NKR52_Meniere_PICO 4_Betahistin

Characteristics of studies

Characteristics of included studies

Adrion 2016

Methods	**Study design:** Randomized controlled trial **Study grouping:** Parallel group
Participants	**Baseline Characteristics** Intervention 1 ● *Age*: 56.1 ● *Boys %*: 53 Intervention 2 ● *Age*: 56.1 ● *Boys %*: 47 Control ● *Age*: 54.4 ● *Boys %*: 47 Overall ● *Age*: ● *Boys %*: **Included criteria:** Patients aged 18-80 years were eligible for enrolment if they presented with two or more definitive spontaneous episodes of vertigo of at least 20 minutes' duration, had audiometrically documented hearing loss on at least one occasion, and tinnitus or aural full-ness in the treated ear, excluding other possible causes of vertigo. These factors made up a diagnosis of definite unilateral or bilateral Meniere's disease, fulfilling the criteria of the 1995 American Academy of Otolaryngolo-gy-Head and Neck Surgery (AAO-HNS) guideline.39 Fur-thermore, patients had to be in an active phase of the disease, with at least two vertigo attacks per month in at least three consecutive months before enrolment. Female patients of childbearing potential were only included if they had a negative serum pregnancy test within seven days before initiation of treatment and were willing to practice acceptable methods of birth control during treatment and for three months after treatment. **Excluded criteria:** Exclusion criteria were diagnosis of other central or peripheral vestibular disorders such as vestibular migraine, benign paroxysmal positioning vertigo, par-oxysmal brainstem attacks, as well as phobic postural vertigo. Patients were excluded if they had known con-traindications or sensitivity to betahistine, such as bronchial asthma, pheochromocytoma, treatment with other antihistaminic drugs, ulcer of the stomach or duo-dendum, or severe dysfunction of liver or kidney. Safety related exclusion criteria were severe coronary heart disease or heart failure, persistent uncontrolled hyper-tension with systolic blood pressure higher than 180 mm Hg or diastolic blood pressure higher than 110 mm Hg, life expectancy less than 12 months, other serious illness, or a complex disease that might confound treat-ment assessment. General exclusion criteria were participation in another trial with an investigational drug or device within the past 30 days, previous partic-ipation in the present study, or planned participation in another trial. We excluded pregnant and breastfeeding women and women contemplating pregnancy during the trial from enrolment. **Pretreatment:** No apparent differences at baseline
Interventions	**Intervention Characteristics** Intervention 1 ● *Description*: 24 mg betahistine x 2 ● *Length of treatment*: 9 months ● *Longest follow-up after end of treatment*: 0 Intervention 2 ● *Description*: 48 mg betahistine x 3 ● *Length of treatment*: 9 months ● *Longest follow-up after end of treatment*: 0 Control ● *Description*: placebo tables (mannitol and aerosol) ● *Length of treatment*: 9 months ● *Longest follow-up after end of treatment*: 0
Outcomes	*Anfaldshyppighed, CI* ● **Outcome type**: ContinuousOutcome *Alvorlige bivirkninger, n* ● **Outcome type**: DichotomousOutcome *Sværhedsgraden af tinnitus, CI* ● **Outcome type**: ContinuousOutcome *Livskvalitet, CI* ● **Outcome type**: ContinuousOutcome *Activities of daily life (DHI), CI* ● **Outcome type**: ContinuousOutcome *Tone audometri, 250Hz CI* ● **Outcome type**: ContinuousOutcome

