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| --- | --- | --- | --- | --- | --- | --- |
| Supplementary eTable 1: Patient-related criteria for being included in 16 randomized, placebo-controlled trials on botulinum toxin A for chronic tension-type or cervicogenic headache | | | | | | |
| Primary author – year | Ability to differentiate from migraine/other headaches | No other headache, or  migraine <1/mo | No other pain problems  being treated | No disease/treatment  interfering with  neuromuscular transmission 2) | No somatic or psychiatric disorder,  drug/alcohol abuse, or  drug-induced headache last 2 years | No pregnancy, inadequate contraception nor breastfeeding |
| Trials on CTTH | | | | | | |
| Smuts 1999 | - | + | - | - | + | - |
| Rollnik 2000 | - | + | - | + | + | + |
| Schmitt 2001 | - | + | - | - | + | + |
| Rollnik 2001 | - | + | - | + | + | + |
| Kokoska 2004 | - | + | - | + | - | + |
| Padberg 2004 | - | + | - | + | - | + |
| Relja 2004 | - | - | - | - | - | - |
| Schulte-Mattler 2004 | - | + | - | - | + | + |
| Silberstein 2006 | + | + | +1) | + | + | + |
| Straube 2008 | + | + | + 1, 2) | + | + | + |
| Hamdy 2009 | + | + | - | + | + | + |
| Harden 2009 | - | + | + 4) | + | + | + |
| Trials on CEH | | | | | | |
| Freund 2000 | - | - | - | - | + | - |
| Schnider 2001 | + | - | - | - | + 5) | + |
| Linde 2011 | + | - | - | + | + | + |
| Karadas 2012 | - | - | + | + | + | + |
| Number of trials: | 5 | 11 | 4 | 10 | 13 | 13 |

*Legend to supplementary eTable 1:*1) Treatment at a constant rate 3 months prior to the trial or the visit 2) Maximum oneanalgesic. No prophylactic treatment permitted, and this should be discontinued 6 w before randomization. 2) This includes myasthenia gravis, ALS, muscular atrophy, infection at injection sites or use of aminoglycosides.4) Physical/occupational therapy, daily opioid prophylaxis **3)** IHS criteria for excessive consumption.

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| Supplementary eTable 2. Drug related exclusion criteria in 16 randomized, placebo-controlled trials on botulinum toxin A treatment for chronic tension type or cervicogenic headache | | | | | | | |
| Primary author - year | Previously  BONTX treated | Local anesthetic/corticosteroid injection last month | Caffeine or  ergotamine  > 3 days/w | Headache  Prophylaxis | Daily use of opoids | Neuroleptics/  antidepressants/  antiepileptics/ sedatives | No anticoagulation |
| Trials on CTTH | | | | | | | |
| Smuts JA 1999 | + | - | - | - | - | - | - |
| Rollnik JD 2000 | - | - | - | - | - | + | + |
| Schmitt WJ 2001 | + | - | - | - | - | - | - |
| Rollnik JD 2001 | - | - | - | - | - | + | + |
| Kokoska 2004 | + | - | - | - | - | - | - |
| Padberg M 2004 | + | + | + | - | - | - | - |
| Relja 2004 | - | - | - | - | - | - | - |
| Schulte-Mattler WJ 2004 | - | - | - | - | - | + | + |
| Silberstein SD 2006 | + | + | + | + | +1) | - | - |
| Straube A 2008 | + | - | - | + | - | + | + |
| Hamdy SM 2009 | + | + | - | - | - | - | - |
| Harden RN 2009 | + | - | - | - | + | - | - |
| Trials on CEH | | | | | | | |
| Freund BJ | - | - | - | - | - | - | - |
| Linde M | + | - | - | + | - | - | - |
| Schnider P 2001 | - | - |  |  |  |  |  |
| Karadas Ӧ | + | - | - | - | - | + | + |
| Number of trials: | 9 | 3 | 2 | 3 | 2 | 4 | 5 |

*Legend to supplementary eTable 2:* BONTX= botulinum toxin A. BZD = Benzodiazepines 1) Includes opioids > 3 days a week. 2) Maximum one analgesic

