Supplemental Online Content

VanderPluym JH, Halker Singh RB, Urtecho M, et al. Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. *JAMA*. doi:10.1001/jama.2021.7939

This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Search strategy

Ovid

Database(s): APA PsycInfo 1806 to February Week 3 2021, EBM Reviews - Cochrane Central Register of Controlled Trials January 2021, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 19, 2021, Embase 1974 to 2021 February 24, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to February 24, 2021

Search Strategy:

#	Searches
1	exp Migraine Disorders/dt, th [Drug Therapy, Therapy]
2	migraine*.ti,ab,hw,kw.
3	exp narcotic analgesic agent/
4	exp Analgesics, Opioid/
5	(acetorphine or acetylcodeine or acetylmethadol or Alfentanil or Alphaprodine or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or "Brompton mixture" or Buprenorphine or Butorphanol or ciramadol or cocodamol or Codeine or codydramol or conorfone or cyclazocine or Dextromoramide or Dextropropoxyphene or dextrorphan or dezocine or diamorphine or diconal or dihydrocodeine or dihydroetorphine or Dihydromorphine or dimethylthiambutene or Diphenoxylate or dipipanone or enadoline or eptazocine or ethylketazocine or Ethylketocyclazocine or Ethylmorphine or etonitazene or Etorphine or etoxeridine or faxeladol or Fentanyl or furethidine or gelonida or Heroin or Hydrocodone or isalmadol or isomethadone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or Levorphanol or Meperidine or Meptazinol or metazocine or Methadone or "Methadyl Acetate" or methylsamidorphan or Morphine or "morphinomimetic agent*" or "morphinomimetic drug*" or morphinone or Nalbuphine or narcotic* or nicocodine or nicomorphine or noracymethadol or norbuprenorphine or nordextropropoxyphene or normorphine or norpethidine or norpropoxyphene or "o nortramadol" or oliceridine or opiate or Opiate* or opioid* or Opium or oripavine or Oxycodone or Oxymorphone or pentamorphone or Pentazocine or pethidine or phenadoxone or phenaridine or Phenazocine or phencyclidine or Phenoperidine or picenadol or piminodine or Pirinitramide or piritramide or profadol or Promedol or propiram or sameridine or samidorphan or semorphone or Sufentanil or tapentadol or thebaine or tifluadom or Tilidine or tonazocine or Tramadol or trimeperidine).ti,ab,hw,kw.
6	exp Anti-Inflammatory Agents, Non-Steroidal/
7	exp cyclooxygenase inhibitors/
8	exp cyclooxygenase 2 inhibitors/
9	Aspirin/
10	sulindac/
11	(Aceclofenac or Acemetacin or "Acetylsalicylic acid" or Alclofenac or Aminopyrine or Amodiaquine or Amoxiprin or Ampyrone or Antipyrine or Apazone or Aspirin or Azapropazone or Benorilate or Benorylate or Bromelains or Bromfenac or "BW-755C" or Celecoxib or "Choline magnesium salicylate" or "Choline magnesium trisalicylate" or clinoril or Clofazimine or Clofezone or Clonixin or "COX-1 inhibitor*" or "COX-2

inhibitor*" or "COX-2 selective inhibitor*" or Coxib* or Curcumin or "Cyclooxygenase 1 inhibitor*" or "Cyclooxygenase 2 inhibitor*" or "Cyclooxygenase inhibitor*" or "Cyclo-oxygenase inhibitor*" or Dapsone or Dexibuprofen or Dexketoprofen or Diclofenac or Diflunisal or Dipyrone or Droxicam or Epirizole or Ethenzamide or Etodolac or Etoricoxib or Faislamine or Fenbufen or Fenoprofen or "Flufenamic acid" or Flunoxaprofen or Flurbiprofen or "Glycyrrhizic Acid" or Ibuprofen or Ibuproxam or Indomethacin or Indoprofen or Kebuzone or Ketoprofen or Ketorolac or Licofelone or Lornoxicam or Loxoprofen or Lumiracoxib or "Magnesium salicylate" or "Meclofenamic Acid" or "Mefenamic Acid" or Meloxicam or Mesalamine or Metamizole or "Methyl salicylate" or Mofebutazone or Nabumetone or Naproxen or "Niflumic Acid" or "Nonsteroidal antiinflammator*" or "Nonsteroidal anti-inflammator*" or "Non-steroidal antiinflammator*" or "Non-steroidal anti-inflammator*" or "Nordihydroguaiaretic Acid" or NSAID* or osenal or Oxametacin or Oxaprozin or Oxyphenbutazone or Parecoxib or "Pentosan Sulfuric Polyester" or Phenazone or Phenylbutazone or Piroxicam or Pirprofen or Prenazone or Proglumetacin or Rofecoxib or Salicylamide or Salicylate or Sulfasalazine or Sulfinpyrazone or Sulindac or Suprofen or Tenoxicam or "Tiaprofenic acid" or "Tolfenamic acid" or Tolmetin or Valdecoxib).ti,ab,hw,kw.

12 exp Tryptamines/

13 exp triptan derivative/

14 ("5-ht" or "5-hydroxytryptamine*" or "5-methoxytryptamine*" or dimethyltryptamine* or enteramine* or hippophaine* or hydroxytryptamine* or indolylethylamine* or meksamine* or methoxydimethyltryptamine* or methoxytryptamine* or methylbufotenin or mexamine* or Serotonin or triptan* or tryptamine*).ti,ab,hw,kw.

15 exp Ergot Alkaloids/

16 (Bromocriptine* or Cabergoline* or "clavine alkaloid*" or "clavines alkaloid*" or Dihydroergocornine* or Dihydroergocristine* or Dihydroergocryptine* or Dihydroergotamine* or Dihydroergotoxine* or Ergoline* or "Ergoloid Mesylate*" or Ergonovine* or "ergot agent*" or "ergot alkaloid*" or "ergot drug*" or "ergot medication*" or Ergotamine* or Ergotamines or "ergotoxine alkaloid*" or "ergots alkaloid*" or Lisuride* or "Lysergic Acid" or "Lysergic Acid Diethylamide*" or Metergoline* or Methylergonovine* or Methysergide* or Nicergoline* or Pergolide*).ti,ab,hw,kw.

17 exp Analgesics/

18 (Acetaminophen or Adenosine or Amantadine or Amitriptyline or analgesic* or analgetic* or anbesol or anodyne* or anpirtoline or antalgic* or antinociceptive* or antrafenine or auralgan or axomadol or befiradol or bicifadine or brivaracetam or brivoligide or bromadoline or "Calcitonin Gene-Related Peptide Receptor Antagonist*" or cannabidivarin or capsaicin or Carbachol or Carbamazepine or cebranopadol or cibinetide or cizolirtine or Clonidine or crobenetine or Cyclazocine or dapansutrile or dasolampanel or davasaicin or deacetyllappaconitine or "Dentin Desensitizing" or "desensitizing agent*" or "desensitizing drug*" or "desensitizing medication*" or Dexmedetomidine or difelikefalin or Dihydroergotamine or dimiracetam or dizatrifone or doxpicomine or drinidene or Dronabino or Duloxetine or ecopladib or edronocaine or efipladib or elismetrep or "embelate potassium" or enkephalin or epibatidine or equagesic or Ergotamine or ethoheptazine or fadolmidine or fasinumab or "floctafenic acid" or floctafenine or flunixin or "flunixin meglumine" or flupirtine or Flurbiprofen or frakefamide or fulranumab or

funapide or Gabapentin or gefapixant or giripladib or "glafenic acid" or Glafenine or "gw 493838" or "gw 842166" or hasamal or ibudilast or Ibuprofen or indantadol or Interleukin or Ketamine or lacosamide or lappaconitine or lenabasum or letimide or lexanopadol or "Magnesium Sulfate" or mavatrep or Medetomidine or Methotrimeprazine or Milnacipran or Mitoxantrone or Nefopam or neurotropin or "Nitrous Oxide" or nuvanil or olodanrigan or olorinab or olvanil or "omega conotoxin" or panidex or "pf 3557156" or "pf 4136309" or "pf 4480682" or "pf 592379" or "pf 738502" or Phenacetin or Pizotyline or pravadoline or Pregabalin or Quinine or ralfinamide or retigabine or ruzadolane or sampirtine or senrebotase or shogaol or strascogesic or tanezumab or tazadolene or tebanicline or tetrodotoxin or tivanisiran or traxoprodil or vedaclidine or vixotrigine or Xylazine).ti,ab,hw,kw.

19 exp Muscle Relaxants, Central/

20 exp muscle relaxant agent/

21 (afloqualone or alcuronium or "atracurium besilate" or azumolene or baclofen or Baclofent or botulinum or branaplam or Carisoprodol or "chandonium iodide" or Chlormezanone or Chlorphenesin or chlorproethazine or Chlorzoxazone or cisatracurium or curare or curaremimetic* or curariform or curarizing or Dantrolene or decamethonium or "depolarizing neuromuscular" or deutolperisone or diadonium or Diazepam or "dihydro beta erythroidine" or dimethyltubocurarine or doxacurium or duador or eperisone or fazadinium or febarbamate or flumetramide or gallamine or gantacurium or "hexafluronium bromide" or idrocilamide or inaperisone or lanperisone or "mebezonium iodide" or Medazepam or Mephenesin or Meprobamate or metaxalone or Methocarbamol or mivacurium or "Muscle relaxant*" or "muscle relaxing" or "musculotropic relaxant*" or "musculotropic relaxing" or myorelaxant or myotonolytic* or nefopam or nelezaprine or "neuromuscular agent*" or "neuromuscular blocker*" or "neuromuscular blocking" or "neuromuscular depolarizing agent*" or "neuromuscular depolarizing drug*" or "neuromuscular depolarizing medication*" or "neuromuscular drug*" or "neuromuscular medication*" or "neuromuscular nondepolarizing agent*" or "neuromuscular nondepolarizing drug*" or "neuromuscular nondepolarizing medication*" or "neuromuscular synapse blocking agent*" or "neuromuscular synapse blocking drug*" or "neuromuscular synapse blocking medication*" or "nondepolarizing neuromuscular blocking agent*" or "nondepolarizing neuromuscular blocking drug*" or "nondepolarizing neuromuscular blocking medication*" or norgesic or Orphenadrine or pancuronium or phenprobamate or pipecuronium or promoxolane or pyrocurine or Quinine or "rapacuronium bromide" or rocuronium or silperisone or styramate or suxamethonium or "tiemonium methylsulfate" or tizanidine or Tolperisone or toxiferine or "tubocurarine chloride" or vecuronium or vesamicol or Xylazine or Zoxazolamine).ti,ab,hw,kw.

22 exp Antiemetics/

23 exp Nausea/dt [Drug Therapy]

24 exp Vomiting/dt [Drug Therapy]

25 (((drug* or agent* or medication*) adj3 (nausea or vomit*)) or alizapride or "anti emetic*" or antiemetic* or antimetic* or "anti-metic*" or antinausea* or "anti-nausea*" or antivomit* or "anti-vomit*" or Aprepitant or azasetron or batanopride or belidral or bendectin or benzquinamide or bromopride or buclizine or casopitant or chlorcyclizine or chlorphenethazine or Chlorpromazine or cinnarizine or cisapride or clebopride or Cyclizine

or dazopride or debendox or Dexamethasone or Diazepam or difenidol or Dimenhydrinate or Diphenhydramine or dixyrazine or "dolasetron mesilate" or Domperidone or Doxylamine or dronabinol or Droperidol or exepanol or ezlopitant or fabesetron or fosaprepitant or fosnetupitant or Granisetron or Haloperidol or hydrodolasetron or icospiramide or indisetron or lerisetron or lintopride or Lorazepam or lurosetron or maropitant or Meclizine or meclozine or Methylprednisolone or Metoclopramide or metopimazine or nabilone or netupitant or norchlorpromazine or Olanzapine or Ondansetron or Palonosetron or pancopride or Prochlorperazine or Promazine or promethazine or ramosetron or renzapride or ricasetron or rolapitant or Scopolamine or sulpiride or telmapitant or tetrahydrocannabinol or Thiethylperazine or transmer or Trifluoperazine or Triflupromazine or trimethobenzamide or Tropisetron or vestipitant or vofopitant or zacopride).ti,ab,hw,kw.

26 exp Cannabis/

27 exp cannabinoid/

28 exp "cannabis use"/

29 exp Marijuana Smoking/

30 exp Cannabinoids/

31 exp Cannabidiol/

32 ("1 butyl 3 1 naphthoyl indole" or "11 hydroxydronabinol" or "2 arachidonoylglycerol" or "2 methyl 3 1 naphthoyl 1 propylindole" or "3 1 naphthoyl 1 pentylindole" or "3 2 iodo 5 nitrobenzoyl 1 1 methyl 2 piperidinylmethyl indole" or "3 hydroxy delta9 tetrahydrocannabinol" or "ajulemic acid" or anandamide or bhang or bhangs or cannabi or cannabichromene or cannabidiol or cannabielsoin or cannabigerol or cannabinoid or cannabinol or cannabis or cannador or charas or Cindica or deacetyllevonantradol or dexanabinol or dextronantradol or dronabinol or endocannabinoid or ganja or ganjas or hashish or hashishs or hemp or hemps or levonantradol or marihuana* or marijuana* or methanandamide or "n oleoylethanolamine" or nabilone or nabiximols or nantradol or "noladin ether" or palmidrol or tetrahydrocannabinol or "tetrahydrocannabinolic acid" or virodhamine).mp.

33 exp Biofeedback, Psychology/

34 ("alpha feedback*" or biofeedback* or "bogus physiological feedback*" or "brainwave feedback*" or "eeg feedback*" or "electroencephalography feedback*" or "electromyography feedback*" or "false physiological feedback*" or myofeedback* or neurofeedback* or "psychophysiologic feedback*").ti,ab,hw,kw.

35 Electric Stimulation Therapy/

36 exp neuromodulation/

37 (((Electric* or electro or galvano or Transcutaneous*) adj3 (stimulat* or stimulus)) or electrostimulation* or electrostimulus or electrotherap* or "E-stim" or ESTIM or FES or galvanostimulation* or galvanostimulus or Neuromodulation or neuromodulatory).ti,ab,hw,kw.

38 exp Cognitive Therapy/

39 exp Cognitive Behavior Therapy/

40 (CBT or "Cognitive behavioral therap*" or "Cognitive therap*").ti,ab,hw,kw.

41 exp Acupuncture/

42 exp Acupuncture Therapy/

43 (acupressure or acupuncture or "auricular needl*" or auriculotherapy or "ear needl*" or electroacupuncture or moxibustion or Shiatsu or "Tui Na").ti,ab,hw,kw.

44 exp exercise/

45 exp exercise therapy/

46 (aerobics or anaerobics or bicycling or biking or "endurance training" or exercis* or "fitness training" or isometrics or "physical exertion" or "physical activit*" or "resistance training" or running or "strength training" or swimming or walking or weightlifting).ti,ab,hw,kw.

47 (drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or therap* or treat*).ti,ab,hw,kw.

48 or/3-47

49 2 and 48

50 1 or 49

51 exp evidence based medicine/

52 exp meta analysis/

53 exp Meta-Analysis as Topic/

54 exp "systematic review"/

55 exp Guideline/ or exp Practice Guideline/

56 exp controlled study/

57 exp Randomized Controlled Trial/

58 exp triple blind procedure/

59 exp Double-Blind Method/

60 exp Single-Blind Method/

61 exp latin square design/

62 exp Placebos/

63 exp Placebo Effect/

64 exp comparative study/

65 exp intervention studies/

66 exp Cross-Sectional Studies/

67 exp Cross-Over Studies/

68 exp Cohort Studies/

69 exp longitudinal study/

70 exp retrospective study/

71 exp prospective study/

72 exp clinical trial/

73 clinical study/

74 exp case-control studies/

75 exp confidence interval/

76 exp multivariate analysis/

77	((evidence adj based) or (meta adj analys*) or (systematic* adj3 review*) or guideline* or (control* adj3 study) or (control* adj3 trial) or (randomized adj3 study) or (randomized adj3 trial) or (randomised adj3 study) or (randomised adj3 trial) or "pragmatic clinical trial" or (doubl* adj blind*) or (doubl* adj mask*) or (singl* adj blind*) or (singl* adj mask*) or (tripl* adj blind*) or (tripl* adj mask*) or (trebl* adj blind*) or (trebl* adj mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* adj2 study) or (intervention* adj2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or "cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") adj3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*)).mp,pt.
78	or/51-77
79	50 and 78
80	limit 79 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") [Limit not valid in APA PsycInfo,CCTR,CDSR,Embase; records were retained]
81	limit 80 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in APA PsycInfo,CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
82	limit 79 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)") [Limit not valid in APA PsycInfo,CCTR,CDSR,Embase; records were retained]
83	limit 82 to (embryo or infant or child or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>) [Limit not valid in APA PsycInfo,CCTR,CDSR,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]
84	83 not 81
85	79 not 84
86	migraine*.ti.
87	85 and 86
88	limit 87 to (dissertation abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or

newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in APA PsycInfo,CCTR,CDSR,Embase,Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]

89 from 88 keep 195-218

90 (87 not 88) or 89

91 limit 90 to yr="2018 -Current"

92 remove duplicates from 91

93 limit 90 to yr="2015-2017"

94 remove duplicates from 93

95 limit 90 to yr="2010-2014"

96 remove duplicates from 95

97 limit 90 to yr="2002-2009"

98 remove duplicates from 97

99 90 not (91 or 93 or 95 or 97)

100 remove duplicates from 99

101 92 or 94 or 96 or 98 or 100

Scopus

1 TITLE(migraine*)

2 TITLE-ABS-KEY(acetorphine or acetylcodeine or acetylmethadol or Alfentanil or Alphaprodine or anileridine or apadoline or azidomorphine or benzhydrocodone or bezitramide or bremazocine or "Brompton mixture" or Buprenorphine or Butorphanol or ciramadol or cocodamol or Codeine or codydramol or conorfone or cyclazocine or Dextromoramide or Dextropropoxyphene or dextrorphan or dezocine or diamorphine or diconal or dihydrocodeine or dihydroetorphine or Dihydromorphine or dimethylthiambutene or Diphenoxylate or dipipanone or enadoline or eptazocine or ethylketazocine or Ethylketocyclazocine or Ethylmorphine or etonitazene or Etorphine or etoxeridine or faxeladol or Fentanyl or furethidine or gelonida or Heroin or Hydrocodone or isalmadol or isomethadone or ketazocine or ketobemidone or ketogan or kyotorphin or lefetamine or levacetylmethadol or levomethadone or Levorphanol or Meperidine or Meptazinol or metazocine or Methadone or "Methadyl Acetate" or methylsamidorphan or Morphine or "morphinomimetic agent*" or "morphinomimetic drug*" or morphinone or Nalbuphine or narcotic* or nicocodine or nicomorphine or noracymethadol or norbuprenorphine or nordextropropoxyphene or normorphine or norpethidine or norpropoxyphene or "o nortramadol" or oliceridine or opiate or Opiate* or opioid* or Opium or oripavine or Oxycodone or Oxymorphone or pentamorphone or Pentazocine or pethidine or phenadoxone or phenaridine or Phenazocine or phencyclidine or Phenoperidine or picenadol or piminodine or Pirinitramide or piritramide or profadol or Promedol or propiram or sameridine or samidorphan or semorphone or Sufentanil or tapentadol or thebaine or tifluadom or Tilidine or tonazocine or Tramadol or trimeperidine)

3 TITLE-ABS-KEY(Aceclofenac or Acemetacin or "Acetylsalicylic acid" or Alclofenac or Aminopyrine or Amodiaquine or Amoxiprin or Ampyrone or Antipyrine or Apazone or Aspirin or Azapropazone or Benorilate or Benorylate or Bromelains or Bromfenac or "BW-755C" or Celecoxib or "Choline magnesium salicylate" or "Choline magnesium trisalicylate" or clinoril or Clofazimine or Clofezone or Clonixin or "COX-1 inhibitor*" or "COX-2 inhibitor*" or "COX-2 selective inhibitor*" or Coxib* or Curcumin or "Cyclooxygenase 1 inhibitor*" or "Cyclooxygenase 2 inhibitor*" or "Cyclooxygenase inhibitor*" or "Cyclo-oxygenase inhibitor*" or Dapsone or Dexibuprofen or Dexketoprofen or Diclofenac or Diflunisal or Dipyrone or Droxicam or Epirizole or Ethenzamide or Etodolac or Etoricoxib or Faislamine or Fenbufen or Fenoprofen or "Flufenamic acid" or Flunoxaprofen or Flurbiprofen or "Glycyrrhizic Acid" or Ibuprofen or Ibuproxam or Indomethacin or Indoprofen or Kebuzone or Ketoprofen or Ketorolac or Licofelone or Lornoxicam or Loxoprofen or Lumiracoxib or "Magnesium salicylate" or "Meclofenamic Acid" or "Mefenamic Acid" or Meloxicam or Mesalamine or Metamizole or "Methyl salicylate" or Mofebutazone or Nabumetone or Naproxen or "Niflumic Acid" or "Nonsteroidal antiinflammator*" or "Nonsteroidal anti-inflammator*" or "Non-steroidal antiinflammator*" or "Non-steroidal anti-inflammator*" or "Nordihydroguaiaretic Acid" or NSAID* or osenal or Oxametacin or Oxaprozin or Oxyphenbutazone or Parecoxib or "Pentosan Sulfuric Polyester" or Phenazone or Phenylbutazone or Piroxicam or Pirprofen or Prenazone or Proglumetacin or Rofecoxib or Salicylamide or Salicylate or Sulfasalazine or Sulfinpyrazone or Sulindac or Suprofen or Tenoxicam or "Tiaprofenic acid" or "Tolfenamic acid" or Tolmetin or Valdecoxib)

4 TITLE-ABS-KEY("5-ht" or "5-hydroxytryptamine*" or "5-methoxytryptamine*" or dimethyltryptamine* or enteramine* or hippophaine* or hydroxytryptamine* or indolylethylamine* or meksamine* or methoxydimethyltryptamine* or methoxytryptamine* or methylbufotenin or mexamine* or Serotonin or triptan* or tryptamine*)

5 TITLE-ABS-KEY(Bromocriptine* or Cabergoline* or "clavine alkaloid*" or "clavines alkaloid*" or Dihydroergocornine* or Dihydroergocristine* or Dihydroergocryptine* or Dihydroergotamine* or Dihydroergotoxine* or Ergoline* or "Ergoloid Mesylate*" or Ergonovine* or "ergot agent*" or "ergot alkaloid*" or "ergot drug*" or "ergot medication*" or Ergotamine* or Ergotamines or "ergotoxine alkaloid*" or "ergots alkaloid*" or Lisuride* or "Lysergic Acid" or "Lysergic Acid Diethylamide*" or Metergoline* or Methylergonovine* or Methysergide* or Nicergoline* or Pergolide*)

6 TITLE-ABS-KEY(Acetaminophen or Adenosine or Amantadine or Amitriptyline or analgesic* or analgetic* or anbesol or anodyne* or anpirtoline or antalgic* or antinociceptive* or antrafenine or auralgan or axomadol or befiradol or bicifadine or brivaracetam or brivoligide or bromadoline or "Calcitonin Gene-Related Peptide Receptor Antagonist*" or cannabidivarin or capsaicin or Carbachol or Carbamazepine or cebranopadol or cibinetide or cizolirtine or Clonidine or crobenetine or Cyclazocine or dapansutrile or dasolampanel or davasaicin or deacetyllappaconitine or "Dentin Desensitizing" or "desensitizing agent*" or "desensitizing drug*" or "desensitizing medication*" or Dexmedetomidine or difelikefalin or Dihydroergotamine or dimiracetam or dizatrifone or doxpicomine or drinidene or Dronabino or Duloxetine or ecopladib or edronocaine or efipladib or elismetrep or "embelate potassium" or enkephalin or epibatidine or equagesic or Ergotamine or ethoheptazine or fadolmidine or fasinumab or

"floctafenic acid" or floctafenine or flunixin or "flunixin meglumine" or flupirtine or Flurbiprofen or frakefamide or fulranumab or funapide or Gabapentin or gefapixant or giripladib or "glafenic acid" or Glafenine or "gw 493838" or "gw 842166" or hasamal or ibudilast or Ibuprofen or indantadol or Interleukin or Ketamine or lacosamide or lappaconitine or lenabasum or letimide or lexanopadol or "Magnesium Sulfate" or mavatrep or Medetomidine or Methotrimeprazine or Milnacipran or Mitoxantrone or Nefopam or neurotropin or "Nitrous Oxide" or nuvanil or olodanrigan or olorinab or olvanil or "omega conotoxin" or panidex or "pf 3557156" or "pf 4136309" or "pf 4480682" or "pf 592379" or "pf 738502" or Phenacetin or Pizotyline or pravadoline or Pregabalin or Quinine or ralfinamide or retigabine or ruzadolane or sampirtine or senrebotase or shogaol or strascogesic or tanezumab or tazadolene or tebanicline or tetrodotoxin or tivanisiran or traxoprodil or vedaclidine or vixotrigine or Xylazine)

7 TITLE-ABS-KEY(afloqualone or alcuronium or "atracurium besilate" or azumolene or baclofen or Baclofent or botulinum or branaplam or Carisoprodol or "chandonium iodide" or Chlormezanone or Chlorphenesin or chlorproethazine or Chlorzoxazone or cisatracurium or curare or curaremimetic* or curariform or curarizing or Dantrolene or decamethonium or "depolarizing neuromuscular" or deutolperisone or diadonium or Diazepam or "dihydro beta erythroidine" or dimethyltubocurarine or doxacurium or duador or eperisone or fazadinium or febarbamate or flumetramide or gallamine or gantacurium or "hexafluronium bromide" or idrocilamide or inaperisone or lanperisone or "mebezonium iodide" or Medazepam or Mephenesin or Meprobamate or metaxalone or Methocarbamol or mivacurium or "Muscle relaxant*" or "muscle relaxing" or "musculotropic relaxant*" or "musculotropic relaxing" or myorelaxant or myotonolytic* or nefopam or nelezaprine or "neuromuscular agent*" or "neuromuscular blocker*" or "neuromuscular blocking" or "neuromuscular depolarizing agent*" or "neuromuscular depolarizing drug*" or "neuromuscular depolarizing medication*" or "neuromuscular drug*" or "neuromuscular medication*" or "neuromuscular nondepolarizing agent*" or "neuromuscular nondepolarizing drug*" or "neuromuscular nondepolarizing medication*" or "neuromuscular synapse blocking agent*" or "neuromuscular synapse blocking drug*" or "neuromuscular synapse blocking medication*" or "nondepolarizing neuromuscular blocking agent*" or "nondepolarizing neuromuscular blocking drug*" or "nondepolarizing neuromuscular blocking medication*" or norgesic or Orphenadrine or pancuronium or phenprobamate or pipecuronium or promoxolane or pyrocurine or Quinine or "rapacuronium bromide" or rocuronium or silperisone or styramate or suxamethonium or "tiemonium methylsulfate" or tizanidine or Tolperisone or toxiferine or "tubocurarine chloride" or vecuronium or vesamicol or Xylazine or Zoxazolamine)

8 TITLE-ABS-KEY(((drug* or agent* or medication*) W/3 (nausea or vomit*)) or alizapride or "anti emetic*" or antiemetic* or antimetic* or "anti-metic*" or antinausea* or "anti-nausea*" or antivomit* or "anti-vomit*" or Aprepitant or azasetron or batanopride or belidral or bendectin or benzquinamide or bromopride or buclizine or casopitant or chlorcyclizine or chlorphenethazine or Chlorpromazine or cinnarizine or cisapride or clebopride or Cyclizine or dazopride or debendox or Dexamethasone or Diazepam or difenidol or Dimenhydrinate or Diphenhydramine or dixyrazine or "dolasetron mesilate" or Domperidone or Doxylamine or dronabinol or Droperidol or exepanol or ezlopitant or fabesetron or fosaprepitant or fosnetupitant or Granisetron or Haloperidol or hydrodolasetron or icospiramide or indisetron or lerisetron or lintopride or

Lorazepam or lurosetron or maropitant or Meclizine or meclozine or Methylprednisolone or Metoclopramide or metopimazine or nabilone or netupitant or norchlorpromazine or Olanzapine or Ondansetron or Palonosetron or pancopride or Prochlorperazine or Promazine or promethazine or ramosetron or renzapride or ricasetron or rolapitant or Scopolamine or sulpiride or telmapitant or tetrahydrocannabinol or Thiethylperazine or transmer or Trifluoperazine or Triflupromazine or trimethobenzamide or Tropisetron or vestipitant or vofopitant or zacopride)

9 TITLE-ABS-KEY("1 butyl 3 1 naphthoyl indole" or "11 hydroxydronabinol" or "2 arachidonoylglycerol" or "2 methyl 3 1 naphthoyl 1 propylindole" or "3 1 naphthoyl 1 pentylindole" or "3 2 iodo 5 nitrobenzoyl 1 1 methyl 2 piperidinylmethyl indole" or "3 hydroxy delta9 tetrahydrocannabinol" or "ajulemic acid" or anandamide or bhang or bhangs or cannabi or cannabichromene or cannabidiol or cannabielsoin or cannabigerol or cannabinoid or cannabinol or cannabis or cannador or charas or Cindica or deacetyllevonantradol or dexanabinol or dextronantradol or dronabinol or endocannabinoid or ganja or ganjas or hashish or hashishs or hemp or hemps or levonantradol or marihuana* or marijuana* or methanandamide or "n oleoylethanolamine" or nabilone or nabiximols or nantradol or "noladin ether" or palmidrol or tetrahydrocannabinol or "tetrahydrocannabinolic acid" or virodhamine)

10 TITLE-ABS-KEY("alpha feedback*" or biofeedback* or "bogus physiological feedback*" or "brainwave feedback*" or "eeg feedback*" or "electroencephalography feedback*" or "electromyography feedback*" or "false physiological feedback*" or myofeedback* or neurofeedback* or "psychophysiologic feedback*")

11 TITLE-ABS-KEY(((Electric* or electro or galvano or Transcutaneous*) W/3 (stimulat* or stimulus)) or electrostimulation* or electrostimulus or electrotherap* or "E-stim" or ESTIM or FES or galvanostimulation* or galvanostimulus or Neuromodulation or neuromodulatory)

12 TITLE-ABS-KEY(CBT or "Cognitive behavioral therap*" or "Cognitive therap*")

13 TITLE-ABS-KEY(acupressure or acupuncture or "auricular needl*" or auriculotherapy or "ear needl*" or electroacupuncture or moxibustion or Shiatsu or "Tui Na")

14 TITLE-ABS-KEY(aerobics or anaerobics or bicycling or biking or "endurance training" or exercis* or "fitness training" or isometrics or "physical exertion" or "physical activit*" or "resistance training" or running or "strength training" or swimming or walking or weightlifting)

15 TITLE-ABS-KEY(drug* or pharmacotherap* or medication* or agent* or chemotherap* or intervention* or manag* or therap* or treat*)

16 TITLE-ABS-KEY((evidence W/1 based) or (meta W/1 analys*) or (systematic* W/3 review*) or guideline* or (control* W/3 study) or (control* W/3 trial) or (randomized W/3 study) or (randomized W/3 trial) or (randomised W/3 study) or (randomised W/3 trial) or "pragmatic clinical trial" or (doubl* W/1 blind*) or (doubl* W/1 mask*) or (singl* W/1 blind*) or (singl* W/1 mask*) or (tripl* W/1 blind*) or (tripl* W/1 mask*) or (trebl* W/1 blind*) or (trebl* W/1 mask*) or "latin square" or placebo* or nocebo* or multivariate or "comparative study" or "comparative survey" or "comparative analysis" or (intervention* W/2 study) or (intervention* W/2 trial) or "cross-sectional study" or "cross-sectional analysis" or "cross-sectional survey" or "cross-sectional design" or "prevalence study" or "prevalence analysis" or "prevalence survey" or "disease frequency study" or "disease frequency analysis" or "disease frequency survey" or crossover or

"cross-over" or cohort* or "longitudinal study" or "longitudinal survey" or "longitudinal analysis" or "longitudinal evaluation" or longitudinal* or ((retrospective or "ex post facto") W/3 (study or survey or analysis or design)) or retrospectiv* or "prospective study" or "prospective survey" or "prospective analysis" or prospectiv* or "concurrent study" or "concurrent survey" or "concurrent analysis" or "clinical study" or "clinical trial" or "case control study" or "case base study" or "case referrent study" or "case referent study" or "case referent study" or "case compeer study" or "case comparison study" or "matched case control" or "multicenter study" or "multi-center study" or "odds ratio" or "confidence interval" or "change analysis" or ((study or trial or random* or control*) and compar*))

17 1 and (2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15) and 16

18 TITLE-ABS-KEY(newborn* or neonat* or infant* or toddler* or child* or adolescent* or paediatric* or pediatric* or girl or girls or boy or boys or teen or teens or teenager* or preschooler* or "pre-schooler*" or preteen or preteens or "pre-teen" or "pre-teens" or youth or youths) AND NOT TITLE-ABS-KEY(adult or adults or "middle age" or "middle aged" OR elderly OR geriatric* OR "old people" OR "old person*" OR "older people" OR "older person*" OR "very old")