	Tone audometri, 500Hz ● **Outcome type**: ContinuousOutcome *Tone audometri 1000Hz* ● **Outcome type**: ContinuousOutcome *Tone audometri, 2000Hz* ● **Outcome type**: ContinuousOutcome
Identification	**Sponsorship source:** Funding: This study was not industry sponsored. The study was supported by grants from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung (BMBF), support code 01KG0708; sponsor's protocol code no 04T-617). This work was supported by the German Centre for Vertigo and Balance Disorders (DSGZ), University Hospital Munich, Campus Grosshadern, Munich, Germany. The funder had no role in the design, management, data collection, analyses, or interpretation of the data or in the writing of the manuscript or the decision to submit for publication **Country:** Germany **Setting:** Multicentre study, 14 German university hospitals. **Comments:** EudraCT no 2005-000752-32; ISRCTN no ISRCTN44359668 **Authors name:** Christine Adrion **Institution:** German Center for Vertigo and Balance Disorders, University Hospital Munich, Campus Grosshadern, Munich, Germany **Email:** Correspondence to: M Strupp Michael.Strupp@med. uni-muenchen.de **Address:** German Center for Vertigo and Balance Disorders, University Hospital Munich, Campus Grosshadern, Munich, Germany
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The concealed allocation was performed by an internet based rando- misation schedule (https://wwwapp.ibe.med.uni- muenchen.de/randoulette), stratified by study site. The"
Allocation concealment (selection bias)	Low risk	Quote: "Each site received a pool of study medication kits including the treatment assignment in a sealed opaque emergency envelope. If"
Blinding of participants and personnel (performance bias)	Low risk	Quote: "Patients, clinicians, core labo- ratories, and trial staff (data analysts, statisticians) were blind to treatment allocation."
Blinding of outcome assessment (detection bias)	Low risk	Quote: "trial. Patients, clinicians, core labo- ratories, and trial staff (data analysts, statisticians) were blind to treatment allocation."
Incomplete outcome data (attrition bias)	Low risk	Judgement Comment: No apparent sources of bias
Selective reporting (reporting bias)	Low risk	Judgement Comment: No apperent sources of bias
Other bias	Low risk	Judgement Comment: No apperent sources of bias

Footnotes

Characteristics of excluded studies

Albu 2015

Reason for exclusion	Wrong intervention

Albu 2016

Reason for exclusion	Test of a combination of treatments

Gananca 2009

Reason for exclusion	Wrong comparator

Kitahara 2016

Reason for exclusion	Wrong intervention

Lezius 2011

Reason for exclusion	Wrong study design

Monzani 2012

Reason for exclusion	Wrong study design

Scholtz 2017

Reason for exclusion	Not full article

Sokolova 2014

Reason for exclusion	Test of a combination of treatments

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

Additional tables

References to studies

Included studies

Adrion 2016

Adrion, Christine; Fischer, Carolin Simone; Wagner, Judith; Gurkov, Robert; Mansmann, Ulrich; Strupp, Michael; BEMED, Study Group. Efficacy and safety of betahistine treatment in patients with Meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial). BMJ (Clinical research ed.) 2016;352(Journal Article):h6816. [DOI: https://dx.doi.org/10.1136/bmj.h6816]

Excluded studies

Albu 2015

Albu, Silviu; Chirtes, Felician; Trombitas, Veronica; Nagy, Alina; Marceanu, Luigi; Babighian, Gregorio; Trabalzini, Franco. Intratympanic dexamethasone versus high dosage of betahistine in the treatment of intractable unilateral Meniere disease. American Journal of Otolaryngology 2015;36(2):205-9. [DOI: https://dx.doi.org/10.1016/j.amjoto.2014.10.032]

Albu 2016

Albu, Silviu; Nagy, Alina; Doros, Caius; Marceanu, Luigi; Cozma, Sebastian; Musat, Gabriela; Trabalzini, Franco. Treatment of Meniere's disease with intratympanic dexamethazone plus high dosage of betahistine. American Journal of Otolaryngology 2016;37(3):225-30. [DOI: https://dx.doi.org/10.1016/j.amjoto.2015.12.007]

Gananca 2009

Gananca, Mauricio Malavasi; Caovilla, Heloisa Helena; Gananca, Fernando Freitas. Comparable efficacy and tolerability between twice daily and three times daily betahistine for Meniere's disease. Acta Oto-Laryngologica 2009;129(5):487-92. [DOI: https://dx.doi.org/10.1080/00016480802273082]

