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Scientific Symposium EVER
New evidence for Multi-modal Treatment Concepts in Post-Stroke Recovery

Official Symposium of the
4th European Stroke Organisation Conference (ESOC 2018)
16-18 May, 2018 | Gothenburg, Sweden

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Program of the symposium

New evidence for Multi-modal Treatment Concepts in Post-Stroke Recovery

Thursday, 17 May 2018, 12:45-14:15 (Meeting Hall E1)
Chairman: Wolf-Dieter Heiss, Germany

Intro

Neuroprotection and neurorepair after stroke: example cerebrolysin

Noninvasive brain stimulation & multi-modal treatment concepts

From neurobiology to evidence based medicine concepts in neurorehabilitation after stroke

New evidence from a recent meta-analysis in acute ischemic stroke

Intro

Wolf-Dieter Heiss (chairman)

Director of the Department of Neurology, University of Cologne and of Department of General Neurology at the Max-Planck-Institute for Neurological Research, Cologne, Germany

The symposium began with Dr. Heiss's welcome speech in which he outlined the general therapeutic landscape of ischemic stroke indicating in particular the limits of modern ischemic stroke therapies: thrombolysis and thrombectomy. This symposium is targeting the new, still evolving concepts in the clinical approach to ischemic stroke, said Dr. Heiss.

Neuroprotection and neurorepair after stroke: example cerebrolysin

Michael Brainin

Danube University Krems, Krems, Austria

ABSTRACT:

Cerebrolysin is a neuropeptide preparation with neurotrophic factor-like effects and has shown to promote recovery after brain injury. Its preclinical profile promises wide applications due to multi-target effects. Currently, Cerebrolysin is used for treatment of cerebral ischemia and neurodegeneration. In stroke, early clinical trials were performed mostly in mildly affected stroke populations which usually have a favourable prognosis. Due to this selection, a floor or ceiling effect of recovery measures in the mild cases did not show a statistical benefit among treatment groups at the chosen study endpoints in time. More detailed subgroup analyses of more severely affected patients reveals a strikingly positive effect for enhanced recovery. Based on the findings from several studies it became evident that the effect sizes of Cerebrolysin were increasing with stroke severity. Other controlled studies showed that Cerebrolysin can be safely used in combination with thrombolysis. More recently, Cerebrolysin has been tested not only for neuroprotection but also for its neurorecovery potential. Recent trials showed a beneficial effect for functional recovery when combined with neurorehabilitation versus neurorehabilitation alone. Also when using this combined or pragmatic approach for neurorecovery beneficial effects are most clearly demonstrated in moderately to severely affected patients. This gives lead to the planning of a more rigorous study design in the future. Moreover, in all studies Cerebrolysin was applied safe and was well tolerated.

Dr. Brainin addressed the etiology of the ischemic stroke and inducted the time as a key factor for effective treatment of the ischemic penumbra **(Fig. 1)**.

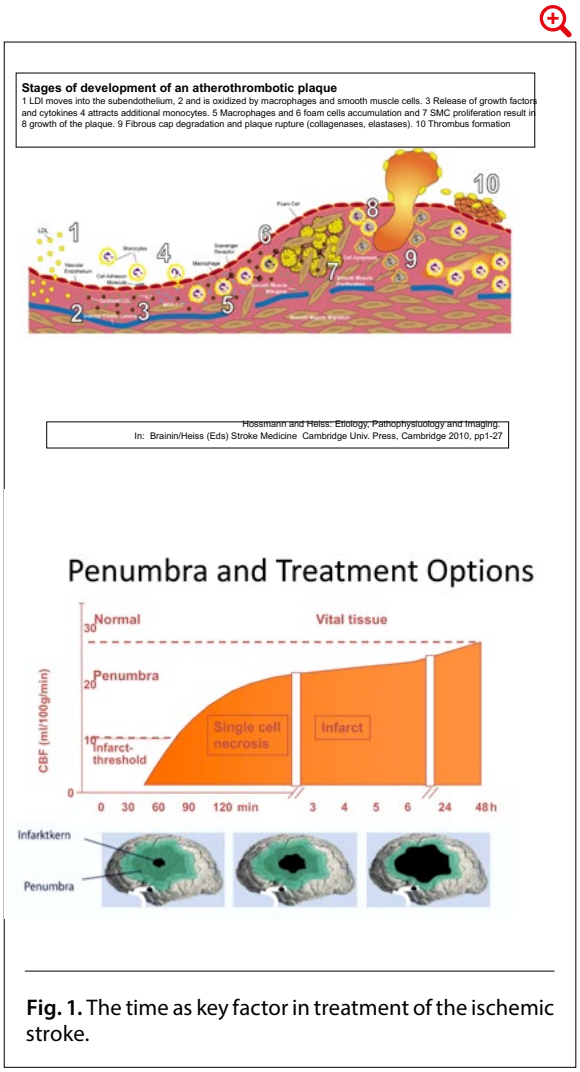

Fig. 1. The time as key factor in treatment of the ischemic stroke.

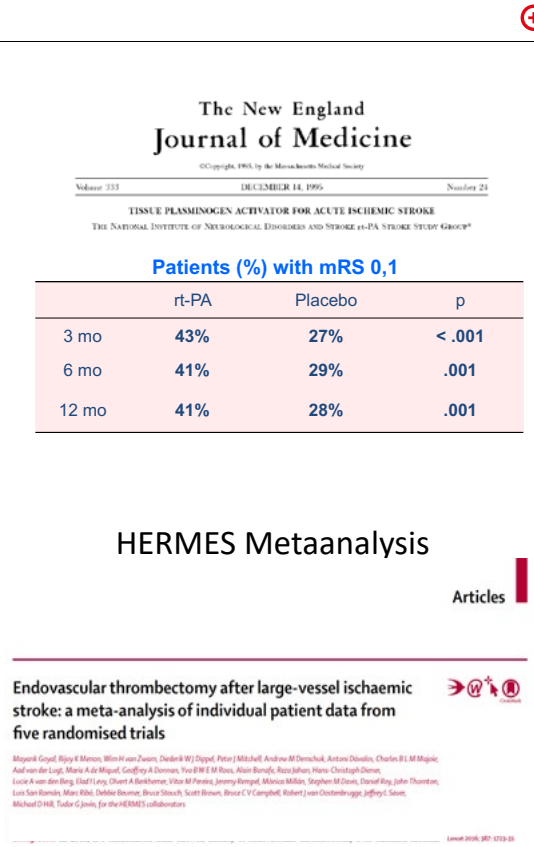

Fig. 2. Gold standards in the ischemic stroke therapy: thrombolysis and thrombectomy

The first modern approach to rescuing ischemic penumbra was introduced 20 years ago. Thrombolysis is the mainstay of the treatment today. Recently, we achieved significant success in thrombectomy, which is the treatment of choice for large vessels thrombosis. Of importance is the fact that this approach can be applied indiscriminately among broad group of patients, with different age, sex, thrombolytic and non-thrmobolytic, with wide range of severities, localization, and onset to randomization **(Fig. 2)**.

At the same time, during last decades, 1026 experimental treatments focused on neuroprotection failed. 114 clinically tested drugs and 912 experimental drugs did not show required clinical effect. The recent review publication addressing this issue by Neuhaus et al., (2017) stated that *"…with the advent of endovascular thrombectomy and ability to investigate patients in much greater detail through advanced imaging modalities, neuroprotective agents can and should be reexamined as adjunct therapies to recanalization"*. Among the new agents that seem to be good candidates for further clinical development are: stem cells, natural and synthetic biologicals (HGF), brain peptide preparations (Cerebrolysin), anti-inflammatory cytokines (TNF alpha, IL10), and reduction of toll-like receptor signaling (DAMPs). Dr. Brainin pointed also to STAIR criteria of conducting validation in experimental phase of drug development. We should adhere to these rules in first place when considering new therapeutic approaches. This is because the STAIR criteria aim at most accurate emulation of clinical tests in the experimental environment. As an example of the STAIR-adhering approach to investigating new treatments, Dr. Brainin described the study performed by M. Chopp's group in Henry Ford Hospital in Detroit (Zhang et al., 2016). In this study, investigators assessed the dose response effect of Cerebrolysin in adult ischemic stroke rats **(Fig. 3)**.

Dose response study Protocol (Zhang et al. 2016)

PI: M. Chopp
Model: Embolic middle cerebral artery occlusion (MCAO)

Young adult rats: n=20/group; 10 males + 10 females
Animals were randomized into one of five dosage groups

Cerebrolysin Dosages (IP):
0.8 ml/kg (0.13 ml/kg in humans)
2.5 ml/kg (0.45 ml/kg in humans)
5.0 ml/kg (0.8 ml/kg in humans)
7.5 ml/kg (1.2 ml/kg in humans)
Control, saline

Treatment: 4h after MCAO, Every 24 h for 10 Days

Parameters:
Longa Score before the initial treatment, mNSS, foot-fault, adhesive removal test, Days 1, 7, 14, 21, 28 after MCAO

Combined Analysis

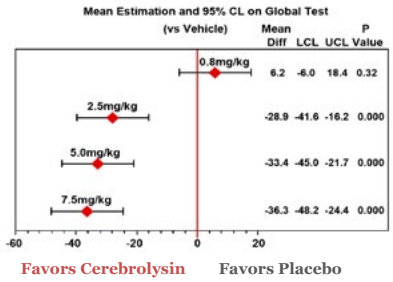

Fig. 3. Dose response effect of Cerebrolysin in the advanced rat stroke model

The various sensorimotor tests used in the evaluation of the treatment effects, including mNSS which is experimental equivalent of NIHSS, showed dose-response relationship and this result was further confirmed by the combined analysis. There was also a noticeable impact on the infarct volume and it correlated with increased dose of Cerebrolysin.

