberstein 2006 ⁸⁶ Country: USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 213 Mean Age (Years): 40.5 Gender (% female): 85.8 History of migraine: NR Type of migraine: Episodic	Topiramate-200 mg daily Placebo
Reference: Silberstein 2007 ⁸⁷ Country: USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 328 Mean Age (Years): 38.2 Gender (% female): 85.3 History of migraine: 9.2 years Type of migraine: Chronic	Topiramate-100 mg/day Placebo
Reference: Silberstein 2004 ⁸⁸ Country: USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 487 Mean Age (Years): 40 Gender (% female): 89 History of migraine: NR Type of migraine: Episodic	Topiramate-50 mg/day Topiramate-100 mg/day Topiramate-200 mg/day Placebo

Study Details	Patients	Interventions
Reference: Silvestrini 2003 ⁸⁹ Country: Italy Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 28 Mean Age (Years): 43.5 Gender (% female): 64 History of migraine: NR Type of migraine: Chronic migraine + Medication overuse headache	Topiramate-50 mg daily Placebo
Reference: Storey 2001 ⁹⁰ Country: USA Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 40 Mean Age (Years): 38.2 Gender (% female): 97.5 History of migraine: NR Type of migraine: Episodic	Topiramate-200 mg daily Placebo
Transcutaneous supraorbital nerve stimulation		
Reference: Schoenen 2013 ¹⁷ Country: Belgium Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 67 Mean Age (Years): 37 Gender (% female): 91 History of migraine: 16 years Type of migraine: Episodic	Transcutaneous supraorbital nerve stimulation-Cefaly Sham
Valproate/Valproic Acid		
Reference: Ebrahimi-Monfared 2017 ¹⁰ Country: Iran Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 126 Mean Age (Years): 38.9 Gender (% female): 51 History of migraine: 7.4 years Type of migraine: Chronic	Valproate/Valproic acid-200 mg daily Melatonin-3 mg Placebo
Reference: Freitag 2002 ¹¹ Country: USA Study Design: Parallel Overall RoB: Low	Number of Randomized Patients: 239 Mean Age (Years): 41 Gender (% female): 79 History of migraine: 20 years Type of migraine: Episodic	Valproate/Valproic acid-500 to 1000 mg/day Placebo
Reference: Jensen 1994 ¹² Country: Denmark Study Design: Crossover Overall RoB: High	Number of Randomized Patients: 43 Mean Age (Years): 46 Gender (% female): 86 History of migraine: NR Type of migraine: Episodic	Valproate/Valproic acid-1000 to 1500 mg/day Placebo

Study Details	Patients	Interventions
Reference: Klapper 1997 ¹³ Country: USA Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 176 Mean Age (Years): 40.8 Gender (% female): 89 History of migraine: 21.6 years Type of migraine: Episodic	Valproate/Valproic acid-500 mg/day Valproate/Valproic acid-1000 mg/day Valproate/Valproic acid-1500 mg/day Placebo
Reference: Mathew 1995 ¹⁴ Country: USA Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 107 Mean Age (Years): 45.6 Gender (% female): 78 History of migraine: NR Type of migraine: Episodic	Valproate/Valproic acid-Titrated between 250 and 750 mg/day Placebo
Reference: Sadeghian 2015 ¹⁵ Country: NR Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 105 Mean Age (Years): 35 Gender (% female): 73 History of migraine: 5 months Type of migraine: NR	Valproate/Valproic acid-500 mg/day Levitaracetam-250-500 mg/day Placebo
Reference: Yurekli 2008 ¹⁶ Country: Turkey Study Design: Parallel Overall RoB: Unclear	Number of Randomized Patients: 29 Mean Age (Years): 40.1 Gender (% female): 87.5 History of migraine: NR Type of migraine: Chronic	Valproate/Valproic acid-500 to 1000 mg/day Placebo
Venlafaxine		
Reference: Ozyalcin 2005 ¹⁸ Country: Turkey Study Design: Parallel Overall RoB: High	Number of Randomized Patients: 60 Mean Age (Years): 36.5 Gender (% female): 90 History of migraine: NR Type of migraine: Episodic	Venlafaxine-75 mg daily Venlafaxine-150 mg Placebo

NR: not reported; RoB: risk of bias; UK: United Kingdom; USA: United States of America

