

## Cerebrolysin for acute ischaemic stroke

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### Abstract

© 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Background: Cerebrolysin is a mixture of low-molecular-weight peptides and amino acids derived from pigs' brain tissue, which has potential neuroprotective and neurotrophic properties. It is widely used in the treatment of acute ischaemic stroke in Russia, Eastern Europe, China, and other Asian and post-Soviet countries. Objectives: To assess the benefits and risks of cerebrolysin for treating acute ischaemic stroke. Search methods: In May 2016 we searched the Cochrane Stroke Group Trials Register, CENTRAL, MEDLINE, Embase, Web of Science Core Collection, with Science Citation Index, LILACS, OpenGrey, and a number of Russian Databases. We also searched reference lists, ongoing trials registers and conference proceedings, and contacted the manufacturer of cerebrolysin, EVER Neuro Pharma GmbH (formerly Ebewe Pharma). Selection criteria: Randomised controlled trials (RCTs) comparing cerebrolysin, started within 48 hours of stroke onset and continued for any time, with placebo or no treatment in people with acute ischaemic stroke. Data collection and analysis: Two review authors independently applied inclusion criteria, assessed trial quality and risk of bias, and extracted data. Main results: We identified six RCTs (1501 participants) that met the inclusion criteria. We evaluated risk of bias and judged it to be unclear for generation of allocation sequence in four studies and low in two studies; unclear for allocation concealment in five studies and low in one study; high for incomplete outcome data (attrition bias) in five studies and unclear in one study; unclear for blinding; high for selective reporting in four studies and unclear in two; and high for other sources of bias in three studies and unclear in the rest. The manufacturer of cerebrolysin, pharmaceutical company EVER Neuro Pharma, supported three multi-centre studies, either totally, or providing cerebrolysin and placebo, randomisation codes, research grants, or statisticians. None of the included trials reported on poor functional outcome defined as death or dependence at the end of the follow-up period or early death (within two weeks of stroke onset). All-cause death: we extracted data from five trials (1417 participants). There was no difference in the number of deaths: 46/714 in cerebrolysin group versus 47/703 in placebo group; risk ratio (RR) 0.91 95% confidence interval (CI) 0.61 to 1.35 (5 trials, 1417 participants, moderate-quality evidence). Serious adverse events (SAEs): there was no significant difference in the total number of SAEs with cerebrolysin (RR 1.16, 95% CI 0.81 to 1.67). This comprised no difference in fatal SAEs (RR 0.90, 95% CI 0.59 to 1.38) and an increase in the number of people with non-fatal SAEs (20/667 with cerebrolysin and 8/668 with placebo: RR 2.47, 95% CI 1.09 to 5.58,  $P = 0.03$ ) (3 trials, 1335 participants, moderate-quality evidence). Total number of people with adverse events: three trials reported on this. There was no difference in the total number of people with adverse events: 308/667 in cerebrolysin group versus 307/668 in placebo group; RR 0.97 95% CI 0.86 to 1.09, random-effects model (3 trials, 1335 participants, moderate-quality evidence). Authors' conclusions: The findings of this Cochrane Review do not demonstrate clinical benefits of cerebrolysin for treating acute ischaemic stroke. We found moderate-quality

evidence of an increase in non-fatal SAEs with cerebrolysin use but not in total SAEs.