If we take the concept of ischemic stroke treatment one step further, we shift our attention to processes of neurorepair as potential new therapeutic targets. This should be considered as an alternative approach to neuroprotection, that stimulates regrowth and neuronal repair. It should be used when damage has already occurred (there is no potential benefit from neuroprotection). It appears not to be bound by short time-windows (typical for neuroprotection), when the key structures have already been lost and need to be repaired, either exogenously or through enhancement of endogeneous processes. It seems that the processes of neurorepair are most active during first 14 days after stroke and we should keep this in mind when designing the experimental and clinical studies.

Among agents considered for neurorepair therapies are enhancers of motor recovery, including: antidepressants (SSRI), dopaminergic drugs (L-Dopa) and biologicals (Cerebrolysin). In the recent clinical study (ECOMPASS; Chang et al., 2016) it was shown that Cerebrolysin supports rehabilitation of motor function **(Fig. 4)**.

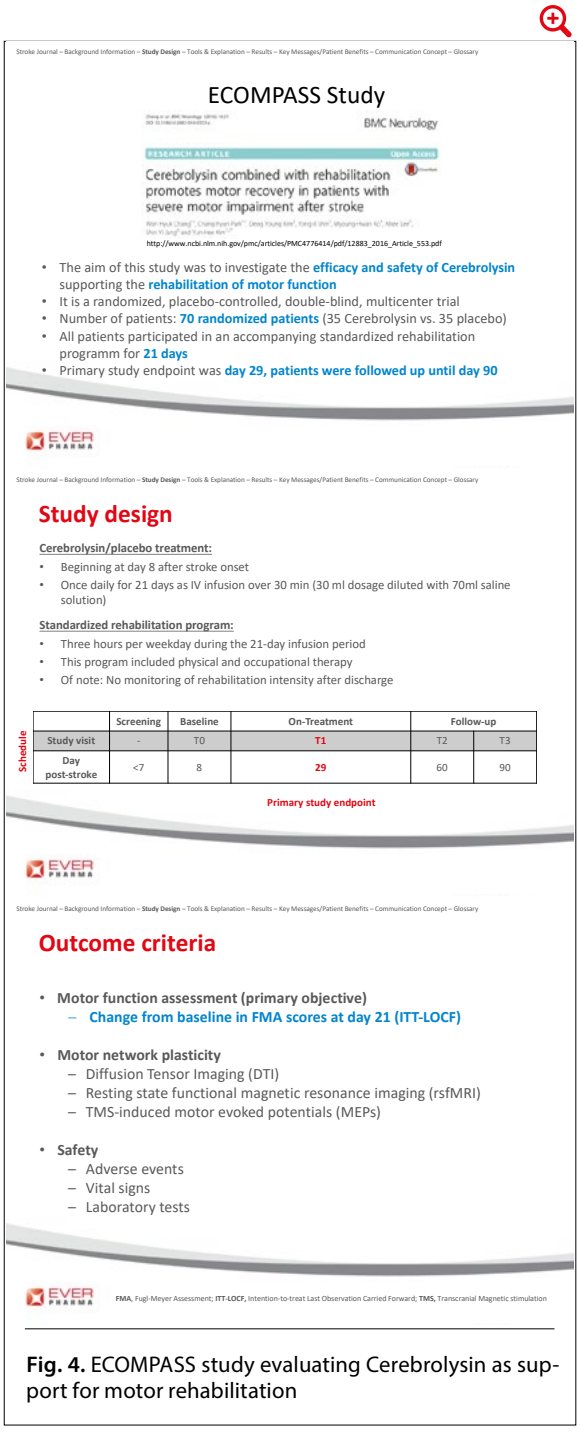

Fig. 4. ECOMPASS study evaluating Cerebrolysin as support for motor rehabilitation

The very important thing about this study is that it used neuroimaging data to further confirm the clinical effects measured with motor outcome scale (FMA scores). This allowed for better understanding the functional outcome results in terms of what is happening in the brain. In the more severe cases, the treatment with Cerebrolysin showed clear benefit in supporting motor rehabilitation for both lower and upper limbs. This result confirmed earlier observations indicating that detection of the clinical benefit of Cerebrolysin is linked with the severity of stroke. This has been explained earlier as a ceiling effect of stroke treatment in the mild stroke cases. The symmetrical functional connectivity as seen on rsfMRI was more pronounced in the Cerebrolysin group indicating better recovery of motor cortical function **(Fig. 5)**.

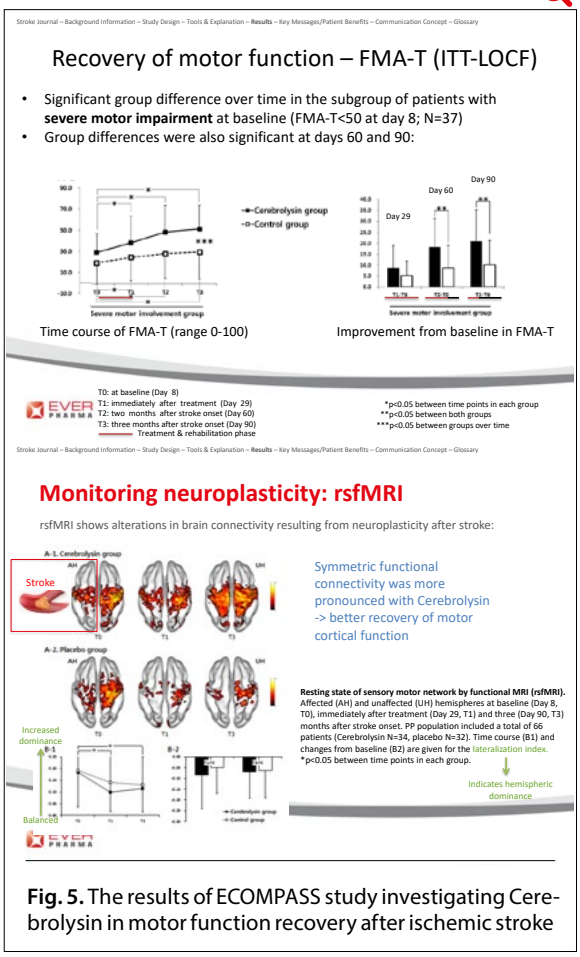

Fig. 5. The results of ECOMPASS study investigating Cerebrolysin in motor function recovery after ischemic stroke

In conclusion, the combination of a standard rehabilitation therapy with Cerebrolysin treatment over three weeks was safe. Cerebrolysin provided additional benefit on motor recovery in stroke patients with severe motor impairment. This result was confirmed by imaging analyses and support the beneficial effect of Cerebrolysin on motor network plasticity.

Dr. Brainin summarized his lecture by underlining that rehabilitation of stroke needs to be redefined by processes of recovery in the brain. This can be seen as a second leg of stroke therapy apart from recanalization. The inclusion and outcome need to be coupled with modern neuroimaging which clearly gives us meaningful additional information. Finally, neurorecovery needs to be further explored which is a view that has been validated with Cerebrolysin studies which indicated a homogenous and effective treatment profile.

Noninvasive brain stimulation & multi-modal treatment concepts in motor rehabilitation

Andreas Winkler

Department of Neurological Rehabilitation,
Clinic Pirawarth, Bad Pirawarth, Austria

ABSTRACT:

In stroke survivors, motor impairment is a leading cause of chronic disability in activities of daily living with 80% experiencing hemiparesis of the contralateral upper limb. While 4 out of 5 stroke patients will be able to walk independently, only 2 out of 5 with upper limb paresis regain functional use. Most troublesome symptoms of upper extremity motor impairment compromise paresis, flaccid or spastic changes in muscle tone, joint laxity, impaired motor control and loss of selective finger movements. These impairments interfere with everyday activities such as reaching, grasping and picking up and holding on to objects.

Rehabilitation training is the most effective way to enhance motor recovery in stroke patients and to minimize impairments. Task specific training is still the gold standard for post-stroke rehabilitation, but effect sizes studied recently in patients with upper extremity impairment (UE) in the subacute stages after stroke were rather small. Special concerns regard stroke patients with more severe initial impairments who in general will not show the same degree of proportional recovery compared to stroke survivors with mild or medium impairment. A multimodal approach in upper extremity rehabilitation combining synergistic effects of different treatment modalities might therefore be beneficial.

Transcranial direct current stimulation (tDCS) is a promising new technique to optimize the effect of task specific training in the context of UE motor recovery. tDCS is a convenient and safe rehabilitation method as it allows modulations in brain plasticity through direct stimulation of the cortex. Cerebrolysin is a neuropeptide preparation with neuroprotective and neurorestorative effects which has shown to support upper extremity motor recovery. Combining tDCS with Cerebrolysin and task specific training might theoretically exhibit synergetic effects in UE motor recovery.

