Normobaric/hyperbaric oxygen

Supplementary table 1: ROB assesment for studies that assessed the effect of oxygen vs placebo

Manuscript	**Randomization process**	**Deviation from intended intervention**	**Missing outcome data**	**Bias in the measurement of the outcome**
Cohen et al, 2009	Low	Some concerns	Low	Low
Fogan et al, 1985	Low	Low	low	Low
Remahld et al, 2002	Low	Low	Low	Low
Petersen et al, 2017	Some concerns	Low	Low	Low

Supplementary table 2: Characteristics of studies that assessed the effect of oxygen vs placebo

Manuscript	**Patients**	**Comparison**	**Intervention**	**Outcome**	**Results**
Cohen 2009	Episodic (75%) or chronic cluster patients, aged 18-70 yo	Placebo (Air)	Oxygen 12 L/min delivered by firm plastic nonbreathing facial mask	Pain free at 15 minutes	Oxygen 116/150 Placebo 29/148

Fogan 1985	19 men with cluster headache not otherwise specified, aged 20-50 yo	Placebo (air)	Oxygen 6 L/min, not otherwise specified	Pain relief score	(substantial or complete relief) oxygen 10/16, placebo 1/16
Remahld 2002	Episodic (75%) or chronic cluster patients, aged 20-62 yo	Placebo (10% oxygen with nitrogen)3	Hyperbaric oxygen	Headache index decreased by 50%	Episodic: 4/12 HBO, 6/12 placebo Chronic: 1/4 HBO, 0/4 Placebo
Petersen 2017	Episodic and cluster headache, aged 18-65 yo (27 chronic and 30 chronic)	Placebo (21% oxygen and 79% nitrogen)	Oxygen 15 L/min, via simple mask, O2optimask and DVO	2-point decrease of pain in a five-point rating scale	Oxygen (DVO): 13/31 (42%) placebo (DVO): 3/8 (27%)

Triptans

Supplementary table 3: ROB assesment for studies included in Tables 5-8 (triptans vs placebo)

Manuscript	**Randomization process**	**Deviation from intended intervention**	**Missing outcome data**	**Bias in the measurement of the outcome**
Ekbom et al, 1993	Low	Low	Low	Low
The Sumatriptan Cluster Headache Study Group (1991)	Low	Low	Low	Low
van Vliet et al, 2003	Some concerns	Some concerns	Low	low
Bahra et al, 2000	Low	Low	Low	Low
Cittadini et al, 2006	Some concerns	Some concerns	Some concerns	Low
Rapoport et al, 2007	Low	Low	Low	Low

Supplementary table 4: Characteristics of studies for tables 5-8 (triptans vs placebo)

Manuscript	**Population**	**Intervention**	**Pts included/pts analyzed**	**Outcome**
Ekbom 1993	Chronic and episodic cluster patients	Sumatriptan subcutaneous injection 6 and 12 mg	157/134	Pain relief to no or mild pain at 10 min, 15 min

The Sumatriptan Cluster Headache Study Group (1991)	Chronic and episodic cluster patients	Sumatriptan subcutaneous injection 6 mg	49/39	Pain relief at 15 min
van Vliet 2003	Chronic and episodic cluster patients	Sumatriptan intranasal 20 mg	118/85	Pain relief at 30 min
Bahra 2000	Chronic and episodic cluster patients	Zolmitriptan oral 5 and 10 mg	153/114	Improvement of headache at 30 min
Cittadini 2006	Chronic and episodic cluster patients	Zolmitriptan intranasal 5 mg and 10 mg	92/69	"headache response" at 30 min
Rapoport 2007	Chronic and episodic cluster patients	Zolmitriptan intranasal 5 mg and 10 mg	83/52	"headache response" at 30 min

Galcanezumab

Supplementary Table 5: risk of bias assessment using ROB2 tool (Galcanezumab vs placebo)

Manuscript	**1. Randomization process**	**2. Deviation from intended intervention**	**3. Missing outcome data**	**4. Bias in the measurement of the outcome**
Goadsby et al, 2019	Low	Some concerns	Some concerns	Low

Supplementary table 6: Study characteristics for table 10 (galcanezumab)