Kitahara 2016

Kitahara, Tadashi; Okamoto, Hidehiko; Fukushima, Munehisa; Sakagami, Masaharu; Ito, Taeko; Yamashita, Akinori; Ota, Ichiro; Yamanaka, Toshiaki. A Two-Year Randomized Trial of Interventions to Decrease Stress Hormone Vasopressin Production in Patients with Meniere's Disease-A Pilot Study. PloS one 2016;11(6):e0158309. [DOI: https://dx.doi.org/10.1371/journal.pone.0158309]

Lezius 2011

Lezius, Franziska; Adrion, Christine; Mansmann, Ulrich; Jahn, Klaus; Strupp, Michael. High-dosage betahistine dihydrochloride between 288 and 480 mg/day in patients with severe Meniere's disease: a case series. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 2011;268(8):1237-1240. [DOI: https://dx.doi.org/10.1007/s00405-011-1647-2]

Monzani 2012

Monzani, D.; Barillari, M. R.; Alicandri Ciufelli, M.; Aggazzotti Cavazza, E.; Neri, V.; Presutti, L.; Genovese, E.. Effect of a fixed combination of nimodipine and betahistine versus betahistine as monotherapy in the long-term treatment of Meniere's disease: a 10-year experience. Acta Otorhinolaryngologica Italica : Organo Ufficiale Della Societa Italiana di Otorinolaringologia e Chirurgia Cervico-Facciale 2012;32(6):393-403. [DOI:]

Scholtz 2017

Scholtz A.W.; Hahn A.; Pritschow B.W.; Weisshaar G.; Medzhidieva D.. Cinnarizine + dimenhydrinate versus betahistine for vertigo. Otolaryngology - Head and Neck Surgery (United States) 2017;157(1):P237. [DOI: http://dx.doi.org/10.1177/0194599817717250]

Sokolova 2014

Sokolova, Larysa; Hoerr, Robert; Mishchenko, Tamara. Treatment of Vertigo: A Randomized, Double-Blind Trial Comparing Efficacy and Safety of Ginkgo biloba Extract EGb 761 and Betahistine. International journal of otolaryngology 2014;2014(Journal Article):682439. [DOI: https://dx.doi.org/10.1155/2014/682439]