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Supplementary eTable 3. Muscles injected with botulinum toxin A in 16 randomized, placebo-controlled trials on botulinum toxin A treatment for chronic tension type or cervicogenic headache | | | | | | | | |
| Primary author - year of publication | **Pericranial and neck muscles** | | | | | | | |
| Frontalis and/or occipitalis | Temporalis | Masseter | Neck and/or shoulder | Trapezius | Sternocleido-mastoideus | Splenius capitis and/or Semispinalis capitis | Not specified |
| Trials on CTTH | | | | | | | | |
| Smuts JA 1999 |  | + |  | + |  |  |  |  |
| Rollnik JD 2000 | + | + |  |  |  |  |  |  |
| Schmitt WJ 2001 | + | + |  | + |  |  |  |  |
| Rollnik JD 2001 | + | + |  |  | + | + | + |  |
| Kokoska 2004 | + |  |  |  |  |  |  |  |
| Padberg M 2004 | + | + | + |  | + | + | + |  |
| Relja 2004 |  |  |  |  |  |  |  | +\* |
| Schulte-Mattler WJ 2004 | + | + |  |  | + | + | + |  |
| Silberstein SD 2006 | + | + |  |  | + | + | + |  |
| Straube A 2008 | + | + |  |  | + |  | + |  |
| Hamdy SM 2009 | + | + |  |  | + | + | + |  |
| Harden RN 2009 |  |  |  | + |  |  |  |  |
| Trials on CEH | | | | | | | | |
| Freund BJ 2000 |  |  |  | + | + |  | + |  |
| Schnider 2001 |  |  |  | + |  |  |  |  |
| Linde M 2011 | + |  |  | + | + | + | + |  |
| Karadas Ӧ 2012 | + | + |  |  | + |  | + |  |
| Number of trials: | 11 | 10 | 1 | 6 | 9 | 6 | 9 | 1 |

*Legend to supplementary eTable 3:* NA= not applicable.\* Relja et al: Pericranial muscles

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Supplementary eTable 4. Primary endpoints applied in each trial** | | | | | | | | | | | | | | | | |
| Endpoint | Smuts 1999 | Rollnik 2000 | Schmitt 2001 | Rollnik 2001 | Kokoska 2004 | Padberg 2004 | Schulte Mattler  2004 | Silberstein 2006 | Straube 2008 | Hamdy 2009 | Harden 2009 | Freund 2000 | Schnider 2001 | Linde 2011\* | Karadas 2012 | No of trials |
| Headache  Intensity |  |  | X |  | x | x | x |  |  | x | x |  |  |  |  | 6 |
| Headache  Frequency |  |  |  |  | x |  |  | x | x | x | x |  |  | x |  | 6 |
| AUC (pain intensity  x duration) |  |  |  | X |  |  |  |  |  |  |  |  |  |  |  | 1 |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Supplementary eTable 5. Secondary or unspecified endpoints applied in more than one trial | | | | | | | | | | | | | | | | | | |
| Endpoint | | Smuts 1999 | Rollnik 2000 | Schmitt 2001 | Rollnik 2001 | Kokoska 2004 | Padberg 2004 | Relja 2004 | Padberg 2004 | Schulte- Mattler 2004 | Silberstein 2006 | Straube 2008 | Hamdy 2009 | Harden 2009 | Freund  2000 | Schnider 2001 | Linde 2011 | Karadas 2012 | No  of trials |
| Headache duration | |  | x | x |  |  | x |  | x | x | x | x | x |  |  | x | x | x | 11 |
| Concomitant/rescue  medication  or medication days | |  | x | x | x | x | x |  | x | x | x | x | x | x |  | x |  |  | 12 |
| Headache frequency | | x | x | x | x |  | x | x | x | x |  |  |  |  |  | x | x |  | 10 |
| Headache intensity | | x | x |  |  |  |  | x |  |  | x | x |  |  | x | x | x | x | 9 |
| Algometry,  tenderness or  pressure pain | |  | x |  |  |  |  | x |  | x |  | x |  | x |  | x | x |  | 7 |
| Daily distress, tension,  anger, or feeling of  depression | |  |  | x |  |  |  |  |  | x | x | x |  | x |  |  |  |  | 5 |
| Patient’s global  assessment of  the treatment | |  | x |  |  |  | x |  | x |  | x | x |  |  |  |  |  |  | 5 |
| HR QOL | | x | x |  |  |  |  |  |  |  | x |  |  |  |  |  | x |  | 4 |
| AROM | |  |  |  |  |  |  |  |  |  |  |  |  | x | x | x | x |  | 4 |
| Interference with,  impact on life | |  | x |  |  |  |  |  |  |  | x | x |  |  |  |  |  |  | 3 |
| Headache localization | |  | x |  | x |  |  |  |  |  | x |  |  |  |  |  |  |  | 3 |
| Nausea, vomiting,  increased sensitivity  to light and/or noise | |  |  |  |  |  |  |  |  |  |  | x | x |  |  |  |  |  | 2 |
| Worsed by phys. act. | |  |  |  |  |  |  |  |  |  |  | x | x |  |  |  |  |  | 2 |
| Non-TTH episodes | |  |  |  |  |  |  |  |  |  |  | x | x |  |  |  |  |  | 2 |
| Duration of headache  and neck pain | |  |  |  |  |  |  |  |  |  |  |  |  |  |  | x | x |  | 2 |
| Number of secondary endpoints  within each trial | | 3 | 9 | 4 | 3 | 1 | 4 | 3 | 4 | 5 | 8 | 10 | 5 | 4 | 2 | 7 | 7 | 2 |  |