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## References

- [1] Amiri-Nikpour MR, Nazarbaghi S, Ahmadi-Salmasi B, Mokari T, Tahamtan U, Rezaei Y. Cerebrolysin effects on neurological outcomes and cerebral blood flow in acute ischemic stroke. *Neuropsychiatric Disease and Treatment* 2014;10:2299-306. 4479442
- [2] Bornstein NM. CASTA - the background for the study and protocol design. *International Journal of Stroke* 2010;5(Suppl 2):50. 2799412
- [3] Brainin M, Heiss WD, Bornstein N, Tuomilehto J, Hong Z. CASTA - results of a double-blind, placebo-controlled, randomized trial with cerebrolysin on patients with acute ischaemic stroke in Asia. *Cerebrovascular Diseases* 2012;33(Suppl 2):459-60. 4479443
- [4] Heiss WD, Brainin M, Bornstein N, Zhen H. Cerebrolysin in patients with acute ischemic stroke - the CASTA study. *International Journal of Stroke* 2010;5(Suppl 2):71. 4479444
- [5] Heiss WD, Brainin M, Bornstein NM, Tuomilehto J, Hong Z, Cerebrolysin Acute Stroke Treatment in Asia (CASTA) Investigators. Cerebrolysin in patients with acute ischemic stroke in Asia: results of a double-blind, placebo-controlled randomized trial. *Stroke* 2012;43(3):630-6. 2799415
- [6] Hong Z, Moessler H, Bornstein N, Brainin M, Heiss W-D, CASTA Investigators. A double-blind, placebo-controlled, randomized trial to evaluate the safety and efficacy of cerebrolysin in patients with acute ischaemic stroke in Asia - CASTA. *International Journal of Stroke* 2009;4(5):406-12. 4479445
- [7] Zhen H. The safety and efficacy of cerebrolysin in patients with acute ischemic stroke (CASTA). [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) 2014. 4479446
- [8] Lang W, Stadler CH, Poljakovic Z, Fleet D, Lyse Study Group. A prospective, randomized, placebo-controlled, double-blind trial about safety and efficacy combined treatment with alteplase (rt-PA) and cerebrolysin in acute ischaemic hemispheric stroke. *International Journal of Stroke* 2012;8(2):95-104. 4479447
- [9] Windisch M, Lang W. Combined treatment with alteplase (rt-PA) and cerebrolysin in acute ischemic hemispheric stroke (CERE-LYSE-1). [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) 2014. 4479448
- [10] Ladurner G. Neuroprotection in acute ischaemic stroke. *Stroke* 2001 2001;32:323. 4479450
- [11] Ladurner G, Gmeinbauer R, Moessler H. Cerebrolysin in acute ischaemic stroke: a randomized, placebo-controlled trial with a neuroprotective agent. *Cerebrovascular Diseases* 2001;11(4):75. 2799404
- [12] Ladurner G, Kalvach P, Moessler H, Cerebrolysin Study Group. Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial. *Journal of Neural Transmission* 2005;112(3):415-28. 4479449
- [13] Skvortsova VI, Shamalov NA, Stakhovskaya LV, Gubsky LV, Tikhonova IV, Smichkov AS. Cerebrolysin in acute ischaemic stroke: results of randomised, double blind, placebo-controlled study. *Cerebrovascular Diseases* 2005;19(Suppl 2):76. 2799458
- [14] Skvortsova VI, Stakhovskaia LV, Gubskii LV, Shamalov NA, Tikhonova IV, Smychkov AS. A randomized, double-blind, placebo-controlled study of Cerebrolysin safety and efficacy in the treatment of acute ischemic stroke. *Zhurnal nevrologii i psikhiiatrii imeni S.S. Korsakova / Ministerstvo zdравookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikhiatrov* 2004;Suppl 11:51-5. 4479451
- [15] Skvortsova VI, Stakhovskaya LV, Gubsky LV, Shamalov NA, Tikhonova IV, Smychkov AS. Evaluation of safety and efficacy of cerebrolysin for treating acute ischaemic stroke [Recept] 2007;5(55):94-8. 4479452
- [16] Xue LX, Zhang T, Zhao YW, Geng Z, Chen JJ, Chen H. Efficacy and safety comparison of DL-3-n-butylphthalide and cerebrolysin: effects on neurological and behavioral outcomes in acute ischemic stroke. *Experimental and Therapeutic Medicine* 2016;11(5):2015-20. 4479454
- [17] Barolin GS, Koppi S, Kapeller E. Old and new aspects of stroke treatment with emphasis on metabolically active medication and rehabilitative outcome. *Eurorehab* 1996;3:135-43. 4479456
- [18] Bavarsad Shahripour R, Shalil Ahmadi A. The efficacy of cerebrolysin in patients with acute ischemic stroke. *Proceedings of the 20th European Stroke Conference*. 2011 May 24-27; Hamburg, Germany 2011. 4479457