Table D-2. Studies Included in Maps 2 or 3

Study	Included for Map 2 or 3
ACE-inhibitor/ARB	
Diener 2009 ⁹¹	Map 2
Schrader 2001 ⁵⁰	Map 2
Sonbolestan 2013 ⁹²	Map 2
Stovner 2014 ²⁷	Map 2, Map 3
Tronvik 2003 ²⁸	Map 2
Alpha agonist	
Adam 1978 ⁹³	Map 2
Boisen 1978 ⁹⁴	Map 2
Martucci 1985 ⁹⁵	Map 2, Map 3
Mondrup 1977 ⁹⁶	Map 2
Ryan 1975 ⁹⁷	Map 2
Shafar 1972 ⁹⁸	Map 2
Anti-epileptic	
Afshari 2012 ⁹⁹	Map 3
Ali 2010 ¹⁰⁰	Map 3
Ashtari 2008 ¹⁰¹	Map 3
Bavrasad 2010 ¹⁰²	Map 3
Blumenfeld 2008 ¹⁰³	Map 3
Bostani 2013 ¹⁰⁴	Map 3
Brandes 2004 ⁷⁸	Map 2, Map 3
Cady 2011 ¹⁰⁵	Map 3
Cady 2012 ¹⁰⁶	Map 3
Chitsaz 2012a ¹⁰⁷	Map 3
Chitsaz 2012b ¹⁰⁸	Map 3
Choudhary 2017 ¹⁰⁹	Map 3
Cosentino 2013 ¹¹⁰	Map 3
Dakhale 2019 ¹¹¹	Map 3
Di 2000 ¹¹²	Map 2
Diener 2004 ⁷²	Map 2, Map 3
Diener 2007a ⁸⁰	Map 2
Diener 2007b ⁸¹	Map 2
Dodick 2009 ¹¹³	Map 3
Ebrahimi-Monfared 2017 ¹⁰	Map 2, Map 3
Facco 2013 ¹¹⁴	Map 3
Freitag 2002 ¹¹	Map 2
Gupta 2007 ⁸²	Map 2, Map 3
Hering 1992 ¹¹⁵	Map 2

Study	Included for Map 2 or 3
Hesami 2018a ¹¹⁶	Map 3
Hesami 2018b ¹¹⁷	Map 3
Jensen 1994 ¹²	Map 2
Kalita 2013 ¹¹⁸	Map 3
Kaniecki 1997 ¹¹⁹	Map 3
Karimi 2019 ¹²⁰	Map 3
Kashipazha 2017 ¹²¹	Map 3
Keskinbora 2008 ¹²²	Map 3
Klapper 1997 ¹³	Map 2, Map 3
Krymchantowski 2012x ¹²³	Map 3
Lai 2017 ¹²⁴	Map 3
Lipton 2011 ⁸³	Map 2
Liu 2017 ¹²⁵	Map 3
Lo 2010 ¹²⁶	Map 3
Luo 2012 ¹²⁷	Map 3
Mansoureh 2008 ¹²⁸	Map 3
Mathew 1995 ¹⁴	Map 2
Mathew 2001 ¹²⁹	Map 2
Mathew 2009 ¹³⁰	Map 3
Mei 2004 ⁸⁴	Map 2
Mei 2006 ⁸⁵	Map 2
Millán 2008 ¹³¹	Map 3
Millán-Guerrero 2007 ¹³²	Map 3
Mitsikostas 1997 ¹³³	Map 3
Mohammadianinejad 2011 ¹³⁴	Map 3
Naderinabi 2017 ¹³⁵	Map 3
Rahimdel 2015 ¹³⁶	Map 3
Rodríguez 2010 ¹³⁷	Map 3
Sadeghian 2015 ¹⁵	Map 2, Map 3
Shaygannejad 2006 ¹³⁸	Map 3
Silberstein 2004 ⁸⁸	Map 2, Map 3
Silberstein 2006 ⁸⁶	Map 2
Silberstein 2007 ⁸⁷	Map 2
Silberstein 2008 ¹³⁹	Map 2
Silvestrini 2003 ⁸⁹	Map 2
Spira 2003 ¹⁴⁰	Map 2
Steiner 1997 ¹⁴¹	Map 2
Storey 2001 ⁹⁰	Map 2
Varkey 2011 ¹⁴²	Map 3