19 17 and not 18

20 DOCTYPE(ed) OR DOCTYPE(bk) OR DOCTYPE(er) OR DOCTYPE(no) OR DOCTYPE(sh)

21 19 and not 20

22 INDEX(embase) OR INDEX(medline) OR PMID(0* OR 1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9*)

23 21 and not 22

Clinicaltrials.gov

Condition or disease: " migraine"

Limited to Adult, Older Adult

eTable 2. List of the excluded interventions

Medications with terminated development or in development:

- Zatosetron
- Telcagepant
- Tonabersat
- BI 44370
- PNU-142633
- Dapitant
- Lanepitant
- Selurampanel
- MK-3207
- NXN-188
- Bemesetron
- Tezampanel

Not available in US:

- Flunarizine
- Dipyrone
- Civamide
- Flupirtine

eTable 3. Definition of pain and function outcomes

Outcome	Definition
Pain free	No pain at defined assessment time (e.g. 2 hours)
Pain relief	Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time (e.g. 2 hours)
Sustained pain free	No pain at initial assessment (e.g. 2 hours) and remains at followup assessment (e.g. 1 day) with no use of rescue medication or relapse (recurrence) within that time frame
Sustained pain relief	Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time (e.g. 2 hours) and remains improved at followup assessment (e.g. 1 day) with no use of rescue medication or relapse (recurrence) within that time frame
Improved function	Improvement of function from moderate to severe at baseline to mild or none at defined assessment time (e.g. 2 hours)
Restored function	No restriction to perform work or usual activities at a defined assessment time (e.g. 2 hours)

eTable 4. Pain and function scales included in the anaysis

Domain	Scale	Scale characteristics
Function	**Function disability score**	Scoring: 0-3. 3, performance of daily activities is severely impaired; 2, working ability severely reduced; 1, working ability mildly reduced; 0, able to function normally. Higher score represents more disruption of daily activities.
	Clinical disability score	Scoring: 4-point scale (none, mild, moderate, and severe). Total scores range from 0 to 100. Higher score represents more disability.
Pain	**Visual analog scale (VAS)**	Scoring: 0-100 or 0-10 from no pain to worst imaginable pain. Higher score represents more severe pain.
	Short-Form of McGill pain questionnaire	Scoring: 15 items with 2 categories (sensory and affective). Each item scores 0-3. 3, severe; 2, moderate; 1, mild; 0, none. Higher score represents more severe pain.
	Subjective pain level (SPL)	Scoring: 0-10. Higher scores represent severity.
	Pain intensity scale	Scoring: 0-10 or 0-4 from no pain to worst imaginable pain. Higher score represents more severe pain.
	Pain relief scale	Scoring: 0-4 or 1-5 from complete relief to no relief. Higher score represents less or no pain relief.
	Headache severity scale	Scoring: 0-10 or 0-3 from no pain to worst imaginable pain. Higher score represents more severe headache.

eTable 5. Categories of adverse events

Type of adverse events	Example
Cardiovascular adverse event	Bradycardia, chest discomfort, palpitation, presyncope, vasodilation
Dermatological adverse event	Skin rash, application site pain/discomfort, burning sensation, local irritation
Ear, nose and throat adverse event	Ear and labyrinth disorders, hyperacusia, lump in throat or burning throat, nasal congestion, nasal irritation, oropharyngeal pain, pharyngitis
Endocrine adverse event	Recurrent thyroid cancer
Gastrointestinal adverse event	Abdominal discomfort/pain, altered taste, anorexia, abnormal taste constipation, diarrhea, dry mouth, dyspepsia, nausea, vomiting
Genitourinary adverse event	Urinary tract infection, diuresis, nephrolithiasis
Hematologic adverse event	Blood and lymphatic system disorders, bleeding
Immunologic adverse event	Allergy Hypersensitivity, infections and infestations, influenza, shingles, anaphylaxis, viral meningitis
Musculoskeletal adverse event	Muscle cramp/spasms/tightness, myalgia
Neurological adverse event	Akathisia, chills, confusion, disorientation, dizziness, dystonic reaction, fatigue, headache, sedation, seizure, vertigo, tremor
Ophthalmological adverse event	Blurred vision, eyelid swelling, visual disturbances, optic neuritis, lacrimation
Psychological adverse event	Anxiety, restlessness, euphoria, mood change, nervousness
Respiratory adverse event	Cough, respiratory tract infection, shortness of breath
Sleep-related adverse event	Sleepiness
Other adverse event	Edema, heat sensation, warmth, flushing, cold hands
Total number of adverse events	Total incidence of adverse events

eTable 6. Definition and approaches to grade strength of evidence

Strength of Evidence (SOE)[a]	Definition
High	Confidence that the estimate of effect lies close to the true effect (the body of evidence has few or no deficiencies and is judged to be stable).
Moderate	Moderate confidence that the estimate of effect lies close to the true effect (the body of evidence has some deficiencies and is judged to be likely stable)
Low	Limited confidence that the estimate of effect lies close to the true effect (the body of evidence has major or numerous deficiencies and is likely unstable)
Insufficient	No evidence, unable to estimate an effect, or no confidence in the estimate of effect

[a]The strength of evidence (SOE) was graded for the outcomes of pain free, pain relief, sustained pain free, sustained pain relief, function relief, and restored function, pain scale, and function scale. These outcomes were chosen because they were deemed clinically important from a patient's perspective and highly relevant for decision making. The AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews for assessing SOE was followed.[1]

Randomized clinical trials (RCTs) started as high SOE. Domains that could decrease this initial SOE were the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the question at hand (focusing on whether the outcomes were important to patients vs surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias.

SOE ratings were lowed for the risk of bias when the studies in a particular comparison had high or unclear risk of bias; imprecision when the number of events was small (<300) or when confidence intervals included substantial benefits and harms (defined as 0.25 relative risk reduction or increase); inconsistency when the I^2 exceeded an arbitrary cutoff >60 percent; and when reporting and publication bias were suspected.

eTable 7. Results of systematic reviews evaluating triptans and nonsteroidal anti-inflammatory drugs (NSAIDs)
eTable 7.1. Results of systematic reviews evaluating triptans

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
Ashcroft, 2004[2]	Naratriptan (Compared with various interventions)	10 RCT (4,499)	Search in 2002 No clear description of study selection methods, risk of bias or excluded studies	Compared with placebo for pain-free response at 2 and 4 hours, naratriptan 2.5 mg were RRs of 2.52 (1.78–3.57) and 2.58 (1.99–3.35) -Naratriptan 2.5 mg was more effective than naratriptan 1 mg and less effective in pain-free response than either rizatriptan 10 mg at 4 hours, RR0.68 (0.55–0.85) or sumatriptan100 mg at 4 hours, RR 0.79 (0.67–0.93) - Significantly fewer patients experienced adverse effects with naratriptan 2.5 mg than with rizatriptan 10 mg, RR 0.73 (0.56–0.97) or sumatriptan 100 mg, RR 0.68 (0.55–0.86)
Bird, 2014 [3]	Zolmitriptan	25 RCTs (20,162)	Search in 2014 - Fulfills all AMSTAR criteria	-For all efficacy outcomes, zolmitriptan surpassed placebo. For oral zolmitriptan 2.5 mg, NNTs were 5.0, 3.2, 7.7, and 4.1 for pain free at two hours, headache relief at two hours, sustained pain-free during the 1 day post dose, and sustained headache

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
				relief during the 1 day post dose, respectively -Adverse events were transient and mild and were more common with zolmitriptan than placebo
Chen, 2007 [4] (study level meta-analysis) Two pooled analyses (Caddy 2002[5] and Dahlof 2006[6])	Almotriptan (compared with various interventions)	8 RCTs (4,995)	Search in 2007 -Review authors with industry ties. Duplication of review procedures is not clearly described, no list or clear description of excluded studies	-Almotriptan 12.5 mg was significantly more effective than placebo for all efficacy outcomes (absolute rate differences ranged from 0.01 to 0.28) - No significant differences in efficacy outcomes comparing almotriptan 12.5 mg against sumatriptan 100 mg and zolmitriptan 2.5 mg, but almotriptan 12.5 mg was associated with significantly fewer adverse events than sumatriptan 100 mg -Almotriptan 12.5 mg was significantly less effective than almotriptan 25 mg for 1-hour pain-free response but with fewer patients experiencing adverse events -Conclusions from pooled analyses were similar to study level analyses

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
Derry, 2012[7]	Oral sumatriptan (alone or in combination with an antiemetic compared with various interventions)	61 RCTs (37,250)	Search in 2011 but re-evaluation suggested stability of findings. - Fulfills all AMSTAR criteria	-NNTs 6.1, 7.5, and 4.0 for pain-free at two hours and headache relief at one and two hours, respectively -25 and 50 mg are likely similar. 100 mg more effective. -Relief of associated symptoms (nausea, photophobia, phonophobia) and use of rescue medication were better with sumatriptan than with placebo -Adverse events were transient and mild and were more common with the sumatriptan than with placebo
Derry, 2012[8]	Subcutaneous sumatriptan (alone or in combination with an antiemetic compared with various interventions)	35 RCTs (9,365)	Search in 2011 but re-evaluation suggested stability of findings - Fulfills all AMSTAR criteria	-Sumatriptan 6 mg vs placebo: NNTs were 2.9, 2.3, 2.2, and 2.1 for pain-free at one and two hours, and headache relief at one and two hours, respectively, and 6.1 for sustained pain-free at 1 day. Similar results for other doses -Relief of headache-associated symptoms and use of rescue medications were greater with sumatriptan than with placebo
Ferrari, 2001[9]	Rizatriptan	7 RCTs (4,814)	Search in 2001 - Fulfills most AMSTAR criteria, does not include clear risk of bias evaluation or a list of excluded studies	-Rizatriptan 10 mg was significantly more effective than placebo or rizatriptan 5 mg on pain relief and pain free at 2 hours and 1 day.
Mandema, 2005[10]	Eletriptan (Compared with sumatriptan)	19 RCTs (11,400)	Search in 2002	- Eletriptan 40 mg was associated with statistically

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
			Only searched Medline with no clear description of study selection methods, risk of bias or excluded studies	significant efficacy compare with sumatriptan 100 mg at any point in time up to 4 h after treatment with an absolute difference at 2 h of 9.1% (7.4–11.5%) more patients achieving pain relief and 7.3% (5.8–8.6%) more patient achieving pain free
Menshawy, 2017[11]	Intranasal sumatriptan	16 RCTs (5,925)	Search in 2016 - Fulfills all AMSTAR criteria, no list or clear description of excluded studies	-Intranasal sumatriptan was superior to placebo in pain relief at 2 h (RR = 1.70, 1.31,2.21) and headache relief at 30 min (RR = 1.31, 1.08, 1.59) and 2 h (RR = 1.58, 1.35, 1.84) -Intranasal sumatriptan was associated with six-fold increase taste disturbances vs placebo
Poolsup, 2005[12]	Frovatriptan	5 RCTs (2,866)	Search in 2005 - Fulfills most AMSTAR criteria, does not include clear risk of bias evaluation or a list of excluded studies	-Frovatriptan 2.5 mg was more effective than placebo in rendering patient pain-free at 4 h and reducing headache severity and symptoms associated with migraine at 2 h.

h = hour; mg = milligram; NNT = number needed to treat; RCT = randomized clinical trial; RR = relative risk

eTable 7.2. Results of systematic reviews evaluating nonsteroidal anti-inflammatory drugs (NSAIDs)

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
Derry, 2013[13]	Oral diclofenac (alone or in combination with an antiemetic compared with various interventions)	5 RCTs (1,356)	Search in 2011 -Fulfills all AMSTAR criteria	- A single dose of diclofenac potassium 50 mg, the NNTs were 6.2, 8.9, and 9.5 for pain-free at two hours, headache relief at two hours, and pain-free responses at 1 day, respectively. -Associated symptoms of nausea, photophobia and phonophobia, and functional disability were reduced within two hours. -Adverse events were mild and transient
Kirthi, 2013[14]	Aspirin (alone or in combination with an antiemetic compared with various interventions)	13 RCTs (4,222)	Search in 2013 -Fulfills all AMSTAR criteria	-Aspirin 900 mg or 1000 mg vs placebo was effective with NNTs of 8.1, 4.9 and 6.6 for 2-hour pain-free, 2-hour headache relief, and 24-hour headache relief. -Sumatriptan 50 mg did not differ from aspirin alone for 2-hour pain-free and headache relief, while sumatriptan 100 mg was better than the combination of aspirin plus metoclopramide for 2-hour pain-free, but not headache relief.
Rabbie, 2013[15]	Ibuprofen (alone or in combination with an antiemetic compared with various interventions)	9 RCTs (4,373)	Search in 2013 but re-evaluation suggested stability of findings -Fulfills all AMSTAR criteria	-Ibuprofen 400 mg vs placebo: NNTs for 2-hour pain-free (26% versus 12% with placebo), 2-hour headache relief (57% versus 25%) and 24-hour sustained headache relief (45%

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
				versus 19%) were 7.2, 3.2 and 4.0, respectively. -Ibuprofen 400 mg did not differ from rofecoxib 25 mg and was better than ibuprofen 200 mg.
Taggart, 2013[16]	Ketorolac	8 RCTs (321)	Search in 2010 -Fulfills all AMSTAR criteria, no list or clear description of excluded studies	-Ketorolac and meperidine resulted in similar pain scores at 60 minutes. -Ketorolac was more effective than intranasal sumatriptan. - Ketorolac was not significantly more effective in pain relief at 60 minutes compare with phenothiazine agents. -Side effect profiles were similar between Ketorolac and comparison groups

mg = milligram; NNT = number needed to treat; RCT = randomized clinical trial

eTable 7.3. Results of systematic reviews evaluating multiple treatments

Systematic Review	Interventions	Studies (Patients)	Methodology*	Main Findings
Law, 2016[17]	Sumatriptan plus naproxen	12 RCTs (7,345)	Search in 2015 -Fulfills all AMSTAR criteria	-At two hours and compare with placebo, NNT for pain-free response was 3.1 for mild pain (50% response vs 18%), and 4.9 for moderate or severe pain (28% response vs 8%). -Treating early, when pain was still mild, was significantly better than treating once pain was moderate or severe. -Adverse events were mostly mild or moderate and rarely led to withdrawal. -Combination treatment was superior to either monotherapy.
Xu, 2016[18] (Network meta-analyses)	Triptans, NSAIDs and combination of triptans and NSAIDs	88 RCTs (44,222)	Searches in 1993-2016 Well-connected network geometry Bayesian framework- Fulfills all AMSTAR criteria, no list or clear description of excluded studies	-Sumatriptan and naproxen was effective, well tolerated and can be used for patients with partial response to either agent.

mg = milligram; MOH = medication overdose headache; NMA = network meta-analysis; RCT = randomized clinical trial

* Credibility was assessed using the AMSTAR tool (A measurement tool to assess systematic reviews)

eTable 8. Characteristics of included studies evaluating CGRP, 5-HT1F, antiemetics, ergot alkaloids, opioids, other pharmacological interventions, and nonpharmacological interventions

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Aggarwal, 2020[19]	Crossover RCT in United States of America, 04/2017 to 02/2018	Outpatient	Timolol	Eye drop, 0.5% solution, once	2 hours	26 Patients aged 41±10.5 years, 96% female
			Placebo	Eye drop, once		
Alemder, 2007[20]	Crossover RCT in Turkey	ED	Tramadol	IV, 100 mg in 100 ml saline solution, once for 30 minutes	1 day	17 Patients aged 42 ± 11.5 years, 76.5% female, 100% White
			Placebo	IV, 100 ml saline solution, once for 30 minutes	1 day	17 Patients aged 37.1 ± 9 years, 88.2% female, 100% White
Amiri, 2017[21]	RCT in Iran	ED	Granisetron	IV, 2 mg, once	4 hours	148 Patients aged 33.5 years, 68.2% female
			Metoclopramide	IV, 10 mg, once	4 hours	
Antal, 2020[22]	RCT in Germany	Outpatient	t ACS (Transcranial Alternating Current Stimulation)	Transcranial stimulation over the visual cortex, 0.4 mA, 140 Hz, for 15 min	2 days	16 Patients aged 31.1±8.9 years
			Sham stimulation	Sham stimulation over the visual cortex, for 15 min	2 days	9 Patients aged 28.1±10.5 years
Ashina, 2021[23]	RCT in Europe, North America, and Asia	Outpatient	Lasmiditan 200 mg	Oral, 200mg, once for four attacks	2 days	486 Patients, aged 42±12 years, 86% female, 77% White
			Lasmiditan 100 mg	Oral, 100 mg, once for four attacks	2 days	485 Patients, aged 42±12 years, 83% female, 77% White
			Placebo	Oral, placebo once for 3 attacks and Lasmiditan 50 mg for either the third or fourth attack	2 days	500 Patients, aged 41±12 years, 83% female, 77% White

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Aurora, 2011[24]	RCT in United States of America, 07/2008 to 03/2009	Outpatient	Dihydroergotamine	Inhaled (orally), 0.6 mg emitted dose (1 mg nominal dose, or 0.5 mg systemic) once immediately after attack	2 days	450 Patients aged 40.5 ± 11.3 years, 91.9% female, 8.9% African American, 88.1% White, 1.3% Asian, BMI 28 ± 6.6
			Placebo	Inhaled (orally), once immediately after attack	2 days	453 Patients aged 39.6 ± 11.7 years, 91.2% female, 11.8% African American, 84.4% White, 3.0% Asian, BMI 27.9 ± 6.4
Aurora, 2009[25]	RCT in United States of America, 07/2006 to 02/2007	Outpatient	Placebo	Inhaled (orally), four times after attack	28 days	18 Patients aged 43.6 ± 9.4 years, 77.8% female, 94.4% White, 5.6% Asian
			Dihydroergotamine mesylate 0.5 mg	Inhaled (orally), 0.5 mg systemic dose (1 mg nominal dose), twice after attack	28 days	35 Patients aged 41.3 ± 10.9 years, 85.7% female, 5.7% African American, 88.6% White, 5.7% Asian
			Dihydroergotamine mesylate 1 mg	Inhaled (orally), 1 mg systemic dose (2mg nominal dose), twice after attack	28 days	33 Patients aged 40 ± 10.6 years, 81.8% female, 84.8% White, 6.1% Asian
Avcu, 2017 [26]	RCT in Turkey, 01/2014 to 10/2014	ED	Lidocaine 10%	Intranasal, 10%, once or twice after attack	3 days	81 Patients aged 36 ± 12 years, 69.1% female
			Placebo	Intranasal, 0.9% saline, once or twice after attack	3 days	81 Patients aged 35 ± 11 years, 85.2% female
Banerjee, 1991[27]	RCT in United Kingdom	Outpatient	Propranolol	Oral, 40 mg, one to three times after attack	2 days	25 Patients aged 35 ± 11.75 years, 84% female
			Placebo	Oral, one to three times after attack	2 days	

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Bell, 1990[28]	RCT in Canada	ED	Chlorpromazine	IV, 12.5 mg, once to three times after attack	1 day	76 Patients, 78.9% female
			Dihydroergotamine	IV, 1 mg, once or twice after attack	1 day	
			Lidocaine	IV, 50 mg, one to three times after attack	1 day	
Bigal, 2002[29]	RCT in Brazil, 01/01/1997 to 12/31/1999	ED	Chlorpromazine	IV, 0.1 mg/kg in 10 ml 0.9% saline, once after attack	1 day	68 Patients aged 34.65 years, 74.20% female
			Placebo	IV, 10 ml 0.9% saline, once after attack	1 day	60 Patients aged 27.70 years, 68.85% female
Bigal, 2002[30]	RCT in Brazil, 04/01/1997 to 12/31/1999	Outpatient	Magnesium sulfate	IV, 1 gr in 10 ml 0.9% saline, once after attack	1 day	60 Patients aged 29.30 years, 74.80% female
			Placebo	IV, 10 ml 0.9% saline, once after attack	1 day	60 Patients aged 27.60 years, 68.40% female
Blanda, 2001[31]	RCT in United States of America, 07/27/1997 to 11/11/1997	ED	Lidocaine 4%	Intranasal 0.5ml drops, two or four times for unilateral or bilateral pain, respectively	1 day	27 Patients, 85.2% female
			Placebo	Intranasal, 0.9% saline, 0.5 ml saline drops, two or four times for unilateral or bilateral pain, respectively	1 day	22 Patients, 86.4% female
Borhani, 2010[32]	Crossover RCT in Iran, 03/2007 to 03/2008	Outpatient	Menthol-Placebo	Topical on forehead and temporal area, 1 ml of 10% solution of menthol crystals in ethanol, immediately after attack (Initial two attack treated with menthol and the second two attack treated with placebo)	N/A	17 Patients aged 29.8 ± 6.14 years, 76.5% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Placebo-Menthol	Topical on forehead and temporal area, 1 ml of 0.5% ethanol menthol solution, immediately after attack (Initial two attack treated with placebo and the second two attack treated with menthol)	N/A	18 Patients aged 29.5 ± 6.4 years, 83.3% female
Boureau, 1994[33]	Crossover RCT in France	Outpatient	Acetaminophen 400 mg plus codeine 25 mg	Oral, 400 mg acetaminophen and 25 mg codeine once after attack	2 hours	494 Patients aged 40.1 ± 11.6 years, 76.90% female
			Placebo	Oral, once after attack	2 hours	
Brandes, 2020[34]	RCT in United States of America, United Kingdom, and Germany	Outpatient	Lasmiditan 100 mg	Oral, 100 mg for each new migraine attack of moderate or severe pain intensity within 4 h of pain onset	365 days	1046 Patients aged 42.7 ± 12.3 years, 85.4% female, 18.8% African American, 77.5% White, 0.7% Asian, BMI 31.2 ± 82
			Lasmiditan 200 mg	Oral, 200 mg for each new migraine attack of moderate or severe pain intensity within 4 h of pain onset	365 days	1125 Patients aged 43.8 ± 12.5 years, 85.3% female, 16.6% African American, 79.3% White, 0.6% Asian, BMI 31.0 ± 8.2
Callaham, 1986[35]	RCT in United States of America, 06/1982 to 06/1984	ED	Dihydroergotamine	IV, 0.75 mg, once after attack	2 days	19 Patients
			Placebo	IV, once after attack	2 days	15 Patients

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Cameron, 1995[36]	RCT in Canada, 1990 to 1992	ED	Chlorpromazine	IV, 0.1 mg/kg, once (up to three times if needed during the first hour)	2 days	47 Patients aged 32.60 ± 9.5 years, 80.90% female
			Metoclopramide	IV, 0.1 mg/kg, once (up to three times if needed during the first hour)	2 days	44 Patients aged 31.60 ± 8.75 years, 79.50% female
Carleton, 1998[37]	RCT in the United States of America, 11/1991 to 08/1992	ED	Dihydroergotamine mesylate plus hydroxyzine hydrochloride	IM, dihydroergotamine mesylate, 1 mg, once (second dose after 1 hour if necessary), Hydroxyzine hydrochloride: Intramuscular, 0.70 mg/kg, once (second dose of 0.35 mg/kg after 1 hour if necessary)	1 day after discharge	85 Patients aged 32.52 ± 8.82 years, 82.40% female
			Meperidine plus hydroxyzine hydrochloride	IM meperidine, 1.5 mg/kg, once (second dose of 0.75 mg/kg after 1 hour if necessary), Hydroxyzine hydrochloride: Intramuscular, 0.70 mg/kg, once (second dose of 0.35 mg/kg after 1 hour if necessary)	1 day after discharge	85 Patients aged 32.36 ± 8.78 years, 82.40% female
Cete, 2005[38]	RCT in Turkey	ED	Metoclopramide plus normal saline	IV, 10 mg in 100 ml normal saline, once for 10 minutes	1 day after discharge	37 Patients aged 40 ± 13 years, 89% female
			Magnesium sulfate plus normal saline	IV, 2 g in 100 ml normal saline, once for 10 minutes	1 day after discharge	36 Patients aged 40 ± 12 years, 75% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Placebo	IV, 100 mL normal saline once for 10 minutes	1 day after discharge	40 Patients aged 40 ± 11 years, 88% female
Chou, 2019[39]	RCT in the United States of America, 02/01/2016 to 03/31/2017	ED	Verum external trigeminal nerve stimulation	Transcutaneously, 1.284 C (total maximum dose), high frequency pulse of 100 Hz with pulse width of 250 µs for 1 hour	1 day	52 Patients aged 39.71 ± 13.62 years, 83% female
			Sham external trigeminal nerve stimulation	Transcutaneously, low frequency pulse of 3 Hz with pulse width of 250 µs for 1 hour	1 day	54 Patients aged 40.09 ± 12.65 years, 91% female
Coppola, 1995[40]	RCT in the United States of America, 11/1991 to 06/1993	ED	Metoclopramide hydrochloride	IV, 10 mg in 2 mL, once for 2 minutes	2 days after discharge	24 Patients
			Prochlorperazine	IV, 10 mg in 2 mL, once for 2 minutes	2 days after discharge	22 Patients
			Placebo	IV, 2 mL, normal saline, once for 2 minutes	2 days after discharge	24 Patients
Corbo, 2001[41]	RCT in the United States of America	ED	Metoclopramide plus magnesium sulfate	IV, Metoclopramide: 20 mg, once for 2 minutes every 15 minutes as needed for pain up to a total of 3 doses or relief of pain, Magnesium sulfate: 2 g in a 10% normal saline solution (a total solution of 50 ml), once for 10 minutes every 15 minutes as needed for pain up to a total of 3 doses or relief of pain	1 day	21 Patients aged 39 ± 12 years, 95% female

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			Metoclopramide plus placebo	IV, Metoclopramide: 20 mg, once for 2 minutes every 15 minutes as needed for pain up to a total of 3 doses or relief of pain, placebo: 50 ml normal saline, once for 10 minutes every 15 minutes as needed for pain up to a total of 3 doses or relief of pain	1 day	23 Patients aged 37 ± 8 years, 96% female
Croop, 2019[42]	RCT in the United States of America, 02/27/2018 to 08/28/2018	Outpatient	Rimegepant	Sublingual, 75 mg, once	7-9 days	732 Patients aged 40.3 ± 12.1 years, 85% female, 74% White, 21% African American, 1% Asian, 1% American Indian or Alaska Native, 2% Native Hawaiian or other Pacific Islander, 1% Multiple, BMI 31.1 ± 8.2
			Placebo	Sublingual, once	7-9 days	734 Patients aged 40 ± 11.9 years, 85% female, 76% White, 18% African American, 3% Asian, <1% American Indian or Alaska Native, 1% Native Hawaiian or other Pacific Islander, 1% Multiple, BMI 30.6 ± 8
Demirkaya, 2001[43]	Crossover RCT in Turkey	Outpatient	Magnesium sulfate	IV, 1 g, once for 15 minutes	1 day	15 Patients (Magnesium sulfate), 15 Patients

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			Placebo	IV, 10 mL, 0.9% saline, once, once. After 3o minutes IV, 1 gr of Magnesium sulfate over 15 minutes for those with persistent complaints of pain, nausea, and vomiting	1 day	(Placebo), age 35 ± 8.9 years (entire population)
Derosier, 2010[44]	Crossover RCT in the United States of America, 12/2007 to 08/2009	Outpatient	Butalbital, acetaminophen, caffeine	Oral, butalbital 50 mg, acetaminophen 325 mg, and caffeine 40 mg, once	2 days	Entire population: 392 Patients (Butalbital, Acetaminophen, Caffeine), 405 Patients (Placebo), age 42.6 ± 7.8 years, 88% female , 83% White (entire population), 14% African American , BMI 27.3 ± 7
			Placebo	Oral, once	2 days	
Dexter, 1985[45]	RCT in the United Kingdom	Outpatient	Paracetamol plus metoclopramide	Oral, 2 tablets, paracetamol 500 mg, metoclopramide 5 mg, once (up to three times)	112 days	22 Patients aged 32 years, 77.27% female
			Placebo	Oral, once (up to three times)	112 days	27 Patients aged 33 years, 59.26% female
Diamond, 1976[46]	Crossover RCT in the United States of America	Outpatient	Isometheptene mucate, acetaminophen, and dichloralphenazone	Oral, isometheptene mucate 65 mg, acetaminophen 325 mg, and dichloralphenazone 100 mg, twice (up to five times)	14-60 days	Entire population: 168 Patients aged 49 ± 9.75 years, 71.4% female

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			Acetaminophen	Oral, 325 mg, twice (up to five times)	14-60 days	
			Placebo	Oral, corn starch and talc, twice (up to five times)	14-60 days	
Diener, 2002[47]	RCT in Australia, Denmark, Finland, France, Germany, Netherlands, Norway, Spain, Sweden, UK, London, Israel, South Africa, Poland	Outpatient	Caffeine plus ergotamine	Oral, 1 mg ergotamine tartrate with 100 mg caffeine, once or twice	7-14 days	203 Patients aged 42 ± 11 years, 86% female
			Placebo	Oral, once or twice	7-14 days	106 Patients aged 40 ± 10 years, 86% female
Dodick, 2019[48]	RCT in United States of America, 07/22/2016 to 12/14/2017	Outpatient	Ubrogepant 100 mg	Oral, 100 mg (2 tablets of ubrogepant 50 mg), once. An optional second dose of either 2 tablets of placebo, 2 tablets of 5o mg ubrogepant was allowed.	4 weeks	557 Patients aged 40.6±12 years, 86.2% female, 80.8% White, BMI 30.4±8
			Ubrogepant 50 mg	Oral, 50 mg (one tablet ubrogepant 50 mg and one tablet placebo), once. An optional second dose of either 2 tablets of placebo, or one tablet of 5o mg ubrogepant and one tablet of placebo was allowed.		556 Patients aged 40.1±11.7 years, 89.7% female, 82.2% White, BMI 30.2±8.1

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Placebo	Oral, 2 tablets, once. An optional second dose of 2 tablets of placebo was allowed.		559 Patients aged 40.9±11.7 years, 88.7% female, 84.5% White, BMI 30±7.4
Dogan, 2019 [49]	RCT in Turkey, 12/2014 to 01/2017	ED	Metoclopramide	IV, 10 mg in 100 mL normal saline solution, once for 10 minutes	1-3 days	74 Patients aged 35 ± 13.3 years, 67.6% female
			Placebo	IV, 100 mL normal saline, once for 10 minutes	1-3 days	74 Patients aged 33 ± 13.3 years, 62.2% female
Donaldson, 2008 [50]	RCT in United States of America, 11/2004 to 11/2005	ED	Placebo	IV, 24 mg (5ml) once	30 days	53 Patients aged 35.17 years, 73.6% female
			Dexamethasone	IV, 24 mg (5ml) once	30 days	62 Patients aged 37.48 years, 87.1% female
Etchison, 2018 [51]	RCT in United States of America, 03/2016 to 03/2017	ED	Ketamine	IV, 0.2 mg/kg in 30 ml aliquots, once for 1 minute	1 hour	16 Patients aged 38.5 ± 13.75 years, 81% female, 19% African American, 62% White, 19% other
			Placebo	IV, 0.2 mg/kg saline in 30 ml aliquots, once for 1 minute	1 hour	18 Patients aged 30.5 ± 8.3 years, 72% female, 11% African American, 72% White, 17% other
Farahmand, 2018[52]	RCT in Iran, 03/2015 to 05/2016	Outpatient	Verum acupuncture	Skin, sterile metallic needles with a width of 0.25 mm and length of 13 mm, which enter certain points in the ear's skin	1 day	30 Patients (Acupuncture), 30 Patients (Acupuncture placebo) aged 31.4 ± 7.6 years, 83.3% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Sham acupuncture	Skin, sterile metallic needles with a width of 0.25 mm and length of 13 mm, inserted into inappropriate acupoints (stomach, and spleen), once	1 day	
Farkkila, 2012[53]	RCT in Finland, Germany, France, Spain and Belgium, 07/08/2009 to 02/18/2010	Outpatient	Placebo	Oral, once	14 days	103 Patients aged 40.5 ± 10.3 years, 87% female, 100% White
			Lasmiditan 50 mg	Oral, 50 mg, once	14 days	106 Patients aged 40.4 ± 12.5 years, 84% female, 99% White
			Lasmiditan 100 mg	Oral, 100 mg, once	14 days	104 Patients aged 42 ± 10.6 years, 83% female, 99% White
			Lasmiditan 200 mg	Oral, 200 mg, once	14 days	100 Patients aged 39.5 ± 10.3 years, 92% female, 99% White
			Lasmiditan 400 mg	Oral, 400 mg, once	14 days	99 Patients aged 38.7 ± 10.3 years, 93% female, 99% White
Fernando, 2019[54]	RCT in United States of America, 11/2016 to 12/2017	ED	Buccally absorbed prochlorperazine (BAP)	Buccally (under the upper lip), 6 mg of BAP + 2.25 mL IV normal saline solution	1-2 days	40 Patients aged 38.8 ± 12.3 years, 87% female
			Intravenous prochlorperazine (IVP)	IV, 10 mg of IVP in a volume of 2.25 mL + buccal saccharine pills	1-2 days	40 Patients aged 37.3 ± 12.2 years, 65% female
Ferrari, 2010[55]	RCT in The Netherlands, Finland,	Outpatient	Placebo	IV, 60 mL infusion, once for 20 minutes	1 day	42 Patients aged 40.3 ± 7.3 years, 90.5% female, 100% White