*Legend to Supplementary eTable 5:* HR QOL= Health-related quality of life, AROM= active range of movement. Pressure pain= pressure pain threshold scores

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| Supplementary eTable 6. Specific item scores and sum scores of Oxford Pain Validity Scale (OPVS) in 16 randomized placebo-controlled trials on botulinum toxin A treatment for chronic tension type or cervicogenic headache | | | | | | | | | |
| Primary author and  year of publication | Blinding (0,3,6) | Group Size  (0-3) | Outcome measure  (0,2) | Internal sensitivity  (0,1) | Data analysis: | | | | Sum score  (0-16) |
| Definition of outcomes (0,1) | Data presentation Location &Dispersion (0,1) | Statistical testing  (0,1) | Dropouts  (0,1) |
| Trials on CTTH | | | | | | | | | |
| Smuts 1999 | 0 | 3 | 2 | 1 | 1 | 1 | 0 | 1 | 9 |
| Rollnik 2000 | 0 | 1 | 2 | 1 | 1 | 1 | 1 | 0 | 7 |
| Schmit 2001 | 6 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | *16* |
| Rollnik 2001\* | NA | NA | NA | NA | NA | NA | NA | NA | NA |
| Kokoska 2004 | 6 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 16 |
| Padberg 2004 | 6 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 16 |
| Relja 2004 | 0 | 0 | 2 | 1 | 1 | 1 | 0 | 0 | 5 |
| Schulte-Mattler 2004 | 0 | 3 | 2 | 1 | 1 | 1 | 1 | 1 | 10 |
| Silberstein 2006 | 6 | 3 | 2 | 1 | 1 | 0 | 1 | 1 | 15 |
| Straube 2008 | 3 | 3 | 2 | 1 | 1 | 1 | 0 | 1 | 12 |
| Hamdy 2009 | 3 | 1 | 2 | 1 | 1 | 1 | 0 | 0 | 9 |
| Harden 2009 | 0 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 8 |
| Trials on CEH | | | | | | | | | |
| Freund 2000 | 6 | 2 | 2 | 1 | 1 | 1 | 0 | 0 | 13 |
| Schnider 2001 | 0 | 2 | 0 | 1 | 1 | 1 | 1 | 1 | 7 |
| Linde 2011 | 6 | 1 | 2 | 1 | 1 | 1 | 1 | 1 | 14 |
| Karadas 2012 | 0 | 3 | 2 | 1 | 1 | 1 | 0 | 0 | 8 |

*Legend to supplementary eTable 6:*NA= not applicable.\*Too small sample size to be assessed.

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| Supplementary eTable 7. Separate item scores of Modified Jadad Quality Scale in 16 randomized placebo-controlled trials on botulinum toxin A treatment for chronic tension type or cervicogenic headache | | | | | | | | | | | | | | | |
| Primary author and  year of publication | Described as randomized  (+1/0) | | Appropriate randomization  (+1/0/-1) | | Described as double-or single- blind  (+1/+0,5/0) | | | Appropriate blinding  (+1/0/-1) | | Withdrawals and dropouts described  (+1/0) | | Inclusion and exclusion criteria described (+1/0) | Methods to  assess AE  described  (+1/0) | Statistical analysis described  (+1/0) | Sum score  (0-8) |
| Trials on CTTH | | | | | | | | | | | | | | | |
| Smuts 1999 | | 1 | | 0 | | 1 | 0 | | 1 | | 1 | | 0 | 1 | 5 |
| Rollnik 2000 | | 1 | | 0 | | 1 | 0 | | 0 | | 1 | | 0 | 1 | 4 |
| Schmitt 2001 | | 1 | | 1 | | 1 | 1 | | 1 | | 1 | | 0 | 1 | 7 |
| Rollnik 2001 | | 1 | | 0 | | 1 | 0 | | 0 | | 1 | | 0 | 1 | 4 |
| Kokoska 2004 | | 1 | | 1 | | 1 | 1 | | 1 | | 1 | | 0 | 1 | 7 |
| Padberg 2004 | | 1 | | 0 | | 1 | 1 | | 1 | | 1 | | 0 | 1 | 6 |
| Relja 2004 | | 1 | | 0 | | 1 | 0 | | 0 | | 1 | | 0 | 1 | 4 |
| Schulte-Mattler 2004 | | 1 | | 1 | | 1 | 0 | | 0 | | 1 | | 1 | 1 | 6 |
| Silberstein 2011 | | 1 | | 0 | | 1 | 1 | | 1 | | 1 | | 1 | 1 | 7 |
| Straube 2008 | | 1 | | 1 | | 1 | -1 | | 1 | | 1 | | 1 | 1 | 6 |
| Hamdy 2009 | | 1 | | 1 | | 0.5 | 0 | | 0 | | 1 | | 1 | 1 | 5.5 |
| Harden 2009 | | 1 | | 0 | | 1 | 0 | | 1 | | 1 | | 0 | 1 | 5 |
| Trials on CEH | | | | | | | | | | | | | | | |
| Freund 2000 | | 1 | | 1 | | 1 | 1 | | 1 | | 1 | | 0 | 1 | 7 |
| Schnider 2001 | | 1 | | 0 | | 1 | 0 | | 1 | | 1 | | 1 | 1 | 6 |
| Linde 2011 | | 1 | | 1 | | 1 | 1 | | 1 | | 1 | | 1 | 1 | 8 |
| Karadas 2012 | | 0 | | 0 | | 0 | -1 | | 0 | | 1 | | 0 | 1 | 1 |