In a retrospective analysis we studied stroke patients under routine conditions with moderate to severe impairment of UE motor function (SA FE-Score > 4 pts.; ARAT-Score >12 pts.). Eligible patients were stratified into three groups: group one received a triple-therapy consisting of daily task oriented training (TOT, 30 minutes 5 days/week), anodal tDCS (20minutes, 5 days/week) plus daily administration of Cerebrolysin 30ml iv. Group two received a combination of TOT plus anodal tDCS, patients in group three were treated as usual by TOT. After two weeks of treatment we assessed differences in functional UE recovery between treatment groups by measuring changes in proportional recovery using the ARAT-Score. To our knowledge, the effects of the combination of these potentially synergetic acting therapeutic modalities on functional UE recovery have never been studied before.

Dr Winkler undertook a broad topic of noninvasive brain stimulation and its relation to multimodal treatment therapies in stroke. While there is a progress in the field of acute stroke therapy, which translates into decrease in number of patients needing rehabilitation, there are still challenges for the rehabilitation itself that need to be effectively addressed. More than 80 % of patients suffer from motor weakness/hemiparesis. 30% are unable to walk, remain severely disabled or suffer from aphasia. Moreover, up to 10% develop post stroke dementia within 6 months of stroke onset. Additionally, upper limb recovery after stroke is unacceptably poor. Arms recover worse than legs – two out of five patients with upper limb paresis regain functional use while four out of five can walk independently. About 60% of patients with non-functional arms one week post-stroke don't recover and four years post-stroke only 50% had fair to good arm function.

In reevaluating our rehabilitation approaches, we must consider time as very important factor of success **(Fig. 1)**. Time is important in both acute and post-acute phases. Patients attend rehabilitation facilities usually weeks after stroke, when neuroprotection and recanalization cannot provide any further help. However, there is still possibility to explore and utilize process of endogenous neuroplasticity. In fact, we need to be very specific and careful in our pro-plasticity approaches in order to avoid fixing the maladaptation. The first few weeks of rehabilitation appear to be most important for recovery of functions.

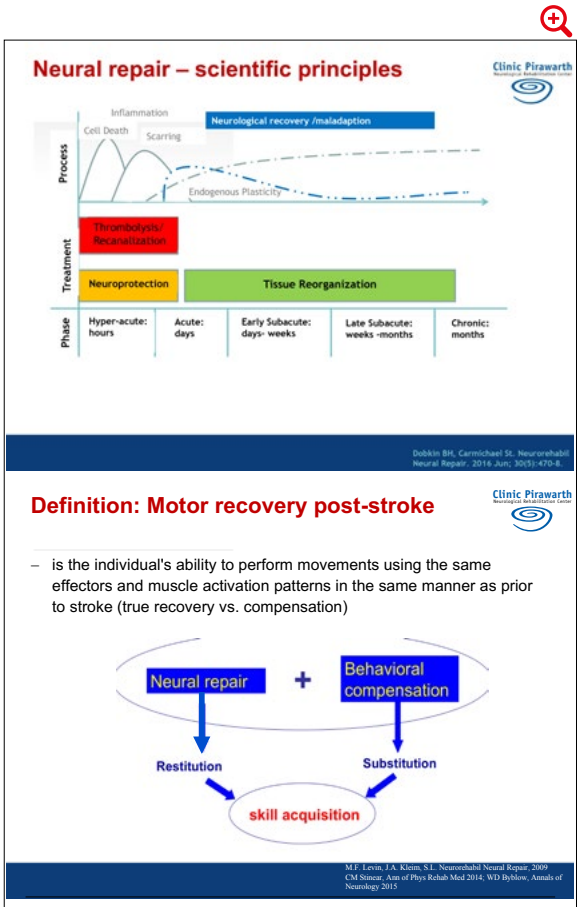

Fig. 1. Neural repair after stroke and what it means to recover motor functions

With regard to motor recovery, we always have to be aware what it means in order to properly set up the rehabilitation program. Real recovery through neurorepair is something completely different from behavioral compensation. Interestingly, about 90% of motor rehabilitation efforts concentrates around behavioral compensation and therefore we lose opportunity for real recovery after stroke. The optimal time window for real recovery is just a few weeks. A good example of compensatory mechanisms displayed by brain itself are jerky movements that appear to be the brain's efforts to activate additional sensorimotor areas reflective of the lost function. Due to high variability of motor recovery in the early phase it is difficult to predict the outcome of rehabilitation, especially in long-term observation. The individual's ability to perform movements using the same effectors and muscle activation patterns in the same manner as prior to stroke (true recovery vs. compensation) varies to great extent. The PREP algorithm is today the best tool to predict the outcome of motor rehabilitation after stroke **(Fig. 2)**.

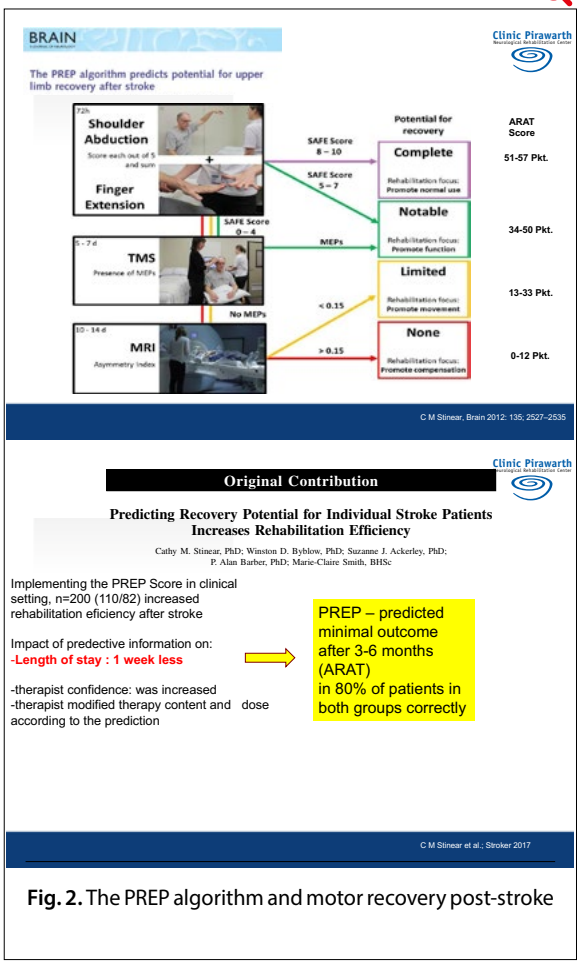

Fig. 2. The PREP algorithm and motor recovery post-stroke

In fact, we can say that resolution of upper limb impairment follows the „proportional recovery rule“ regardless of initial impairment, but only for patients with intact corticomotor function and only for patients with mild stroke. The major question for us is how to move 30% of patients with poor recovery to the group of proportional recovery and also how to increase the population benefiting from our rehabilitation processes. Another important question relates to dose of rehabilitation required to effectively stimulate recovery. We have very poor idea about this aspect of recovery. In the ICARE trial, there was no advantage of providing more than twice the mean dose (mean, 27 hours) of therapy compared with the average 11 hours received by the observation-only group (Winstein, JAMA ,2016). It may be that spontaneous recovery may have been greater than any treatment effect. Within 6 to 10 weeks after stroke, time from stroke occurrence is independently associated with spontaneous recovery of impairments and activities, explaining 16% to 42% of the observed improvements. Still, the therapeutic dose in rehabilitation appears to be too low for achieving the beneficial effects. But is it possible to give our patients, especially children, very high doses of rehabilitation lasting several hours a day? We have to find less exhausting and more effective way to rehabilitate our patients. One such approach relies on reopening the plasticity period after stroke by inducing another ischemic period. This appears to work in animal models as documented in the works published by Dr. Zeiler's group from Johns Hopkins University **(Fig. 3)**.