- [19] Bayer E. Therapeutic use of a brain hydrolysate. *Medizinische Welt* 1980;31(17):636-7. 4479459
- [20] Belkin AA. Navigation brain stimulation for evaluation of the neuroprotective drug efficiency in patients after ischemic stroke. [ClinicalTrials.gov](http://ClinicalTrials.gov) (accessed 19 July 2016). 4479461
- [21] Belkin AA, Alashev AM. Comprehensive reparative therapy in ischemic stroke complex repair in ischemic stroke - arm. [ClinicalTrials.gov](http://ClinicalTrials.gov) Accessed 19 July 2016. 4479463

- [22] Chang WH, Park CH, Kim DY, Shin YI, Ko MH, Lee A, et al. Cerebrolysin combined with rehabilitation promotes motor recovery in patients with severe motor impairment after stroke. Effects of cerebrolysin on motor recovery in patients with subacute stroke (E-COMPASS). *BMC Neurology* 2016;2(16):31. [DOI: 10.1186/s12883-016-0553-z]4479465
- [23] Cuparnecu B. Efficacy of cerebrolysin in patients with ischaemic stroke of the middle cerebral artery. *Pharmacology and Toxicology* 2001;89 Suppl 1:136. 4479466
- [24] Domzal T, Zaleska B. Cerebrolysin in treatment of acute ischemic stroke. *Neurologia i Neurochirurgia Polska* 1995;29(3):325-31. 4479468
- [25] Kim YH. Effects of cerebrolysin combined with rehabilitation on motor recovery in stroke. [www.strokecenter.org](http://www.strokecenter.org) (accessed 18 July 2016). 4479470
- [26] Ershov VI. Comparative aspects of using neuroprotectors in the management of patients with ischemic stroke. *Zhurnal Nevrologii I Psikhiatrii Imeni S.S. Korsakova* 2011;111(8 Pt 2):41-4. 4479471
- [27] Ershov VI. Comparative characteristics of efficacy of neuroprotectors for treating ischaemic stroke. *Nevrologicheskyy Vestnik. Zhurnal im. VM Bekhtereva* 2009;41(3):65-9. 4479472
- [28] Guekht A, Heiss WD, Bajenaru OA, Popescu C, Gusev E, Vester JC, et al. Cerebrolysin and recovery after stroke (CARS): a meta-analysis of two randomized, controlled, double-blind trials assessing the combination of Cerebrolysin and standardized rehabilitation on motor recovery. *European Journal of Neurology* 2015;22:598. 4479474
- [29] Guekht A, Heiss D, Gusev E, Vester J, Doppler E, Muresanu D. Cerebrolysin and recovery after stroke (CARS 2): a randomized, placebo-controlled, double-blind, multicenter clinical study. *Journal of the Neurological Sciences* 2015;357:e103. 4479476
- [30] Haffner Z, Gmeinbauer R, Moessler H. A randomized, double-blind, placebo-controlled trial with cerebrolysin in acute ischaemic stroke. *Cerebrovascular Diseases* 2001;11 Suppl 4:76. 4479477
- [31] Jianu DC, Muresanu DF, Bajenaru O, Popescu BO, Deme SM, Moessler H, et al. Cerebrolysin adjuvant treatment in Broca's aphasics following first acute ischemic stroke of the left middle cerebral artery. *Journal of Medicine and Life* 2010;3(3):297-307. 2799435
- [32] Jianu DC, Jianu SN, Petrica L, Deme SM, Dan F, Falup Pecurariu C, et al. Cerebrolysin adjuvant treatment in Broca's aphasics following first acute ischemic stroke of the left middle cerebral artery. *International Journal of Stroke* 2015;10:187. 4479479
- [33] Kim YH, Kim DY, Shin YI, Ko MH, Chang WH, Lee AH. Effects of cerebrolysin on motor recovery in patients with subacute stroke. *International Journal of Stroke* 2014;9:107-8. 4479480
- [34] Kim YH, Park CH, Kim DY, Shin YI, Ko MH, Chang WH, et al. Effects of cerebrolysin on motor recovery of stroke patients: a diffusion tensor imaging study. *International Journal of Stroke* 2014;9:49-9. 4479481
- [35] Kim YH, Kim DY, Shin YI, Ko MH, Chang WH, Lee AH. Effects of cerebrolysin on motor recovery in patients with severe stroke motor impairment after stroke. *International Journal of Stroke* 2015;10(Suppl 2):90. 4479483
- [36] Martinez Sanchez BR, Hernandez Hernandez JJ, Franco Del Aguila DI, Gryzbowski Gainza E, Paz Ballesteros WC, Herrera Rojas J, et al. An open label, one arm study to evaluate the efficacy and safety of cerebrolysin in patients with acute severe ischemic stroke in Mexico. *Value in Health* 2015;18(7):A827-8. 4479485
- [37] Muresanu D, Heiss WD, Bajenaru O, Popescu CD, Vester J, Guekht A. Cerebrolysin and recovery after stroke (CARS): a randomized, placebo-controlled, double-blind, multicenter, phase II clinical study. *International Journal of Stroke* 2015;10(Suppl 2):92. 4479487