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
	Germany, 08/2006 to 07/2007		Lasmiditan 2.5 mg	IV, 2.5 mg in 60 mL infusion, once for 20 minutes	1 day	4 Patients aged 46.8 ± 7.3 years, 75% female, 100% White
			Lasmiditan 5 mg	IV, 5 mg in 60 mL infusion, once for 20 minutes	1 day	12 Patients aged 39.2 ± 7.3 years, 83.3% female, 91.7% White, 8.3% Non-Caucasian
			Lasmiditan 10 mg	IV, 10 mg in 60 mL infusion, once for 20 minutes	1 day	24 Patients aged 34.2 ± 7.3 years, 87.5% female, 83.3% White, 16.7% Non-Caucasian
			Lasmiditan 20 mg	IV, 20 mg in 60 mL infusion, once for 20 minutes	1 day	28 Patients aged 38.9 ± 7.3 years, 85.7% female, 100% White
			Lasmiditan 30 mg	IV, 30 mg in 60 mL infusion, once for 20 minutes	1 day	16 Patients aged 40.3 ± 7.3 years, 87.5% female, 100% white
			Lasmiditan 45 mg	IV, 45 mg in 60 mL infusion, once for 20 minutes	1 day	4 Patients aged 40.8 ± 7.3 years, 75% female, 100% White
Foroughipour, 2013[56]	RCT in Iran, during 2011	ED	Valproate	IV, 900 mg (diluted in 150 cc normal saline) (Patients at a minimum weight of 90 kg received 1200 mg), once for 10 minutes	3 days	20 Patients aged 33.9 ± 13.34 years, 89% female
			Dexamethasone	IV, 16 mg (diluted in 150 cc normal saline) (Patients at a minimum weight of 90 kg received 20 mg), once for 10 minutes	3 days	20 Patients aged 32.5 ± 11.12 years, 92% female

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Freitag, 1993[57]	RCT in United States of America	ED	Transnasal butorphanol	Intranasal, 1 mg, twice	6 hours	32 Patients aged 39.4 ± 9.25 years, 97% White, 3% African American
			Methadone	IM, 10 mg, once	6 hours	32 Patients aged 38.4 ± 9.5 years, 91% White, 6% African American
			Placebo	Intranasal spray, twice, and IM, once	6 hours	32 Patients aged 37.2 ± 11.75 years, 97% White, 3% African American
Friedman, 2007[58]	RCT in United States of America, 07/2005 to 07/2006	ED	Dexamethasone sodium phosphate	IV, 10 mg	1 day	106 Patients aged 36 ± 10 years, 82% female, 27% African American, 6% White, 69% Latino
			Placebo	IV	1 day	99 Patients aged 37 ± 11 years, 88% female, 22% African American, 2% White, 70% Latino
Friedman, 1989[59]	RCT in United States of America	Outpatient	Cafergot P-B	Oral, 2 tablets at the first signs of a migraine, one tablet after 0.5 hour and another after 1 hour of the first dose. One tablet after 1.5 hour and another after 2 hours of the first dose if needed for a maximum dose of 6 tablets.	3 hours	Entire population: 254 Patients aged 34.4 years, 87.4% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Cafergot	Oral, 2 tablets at the first signs of a migraine, one tablet after 0.5 hour and another after 1 hour of the first dose. One tablet after 1.5 hour and another after 2 hours of the first dose if needed for a maximum dose of 6 tablets.	3 hours	
			Placebo	Oral, 2 tablets at the first signs of a migraine, one tablet after 0.5 hour and another after 1 hour of the first dose. One tablet after 1.5 hour and another after 2 hours of the first dose if needed for a maximum dose of 6 tablets.	3 hours	
Friedman, 2008[60]	RCT in United States of America, 08/2006 to 03/2007	ED	Prochlorperazine	IV, 10 mg, once for 15 minutes	1 day	39 Patients aged 34 ± 10 years, 85% female, 36% African American, 51% White, 3% Asian, 62% Hispanic/Latino, 10% other
			Metoclopramide	IV, 20 mg, once for 15 minutes	1 day	38 Patients aged 38 ± 12 years, 95% female, 42% African American, 53% White, 68% Hispanic/Latino, 5% other

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Friedman, 2011[61]	RCT in United States of America, 05/2008 to 02/2010	ED	Metoclopramide 10 mg plus diphenhydramine	IV, 10 mg metoclopramide plus 25 mg diphenhydramine, once for 20 minutes	2 days	113 Patients aged 39 ± 11 years, 83% female, 28% African American, 18% White, 70% Hispanic, 0.9% previous opioid use
			Metoclopramide 20 mg plus diphenhydramine	IV, 20 mg metoclopramide plus 25 mg diphenhydramine, once for 20 minutes	2 days	118 Patients aged 37 ± 10 years, 87% female, 28% African American, 20% White, 1% Asian, 70% Hispanic, 3.4% previous opioid use
			Metoclopramide 40 mg plus diphenhydramine	IV, 40 mg metoclopramide plus 25 mg diphenhydramine, once for 20 minutes	2 days	118 Patients aged 38 ± 12 years, 82% female, 20% African American, 19% White, 1% Asian, 76% Hispanic, 3.4% previous opioid use
Friedman, 2016[62]	RCT in United States of America, 04/2013 to 12/2015	ED	Diphenhydramine plus metoclopramide	IV, diphenhydramine 50 mg plus metoclopramide 10 mg, once	2 days	104 Patients aged 41 ± 11 years, 85% female
			Placebo plus metoclopramide	IV, placebo (saline solution) plus metoclopramide 10 mg, once	2 days	104 Patients aged 36 ± 10 years, 89% female
Friedman, 2018[63]	RCT in United States of America, 08/2015 to 01/2018	ED	Sham injection	Intradermally, 0.5 mL bupivacaine 0.5% bilaterally (1 mL total), once	2 days	15 Patients aged 40 ± 12 years, 80% female
			Greater occipital nerve block	Intradermally, 3 mL bupivacaine 0.5% bilaterally (6 mL total), once	2 days	13 Patients aged 35 ± 10 years, 92% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Friedman, 2017[64]	RCT in United States of America, 03/2015 to 06/2016	ED	Prochlorperazine plus diphenhydramine	IV, 10 mg prochlorperazine plus 25 mg diphenhydramine, once for 5 minutes (additional optional dose after one hour)	90 days	63 Patients aged 32 ± 9 years, 79% female,
			Hydromorphone plus normal saline placebo	IV, 1 mg hydromorphone, once for 5 minutes (additional optional dose after one hour)	90 days	64 Patients aged 35 ± 11 years, 88% female,
Friedman, 2020[65]	RCT in USA, 11/2017 to 03/2020	ED	Greater occipital nerve block	Adjacent to the greater occipital nerve, Total of 6 mL of bupivacaine 0.5% (3 ml each side) once, in addition to an IV drip of normal saline placebo administered over 15 min	2 days	51 Patients aged 39±11 years, 86% female
			Metoclopramide	Sham great occipital nerve block, total of 6 ml of normal saline injected adjacent to the greater occipital nerve bilaterally (3 ml each side), in addition to an IV drip of 10 mg metoclopramide administered over 15 min.	2 days	48 Patients aged 38±11 years, 71% female
Fuglsang, 2018[66]	Crossover RCT in Denmark,	Outpatient	Active partial rebreathing device	Oral, twice for 40 minutes (20 minutes at the onset of the aura followed by 20 minutes after 40 minutes)	1 day	Entire population: 11 Patients aged 35.5 ± 12 years, 72.7% female, 100% Caucasian

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	11/2016 to 10/2017		Sham partial rebreathing device	Oral, twice for 40 minutes (20 minutes at the onset of the aura followed by 20 minutes after 40 minutes)	1 day	
Gaffigan, 2015[67]	RCT in United States of America, 06/2013 to 02/2014	ED	Diphenhydramine plus haloperidol	IV, diphenhydramine 25 mg plus haloperidol 5 mg, once for 2 minutes	14 days	31 Patients aged 29 ± 8 years, 87% female
			Diphenhydramine plus metoclopramide	IV, diphenhydramine 25 mg plus metoclopramide 10 mg, once for 2 minutes	14 days	33 Patients aged 29 ± 8 years, 76% female
Gallagher, 1996[68]	RCT in United States of America, 04/1993 to 06/1994	Outpatient	Dihydroergotamine mesylate 3 mg	Intranasal, 3 mg, 3 times in each nostril	1 day	Entire population: 348 Patients aged 40 ± 7.8 years
			Dihydroergotamine mesylate 2 mg	Intranasal, 2 mg, 3 times in each nostril	1 day	
			Placebo	Intranasal, 3 times in each nostril	1 day	
Gerhardt, 2011[69]	RCT in United States of America, 01/2002 to 04/2003	Outpatient	Secobarbital	Oral, 100 mg, once or twice	3 days	14 Patients aged 45 ± 1.25 years, 94% female
			Placebo	Oral, once or twice	3 days	16 Patients aged 44 ± 3.25 years, 100% female
Goadsby, 2019[70]	RCT in United States of America, UK and Germany, 05/19/2016 to 06/29/2017	Outpatient	Lasmiditan 200 mg	Oral, 200 mg, once within 4 hours of onset of migraine attack	7 days	721 Patients aged 41.8 ± 12.4 years, 82.6% female, 80.4% White, BMI 30.1 ± 8.2
			Lasmiditan 100 mg	Oral, 100 mg, once within 4 hours of onset of migraine attack	7 days	721 Patients aged 43.4 ± 12.6 years, 84.9% female, 80.2% White, BMI 30.1± 8.3

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Lasmiditan 50 mg	Oral, 50 mg, once within 4 hours of onset of migraine attack	7 days	716 Patients aged 42.8 ± 13.2 years, 84.7% female, 80.1% White, BMI 29.7 ± 7.6
			Placebo	Oral, once within 4 hours of onset of migraine attack	7 days	711 Patients aged 42.6 ± 12.9 years, 84.5% female, 80% White, BMI 30.4 ± 11.1
Hakkarainen, 1982[71]	Crossover RCT, in Finland	Outpatient	Ergotamine 1 mg	Rectal, once after attack	NR	Entire population: 24 Patients aged 36.3 ± 9 years, 100% female
			Metoclopramide 20 mg	Rectal, once after attack		
			Ergotamine 1 mg plus metoclopramide 20 mg	Rectal, once after attack		
			Ergotamine 2 mg plus metoclopramide 20 mg	Rectal, once after attack		
Hoffert, 1992[72]	Crossover RCT in United States of America	Outpatient	Nifedipine	Oral, 20 mg, at onset of the aura. If aura persisted allowed to repeat dose every 20 minutes to the maximum dose	NR	Entire population: 14 Patients (Nifedipine), 13 Patients (Placebo) aged 33 ± 5.75, 66.6% female
			Placebo	Oral, at onset of the aura. If aura persisted allowed to repeat dose every 20 minutes to the maximum dose		

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Hoffert, 1995[73]	RCT in Unites States of America	Outpatient	Butorphanol	Intranasal, 1 mg per spray, immediately after attack, additional doses were allowed within 30-90 minutes if pain relief had not been achieved then every 2-4 hours as needed, with a maximum of 12 sprays allowed over 1 day	2 days	107 Patients aged 41 ± 7 years, 85% female, 90% White, 7% African American, 1% Asian, 1% Hispanic
			Placebo	Intranasal, immediately after attack, additional doses were allowed within 30-90 minutes if pain relief had not been achieved then every 2-4 hours as needed, with a maximum of 12 sprays allowed over 1 day		50 Patients aged 40.6 ± 10.25 years, 82% female, 96% White, 4% African American

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Hokenek, 2020[74]	RCT in Turkey, 06/2019 to 10/2019	ED	Sham stimulation	Transcutaneous electrical nerve stimulation (electrodes over supraorbital nerve), device include 27 kΩ resistance and 47 nF capacitance connected in parallel to the load, a pulse repetition frequency of 50 Hz, a pulse width of 125 μs, an impulse amplitude of 60 voltage, and a pulse energy of 18.4 μJ (±10%) on an oscilloscope, with empty battery and the device was electrically inactive), once for 20 minutes	2 hours	41 Patients aged 33.62±10.2 years

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			External trigeminal nerve stimulation	Transcutaneous electrical nerve stimulation (electrodes over supraorbital nerve), device include 27 kΩ resistance and 47 nF capacitance connected in parallel to the load, a pulse repetition frequency of 50 Hz, a pulse width of 125 μs, an impulse amplitude of 60 voltage and a pulse energy of 18.4 μJ (±10%) on an oscilloscope, with fully charged battery), once for 20 minutes		42 Patients aged 35.62±8.77 years
Honkaniemi, 2006[75]	RCT in Finland, 01/2002 to 02/2005	Inpatient	Haloperidol	IV, 5 mg in 500 mL normal saline over 20-30 minutes	30 days	Entire population:20 Patients (in each study group) aged 36 years, 85% female, 17% previous opioid use
			Placebo	IV, 500 mL normal saline over 20-30 minutes (if no relief in pain 1-3 hours after the infusion then received haloperidol as an open trial)	30 days	
Jones, 1994[76]	RCT in United States of America	ED	Prochlorperazine	Rectal, 25 mg, once	2 hours	10 Patients aged 30.5 ± 2.5 years, 100% female
			Placebo	Rectal, once	2 hours	10 Patients aged 28.4 ± 2.3 years, 90% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Jones, 1996[77]	RCT in United States of America, 02/1991 to 07/1991	ED	Prochlorperazine edisylate	IM, 10 mg, once	2 days	28 Patients (Prochlorperazine edisylate), 29 Patients (Metoclopramide hydrochloride), 29 Patients (Saline), aged 32.1 ± 2.1 years, 73% female
			Metoclopramide hydrochloride	IM, 10 mg, once	2 days	
			Placebo	IM, 2 mL, once	2 days	
Jones, 2019[78]	RCT in United States of America, 01/2017 to 09/2017	ED	Fluid group	IV, 1 L of 0.9% saline solution over 1 hour	2 days	25 Patients aged 34 ± 3.75 years,76% female, 40% White, 40% African American, 40% Hispanic
			Control group	IV, 0.9% saline solution at 10 mL/hour over 1 hour	2 days	25 Patients aged 37 ± 5 years, 92% female, 42% White, 33% African American, 29% Hispanic
Kandil, 2020[79]	RCT in USA, 08/2019 to 03/2020	ED	Magnesium sulfate	IV, 2 g/50 mL dextrose 5% in water, once over 20 min	2 hours	61 Patients aged 34±15.6 years, 72% female, 49% White, 41% Black, 10% Hispanic, BMI 31.2±7.7
			Prochlorperazine	IV, 10 mg/50 mL dextrose 5% in water, once over 20 min	2 hours	52 Patients aged 37.5±15.2 years, 88% female, 27% White, 54% Black, 17% Hispanic, BMI 33.4±7.2
			Metoclopramide	IV, 10 mg/50 mL dextrose 5% in water, once over 20 min	2 hours	44 Patients aged 37.5±13.7 years, 75% female, 52% White, 36% Black, 11% Hispanic, BMI 30.1±6.1
		Outpatient	Ergotamine	Suppositories, 2 mg, once	2 days	

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Kangasniemi, 1992[80]	Crossover RCT in Finland, 01/1987 to 01/1988		Placebo	Suppositories, once	2 days	Entire population: 52 Patients in each group aged 39 ± 10.25 years, 88% female
Kapicioglu, 1997[81]	RCT in Turkey	Outpatient	Octreotide	Subcutaneous, 100 mg	1 day	17 Patients aged 39.7 years, 70.5% female
			Placebo	Subcutaneous, isotonic saline	1 day	12 Patients aged 37.11 years, 75% female
Karimi, 2017[82]	RCT in Iran, 10/2014 to 06/2016	ED	Dexamethasone	IV, 8 mg, once	1 day	40 Patients aged 33.4 ± 9.2 years, 85% female
			Valproate sodium	IV, 400 mg (diluted into 4 mL of normal saline), once	1 day	40 Patients aged 33.9 ± 9.5 years, 77.5% female
Klapper, 1993[83]	RCT in United States of America	Outpatient	Dihydroergotamine plus metoclopramide plus placebo	IV, 1 mg dihydroergotamine plus 10 mg metoclopramide, IM, placebo	1 hour	14 Patients
			Meperidine plus hydroxyzine plus placebo	IM, 75 mg meperidine plus 75 mg hydroxyzine, IV, placebo	1 hour	14 Patients
Korucu, 2018[84]	RCT in Turkey, 01/2016 to 12/2016	ED	Greater occipital nerve blockade	Subcutaneous, 1 mL of 0.5% bupivacaine and 1 mL of normal saline, single injection (if the headache was on one side) or a double injection (if the headache was on both sides (total 4 mL)	45 minutes	20 Patients median age 40 ± 8.9 years, 90% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Dexketoprofen trometamol 50 mg plus metoclopramide10 mg	IV, 50 mg dexketoprofen plus 10 mg metoclopramide diluted in 100ml normal saline	45 minutes	20 Patients median age 35 ± 8.14, 75% female
			Placebo	Subcutaneous, 2 mL of normal saline, single injection (if the headache was on one side) or a double injection (if the headache was on both sides (total 4 mL)	45 minutes	20 Patients median age 40 ± 10.4 years, 90% female
Kuca, 2018[85]	RCT in United States of America, 04/27/2015 to 08/12/2016	Outpatient	Lasmiditan 200 mg	Oral, 200 mg, once	7 days	745 Patients aged 41.4 ± 12 years, 84.6 % female, 73.9% White, BMI 31 ± 8.2
			Lasmiditan 100 mg	Oral, 100 mg, once	7 days	744 Patients aged 42.2 ± 11.7 years, 81.3 % female, 74.8% White, BMI 30 ± 8
			Placebo	Oral, once	7 days	742 Patients aged 42.4 ± 12.3 years, 85.1 % female, 77.6% White, BMI 30.3 ± 7.5
Lane, 1989[86]	RCT in Canada	ED	Chlorpromazine	IV, 25 mg diluted to 10 mL plus 10 mL normal saline, every 15 minutes as needed up to a total of three doses	1 hour	24 Patients aged 31 ± 6.5 years, 87.5% female, 75% previously used opioid

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Dimenhydrinate plus meperidine	IV, 50mg dimenhydrinate diluted to 10 mL plus 100 mg meperidine diluted to 10 mL, every 15 minutes as needed up to a total of three doses	1 hour	22 Patients aged 31.09 ± 7.25 years, 81.8 % female, 68.1 % previously used opioid
Levy, 2005[87]	Crossover RCT in UK	Outpatient	Octreotide	Subcutaneous, 100 µg in 1 mL normal saline, once	2 days	Entire population: 43 Patients aged 48 ± 12 years, female 95%
			Placebo	Subcutaneous, 1 mL normal saline, once	2 days	
Li, 2009 [88]	RCT in China	Outpatient	Verum Acupuncture	Skin by filiform Huatao needles, at the following acupoints Waiguan (TE 5), Yanglingquan (GB 34), Qiuxu (GB 40), Jiaosun (TE 20), and Fengchi (GB 20) used bilaterally. once, for 30 minutes	1 day	58 Patients aged 41.84 years ± 14.21, 56.9% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Sham Acupuncture 1	Skin by filiform Huatao needles, at nonacupoints located halfway between the triple Energizer and Small Intestine meridians lateral to the acupoints Waiguan (TE 5) horizontally; halfway between the line from Qiuxu (GB 40) to Jiexi (ST 41); halfway between the gallbladder and bladder meridians lateral to Yanglingquan (GB 34) horizontally; halfway between the line from Jiaosun (TE 20) to Shuaigu (GB 8); and halfway between the line from Fengchi (GB 20) to Anmian (extra point) bilaterally. Once for 30 minutes	1 day	60 Patients aged 39.65 ± 12.83 years, 55% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Sham Acupuncture 2	Skin by filiform Huatao needles, at nonacupoints located medial arm on the anterior border of the insertion of the deltoid muscle at the junction of the deltoid and biceps muscles; the inside of the mid-thigh region 2 cm lateral to half the distance from the anterior superior iliac spine to the lateral superior corner of the patella on the rectus femoris;13 the edge of the tibia 1 to 2 cm lateral to the Zusanli (ST 36) point horizontally; halfway between the tip of the elbow and the axillae and halfway between the epicondylus medialis of the humerus and ulnar side of the wrist bilaterally.once for 30 minutes	1 day	57 Patients aged 39.49 ± 11.6 years, 70.2% female
Lipton, 2000[89]	RCT in United Stated of America, 03/11/1998 to 08/10/1998	Outpatient	Acetaminophen	Oral, 1000 mg, once	6 hours	176 Patients aged 37.3 ± 10.4 years, 76.9% female, 23.8% African American, 75.5% White, 0.7% others

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Placebo	Oral, once	6 hours	175 Patients aged 36 ± 9.3 years, 83.1% female, 28.9% African American, 69.7% white, 1.4% others
Lipton, 2010[90]	RCT (non-inferiority) in United States of America, 08/2006 to 02/2008	Outpatient	Single-pulse transcranial magnetic stimulation (sTMS)	Transcranial (below the occipital bone), pulse of nominally 0·9 T peak (measured 1 cm from the device surface) with a rise time of roughly 180 μs and a total pulse length of less than 1 ms, two pulses about 30 s apart (treat up to 3 attacks)	90 days	102 Patients aged 38.8 ± 11.2 years, 82% female
			Sham stimulation	Transcranial (below the occipital bone), two pulses about 30 s apart (treat up to 3 attacks)	90 days	99 Patients aged 40.1 ± 10.8 years, 77% female
Lipton, 2019[91]	RCT in United States of America, 07/2017 to 01/2018	Outpatient	Rimegepant	Oral, 75 mg, once	7 days	594 Patients aged 40.2 ± 11.9 years, 89.2% female, 20.7% African American, 73.4% White, 1.5% Asian, 14.3% Hispanic, 4.47% others, BMI 31.0 ± 7.9
			Placebo	Oral, once	7 days	592 Patients aged 40.9 ± 12.1 years, 88.2% female, 22.1% African American, 74.6% White, 1.5% Asian, 15.5% Hispanic, 1.8% others, BMI 31.8 ± 8.5

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Lipton, 2019[92]	RCT in United States of America, 08/26/2016 to 02/26/2018	Outpatient	Ubrogepant 50 mg	Oral, 50 mg, once within 4 hours of a qualifying migraine attack	42 days	562 Patients aged 41.2±12.5 years, 91% female, 16.8% African American, 81.6% White, 0.4% Asian, 21.9% Hispanic, 0.4% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 0.6% multiple, BMI 30.5±7.5, 3.9% previous opioid use
			Ubrogepant 25 mg	Oral, 25 mg, once within 4 hours of a qualifying migraine attack	42 days	561 Patients aged 41.6±12.4 years, 90.2% female, 14% African American, 83.5% White, 1.3% Asian, 23% Hispanic, 0.2% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 0.8% multiple, BMI 29.6±7, 3.6 % previous opioid use

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Placebo	Oral, once within 4 hours of a qualifying migraine attack	42 days	563 Patients aged 41.7±12.1 years, 88.6% female, 16.4% African American, 80% White, 1.4% Asian, 19.8% Hispanic, 0.6% American Indian or Alaska Native, 0.2% Native Hawaiian or other Pacific Islander, 1.4% multiple, BMI 29.8±7.7, 3.8% previous opioid use
Maizels, 1996[93]	RCT in United States of America, 12/1994 to 10/1995	Urgent Care	Lidocaine	Intranasal, 0.5 mL of 4% lidocaine topical solution dripped in one nostril over 30 seconds (1 mL in case the headache is bilateral dripped over 1 minute), 1-2 times	1 day	53 Patients median age 43 ± 11.9 years, 87% female
			Placebo	Intranasal, 0.5 mL, normal saline dripped in one nostril over 30 seconds (1 mL in case the headache is bilateral dripped over 1 minute), 1-2 times	1 day	28 Patients median age 40 ± 11.5 years, 75% female
Maizels, 1999[94]	RCT in United States of America, 01/1997 to 01/1998	Outpatient	Lidocaine	Intranasal, 0.5 mL of 4% lidocaine topical solution dripped in one nostril over 30 seconds (1 mL in case the headache is bilateral dripped over 1 minute), 1-2 times	30 days (RCT),180 days (open label)	66 Patients aged 44.5 ± 9.1 years, 83.1% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Placebo	Intranasal, 0.5 mL, normal saline dripped in one nostril over 30 seconds (1 mL in case the headache is bilateral dripped over 1 minute), 1-2 times	30 days (RCT),180 days (open label)	65 Patients aged 47 ± 10.2 years, 87.9% female
Marcus, 2008[95]	RCT in United States of America	ED	Integrated EMDR (eye movement desensitization reprocessing)	Behavioral intervention, Participant's use of diaphragmatic breathing coupled with head compression by the provider, once for 12-60 minutes	7 days	26 Patients aged 38.33 ± 10.57 years, 95.2% female, 30% White
			Usual Care	Variable interventions (oral / injection; depending on drug type), Variable dosage depends on the drug, once	7 days	26 Patients aged 37.95 ± 9.57 years, 95.5% female, 68.2% White
Marcus, 2014[96]	RCT in United States of America, 10/2011 to 05/ 2012	Outpatient	Placebo	Oral, once	7 days	229 Patients aged 37.9 ± 11.36 years, 86% female, 12% African American, 84% White, 3% others
			Rimegepant 10 mg	Oral, 10 mg, once	7 days	85 Patients aged 41.1 ± 10.36 years, 79% female, 14% African American, 79% White, 7% others
			Rimegepant 25 mg	Oral, 25 mg, once	7 days	68 Patients aged 36.5 ± 11.92 years, 90% female, 10% African American, 87% White, 3% others

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Rimegepant 75 mg	Oral, 75 mg, once	7 days	91 Patients aged 38.5 ± 11.87 years, 89% female, 7% African American, 90% White, 3% others
			Rimegepant 150 mg	Oral, 150 mg, once	7 days	90 Patients aged 39.2 ± 11.26 years, 70% female, 20% African American, 72% White, 8% others
			Rimegepant 300 mg	Oral, 300 mg, once	7 days	121 Patients aged 41.9 ± 11.46 years, 84% female, 13% African American, 84% White, 1% others
			Rimegepant 600 mg	Oral, 600 mg, once	7 days	92 Patients aged 39.3 ± 13.01 years, 83% female, 11% African American, 87% White, 2% others
Mazaheri, 2015[97]	RCT in Iran, 04/2012 to 06/2014	ED	Valproate Sodium	IV, 400 mg (plus 50 mL saline normal solution) for 15 minutes, once	2 hours	43 Patients aged 37.29 ± 11.7 years, 82.9% female
			Dexamethasone	IV, 16 mg (plus 50 mL saline normal solution) for 15 minutes, once	2 hours	43 Patients aged 32.05 ± 9.1 years, 81.1% female
McEwen, 1987[98]	RCT in Canada, 03/1985 to 11/1985	ED	Chlorpromazine	IM, 50 mg/2mL (1 mg/kg), once	1 day	19 Patients aged 30 years, 94.7% female
			Normal saline	IM, 2 mL, normal saline, once	1 day	17 Patients aged 36 years, 88.2% female
Meek, 2020[99]	RCT in Australia, 03/01/2016 to 10/31/2018	ED	Propofol	IV, Maximum dose 140 mg over 40 min (Initial dose of 40 mg followed by up to five doses of 20 mg, over 5 min a part)	2 days	21 Patients, aged 35±9.6 years, 81% female

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			Placebo	IV, maximum dose 14 ml (20% Intralipid), over 40 min (Initial dose of 4 ml followed by up to five doses of 2 ml, over 5 min a part)	2 days	19 Patients, aged 35±11.9 years, 84% female
Miller, 2009[100]	RCT in United States of America, 02/2006 to 02/2007	ED	Prochlorperazine	IV, 10 mg once for 2 minutes	3 days	20 Patients aged 27.5 ± 5.8 years, 70% female
			Octreotide	IV, 100 µg, once for 2 minutes	3 days	24 Patients aged 31.1 ± 11.1 years, 78% female
Mitra, 2020[101]	RCT in Australia	ED	Propofol	IV, 1 mg/kg, slowly for 1 min	N/A	15 Patients aged 32.9±10.3 years, 47% female
			Standard therapy (chlorpromazine, metoclopramide, ondansetron, lignocaine, magnesium sulphate, or morphine)	N/A	N/A	15 Patients aged 37.9±9.4 years, 89% female.
Molaie, 1987[102]	RCT in United States of America	ED	Verapamil hydrochloride	IV, 2 cc (10 mg), once	1 hour	6 Patients (verapamil hydrochloride), 6 Patients (placebo), aged 33.75 ± 8.3 years, 50% female
			Placebo	IV, 2 cc, once	1 hour	
Motamed, 2020[103]	RCT in Iran, 10/2017 to 11/2018	ED	Metoclopramide plus Magnesium sulphate	IV, 2 g magnesium sulfate plus 10 mg metoclopramide once	45 minutes	40 Patients aged 20-30 (12.5%), 31-40 (52.5%), >40 (35%) years, 50% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Metoclopramide plus placebo	IV, 10 mg metoclopramide plus placebo once	45 minutes	40 Patients aged 20-30 (22.5%), 31-40 (42.5%), >40 (35%) years, 50% female
Niazi, 2007[104]	Crossover RCT in Iran	Outpatient	Rose damascene oil	Skin, 2 cc of the rose damascene oil on forehead and temporal zones at onset of migraine attacks	1 day	Entire population: 40 Patients aged 34.89 ± 10.81 years, BMI 25.50 ± 4.77
			Placebo	Skin, 2 cc of the paraffin oil forehead and temporal zones at the onset of migraine attacks	1 day	
Prior, 2010[105]	RCT in United States of America, 02/1999 to 06/1999	Outpatient	Acetaminophen	Oral, 1000 mg, once	3 days	190 Patients aged 38.1 ± 11 years, 80.8% female, 87% White
			Placebo	Oral, placebo, once	3 days	188 Patients aged 39.8 ± 11.8 years, 85.8% female, 85.8% White
Rafieian-Kopaei, 2019[106]	RCT in Iran	Outpatient	Lidocaine	Intranasal, 4%, once-twice	60 days	41 Patients aged 30.6 ± 6.3 years, 76.3% female
			Peppermint essential oil	Intranasal, 1.5%, once-twice	60 days	38 Patients aged 30.42 ± 7.2 years, 76.3.6% female
			Placebo	Intranasal, once-twice	60 days	41 Patients aged 31.8 ± 5.8 years, 68.3% female
Rapoport, 1995[107]	RCT in the United States of America	Outpatient	Dihydroergotamine	Intranasal, 2 mg in 0.5 mL, divided into 2 sprays delivered in 15 minutes interval	4 hours	114 Patients (Dihydroergotamine), 115 Patients (Placebo), age