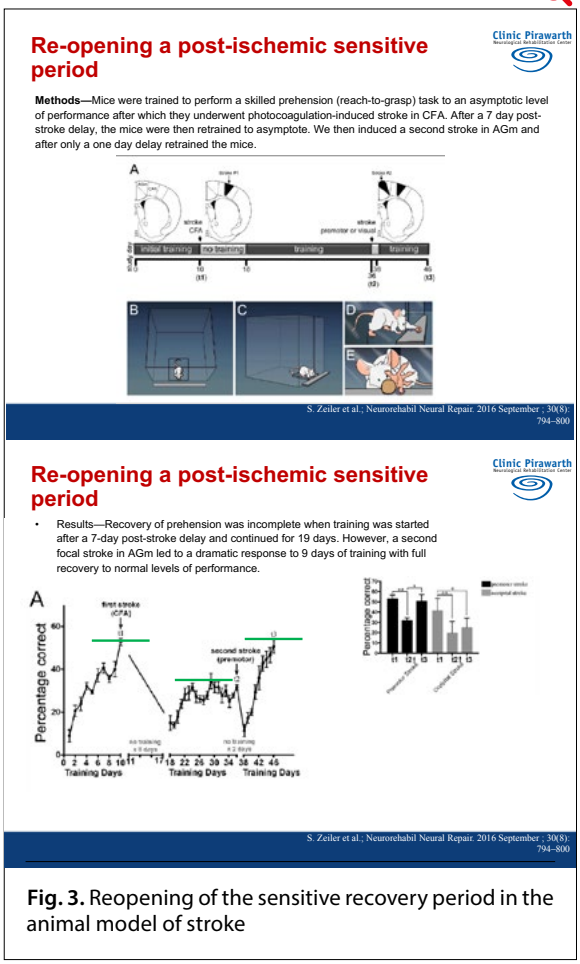

Fig. 3. Reopening of the sensitive recovery period in the animal model of stroke

Is it possible to translate this animal experiments into clinical practice without inducing another ischemic stroke to our patients? One possible answer is the combination of various approaches to stimulate neuroplasticity processes. In Dr. Winkler's clinic non-invasive brain stimulation (NIBS) techniques have been chosen as easy to use method to stimulate plasticity in various brain regions related to true recovery post-stroke. In the transcranial direct current stimulation (tDCS) a weak electrical current (1-2mA) is delivered to the scalp using two surface electrodes to induce a polarity-dependent shift in neuronal resting membrane, thereby promoting changes in cortical excitability (neuromodulation local/motor network): anodal (facilitating) and cathodal (inhibiting). The after-effects of tDCS (90') involve induction of synaptic plasticity that mimic long-term potentiation, which is critical for learning, neuroplasticity and rehabilitation. Additionally, tDCS has an excellent safety profile. Among physiological effects of tDCS are: induction of calcium-dependent plasticity, activation of glutamatergic neurons, non-linearity effects. The remote effects are present and these involve functional connectivity which is very important for recovery pathway establishment.

Another way to enhance post-stroke plasticity is to use appropriate medications. Several classes of drugs could be considered: acetylcholinesterase inhibitors, amphetamine, dopamin (DARS Trial 2017), SSRI`s (FLAME 2011, TALOS 2017) and neuropeptides (Cerebrolysin®- CARS Trial). Dr. Winkler indicated that Cerebrolysin probably induces a favorable milieu for enhanced plasticity and motor recovery, as evidenced by several clinical trials conducted in recent years. The last of them, CARS trial, showed an improvement of upper limb motor functions in combination with motor rehabilitation as measured with ARAT. The proportional recovery among patients receiving Cerebrolysin was greatly improved **(Fig. 4)**.

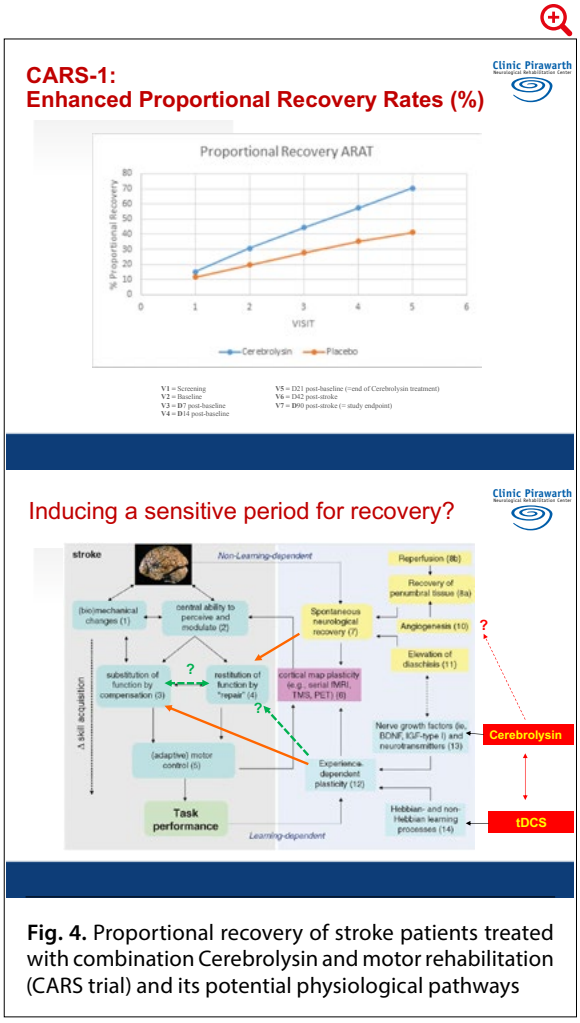

Fig. 4. Proportional recovery of stroke patients treated with combination Cerebrolysin and motor rehabilitation (CARS trial) and its potential physiological pathways

At the end of his lecture, Dr. Winkler described the case study from his clinic in which the multimodal therapy targeting post-stroke plasticity appeared to improve motor recovery of already chronic stroke patient, who experienced not one, but two strokes **(Fig. 5)**. The therapy led to 60% proportional recovery of motor functions.

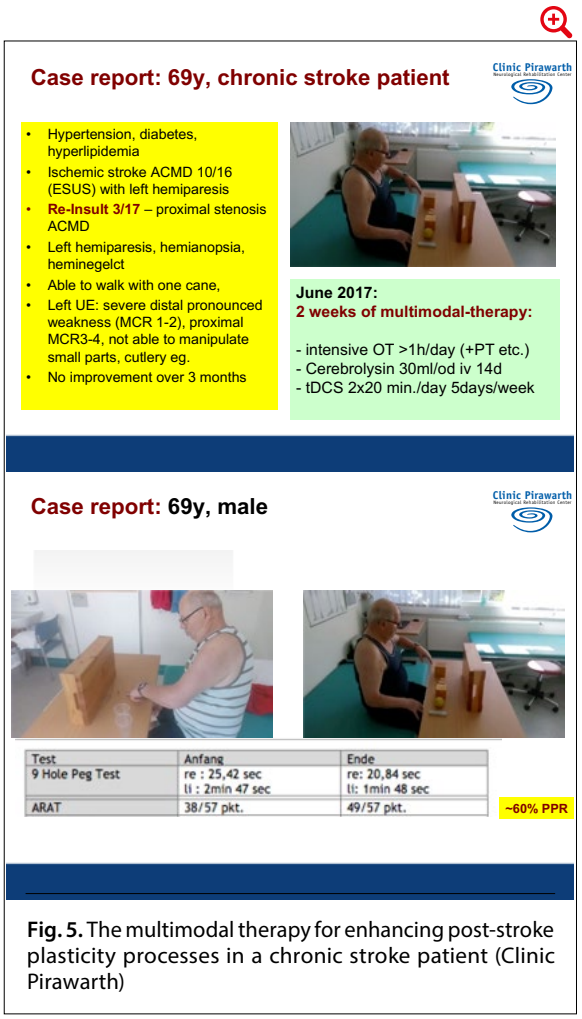

Fig. 5. The multimodal therapy for enhancing post-stroke plasticity processes in a chronic stroke patient (Clinic Pirawarth)

This result gave the investigators an idea to look retrospectively at their patients treated with Cerebrolysin in the context of multimodal therapy supporting motor recovery after stroke in its post-acute phase (the chronic phase of stroke). The study compared three arms: first, employing daily task specific training, second adding to it tDCS, and third adding to it tDCS and Cerebrolysin. The primary endpoint was ARAT score at day 14 determined as proportional recovery score (PRS%). The combination groups, especially Cerebrolysin group, showed the recovery of motor functions that was three times higher from the conventional daily task specific training (group C improved by 31% proportional recovery in the chronic phase; Fig 6). This result gave clear rationale for designing a larger, prospective RCT which will further explore the multimodal treatment of post-acute stroke patients with combination motor training, tDCS and Cerebrolysin **(Fig. 6)**.

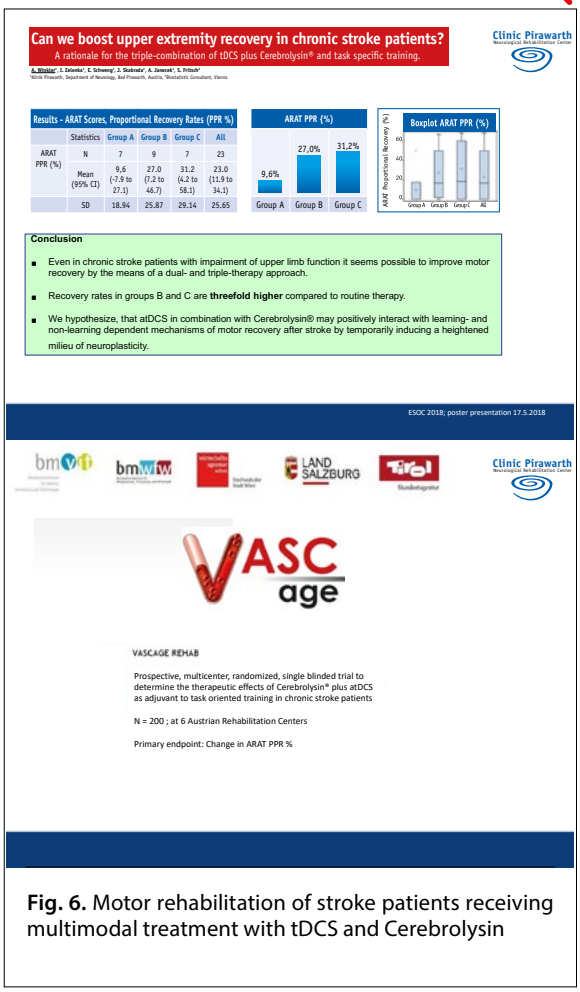

Fig. 6. Motor rehabilitation of stroke patients receiving multimodal treatment with tDCS and Cerebrolysin

From neurobiology to evidence based medicine concepts in neurorehabilitation after stroke

Dafin Muresanu

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University of Medicine and Pharmacy "Iuliu Hatieganu",
Cluj-Napoca, Romania

ABSTRACT:

Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes.

Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone. Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data shows that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization-related complications cause over 50% of stroke patients' deaths, rehabilitation plays an important role in stroke care. It is getting clearer that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke. The results of recently published large and well-controlled clinical studies show a positive effect of Cerebrolysin on neurological recovery after acute ischemic stroke.

The newly published CARS study assessed the efficacy and safety of Cerebrolysin in combination with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper-limb motor functions. Cerebrolysin was administered for 21 days, starting within 48-72 hours after ischemic stroke. The study showed a statistically significant group difference in the upper-limb motor function (ARAT) at day 90 – primary end point. Cerebrolysin was also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with Cerebrolysin showed less depressive symptoms and better quality of life. In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of Cerebrolysin. Analysis of the safety parameters did not show any clinical statistically significant differences between the treatment groups. The results indicate that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach.

Furthermore, CARS 1 and CARS 2 meta-analysis provides evidence that Cerebrolysin has a beneficial effect on motor function recovery in early rehabilitation patients after stroke. All pre-planned primary metaanalytic results were statistically significant.

The enhancement and improving of the rehabilitation process by using pharmacological agents was the leading theme of Dr. Muresanu's talk. Rehabilitation is defined as a process through which each disabled person reaches the maximum physical, functional, cognitive and psychosocial recovery possible within the limits of their disability and individual biological reserve. These also determine the observed heterogeneity of the response to same rehabilitation efforts. There are two leading models that we have to consider in therapy of stroke: medical and rehabilitation model. In the rehabilitation model, the personalization of therapy plays very important role which differs it from the medical model. We are striving to bring more evidence based medicine to neurorehabilitatian and, at the same time, develop rehabilitation as a science. One of the major advances in science of neurorehabilitation developed in the last decade is concept of anti-correlation. After an acute brain lesion there is always an endogenous continuous brain defense response consisting of two main anti-correlated sequences: an immediate one, aiming to reduce brain damage (neuroprotection/impairment) and a later one, aiming to repair the brain damage (neurorepair/neurorecovery/disability). The stage of neuroprotection is short and rather weak. Often, with the highest level of protection the level of recovery is negligible. When the processes of neuroprotection are getting silenced over time, the processes of neurorepair are accelerating. And this anticorelation makes a lot of sense from physiological standpoint. Dr Muresanu gave examples of anti-correlated mechanisms observed at molecular and cellular, circuitry and dynamic network levels within the central nervous system. The concept of endogenous neuromodulation describes the capacity of the brain to balance anti-correlated processes. Neuromodulation balances pro-survival signaling mechanisms versus pro-death signaling mechanisms at the cellular and molecular level, long-term potentiation versus long-term depression at the local circuits level and synchronization versus desynchronization at the dynamic network level. Every level in turn comprises several sub-levels, and each of them is characterized further by a multitude of anti-correlated processes.

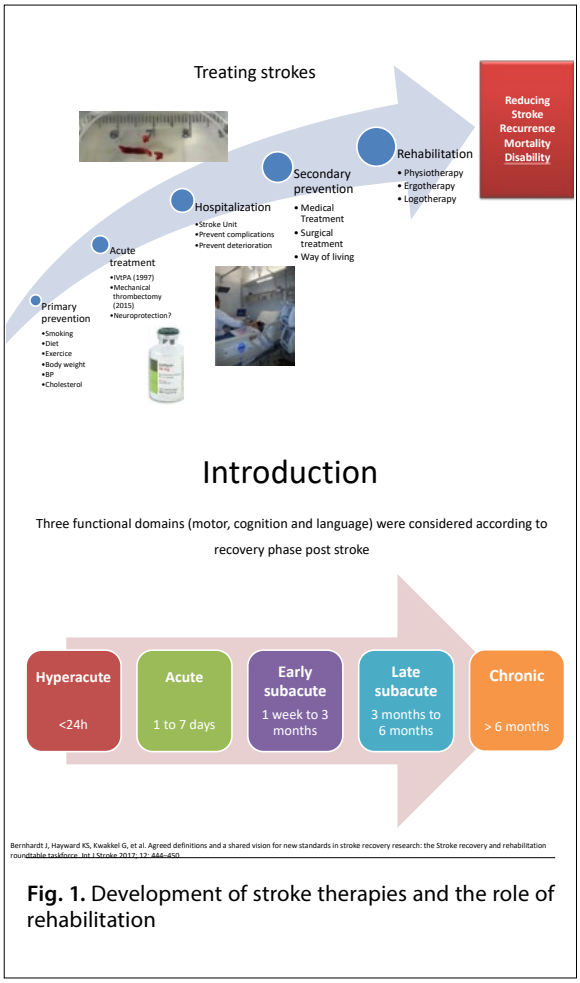
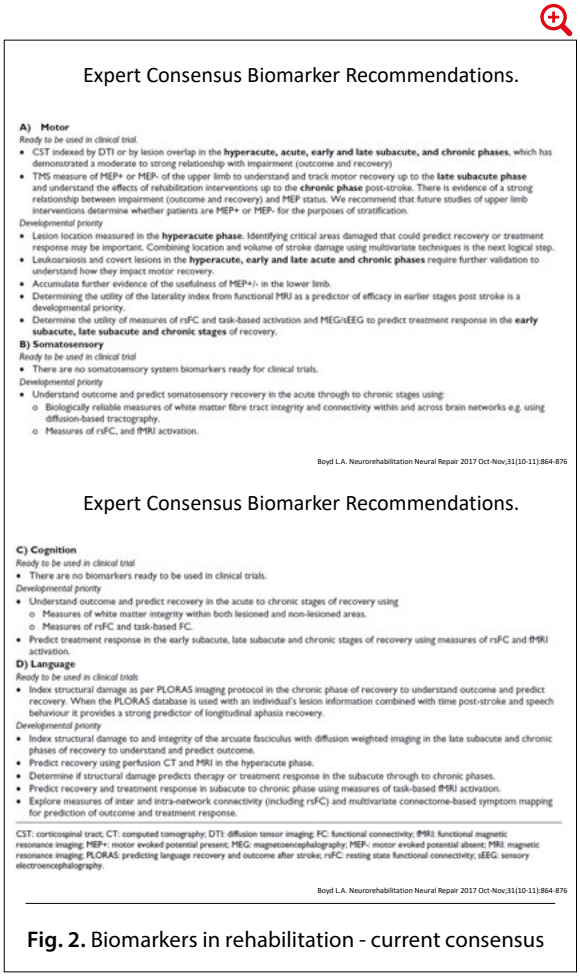


Fig. 1. Development of stroke therapies and the role of rehabilitation

When we consider all the progresses made in stroke treatment, we see that properly conducted therapeutic procedures help many patients, but there is still open question of rehabilitation as probably the least understood stage of stroke therapy **(Fig. 1)**.

The timing and intensity of acute rehabilitation are important issues in assessing post-stroke functional outcomes but remain controversial. Early mobilization after stroke is recommended in many clinical practice guidelines worldwide, but at the same time we understand that it is very much an individualized process. In evaluating the rehabilitation process the biomarkers play increasingly important role **(Fig. 2)**.



Expert Consensus Biomarker Recommendations.

A) Motor

Ready to be used in clinical trial.

- CST indexed by DTI or by lesion overlap in the **hyperacute, acute, early and late subacute, and chronic phases**, which has demonstrated a moderate to strong relationship with impairment (outcome and recovery)
- TMS measure of MEP+ or MEP- of the upper limb to understand and track motor recovery up to the **late subacute phase** and understand the effects of rehabilitation interventions up to the **chronic phase** post-stroke. There is evidence of a strong relationship between impairment (outcome and recovery) and MEP status. We recommend that future studies of upper limb interventions determine whether patients are MEP+ or MEP- for the purposes of stratification.

Developmental priority

- Lesion location measured in the **hyperacute phase**. Identifying critical areas damaged that could predict recovery or treatment response may be important. Combining location and volume of stroke damage using multivariate techniques is the next logical step.
- Leukoaraiosis and covert lesions in the **hyperacute, early and late acute and chronic phases** require further validation to understand how they impact motor recovery.
- Accumulate further evidence of the usefulness of MEP+/- in the lower limb.
- Determining the utility of the laterality index from functional MRI as a predictor of efficacy in earlier stages post stroke is a developmental priority.
- Determine the utility of measures of rsFC and task-based activation and MEG/sEEG to predict treatment response in the **early subacute, late subacute and chronic stages** of recovery.

B) Somatosensory

Ready to be used in clinical trial

- There are no somatosensory system biomarkers ready for clinical trials.

Developmental priority

- Understand outcome and predict somatosensory recovery in the acute through to chronic stages using:
  - Biologically reliable measures of white matter fibre tract integrity and connectivity within and across brain networks e.g. using diffusion-based tractography.
  - Measures of rsFC, and fMRI activation.

Boyd L.A. Neurorehabilitation Neural Repair 2017 Oct-Nov;31(10-11):864-876

Expert Consensus Biomarker Recommendations.