Study	Included for Map 2 or 3
Xu 2017 ¹⁴³	Map 3
Yang 2011 ¹⁴⁴	Map 3
Yurekli 2008 ¹⁶	Map 2
Zain 2013 ¹⁴⁵	Map 3
de Tommaso 2007 ⁷⁹	Map 2, Map 3
Storey 2001 ⁹⁰	Map 2
Varkey 2011 ¹⁴²	Map 3
Xu 2017 ¹⁴³	Map 3
Yang 2011 ¹⁴⁴	Map 3
Yurekli 2008 ¹⁶	Map 2
Zain 2013 ¹⁴⁵	Map 3
de Tommaso 2007 ⁷⁹	Map 2, Map 3
Beta-blocker	
Albers 1989 ¹⁴⁶	Map 3
al-Qassab 1993 ⁶⁹	Map 2, Map 3
Andersson 1983 ⁵¹	Map 2
Ashtari 2008 ¹⁰¹	Map 3
Bayer 2019 ⁵²	Map 2
Bordini 1997 ¹⁴⁷	Map 3
Borgesén 1976 ¹⁴⁸	Map 2
Carroll 1990 ¹⁴⁹	Map 3
Dahlof 1987 ⁷⁰	Map 2, Map 3
Dakhale 2019 ¹¹¹	Map 3
Diener 1996 ⁷¹	Map 2, Map 3
Diener 2001 ¹⁵⁰	Map 3
Diener 2002 ¹⁵¹	Map 3
Diener 2004 ⁷²	Map 2, Map 3
Domingues 2009 ¹⁵²	Map 3
Forssman 1976 ⁷³	Map 2
Forssman 1983 ¹⁵³	Map 2, Map 3
Gawel 1992 ¹⁵⁴	Map 3
Gerber 1995 ¹⁵⁵	Map 3
Ghobadi 2013 ¹⁵⁶	Map 3
Hesse 1994 ¹⁵⁷	Map 3
Johannsson 1987 ¹⁵⁸	Map 2
Johnson 1986 ¹⁵⁹	Map 2, Map 3
Kangasniemi 1984 ¹⁶⁰	Map 3
Kaniecki 1997 ¹¹⁹	Map 3
Kaushik 2005 ¹⁶¹	Map 3

Study	Included for Map 2 or 3
Kjaersgkd Rasmussen 1994 ¹⁶²	Map 3
Mathew 1981 ¹⁶³	Map 2, Map 3
Mikkelsen 1986 ¹⁶⁴	Map 2, Map 3
Millán-Guerrero 2014 ¹⁶⁵	Map 3
Nadelmann 1986 ¹⁶⁶	Map 2
Nambiar 2011 ¹⁶⁷	Map 3
Pradalier 1989 ⁷⁴	Map 2
Ryan 1984 ¹⁶⁸	Map 3
Salviz 2016 ¹⁶⁹	Map 3
Sargent 1985 ⁷⁵	Map 2, Map 3
Schellenberg 2008 ¹⁷⁰	Map 3
Shimell 1990 ¹⁷¹	Map 3
Sorensen 1991 ¹⁷²	Map 3
Steiner 1988 ⁵³	Map 2
Stellar 1984 ¹⁷³	Map 2
Stovner 2014 ²⁷	Map 2, Map 3
Streng 2006 ¹⁷⁴	Map 3
Sudilovsky 1987 ¹⁷⁵	Map 3
Tfelt-Hansen 1984 ⁷⁶	Map 2, Map 3
Van 1997 ¹⁷⁶	Map 2, Map 3
Weber 1972 ¹⁷⁷	Map 2
Wideroe 1974 ⁷⁷	Map 2
Ziegler 1987 ¹⁷⁸	Map 2, Map 3
Ziegler 1993 ¹⁷⁹	Map 2, Map 3
Botulinum Toxin Type A	
Anand 2006 ⁵⁵	Map 2
Aurora 2007 ⁵⁷	Map 2
Aurora 2010 ⁵⁶	Map 2
Barrientos 2003 ⁵⁸	Map 2
Blumenfeld 2008 ¹⁰³	Map 3
Cady 2008 ⁵⁹	Map 2
Cady 2011 ¹⁰⁵	Map 3
Chankrachang 2011 ¹⁸⁰	Map 2, Map 3
Chitsaz 2012a ¹⁰⁷	Map 3
Diener 2010 ⁶⁰	Map 2
Elkind 2006 ⁴	Map 2, Map 3
Evers 2004 ⁶¹	Map 2, Map 3
Freitag 2008 ⁶²	Map 2
Hou 2015 ⁶³	Map 2, Map 3