- [38] Muresanu DF, Heiss WD, Hoemberg V, Bajenaru O, Popescu CD, Vester JC, et al. Cerebrolysin and Recovery After Stroke (CARS): a randomized, placebo-controlled, double-blind, multicenter trial. *Stroke* 2016;47(1):151-9. 4479488
- [39] Pushkarev K, Tsoy R. Neuroprotective therapy for lacunar stroke - which is better Ceraxon or Cerebrolysin?. *European Journal of Neurology* 2015;22:775. 4479490
- [40] Shamalov NA, Stakhovskaya LV, Gubsky LV, Tikhonova IV, Smichkov AS, Skvortsova VI, et al. Effects of the neuroprotective drug cerebrolysin on the infarct volume after acute ischemic stroke. *Cerebrovascular Diseases* 2005;19 Suppl 2:107. 4479491
- [41] Shamalov NA, Stakhovskaia LV, Burenchev DV, Kichuk IV, Tvorogova TV, Botsina AI, et al. The effect of cerebrolysin in dosage 50 ml on the volume of lesion in ischemic stroke. *Zhurnal nevrologii i psikhiatrii imeni S.S. Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikhiatrov* 2010;110(12 Pt 2):34-7. 4479492
- [42] Shishkova V, Zotova LI, Remennik AYU. Association between BDNF-196 G>A and BDNF-270 C>T polymorphisms, BDNF concentration, and cerebrolysin treatment outcome after ischemic stroke. *International Journal of Stroke* 2015;10 Suppl 2:170. 4479494
- [43] Skvortsova VI, Stakhovskaia LV, Shamalov NA, Kerbikov OB. Results of the multicenter prospective study of cerebrolysin safety and efficacy in acute stroke. *Zhurnal Nevrologii I Psikhiatrii Imeni SS Korsakova* 2006;Suppl 16:41-5. 4479495

- [44] Stan AD, Badisor A, Birla C, Blesneag AV, Opincariu I, Iancu M, et al. The influence of neurotrophic factors treatment on stroke volume. *Romanian Journal of Neurology* 2013;XII(3):124-9. 4479496
- [45] Vilenskii BS, Semenova GM, Shirokov EA. The application of cerebrolysin in ischemic stroke. *Zhurnal nevrologii i psikiatrii imeni S.S. Korsakova / Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikiatrov* 1999;99(4):65-9. 4479498
- [46] Yavorskaya VA, Bondar OB. Clinical features of cerebrolysin application in patients in acute period of ischemic stroke. *International Journal of Stroke* 2008;3 Suppl 1:141. 4479499
- [47] Zhu GX, Hong Z, Yao JL, Yu LY. Double-blind and randomized placebo-controlled trial of cerebrolysin in improvement of nerve function and living ability in patients with ischemic stroke. *Chinese Journal of Clinical Rehabilitation* 2003;7(22):3084-5. 4479500
- [48] Dobi D, Xhaxho S, Kapisyzi M, Papadhopulli Z. The effect of cerebrolysin in acute ischemic stroke. *Revue Neurologique* 2010;166(3):355. 4479502
- [49] Hong Z, Zhu G, Chen H. The clinical efficacy of cerebrolysin in the treatment of acute ischemic stroke. *Chinese Journal of Geriatric Heart Brain and Vessel Diseases* 2005;7(5):331-3. 4479503
- [50] IRCT138803272042N1 . The efficacy of cerebrolysin in the treatment of acute ischemic stroke. *Iranian Registry of Clinical Trials* (en.search.irct.ir/view/1090) (accessed 15 December 2014). 2799492
- [51] Nazarbaghi S, Nikpoor MA. Efficiency of cerebrolysin in treatment of patients with acute ischemic stroke. *International Journal of Stroke* 2014;9 Suppl 3:91-2. 4479504
- [52] Jech M, Shamalov NA, Moessler H, Skvortsova VI. Safety and efficacy of cerebrolysin as adjuvant therapy in patients suffering from acute ischemic stroke. *Cerebrovascular Diseases* 2009;27(Suppl 6):84. 4479505
- [53] Skvortsova VI, Shamalov NA, Moessler H, Doppler E. Safety and efficacy of cerebrolysin as adjuvant therapy in patients suffering from acute ischemic stroke. *European Journal of Neurology* 2008;15 Suppl 3:253. 4479506
- [54] Skvortsova VI, Shamalov NA, Moessler H, Novak PH. Beneficial effects of the neurotrophic drug cerebrolysin on the infarct volume after acute stroke. *Cerebrovascular Diseases* 2008;25 Suppl 2:145. 4479507
- [55] Skvortsova VI, Shamalov NA, Moessler H, Novak PH. Positive impacts of the neurotrophic drug cerebrolysin on the infarct volume after acute stroke. *International Journal of Stroke* 2008;3 Suppl 1:137. 4479508
- [56] Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, et al. Heart disease and stroke disease statistics - 2014 update: a report from the American Heart Association. *Circulation* 2014;129(3):e28-e292.