C) Cognition

Ready to be used in clinical trial

- There are no biomarkers ready to be used in clinical trials.

Developmental priority

- Understand outcome and predict recovery in the acute to chronic stages of recovery using
  - Measures of white matter integrity within both lesioned and non-lesioned areas.
  - Measures of rsFC and task-based FC.
- Predict treatment response in the early subacute, late subacute and chronic stages of recovery using measures of rsFC and fMRI activation.

D) Language

Ready to be used in clinical trials

- Index structural damage as per PLORAS imaging protocol in the chronic phase of recovery to understand outcome and predict recovery. When the PLORAS database is used with an individual's lesion information combined with time post-stroke and speech behaviour it provides a strong predictor of longitudinal aphasia recovery.

Developmental priority

- Index structural damage to and integrity of the arcuate fasciculus with diffusion weighted imaging in the late subacute and chronic phases of recovery to understand and predict outcome.
- Predict recovery using perfusion CT and MRI in the hyperacute phase.
- Determine if structural damage predicts therapy or treatment response in the subacute through to chronic phases.
- Predict recovery and treatment response in subacute to chronic phase using measures of task-based fMRI activation.
- Explore measures of inter and intra-network connectivity (including rsFC) and multivariate connectome-based symptom mapping for prediction of outcome and treatment response.

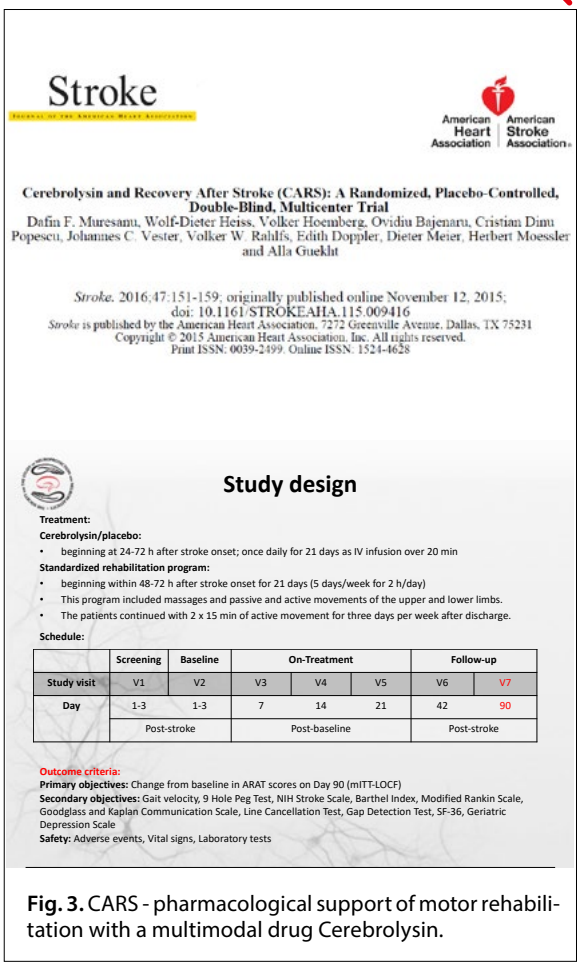
CST: corticospinal tract; CT: computed tomography; DTI: diffusion tensor imaging; FC: functional connectivity; fMRI: functional magnetic resonance imaging; MEP+: motor evoked potential present; MEG: magnetoencephalography; MEP-: motor evoked potential absent; MRI: magnetic resonance imaging; PLORAS: predicting language recovery and outcome after stroke; rsFC: resting state functional connectivity; sEEG: sensory electroencephalography.

Boyd L.A. Neurorehabilitation Neural Repair 2017 Oct-Nov;31(10-11):864-876

Fig. 2. Biomarkers in rehabilitation - current consensus

For stroke patients, upper limb deficits are of special concern. Upper limb impairment has devastating consequences on quality of life, not only impeding the returning to previous activities, but also interfering with the ADLs like eating, dressing and washing. Therefore, the recovery of upper limb deficits became a core objective of rehabilitation after stroke. Nakayama et al., (1994) showed that: at 30 days 80% of patients reached the maximum level of their recovery in upper limb and at 9 weeks 95% of patients reached the maximum level of their recovery. After 11 weeks, no improvement was noted in the spontaneous recovery of upper limb. The speed and amount of recovery of upper limb was dependent on severity of initial deficits, with 79% of patients with mild paresis having a complete recovery and only 18% of patients with severe paresis recovering the functions of upper limb completely. Progress of time is responsible for 16% to 42% of the observed improvements in the first 6 to 10 weeks after stroke onset. A complete motor recovery occurred in less than 15% of the patients, both for the upper and lower extremities and only a quarter of stroke survivors are able to return to the previous activities (Kwakkel et al., 2016). Regarding the pharmacological support of rehabilitation, Dr. Muresanu indicated that historically the monomodal neuroprotective suppressive drugs with single or pleiotropic mechanism of action failed in clinical trials. Some monomodal pleiotropic drugs stimulating only neuroplasticity during neurorehabilitation are still an interesting option, while multimodal drugs with immediate pleiotropic neuroprotective effect, that modulate acute neuroprotection and long term recovery, are of special interest (Muresanu et al., 2012).

Cerebrolysin is an example of pharmacological agent belonging to the last group of multimodal drugs. Dr. Muresanu went on to detail CARS study experience which, in his opinion, set a new standard for the concept of pharmacological support of motor rehabilitation **(Fig. 3)**.


Stroke

American Heart Association | American Stroke Association

Cerebrolysin and Recovery After Stroke (CARS): A Randomized, Placebo-Controlled, Double-Blind, Multicenter Trial

Dafin F. Muresanu, Wolf-Dieter Heiss, Volker Hoemberg, Ovidiu Bajenaru, Cristian Dinu Popescu, Johannes C. Vester, Volker W. Rahlfs, Edith Doppler, Dieter Meier, Herbert Moessler and Alla Guekht

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Study design

Treatment:

Cerebrolysin/placebo:

- beginning at 24-72 h after stroke onset; once daily for 21 days as IV infusion over 20 min

Standardized rehabilitation program:

- beginning within 48-72 h after stroke onset for 21 days (5 days/week for 2 h/day)
- This program included massages and passive and active movements of the upper and lower limbs.
- The patients continued with 2 x 15 min of active movement for three days per week after discharge.

Schedule:

	Screening	Baseline	On-Treatment			Follow-up	
Study visit	V1	V2	V3	V4	V5	V6	V7
Day	1-3	1-3	7	14	21	42	90
	Post-stroke		Post-baseline			Post-stroke	

Outcome criteria:

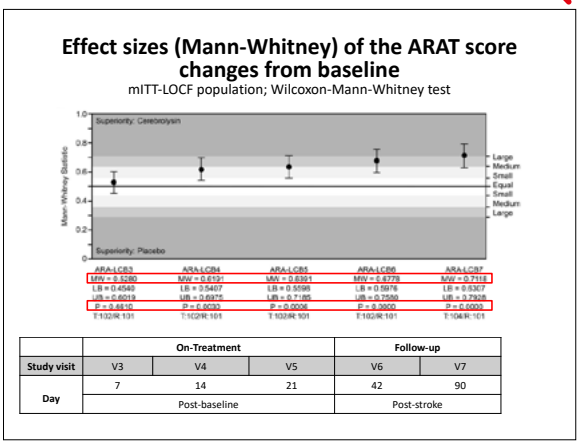
Primary objectives: Change from baseline in ARAT scores on Day 90 (mITT-LOCF)

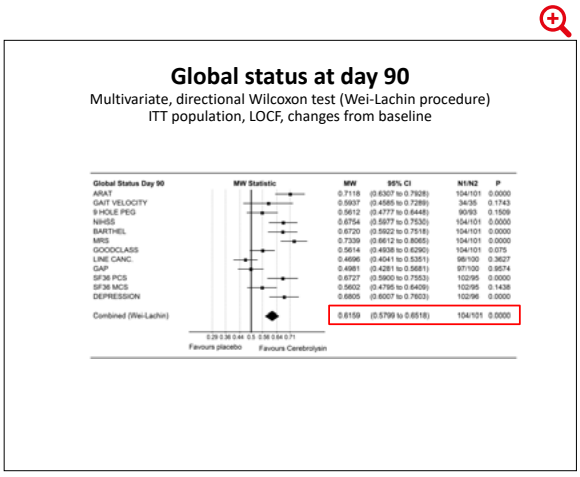
Secondary objectives: Gait velocity, 9 Hole Peg Test, NIH Stroke Scale, Barthel Index, Modified Rankin Scale, Goodglass and Kaplan Communication Scale, Line Cancellation Test, Gap Detection Test, SF-36, Geriatric Depression Scale

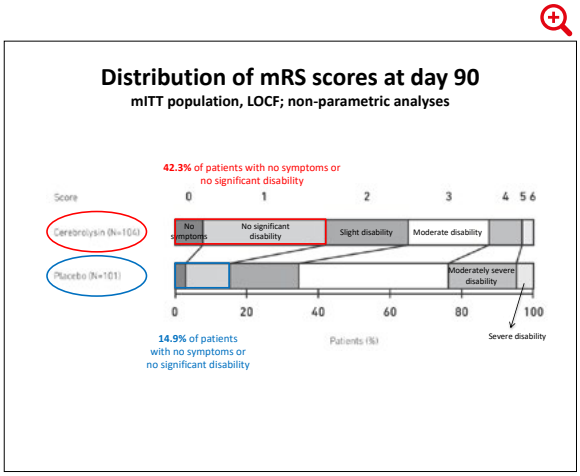
Safety: Adverse events, Vital signs, Laboratory tests