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Placebo	Intranasal, 0.5 mL, divided into 2 sprays delivered in 15 minutes interval	4 hours	range 18-62, 70% female 0% White
Reutens, 1991[108]	RCT in Australia, 04/1989 to 12/1989	ED	Lidocaine	IV, 66 mg, once for 2 minutes	20 minutes	13 Patients aged 40 years, 92% female
			Placebo	IV, once for 2 minutes	20 minutes	12 Patients aged 30 years, 67% female
Richman, 2002[109]	RCT in United States of America	ED	Droperidol	IM, 2.5 mg, once	0.5 hour	15 Patients aged 30.7 ± 8.9 years, 73% female
			Meperidine	IM, 1.5 mg/ kg, once	0.5 hour	14 Patients aged 32.7 ± 9.9 years, 71% female
Rowat, 1991[110]	RCT in Canada	ED	Granisetron 40 µg/kg	IV, 20 mL (1000 µg/ mL diluted in 0.9% saline), once for 3 minutes	3 ±1 days	10 Patients aged 39.5 ± 11.8 years, 50% female, weight 72.4 ± 11.7
			Granisetron 80 µg/kg	IV, 20 mL (2000 µg/ mL diluted in 0.9% saline), once for 3 minutes	3 ±1 days	10 Patients aged 38.2 ± 13.8 years, 80% female, weight 59.8 ± 9.2
			Placebo	IV, once for 3 minutes	3 ±1 days	8 Patients aged 41.3 ± 8.6 years, 87.5% female, weight 63.1 ± 11.9
Ryan, 1970[111]	Crossover RCT in United States of America	Outpatient	Ergostine 1 mg plus caffeine 100 mg	Oral, 1 mg ergostine plus 100 mg caffeine, medication was taken at first sign of headache (2 tablets) followed by 1 tablet every ½ hour until attack was aborted or a maximum of six tablets had been taken	1 day	Entire population: 48 Patients aged 46 ± 12.25 years, 68.7% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Ergotamine tartrate 1 mg plus caffeine 100 mg	Oral, 1 mg ergotamine tartrate plus 100 mg caffeine, medication was taken at first sign of headache (2 tablets) followed by 1 tablet every ½ hour until attack was aborted or a maximum of six tablets had been taken	1 day	
			Placebo	Oral, medication was taken at first sign of headache (2 tablets) followed by 1 tablet every ½ hour until attack was aborted or a maximum of six tablets had been taken	1 day	
Salazar, 2011[112]	RCT in Spain, 01/2007 to 03/2009	ED	Metoclopramide	IV, 10 mg diluted in 100 cc of saline, once	2 days	43 Patients aged 35 years, 53.48% female
			Paracetamol	IV, 1g diluted in 100 mL of saline, once	2 days	45 Patients aged 42 years, 51.11% female
Scherl, 1995[113]	RCT in United States of America	Outpatient	Dihydroergotamine plus metoclopramide	IV, 0.5 mg dihydroergotamine with 10 mg metoclopramide, once	1 day	14 Patients (dihydroergotamine plus metoclopramide), 13 patients (meperidine plus promethazine), aged 30.6 ± 7.6 years, 70.4% female
			Meperidine plus promethazine	IM, 75 mg meperidine with 25 mg promethazine, once	1 day	
Shahrami, 2015[114]	RCT in Iran, 2011	ED	Dexamethasone plus metoclopramide	IV, 8 mg dexamethasone and 10 mg metoclopramide in 100 mL normal saline solution, once for 15 minutes	2 hours	35 Patients aged 38 ± 11.2 years, 60% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Magnesium sulfate	IV, 1 g in 100 mL normal saline, once for 15 minutes	2 hours	35 Patients aged 36 ± 12.6 years, 45.7% female
Sharma, 2002[115]	RCT in India	Outpatient	Buccal prochlorperazine	Oral, 3 mg, once	N/A	Entire population: 45 Patients aged 18 to 50 years, 62.2% female
			Buccal placebo	Oral, once	N/A	
			Ergotamine tartrate plus caffeine	Oral, 1 mg ergotamine tartrate plus 100 mg caffeine, once	N/A	
Silberstein, 2005[116]	RCT in United States of America	Outpatient	Acetaminophen plus tramadol	Oral, 75 mg/650 mg, once	1 day	188 Patients aged 39.2 ± 11.29 years, 87% female, 83.8% White, 10.4% Black, 1.3% Asian, 4.5% Other
			Placebo	Oral, once	1 day	187 Patients aged 39.1 ± 10.47 years, 83.4% female, 87.6% White, 6% Black, 2% Asian, 4.6% Other
Silberstein, 2003[117]	RCT in United States of America, 12/19/1997 to 06/15/1998	Outpatient	Droperidol 0.1 mg	IM, 0.1 mg, once	7 days	63 Patients aged 42 ± 10.5 years, 81% female
			Droperidol 2.75 mg	IM, 2.75 mg, once	7 days	61 Patients aged 41 ± 9.1 years, 80% female
			Droperidol 5.5 mg	IM, 5.5 mg, once	7 days	59 Patients aged 41 ± 10.8 years, 81% female
			Droperidol 8.25 mg	IM, 8.25 mg, once	7 days	61 Patients aged 42 ± 10 years, 77% female
			Placebo	IM, once	7 days	61 Patients aged 41 ± 9.7 years, 85% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Soleimanpour, 2012[118]	RCT in Iran	ED	Propofol	IV, 10 mg, every 5-10 minutes (maximum dose of 80 mg), rate of 1 mL for 10 seconds	N/A	45 Patients aged 35.65 ± 12.55 years, 66.6% female
			Dexamethasone	IV, 4 mg/mL with dose of 0.15 mg/kg (maximum dose of 16 mg), rate of 1 mL for 10 seconds	N/A	45 Patients aged 36.27 ± 13.38 years, 62.22% female
Stiell, 1991[119]	RCT in Canada, 02/1990 to 09/1990	ED	Methotrimeprazine	IM, 37.5 mg, once	2 days	37 Patients aged 30.9±7.3 years, 67.6% female
			Meperidine plus dimenhydrinate	IM, 75 mg meperidine with 50 mg dimenhydrinate, once	2 days	37 Patients aged 32.5±8.9 years, 83.8% female
Taheraghdam, 2011[120]	RCT in Iran, 09/2008 to 05/2009	ED	Dexamethasone	IV, 8 mg, once	1 day	93 Patients aged 45.93±16.1 years, 55.9% female
			Morphine	IV, 0.1 mg/kg, once	1 day	97 Patients aged 42.34±16.2 years, 67% female
Tanen, 2003[121]	RCT in United States of America, 01/2002 to 08/2002	ED	Sodium valproate	IV, 500 mg, once for 2 minutes	0.5 days	20 Patients aged 31±9.3, 58% female
			Prochlorperazine	IV, 10 mg, once for 2 minutes	0.5 days	20 Patients aged 38.8±11, 79.2% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
Tassorelli, 2018[122]	RCT in Italy, 01/11/2016 to 03/31/2017	Outpatient	Noninvasive vagus nerve stimulation	Transdermal, a low-voltage electrical signal comprising a 5-kHz sine wave burst lasting for 1 ms (5 sine waves, each lasting 200 μs), with such bursts repeated once every 40 ms (25 Hz), generating a 24-V peak voltage and 60-mA peak output current for 2 minutes	5 days	122 Patients aged 38.8±11 years, 79.24% female, 100% White
			Sham stimulation	Transdermal, a low-frequency (0.1 Hz) biphasic signal for 2 minutes	5 days	126 Patients aged 39.6±11.8 years, 30% female, 100% White
Tek, 1990[123]	RCT in United States of America, 08/1987 to 04/1988	ED	Metoclopramide	IV, 10 mg, once	2 days	24 Patients age range 18-60
			Placebo	IV, 2 mL, once	2 days	26 Patients age range 18-60
Treves, 1998[124]	RCT in Brazil	Outpatient	Dihydroergotamine 1 mg	Intranasal, 1 mg, 2 to 4 times	N/A	19 Patients aged 33.3±12.3 years, 78.9% female
			Dihydroergotamine 0.5 mg	Intranasal, 0.5 mg, 2 to 4 times	N/A	17 Patients aged 33.7±10 years, 41.2% female
			Placebo	Intranasal, 2 to 4 times	N/A	16 Patients aged 34.8±13.7 years, 62.5% female
Triner, 1999[125]	RCT in United States of America,	ED	Nitrous oxide plus oxygen	Inhalation, 50% (NO) 50% Oxygen, once for 20 minutes	0.5 days	10 Patients aged 34.5± 11.8 years, 80% female, 70% White

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
	07/10/1995 to 11/30/1995		Oxygen	Inhalation, 100% Oxygen, once for 20 minutes	0.5 days	12 Patients aged 28.1 ± 5.5 years, 91.6% female, 80% White
Tulunay, 1987[126]	Crossover RCT in Turkey	Outpatient	Dihydroergotamine	Intranasal (Puff), 4 mg/mL of DHE in an aqueous solution of 1 % caffeine and 5% glucose, 2 to 3 times	0.5 days	17 Patients aged 26.1 ± 3.34 years, 58.6% female
			Placebo	Intranasal (Puff), 2 to 3 times	0.5 days	
Voss, 2016[127]	RCT in United States of America	Outpatient	Ubrogepant 1 mg	Oral, 1 mg, once	14 days	138 Patients aged 39.6 ± 10.7 years, 88.8% female, BMI 29.4±7.3
			Ubrogepant 10 mg	Oral, 10 mg, once	14 days	139 Patients aged 41.1 ± 10.9 years, 85.2% female, 29.6±7.1
			Placebo	Oral, once	14 days	139Patients aged 40.5 ± 11.7 years, 87.65% female, BMI 28.5±7
			Ubrogepant 25 mg	Oral, 25 mg, once	14 days	139 Patients aged 41.4 ± 11.5 years, 86.8% female, BMI 29.2±8.1
			Ubrogepant 50 mg	Oral, 50 mg, once	14 days	139 Patients aged 40.7 ± 12.3 years, 88.2% female, BMI 27.8±8.1
			Ubrogepant 100 mg	Oral, 100 mg, once	14 days	140 Patients aged 41.9 ± 11 years, 83.3% female, BMI 29.2±7
Wang, 2012[128]		Outpatient	Verum Acupuncture	Skin, once for 30 minutes	3 days	75 Patients aged 37.8 ± 10.6 years, 89.3% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
	RCT in China 03/2007 to 02/2009		Sham Acupuncture	Skin, once for 30 minutes	3 days	75 Patients aged 38.6 ± 12.6 years, 84% female
Yang, 2012[129]	RCT in China, 07/2008 to 09/2009	Outpatient	Traditional acupuncture group	Received specific stimulation of traditional acupoints by electroacupuncture treatment (EAT) for 30 minutes, stimulation frequency was 2/100 Hz, and the stimulation intensity varied from 0.1 to 1.0 mA as long as the patients felt comfortable	1 hour	Entire population: 30 Patients aged 32.87 ± 8.71 years, 60% female
			Sham acupuncture group	Received nonspecific stimulation by electroacupuncture treatment (EAT) for 30 minutes, stimulation frequency was 2/100 Hz, and the stimulation intensity varied from 0.1 to 1.0 mA as long as the patients felt comfortable	1 hour	
			No treatment	Received no treatment	1 hour	
Yarnitsky, 2017[130]	Crossover RCT in Israel, 06/2015 to 03/2016	Outpatient	Active remote electrical stimulation (pulse width 50 μs)	Transcutaneously, at 80-120 Hz frequency, with pulse width of 50 μs for 20 minutes	60 days	Entire population: 86 Patients aged 45.9 ± 11.7 years, 80% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Active remote electrical stimulation (pulse width 100 μs)	Transcutaneously, at 80-120 Hz frequency, with pulse width of 100 μs for 20 minutes	60 days	
			Active remote electrical stimulation (pulse width 150 μs)	Transcutaneously, at 80-120 Hz frequency, with pulse width of 150 μs for 20 minutes	60 days	
			Active remote electrical stimulation (pulse width 200 μs)	Transcutaneously, at 80-120 Hz frequency, with pulse width of 200 μs for 20 minutes	60 days	
			Sham remote electrical stimulation	Transcutaneously, at 0.1 Hz frequency, with pulse width of 45 μs for 20 minutes	60 days	
Yarnitsky, 2019[131]	RCT in United States of America, Israel, 12/17/2017 to 10/07/2018	Outpatient	Remote electrical neuromodulation-active group	Applied to lateral arm, once for 30 to 45 minutes	2 days	126 Patients aged 44 ± 12.25 years, 80.9% female, 86.5% While
			Sham stimulation	Applied to lateral arm, once for 30 to 45 minutes	2 days	126 Patients aged 42 ± 11.81 years, 80.9% female
Zargaran, 2018[132]	Crossover RCT in Iran 12/2014 to 05/2015	Outpatient	Chamomile oil	Cutaneous gel, 2mL, twice	1 day	50 Patients aged 37.94 ± 9.77 years, 86.8% female
			Placebo	Cutaneous gel, 2mL, twice	1 day	50 Patients aged 36.03 ± 8.79 years, 70.5% female
Ziegler, 1994[133]	RCT in United States of America	Outpatient	Dihydroergotamine	Intranasal, 0.5 mg (per nostril repeated after 15 minutes), once to twice for 4 hours	14 days	54Patients aged 39.3 ± 10.5 years, 83.3% female

Author, Year	Country, Study Design, Study Period	Study Setting (outpatient, inpatient, ED)	Intervention(s) and Comparison	Route of Administration, Dose and Duration	Length of Followup	Patient Characteristics
			Placebo	Intranasal, once to twice for 4 hours	14 days	58 Patients aged 36.7 ±10.75 years, 75% female

BAP = buccally absorbed prochlorperazine; BMI = body mass index; C = centigrade; cm = centimeter; cc = cubic centimeter; ED = emergency department; Hz = hertz; IV = intravenous; IVP = intravenous prochlorperazine; IM = intramuscular; kHz = kilohertz; gr = gram; kg = kilogram; mA = milliampere; µg = microgram; µg/ mL = microgram/milliliter; µs = microsecond; mg = milligram; mg/kg = milligram/kilogram; mg/mL = milligram /milliliter; mL = milliliter; mL/hour = milliliter/hour; ms = millisecond; N/A = not available; NO = nitrous oxide; RCT = randomized clinical trial s = second; T = temperature

eTable 9. Adverse events

eTable 9.1. Adverse events: calcitonin gene-related peptide receptor antagonists

Comparison	Adverse Events	Findings	Study Design
Rimegepant vs. Placebo	Cardiovascular AE	Rate Ratio: 0.42; 95% CI: 0.01 to 21.10; I^2=N/A	1 RCT[96]
	Gastrointestinal AE	Rate Ratio: 1.69; 95% CI: 1.00 to 2.87; I^2=N/A	3 RCTs[42,91,96]
	Genitourinary AE	Rate Ratio: 1.77; 95% CI: 0.81 to 3.88; I^2=N/A	2 RCTs[42,91]
	Musculoskeletal AE	Rate Ratio: 1.67; 95% CI: 0.08 to 37.13; I^2=N/A	1 RCT[96]
	Neurological AE	Rate Ratio: 0.90; 95% CI: 0.40 to 2.00; I^2=N/A	2 RCTs[42,96]
	Other AE	Rate Ratio: 0.42; 95% CI: 0.01 to 21.10; I^2=N/A	1 RCT[96]
	Serious AE	Rate Ratio: 0.54; 95% CI: 0.13 to 2.28; I^2=0.00%	3 RCTs [42,91,96]
	Total AE	Rate Ratio: 1.23; 95% CI: 1.00 to 1.50; I^2=N/A	3 RCTs[42,91,96]
	Withdrawal due to AE	RR: 3.01; 95% CI: 0.12 to 73.72; I^2=N/A	1 RCT[42]
Ubrogepant vs. Placebo	Cardiovascular AE	Rate Ratio: 2.00; 95% CI: 0.11 to 36.61; I^2=N/A	1 RCT[127]
	ENT AE	Rate Ratio: 8.02; 95% CI: 1.06 to 60.48; I^2=N/A	1 RCT[92]
	Dermatological AE	Rate Ratio: 0.10; 95% CI: 0.00 to 2.98; I^2=N/A	1 RCT[127]
	Gastrointestinal AE	Rate Ratio: 1.46; 95% CI: 0.99 to 2.16; I^2=0%	3 RCT[48,92,127]
	Neurological AE	Rate Ratio: 1.19; 95% CI: 0.76 to 1.85; I^2=0%	3 RCT[48,92,127]
	Other AE	Rate Ratio: 0.20; 95% CI: 0.00 to 10.08; I^2=N/A	1 RCT[127]
	Serious AE	Rate Ratio: 2.54; 95% CI: 0.28 to 23.11; I^2=N/A	2 RCTs [48,92]
	Total AE	Rate Ratio: 1.11; 95% CI: 0.96 to 1.28; I^2=0%	3 RCT[48,92,127]
	Withdrawal due to AE	RR: 0.63; 95% CI: 0.17 to 2.33; I^2=4.68	2 RCT[48,92]

AE = adverse event; CI = confidence interval; ENT = ear, nose, throat; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk

eTable 9.2. Adverse events: 5-HT1F receptor agonist

Comparison	Adverse Events	Findings	Study Design
Lasmiditan vs. Placebo	Cardiovascular AE	Rate Ratio: 1.83; 95% CI: 0.56 to 6.01; I^2 = 0.00%	3 RCTs[55,70,85]
	Gastrointestinal AE	Rate Ratio: 2.32; 95% CI: 1.32 to 4.07; I^2 = 0.00%	4 RCTs[23,53,70,85]
	Neurological AE	Rate Ratio: 4.90; 95% CI: 3.13 to 7.66; I^2 = 62.50%	4 RCTs[53,55,70,85]
	Other AE	Rate Ratio: 4.77; 95% CI: 0.26 to 87.36; I^2 = N/A	2 RCT[23,55]
	Serious AE	Rate Ratio: 2.18; 95% CI; 1.18 to 4.02; I^2=66.60%	3 RCTs[23,53,85]
	Total AE	Rate Ratio: 2.67; 95% CI: 2.10 to 3.39; I^2 = 0.00%	4 RCTs[53,55,70,85]
	Withdrawal	RR: 1.16; 95% CI: 0.90 to 1.49; I^2 = 53.64%	4 RCTs[23,53,70,85]
	Withdrawal due to AE	RR: 5.89; 95% CI: 2.66 to 13.04; I^2 =0.00%	2 RCT[23,85]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk

eTable 9.3. Adverse events: antiemetic

Comparison	Adverse Events	Findings	Study Design
Chlorpromazine vs. Placebo	Cardiovascular AE	Rate Ratio: 2.98; 95% CI: 0.82 to 10.84; I^2=N/A	1 RCT[98]
	Neurological AE	Rate Ratio: 2.09; 95% CI: 0.96 to 4.56; I^2=N/A	1 RCT[98]
	Total AE	Rate Ratio: 1.61; 95% CI: 0.54 to 4.81; I^2=N/A	1 RCT[98]
	Withdrawal	RR: 1.06; 95% CI: 0.62 to 1.79; I^2=41.60%%	2 RCTs[29,98]
Diphenhydramine plus metoclopramide vs. Diphenhydramine plus haloperidol	Neurological AE	Rate Ratio: 0.38; 95% CI: 0.12 to 1.20; I^2=N/A	1 RCT[67]
	Sleep-related AE	Rate Ratio: 1.69; 95% CI: 0.57 to 5.05; I^2=N/A	1 RCT[67]
	Total AE	Rate Ratio: 0.77; 95% CI: 0.38 to 1.57; I^2=N/A	1 RCT[67]
Droperidol vs. Placebo	Dermatological AE	Rate Ratio: 0.43; 95% CI: 0.19 to 0.93; I^2=N/A	1 RCT[117]
	Gastrointestinal AE	Rate Ratio: 1.25; 95% CI: 0.43 to 3.66; I^2=N/A	1 RCT[117]
	Neurological AE	Rate Ratio: 1.52; 95% CI: 1.03 to 2.23; I^2=N/A	1 RCT[117]
	Psychological AE	Rate Ratio: 7.25; 95% CI: 1.77 to 29.68; I^2=N/A	1 RCT[117]
	Total AE	Rate Ratio: 1.61; 95% CI: 1.18 to 2.20; I^2=N/A	1 RCT[117]
Granisetron vs. Placebo	Cardiovascular AE	Rate Ratio: 0.80; 95% CI: 0.15 to 4.37; I^2=N/A	1 RCT[110]
	Dermatological AE	Rate Ratio: 0.27; 95% CI: 0.03 to 2.56; I^2=N/A	1 RCT[110]
	Gastrointestinal AE	Rate Ratio: 1.87; 95% CI: 0.54 to 6.50; I^2=N/A	1 RCT[110]
	Neurological AE	Rate Ratio: 1.20; 95% CI: 0.22 to 6.55; I^2=N/A	1 RCT[110]
	Other AE	Rate Ratio: 0.80; 95% CI: 0.05 to 12.79; I^2=N/A	1 RCT[110]
	Serious AE	Rate Ratio: 0.40; 95% CI 0.01 to 20.16; I^2 =N/A	1 RCT[110]
	Total AE	Rate Ratio: 1.10; 95% CI: 0.34 to 3.56; I^2=N/A	1 RCT[110]
Haloperidol vs. Placebo	Total AE	Rate Ratio: 6; 95% CI: 2.12 to 120.65; I^2=N/A	1 RCT[75]
Magnesium sulfate vs. Dexamethasone plus metoclopramide	Gastrointestinal AE	Rate Ratio: 0.80; 95% CI: 0.21 to 2.98; I^2=N/A	1 RCT[114]
	Total AE	Rate Ratio: 0.57; 95% CI: 0.17 to 1.95; I^2=N/A	1 RCT[114]
Metoclopramide vs. Chlorpromazine	Gastrointestinal AE	Rate Ratio: 1.60; 95% CI: 0.27 to 9.59; I^2=N/A	1 RCT[36]
	Neurological AE	Rate Ratio: 0.98; 95% CI: 0.43 to 2.22; I^2=N/A	1 RCT[36]
	Psychological AE	Rate Ratio: 1.07; 95% CI: 0.07 to 17.08; I^2=N/A	1 RCT[36]
	Total AE	Rate Ratio: 0.84; 95% CI: 0.43 to 1.66; I^2=N/A	1 RCT[36]

Comparison	Adverse Events	Findings	Study Design
Metoclopramide vs. Diphenhydramine plus metoclopramide	Neurological AE	Rate Ratio: 0.97; 95% CI: 0.58 to 1.61; I^2=N/A	1 RCT[62]
	Total AE	Rate Ratio: 0.97; 95% CI: 0.58 to 1.61; I^2=N/A	1 RCT[62]
	Withdrawal	Rate Ratio: 0.20; 95% CI: 0.02 to 1.68; I^2=N/A	1 RCT[62]
Metoclopramide vs. Magnesium sulfate plus metoclopramide	Neurological AE	Rate Ratio: 0.30; 95% CI: 0.03 to 2.93; I^2=N/A	1 RCT[41]
	Other AE	Rate Ratio: 0.42; 95% CI: 0.14 to 1.19; I^2=N/A	1 RCT[41]
	Total AE	Rate Ratio: 0.39; 95% CI: 0.15 to 1.02; I^2=N/A	1 RCT[41]
	Withdrawal	RR: 0.61; 95% CI: 0.11 to 3.29; I^2=N/A	1 RCT[41]
Metoclopramide vs. Magnesium sulfate	Total AE	Rate Ratio: 0.92; 95% CI: 0.15 to 5.53; I^2=N/A	1 RCT [79]
Metoclopramide vs. Placebo	Neurological AE	Rate Ratio: 0.21; 95% CI: 0.37 to 4.03; I^2=N/A	2 RCTs[49,123]
	Serious AE	Rate Ratio: 1.08; 95% CI 0.02 to 54.60; I^2 =N/A	1 RCT[123]
	Total AE	Rate Ratio: 1.21; 95% CI: 0.37 to 4.03; I^2=N/A	2 RCTs[49,123]
Metoclopramide plus paracetamol vs. Placebo	Withdrawal	RR: 1.64; 95% CI: 0.41 to 6.55; I^2=N/A	1 RCT[45]
Paracetamol vs. Metoclopramide	Total AE	Rate Ratio: 0.09; 95% CI: 0.01 to 0.67; I^2=N/A	1 RCT[112]
Prochlorperazine vs. Magnesium sulfate	Total AE	Rate Ratio: 2.35; 95% CI: 0.59 to 9.38; I^2=N/A	1 RCT [79]
Prochlorperazine vs. Metoclopramide	Neurological AE	Rate Ratio: 0.95; 95% CI: 0.50 to 1.81; I^2=0.00%	3 RCTs[40,60,77]
	Total AE	Rate Ratio: 1.39; 95% CI: 0.73 to 2.67; I^2=0.00%	4 RCTs[40,60,77,79]
	Withdrawal	RR: 2.92; 95% CI: 0.32 to 26.88; I^2=N/A	1 RCT[60]
	Withdrawal due to AE	RR: 1.09; 95% CI: 0.17 to 7.10; I^2=N/A	1 RCT[60]
Prochlorperazine vs. Octreotide	Neurological AE	Rate Ratio: 4.2; 95% CI: 0.87 to 20.22; I^2=N/A	1 RCT[100]
	Total AE	Rate Ratio: 3.36; 95% CI: 1.21 to 9.33; I^2=N/A	1 RCT[100]
	Withdrawal	RR: 0.40; 95% CI: 0.02 to 9.24; I^2=N/A	1 RCT[100]
	Withdrawal due to AE	RR:0.40; 95% CI: 0.02 to 9.24; I^2=N/A	1 RCT[100]
Prochlorperazine vs. Placebo	Neurological AE	Rate Ratio: 6.07; 95% CI: 1.39 to 26.55; I^2=N/A	1 RCT[115]
	Total AE	Rate Ratio: 6.48; 95% CI: 1.49 to 28.17; I^2=N/A	1 RCT[115]
	Withdrawal	Rate Ratio: 1.89; 95% CI: 0.57 to 6.22; I^2=N/A	1 RCT[115]
Valproate vs. Prochlorperazine	Withdrawal	RR: 3; 95% CI: 0.13 to 69.52; I^2=N/A	1 RCT[121]

AE = adverse event; CI = confidence interval; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk

eTable 9.4. Adverse events: ergot alkaloids

Comparison	Adverse Events	Findings	Study Design
Dihydroergotamine vs. Chlorpromazine	Gastrointestinal AE	Rate Ratio: 2.54; 95% CI: 0.81 to 7.97; I^2=N/A	1 RCT[28]
	Total AE	Rate Ratio: 2.54; 95% CI: 0.81 to 7.97; I^2=N/A	1 RCT[28]
Dihydroergotamine vs. Lidocaine	Gastrointestinal AE	Rate Ratio: 0.45; 95% CI: 0.16 to 1.31; I^2=N/A	1 RCT[28]
	Total AE	Rate Ratio: 0.45; 95% CI: 0.16 to 1.31; I^2=N/A	1 RCT[28]
Dihydroergotamine vs. Placebo	Cardiovascular AE	Rate Ratio: 0.46; 95% CI: 0.12 to 1.78; I^2=N/A	1 RCT[133]
	ENT AE	Rate Ratio: 0.58; 95% CI: 0.24 to 1.37; I^2=N/A	1 RCT[24]
	Gastrointestinal AE	Rate Ratio: 2.78; 95% CI: 1.70 to 4.55; I^2=0.3%	3 RCTs[24,25,35]
	Neurological AE	Rate Ratio: 0.90; 95% CI: 0.17 to 4.71; I^2=0.0%	3 RCTs[24,25,35]
	Respiratory AE	Rate Ratio: 1.30; 95% CI: 0.69 to 2.45; I^2=N/A	1 RCT[24]
	Serious AE	Rate Ratio: 0.69; 95% CI: -0.03 to 16.62; I^2 = 0.00%	4 RCTs[24,25,35,133]
	Total AE	Rate Ratio: 2.17; 95% CI: 0.65 to 7.31; I^2=66%	4 RCTs[24,25,35,133]
	Withdrawal AE	RR: 2.81; 95% CI: 0.61 to 12.93; I^2=0.00%	4 RCTs[24,25,124,133]
Ergotamine vs. Placebo	Neurological AE	Rate Ratio: 1.21; 95% CI: 0.11 to 13.39; I^2=N/A	1 RCT[115]
	Total AE	Rate Ratio: 1.21; 95% CI: 0.11 to 13.39; I^2=N/A	1 RCT[115]
	Withdrawal	Rate Ratio: 1.67; 95% CI: 0.56 to 4.98; I^2=N/A	2 RCTs[80,115]
Ergotamine vs. Prochlorperazine	Neurological AE	Rate Ratio: 0.20; 95% CI: 0.03 to 1.52; I^2=N/A	1 RCT[115]
	Total AE	Rate Ratio: 0.19; 95% CI: 0.02 to 1.41; I^2=N/A	1 RCT[115]
	Withdrawal	Rate Ratio: 1.28; 95% CI: 0.45 to 3.70; I^2=N/A	1 RCT[115]
Ergotamine plus caffeine vs. Placebo	Gastrointestinal AE	Rate Ratio: 1.00; 95% CI: 0.50 to 2.01; I^2=N/A	1 RCT[47]
	Neurological AE	Rate Ratio: 1.24; 95% CI: 0.54 to 2.83; I^2=N/A	1 RCT[47]
	Other AE	Rate Ratio: 2.61; 95% CI: 0.31 to 22.35; I^2=N/A	1 RCT[47]
	Total AE	Rate Ratio: 2.34; 95% CI: 0.00 to 91814.93; I^2=77%	2 RCTs[47,59]
	Withdrawal	Rate Ratio: 0.78; 95% CI: 0.23 to 2.72; I^2=N/A	1RCT[47]
	Withdrawal due to AE	RR: 2.00; 95% CI: 0.54 to 7.35; I^2=67.50%	2 RCTs[47,59]
Ergotamine plus caffeine plus pentobarbital plus bellafoline vs.	Gastrointestinal AE	Rate Ratio: 0.52; 95% CI: 0.12 to 2.17 I^2=N/A	1 RCT[59]
	Total AE	Rate Ratio: 0.94; 95% CI: 0.42 to 2.14; I^2=N/A	1 RCT[59]

Comparison	Adverse Events	Findings	Study Design
Ergotamine plus caffeine	Withdrawal due to AE	RR: 0.43; 95% CI: 0.08 to 2.25; I^2=N/A	1 RCT[59]
Ergotamine plus caffeine plus pentobarbital plus bellafoline vs. Placebo	Total AE	Rate Ratio: 6.00; 95% CI: 1.34 to 26.81; I^2=N/A	1 RCT[59]
	Withdrawal due to AE	RR: 5.00; 95% CI: 0.25 to 101.68; I^2=N/A	1 RCT[59]

AE = adverse event; CI = confidence interval; ENT = ear, nose, throat; N/A = not applicable; RCT = randomized clinical trial

eTable 9.5. Adverse events: opioids

Comparison	Adverse Events	Findings	Study Design
Butorphanol vs. Placebo	ENT AE	Rate Ratio: 4.21; 95% CI: 0.53 to 33.2; I^2=N/A	1 RCT[73]
	Gastrointestinal AE	Rate Ratio: 3.05; 95% CI: 1.61 to 5.80; I^2=0.00%	2 RCTs[57,73]
	Neurological AE	Rate Ratio: 8.31; 95% CI: 4.47 to 15.47; I^2=11.50%	2 RCTs[57,73]
	Ophthalmological AE	Rate Ratio: 4.00; 95% CI: 0.45 to 35.97; I^2=N/A	1 RCT[57]
	Psychological AE	Rate Ratio: 1.64; 95% CI: 0.54 to 4.97; I^2=N/A	1 RCT[73]
	Total AE	Rate Ratio: 6.08; 95% CI: 4.19 to 8.82; I^2=94.00%	2 RCTs[57,73]
Hydromorphone vs. Diphenhydramine plus prochlorperazine	Total AE	Rate Ratio: 2.95; 95% CI: 0.80 to 10.91; I^2=N/A	1 RCT[64]
	Withdrawal	RR: 0.33; 95% CI: 0.01 to 7.91; I^2=N/A	1 RCT[64]
Hydroxyzine plus meperidine vs. Dihydroergotamine plus hydroxyzine	Total AE	Rate Ratio: 1.31; 95% CI: 0.92 to 1.86; I^2=N/A	1 RCT[37]
Meperidine vs. Droperidol	Neurological AE	Rate Ratio: 0.71; 95% CI: 0.12 to 4.27; I^2=N/A	1 RCT[109]
	Total AE	Rate Ratio: 0.71; 95% CI: 0.12 to 4.27; I^2=N/A	1 RCT[109]
Meperidine plus dimenhydrinate vs. Chlorpromazine	Gastrointestinal AE	Rate Ratio: 0.73; 95% CI: 0.12 to 4.35; I^2=N/A	1 RCT[86]
	Neurological AE	Rate Ratio: 0.78; 95% CI: 0.25 to 2.46; I^2=N/A	1 RCT[86]
	Total AE	Rate Ratio: 0.51; 95% CI: 0.21 to 1.25; I^2=N/A	1 RCT[86]
Meperidine plus hydroxyzine vs. Dihydroergotamine plus hydroxyzine	Gastrointestinal AE	Rate Ratio: 0.40; 95% CI: 0.13 to 1.28; I^2=N/A	1 RCT[37]
	Neurological AE	Rate Ratio: 1.74; 95% CI: 1.18 to 2.58; I^2=N/A	1 RCT[37]
	Total AE	Rate Ratio: 1.31; 95% CI: 0.92 to 1.86; I^2=N/A	1 RCT[37]
	Withdrawal due to AE	RR: 1.00; 95% CI: 0.37 to 2.73; I^2=N/A	1 RCT[37]
Meperidine plus hydroxyzine vs. Dihydroergotamine plus metoclopramide	Serious AE	Rate Ratio: 1.00; 95% CI: 0.02 to 50.40; I^2=N/A	1 RCT[83]
Meperidine plus promethazine vs. Dihydroergotamine plus metoclopramide	Cardiovascular AE	Rate Ratio: 8.62; 95% CI: 1.08 to 68.88; I^2=N/A	1 RCT[113]
	Gastrointestinal AE	Rate Ratio: 1.79; 95% CI: 0.43 to 7.51; I^2=N/A	1 RCT[113]
	Neurological AE	Rate Ratio: 4.85; 95% CI: 1.64 to 14.32; I^2=N/A	1 RCT[113]
	Total AE	Rate Ratio: 4.17; 95% CI: 1.92 to 9.08; I^2=N/A	1 RCT[113]
Methadone vs. Butorphanol	Gastrointestinal AE	Rate Ratio: 0.17; 95% CI: 0.02 to 1.38; I^2=N/A	1 RCT[57]