- [57] Alper BS, Malone-Moses M, McLellan JS, Prasad K, Manheimer E. Thrombolysis in acute ischaemic stroke: time for a rethink?. *BMJ* 2015;350:h1075. [DOI: <http://dx.doi.org/10.1136/bmj.h1075>]
- [58] Alvarez XA, Lombardi VR, Corzo L, Pérez P, Pichel V, Laredo M, et al. Oral cerebrolysin enhances brain alpha activity and improves cognitive performance in elderly control subjects. *Journal of Neural Transmission* 2000;59 Suppl:315-28.
- [59] Appelros P, Terént A. Thrombolysis in acute stroke. *Lancet* 2015;385(9976):1394. [DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)60714-0](http://dx.doi.org/10.1016/S0140-6736(15)60714-0)]
- [60] Bajenaru O, Tiu C, Moessler H, Antochi F, Muresanu D, Popescu BO, et al. Efficacy and safety of cerebrolysin in patients with hemorrhagic stroke. *Journal of Medicine and Life* 2010;3(2):137-43.
- [61] Blood pressure in Acute Stroke Collaboration (BASC). Vasoactive drugs for acute stroke. *Cochrane Database of Systematic Reviews* 2000, Issue 4. [DOI: 10.1002/14651858.CD002839]
- [62] Blood pressure in Acute Stroke Collaboration (BASC). Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database of Systematic Reviews* 2001, Issue 3. [DOI: 10.1002/14651858.CD000039]
- [63] Bath PMW, Willmot M, Leonardi-Bee J, Bath-Hextall FJ. Nitric oxide donors (nitrates), L-arginine, or nitric oxide synthase inhibitors for acute stroke. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD000398]
- [64] Bath PMW. Theophylline, aminophylline, caffeine and analogues for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD000211.pub2]
- [65] Bath PMW, Bath-Hextall FJ. Pentoxifylline, propentofylline and pentifylline for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD000162.pub2]
- [66] Bath PMW. Prostacyclin and analogues for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD000177.pub2]
- [67] Bath PMW, Sprigg N, England T. Colony stimulating factors (including erythropoietin, granulocyte colony stimulating factor and analogues) for stroke. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD005207.pub4]
- [68] Bath PMW, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database of Systematic Reviews* 2014, Issue 10. [DOI: 10.1002/14651858.CD000039.pub3]
- [69] Bereczki D, Fekete I, Prado GF, Liu M. Mannitol for acute stroke. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD001153.pub2]

- [70] Bereczki D, Fekete I. Vinpocetine for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD000480.pub2]
- [71] Berge E, Sandercock P. Anticoagulants versus antiplatelet agents for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD003242]
- [72] Boncoraglio GB, Bersano A, Candelise L, Reynolds BA, Paratti EA. Stem cell transplantation for ischemic stroke. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: 10.1002/14651858.CD007231.pub2]
- [73] Bonita R. Epidemiology of stroke. *Lancet* 1992;339(8789):342-4.