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| Supplementary eTable 8: Item specific and total assessment by the revised Cochrane Collaboration’s tool for assessing risk of bias (RoB 2)  in 16 randomized placebo-controlled trials on botulinum toxin A treatment for chronic tension type or cervicogenic headache | | | | | | |
| Primary author | Randomzation | Deviation and effect of assignment to intervention | Missing outcome data | Measurement of outcome | Selection in the outcome data | Overall |
| Trials on CTTH | | | | | | |
| Smuts 1999 | HR | SC | HR | HR | SC | HR |
| Rollnik 2000 | HR | SC | HR | SC | SC | HR |
| Schmitt 2001 | LR | SC | LR | SC | SC | SC |
| Rollnik 2001 | HR | SC | HR | SC | SC | HR |
| Kokoska 2004 | SC | SC | LR | SC | SC | SC |
| Padberg 2004 | SC | SC | SC | LR | SC | SC |
| Relja 2004 | SC | SC | HR | HR | HR | HR |
| Schulte-Mattler 2004 | SC | SC | SC | LR | LR | SC |
| Silberstein 2011 | SC | LR | SC | LR | SC | SC |
| Straube 2008 | SC | SC | SC | LR | SC | SC |
| Hamdy 2009 | HR | SC | HR | HR | SC | HR |
| Harden 2009 | SC | LR | HR | SC | SC | HR |
| Trials on CEH | | | | | | |
| Freund 2000 | SC | SC | SC | LR | SC | SC |
| Schnider 2001 | HR | SC | SC | SC | SC | HR |
| Linde 2011 | SC | LR | SC | LR | SC | SC |
| Karadas 2012 | SC | SC | LR | HR | SC | HR |

*Legend to Supplementary eTable 8:* HR= high risk of bias, SC = some concerns of risk of bias, and LR= low risk of bias