Comparison	Adverse Events	Findings	Study Design
	Neurological AE	Rate Ratio: 0.81; 95% CI: 0.49 to 1.31; I^2=N/A	1 RCT[57]
	Ophthalmological AE	Rate Ratio: 0.50; 95% CI: 0.09 to 2.73; I^2=N/A	1 RCT[57]
	Psychological AE	Rate Ratio: 0.20; 95% CI: 0.02 to 1.71; I^2=N/A	1 RCT[57]
	Total AE	Rate Ratio: 0.86; 95% CI: 0.50 to 1.47; I^2=N/A	1 RCT[57]
Methadone vs. Placebo	Gastrointestinal AE	Rate Ratio: 0.50; 95% CI: 0.05 to 5.51; I^2=N/A	1 RCT[57]
	Neurological AE	Rate Ratio: 4.83; 95% CI: 2.01 to 11.64; I^2=N/A	1 RCT[57]
	Ophthalmological AE	Rate Ratio: 2.00; 95% CI: 0.18 to 22.06; I^2=N/A	1 RCT[57]
	Total AE	Rate Ratio: 1.79; 95% CI: 0.93 to 3.44; I^2=N/A	1 RCT[57]
Methotrimeprazine vs. Dimenhydrinate plus meperidine	Cardiovascular AE	Rate Ratio: 10.00; 95% CI: 1.28 to 78.12; I^2=N/A	1 RCT[119]
	Gastrointestinal AE	Rate Ratio: 0.80; 95% CI: 0.32 to 2.03; I^2=N/A	1 RCT[119]
	Neurological AE	Rate Ratio: 1.31; 95% CI: 0.85 to 2.04; I^2=N/A	1 RCT[119]
	Total AE	Rate Ratio: 1.39; 95% CI: 0.95 to 2.03; I^2=N/A	1 RCT[119]
Tramadol plus acetaminophen vs. Placebo	Serious AE	Rate Ratio: 0.99; 95% CI: 0.02 to 50.13; I^2=N/A	1 RCT[116]
	Total AE	Rate Ratio: 2.49; 95% CI: 1.48 to 4.18; I^2=N/A	1 RCT[116]
	Withdrawal	RR: 0.94; 95% CI: 0.62 to 1.43; I^2=N/A	1 RCT[116]
	Withdrawal due to AE	RR: 0.99; 95% CI: 0.06 to 15.79; I^2=N/A	1 RCT[116]

AE = adverse event; CI = confidence interval; ENT = ear, nose, and throat; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk

eTable 9.6. Adverse events: other pharmacological interventions

Comparison	Adverse Events	Findings	Study Design
Acetaminophen vs. Placebo	ENT AE	Rate Ratio: 0.91; 95% CI: 0.57 to 1.45; I^2=N/A	1 RCT[105]
	Gastrointestinal AE	Rate Ratio: 0.81; 95% CI: 0.62 to 1.07; I^2=72.8	2 RCTs[89,105]
	Neurological AE	Rate Ratio: 0.90; 95% CI: 0.60 to 1.37; I^2=0.00%	2 RCTs[89,105]
	Other AE	Rate Ratio: 0.75; 95% CI: 0.45 to 1.27; I^2=N/A	1 RCT[89]
	Serious AE	Rate Ratio: 0.99; 95% CI 0.06 to 15.86; I^2=0.00%	2 RCTs[89,105]
	Total AE	Rate Ratio: 0.82; 95% CI: 0.64 to 1.06; I^2=0.00%	2 RCTs[89,105]
	Withdrawal	RR: 0.69; 95% CI: 0.54 to 0.88; I^2=0.00%	2 RCTs[89,105]
	Withdrawal due to AE	RR: 1.98; 95% CI: 0.18 to 21.64; I^2=N/A	1 RCT[105]
Chlorpromazine vs. Lidocaine	Gastrointestinal AE	Rate Ratio: 0.87; 95% CI: 0.23 to 3.23; I^2=N/A	1 RCT[28]
	Total AE	Rate Ratio: 0.87; 95% CI: 0.23 to 3.23; I^2=N/A	1 RCT[28]
Dexamethasone vs. Placebo	Gastrointestinal AE	Rate Ratio: 0.95; 95% CI: 0.39 to 2.34; I^2=N/A	1 RCT[50]
	Immunological AE	Rate Ratio: 8.41; 95% CI: 1.06 to 66.35; I^2=N/A	1 RCT[58]
	Musculoskeletal AE	Rate Ratio: 0.28; 95% CI: 0.03 to 2.74; I^2=N/A	1 RCT[50]
	Neurological AE	Rate Ratio: 1.21; 95% CI: 0.55 to 2.65; I^2=0.00%	2 RCTs[50,58]
	Psychological AE	Rate Ratio: 0.85; 95% CI: 0.12 to 6.07; I^2=N/A	1 RCT[50]
	Total AE	Rate Ratio: 0.80; 95% CI: 0.51 to 1.26; I^2=0.00%	2 RCTs[50,58]
	Withdrawal	RR: 0.39; 95% CI: 0.14 to 1.05; I^2=N/A	1 RCT[50,58]
Greater occipital nerve block vs. Placebo	Musculoskeletal AE	Rate Ratio: 1.15; 95% CI: 0.07 to 18.45; I^2=N/A	1 RCT[63]
	Total AE	Rate Ratio: 2.31; 95% CI: 0.42 to 12.60; I^2=N/A	1 RCT[63]
Greater occipital nerve block vs. Metoclopramide	Dermatological AE	Rate Ratio: 1.88; 95% CI: 0.17 to 20.83; I^2=N/A	1 RCT[65]
	Neurological AE	Rate Ratio: 1.29; 95% CI: 0.52 to 3.22; I^2=N/A	1 RCT[65]
	Gastrointestinal AE	Rate Ratio: 3.76; 95% CI: 0.17 to 83.33; I^2=N/A	1 RCT[65]
	Total AE	Rate Ratio: 1.57; 95% CI: 0.69 to 3.58; I^2=N/A	1 RCT[65]
Ketamine vs. Placebo	Serious AE	Rate Ratio: 1.13; 95% CI 0.02 to 56.70; I^2 =N/A	1 RCT[51]
Lidocaine vs. Placebo	Dermatological AE	Rate Ratio: 4.44; 95% CI: 2.16 to 9.16; I^2=N/A	1 RCT[26]
	Neurological AE	Rate Ratio: 1.22; 95% CI: 0.34 to 4.33; I^2=N/A	1 RCT[31]

Comparison	Adverse Events	Findings	Study Design
	Serious AE	Rate Ratio: 1.00; 95% CI 0.02 to 50.40; I^2 =N/A	1 RCT[26]
	Total AE	Rate Ratio: 3.30; 95% CI: 1.76 to 6.17; I^2=68.10%	2 RCTs[26,31]
	Withdrawal	RR: 0.16; 95% CI: 0.01 to 3.25; I^2=N/A	1 RCT[31]
Propofol vs. Placebo	Neurological AE	Rate Ratio: 5.43; 95% CI: 0.27 to 108.37; I^2=N/A	1 RCT[99]
	Cardiovascular AE	Rate Ratio: 3.62; 95% CI: 0.16 to 80.25; I^2=N/A	1 RCT[99]
	Total AE	Rate Ratio: 9.05; 95% CI: 0.49 to 165.60; I^2=N/A	1 RCT[99]
	Withdrawal due to AE	RR: 8.18; 95% CI: 0.47 to 142.62; I^2=N/A	1 RCT[99]
	Withdrawal	RR: 1.16; 95% CI: 0.54 to 2.51; I^2=N/A	1 RCT[99]
Octreotide vs. Placebo	Gastrointestinal AE	Rate Ratio: 5.75; 95% CI: 0.67 to 49.22; I^2=N/A	1 RCT[87]
	Serious AE	Rate Ratio: 1.15; 95% CI 0.02 to 57.96; I^2=N/A	1 RCT[87]
	Total AE	Rate Ratio: 1.73; 95% CI: 0.49 to 6.11; I^2=N/A	1 RCT[87]
	Withdrawal	RR: 1.15; 95% CI: 0.08 to 17.22; I^2=N/A	1 RCT[87]
Valproate vs. Dexamethasone	Gastrointestinal AE	Rate Ratio: 1.50; 95% CI: 0.25 to 8.98; I^2=N/A	1 RCT[97]
	Neurological AE	Rate Ratio: 4.00; 95% CI: 0.45 to 35.79; I^2=N/A	1 RCT[97]
	Serious AE	Rate Ratio: 1.00; 95% CI 0.02 to 50.40; I^2=N/A	1 RCT[97]
	Total AE	Rate Ratio: 2.33; 95% CI: 0.60 to 9.02; I^2=N/A	1 RCT[97]
	Withdrawal	RR: 0.64; 95% CI: 0.29 to 1.40; I^2=79.10%	3 RCTs[56,82,97]

AE = adverse event; CI = confidence interval; ENT = ear, nose, and throat; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk

eTable 9.7. Adverse events: nonpharmacologic therapy

Comparison	Adverse Events	Findings	Study Design
Acupuncture vs. Sham acupuncture	Hematological AE	Rate Ratio: 1.50; 95% CI: 0.25 to 8.89; I^2=N/A	1 RCT[128]
	Serious AE	RR: 1.03; 95% CI: 0.02 to 52.13; I^2 = N/A	1 RCT[88]
	Total AE	Rate Ratio: 1.75; 95% CI: 0.51 to 5.98; I^2=N/A	1 RCT[128]
	Withdrawal	RR: 0.55; 95% CI: 0.23 to 1.33; I^2=0.00%	2 RCTs[88,128]
	Withdrawal due to AE	RR: 0.52; 95% CI: 0.05 to 5.55; I^2=N/A	1 RCT[88]
External trigeminal nerve stimulation vs. Sham external trigeminal nerve stimulation	Neurological AE	Rate Ratio: 2.22; 95% CI: 0.58 to 8.88; I^2=0.00%	2 RCTs[39,74]
	Serious AE	Rate Ratio: 1.04; 95% CI: 0.02 to 52.34; I^2=N/A	1 RCT[39]
	Total AE	Rate Ratio: 2.46; 95% CI: 0.62 to 9.72; I^2=0.00%	2 RCTs[39,74]
	Withdrawal due to AE	RR: 1.46; 95% CI: 0.26 to 8.31; I^2=N/A	1 RCT[74]
Eye movement desensitization reprocessing vs. Usual care	Withdrawal	RR: 1.25; 95% CI: 0.38 to 4.14; I^2=N/A	1 RCT[95]
Magnetic stimulation vs. Sham stimulation	ENT AE	Rate Ratio: 1.94; 95% CI: 0.18 to 21.41; I^2=N/A	1 RCT[90]
	Gastrointestinal AE	Rate Ratio: 0.97; 95% CI: 0.06 to 15.52; I^2=N/A	1 RCT[90]
	Neurological AE	Rate Ratio: 1.94; 95% CI: 0.49 to 7.76; I^2=N/A	1 RCT[90]
	Serious AE	Rate Ratio: 0.97; 95% CI: 0.02 to 48.91; I^2=N/A	1 RCT[90]
	Total AE	Rate Ratio: 1.51; 95% CI: 0.65 to 3.49; I^2=N/A	1 RCT[90]
	Withdrawal	RR: 1.14; 95% CI: 0.64 to 2.05; I^2=N/A	1 RCT[90]
Noninvasive vagus nerve stimulation vs. Sham stimulation	Dermatological AE	Rate Ratio: 0.44; 95% CI: 0.11 to 1.71; I^2=N/A	1 RCT[122]
	ENT AE	Rate Ratio: 0.69; 95% CI: 0.12 to 4.12; I^2=N/A	1 RCT[122]
	Serious AE	Rate Ratio: 1.04; 95% CI: 0.02 to 52.05; I^2= N/A	1 RCT[122]
	Total AE	Rate Ratio: 0.99; 95% CI: 0.55 to 1.77; I^2=N/A	1 RCT[122]
	Withdrawal	RR: 0.69; 95% CI: 0.12 to 4.05; I^2=N/A	1 RCT[122]
	Withdrawal due to AE	RR: 0.21; 95% CI: 0.01 to 4.26; I^2=N/A	1 RCT[122]
Remote electrical neuromodulation vs. Sham stimulation	Dermatological AE	Rate Ratio: 3.00; 95% CI: 0.31 to 28.84; I^2=N/A	1 RCT[131]
	Musculoskeletal AE	Rate Ratio: 1.00; 95% CI: 0.06 to 15.99; I^2=N/A	1 RCT[131]
	Neurological AE	Rate Ratio: 3.00; 95% CI: 0.31 to 28.84; I^2=N/A	1 RCT[131]

Comparison	Adverse Events	Findings	Study Design
	Other AE	Rate Ratio: 3.00; 95% CI: 0.31 to 28.84; I^2=N/A	1 RCT[131]
	Serious AE	Rate Ratio: 1.00; 95% CI: 0.02 to 50.40; I^2=N/A	1 RCT[131]
	Total AE	Rate Ratio: 1.27; 95% CI: 0.64 to 2.49; I^2=N/A	1 RCT[131]
	Withdrawal	RR: 1.17; 95% CI: 0.71 to 1.93; I^2=N/A	1 RCT[131]

AE = adverse event; CI = confidence interval; ENT = ear, nose, and throat; N/A = not applicable; RCT = randomized clinical trial; RR = relative risk

eTable 10. Subgroup analysis

eTable 10.1 Subgroup analysis by risk of bias for calcitonin gene-related peptide receptor antagonists

Comparison	Outcome	Risk of Bias	Findings
Rimegepant vs. Placebo	Pain Free 2 hours	Moderate ROB	RR: 1.64; 95% CI: 1.22 to 2.18; I^2=N/A
		High ROB	RR: 1.89; 95% CI: 1.53 to 2.33; I^2=0.00%
		Overall	RR: 1.80; 95% CI: 1.52 to 2.13; I^2=0.00%
	Pain Relief 2 hours	Moderate ROB	RR: 1.36; 95% CI: 1.20 to 1.54; I^2=N/A
		High ROB	RR: 1.36; 95% CI: 1.24 to 1.49; I^2=0.00%
		Overall	RR: 1.36; 95% CI: 1.26 to 1.46; I^2=0.00%
	Restored Function 2 hours	Moderate ROB	RR: 1.40; 95% CI: 1.14 to 1.70; I^2=N/A
		High ROB	RR: 1.45; 95% CI: 1.23 to 1.71; I^2=N/A
		Overall	RR: 1.43; 95% CI: 1.26 to 1.62; I^2=0.00%
	Sustained Pain Free 1 day	Moderate ROB	RR: 1.73; 95% CI: 1.18 to 2.54; I^2=N/A
		High ROB	RR: 3.15; 95% CI: 1.88 to 5.28; I^2=N/A
		Overall	RR: 2.24; 95% CI: 1.65 to 3.05; I^2=70.86%
	Sustained Pain Free 1 week	Moderate ROB	RR: 1.65; 95% CI: 1.08 to 2.52; I^2=N/A
		High ROB	RR: 3.10; 95% CI: 1.85 to 5.19; I^2=N/A
		Overall	RR: 2.23; 95% CI: 1.60 to 3.09; I^2=71.31%

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias

eTable 10.2 Subgroup analysis by route of administration for calcitonin gene-related peptide receptor antagonists

Comparison	Outcome	Subgroup	Findings
Rimegepant vs. Placebo	Pain Free 2 hours	Oral	RR:1.71; 95% CI: 1.37 to 2.14; I^2=0.00%
		Sublingual	RR:1.92; 95% CI: 1.48 to 2.50; I^2=N/A
	Pain Relief 2 hours	Oral	RR:1.36; 95% CI: 1.24 to 1.50; I^2=0.00%
		Sublingual	RR:1.35; 95% CI: 1.21 to 1.51; I^2=N/A
	Restored Function 2 hours	Oral	RR:1.40; 95% CI: 1.14 to 1.70; I^2=N/A
		Sublingual	RR:1.45; 95% CI: 1.22 to 1.74; I^2=N/A
	Restored Function 1 week	Oral	RR:1.73; 95% CI: 1.39 to 2.15; I^2=N/A
		Sublingual	RR:1.66; 95% CI: 1.32 to 2.09; I^2=N/A
	Sustained Pain Free 1 day	Oral	RR:2.24; 95% CI: 1.64 to 13.04; I^2=70.86%
		Sublingual	RR:1.70; 95% CI: 1.46 to 1.97; I^2=N/A

CI = confidence interval; IV = intravenous; N/A = not applicable; RR = relative risk

eTable 10.3. Subgroup analysis by dosage for calcitonin gene-related peptide receptor antagonists

Comparison	Outcome	Findings
Rimegepant 10 mg vs. Placebo	Pain Free at 2 hours	RR: 1.30; 95% CI: 0.74 to 2.29; I^2=N/A
	Pain Relief at 2 hours	RR: 1.09; 95% CI: 0.84 to 1.41; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.62; 95% CI: 0.74 to 3.55; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.44; 95% CI: 0.63 to 3.27; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.19; 95% CI: 0.89 to 1.59; I^2=N/A
Rimegepant 25 mg vs. Placebo	Pain Free at 2 hours	RR: 1.30; 95% CI: 0.71 to 2.40; I^2=N/A
	Pain Relief at 2 hours	RR: 1.20; 95% CI: 0.92 to 1.55; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.25; 95% CI: 1.06 to 4.77; I^2=N/A
	Sustained Pain Free at 1 week	RR: 2.02; 95% CI: 0.93 to 4.41; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.29; 95% CI: 0.96 to 1.74; I^2=N/A
Rimegepant 75 mg vs. Placebo	Pain Free at 2 hours	RR: 2.19; 95% CI: 1.39 to 3.46; I^2=N/A
	Pain Relief at 2 hours	RR: 1.50; 95% CI: 1.23 to 1.83; I^2=N/A
	Sustained Pain Free at 1 day	RR: 4.03; 95% CI: 2.21 to 7.32; I^2=N/A
	Sustained Pain Free at 1 week	RR: 4.03; 95% CI: 2.21 to 7.32; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.76; 95% CI: 1.40 to 2.19; I^2=N/A
Rimegepant 150 mg vs. Placebo	Pain Free at 2 hours	RR: 2.30; 95% CI: 1.47 to 3.60; I^2=N/A
	Pain Relief at 2 hours	RR: 1.27; 95% CI: 1.01 to 1.60; I^2=N/A
	Sustained Pain Free at 1 day	RR: 4.07; 95% CI: 2.24 to 7.40; I^2=N/A
	Sustained Pain Free at 1 week	RR: 4.07; 95% CI: 2.24 to 7.40; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.51; 95% CI: 1.18 to 1.93; I^2=N/A
Rimegepant 300 mg vs. Placebo	Pain Free at 2 hours	RR: 2.01; 95% CI: 1.30 to 3.12; I^2=N/A
	Pain Relief at 2 hours	RR: 1.53; 95% CI: 1.27 to 1.84; I^2=N/A
	Sustained Pain Free at 1 day	RR: 3.66; 95% CI: 2.04 to 6.56; I^2=N/A
	Sustained Pain Free at 1 week	RR: 3.66; 95% CI: 2.04 to 6.56; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.83; 95% CI: 1.49 to 2.24; I^2=N/A
Rimegepant 600 mg vs. Placebo	Pain Free at 2 hours	RR: 1.61; 95% CI: 0.97 to 2.67; I^2=N/A
	Pain Relief at 2 hours	RR: 1.53; 95% CI: 1.26 to 1.86; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.82; 95% CI: 1.47 to 5.41; I^2=N/A
	Sustained Pain Free at 1 week	RR: 2.82; 95% CI: 1.47 to 5.41; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.68; 95% CI: 1.34 to 2.11; I^2=N/A
Rimegepant 25 mg vs. Rimegepant 10 mg	Pain Free at 2 hours	RR: 1.00; 95% CI: 0.50 to 1.99; I^2=N/A
	Pain Relief at 2 hours	RR: 1.10; 95% CI: 0.81 to 1.50; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.39; 95% CI: 0.60 to 3.22; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.41; 95% CI: 0.57 to 3.45; I^2=N/A

Comparison	Outcome	Findings
	Sustained Pain Relief at 1 day	RR: 1.09; 95% CI: 0.77 to 1.53; I^2=N/A
Rimegepant 25 mg vs. Rimegepant 150 mg	Pain Free at 2 hours	RR: 0.57; 95% CI: 0.31 to 1.03; I^2=N/A
	Pain Relief at 2 hours	RR: 0.94; 95% CI: 0.71 to 1.25; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.55; 95% CI: 0.28 to 1.07; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.50; 95% CI: 0.25 to 1.00; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.86; 95% CI: 0.63 to 1.16; I^2=N/A
Rimegepant 75 mg vs. Rimegepant 10 mg	Pain Free at 2 hours	RR: 1.68; 95% CI: 0.96 to 2.94; I^2=N/A
	Pain Relief at 2 hours	RR: 1.38; 95% CI: 1.07 to 1.78; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.49; 95% CI: 1.23 to 5.05; I^2=N/A
	Sustained Pain Free at 1 week	RR: 2.80; 95% CI: 1.33 to 5.89; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.47; 95% CI: 1.12 to 1.95; I^2=N/A
Rimegepant 75 mg vs. Rimegepant 25 mg	Pain Free at 2 hours	RR: 1.68; 95% CI: 0.92 to 3.07; I^2=N/A
	Pain Relief at 2 hours	RR: 1.25; 95% CI: 0.97 to 1.62; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.79; 95% CI: 0.92 to 3.50; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.99; 95% CI: 0.99 to 4.01; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.36; 95% CI: 1.02 to 1.81; I^2=N/A
Rimegepant 75 mg vs. Rimegepant 150 mg	Pain Free at 2 hours	RR: 0.95; 95% CI: 0.61 to 1.48; I^2=N/A
	Pain Relief at 2 hours	RR: 1.18; 95% CI: 0.94 to 1.48; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.99; 95% CI: 0.61 to 1.61; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.99; 95% CI: 0.61 to 1.61; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.16; 95% CI: 0.92 to 1.47; I^2=N/A
Rimegepant 75 mg vs. Rimegepant 300 mg	Pain Free at 2 hours	RR: 1.09; 95% CI: 0.71 to 1.67; I^2=N/A
	Pain Relief at 2 hours	RR: 0.98; 95% CI: 0.82 to 1.18; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.10; 95% CI: 0.69 to 1.76; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.10; 95% CI: 0.69 to 1.76; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.96; 95% CI: 0.79 to 1.16; I^2=N/A
Rimegepant 75 mg vs. Rimegepant 600 mg	Pain Free at 2 hours	RR: 1.36; 95% CI: 0.83 to 2.25; I^2=N/A
	Pain Relief at 2 hours	RR: 0.98; 95% CI: 0.81 to 1.19; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.43; 95% CI: 0.82 to 2.47; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.43; 95% CI: 0.82 to 2.47; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.05; 95% CI: 0.84 to 1.30; I^2=N/A
Rimegepant 150 mg vs. Rimegepant 10 mg	Pain Free at 2 hours	RR: 1.76; 95% CI: 1.01 to 3.06; I^2=N/A
	Pain Relief at 2 hours	RR: 1.17; 95% CI: 0.89 to 1.54; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.52; 95% CI: 1.24 to 5.10; I^2=N/A
	Sustained Pain Free at 1 week	RR: 2.83; 95% CI: 1.35 to 5.96; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.27; 95% CI: 0.94 to 1.71; I^2=N/A
	Pain Free at 2 hours	RR: 1.55; 95% CI: 0.90 to 2.66; I^2=N/A

Comparison	Outcome	Findings
Rimegepant 300 mg vs. Rimegepant 10 mg	Pain Relief at 2 hours	RR: 1.40; 95% CI: 1.10 to 1.80; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.26; 95% CI: 1.13 to 4.53; I^2=N/A
	Sustained Pain Free at 1 week	RR: 2.55; 95% CI: 1.22 to 5.29; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.53; 95% CI: 1.18 to 2.00; I^2=N/A
Rimegepant 300 mg vs. Rimegepant 25 mg	Pain Free at 2 hours	RR: 1.55; 95% CI: 0.86 to 2.79; I^2=N/A
	Pain Relief at 2 hours	RR: 1.28; 95% CI: 1.00 to 1.63; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.63; 95% CI: 0.85 to 3.14; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.81; 95% CI: 0.91 to 3.60; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.41; 95% CI: 1.08 to 1.86; I^2=N/A
Rimegepant 300 mg vs. Rimegepant 150 mg	Pain Free at 2 hours	RR: 0.88; 95% CI: 0.57 to 1.34; I^2=N/A
	Pain Relief at 2 hours	RR: 1.20; 95% CI: 0.97 to 1.49; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.90; 95% CI: 0.56 to 1.43; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.90; 95% CI: 0.56 to 1.43; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.21; 95% CI: 0.97 to 1.50; I^2=N/A
Rimegepant 600 mg vs. Rimegepant 10 mg	Pain Free at 2 hours	RR: 1.23; 95% CI: 0.68 to 2.25; I^2=N/A
	Pain Relief at 2 hours	RR: 1.41; 95% CI: 1.09 to 1.82; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.75; 95% CI: 0.82 to 3.70; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.96; 95% CI: 0.89 to 4.31; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.41; 95% CI: 1.06 to 1.87; I^2=N/A
Rimegepant 600 mg vs. Rimegepant 25 mg	Pain Free at 2 hours	RR: 1.23; 95% CI: 0.65 to 2.34; I^2=N/A
	Pain Relief at 2 hours	RR: 1.28; 95% CI: 0.99 to 1.65; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.26; 95% CI: 0.61 to 2.57; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.40; 95% CI: 0.66 to 2.94; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.30; 95% CI: 0.97 to 1.74; I^2=N/A
Rimegepant 600 mg vs. Rimegepant 150 mg	Pain Free at 2 hours	RR: 0.70; 95% CI: 0.43 to 1.15; I^2=N/A
	Pain Relief at 2 hours	RR: 1.20; 95% CI: 0.96 to 1.50; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.69; 95% CI: 0.40 to 1.20; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.69; 95% CI: 0.40 to 1.20; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.11; 95% CI: 0.88 to 1.41; I^2=N/A
Rimegepant 600 mg vs. Rimegepant 300 mg	Pain Free at 2 hours	RR: 0.80; 95% CI: 0.49 to 1.29; I^2=N/A
	Pain Relief at 2 hours	RR: 1.00; 95% CI: 0.84 to 1.20; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.77; 95% CI: 0.45 to 1.31; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.77; 95% CI: 0.45 to 1.31; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.92; 95% CI: 0.75 to 1.12; I^2=N/A
	Pain Relief at 2 hours	RR: 1.74; 95% CI: 1.51 to 2.00; I^2=0.00%
	Restored Function at 2 hours	RR: 1.69; 95% CI: 1.36 to 2.09; I^2=53.80%
	Sustained Pain Free at 1 day	RR: 2.07; 95% CI: 1.18 to 3.65; I^2=N/A

Comparison	Outcome	Findings
	Sustained Pain Free at 1 week	RR: 2.20; 95% CI: 1.49 to 3.23; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.82; 95% CI: 1.48 to 2.25; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.87; 95% CI: 1.49 to 2.33; I^2=N/A
Ubrogepant 1 mg vs. Placebo	Pain Free at 2 hours	RR: 0.60; 95% CI: 0.23 to 1.62; I^2=N/A
	Pain Relief at 2 hours	RR: 0.81; 95% CI: 0.57 to 1.14; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.72; 95% CI: 0.23 to 2.21; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.72; 95% CI: 0.23 to 2.21; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.60; 95% CI: 0.36 to 1.00; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 0.65; 95% CI: 0.38 to 1.11; I^2=N/A
Ubrogepant 10 mg vs. Placebo	Pain Free at 2 hours	RR: 1.60; 95% CI: 0.75 to 3.40; I^2=N/A
	Pain Relief at 2 hours	RR: 1.14; 95% CI: 0.85 to 1.54; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.43; 95% CI: 0.56 to 3.65; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.43; 95% CI: 0.56 to 3.65; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.22; 95% CI: 0.81 to 1.83; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.25; 95% CI: 0.81 to 1.94; I^2=N/A
Ubrogepant 25 mg vs. Placebo	Pain Free at 2 hours	RR: 1.50; 95% CI: 1.14 to 1.97; I^2=27.20%
	Pain Relief at 2 hours	RR: 1.18; 95% CI: 1.04 to 1.34; I^2=0.00%
	Pain Relief at 1 day	RR: 1.49; 95% CI: 1.18 to 1.88; I^2=N/A
	Restored Function at 2 hours	RR: 1.19; 95% CI: 1.00 to 1.42; I^2=N/A
	Restores Function at 1 day	RR: 1.13; 95% CI: 1.01 to 1.26; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.60; 95% CI: 1.11 to 2.29; I^2=0.00%
	Sustained Pain Free at 1 week	RR: 2.14; 95% CI: 0.90 to 5.09; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.28; 95% CI: 0.86 to 1.91; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.39; 95% CI: 0.91 to 2.13; I^2=N/A
Ubrogepant 50 mg vs. Placebo	Pain Free at 2 hours	RR: 1.59; 95% CI: 1.29 to 1.95; I^2=0.00%
	Pain Relief at 2 hours	RR: 1.23; 95% CI: 1.13 to 1.35; I^2=10.90%
	Pain Relief at 1 day	RR: 1.78; 95% CI: 1.42 to 2.23; I^2=N/A
	Restored Function at 2 hours	RR: 1.23; 95% CI: 1.08 to 1.40; I^2=0.00%
	Restores Function at 1 day	RR: 1.18; 95% CI: 1.10 to 1.28; I^2=0.00%
	Sustained Pain Free at 1 day	RR: 1.63; 95% CI: 1.26 to 2.12; I^2=0.00%
	Sustained Pain Free at 1 week	RR: 2.14; 95% CI: 0.90 to 5.09; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.59; 95% CI: 1.30 to 1.94; I^2=0.00%
	Sustained Pain Relief at 1 week	RR: 1.61; 95% CI: 1.07 to 2.42; I^2=N/A
Ubrogepant 100 mg vs. Placebo	Pain Free at 2 hours	RR: 1.89; 95% CI: 1.43 to 2.52; I^2=0.00%
	Pain Relief at 2 hours	RR: 1.22; 95% CI: 1.09 to 1.38; I^2=0.00%
	Restored Function at 2 hours	RR: 1.42; 95% CI: 1.18 to 1.71; I^2=N/A
	Restored Function at 1 day	RR: 1.16; 95% CI: 1.05 to 1.29; I^2=N/A

Comparison	Outcome	Findings
	Sustained Pain Free at 1 day	RR: 1.96; 95% CI: 1.40 to 2.75; I^2=37.20%
	Sustained Pain Free at 1 week	RR: 2.98; 95% CI: 1.31 to 6.78; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.70; 95% CI: 1.40 to 2.06; I^2=0.00%
	Sustained Pain Relief at 1 week	RR: 1.56; 95% CI: 1.03 to 2.35; I^2=N/A
Ubrogepant 10 mg vs. Ubrogepant 1 mg	Pain Free at 2 hours	RR: 2.65; 95% CI: 1.07 to 6.57; I^2=N/A
	Pain Relief at 2 hours	RR: 1.41; 95% CI: 1.02 to 1.97; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.99; 95% CI: 0.70 to 5.66; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.99; 95% CI: 0.70 to 5.66; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 2.04; 95% CI: 1.24 to 3.34; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.93; 95% CI: 1.15 to 3.24; I^2=N/A
Ubrogepant 25 mg vs. Ubrogepant 1 mg	Pain Free at 2 hours	RR: 3.64; 95% CI: 1.52 to 8.70; I^2=N/A
	Pain Relief at 2 hours	RR: 1.37; 95% CI: 0.98 to 1.90; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.98; 95% CI: 1.11 to 7.97; I^2=N/A
	Sustained Pain Free at 1 week	RR: 2.98; 95% CI: 1.11 to 7.97; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 2.14; 95% CI: 1.31 to 3.50; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 2.15; 95% CI: 1.30 to 3.57; I^2=N/A
Ubrogepant 25 mg vs. Ubrogepant 10 mg	Pain Free at 2 hours	RR: 1.38; 95% CI: 0.75 to 2.50; I^2=N/A
	Pain Relief at 2 hours	RR: 0.96; 95% CI: 0.72 to 1.28; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.50; 95% CI: 0.70 to 3.22; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.50; 95% CI: 0.70 to 3.22; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.05; 95% CI: 0.73 to 1.52; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.11; 95% CI: 0.75 to 1.65; I^2=N/A
Ubrogepant 25 mg vs. Ubrogepant 100 mg	Pain Free at 2 hours	RR: 0.85; 95% CI: 0.51 to 1.43; I^2=N/A
	Pain Relief at 2 hours	RR: 0.92; 95% CI: 0.70 to 1.22; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.69; 95% CI: 0.37 to 1.27; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.72; 95% CI: 0.39 to 1.34; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.88; 95% CI: 0.62 to 1.24; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 0.89; 95% CI: 0.62 to 1.28; I^2=N/A
Ubrogepant 50 mg vs. Ubrogepant 1 mg	Pain Free at 2 hours	RR: 3.64; 95% CI: 1.52 to 8.70; I^2=N/A
	Pain Relief at 2 hours	RR: 1.49; 95% CI: 1.08 to 2.06; I^2=N/A
	Sustained Pain Free at 1 day	RR: 3.18; 95% CI: 1.20 to 8.43; I^2=N/A
	Sustained Pain Free at 1 week	RR: 2.98; 95% CI: 1.11 to 7.97; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 2.51; 95% CI: 1.56 to 4.04; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 2.48; 95% CI: 1.52 to 4.06; I^2=N/A
Ubrogepant 50 mg vs. Ubrogepant 10 mg	Pain Free at 2 hours	RR: 1.38; 95% CI: 0.75 to 2.50; I^2=N/A
	Pain Relief at 2 hours	RR: 1.05; 95% CI: 0.80 to 1.39; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.60; 95% CI: 0.75 to 3.40; I^2=N/A