- [74] Brunström M, Carlberg B. Thrombolysis in acute stroke. *Lancet* 2015;385(9976):1394-5. [DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)60715-2](http://dx.doi.org/10.1016/S0140-6736(15)60715-2)]
- [75] Candelise L, Ciccone A. Gangliosides for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD000094]
- [76] Chang TS, Jensen MB. Haemodilution for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2014, Issue 8. [DOI: 10.1002/14651858.CD000103.pub2]
- [77] Chen X, Zhou M, Li Q, Yang J, Zhang Y, Zhang D, et al. Sanchi for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD006305.pub2]
- [78] Chen N, Yang M, Guo J, Zhou M, Zhu C, He L. Cerebrolysin for vascular dementia. *Cochrane Database of Systematic Reviews* 2013, Issue 1. [DOI: 10.1002/14651858.CD008900.pub2]
- [79] Chukanova EI. The effect of cerebrolysin on the clinical symptoms and the course of ischemic encephalopathy. *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 2005;105(1):42-5.
- [80] Ciccone A, Motto C, Abraha I, Cozzolino F, Santilli I. Glycoprotein IIb/IIIa inhibitors for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD005208.pub3]
- [81] Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [handbook.cochrane.org](http://handbook.cochrane.org).
- [82] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014;384(9958):1929-35.
- [83] The European Ad Hoc Consensus Group. Neuroprotection as initial therapy in acute stroke. Third report of an Ad Hoc Consensus Group Meeting. *Cerebrovascular Diseases* 1998;8(1):59-72.
- [84] Feng S, Yang Q, Liu M, Li W, Yuan W, Zhang S, et al. Edaravone for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2011, Issue 12. [DOI: 10.1002/14651858.CD007230.pub2]
- [85] Fragoso Y, Dantas DC. Cerebrolysin for Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003801]
- [86] French B, Thomas LH, Leathley MJ, Sutton CJ, McAdam J, Forster A, et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD006073]
- [87] Gafurov BG, Alikulova NA. Clinical and pathogenetical peculiarities and treatment policy in ischemic stroke of elderly and old age [Russian]. *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 2004;104 Suppl 11:44-6.
- [88] Gandolfo C, Sandercock P, Conti M. Lubeluzole for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2002, Issue 1. [DOI: 10.1002/14651858.CD001924]
- [89] Essential Medicines List for 2016. Government of the Russian Federation RASPORIESE 26 December 2015. [government.ru/media/files/MzyVOMmm2FoDAP7AWAAVLLpjoLoiShib.pdf](http://government.ru/media/files/MzyVOMmm2FoDAP7AWAAVLLpjoLoiShib.pdf) (accessed 12 August 2016).
- [90] McMaster University (developed by Evidence Prime, Inc.). Available from [www.gradepr.org](http://www.gradepr.org). GRADEPro Guideline Development Tool. McMaster University (developed by Evidence Prime, Inc.). Available from [www.gradepr.org](http://www.gradepr.org), 2015.
- [91] Gromova OA, Tret'iakov VE, Moshkovski SA, Gusev EI, Nikonov AA, Val'kova LA, et al. An oligopeptide membrane fraction of cerebrolysin. *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 2006;106(7):68-70.
- [92] Gusev EI, Skvortsova VI, Stakhovskaia LV. Epidemiology of stroke in Russia. *Zhurnal Nevrologii i Psikhiatrii Imeni S.S. Korsakova* 2003;Suppl 8:4-9.
- [93] Gusev EI, Martynov MYu, Kamtchatnov PR. Ischemic stroke: current status [Ishemicheskyy insult. Sovremennoye sostoyaniye problemy]. *Nevrologiya* 2013;83(5):2-7.
- [94] Guyatt GH, Oxman AD, Vist G, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-6.
- [95] Hao Z, Liu M, Counsell C, Wardlaw JM, Lin S, Zhao X. Fibrinogen depleting agents for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2012, Issue 3. [DOI: 10.1002/14651858.CD000091.pub2]
- [96] Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.

- [97] Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [handbook.cochrane.org](http://handbook.cochrane.org).
- [98] Hong Z, Moessler H, Bornstein N, Brainin M, Heiss W-D, CASTA Investigators. A double-blind, placebo-controlled, randomized trial to evaluate the safety and efficacy of cerebrolysin in patients with acute ischaemic stroke in Asia - CASTA. *International Journal of Stroke* 2009;4(5):406-12.
- [99] Horn J, Limburg M. Calcium antagonists for acute ischemic stroke. *Cochrane Database of Systematic Reviews* 2000, Issue 1. [DOI: 10.1002/14651858.CD001928]
- [100] ICH Expert Working Group. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. Post-approval safety data management: definitions and standards for expedited reporting E2D. ICH harmonised tripartite guideline, Step 4 version 2003.