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| Supplementary eTable 9. Numbers and proportions of side effects in general and number of trial-specific, adverse events among patients treated with botulinum toxin A or placebo in 12 randomized placebo-controlled trials due to chronic tension type or cervicogenic headache. | | | | | | | | | | | | | | | | | | |
| Trials- primary author | Treatment | Dose\* | N | Side effects | Proportion  (%) | Dizzy | Injection site: pain/  burning/  itching | Muscle weakness | Nausea | Neck pain | Neck stiffness | Paraesthesia/Numb-ness | Headache | Pain | Dysphagia | Ptosis | Asthenia | Others |
| All trials | Btx |  | 531 | 162 | 31 | 11 | 18 | 37 | 5 | 16 | 9 | 5 | 21 | 9 | 6 | 5 | 7 | 13 |
| All trials | Plac |  | 331 | 51 | 15 | 4 | 20 | 2 | 3 | 1 | 1 | 0 | 10 | 2 | 1 | 0 | 0 | 7 |
| Trials on CTTH | | | | | | | | | | | | | | | | | | |
| Schmitt  2001 | Btx | 20 | 30 | 12 | 40 | 2 | 2 |  |  |  |  |  | 4 |  |  |  |  | 4 |
| Schmitt  2001 | Plac | 0 | 29 | 8 | 28 | 1 | 1 |  |  |  |  |  | 4 |  |  |  |  | 2 |
| Kokoska 2004 | Btx | 50 | 20 | 3 | 15 |  |  | 0 |  |  |  |  |  |  |  | 3 |  | 0 |
| Kokoska 2004 | Plac | 0 | 20 | 0 | 0 |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Padberg  2004 | Btx | 100 | 19 | 8 | 42 | 0 | 5 | 1 | 1 |  |  | 1 |  |  |  |  |  | 0 |
| Padberg  2004 | Plac | 0 | 21 | 13 | 62 | 1 | 9 | 0 | 1 |  |  | 0 |  |  |  |  |  | 2 |
| Schulte-Mattler  2004 | Btx | 200 | 53 | 8 | 15 |  |  | 7 |  | 1 |  |  |  |  |  |  |  |  |
| Schulte-Mattler  2004 | Plac | 0 | 54 | 0 | 0 |  |  | 0 |  | 0 |  |  |  |  |  |  |  |  |
| Silberstein  2006 | Btx | 150 | 47 | 12 | 26 | 0 | 2 | 3 | 0 | 3 | 1 | 0 | 0 | 1 | 0 |  | 0 | 2 |
| Silberstein  2006 | Btx | 100 | 51 | 35 | 69 | 4 | 1 | 10 | 0 | 4 | 5 | 0 | 4 | 4 | 1 |  | 2 | 0 |
| Silberstein  2006 | Btx | 100 | 52 | 14 | 27 | 1 | 1 | 2 | 0 | 2 | 0 | 1 | 2 | 3 | 0 |  | 0 | 2 |
| Silberstein  2006 | Btx | 86 | 51 | 20 | 39 | 0 | 1 | 3 | 1 | 3 | 0 | 3 | 2 | 0 | 3 |  | 3 | 1 |
| Silberstein  2006 | Btx | 50 | 49 | 16 | 33 | 1 | 1 | 1 | 2 | 3 | 2 | 0 | 2 | 0 | 0 |  | 2 | 2 |
| Silberstein  2006 | Plac | 0 | 50 | 10 | 20 | 0 | 5 | 1 | 0 | 1 | 0 | 0 | 2 | 1 | 0 |  | 0 | 0 |
| Straube  2008 | Btx | 168 | 26 | 8 | 31 |  |  | 5 |  |  |  |  |  |  | 2 | 1 |  |  |
| Straube  2008 | Btx | 84 | 33 | 2 | 6 |  |  | 2 |  |  |  |  |  |  |  | 0 |  |  |
| Straube  2008 | Plac | 0 | 60 | 2 | 3 |  |  | 1 |  |  |  |  |  |  | 1 | 0 |  |  |
| Hamdy  2009 | Btx | < 80 | 14 | 3 | 21 |  | 1 |  |  |  |  |  |  |  |  | 1 |  | 1 |
| Hamdy  2009 | Plac | 0 | 14 | 3 | 21 |  | 2 |  |  |  |  |  |  |  |  | 0 |  | 1 |
| Harden  2009 | Btx | 100 | 12 | 1 | 8 |  |  | 1 |  |  |  |  |  |  |  |  |  |  |
| Harden  2009 | Plac | 0 | 11 | 0 | 0 |  |  | 0 |  |  |  |  |  |  |  |  |  |  |
| Trials on CEH | | | | | | | | | | | | | | | | | | |
| Freund  2000 | Btx | 100 | 14 | 0 | 0 |  |  | 0 |  |  |  |  |  |  |  |  |  |  |
| Freund  2000 | Plac | 0 | 12 | 0 | 0 |  |  | 0 |  |  |  |  |  |  |  |  |  |  |
| Schnider 2001 | Btx | 90 | 17 | 1 | 6 |  | 1 | 0 |  |  |  |  |  |  | 0 |  |  |  |
| Schnider 2001 | Plac | 0 | 16 | 0 | 0 |  | 0 | 0 |  |  |  |  |  |  | 0 |  |  |  |
| Linde  2011 | Btx | 100 | 23 | 13 | 57 | 1 | 1 | 1 | 1 |  | 1 |  | 7 |  |  |  |  | 1 |
| Linde  2011 | Plac | 0 | 24 | 9 | 38 | 1 | 1 | 0 | 2 |  | 0 |  | 4 |  |  |  |  | 1 |
| Karadas  2012 | Btx | 60 | 20 | 6 | 30 | 2 | 2 | 1 |  |  | 0 |  |  | 1 |  |  |  | 0 |
| Karadas  2012 | Plac | 0 | 20 | 6 | 30 | 1 | 2 | 0 |  |  | 1 |  |  | 1 |  |  |  | 1 |

Legend to supplementary eTable 9: BTX= Botulinum toxin A. Plac.= placebo, NA= Not applicable.

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| Supplementary eTable 10. Data-analysis with different meta-analysis models | | |
| Meta-analysis model | **Analysis group** | **SMD (95% CI)** |
| Fixed effect | CTTH: Headache frequency | -0.26 (-0.48 to -0.04 |
| Fixed effect | CTTH: Pain intensity | -0.28 (-0.49 to -0.07) |
| Fixed effect | CEH: Headache frequency | -0.58 (-0.89 to -0.28) |
| Fixed effect | CEH: Pain intensity | -0.37 (-0.65 to -0.09) |
| DerSimonian-Laird random effects | CTTH: Headache frequency | -0.34 (-0.71 to 0.02) |
| DerSimonian-Laird random effects | CTTH: Pain intensity | -0.35 (-0.69 to 0.00) |
| DerSimonian-Laird random effects | CEH: Headache frequency | -0.74 (-1.42 to -0.05) |
| DerSimonian-Laird random effects | CEH: Pain intensity | -0.38 (-0.74 to -0.03) |
| Mandel-Paule empirical Bayes estimator | CTTH: Headache frequency | -0.37 (-0.81 to 0.08) |
| Mandel-Paule empirical Bayes estimator | CTTH: Pain intensity | -0.36 (-0.75 to 0.03) |
| Mandel-Paule empirical Bayes estimator | CEH: Headache frequency | -0.74 (-1.44 to -0.04) |
| Mandel-Paule empirical Bayes estimator | CEH: Pain intensity | -0.38 (-0.75 to -0.02) |