Comparison	Outcome	Findings
	Sustained Pain Free at 1 week	RR: 1.50; 95% CI: 0.70 to 3.22; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.23; 95% CI: 0.87 to 1.75; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.29; 95% CI: 0.88 to 1.87; I^2=N/A
Ubrogepant 50 mg vs. Ubrogepant 25 mg	Pain Free at 2 hours	RR: 1.10; 95% CI: 0.87 to 1.39; I^2=0.00%
	Pain Relief at 2 hours	RR: 1.10; 95% CI: 0.99 to 1.23; I^2=0.00%
	Pain Relief at 1 day	RR: 1.19; 95% CI: 0.98 to 1.45; I^2=N/A
	Restored Function at 2 hours	RR: 1.01; 95% CI: 0.86 to 1.20; I^2=N/A
	Restored Function at 1 day	RR: 1.09; 95% CI: 0.99 to 1.20; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.17; 95% CI: 0.87 to 1.58; I^2=0.00%
	Sustained Pain Free at 1 week	RR: 1.00; 95% CI: 0.51 to 1.97; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.17; 95% CI: 0.83 to 1.65; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.15; 95% CI: 0.81 to 1.65; I^2=N/A
Ubrogepant 50 mg vs. Ubrogepant 100 mg	Pain Free at 2 hours	RR: 0.85; 95% CI: 0.67 to 1.09; I^2=0.00%
	Pain Relief at 2 hours	RR: 0.95; 95% CI: 0.85 to 1.06; I^2=0.00%
	Restored Function at 2 hours	RR: 0.89; 95% CI: 0.75 to 1.05; I^2=N/A
	Restores Function at 1 day	RR: 0.98; 95% CI: 0.89 to 1.08; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.77; 95% CI: 0.57 to 1.03; I^2=0.00%
	Sustained Pain Free at 1 week	RR: 0.72; 95% CI: 0.39 to 1.34; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.94; 95% CI: 0.80 to 1.10; I^2=0.00%
	Sustained Pain Relief at 1 week	RR: 1.03; 95% CI: 0.73 to 1.45; I^2=N/A
Ubrogepant 100 mg vs. Ubrogepant 1 mg	Pain Free at 2 hours	RR: 4.27; 95% CI: 1.81 to 10.05; I^2=N/A
	Pain Relief at 2 hours	RR: 1.48; 95% CI: 1.07 to 2.04; I^2=N/A
	Sustained Pain Free at 1 day	RR: 4.34; 95% CI: 1.69 to 11.13; I^2=N/A
	Sustained Pain Free at 1 week	RR: 4.14; 95% CI: 1.61 to 10.67; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 2.44; 95% CI: 1.51 to 3.93; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 2.41; 95% CI: 1.47 to 3.95; I^2=N/A
Ubrogepant 100 mg vs. Ubrogepant 10 mg	Pain Free at 2 hours	RR: 1.61; 95% CI: 0.91 to 2.87; I^2=N/A
	Pain Relief at 2 hours	RR: 1.05; 95% CI: 0.79 to 1.38; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.18; 95% CI: 1.07 to 4.44; I^2=N/A
	Sustained Pain Free at 1 week	RR: 2.09; 95% CI: 1.02 to 4.26; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.20; 95% CI: 0.84 to 1.70; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.25; 95% CI: 0.86 to 1.82; I^2=N/A

CI = confidence interval; kg = kilograms; mg = milligrams; N/A = not applicable; RR = risk ratio; ug = micrograms

eTable 10.4 Subgroup analysis by risk of bias for 5-HT1F receptor agonist

Comparison	Outcome	Risk of Bias	Findings
Lasmiditan vs. Placebo	Pain Free 2 hours	Low ROB	RR: 1.54; 95% CI: 1.29 to 1.83; I^2=0.00%
		Moderate ROB	RR: 1.92; 95% CI: 1.53 to 2.42; I^2=N/A
		High ROB	RR: 3.18; 95% CI: 2.28 to 4.43; I^2=N/A
		Overall	RR: 1.95; 95% CI: 1.25 to 3.04; I^2=75.60%
	Pain Relief 2 hours	Low ROB	RR: 1.35; 95% CI: 1.23 to 1.49; I^2=51.20%
		Moderate ROB	RR: 1.41; 95% CI: 1.25 to 1.59; I^2=N/A
		High ROB	RR: 1.52; 95% CI: 1.34 to 1.74; I^2=N/A
		Overall	RR: 1.42; 95% CI: 1.23 to 1.63; I^2=38.90%
	Restored Function 2 hours	Low ROB	RR: 1.35; 95% CI: 1.15 to 1.60; I^2=N/A
		Moderate ROB	RR: 1.51; 95% CI: 1.25 to 1.82; I^2=N/A
		High ROB	RR: 1.95; 95% CI: 1.42 to 2.70; I^2=N/A
		Overall	RR: 1.49; 95% CI: 1.42 to 1.67; I^2=50.30%

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias; SMD = standardized mean difference

eTable 10.5 Subgroup analysis by route of administration for 5-HT1F receptor agonist

Comparison	Outcome	Subgroup	Findings
Lasmiditan vs. Placebo	Pain Free 2 hours	IV	RR:1.18; 95% CI: 0.57 to 2.48; I^2=N/A
		Oral	RR:2.08; 95% CI: 1.20 to 3.60; I^2=80.00%
	Pain Relief 2 hours	IV	RR:1.23; 95% CI: 0.84 to 1.80; I^2=N/A
		Oral	RR:1.43; 95% CI: 1.19 to 1.72; I^2=50.70%
	Sustained Pain Free 1 day	IV	RR:0.82; 95% CI: 0.35 to 1.93; I^2=N/A
		Oral	RR:1.79; 95% CI: 1.46 to 2.21; I^2=91.20%

CI = confidence interval; IV = intravenous; N/A = not applicable; RR = relative risk

eTable 10.6 Subgroup analysis by age for 5-HT1F receptor agonist

Comparison	Outcome	Subgroup	Findings*
Lasmiditan 50 mg vs. Placebo	Pain Free at 2 hours	< 65 years	OR: 1.38; 95% CI: 1.07 to 1.78; I^2=N/A
		≥ 65 years	OR: 0.90; 95% CI: 0.30 to 2.84; I^2=N/A
Lasmiditan 100 mg vs. Placebo	Pain Free at 2 hours	< 65 years	OR: 1.67; 95% CI: 1.40 to 2.01; I^2=N/A
		≥ 65 years	OR: 0.79; 95% CI: 0.33 to 1.95; I^2=N/A
Lasmiditan 200 mg vs. Placebo	Pain Free at 2 hours	< 65 years	OR: 1.75; 95% CI: 1.46 to 2.09; I^2=N/A
		≥ 65 years	OR: 1.56; 95% CI: 0.52 to 4.58; I^2=N/A

CI = confidence interval; N/A = not applicable; OR = odds ratio

* Tepper et al.[134] reported OR instead of RR. No conversion to RR was made.

eTable 10.7 Subgroup analysis by gender for 5-HT1F receptor agonist

Comparison	Outcome	Subgroup	Findings*
Lasmiditan 50 mg vs. Placebo	Pain Free at 2 hours	Female	OR: 1.48; 95% CI: 1.15 to 1.93; I^2=N/A
		Male	OR: 0.79; 95% CI: 0.41 to 1.48; I^2=N/A
Lasmiditan 100 mg vs. Placebo	Pain Free at 2 hours	Female	OR: 1.59; 95% CI: 1.31 to 1.92; I^2=N/A
		Male	OR: 1.96; 95% CI: 1.26 to 3.09; I^2=N/A
Lasmiditan 200 mg vs. Placebo	Pain Free at 2 hours	Female	OR: 1.75; 95% CI: 1.45 to 2.12; I^2=N/A
		Male	OR: 1.59; 95% CI: 1.01 to 2.48; I^2=N/A

CI = confidence interval; N/A = not applicable; OR = odds ratio

* Tepper et al.[134] reported OR instead of RR. No conversion to RR was made.

eTable 10.8 Subgroup analysis by race for 5-HT1F receptor agonist

Comparison	Outcome	Subgroup*	Findings*
Lasmiditan 50 mg vs. Placebo	Pain Free at 2 hours	Caucasian	OR: 1.51; 95% CI: 1.10 to 1.90; I^2=N/A
		non-Caucasian	OR: 0.99; 95% CI: 0.62 to 1.71; I^2=N/A
Lasmiditan 100 mg vs. Placebo	Pain Free at 2 hours	Caucasian	OR: 1.79; 95% CI: 1.51 to 2.20; I^2=N/A
		non-Caucasian	OR: 1.09; 95% CI: 0.71 to 1.49; I^2=N/A
Lasmiditan 200 mg vs. Placebo	Pain Free at 2 hours	Caucasian	OR: 2.00; 95% CI: 1.59 to 2.39; I^2=N/A
		non-Caucasian	OR: 0.99; 95% CI: 0.71 to 1.51; I^2=N/A

CI = confidence interval; N/A = not applicable; OR = odds ratio

* Tepper et al.[134] reported OR instead of RR. No conversion to RR was made.

eTable 10.9 Subgroup analysis by body mass index for 5-HT1F receptor agonist

Comparison	Outcome	Subgroup*	Findings*
Lasmiditan 50 mg vs. Placebo	Pain Free at 2 hours	≥ 30 kg/m^2	OR: 1.15; 95% CI: 0.79 to 1.65; I^2=N/A
		< 30 kg/m^2	OR: 0.99; 95% CI: 0.62 to 1.71; I^2=N/A
Lasmiditan 100 mg vs. Placebo	Pain Free at 2 hours	≥ 30 kg/m^2	OR: 1.53; 95% CI: 1.18 to 1.98; I^2=N/A
		< 30 kg/m^2	OR: 1.73; 95% CI: 1.37 to 2.20; I^2=N/A
Lasmiditan 200 mg vs. Placebo	Pain Free at 2 hours	≥ 30 kg/m^2	OR: 1.60; 95% CI: 1.21 to 2.06; I^2=N/A
		< 30 kg/m^2	OR: 1.85; 95% CI: 1.45 to 2.34; I^2=N/A

CI = confidence interval; N/A = not applicable; OR = odds ratio

* Tepper et al.[134] reported OR instead of RR. No conversion to RR was made.

eTable 10.10 Subgroup analysis by prior response to triptans for 5-HT1F receptor agonist

Comparison	Outcome	Subgroup*	Findings
Lasmiditan vs. Placebo	Pain Free at 2 hours	Triptan-naive	RR: 2.01; 95% CI: 1.52 to 2.67; I^2=N/A
		Good	RR: 2.28; 95% CI:1.47 to 3.53; I^2=N/A
		Insufficient	RR: 1.52, 95% CI: 1.29 to 1.80; I^2=N/A
	Pain Relief at 2 hours	Triptan-naive	RR: 1.59; 95% CI: 1.39 to 1.83; I^2=N/A
		Good	RR:1.47; 95% CI: 1.20 to 1.79; I^2=N/A
		Insufficient	RR: 1.24; 95% CI: 1.13 to 1.36; I^2=N/A

CI = confidence interval; N/A = not applicable; RR = relative risk

* An overall response of “good” or “poor/none” to the most recent use of triptan at baseline were defined as “good” or “insufficient”.

eTable 10.11 Subgroup analysis by dosage compare for 5-HT1F receptor agonist

Comparison	Outcome	Findings
Lasmiditan 2.5 mg vs. Placebo	Pain Free at 2 hours	RR: 0.50; 95% CI: 0.03 to 7.51; I^2= N/A
	Pain Relief at 2 hours	RR: 1.10; 95% CI: 0.39 to 3.11; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.57; 95% CI: 0.03 to 8.60; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 2.42; 95% CI: 1.17 to 4.99; I^2=N/A
Lasmiditan 5 mg vs. Placebo	Pain Free at 2 hours	RR: 0.19; 95% CI: 0.01 to 3.14; I^2=N/A
	Pain Relief at 2 hours	RR: 0.37; 95% CI: 0.09 to 1.36; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.22; 95% CI: 0.01 to 3.61; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.07; 95% CI: 0.42 to 2.69; I^2=N/A
Lasmiditan 10 mg vs. Placebo	Pain Free at 2 hours	RR: 1.09; 95% CI: 0.40 to 2.97; I^2=N/A
	Pain Relief at 2 hours	RR: 1.19; 95% CI: 0.73 to 1.96; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.75; 95% CI: 0.21 to 2.63; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.75; 95% CI: 0.97 to 3.13; I^2=N/A
Lasmiditan 20 mg vs. Placebo	Pain Free at 2 hours	RR: 1.50; 95% CI: 0.64 to 3.53; I^2=N/A
	Pain Relief at 2 hours	RR: 1.42; 95% CI: 0.92 to 2.19; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.07; 95% CI: 0.37 to 3.04; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.84; 95% CI: 1.06 to 3.21; I^2=N/A
Lasmiditan 30 mg vs. Placebo	Pain Free at 2 hours	RR: 1.97; 95% CI: 0.81 to 4.78; I^2= N/A
	Pain Relief at 2 hours	RR: 1.52; 95% CI: 0.95 to 2.42; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.12; 95% CI: 0.33 to 3.82; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 2.22; 95% CI: 1.26 to 3.88; I^2=N/A
Lasmiditan 45 mg vs. Placebo	Pain Free at 2 hours	RR: 1.31; 95% CI: 0.21 to 8.01; I^2=N/A
	Pain Relief at 2 hours	RR: 1.65; 95% CI: 0.86 to 3.19; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.50; 95% CI: 0.24 to 9.32; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.80; 95% CI: 0.13 to 4.67; I^2=N/A
Lasmiditan 50 mg vs. Placebo	Function Scale at 2 hours	SMD: 1.13; 95% CI: 0.84 to 1.43; I^2=N/A
	Pain Free at 2 hours	RR: 1.39; 95% CI: 1.13 to 1.72; I^2=0.00%
	Pain Relief at 2 hours	RR: 1.30; 95% CI: 1.16 to 1.46; I^2=0.00%
	Pain Scale at 2 hours	SMD: 1.04; 95% CI: 0.75 to 1.34; I^2=N/A
	Restored Function at 2 hours	RR: 1.29; 95% CI: 1.07 to 1.57; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.32; 95% CI: 1.01 to 1.75; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.29; 95% CI: 0.96 to 1.75; I^2=N/A
	Function Scale at 2 hours	SMD: 1.74; 95% CI: 1.42 to 2.06; I^2=N/A

Comparison	Outcome	Findings
Lasmiditan 100 mg vs. Placebo	Pain Free at 2 hours	RR: 1.78; 95% CI: 1.54 to 2.07; I^2=73.81%
	Pain Free at 1 day	RR: 1.79; 95% CI: 1.51 to 2.11; I^2=N/A
	Pain Relief at 2 hours	RR: 1.44; 95% CI: 1.33 to 1.55; I^2=62.23%
	Pain Relief at 1 day	RR: 1.16; 95% CI: 1.06 to 1.27; I^2=N/A
	Pain Scale at 2 hours	SMD: 0.57; 95% CI: 0.30 to 0.85; I^2=N/A
	Restored Function at 2 hours	RR: 1.48; 95% CI: 1.30 to 1.68; I^2=28.15%
	Sustained Pain Free at 1 day	RR: 1.64; 95% CI: 1.29 to 2.08; I^2=87.56%
	Sustained Pain Free at 1 week	RR: 1.42; 95% CI: 1.09 to 1.85; I^2=60.31%
	Sustained Pain Relief at 1 day	RR: 1.97; 95% CI: 1.38 to 2.82; I^2=N/A
Lasmiditan 200 mg vs. Placebo	Function Scale at 2 hours	SMD: 8.46; 95% CI: 7.59 to 9.34; I^2=N/A
	Pain Free at 2 hours	RR: 2.14; 95% CI: 1.86 to 2.46; I^2=72.52%
	Pain Free at 1 day	RR: 1.83; 95% CI: 1.55 to 2.16; I^2=N/A
	Pain Relief at 2 hours	RR: 1.42; 95% CI: 1.32 to 1.53; I^2=17.28%
	Pain Relief at 1 day	RR: 1.27; 95% CI: 1.17 to 1.39; I^2=N/A
	Pain Scale at 2 hours	SMD: 7.11; 95% CI: 6.36 to 7.85; I^2=N/A
	Restored Function at 2 hours	RR: 1.55; 95% CI: 1.36 to 1.76; I^2=36.98%
	Sustained Pain Free at 1 day	RR: 2.10; 95% CI: 1.67 to 2.63; I^2=89.87%
	Sustained Pain Free at 1 week	RR: 2.03; 95% CI: 1.59 to 2.59; I^2=86.50%
	Sustained Pain Relief at 1 day	RR: 2.44; 95% CI: 1.73 to 3.45; I^2=N/A
Lasmiditan 400 mg vs. Placebo	Function Scale at 2 hours	SMD: 10.15; 95% CI: 9.12 to 11.18; I^2=N/A
	Pain Free at 2 hours	RR: 3.29; 95% CI: 1.37 to 7.91; I^2=N/A
	Pain Relief at 2 hours	RR: 2.18; 95% CI: 1.40 to 3.38; I^2=N/A
	Pain Scale at 2 hours	SMD: 8.14; 95% CI: 7.30 to 8.98; I^2=N/A
Lasmiditan 2.5 mg vs. Lasmiditan 10 mg	Pain Free at 2 hours	RR: 0.45; 95% CI: 0.03 to 6.97; I^2=N/A
	Pain Relief at 2 hours	RR: 0.92; 95% CI: 0.32 to 2.63; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.71; 95% CI: 0.04 to 11.78; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.38; 95% CI: 0.70 to 2.71; I^2=N/A
Lasmiditan 5 mg vs. Lasmiditan 2.5 mg	Sustained Pain Relief at 1 day	RR: 0.44; 95% CI: 0.16 to 1.18; I^2= N/A
Lasmiditan 5 mg vs. Lasmiditan 10 mg	Pain Free at 2 hours	RR: 0.17; 95% CI: 0.01 to 2.92; I^2=N/A
	Pain Relief at 2 hours	RR: 0.31; 95% CI: 0.08 to 1.15; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.27; 95% CI: 0.01 to 4.92; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.61; 95% CI: 0.25 to 1.48; I^2=N/A

Comparison	Outcome	Findings
Lasmiditan 5 mg vs. Lasmiditan 20 mg	Pain Free at 2 hours	RR: 0.13; 95% CI: 0.01 to 2.10; I^2=N/A
	Pain Relief at 2 hours	RR: 0.26; 95% CI: 0.07 to 0.94; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.20; 95% CI: 0.01 to 3.40; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.58; 95% CI: 0.24 to 1.38; I^2=N/A
Lasmiditan 5 mg vs. Lasmiditan 30 mg	Pain Free at 2 hours	RR: 0.10; 95% CI: 0.01 to 1.63; I^2=N/A
	Pain Relief at 2 hours	RR: 0.24; 95% CI: 0.06 to 0.89; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.18; 95% CI: 0.01 to 3.30; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.48; 95% CI: 0.20 to 1.15; I^2=N/A
Lasmiditan 5 mg vs. Lasmiditan 45 mg	Pain Free at 2 hours	RR: 0.13; 95% CI: 0.01 to 2.65; I^2=N/A
	Pain Relief at 2 hours	RR: 0.22; 95% CI: 0.05 to 0.88; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.12; 95% CI: 0.01 to 2.65; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.33; 95% CI: 0.20 to 8.70; I^2=N/A
Lasmiditan 20 mg vs. Lasmiditan 2.5 mg	Pain Free at 2 hours	RR: 2.93; 95% CI: 0.21 to 43.16; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.89; 95% CI: 0.12 to 29.2; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.76; 95% CI: 0.39 to 1.46; I^2=N/A
Lasmiditan 20 mg vs. Lasmiditan 10 mg	Pain Free at 2 hours	RR: 1.37; 95% CI: 0.52 to 3.63; I^2=N/A
	Pain Relief at 2 hours	RR: 1.18; 95% CI: 0.75 to 1.88; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.42; 95% CI: 0.38 to 5.36; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.05; 95% CI: 0.64 to 1.71; I^2=N/A
Lasmiditan 30 mg vs. Lasmiditan 2.5 mg	Pain Free at 2 hours	RR: 3.82; 95% CI: 0.26 to 56.78; I^2=N/A
	Pain Relief at 2 hours	RR: 1.37; 95% CI: 0.48 to 3.86; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.05; 95% CI: 0.12 to 33.5; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.91; 95% CI: 0.47 to 1.76; I^2= N/A
Lasmiditan 30 mg vs. Lasmiditan 10 mg	Pain Free at 2 hours	RR: 1.80; 95% CI: 0.66 to 4.91; I^2= N/A
	Pain Relief at 2 hours	RR: 1.27; 95% CI: 0.77 to 2.08; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.50; 95% CI: 0.34 to 6.52; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.26; 95% CI: 0.77 to 2.08; I^2=N/A
Lasmiditan 30 mg vs. Lasmiditan 20 mg	Pain Free at 2 hours	RR: 1.31; 95% CI: 0.55 to 3.11; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.05; 95% CI: 0.28 to 3.82; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 1.20; 95% CI: 0.75 to 1.90; I^2=N/A
Lasmiditan 45 mg vs. Lasmiditan 2.5 mg	Pain Free at 2 hours	RR: 3.00; 95% CI: 0.16 to 57.36; I^2=N/A
	Pain Relief at 2 hours	RR: 1.50; 95% CI: 0.48 to 4.65; I^2=N/A
	Sustained Pain Free at 1 day	RR: 3.00; 95% CI: 0.15 to 57.36; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.33; 95% CI: 0.05 to 1.99; I^2=N/A
	Pain Free at 2 hours	RR: 1.20; 95% CI: 0.18 to 7.77; I^2= N/A

Comparison	Outcome	Findings
Lasmiditan 45 mg vs. Lasmiditan 10 mg	Pain Relief at 2 hours	RR: 1.38; 95% CI: 0.70 to 2.72; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.00; 95% CI: 0.27 to 14.78; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.46; 95% CI: 0.08 to 2.62; I^2=N/A
Lasmiditan 45 mg vs. Lasmiditan 20 mg	Pain Free at 2 hours	RR: 0.87; 95% CI: 0.14 to 5.27; I^2=N/A
	Pain Relief at 2 hours	RR: 1.07; 95% CI: 0.69 to 1.64; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.40; 95% CI: 0.21 to 9.12; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.43; 95% CI: 0.07 to 2.46; I^2=N/A
Lasmiditan 45 mg vs. Lasmiditan 30 mg	Pain Free at 2 hours	RR: 0.66; 95% CI: 0.11 to 4.08; I^2=N/A
	Pain Relief at 2 hours	RR: 1.09; 95% CI: 0.56 to 2.10; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.33; 95% CI: 0.18 to 9.65; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.36; 95% CI: 0.06 to 2.04; I^2=N/A
Lasmiditan 50 mg vs. Lasmiditan 100 mg	Function Scale at 2 hours	SMD: 0.68; 95% CI: 0.96 to 0.41; I^2=N/A
	Pain Free at 2 hours	RR: 0.96; 95% CI: 0.79 to 1.16; I^2=0.00%
	Pain Relief at 2 hours	RR: 0.92; 95% CI: 0.83 to 1.02; I^2=80.20%
	Pain Scale at 2 hours	SMD: 0.66; 95% CI: 0.38 to 0.94; I^2=N/A
	Restored Function at 2 hours	RR: 0.97; 95% CI: 0.82 to 1.16; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.04; 95% CI: 0.78 to 1.37; I^2=N/A
	Sustained Pain Free at 1 day	RR: 1.01; 95% CI: 0.78 to 1.31; I^2=N/A
Lasmiditan 50 mg vs. Lasmiditan 200 mg	Function Scale at 2 hours	SMD: 8.66; 95% CI: 9.55 to 7.78; I^2=N/A
	Pain Free at 2 hours	RR: 0.78; 95% CI: 0.65 to 0.93; I^2=0.00%
	Pain Relief at 2 hours	RR: 0.96; 95% CI: 0.87 to 1.06; I^2=0.00%
	Pain Scale at 2 hours	SMD: 6.84; 95% CI: 7.56 to 6.13; I^2=N/A
	Restored Function at 2 hours	RR: 0.90; 95% CI: 0.76 to 1.06; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.81; 95% CI: 0.63 to 1.02; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.80; 95% CI: 0.62 to 1.04; I^2=N/A
Lasmiditan 50 mg vs. Lasmiditan 400 mg	Function Scale at 2 hours	SMD: 10.66; 95% CI: 11.74 to 9.59; I^2= N/A
	Pain Free at 2 hours	RR: 0.54; 95% CI: 0.27 to 1.07; I^2=N/A
	Pain Relief at 2 hours	RR: 0.72; 95% CI: 0.51 to 1.03; I^2=N/A
	Pain Scale at 2 hours	SMD: 8.11; 95% CI: 8.94 to 7.27; I^2=N/A
Lasmiditan 200 mg vs. Lasmiditan 100 mg	Function Scale at 2 hours	SMD: 8.27; 95% CI: 7.42 to 9.13; I^2=N/A
	Pain Free at 2 hours	RR: 1.20; 95% CI: 1.07 to 1.34; I^2=0.00%
	Pain Free at 1 day	RR: 1.03; 95% CI: 0.91 to 1.16; I^2=N/A
	Pain Relief at 2 hours	RR: 0.99; 95% CI: 0.93 to 1.05; I^2=39.27%

Comparison	Outcome	Findings
	Pain Relief at 1 day	RR: 1.10; 95% CI: 1.02 to 1.18; I^2=N/A
	Pain Scale at 2 hours	SMD: 8.56; 95% CI: 7.68 to 9.44; I^2=N/A
	Restored Function at 2 hours	RR: 1.05; 95% CI: 0.94 to 1.18; I^2=0.00%
	Sustained Pain Free at 1 day	RR: 1.28; 95% CI: 1.06 to 1.55; I^2=0.00%
	Sustained Pain Free at 1 week	RR: 1.43; 95% CI: 1.15 to 1.77; I^2=35.72%
	Sustained Pain Relief at 1 day	RR: 1.24; 95% CI: 0.95 to 1.62; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.08; 95% CI: 0.81 to 1.42; I^2=N/A
Lasmiditan 400 mg vs. Lasmiditan 100 mg	Function Scale at 2 hours	SMD: 10.34; 95% CI: 9.31 to 11.39; I^2=N/A
	Pain Free at 2 hours	RR: 1.81; 95% CI: 0.91 to 3.61; I^2=N/A
	Pain Relief at 2 hours	RR: 0.88; 95% CI: 0.66 to 1.19; I^2=N/A
	Pain Scale at 2 hours	SMD: 10.38; 95% CI: 9.33 to 11.4; I^2=N/A
Lasmiditan 400 mg vs. Lasmiditan 200 mg	Function Scale at 2 hours	SMD: 2.00; 95% CI: 1.66 to 2.34; I^2=N/A
	Pain Free at 2 hours	RR: 1.47; 95% CI: 0.77 to 2.82; I^2=N/A
	Pain Relief at 2 hours	RR: 1.26; 95% CI: 0.89 to 1.79; I^2=N/A
	Pain Scale at 2 hours	SMD: 0.73; 95% CI: 0.44 to 1.02; I^2=N/A

CI = confidence interval; mg = milligram; N/A = not available; RR = relative risk; SMD = standardized mean deviation

eTable 10.12 Subgroup analysis by risk of bias for antiemetic

Comparison	Outcome	Risk of Bias	Findings
Metoclopramide vs. Placebo	Pain Relief 2 hours	Low ROB	RR: 1.48; 95% CI: 1.10 to 2.01; I^2=N/A
		High ROB	RR: 3.11; 95% CI: 1.85 to 5.20; I^2=0.00%
		Overall	RR: 1.91; 95% CI: 1.47 to 2.48; I^2=67.30%
	Pain Scale 2 hours	Low ROB	SMD: -0.38; 95% CI: -0.70 to -0.06; I^2=N/A
		High ROB	SMD: 0.71; 95% CI: 0.13 to 1.28; I^2=N/A
		Overall	SMD: -0.12; 95% CI: -0.40 to 0.17; I^2=90.46%
Prochlorperazine vs. Metoclopramide	Pain Relief 2 hours	Moderate ROB	RR: 1.08; 95% CI: 0.85 to 1.35; I^2=N/A
		High ROB	RR: 0.60; 95% CI: 0.38 to 0.95; I^2=N/A
		Overall	RR: 0.89; 95% CI: 0.72 to 1.10; I^2=81.90%

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias; SMD = standardized mean difference

eTable 10.13 Subgroup analysis by dosage for antiemetic

Comparison	Outcome	Findings
Droperidol 0.1 mg vs. Placebo	Pain Free at 2 hours	RR: 1.18; 95% CI: 0.71 to 1.98; I^2=N/A
	Pain Relief at 2 hours	RR: 1.13; 95% CI: 0.86 to 1.50; I^2=N/A
Droperidol 2.75 mg vs. Placebo	Pain Free at 2 hours	RR: 2.11; 95% CI: 1.37 to 3.26; I^2=N/A
	Pain Relief at 2 hours	RR: 1.51; 95% CI: 1.19 to 1.92; I^2=N/A
Droperidol 2.75 mg vs. Droperidol 0.1 mg	Pain Free at 2 hours	RR: 1.78; 95% CI: 1.21 to 2.63; I^2=N/A
	Pain Relief at 2 hours	RR: 1.34; 95% CI: 1.09 to 1.64; I^2=N/A
Droperidol 5.5 mg vs. Placebo	Pain Free at 2 hours	RR: 1.49; 95% CI: 0.92 to 2.42; I^2=N/A
	Pain Relief at 2 hours	RR: 1.42; 95% CI: 1.11 to 1.82; I^2=N/A
Droperidol 5.5 mg vs. Droperidol 0.1 mg	Pain Free at 2 hours	RR: 1.26; 95% CI: 0.81 to 1.97; I^2=N/A
	Pain Relief at 2 hours	RR: 1.25; 95% CI: 1.00 to 1.56; I^2=N/A
Droperidol 5.5 mg vs. Droperidol 2.75 mg	Pain Free at 2 hours	RR: 0.71; 95% CI: 0.50 to 1.00; I^2=N/A
	Pain Relief at 2 hours	RR: 0.94; 95% CI: 0.80 to 1.09; I^2=N/A
Droperidol 8.25 mg vs. Placebo	Pain Free at 2 hours	RR: 1.61; 95% CI: 1.01 to 2.58; I^2=N/A
	Pain Relief at 2 hours	RR: 1.49; 95% CI: 1.17 to 1.89; I^2=N/A
Droperidol 8.25 mg vs. Droperidol 0.1 mg	Pain Free at 2 hours	RR: 1.36; 95% CI: 0.89 to 2.09; I^2=N/A
	Pain Relief at 2 hours	RR: 1.31; 95% CI: 1.06 to 1.61; I^2=N/A
Droperidol 8.25 mg vs. Droperidol 2.75 mg	Pain Free at 2 hours	RR: 0.76; 95% CI: 0.55 to 1.06; I^2=N/A
	Pain Relief at 2 hours	RR: 0.98; 95% CI: 0.85 to 1.13; I^2=N/A
Droperidol 8.25 mg vs. Droperidol 5.5 mg	Pain Free at 2 hours	RR: 1.08; 95% CI: 0.73 to 1.59; I^2=N/A
	Pain Relief at 2 hours	RR: 1.05; 95% CI: 0.89 to 1.23; I^2=N/A
Granisetron 40 µg/ kg vs. Placebo	Pain Free at 2 hours	RR: 2.45; 95% CI: 0.11 to 53.25; I^2=N/A
	Pain Scale at 2 hours	SMD: 1.22; 95% CI: 0.20 to 2.24; I^2=N/A
Granisetron 80 µg/ kg vs. Placebo	Pain Scale at 2 hours	SMD: 1.79; 95% CI: 0.67 to 2.91; I^2=N/A
Granisetron 80 µg/ kg vs. Granisetron 40 µg/ kg	Pain Free at 2 hours	RR: 0.33; 95% CI: 0.02 to 7.32; I^2=N/A
	Pain Scale at 2 hours	SMD: 0.21; 95% CI: -0.67 to 1.09; I^2=N/A
Metoclopramide 20 mg vs. Metoclopramide 10 mg	Pain Free at 2 hours	RR: 1.04; 95% CI: 0.77 to 1.38; I^2=N/A
	Pain Relief at 2 hours	RR: 0.97; 95% CI: 0.85 to 1.10; I^2=N/A
	Pain Scale at 2 hours	SMD: 0.07; 95% CI: -0.18 to 0.33; I^2=N/A
	Restored Function at 2 hours	RR: 0.93; 95% CI: 0.75 to 1.15; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.22; 95% CI: 0.70 to 2.14; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.04; 95% CI: 0.81 to 1.33; I^2=N/A