Studies awaiting classification

Ongoing studies

Other references

Additional references

Other published versions of this review

Classification pending references

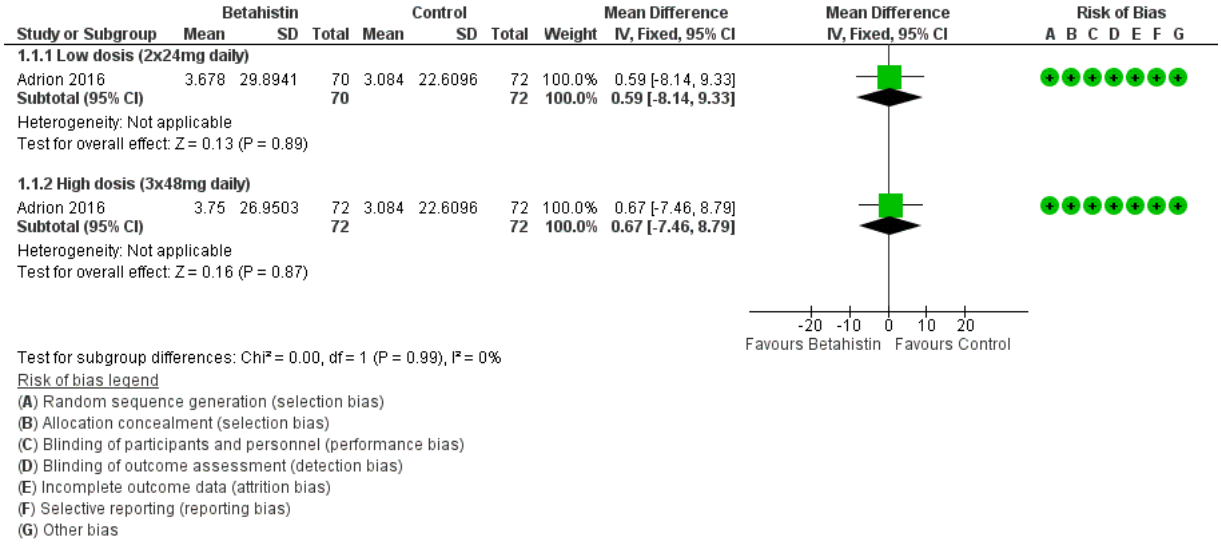
Data and analyses

1 Betahistin vs Control

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Anfaldshyppighed (mean attacks per month) 9 months after starting treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Low dosis (2x24mg daily)	1	142	Mean Difference (IV, Fixed, 95% CI)	0.59 [-8.14, 9.33]
1.1.2 High dosis (3x48mg daily)	1	144	Mean Difference (IV, Fixed, 95% CI)	0.67 [-7.46, 8.79]
1.2 Sværhedsgraden af Tinnitus (dB) 9 months after starting treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Low dosis (2x24mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	1.40 [-5.10, 7.90]
1.2.2 High dosis (3x48mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	-3.34 [-9.74, 3.06]
1.3 Livskvalitet (VDADL, total score) 9 months after starting treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 Low dosis (2x24mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.32, 0.22]
1.3.2 High dosis (3x48mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.33, 0.20]
1.4 Activities of daily life (DHI, total score) 9 months after starting treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 Low dosis (2x24mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.16, 0.33]
1.4.2 High dosis (3x48mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.27, 0.22]
1.5 Tone audometri, 250Hz (hearing loss dB). 9 months after starting treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.5.1 Low dosis (2x24mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	0.33 [-3.13, 3.79]
1.5.2 High dosis (3x48mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	-0.21 [-3.86, 3.43]
1.6 Tone audometri, 500Hz (hearing loss dB). 9 months after starting treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 Low dosis (2x24mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	1.99 [-2.64, 6.62]
1.6.2 High dosis (3x48mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	-0.08 [-4.51, 4.35]
1.7 Tone audometri, 1000Hz (hearing loss dB). 9 months after starting treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.7.1 Low dosis (2x24mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	2.83 [-1.93, 7.59]
1.7.2 High dosis (3x48mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	1.15 [-3.27, 5.56]
1.8 Tone audometri, 2000Hz (hearing loss dB). 9 months after starting treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.8.1 Low dosis (2x24mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	1.67 [-2.41, 5.74]
1.8.2 High dosis (3x48mg daily)	1		Mean Difference (IV, Fixed, 95% CI)	-0.68 [-4.75, 3.39]
1.9 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9.1 Low dosis (2x24mg daily)	1	146	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.53, 2.38]
1.9.2 High dosis (3x48mg daily)	1	146	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.42, 2.06]