Legend to Supplementary eTable 10: The analysis is based on 12 trials. SMD (Standardized mean difference), CI = Confidence interval.

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| Supplementary eTable 11. Meta-regression analysis | | | |
| Analysis group | **Variable** | **Effect size (95% CI)** | **p-value** |
| All studies | **Age** | **0.054 (-0.081 to 0.19)** | **0.331** |
| CTTH: Headache frequency | Age | 0.088 (-0.83 to 0.26 | 0.226 |
| CTTH: Pain intensity | Age | 0.034 (-0.112 to 0.181) | 0.575 |
| CEH: Headache frequency | Age | 0.095 (-0.81 to 1.001) | 0.408 |
| CEH: Pain intensity | Age | 0.088 (-0.099 to 0.276) | 0.180 |
| All studies | **Women** | **-0.030 (-0.054 to -0.006)** | **0.029\*** |
| CTTH: Headache frequency | Women | -0.034 (-0.113 to 0.045 | 0.299 |
| CTTH: Pain intensity | Women | -0.024 (-0.068 to 0.020) | 0.213 |
| CEH: Headache frequency | Women | -0.054 (-0.295 to 0.188) | 0.217 |
| CEH: Pain intensity | Women | -0.032 (-0.106 to 0.041) | 0.200 |
| All studies | **Sample size** | **0.004 (-0.006 to 0.015)** | **0.236** |
| CTTH: Headache frequency | Sample size | 0.007 (-0.011 to 0.024) | 0.345 |
| CTTH: Pain intensity | Sample size | 0.003 (-0.011 to 0.017) | 0.568 |
| CEH: Headache frequency | Sample size | -0.091 (-0.517 to 0.335) | 0.224 |
| CEH: Pain intensity | Sample size | -0.048 (-0.192 to 0.095) | 0.284 |
| All studies | **Study duration** | **-0.016 (-0.082 to 0.049)** | **0.484** |
| CTTH: Headache frequency | Study duration | 0.004 (-0.260 to 0.268) | 0.968 |
| CTTH: Pain intensity | Study duration | -0.029 (-0.137 to 0.079) | 0.525 |
| CEH: Headache frequency | Study duration | -0.024 (-1.972 to 1.923) | 0.900 |
| CEH: Pain intensity | Study duration | 0.007 (-0.236 to 0.250) | 0.913 |
| All studies | **Bont dose** | **0.000 (-0.004 to 0.005)** | **0.697** |
| CTTH: Headache frequency | Bont dose | 0.001 (-0.005 to 0.007) | 0.692 |
| CTTH: Pain intensity | Bont dose | 0.000 (-0.004 to 0.004) | 0.990 |
| CEH: Headache frequency | Bont dose | -0.020 (-0.115 to 0.075 | 0.226 |
| CEH: Pain intensity | Bont dose | -0.014 (-0.044 to 0.016) | 0.179 |

Legend to Supplementary eTable 11: The analysis is based on 12 trials. The unit for study duration is week. For BONTA dosages the 1 unit of onabotulinumtoxin A has been applied and 2,5 units of abobotulinumtoxin A was considered equivalent to 1 unit of onabotulinumtoxin A. \*= statistical significance.