Comparison	Outcome	Findings
Metoclopramide 40 mg vs. Metoclopramide 10 mg	Pain Free at 2 hours	RR: 1.00; 95% CI: 0.74 to 1.34; I^2=N/A
	Pain Relief at 2 hours	RR: 1.03; 95% CI: 0.92 to 1.15; I^2=N/A
	Pain Scale at 2 hours	SMD: 0.21; 95% CI: -0.05 to 0.47; I^2=N/A
	Restored Function at 2 hours	RR: 1.09; 95% CI: 0.90 to 1.32; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.28; 95% CI: 0.73 to 2.22; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.14; 95% CI: 0.90 to 1.44; I^2=N/A
Metoclopramide 40 mg vs. Metoclopramide 20 mg	Pain Free at 2 hours	RR: 0.96; 95% CI: 0.72 to 1.28; I^2=N/A
	Pain Relief at 2 hours	RR: 1.06; 95% CI: 0.94 to 1.20; I^2=N/A
	Pain Scale at 2 hours	SMD: 0.14; 95% CI: -0.12 to 0.40; I^2=N/A
	Restored Function at 2 hours	RR: 1.18; 95% CI: 0.96 to 1.43; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.04; 95% CI: 0.63 to 1.74; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 1.10; 95% CI: 0.87 to 1.37; I^2=N/A

CI = confidence interval; kg = kilograms; mg = milligrams; N/A = not applicable; RR = risk ratio; SMD = standardized mean difference; ug = micrograms

eTable 10.14 Subgroup analysis by risk of bias for ergot alkaloids

Comparison	Outcome	Risk of Bias	Findings
Dihydroergotamine vs. Placebo	Pain Free 2 hours	Low ROB	RR: 2.82; 95% CI: 2.01 to 3.95; I^2=N/A
		High ROB	RR: 4.76; 95% CI: 0.68 to 33.34; I^2=N/A
		Overall	RR: 2.89; 95% CI: 2.07 to 4.03; I^2=0.00%
	Pain Relief 2 hours	Low ROB	RR: 1.70; 95% CI: 1.44 to 2.01; I^2=N/A
		Moderate ROB	RR: 2.45; 95% CI: 1.66 to 3.63; I^2=N/A
		High ROB	RR: 1.75; 95% CI: 0.80 to 3.83; I^2=N/A
		Overall	RR: 1.83; 95% CI: 1.58 to 2.13; I^2=30.30%
	Pain Relief 1 day	Low ROB	RR: 1.63; 95% CI: 1.37 to 1.93; I^2=N/A
		Moderate ROB	RR: 2.42; 95% CI: 1.72 to 3.39; I^2=N/A
		Overall	RR: 1.79; 95% CI: 1.54 to 2.09; I^2=76.40%
	Sustained Pain Free 1 day	Low ROB	RR: 3.48; 95% CI: 2.30 to 5.28; I^2=N/A
		High ROB	RR: 3.97; 95% CI: 0.56 to 28.09; I^2=N/A
		Overall	RR: 3.51; 95% CI: 2.33 to 5.28; I^2=0.00%
	Sustained Pain Free 1 week	Low ROB	RR: 2.93; 95% CI: 1.86 to 4.62; I^2=N/A
		High ROB	RR: 3.44; 95% CI: 0.48 to 24.59; I^2=N/A
		Overall	RR: 2.96; 95% CI: 1.90 to 4.62; I^2=0.00%
	Sustained Pain Relief 1 day	Low ROB	RR: 2.21; 95% CI: 1.74 to 2.81; I^2=N/A
		High ROB	RR: 2.65; 95% CI: 0.68 to 10.29; I^2=N/A
		Overall	RR: 2.23; 95% CI: 1.76 to 2.82; I^2=0.00%
	Sustained Pain Relief 1 week	Low ROB	RR: 2.09; 95% CI: 1.59 to 2.75; I^2=N/A
		High ROB	RR: 2.51; 95% CI: 0.64 to 9.81; I^2=N/A
		Overall	RR: 2.11; 95% CI: 1.62 to 2.77; I^2=0.00%

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias

eTable 10.15 Subgroup analysis by dosage for ergot alkaloids

Comparison	Outcome	Findings
Dihydroergotamine 1 mg vs. Placebo	Pain Free at 2 hours	RR: 5.65; 95% CI: 0.79 to 40.42; I^2=N/A
	Pain Relief at 2 hours	RR: 1.95; 95% CI: 0.87 to 4.36; I^2=N/A
	Sustained Pain Free at 1 day	RR: 5.14; 95% CI: 0.71 to 37.07; I^2=N/A
	Sustained Pain Free at 1 week	RR: 5.14; 95% CI: 0.71 to 37.07; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 2.82; 95% CI: 0.70 to 11.41; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 2.82; 95% CI: 0.70 to 11.41; I^2=N/A
Dihydroergotamine 2 mg vs. Placebo	Pain Free at 2 hours	RR: 3.81; 95% CI: 0.50 to 28.64; I^2=N/A
	Pain Relief at 2 hours	RR: 2.59; 95% CI: 1.81 to 3.71; I^2=45.00%
	Pain Relief at 1 day	RR: 2.68; 95% CI: 1.89 to 3.79; I^2=N/A
	Restored Function at 2 hours	RR: 2.73; 95% CI: 1.62 to 4.60; I^2=N/A
	Restored Function at 1 day	RR: 3.12; 95% CI: 1.98 to 4.91; I^2=N/A
	Sustained Pain Free at 1 day	RR: 2.72; 95% CI: 0.34 to 21.58; I^2=N/A
	Sustained Pain Free at 1 week	RR: 1.63; 95% CI: 0.18 to 14.60; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 2.45; 95% CI: 0.59 to 10.15; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 2.18; 95% CI: 0.51 to 9.20; I^2=N/A
Dihydroergotamine 2 mg vs. Dihydroergotamine 1 mg	Pain Free at 2 hours	RR: 0.67; 95% CI: 0.29 to 1.53; I^2=N/A
	Pain Relief at 2 hours	RR: 0.78; 95% CI: 0.47 to 1.28; I^2=N/A
	Sustained Pain Free at 1 day	RR: 0.53; 95% CI: 0.20 to 1.38; I^2=N/A
	Sustained Pain Free at 1 week	RR: 0.31; 95% CI: 0.09 to 1.05; I^2=N/A
	Sustained Pain Relief at 1 day	RR: 0.86; 95% CI: 0.41 to 1.82; I^2=N/A
	Sustained Pain Relief at 1 week	RR: 0.77; 95% CI: 0.35 to 1.67; I^2=N/A
Dihydroergotamine 3 mg vs. Placebo	Pain Relief at 2 hours	RR: 1.97; 95% CI: 1.27 to 3.04; I^2=0.00%
	Pain Relief at 1 day	RR: 2.13; 95% CI: 1.47 to 3.07; I^2=N/A
	Restored Function at 2 hours	RR: 2.01; 95% CI: 1.15 to 3.51; I^2=N/A
	Restored Function at 1 day	RR: 2.52; 95% CI: 1.57 to 4.04; I^2=N/A
Dihydroergotamine 3 mg vs. Dihydroergotamine 2 mg	Pain Relief at 2 hours	RR: 0.67; 95% CI: 0.51 to 0.89; I^2=N/A
	Pain Relief at 1 day	RR: 0.79; 95% CI: 0.64 to 0.97; I^2=N/A
	Restored Function at 2 hours	RR: 0.73; 95% CI: 0.50 to 1.07; I^2=N/A
	Restored Function at 1 day	RR: 0.80; 95% CI: 0.61 to 1.06; I^2=N/A
Oral ergotamine vs. Placebo	Pain Scale at 2 hours	SMD: 0.13; 95% CI: 1.12 to 0.85; I^2=N/A
Oral ergotamine vs. Buccal PCZ	Pain Scale at 2 hours	SMD: 0.58; 95% CI: 1.45 to 0.28; I2=N/A

CI = confidence interval; mg = milligram; N/A = not available; PCZ = prochlorperazine; RR = relative risk; SMD = standardized mean deviation

eTable 10.16 Subgroup analysis by risk of bias for other pharmacological interventions

Comparison	Outcome	Risk of Bias	Findings
Acetaminophen vs. Placebo	Pain Free 2 hours	Low ROB	RR: 1.69; 95% CI: 0.91 to 3.18; I^2=N/A
		Moderate ROB	RR: 2.05; 95% CI: 1.17 to 3.59; I^2=N/A
		Overall	RR: 1.89; 95% CI: 1.24 to 2.86; I^2=0.00%
	Pain Free 1 day	Low ROB	RR: 1.75; 95% CI: 1.22 to 2.52; I^2=N/A
		Moderate ROB	RR: 1.81; 95% CI: 1.26 to 2.60; I^2=N/A
		Overall	RR: 1.78; 95% CI: 1.38 to 2.30; I^2= 0.00%
	Pain Relief 2 hours	Low ROB	RR: 1.68; 95% CI: 1.28 to 2.20; I^2= N/A
		Moderate ROB	RR: 1.54; 95% CI: 1.18 to 2.01; I^2=N/A
		Overall	RR: 1.61; 95% CI: 1.33 to 1.95; I^2=0.00%
	Pain Relief 1 day	Low ROB	RR: 1.73; 95% CI: 1.34 to 2.24; I^2=N/A
		Moderate ROB	RR: 1.68; 95% CI: 1.31 to 2.15; I^2=N/A
		Overall	RR: 1.71; 95% CI: 1.43 to 2.04; I^2=0.00%
	Pain Scale 2 hours	Low ROB	SMD: 0.42; 95% CI: 0.22 to 0.62; I^2=N/A
		Moderate ROB	SMD: 0.37; 95% CI: 0.16 to 0.58; I^2=N/A
		Overall	SMD: 0.39; 95% CI: 0.25 to 0.54; I^2 =0.00%
	Restored Function 2 hours	Low ROB	RR: 1.48; 95% CI: 0.87 to 2.51; I^2=N/A
		Moderate ROB	RR: 2.08; 95% CI: 1.31 to 3.30; I^2=N/A
		Overall	RR: 1.80; 95% CI: 1.27 to 2.54; I^2=0.00%
	Restored Function 1 day	Low ROB	RR: 1.67; 95% CI: 1.19 to 2.35; I^2=N/A
		Moderate ROB	RR: 1.81; 95% CI: 1.37 to 2.39; I^2=N/A
		Overall	RR: 1.75; 95% CI: 1.41 to 2.17; I^2=0.00%
Lidocaine vs. Placebo	Pain Scale 2 hours	Moderate ROB	SMD: 0.46; 95% CI: 0.10 to 0.82; I^2=72.60%
		High ROB	SMD: -0.30; 95% CI: -0.61 to 0.01; I^2=N/A
		Overall	SMD: 0.02; 95% CI: -0.21 to 0.26; I^2=85.00%
Valproate vs. Dexamethasone	Pain Scale 2 hours	Low ROB	SMD: -0.30; 95% CI: -0.74 to 0.15; I^2=N/A
		High ROB	SMD: -0.03; 95% CI: -0.45 to 0.39; I^2=N/A
		Overall	SMD: -0.16; 95% CI: -0.46 to 0.15; I^2=0.00%
	Pain Scale 1 day	Low ROB	SMD: -0.39; 95% CI: -0.84 to 0.04; I^2=N/A
		High ROB	SMD: 0.36; 95% CI: -0.26 to 0.99; I^2=N/A
		Overall	SMD: -0.15; 95% CI: -0.51 to 0.22; I^2=73.59%

CI = confidence interval; N/A = not applicable; RR = relative risk; ROB = risk of bias; SMD = standardized mean difference

eTable 10.17 Subgroup analysis by study setting for other pharmacological interventions

Comparison	Outcome	Subgroup	Findings
Lidocaine vs. Placebo	Pain Relief 2 hours	ED	RR: 0.54; 95% CI: 0.10 to 2.97; I^2=N/A
		Urgent Care	RR: 2.64; 95% CI: 1.33 to 5.25; I^2=N/A
	Pain Scale 2 hours	ED	SMD: -0.22; 95% CI: -0.49 to 0.05; I^2=5.28%
		Urgent Care	SMD: 0.75; 95% CI: 0.28 to 1.23; I^2=N/A

CI = confidence interval; ED = emergency department; IV = intravenous; N/A = not applicable; RR = relative risk; SMD = standardized mean difference

eTable 10.18 Subgroup analysis by route of administration for other pharmacological interventions

Comparison	Outcome	Findings
Intravenous prochlorperazine vs. Buccally absorbed prochlorperazine	Pain Scale at 2 hours	SMD:0.45; 95% CI: 0.00 to 0.89; I^2=N/A

CI = confidence interval; N/A = not applicable; SMD = standardized mean difference

eTable 10.19 Subgroup analysis by dosage for other interventions

Comparison	Outcome	Findings
Buccal PCZ vs. Placebo	Pain Scale at 2 hours	SMD: 0.45; 95% CI: -0.34 to 1.24; I^2=N/A

CI = confidence interval; µg = microgram; mg = milligram; N/A = not applicable; PCZ = prochlorperazine; RR = relative risk; SMD = standardized mean difference

eTable 10.20 Subgroup analysis by risk of bias for nonpharmacologic therapy

Comparison	Outcome	Risk of Bias	Findings
External trigeminal nerve stimulation vs. Sham	Pain Scale 2 hours	Low ROB	SMD: 0.52; 95% CI: 0.13 to 0.91; I^2 = N/A
		High ROB	SMD: 4.48; 95% CI: 3.67 to 5.30; I^2 = N/A
		Overall	SMD: 1.25; 95% CI: 0.90 to 1.60; I^2 = 98.70%

CI = confidence interval; ROB = risk of bias; SMD = standardized mean difference

eTable 11. Risk of bias (Cochrane Risk of Bias tool for randomized trials [RoB 2.0]) for randomized clinical trials

Author, Year	Overall ROB	ROB from Randomization Process	ROB due to Deviations from Intended Interventions	ROB due to Missing Outcome Data	ROB in Measurement of Outcomes	ROB in Selection of the Reported Results
Aggarwal, 2020 [19]	High	Moderate	Low	High	Low	Low
Alemdar,2007[20]	Moderate	Moderate	Moderate	Moderate	Moderate	Low
Amiri,2017[21]	High	Moderate	Low	High	Low	Low
Antal, 2020 [22]	Moderate	Low	Low	Moderate	Low	Low
Ashina, 2021[23]	High	Moderate	Low	High	Low	Low
Aurora,2009[25]	High	Low	Low	High	Low	Low
Aurora,2011[24]	Low	Low	Low	Low	Low	Low
Avcu,2017[26]	High	High	Low	Low	Moderate	Low
Banerjee,1991[27]	High	Moderate	Low	High	Moderate	Low
Bell,1990[28]	High	Moderate	High	High	Moderate	Low
Bigal,2002[29]	High	High	Low	Moderate	Low	Low
Bigal,2002[30]	High	Moderate	Low	High	Low	Low
Blanda,2001[31]	Moderate	Low	Low	Low	Moderate	Low
Borhani,2010[32]	High	Moderate	Low	High	Low	Low
Boureau,1994[33]	High	Moderate	Low	Low	Moderate	High
Brandes,2020 [34]	Moderate	Moderate	Moderate	Moderate	Moderate	Low
Callaham,1986[35]	High	Moderate	Low	High	Moderate	High
Cameron,1995[36]	Moderate	Low	Low	Low	Moderate	Low
Carleton,1998[37]	High	Low	Low	High	Low	Moderate
Cete,2005[38]	Moderate	Moderate	Low	Moderate	Low	Low
Chou,2019[39]	Low	Low	Low	Low	Low	Low
Coppola,1995[40]	High	Moderate	Low	High	Moderate	Low
Corbo,2001[41]	Low	Low	Low	Low	Low	Low
Croop,2019[42]	High	Low	Low	Low	Low	High
Demirkaya,2001[43]	High	Moderate	High	High	Moderate	Moderate
Derosier,2010[44]	High	Low	Low	High	Moderate	Low
Dexter,1985[45]	High	High	Low	High	Moderate	Moderate
Diamond,1976[46]	High	Moderate	Low	High	Moderate	Moderate
Diener,2002[47]	Low	Low	Low	Low	Low	Low
Dodick, 2019 [48]	Low	Low	Low	Low	Low	Low

Author, Year	Overall ROB	ROB from Randomization Process	ROB due to Deviations from Intended Interventions	ROB due to Missing Outcome Data	ROB in Measurement of Outcomes	ROB in Selection of the Reported Results
Dogan,2019[49]	Low	Low	Low	Low	Low	Low
Donaldson,2008[50]	Moderate	Moderate	Low	Moderate	Low	Low
Etchison,2018[51]	Moderate	Moderate	Low	Low	Low	Low
Farahmand,2018[52]	Moderate	Moderate	Moderate	Low	Low	Low
Farkkila,2012[53]	Low	Low	Low	Low	Low	Low
Fernando,2019[54]	Moderate	Moderate	Low	Moderate	Low	Low
Ferrari,2010[55]	Low	Low	Low	Low	Low	Low
Foroughipour,2013[56]	High	Moderate	Low	High	Low	Low
Freitag,1993[57]	High	Moderate	Low	High	High	Moderate
Friedman,1989[59]	High	Moderate	Low	High	Moderate	Low
Friedman,2007[58]	Low	Low	Low	Low	Low	Low
Friedman,2008[60]	Moderate	Low	Low	Moderate	Low	Low
Friedman,2011[61]	High	Low	Low	High	Low	Low
Friedman,2016[62]	Low	Low	Low	Low	Low	Moderate
Friedman,2017[64]	High	Low	Low	High	Moderate	Low
Friedman,2018[63]	Moderate	Low	Moderate	Low	Low	Moderate
Friedman,2020 [65]	Moderate	Moderate	Low	Low	Low	Low
Fuglsang,2018[66]	High	Low	Low	High	Moderate	Low
Gaffigan,2015[67]	High	Low	Low	High	Low	Low
Gallagher,1996[68]	Moderate	Moderate	Low	Low	Moderate	Low
Gerhardt,2011[69]	High	Moderate	Low	High	Moderate	Low
Goadsby,2019[70]	Low	Low	Low	Low	Low	Low
Hakkarainen,1982[71]	High	Moderate	Low	High	Moderate	Low
Hoffert,1992[72]	High	High	Low	Low	Moderate	High
Hoffert,1995[73]	High	Moderate	Low	High	Moderate	Moderate
Hokenek, 2020 [74]	High	High	Low	Low	Moderate	High
Honkaniemi,2006[75]	High	Moderate	Low	High	Moderate	Low
Jones,1994[76]	High	Moderate	Low	High	Moderate	Low
Jones,1996[77]	High	Moderate	Low	High	Moderate	Low
Jones,2019[78]	High	Moderate	Moderate	High	Low	Low
Kandil, 2020 [79]	Moderate	Low	Low	Low	Moderate	Low

Author, Year	Overall ROB	ROB from Randomization Process	ROB due to Deviations from Intended Interventions	ROB due to Missing Outcome Data	ROB in Measurement of Outcomes	ROB in Selection of the Reported Results
Kangasniemi,1992[80]	High	Moderate	Low	High	Moderate	Low
Kapicioglu,1997[81]	High	Moderate	Low	High	Moderate	High
Karimi,2017[82]	Low	Low	Low	Low	Low	Low
Klapper,1993[83]	High	Moderate	Low	High	Low	Moderate
Korucu,2018[84]	High	Moderate	High	High	Moderate	Low
Kuca,2018[85]	Moderate	Low	Low	Moderate	Low	Low
Lane,1989[86]	High	Moderate	Low	High	Low	Low
Levy,2005[87]	High	Moderate	Low	High	Moderate	Moderate
Li,2009[88]	Moderate	Low	Moderate	Low	Low	Low
Lipton,2000[89]	Moderate	Moderate	Low	Low	Low	Low
Lipton,2010[90]	High	Low	Low	High	Low	Low
Lipton,2019[91]	Moderate	Moderate	Low	Low	Moderate	Low
Lipton 2019 [92]	Low	Low	Low	Low	Low	Low
Maizels,1996[93]	Moderate	Moderate	Low	Moderate	Moderate	Low
Maizels,1999[94]	High	High	Low	Moderate	Low	Low
Marcus,2008[95]	High	High	Moderate	Moderate	Low	Moderate
Marcus,2014[96]	High	High	Low	Low	Moderate	Low
Mazaheri,2015[97]	High	Low	Low	High	Low	Low
McEwen,1987[98]	High	Moderate	Low	High	Low	Low
Meek, 2020 [99]	High	Low	Low	High	Moderate	Moderate
Miller,2009[100]	Moderate	Moderate	Low	Low	Low	Low
Mitra, 2020[101]	Moderate	Low	Moderate	Low	Moderate	Low
Molaie,1987[102]	High	Moderate	Low	High	Moderate	Moderate
Motamed, 2020 [103]	Moderate	Moderate	Low	Low	Low	Low
Niazi,2017[104]	High	Moderate	Low	High	Low	Low
Prior,2010[105]	Low	Low	Low	Low	Low	Low
Rafieian-Kopaei,2019[106]	Moderate	Moderate	Low	Low	Moderate	Moderate
Rapoport,1995[107]	Moderate	Moderate	Low	Low	Moderate	Moderate
Reutens,1991[108]	High	High	Low	High	Moderate	Low
Richman ,2002[109]	High	Moderate	Low	High	Moderate	Low

Author, Year	Overall ROB	ROB from Randomization Process	ROB due to Deviations from Intended Interventions	ROB due to Missing Outcome Data	ROB in Measurement of Outcomes	ROB in Selection of the Reported Results
Rowat,1991[110]	Moderate	Moderate	Low	Moderate	Moderate	Low
Ryan,1970[111]	High	Moderate	Low	High	High	Moderate
Salazar,2011[112]	High	Moderate	Low	High	Moderate	Moderate
Scherl,1995[113]	High	Moderate	Low	High	Moderate	Moderate
Shahrami,2015[114]	High	Moderate	Low	High	Moderate	Low
Sharma,2002[115]	High	Moderate	Low	High	Moderate	Low
Silberstein,2003[117]	High	Low	Low	High	Low	High
Silberstein,2005[116]	High	Moderate	Low	Low	Low	High
Soleimanpour,2012[118]	Moderate	Moderate	Low	Low	Low	Low
Stiell,1991[119]	High	Low	Low	High	Low	Low
Taheraghdam,2011[120]	High	High	Low	High	Moderate	Low
Tanen,2003[121]	Low	Low	Low	Low	Low	Low
Tassorelli,2018[122]	Low	Low	Low	Low	Low	Low
Tek,1990[123]	High	Low	High	Low	Low	Low
Treves,1998[124]	High	Low	Low	High	Moderate	Low
Triner,1999[125]	Moderate	Moderate	Low	Moderate	Low	Low
Tulunay,1987[126]	High	High	Low	High	Moderate	High
Voss,2016[127]	Low	Low	Low	Low	Low	Low
Wang,2012[128]	Moderate	Moderate	Moderate	Low	Low	Low
Yang,2012[129]	High	Moderate	High	High	Moderate	Moderate
Yarnitsky,2017[130]	Moderate	Moderate	Low	Low	Low	Low
Yarnitsky,2019[131]	Low	Low	Low	Low	Low	Low
Zargaran,2018[132]	Moderate	Moderate	Low	Moderate	Low	Low
Ziegler,1994[133]	High	Moderate	Low	High	Moderate	Low

ROB = risk of bias

eTable 12. Effectiveness of treatments other than triptans and nonsteroidal anti-inflammatory drugs

	Pain free	Pain relief	Sustained pain free	Sustained pain relief	Restored function	Improved function	Sustained restored function	Pain scale	Function scale
Calcitonin gene-related peptide receptor antagonists (gepants)									
Rimegepant vs. Placebo	Moderate SOE	Moderate SOE	Moderate SOE	Moderate SOE	Moderate SOE		Moderate SOE		
Ubrogepant vs. Placebo	High SOE	High SOE	Low to high SOE	Low to moderate SOE	High SOE				
5-HT1F receptor agonists (ditans)									
Lasmiditan vs. Placebo	High SOE	High SOE	High SOE	High SOE	High SOE			Moderate SOE	High SOE
Ergot Alkaloids									
Dihydroergotamine vs. Chlorpromazine	Insufficient SOE								
Dihydroergotamine vs. Lidocaine	Insufficient SOE								
Dihydroergotamine vs. Placebo	Moderate SOE	Moderate to high SOE	High SOE	High SOE	Moderate SOE			Insufficient SOE	

	Pain free	Pain relief	Sustained pain free	Sustained pain relief	Restored function	Improved function	Sustained restored function	Pain scale	Function scale
Ergotamine plus caffeine vs. Placebo	Low SOE	Moderate SOE				Low SOE		Insufficient SOE	
Antiemetics									
Chlorpromazine vs. Placebo	Low SOE	Low SOE				Insufficient SOE			
Diphenhydramine plus metoclopramide vs. Diphenhydramine plus haloperidol								Insufficient	
Droperidol vs. Placebo	Low SOE	Low SOE							
Granisetron vs. Placebo	Insufficient SOE							Insufficient SOE	
Haloperidol vs. Placebo		Low SOE							
Magnesium sulfate vs. Dexamethasone								Low SOE	

	Pain free	Pain relief	Sustained pain free	Sustained pain relief	Restored function	Improved function	Sustained restored function	Pain scale	Function scale
plus metoclopramide									
Metoclopramide vs. Chlorpromazine	Insufficient SOE	Insufficient SOE						Insufficient SOE	
Metoclopramide vs. Diphenhydramine plus metoclopramide			Low SOE	Low SOE				Low SOE	
Metoclopramide vs. Granisetron								Low SOE	
Metoclopramide vs. Magnesium sulfate								Insufficient SOE	
Metoclopramide vs. Magnesium sulfate plus metoclopramide		Low SOE			Low SOE			Insufficient SOE	
Metoclopramide vs. Placebo	Insufficient SOE	Low SOE						Insufficient SOE	

	Pain free	Pain relief	Sustained pain free	Sustained pain relief	Restored function	Improved function	Sustained restored function	Pain scale	Function scale
Prochlorperazine vs. Ergotamine plus caffeine								Insufficient SOE	
Prochlorperazine vs. Magnesium sulfate								Insufficient SOE	
Prochlorperazine vs. Metoclopramide	Low SOE	Insufficient SOE	Insufficient SOE	Insufficient SOE				Insufficient SOE	
Prochlorperazine vs. Octreotide		Low SOE						Low SOE	
Prochlorperazine vs. Placebo	Low SOE	Low SOE						Low SOE	
Prochlorperazine vs. Valproate								Low SOE	
Opioids									
Butorphanol vs. Placebo	Low SOE	Low SOE							
Hydromorphone vs. Diphenhydramine	Low SOE		Low SOE	Low SOE	Insufficient to low SOE				

	Pain free	Pain relief	Sustained pain free	Sustained pain relief	Restored function	Improved function	Sustained restored function	Pain scale	Function scale
plus prochlorperazine									
Meperidine plus dimenhydrinate vs. Chlorpromazine		Insufficient SOE						Low SOE	
Meperidine plus hydroxyzine vs. Dihydroergotamine plus metoclopramide		Low SOE			Low SOE			Insufficient SOE	
Meperidine vs. Droperidol		Insufficient SOE							
Methotrimeprazine vs. Dimenhydrinate plus meperidine								Insufficient SOE	
Morphine vs. Intravenous dexamethasone								Low SOE	
Tramadol vs. Placebo	Insufficient SOE	Insufficient SOE						Insufficient SOE	

	Pain free	Pain relief	Sustained pain free	Sustained pain relief	Restored function	Improved function	Sustained restored function	Pain scale	Function scale
Tramadol plus acetaminophen vs. Placebo	Low SOE	Low SOE	Low SOE	Low SOE					
Other pharmacologic interventions									
Acetaminophen vs. Placebo	Moderate SOE	Moderate SOE			Moderate SOE			Moderate SOE	Moderate SOE
Dexamethasone vs. Placebo	Low SOE		Low SOE		Low SOE				
Greater occipital nerve block vs. Sham	Insufficient SOE	Insufficient SOE						Insufficient SOE	
Ketamine vs. Placebo		Insufficient SOE						Insufficient SOE	Insufficient SOE
Lidocaine vs. Chlorpromazine	Low SOE								
Lidocaine vs. Placebo	Insufficient SOE	Low SOE						Insufficient SOE	Insufficient SOE
Magnesium sulfate vs. Placebo	Insufficient to low SOE	Insufficient to low SOE							

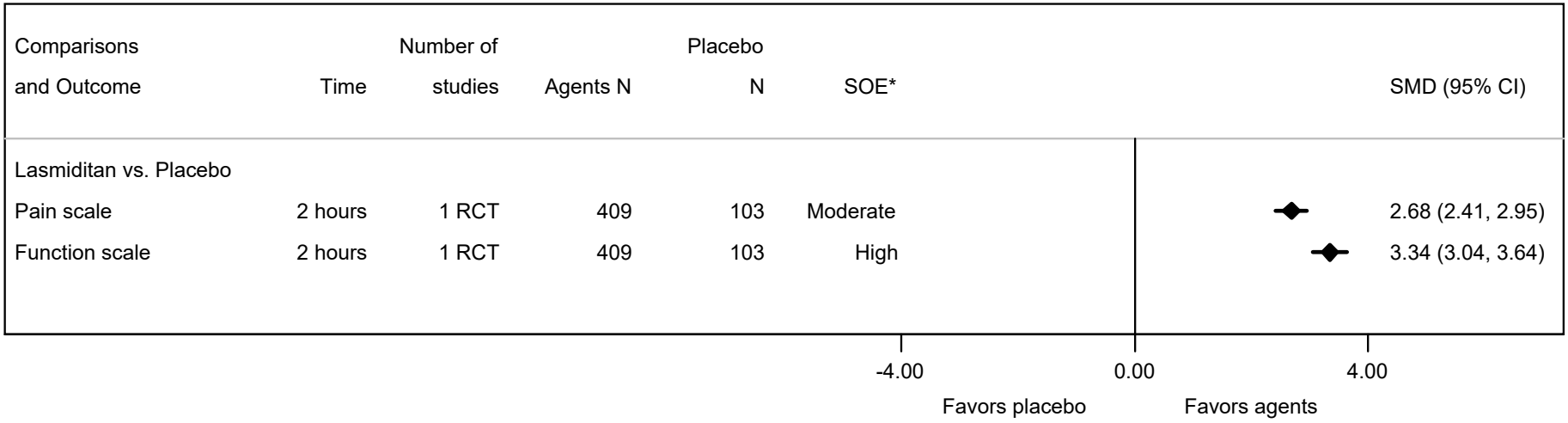
	Pain free	Pain relief	Sustained pain free	Sustained pain relief	Restored function	Improved function	Sustained restored function	Pain scale	Function scale
Octreotide vs. Placebo		Low SOE						Low SOE	
Propofol vs. standard therapy								Insufficient SOE	
Propofol vs. Placebo	Insufficient SOE	Insufficient SOE	Insufficient SOE					Insufficient SOE	
Propofol vs. Dexamethasone								Low SOE	
Secobarbital vs. Placebo		Insufficient SOE						Insufficient SOE	
Valproate vs. Dexamethasone	Insufficient SOE	Low SOE						Insufficient SOE	
Nonpharmacologic (non-drug) Therapy									
Acupuncture vs. Sham	Low SOE	Low SOE	Insufficient SOE					Insufficient to low SOE	
External trigeminal nerve stimulation vs. Sham	Low SOE	Low SOE	Low SOE	Low SOE				Low to moderate SOE	

	Pain free	Pain relief	Sustained pain free	Sustained pain relief	Restored function	Improved function	Sustained restored function	Pain scale	Function scale
Eye movement desensitization reprocessing vs. Usual care	Low SOE							Insufficient to low SOE	
Transcranial magnetic stimulation vs. Sham	Low SOE	Insufficient SOE	Insufficient SOE						
Noninvasive vagus nerve stimulation vs. Sham	Low SOE	Moderate SOE							
Remote electrical neuromodulation vs. Sham	Moderate SOE	Moderate SOE	Moderate SOE	Moderate SOE					