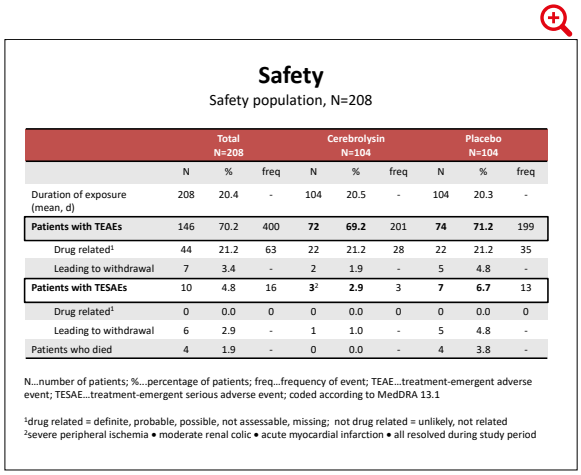
Fig. 3. CARS - pharmacological support of motor rehabilitation with a multimodal drug Cerebrolysin.

The combination of right pharmacological agent and motor rehabilitation allowed for dynamic recovery of upper limb function which was assessed with the ARAT score. This allowed for preventing of complications and could potentially slow down the cognitive decline of the patients. Also the result of mRS was relevant for the combination group and further confirmed efficacy of the treatment and general impact of progress in motor recovery for the functional outcomes **(Fig. 4)**.









Safety

Safety population, N=208

	Total N=208			Cerebrolysin N=104			Placebo N=104		
	N	%	freq	N	%	freq	N	%	freq
Duration of exposure (mean, d)	208	20.4	-	104	20.5	-	104	20.3	-
Patients with TEAEs	146	70.2	400	**72**	**69.2**	201	**74**	**71.2**	199
Drug related[1]	44	21.2	63	22	21.2	28	22	21.2	35
Leading to withdrawal	7	3.4	-	2	1.9	-	5	4.8	-
Patients with TESAEs	10	4.8	16	**3**[2]	**2.9**	3	**7**	**6.7**	13
Drug related[1]	0	0.0	0	0	0.0	0	0	0.0	0
Leading to withdrawal	6	2.9	-	1	1.0	-	5	4.8	-
Patients who died	4	1.9	-	0	0.0	-	4	3.8	-

N...number of patients; %...percentage of patients; freq...frequency of event; TEAE...treatment-emergent adverse event; TESAE...treatment-emergent serious adverse event; coded according to MedDRA 13.1

[1]drug related = definite, probable, possible, not assessable, missing; not drug related = unlikely, not related
[2]severe peripheral ischemia • moderate renal colic • acute myocardial infarction • all resolved during study period

Fig. 4. The results of CARS study confirmed safety and efficacy of the combination Cerebrolysin and motor rehabilitation

The concept of CARS was further corroborated in a parallel study performed on different patients population and the meta-analysis of both trials was recently published (Guekht et al., 2017). The conclusions were almost the same. The combined ARAT score and the early benefit measured with NIHSS at 14 and 21 days, were shown to be significantly improved in the Cerebrolysin group.

Dr. Muresanu finished his presentation by mentioning the results of ECOMPASS study (Chang et al., 2016) in which the mechanistic proof of efficacy was generated for Cerebrolysin in the motor rehabilitation after stroke. The rsfMRI data showed that treatment with Cerebrolysin prevented compensation mechanisms triggered in the contralateral hemisphere after stroke. The compensation, as we know, can disturb or even hinder true recovery of lost motor functions. Cerebrolysin treated patients regained the symmetrical activation of the motor cortical function and that allowed for true recovery of the upper limb functions.

New evidence from a recent meta-analysis in acute ischemic stroke

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ABSTRACT:

This meta-analysis combines the results of nine ischemic stroke trials, assessing efficacy of Cerebrolysin on global neurological improvement during early post-stroke period. Cerebrolysin is a parenterally administered neuropeptide preparation approved for treatment of stroke. Design: All included studies had a prospective, randomized, double-blind, placebo-controlled design. The patients were treated with 30-50 ml Cerebrolysin once daily for 10-21 days, with treatment initiation within 72 hours after onset of ischemic stroke. Data Sources: For five studies original analysis data were available for meta-analysis (individual patient data analysis), for four studies aggregate data were used. Study Selection: The combination by meta-analytic procedures was pre-planned and the methods of synthesis were pre-defined under blinded conditions. Search deadline for the present meta-analysis was December 31st, 2016. Results: The nonparametric Mann-Whitney (MW) effect size for NIHSS on day 30 (or 21), combining the results of nine randomized, controlled trials by means of the robust Wei-Lachin Pooling Procedure [MERT], indicated superiority of Cerebrolysin as compared with placebo (MW 0.60, P<0.0001, N=1879). The combined number-needed-to-treat (NNT) for clinically relevant changes in early NIHSS was 7.7 (95% CI 5.2 to 15.0). The additional full scale ordinal analysis of mRS at day 90 in moderate to severe patients resulted in MW 0.61 with statistical significance in favor of Cerebrolysin (95% CI 0.52 to 0.69, P = 0.0118, N = 314). Safety aspects were comparable to placebo. Conclusion: Our meta-analysis confirms previous evidence that Cerebrolysin has a beneficial effect on early global neurological deficits in patients with acute ischemic stroke.

The lecture was dedicated to discussion of the results of the newly published meta-analysis of nine randomized clinical trials of Cerebrolysin in early post-stroke recovery. Dr. Bornstein is the first author of this publication. Before analyzing the results, Dr. Bornstein introduced the audience to the topic of timing in post-stroke rehabilitation and the evolution of the concept and guidelines for establishing the scientific evidence. Both these topics were relevant for choosing the methodology and for validating the interpretation of Cerebrolysin clinical data in the meta-analysis.

One of the most important aspects of stroke rehabilitation is patients activity. The bed rest causes multitude of complications after stroke and should be avoided whenever possible. At the same time, we need a proper timing of the rehabilitation efforts in order to avoid potentially hazardous incidents while maximizing the recovery processes **(Fig. 1)**.

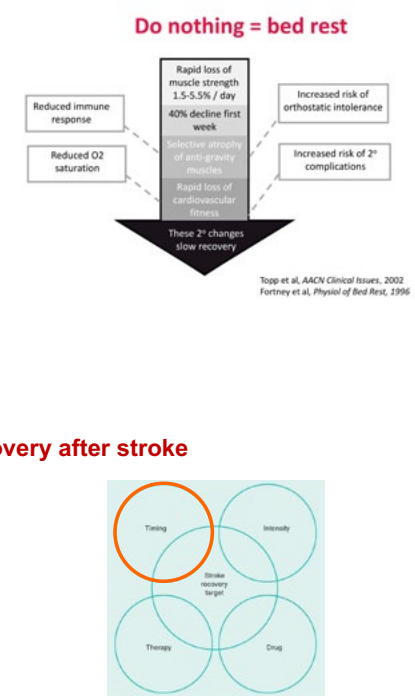

Fig. 1. Bed rest after stroke and timing of the rehabilitation

Every phase of stroke needs a different therapeutic approach. For example, very early mobilization is sometimes bad for a patient. The endogenous mechanisms of neurorepair in the very early stages must be utilized with caution to accelerate true recovery of lost functions. Before the stroke enters the chronic stage, there is a relatively rapid and strong phase lasting for about three months. During this phase, we can observe the process of spontaneous recovery in mild to moderate stroke patients. While there is a chance of stimulating recovery in the chronic phase, we should focus on the early post-acute phase, in which the processes of self-repair are most potent and could be further stimulated for the enhanced recovery.

The critical evaluation of available therapeutic options is necessary for the decision process in stroke rehabilitation. In the past, the hierarchy of medical evidence dictated that randomized, controlled, double blind studies are the gold standard in medicine. However, this paradigm shifted recently into meta-analyses of randomized clinical trials which are the most important tools to evaluate and rate clinical evidence. The concept of RCTs is strong and entails such methodological milestones as: randomization to avoid selection bias, prospective design using controlled condition, blinding, defined population, detailed covariate information, and high integrity of data. However, RCTs have also their weaknesses. Among them are: generally small sample size, protocol driven care, center and patient selection narrowly defined. The good way to overcome these problems is to use meta-analyses of RCTs. They provide level 1 evidence (the highest in rank). Meta-analysis is the statistical combination of results from two or more separate randomized, controlled clinical trials into a single estimate. The major advantage of a meta-analysis is increase in statistical power and improvement in precision.