Appendix 1

**A step by step search strategy table**

| Search | Query | Results | Time |
| --- | --- | --- | --- |
| #27 | Search: ((((((tension headache) OR (Tension-Type Headache)) OR (headache disorders, secondary)) OR (cervicogenic headache)) OR (cervical)) AND (((((Botulinum Toxins) OR (botulinum)) OR (botulinum toxin)) OR (toxin)) OR (toxins))) AND (((((((reduced headache) OR (headache)) OR (reduced headache severity)) OR (severity)) OR (pain relief)) OR (reduced headache days)) OR (headache free days)) Filters: Clinical Trial, Randomized Controlled Trial, Humans | [150](https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28%28tension+headache%29+OR+%28Tension-Type+Headache%29%29+OR+%28headache+disorders%2C+secondary%29%29+OR+%28cervicogenic+headache%29%29+OR+%28cervical%29%29+AND+%28%28%28%28%28Botulinum+Toxins%29+OR+%28botulinum%29%29+OR+%28botulinum+toxin%29%29+OR+%28toxin%29%29+OR+%28toxins%29%29%29+AND+%28%28%28%28%28%28%28reduced+headache%29+OR+%28headache%29%29+OR+%28reduced+headache+severity%29%29+OR+%28severity%29%29+OR+%28pain+relief%29%29+OR+%28reduced+headache+days%29%29+OR+%28headache+free+days%29%29&filter=pubt.clinicaltrial&filter=pubt.randomizedcontrolledtrial&filter=hum_ani.humans&sort=relevance) | 15:23:32 |
| #26 | Search: ((((((tension headache) OR (Tension-Type Headache)) OR (headache disorders, secondary)) OR (cervicogenic headache)) OR (cervical)) AND (((((Botulinum Toxins) OR (botulinum)) OR (botulinum toxin)) OR (toxin)) OR (toxins))) AND (((((((reduced headache) OR (headache)) OR (reduced headache severity)) OR (severity)) OR (pain relief)) OR (reduced headache days)) OR (headache free days)) Filters: Clinical Trial, Randomized Controlled Trial | [152](https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28%28tension+headache%29+OR+%28Tension-Type+Headache%29%29+OR+%28headache+disorders%2C+secondary%29%29+OR+%28cervicogenic+headache%29%29+OR+%28cervical%29%29+AND+%28%28%28%28%28Botulinum+Toxins%29+OR+%28botulinum%29%29+OR+%28botulinum+toxin%29%29+OR+%28toxin%29%29+OR+%28toxins%29%29%29+AND+%28%28%28%28%28%28%28reduced+headache%29+OR+%28headache%29%29+OR+%28reduced+headache+severity%29%29+OR+%28severity%29%29+OR+%28pain+relief%29%29+OR+%28reduced+headache+days%29%29+OR+%28headache+free+days%29%29&filter=pubt.clinicaltrial&filter=pubt.randomizedcontrolledtrial&sort=relevance) | 15:22:53 |
| #25 | Search: ((((((tension headache) OR (Tension-Type Headache)) OR (headache disorders, secondary)) OR (cervicogenic headache)) OR (cervical)) AND (((((Botulinum Toxins) OR (botulinum)) OR (botulinum toxin)) OR (toxin)) OR (toxins))) AND (((((((reduced headache) OR (headache)) OR (reduced headache severity)) OR (severity)) OR (pain relief)) OR (reduced headache days)) OR (headache free days)) Filters: Clinical Trial | [152](https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28%28tension+headache%29+OR+%28Tension-Type+Headache%29%29+OR+%28headache+disorders%2C+secondary%29%29+OR+%28cervicogenic+headache%29%29+OR+%28cervical%29%29+AND+%28%28%28%28%28Botulinum+Toxins%29+OR+%28botulinum%29%29+OR+%28botulinum+toxin%29%29+OR+%28toxin%29%29+OR+%28toxins%29%29%29+AND+%28%28%28%28%28%28%28reduced+headache%29+OR+%28headache%29%29+OR+%28reduced+headache+severity%29%29+OR+%28severity%29%29+OR+%28pain+relief%29%29+OR+%28reduced+headache+days%29%29+OR+%28headache+free+days%29%29&filter=pubt.clinicaltrial&sort=relevance) | 15:22:23 |
| #24 | Search: ((((((tension headache) OR (Tension-Type Headache)) OR (headache disorders, secondary)) OR (cervicogenic headache)) OR (cervical)) AND (((((Botulinum Toxins) OR (botulinum)) OR (botulinum toxin)) OR (toxin)) OR (toxins))) AND (((((((reduced headache) OR (headache)) OR (reduced headache severity)) OR (severity)) OR (pain relief)) OR (reduced headache days)) OR (headache free days)) | [877](https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28%28tension+headache%29+OR+%28Tension-Type+Headache%29%29+OR+%28headache+disorders%2C+secondary%29%29+OR+%28cervicogenic+headache%29%29+OR+%28cervical%29%29+AND+%28%28%28%28%28Botulinum+Toxins%29+OR+%28botulinum%29%29+OR+%28botulinum+toxin%29%29+OR+%28toxin%29%29+OR+%28toxins%29%29%29+AND+%28%28%28%28%28%28%28reduced+headache%29+OR+%28headache%29%29+OR+%28reduced+headache+severity%29%29+OR+%28severity%29%29+OR+%28pain+relief%29%29+OR+%28reduced+headache+days%29%29+OR+%28headache+free+days%29%29&sort=) | 15:21:38 |