- [101] Leonardi-Bee J, Steiner T, Bath-Hextall F. Naftidrofuryl for acute stroke. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD005478.pub2]
- [102] Liu J, Wang LN, Ma X, Ji X. Gamma aminobutyric acid (GABA) receptor agonists for acute stroke. *Cochrane Database of Systematic Reviews* 2016, Issue 10. [DOI: 10.1002/14651858.CD009622.pub4]
- [103] Makarenko AN, Kositsin NS, Nazimov IV, Svinov MM, Goloborod'ko EV, Pasikova NV. A comparative study of antistroke activity of the new drug "cerebral" and its fractions in rats. *Eksperimental'naiia i Klinicheskaia Farmakologija* 2005;68(2):15-20.
- [104] Martynchik SA, Sokolova OV. Medical and economic assessment and rationale for improving organization of inpatient care for cerebral stroke [Medico-economicheskaya otsenka i obosnovaniye sovershenstvovaniya organizatsionnykh form okazaniya stacionarnoy pomoschi pri mozgovom insulte]. *Social Aspects of Population Health* ([vestnik.mednet.ru/content/view/473/30/lang.ru/](http://vestnik.mednet.ru/content/view/473/30/lang.ru/)) 2013; Vol. 30, issue 2.
- [105] Masliah E, Díez-Tejedor E. The pharmacology of neurotrophic treatment with cerebrolysin: brain protection and repair to counteract pathologies of acute and chronic neurological disorders. *Drugs of Today* 2012;48(Suppl A):3-24. [DOI: 10.1358/dot.2012.48(Suppl.A).1739716]
- [106] MedDRA Maintenance and Support Services Organization. *Introductory Guide to MedDRA Version 14.0*. Chantilly, Virginia, March, 2011.
- [107] Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357(9263):1191-4.
- [108] Muir KW, Lees KR. Excitatory amino acid antagonists for acute stroke. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [DOI: 10.1002/14651858.CD001244]
- [109] O'Rourke K, Berge E, Walsh CD, Kelly PJ. Percutaneous vascular interventions for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2010, Issue 10. [DOI: 10.1002/14651858.CD007574.pub2]
- [110] Onishchenko LS, Ga kova ON, Ianishevski SN. Changes in the focus of experimental ischemic stroke under the influence of neuroprotective drugs. *Morfologija* 2006;130(6):40-6.
- [111] Registry of Medicines. Cerebrolysin. [www.rlsnet.ru/tn\\_index\\_id\\_3528.htm#pobochnye-dejstviya](http://www.rlsnet.ru/tn_index_id_3528.htm#pobochnye-dejstviya) (accessed 31 January 2015).
- [112] The Nordic Cochrane Centre, The Cochrane Collaboration. *Review Manager (RevMan). Version 5.3*. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- [113] Ricci S, Celani MG, Cantisani TA, Righetti E. Piracetam for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD000419.pub3]
- [114] Ricci S, Dinia L, Del Sette M, Anzola P, Mazzoli T, Cenciarelli S, et al. Sonothrombolysis for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2012, Issue 10. [DOI: 10.1002/14651858.CD008348.pub3]
- [115] Righetti E, Celani MG, Cantisani T, Sterzi R, Boysen G, Ricci S. Glycerol for acute stroke. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD000096.pub2]
- [116] Riley C, Hutter-Paier B, Windisch M, Doppler E, Moessler H, Wronski R. A peptide preparation protects cells in organotypic brain slices against cell death after glutamate intoxication. *Journal of Neural Transmission* 2006;113(1):103-10.
- [117] Sandercock PAG, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD000024.pub3]
- [118] Sandercock P, Counsell C, Tseng MC. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD000119.pub3]
- [119] Sandercock PAG, Gibson LM, Liu M. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD000248.pub2]
- [120] Sandercock PAG, Soane T. Corticosteroids for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2011, Issue 9. [DOI: 10.1002/14651858.CD000064.pub2]

- [121] Sandercock PAG, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD000029.pub3]
- [122] Sapronov NS, Bul'on VV, Kuznetsova NN, Selina EN. The neuroprotector effect of a new taurine derivative on a model of compression spinal cord trauma in rats [Russian]. *Eksperimental'naiia i Klinicheskaia Farmakologija* 2005;68(6):45-8.