SOE = strength of evidence

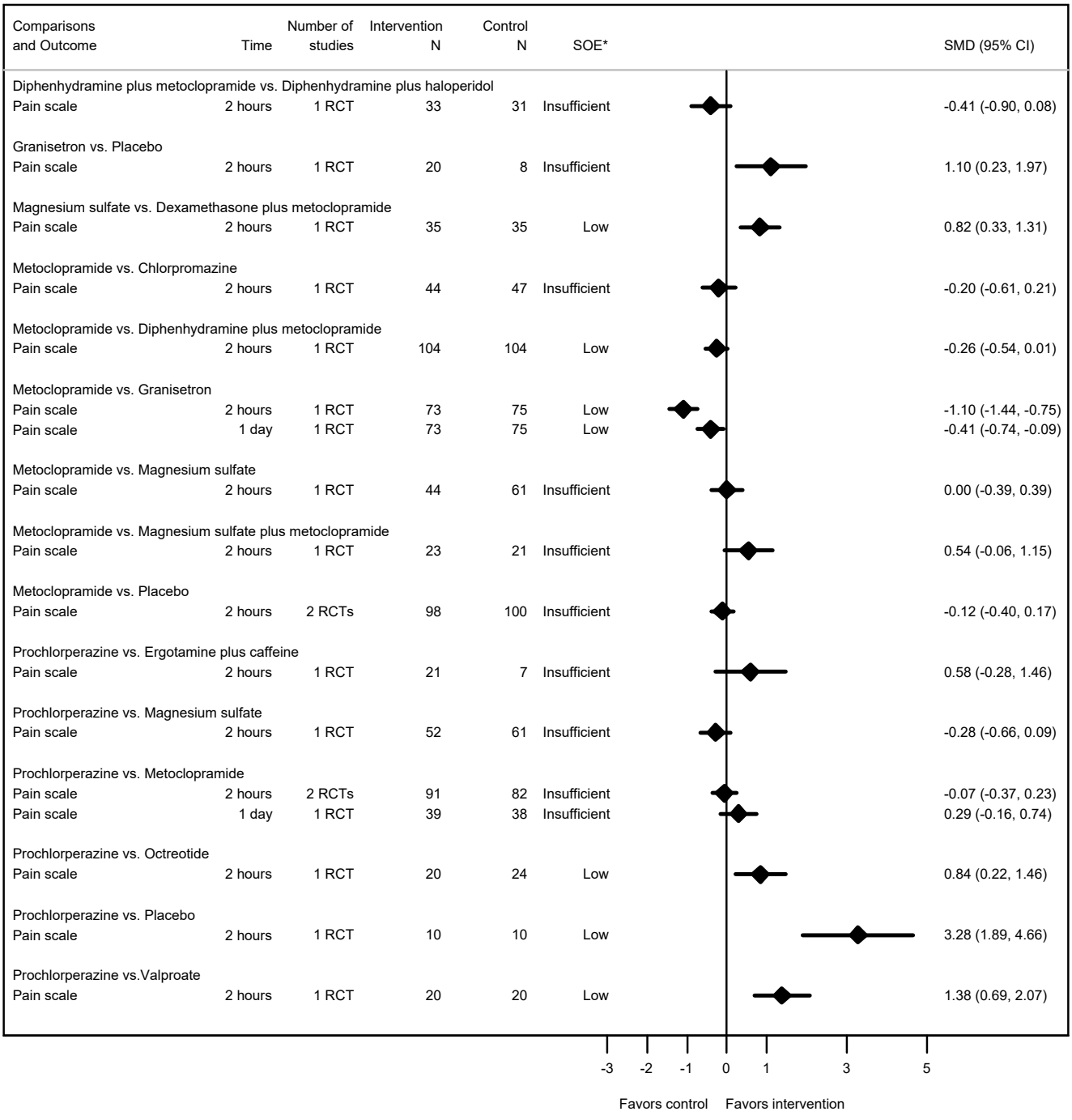
[a]Green indicates statistically significant better outcome when the intervention was compared with the control; red indicates statistically significant worse outcome; and white shows no statistically significant difference.

eFigure 1. Findings of Meta-analysis of 5-HT_{1F} Receptor Agonists on Pain and Function Outcomes measured as Continuous Outcomes for Episodic Migraine in Adults



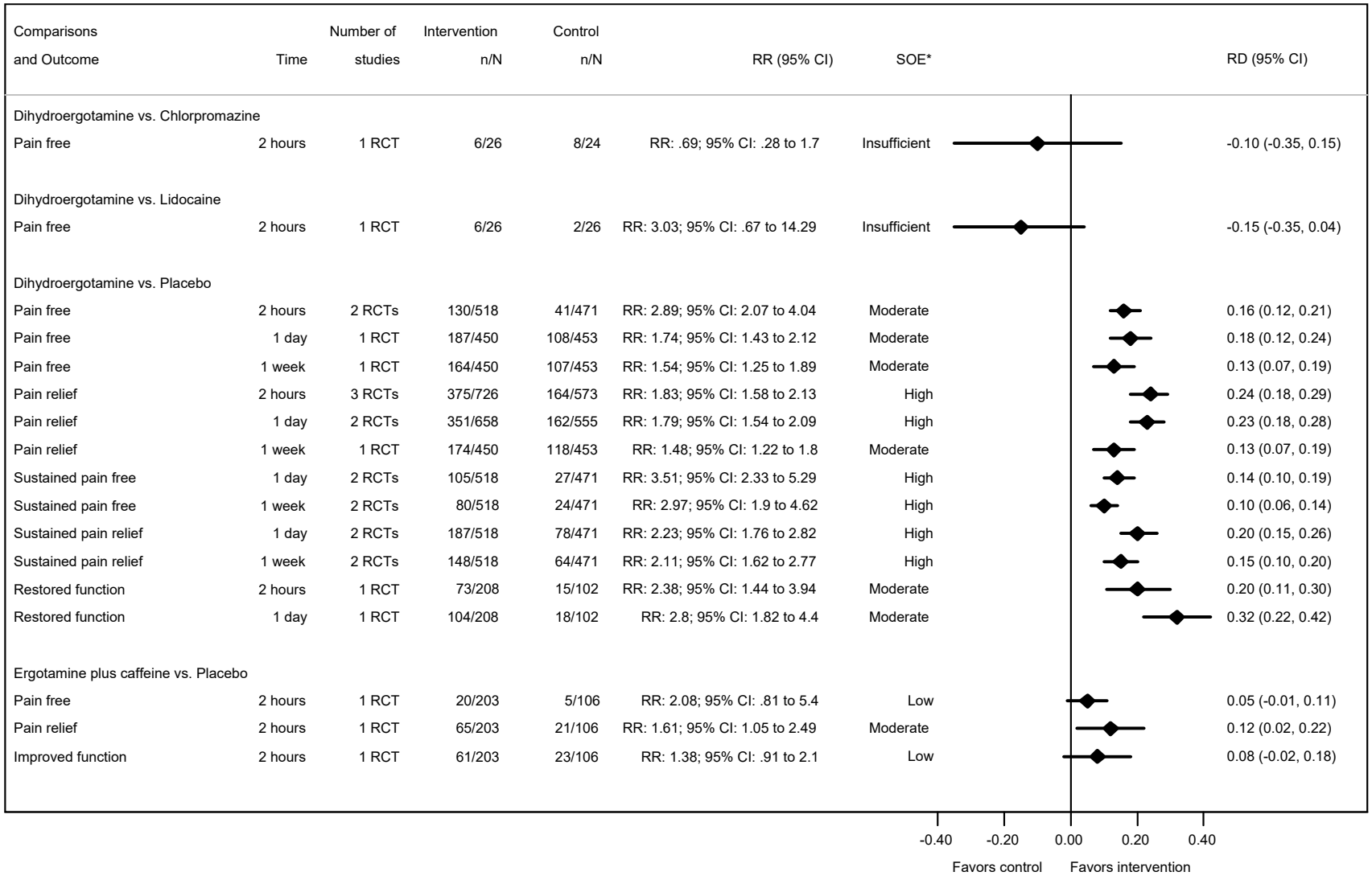
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; SMD = standardized mean difference; SOE = strength of evidence

eFigure 2. Findings of Meta-analysis of Antiemetics on Pain Outcomes measured as Continuous Outcomes for Episodic Migraine in Adults



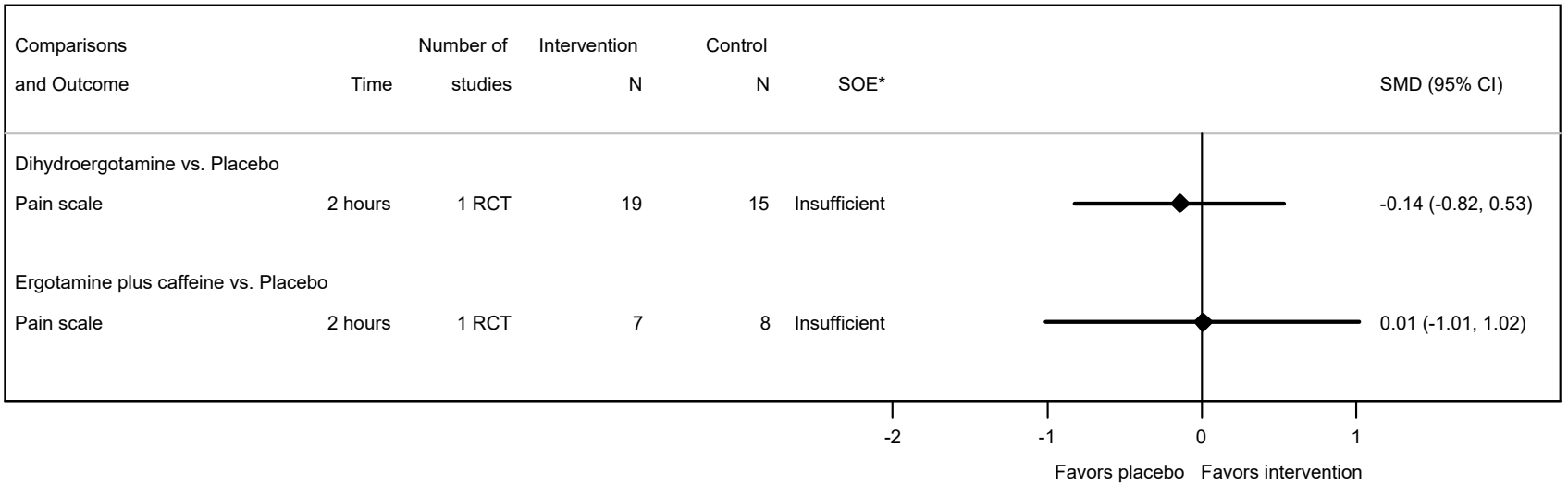
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; SMD = standardized mean difference; SOE = strength of evidence

eFigure 3. Findings of Meta-analysis of Ergot Alkaloids on Pain and Function Outcomes measured as Binary Outcomes for Episodic Migraine in Adults



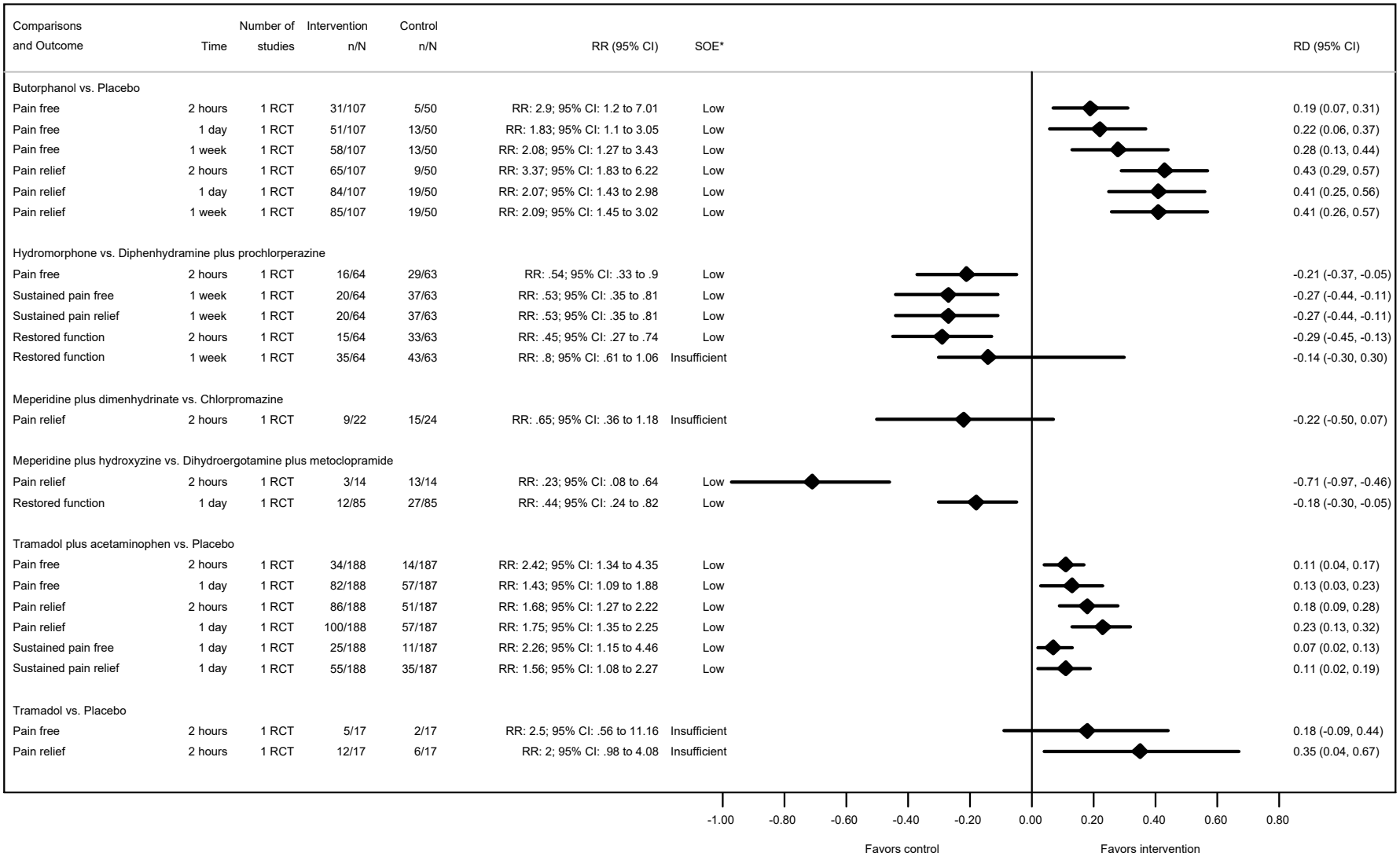
eTable 3 in the supplement lists definitions of outcomes.
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; RD = risk difference; RR = relative risk; SOE = strength of evidence

eFigure 4. Findings of Meta-analysis of Ergot Alkaloids on Pain Outcomes measured as Continuous Outcomes for Episodic Migraine in Adults



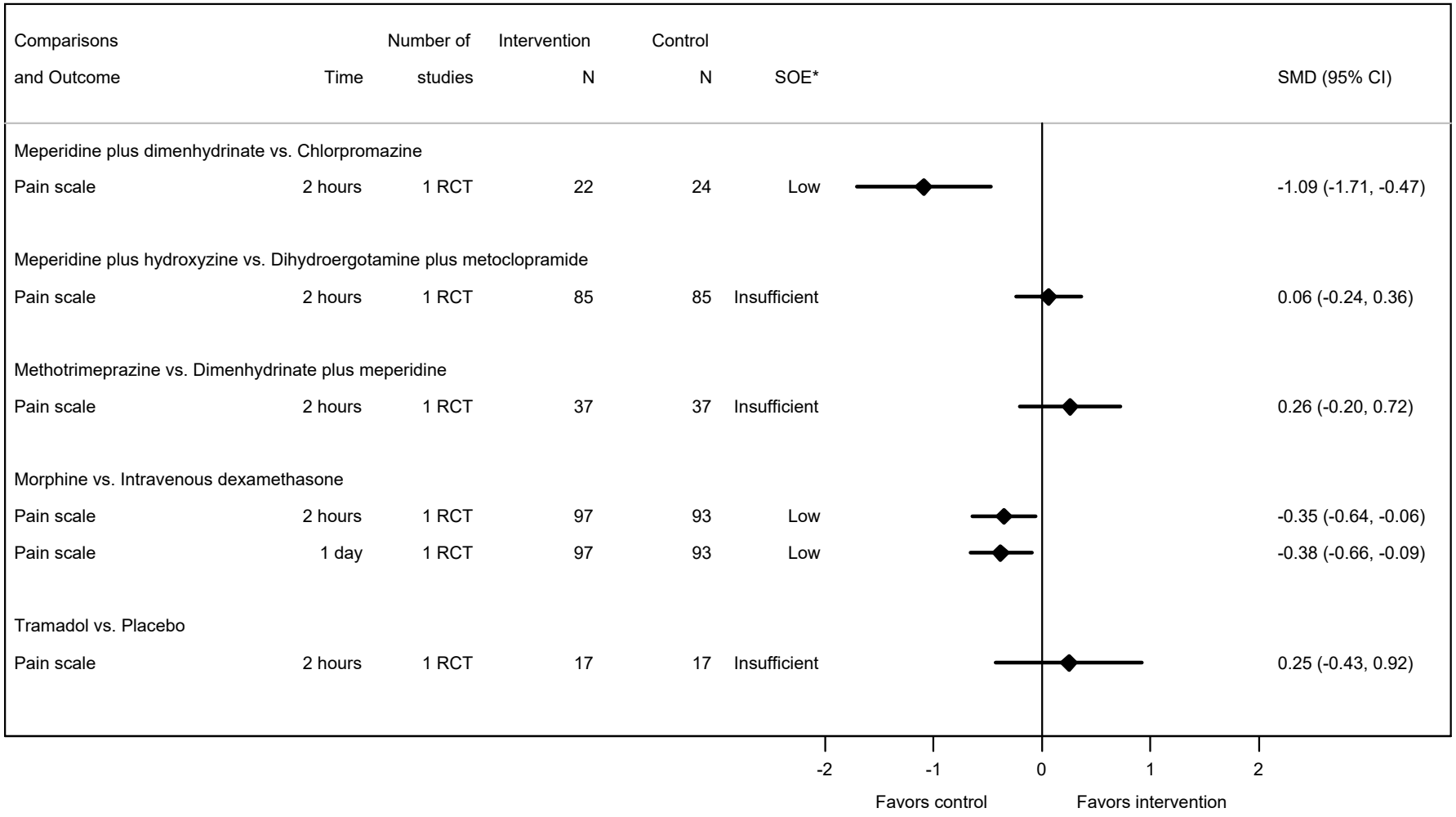
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; SMD = standardized mean difference; SOE = strength of evidence

eFigure 5. Findings of Meta-analysis of Opioids on Pain and Function Outcomes measured as Binary Outcomes for Episodic Migraine in Adults



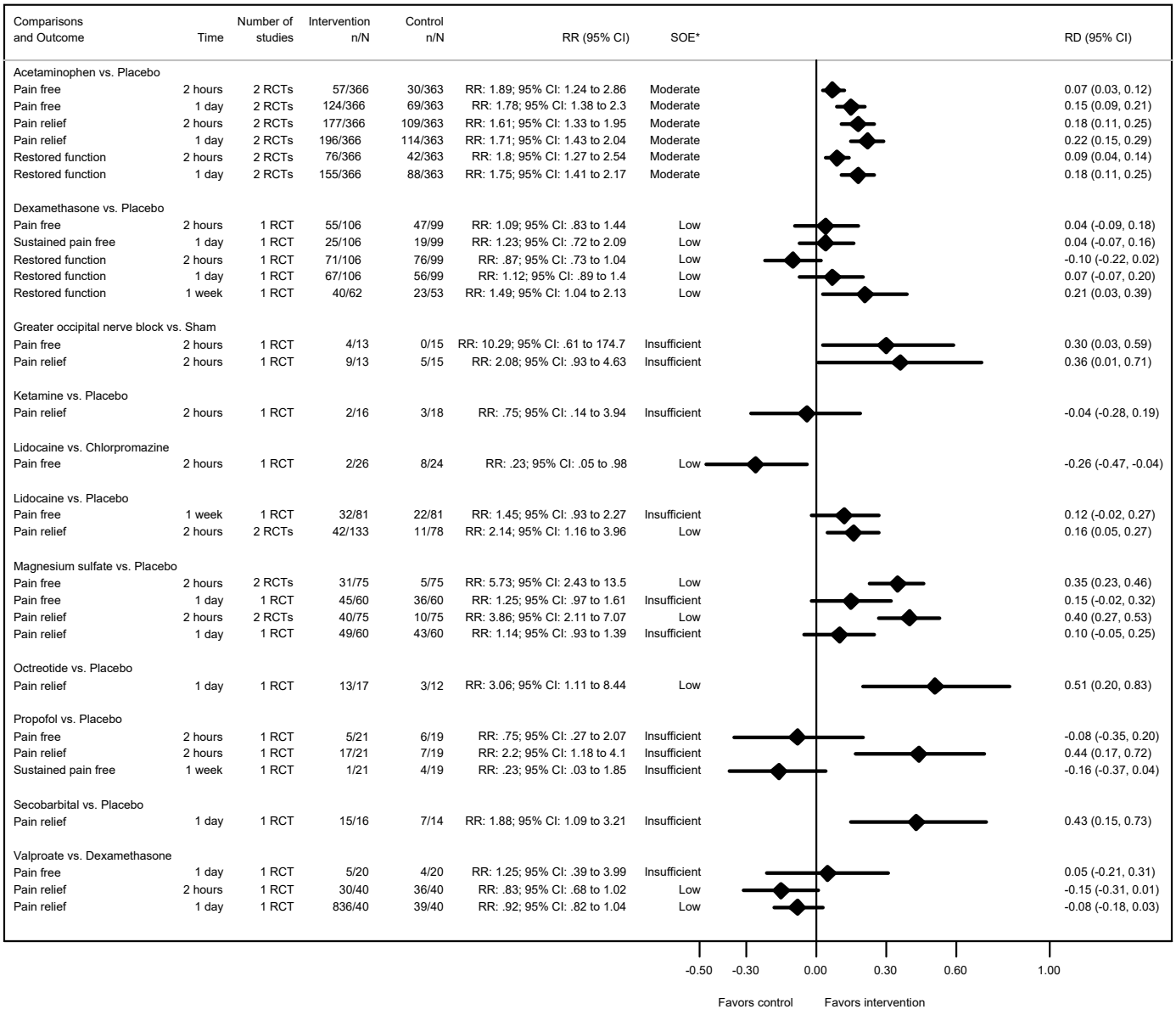
eTable 3 in the supplement lists definitions of outcomes.
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; RD = risk difference; RR = relative risk; SOE = strength of evidence

eFigure 6. Findings of Meta-analysis of Opioids on Pain Outcomes measured as Continuous Outcomes for Episodic Migraine in Adults



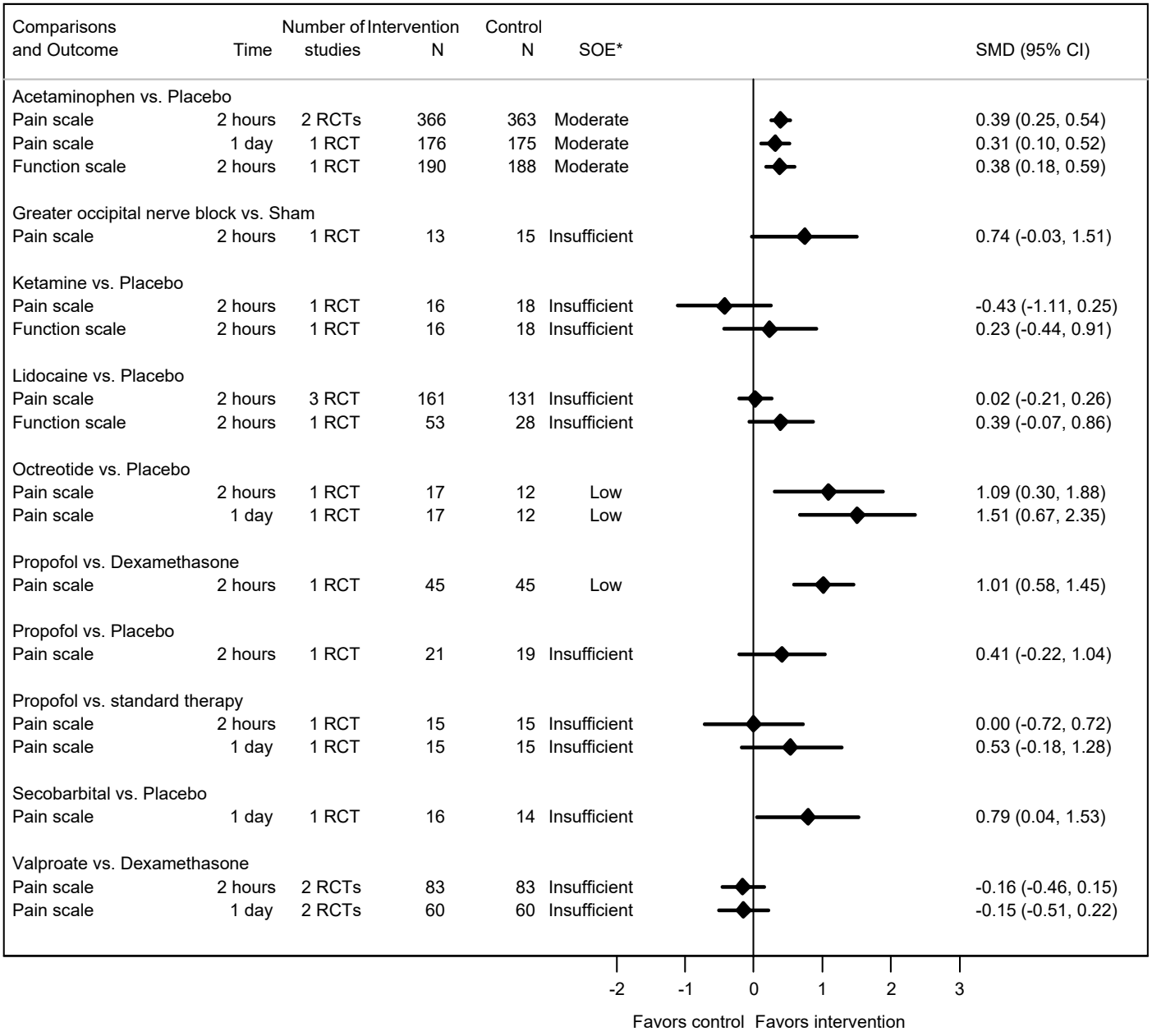
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; SMD = standardized mean difference; SOE = strength of evidence

eFigure 7. Findings of Meta-analysis of Other Pharmacological Interventions on Pain and Function Outcomes measured as Binary Outcomes for Episodic Migraine in Adults



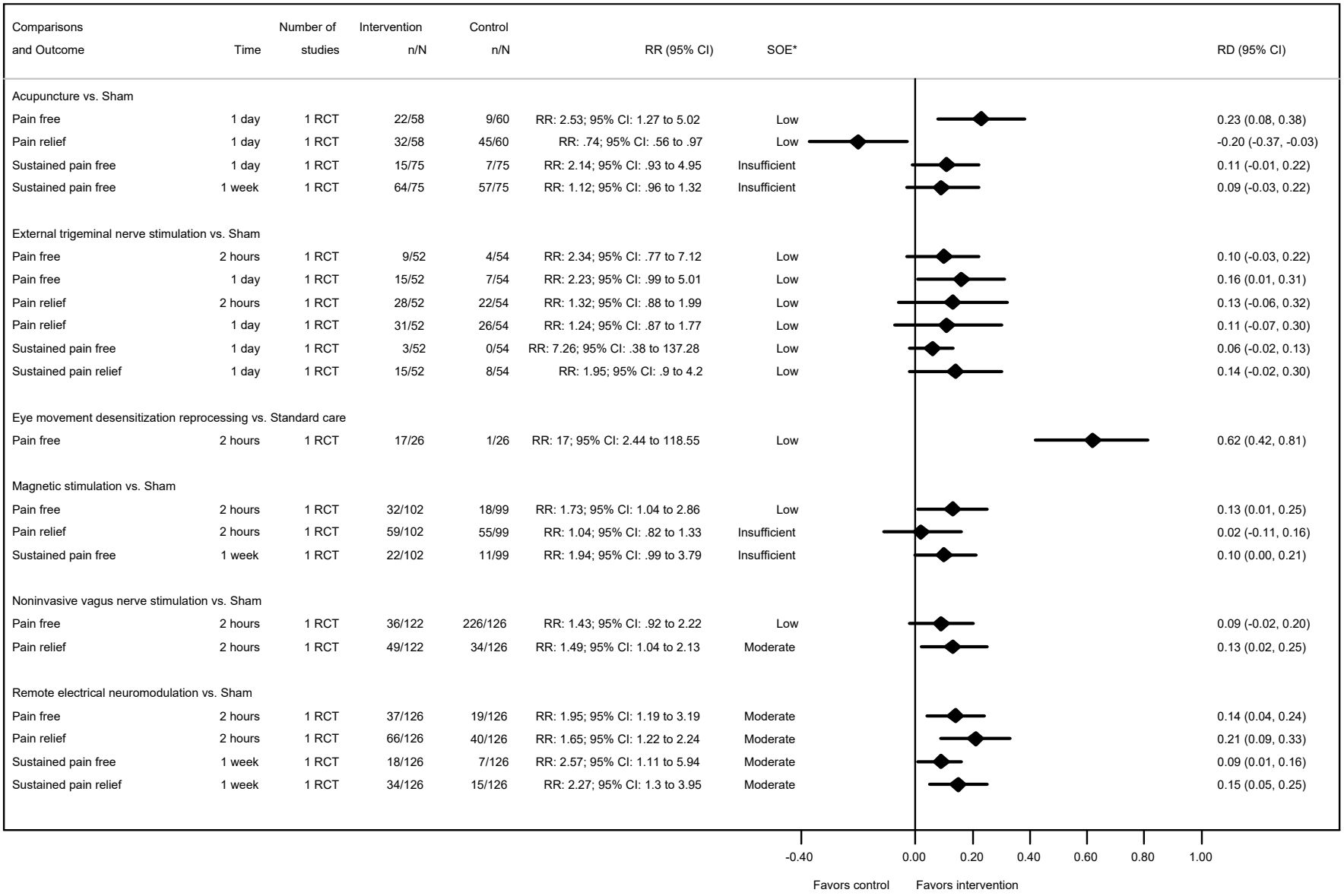
eTable 3 in the supplement lists definitions of outcomes.
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; RD = risk difference; RR = relative risk; SOE = strength of evidence

eFigure 8. Findings of Meta-analysis of Other Pharmacological Interventions on Pain and Function Outcomes measured as Continuous Outcomes for Episodic Migraine in Adults



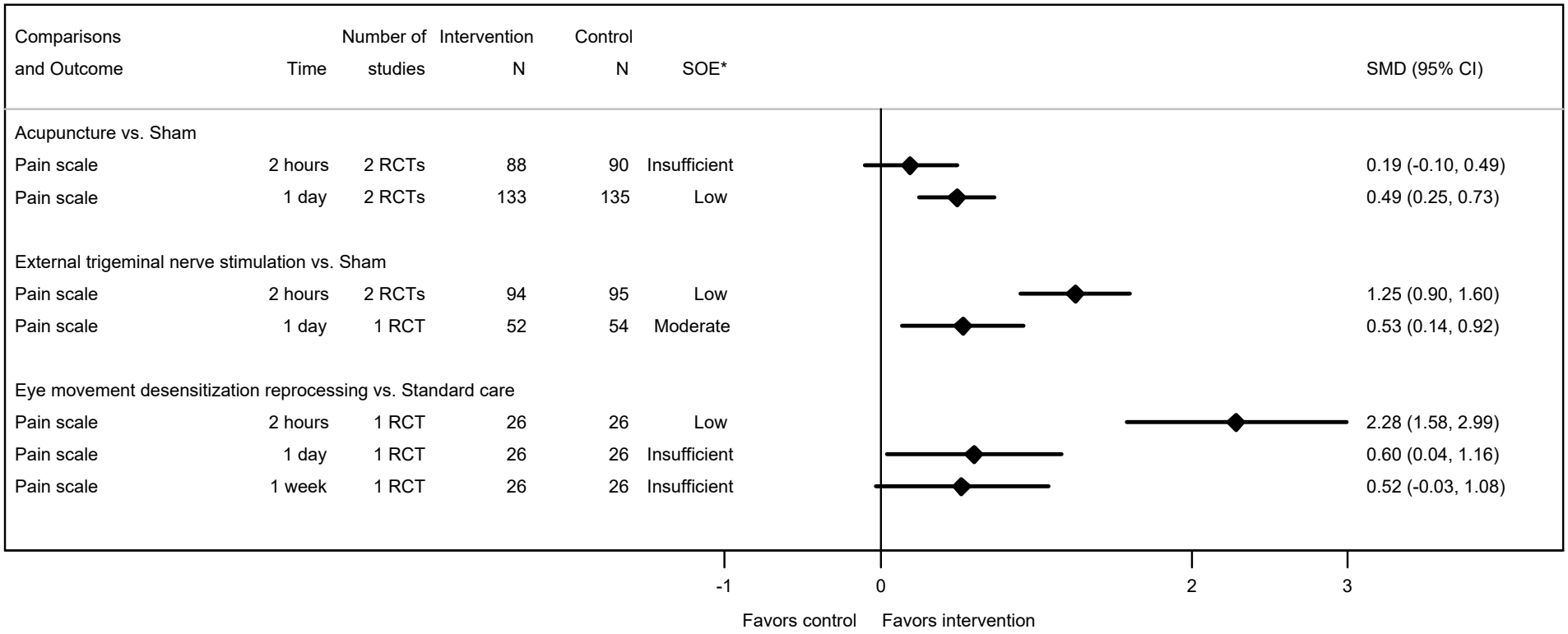
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; SMD = standardized mean difference; SOE = strength of evidence

eFigure 9. Findings of Meta-analysis of Nonpharmacological Interventions on Pain Outcomes measured as Binary Outcomes for Episodic Migraine in Adults



eTable 3 in the supplement lists definitions of outcomes.
eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; RD = risk difference; RR = relative risk; SOE = strength of evidence

eFigure 10. Findings of Meta-analysis of Nonpharmacological Interventions on Pain Outcomes measured as Continuous Outcomes for Episodic Migraine in Adults



eTable 6 in the supplement lists definitions of strength of evidence (SOE) and approaches used to grade SOE.
CI = confidence interval; RCT = randomized clinical trial; SMD = standardized mean difference; SOE = strength of evidence

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