| #23 | Search: (((((tension headache) OR (Tension-Type Headache)) OR (headache disorders, secondary)) OR (cervicogenic headache)) OR (cervical)) AND (((((Botulinum Toxins) OR (botulinum)) OR (botulinum toxin)) OR (toxin)) OR (toxins)) | [4,234](https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28tension+headache%29+OR+%28Tension-Type+Headache%29%29+OR+%28headache+disorders%2C+secondary%29%29+OR+%28cervicogenic+headache%29%29+OR+%28cervical%29%29+AND+%28%28%28%28%28Botulinum+Toxins%29+OR+%28botulinum%29%29+OR+%28botulinum+toxin%29%29+OR+%28toxin%29%29+OR+%28toxins%29%29&sort=) | 15:19:11 |
| #22 | Search: ((((((reduced headache) OR (headache)) OR (reduced headache severity)) OR (severity)) OR (pain relief)) OR (reduced headache days)) OR (headache free days) | [1,695,968](https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28%28%28reduced+headache%29+OR+%28headache%29%29+OR+%28reduced+headache+severity%29%29+OR+%28severity%29%29+OR+%28pain+relief%29%29+OR+%28reduced+headache+days%29%29+OR+%28headache+free+days%29&sort=) | 15:18:49 |
| #21 | Search: ((((Botulinum Toxins) OR (botulinum)) OR (botulinum toxin)) OR (toxin)) OR (toxins) | [380,909](https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28Botulinum+Toxins%29+OR+%28botulinum%29%29+OR+%28botulinum+toxin%29%29+OR+%28toxin%29%29+OR+%28toxins%29&sort=) | 15:18:11 |
| #20 | Search: ((((tension headache) OR (Tension-Type Headache)) OR (headache disorders, secondary)) OR (cervicogenic headache)) OR (cervical) | [597,996](https://pubmed.ncbi.nlm.nih.gov/?term=%28%28%28%28tension+headache%29+OR+%28Tension-Type+Headache%29%29+OR+%28headache+disorders%2C+secondary%29%29+OR+%28cervicogenic+headache%29%29+OR+%28cervical%29&sort=) | 15:13:15 |
| #19 | Search: headache free days | [722](https://pubmed.ncbi.nlm.nih.gov/?term=headache+free+days&sort=relevance) | 15:12:11 |
| #18 | Search: reduced headache days | [1,720](https://pubmed.ncbi.nlm.nih.gov/?term=reduced+headache+days&sort=relevance) | 15:11:55 |
| #17 | Search: pain relief | [49,818](https://pubmed.ncbi.nlm.nih.gov/?term=pain+relief&sort=relevance) | 15:11:40 |
| #16 | Search: severity | [1,575,005](https://pubmed.ncbi.nlm.nih.gov/?term=severity&sort=relevance) | 15:11:29 |
| #15 | Search: reduced headache severity | [2,522](https://pubmed.ncbi.nlm.nih.gov/?term=reduced+headache+severity&sort=relevance) | 15:11:16 |
| #14 | Search: headache | [101,001](https://pubmed.ncbi.nlm.nih.gov/?term=headache&sort=relevance) | 15:10:54 |
| #13 | Search: reduced headache | [9,164](https://pubmed.ncbi.nlm.nih.gov/?term=reduced+headache&sort=relevance) | 15:10:21 |
| #12 | Search: toxins | [378,928](https://pubmed.ncbi.nlm.nih.gov/?term=toxins&sort=relevance) | 15:09:42 |
| #9 | Search: toxin | [378,928](https://pubmed.ncbi.nlm.nih.gov/?term=toxin&sort=relevance) | 15:07:27 |
| #8 | Search: botulinum toxin | [21,777](https://pubmed.ncbi.nlm.nih.gov/?term=botulinum+toxin&sort=relevance) | 15:07:17 |
| #7 | Search: botulinum | [23,789](https://pubmed.ncbi.nlm.nih.gov/?term=botulinum&sort=relevance) | 15:06:57 |
| #6 | Search: Botulinum Toxins | [17,180](https://pubmed.ncbi.nlm.nih.gov/?term=Botulinum+Toxins&sort=relevance) | 15:06:43 |
| #5 | Search: cervical | [589,132](https://pubmed.ncbi.nlm.nih.gov/?term=cervical&sort=relevance) | 15:06:31 |
| #4 | Search: cervicogenic headache | [1,454](https://pubmed.ncbi.nlm.nih.gov/?term=cervicogenic+headache&sort=relevance) | 15:06:19 |
| #3 | Search: headache disorders, secondary | [4,752](https://pubmed.ncbi.nlm.nih.gov/?term=headache+disorders%2C+secondary&sort=relevance) | 15:06:06 |
| #2 | Search: Tension-Type Headache | [3,906](https://pubmed.ncbi.nlm.nih.gov/?term=Tension-Type+Headache&sort=relevance) | 15:05:54 |
| #1 | Search: tension headache | [5,027](https://pubmed.ncbi.nlm.nih.gov/?term=tension+headache&sort=relevance) | 15:05:42 |

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