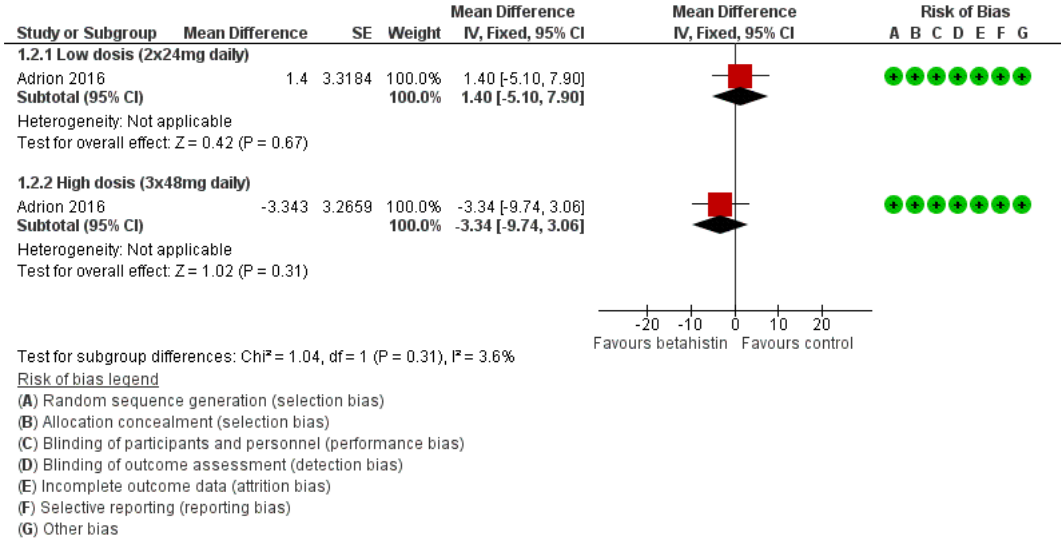
Figures

Figure 1 (Analysis 1.1)



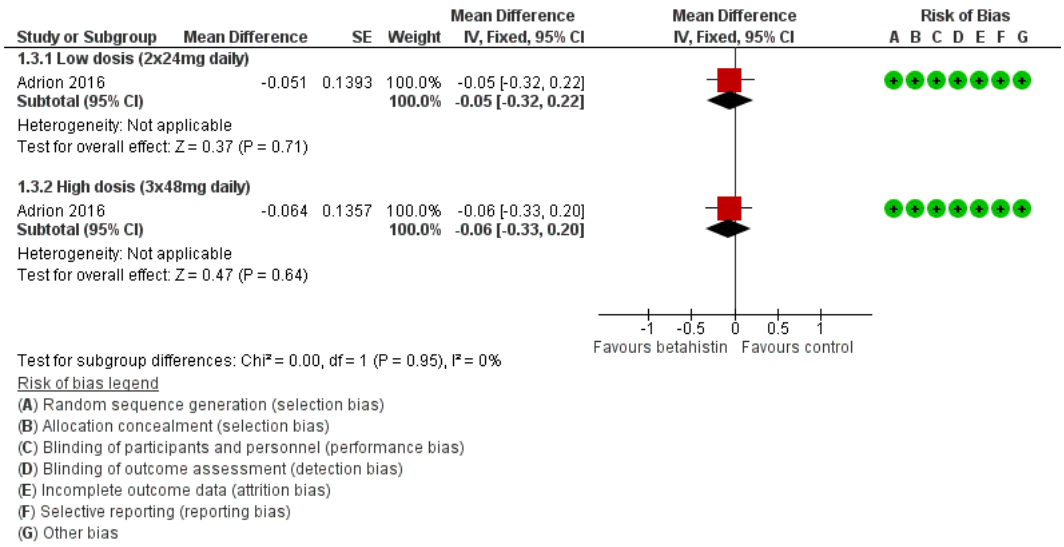
Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.1 Anfaldshyppighed (mean attacks per month) 9 months after starting treatment.

Figure 2 (Analysis 1.2)