- [123] Schauer E, Wronski R, Patockova J, Moessler H, Doppler E, Hutter-Paier B, et al. Neuroprotection of Cerebrolysin in tissue culture models of brain ischemia: post lesion application indicates a wide therapeutic window. *Journal of Neural Transmission* 2006;113(7):855-68.
- [124] Schunemann HJ, Oxman AD, Vist GE, Higgins JPT, Deeks JJ, Glasziou P, et al. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from [www.handbook.cochrane.org](http://www.handbook.cochrane.org). Available from [www.cochrane-handbook.org](http://www.cochrane-handbook.org). The Cochrane Collaboration.
- [125] Shu LLS, San Jose CZ, Pasco PP. The efficacy and safety of cerebrolysin in acute hemorrhagic stroke: a meta analysis. *Cerebrovascular Diseases* 2012;34(Suppl 1):36.
- [126] Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, et al. NXY-059 for the treatment of acute ischemic stroke. *New England Journal of Medicine* 2007;357(6):562-71.
- [127] Suslina ZA, Varakin YY, Vereshchagin NV. Clinical and epidemiological research as a perspective direction of cerebral pathology study (the first report) [Clinico-epidemiologicheskiye issledovaniya - perspektivnoye napravleniye izucheniya cerebralnoi patologii (soobscheniye pervoiye)]. *Annals of Neurology* 2009;3:4-11.
- [128] Tan Y, Liu M, Wu B. Puerarin for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2008, Issue 1. [DOI: 10.1002/14651858.CD004955.pub2]
- [129] Bath PM, Iddenden R, Bath FJ, Orgogozo JM, Tirilazad International Steering Committee. Tirilazad for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD002087]
- [130] Vilenski BS, Iakhno NN. The problem of cerebral stroke: its contemporary state. *Vestnik Rossi sko Akademii Meditsinskikh Nauk* 2006;9-10:18-24.
- [131] Visvanathan A, Dennis M, Whiteley W. Parenteral fluid regimens for improving functional outcome in people with acute stroke. *Cochrane Database of Systematic Reviews* 2015, Issue 9. [DOI: 10.1002/14651858.CD011138.pub2]
- [132] Wardlaw JM, Koumellis P, Liu M. Thrombolysis (different doses, routes of administration and agents) for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2013, Issue 5. [DOI: 10.1002/14651858.CD000514.pub3]
- [133] Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2014, Issue 7. [DOI: 10.1002/14651858.CD000213.pub3]
- [134] World Health Organization. The Atlas of Heart Disease and Stroke. [www.who.int/cardiovascular\\_diseases/resources/atlas/en/](http://www.who.int/cardiovascular_diseases/resources/atlas/en/) (accessed November 2014).
- [135] National Essential Medicines Lists. [www.who.int/selection\\_medicines/country\\_lists](http://www.who.int/selection_medicines/country_lists) (accessed 12 August 2016).
- [136] Wong GK, Zhu XL, Poon WS. Beneficial effect of cerebrolysin on moderate and severe head injury patients: result of a cohort study. *Acta Neurochirurgica Supplement* 2005;95:59-60.
- [137] Yang W, Hao Z, Zhang S, Dong W, Wu T, Liu GJ, et al. Mailuoning for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD007028.pub2]
- [138] Zeng X, Liu M, Yang Y, Li Y, Asplund K. Ginkgo biloba for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD003691.pub2]
- [139] Zhang CL, Chopp M, Cui YS, Wang L, Zhang RL, Zhang L, et al. Cerebrolysin enhances neurogenesis in the ischemic brain and improves functional outcome after stroke. *Journal of Neuroscience Research* 2010;88(15):3275-81.
- [140] Zhuo Q, Yang X, Wu T, Liu G, Zhou L. Tongxinluo capsule for acute stroke. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004584.pub2]
- [141] Ziganshina LE, Abakumova T, Kuchaeva A. Cerebrolysin for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD007026.pub2]
- [142] Ziganshina LE, Abakumova T, Kuchaeva A. Cerebrolysin for acute ischaemic stroke. *International Journal of Risk and Safety in Medicine* 2010;22(4):179-93.
- [143] Ziganshina LE, Abakumova TR. Cerebrolysin for acute ischemic stroke. *Vestnik Rossi Akademii Meditsinskikh Nauk* 2013;1:21-9.
- [144] Ziganshina LE, Abakumova T. Cerebrolysin for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: 10.1002/14651858.CD007026.pub3]