META-ANALYSIS OF RANDOMIZED PLACEBO-CONTROLLED TRIALS WITH CEREBROLYSIN IN MILD-TO-MODERATE ALZHEIMER'S DISEASE

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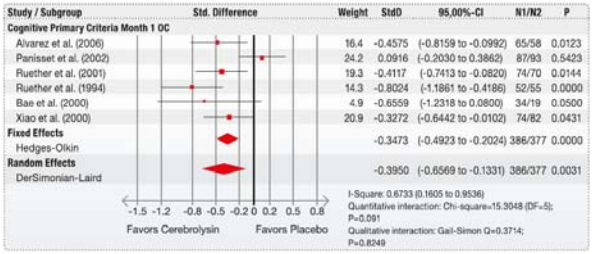
Objectives: Cerebrolysin is a parenterally administered neuropeptide preparation that mimics the pleiotropic effects of neurotrophic factors. The objective of this meta-analysis was to assess the treatment effect of Cerebrolysin in mild-to-moderate Alzheimer's disease in a systematic, consolidated and quantitative approach.

Methods: A comprehensive literature search was performed to identify all randomized, double-blind, placebo-controlled studies using Cerebrolysin. There were no restrictions on language. A mixed meta-analysis was performed using both, individual patient data and/or published (aggregate) data. The effect sizes were calculated for the global clinical change (odds ratio) and the cognitive function (standardized mean difference) as well as for the combined effect of both domains as the global benefit (Mann-Whitney; Wei-Lachin procedure as multivariate generalization of the Wilcoxon-Mann-Whitney test). Meta-analyses were based on the intention-to-treat population using the observed cases approach. Sensitivity analyses were performed with the last observation carried forward approach.

Results

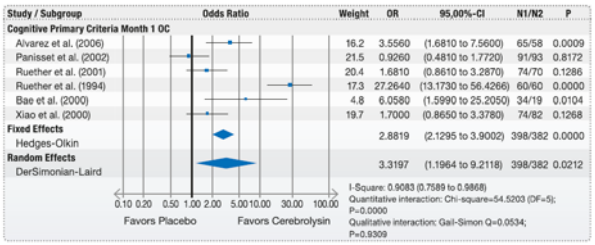
Short-term effects (Month 1)

Cognitive functions:



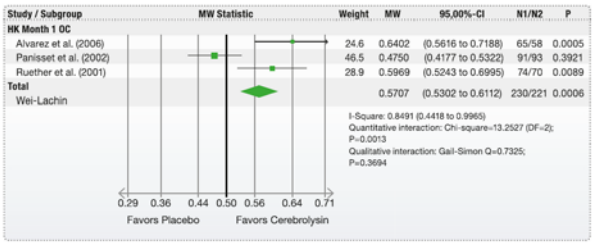
Comparison of Cerebrolysin (30ml/d) vs Placebo. Changes from baseline, effect size: SMD, OC. **Beneficial and statistically significant treatment effects of Cerebrolysin compared to placebo were observed in the cognitive functions as early as after four weeks of treatment.**

Global clinical change:



Comparison of Cerebrolysin (30ml/d) vs Placebo. Effect size: OR, OC. **After a four-week treatment with Cerebrolysin the chance for global clinical improvement was three times higher as compared to placebo. The effect was statistically significant.**

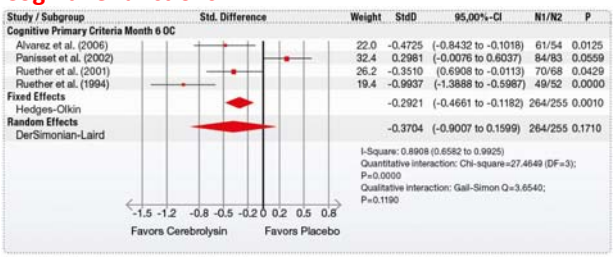
Global benefit:



Comparison of Cerebrolysin (30ml/d) vs Placebo. Multivariate, effect size: MW, OC. **A statistically significant advantage of Cerebrolysin over placebo was observed after four weeks of treatment in the global benefit.**

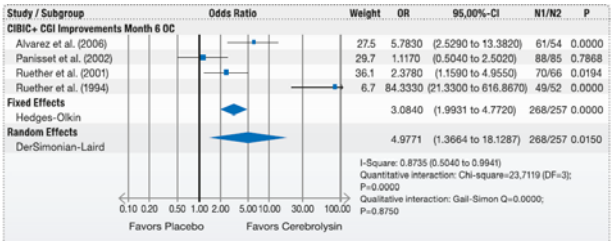
Long-term effects (Month 6)