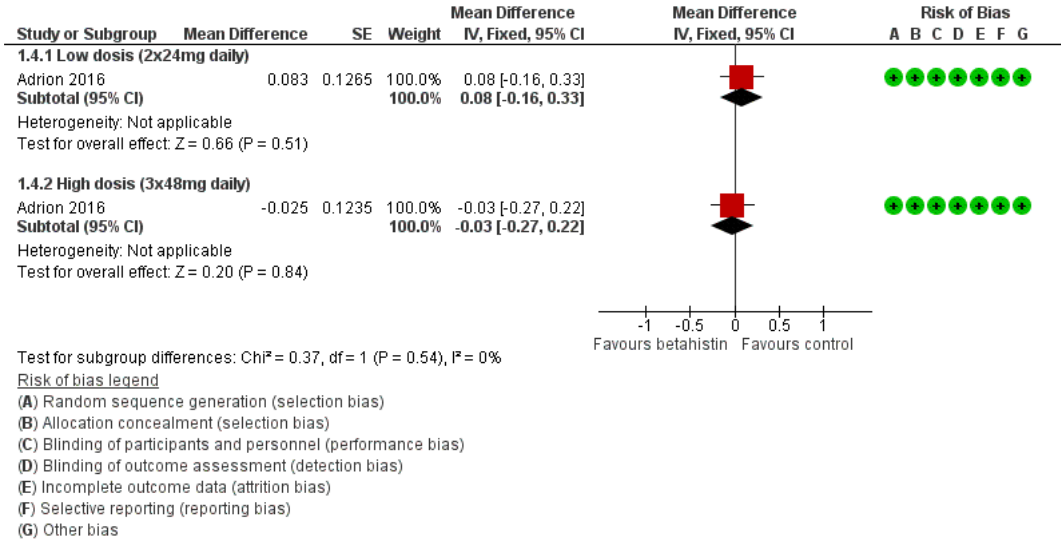
Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.2 Sværhedsgraden af Tinnitus (dB) 9 months after starting treatment.

Figure 3 (Analysis 1.3)



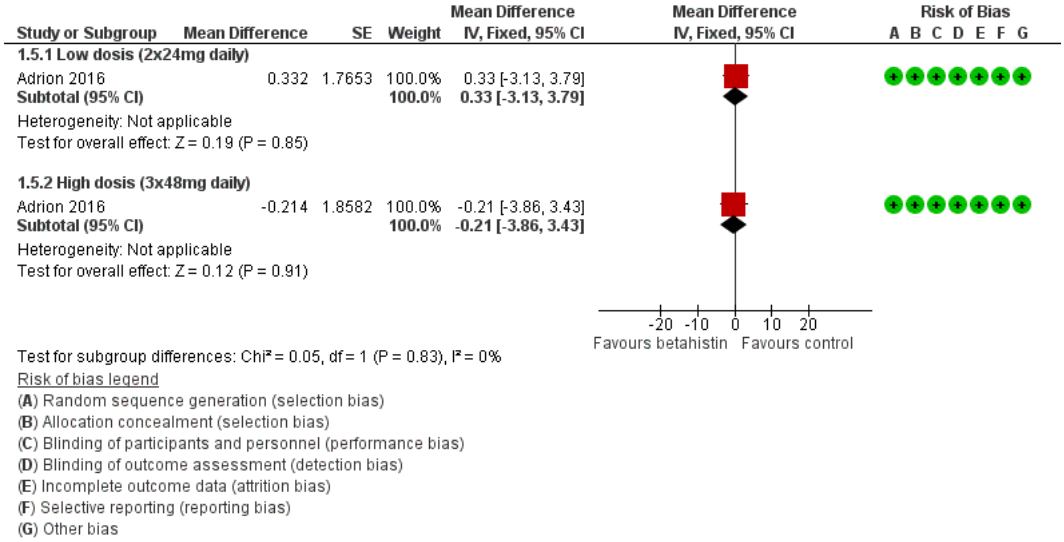
Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.3 Livskvalitet (VDADL, total score) 9 months after starting treatment.

Figure 4 (Analysis 1.4)