Manuscript	Patients	Comparison	Intervention	Outcome
Goadsby et al, 2019	Episodic cluster headache patients (age: 18-65; assigned 49 to galcanezumab, 57 to placebo)	placebo	Galcanezumab 300mg	Frequency of attacks

Prednisone

Supplementary Table 7: risk of bias assessment using ROB2 tool (prednisone)

Manuscript	**1. Randomization process**	**2. Deviation from intended intervention**	**3. Missing outcome data**	**4. Bias in the measurement of the outcome**
Obermann et al, 2021	Low	low	Low	Low

Supplementary table 8: Study characteristics for table 9 (prednisone)

Manuscript	**Patients**	**Intervention**	**Comparison**	**Outcome**
Obermann et al, 2021	Episodic cluster headache patients (age: 18-65; assigned 57 to prednisone, 59 to placebo)	100 mg oral prednisone for 5 days	placebo	Mean number of cluster headache attacks in the first week

Supplementary Table 9: risk of bias assessment using ROB2 tool (VNS)

Manuscript	Randomization process	deviation from intended intervention	missing outcome data	Bias in the measurement of the outcome
Silberstein 2016	Low	Low	Low	Low
Goadsby 2018a	Low	Low	Low	Low
Gaul 2016	Some concerns	Low	Low	Low

Supplementary table 10: Characteristics of studies for tables 11-13 (VNS)

Manuscript	Population	Intervention	Comparator	Outcome	Rescue treatment
Silberstein 2016	Episodic and chronic cluster headache (60 nVNS-treated (38 episodic; 22 chronic) and 73 placebo (47 episodic; 26 chronic)	VNS (5kHz)	placebo	pain relief within 15 minutes from treatment for the first CH attack (pain relief defined as no (0) or mild pain (1) over a 0-4 scale)*	Abortive medications as needed
Goadsby 2018a	Episodic and chronic cluster headache age: >18yo; (48 VNS-treated (14 episodic, 34 chronic) and 44 sham-treated (13 episodic, 31 chronic)	VNS (5kHz)	placebo	pain-free status within 15 from treatment (no pain (0))*	3 additional stimulation allowed if no pain-free at 9 minutes (refrain for abortive medications over the 15 mins following stimulation)
Gaul 2016	Chronic cluster headache; age 18-70 (45 VNS 48 controls)	VNS (5kHz)	standard care	mean number of attacks per week	Abortive medications as needed

Supplementary Table 11: risk of bias assessment using ROB2 tool.

Manuscript	Randomization process	deviation from intended intervention	missing outcome data	Bias in the measurement of the outcome
Goadsby 2019	Low	Low	Low	Low

Supplementary table 12: Characteristics of studies for tables 14 (SPG)

Manuscript	Population	Intervention	Comparator	Outcome	Rescue treatment
Goadsby 2019	Chronic cluster headache patients; age: 18-70 yo; (SPG 45, placebo 48 patients)	SPG stimulation	placebo	Pain relief after 15min of the initiation of attack (from scores 2-4 to scores 0-1)	Abortive medications as needed after 15 min

Supplementary table 13: ROB assessment for ONS with Newcastle-Ottawa scale for cohort studies

Manuscript	Selection	Comparability	Outcome	Patients randomized/analyzed	Weight in the pooled effect
Miller, 2016	**	*	**	51	29%
Wilbrink, 2021	**	**	**	130	71.00%

Supplementary table 14: Characteristics of studies for ONS

Manuscript	Population	Intervention	Outcome	Mean duration of CH	Follow-up	Rescue treatment	Rating scale	Results, mean daily attacks
Miller, 2016	Patients with intractable CCH, 35 men, 16 women	ONS (t 60 Hz with a pulse width of 240 ls; adjusted during follow-up)	Mean change of attack frequency from baseline	14.63 (+/- 11.0)	39.17 months (+/-19.04)	As needed	1-10	MD from baseline: -1.61 (0.88, 2.34)

Wilbrink, 2021	Patients with intractable CCH, 47 men, 83 women	ONS (t 60 Hz with a pulse width of 450 ls; adjusted during follow-up); divided on 30% or 100% of the intensity	Mean change of attack frequency from baseline	7 (6)	24 weeks	As needed	1-10	MD from baseline -42.56 (-80.05 to -1.80)