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Magalhaes 2010 ¹⁸¹	Map 3
Mathew 2009 ¹³⁰	Map 3
Millán-Guerrero 2009 ¹⁸²	Map 3
Naderinabi 2017 ¹³⁵	Map 3
Petri 2009 ¹⁸³	Map 2, Map 3
Pijpers 2019 ⁶⁴	Map 2
Relja 2007 ³	Map 2, Map 3
Sandrini 2011 ⁶⁵	Map 2
Saper 2007 ⁶⁶	Map 2, Map 3
Shehata 2016 ¹⁸⁴	Map 3
Silberstein 2000 ⁶⁷	Map 2, Map 3
Silberstein 2005 ¹⁹	Map 2, Map 3
Vo 2007 ⁶⁸	Map 2
Calcium channel blockers	
Ahuja 1985 ¹⁸⁵	Map 2, Map 3
Albers 1989 ¹⁴⁶	Map 3
Ansell 1988 ¹⁸⁶	Map 2
Gelmers 1989a ¹⁸⁷	Map 2
Gelmers 1989b ¹⁸⁸	Map 2
Ghobadi 2013 ¹⁵⁶	Map 3
Havanka-Kanniainen 1985 ¹⁸⁹	Map 2, Map 3
Lamsudin 1993 ¹⁹⁰	Map 3
Leandri 1990 ¹⁹¹	Map 2
Markley 1984 ¹⁹²	Map 2
McArthur 1989 ¹⁹³	Map 2
Nuti 1996 ¹⁹⁴	Map 3
Stewart 1988 ¹⁹⁵	Map 2
CGRP antagonist	
Ashina 2020 ²⁹	Map 2, Map 3
Bigal 2015a ³⁸	Map 2, Map 3
Bigal 2015b ³⁹	Map 2, Map 3
Detke 2018 ⁴³	Map 2, Map 3
Dodick 2014a ¹⁹⁶	Map 2
Dodick 2014b ⁴⁴	Map 2
Dodick 2018a ³²	Map 2
Dodick 2018b ⁴⁰	Map 2, Map 3
Dodick 2019 ³⁰	Map 2, Map 3
Ferrari 2019 ⁴¹	Map 2, Map 3
Goadsby 2017 ³³	Map 2, Map 3

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Goadsby 2020 ²⁶	Map 2, Map 3
Lipton 2020 ³¹	Map 2, Map 3
Mulleners 2020 ⁴⁵	Map 2
Reuter 2018 ³⁴	Map 2
Sakai 2019 ³⁵	Map 2, Map 3
Sakai 2020 ⁴⁶	Map 2, Map 3
Silberstein 2017 ⁴²	Map 2, Map 3
Skljarevski 2018a ⁴⁷	Map 2, Map 3
Skljarevski 2018b ⁴⁸	Map 2, Map 3
Stauffer 2018 ⁴⁹	Map 2, Map 3
Sun 2016 ³⁶	Map 2, Map 3
Tepper 2017 ³⁷	Map 2, Map 3
Device	
Deng 2020 ²⁰	Map 3
Diener 2019 ⁵⁴	Map 2
Schoenen 2013 ¹⁷	Map 2
Other antidepressant	
Adly 1992 ¹⁹⁷	Map 2
Bank 1994 ¹⁹⁸	Map 3
Bulut 2004 ¹⁹⁹	Map 3
Colucci d'Amato 1999 ²⁰⁰	Map 2
Liu 2017 ¹²⁵	Map 3
Ozyalcin 2005 ¹⁸	Map 2, Map 3
Rampello 2004 ²⁰¹	Map 3
Salviz 2016 ¹⁶⁹	Map 3
Saper 1994 ²⁰²	Map 2
Steiner 1998 ²⁰³	Map 2
Tarlaci 2009 ²⁰⁴	Map 3
Tricyclic antidepressant	
Bank 1994 ¹⁹⁸	Map 3
Bruno 2018 ²⁰⁵	Map 3
Bulut 2004 ¹⁹⁹	Map 3
Couch 1979 ²⁰⁶	Map 2
Couch 2011 ²⁴	Map 2
Dodick 2009 ¹¹³	Map 3
Domingues 2009 ¹⁵²	Map 3
Gomersall 1973 ²⁰⁷	Map 2
Goncalves 2016 ²⁵	Map 2, Map 3
Kalita 2013 ¹¹⁸	Map 3

Study	Included for Map 2 or 3
Keskinbora 2008 ¹²²	Map 3
Krymchantowski 2002 ²⁰⁸	Map 3
Krymchantowski 2012y ¹²³	Map 3
LampI 2009 ²⁰⁹	Map 3
Magalhaes 2010 ¹⁸¹	Map 3
Mathew 1981 ¹⁶³	Map 2, Map 3
Nelson 1998 ²¹⁰	Map 3
Rampello 2004 ²⁰¹	Map 3
Rodríguez 2010 ¹³⁷	Map 3
Santiago 2014 ²¹¹	Map 3
Villani 2017 ²¹²	Map 3
Ziegler 1987 ¹⁷⁸	Map 2, Map 3
Ziegler 1993 ¹⁷⁹	Map 2, Map 3