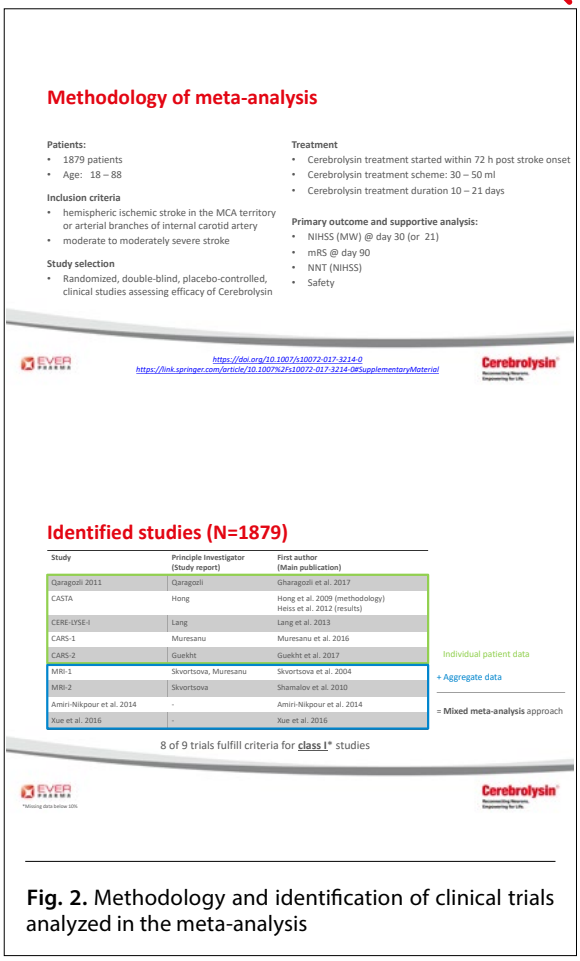

Fig. 2. Methodology and identification of clinical trials analyzed in the meta-analysis

The aim of the meta-analysis of Cerebrolysin RCTs was evaluation of the efficacy and safety of Cerebrolysin in patients with ischemic stroke, with focus on early neurological conditions measured with NIHSS and on functional status using mRS. The specific clinical question the authors asked before conducting this research was "Does 30 to 50 ml Cerebrolysin treatment, initiated within 72 hours post-acute ischemic stroke and administered for at least 1 week, have an effect on early neurological status?".

The general methodology of the meta-analysis was described and Dr. Bornstein listed the studies identified in the process **(Fig. 2)**.

In the primary efficacy analysis (NIHSS at day 30), the early recovery after stroke was assessed. It was shown that patients have a 60% better chance for better outcome when treated with Cerebrolysin. This was confirmed by the rule of leave-one-out which weights the impact of one particular trial on the combined result. This analysis showed strong sign for an overall robustness of results and that the key meta-analysis results were not triggered by a specific study. Additionally, the assessment of the NNT (number needed to treat for clinical benefit) parameter revealed separately and confirmed the higher chance of recovery for patients treated with Cerebrolysin. NNT of 7.7 for Cerebrolysin was comparable to the results obtained earlier when establishing the thrombolysis standard in stroke (NNT=8.0) **(Fig. 3)**.

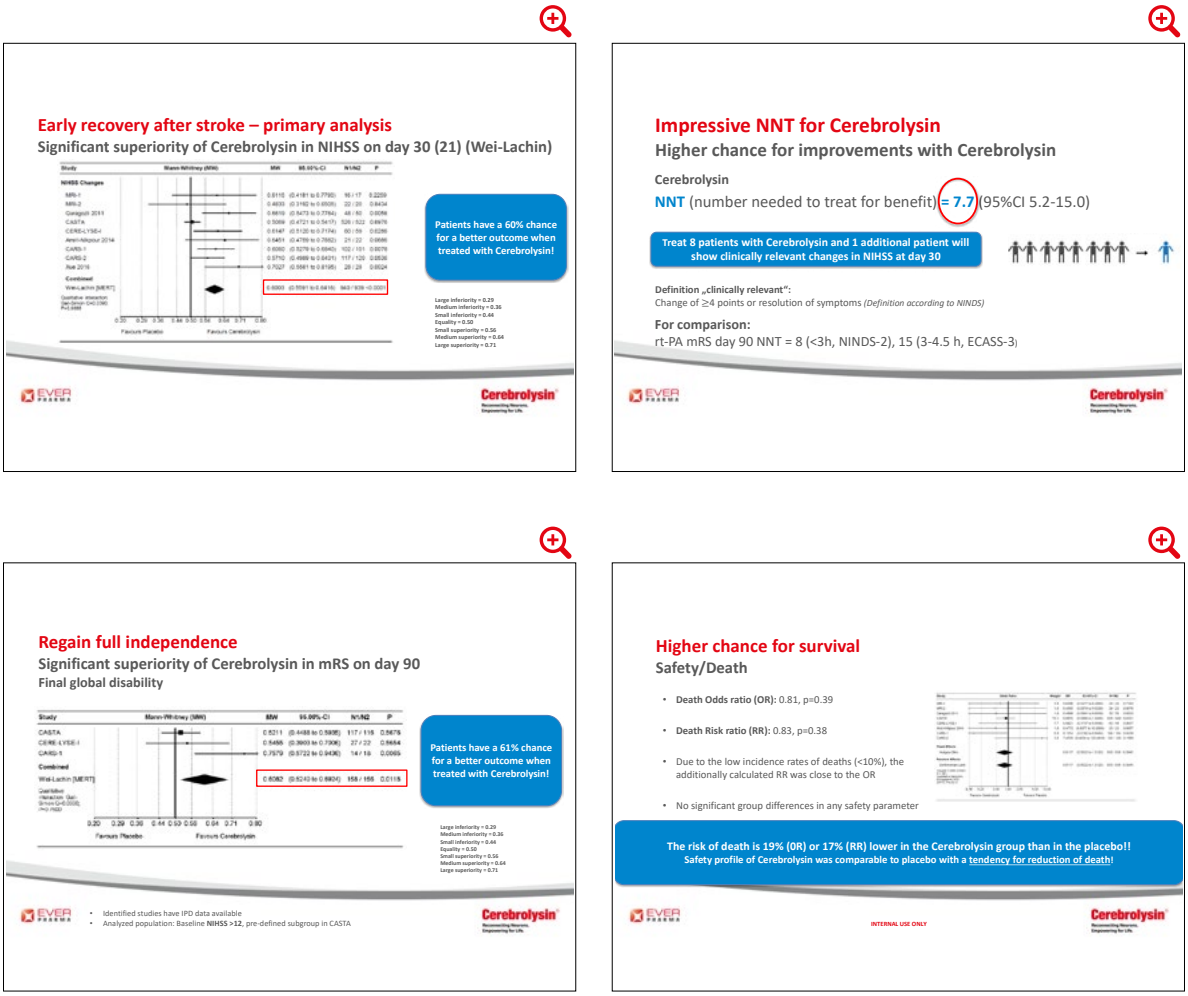

Fig. 3. The results of the meta-analysis of Cerebrolysin RCTs in early stroke recovery

Similar size of the effect was seen in mRS analysis, indicating 61% higher chance for regaining full independence at day 90. Finally, a trend toward improved chances of survival was detected with the risk of death at 19% (OR) or 17% (RR) lower level in the Cerebrolysin group than in the placebo group. Cerebrolysin was safe and well tolerated with the safety profile similar to that of placebo.

This was a strong meta-analysis and the largest meta-analysis of Cerebrolysin in stroke performed to date. It was conducted in response to increased importance of meta-analysis as a method of choice for assessment of evidence in the medical world. Individual patients data (IPD) were available for the majority of studies. Findings were homogenous and showed consistent superiority of Cerebrolysin. No limitations as in other recent meta-analyses were apparent, allowing for valid and robust methodology and generation of correct data. Summarizing his lecture, Dr. Bornstein said that the meta-analysis showed clear superiority of Cerebrolysin at day 30 indicating early recovery and confirming observations from animal models of stroke. The combined NNT for clinically relevant changes in early recovery was 7.7. Statistically significant long term benefits – strongest effects observed in patients with higher baseline severity - were also detected, together with excellent safety profile of Cerebrolysin, with a tendency for reduction of death rate. The benefits of Cerebrolysin treatment can be seen in the early recovery after stroke and higher chance of improvement with Cerebrolysin is consistently documented.

Volume 24; 2018

EVER PHARMA

ABBREVIATED PRESCRIBING INFORMATION. Name of the medicinal product: Cerebrolysin – Solution for injection. Qualitative and quantitative composition: One ml contains 215.2 mg of porcine brain-derived peptide preparation (Cerebrolysin concentrate) in aqueous solution. List of excipients: Sodium hydroxide and water for injection. Therapeutic indications: Organic, metabolic and neurodegenerative disorders of the brain, especially senile dementia of Alzheimer's type – Post-apoplectic complications – Craniocerebral trauma; post-operative trauma, cerebral contusion or concussion. Contraindications: Hypersensitivity to one of the components of the drug, epilepsy, severe renal impairment. Marketing Authorisation Holder: EVER Neuro Pharma GmbH, A-4866 Unterach. Only available on prescription and in pharmacies. More information about pharmaceutical form, posology and method of administration, special warnings and precautions for use, interaction with other medicinal products and other forms of interaction, fertility, pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, overdose, pharmacodynamics properties, pharmacokinetic properties, preclinical safety data, incompatibilities, shelf life, special precautions for storage, nature and contents of the container and special precautions for disposal is available in the summary of product characteristics.

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edited by: Pawel J. Ciesielczyk, PhD; EVER Neuro Pharma GmbH; made by Artists