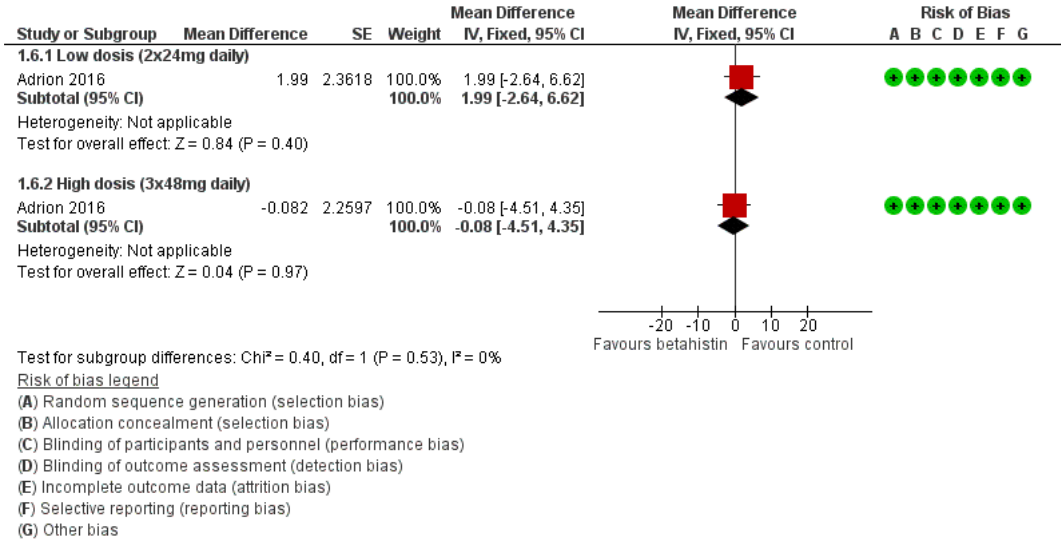
Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.4 Activities of daily life (DHI, total score) 9 months after starting treatment.

Figure 5 (Analysis 1.5)



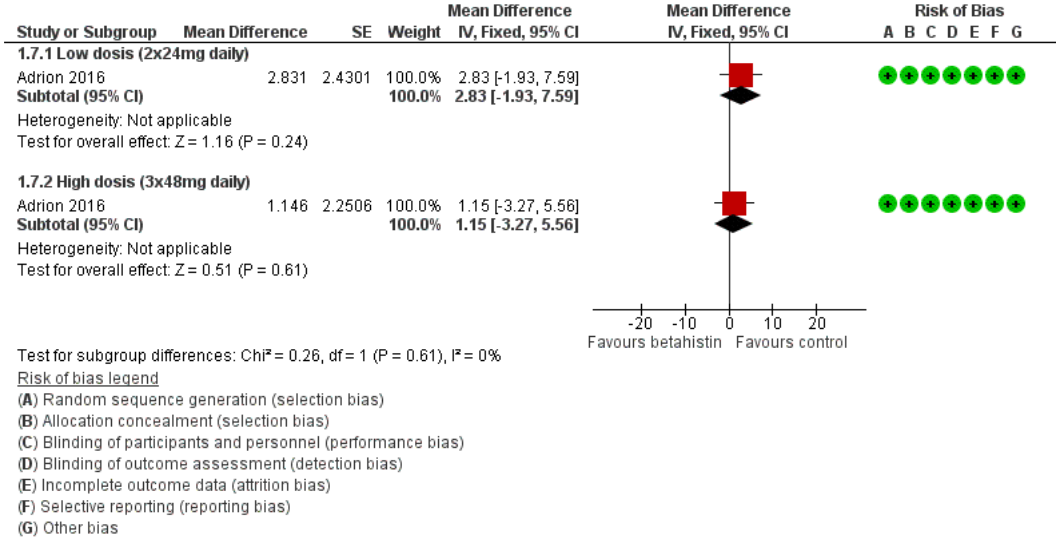
Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.5 Tone audometri, 250Hz (hearing loss dB). 9 months after starting treatment.

Figure 6 (Analysis 1.6)