Cognitive functions:



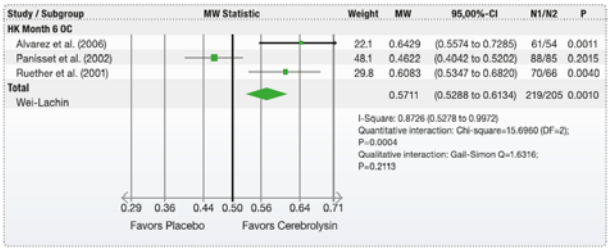
Comparison of Cerebrolysin (30ml/d) vs Placebo. Changes from baseline, effect size: SMD, OC. **At six months treatment effects on cognitive functions were clearly in favor of Cerebrolysin.**

Global clinical change:



Comparison of Cerebrolysin (30ml/d) vs Placebo. Effect size: OR, OC. **At six-month follow-up the chance for global clinical improvement is five times higher as compared to placebo. The effect was statistically significant.**

Global benefit:



Comparison of Cerebrolysin (30ml/d) vs Placebo. Multivariate, effect size: MW, OC. **The statistically significant advantage of Cerebrolysin over placebo in the global benefit was maintained for at least six months.**

Conclusions

- Efficacy of Cerebrolysin in patients with Alzheimer's disease could well be shown in the meta-analysis of six placebo-controlled and double-blind clinical studies with a duration of up to six months and as early as after four weeks of treatment. Sensitivity analyses were in line with these findings *(data not shown).*
- The effect size of Cerebrolysin in cognitive functions at six months is comparable with competitors: Cerebrolysin was between the effect sizes of memantine and donepezil (10mg) but significant safety findings were reported for donepezil *(Birks&Harvey, Cochrane 2006; McShane et al, Cochrane 2006).*
- The safety aspects of Cerebrolysin were comparable to placebo, thus suggesting a favorable benefit-risk ratio in patients with mild-to-moderate Alzheimer's disease *(data not shown).*

Characteristics of Selected Studies

Trial	Trial Duration	Randomized patients (N)	ITT Patients (N)	ITT Patients (%²)	MMSE¹ (mean)	Age (mean)	Female (%)	Data set
Alvarez et al, 2006	6 m	139	123	88.5%	19.7	73.6	70.7	IPD
Panisset et al, 2002	6 m	192	187	97.4 %	20.6	74.2	58.3	IPD
Ruether et al, 2001	6 m	149	144	96.6%	17.3	73.0	58.3	IPD
Ruether et al, 1994	6 m	120	120	100.0%	21.6	71.5	65.8	AD
Total 6m		**600**	**574**	**95.7%**	**19.8**	**73.2**	**62.7**	
Bae et al, 2000	4 w	53	53	100.0%	15.7	71.6	66.2	AD
Xiao et al, 2000	4 w	157	157	100.0%	19.0	70.4	50.3	AD
Total 4w		**810**	**784**	**96.8%**	**19.3**	**72.5**	**60.3**	

¹at baseline, ²of randomized patients; AD, aggregate data; IPD, individual patient data; ITT, intention-to-treat; MMSE, Mini-Mental State Examination (10-20 = moderate severity). All studies have a **minimum of 4 weeks treatment** (20 infusions) with **30 ml Cerebrolysin/day.**

Primary outcome measures of individual studies

Study	Global Benefit: CIBIC+	Global Benefit: CGI	Cognitive Functions: ADAS-cog+	Cognitive Functions: ADAS-cog	Cognitive Functions: MMSE	Cognitive Functions: ZVT
Alvarez et al, 2006	X		X			
Panisset et al, 2002	X			X		
Ruether et al, 2001		X		X		
Bae et al, 2000		X		X		
Xiao et al, 2000		X			X	
Ruether et al, 1994		X				X

Global Clinical Change | Cognitive Functions

CIBIC+, Clinical Interview-based Impression of Change plus caregiver input; CGI, Clinician's Global Impression of Change (Item 2 of CGI); ADAS-cog+, Alzheimer's Disease Assessment Scale – cognitive subpart – modified (14 items); ADAS-cog, Alzheimer's Disease Assessment Scale – cognitive subpart (11 items); MMSE, Mini-Mental State Examination; ZVT, Zahlen-Verbindungs-Test (Trail-Making Test).

This meta-analysis was published by S. Gauthier *et al.*, Dement Geriatr Cogn Disord 2015;39:340-355.