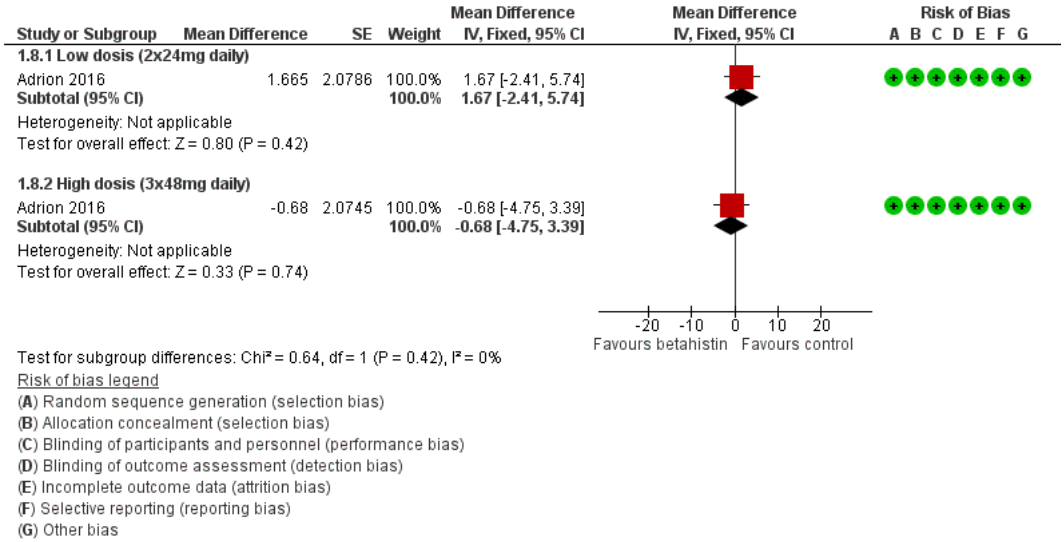
Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.6 Tone audometri, 500Hz (hearing loss dB). 9 months after starting treatment.

Figure 7 (Analysis 1.7)



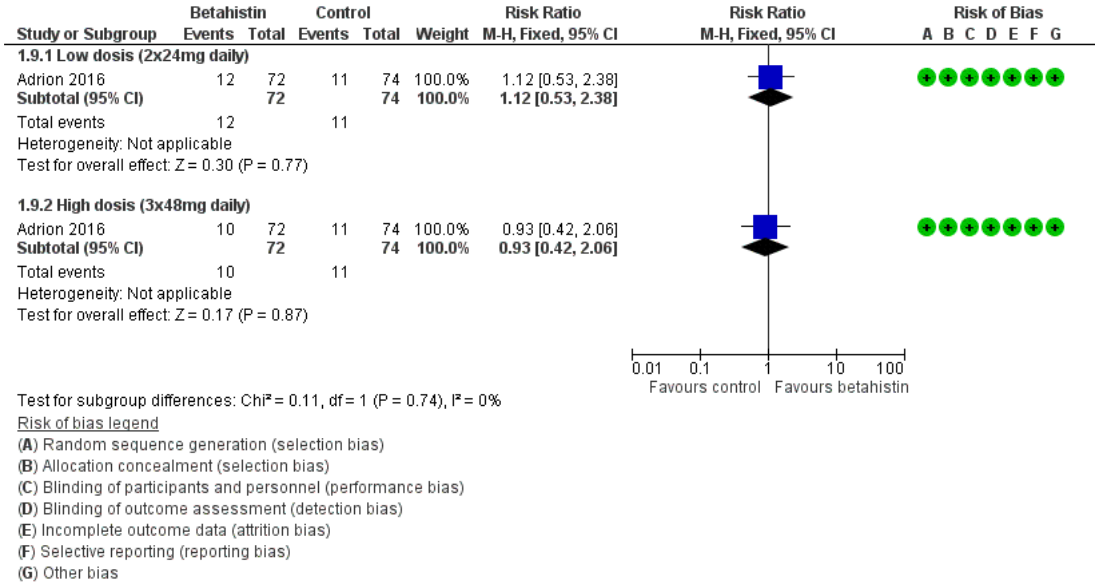
Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.7 Tone audometri, 1000Hz (hearing loss dB). 9 months after starting treatment.

Figure 8 (Analysis 1.8)



Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.8 Tone audometri, 2000Hz (hearing loss dB). 9 months after starting treatment.

Figure 9 (Analysis 1.9)



Forest plot of comparison: 1 Betahistin vs Control, outcome: 1.9 Serious adverse events.