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Safety in pharmacological enhancement of stroke rehabilitation

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Pharmacological enhancement of neurorehabilitation is based on the concept of neuroplasticity. Agents with probably unfavourable effects on recovery (e.g. classical antiepileptic drugs, butyrophenones) should be avoided. The findings of experimental studies in animal models, investigations in healthy subjects and the findings of neurophysiological studies indicate that there is scope for benefit from pharmacological enhancement in stroke rehabilitation in the clinical setting - in addition to rehabilitative therapies. Randomized controlled clinical trials have shown benefit of pharmacological enhancement in stroke rehabilitation for some agents. Nevertheless, the clinical evidence regarding benefits of this treatment approach is still considered weak for the following reason: First, the beneficial findings of some studies were not confirmed by others. Second, several studies were limited by small patient populations and narrow inclusion criteria. Third, there were concerns regarding safety of some agents (i.e., piracetam, and amphetamines). Dopaminergic agents, Selective Serotonin-Reuptake-Inhibitors (SSRI) and acetylcholinesterase-inhibitors are promising candidates. Their safety and efficacy should be further investigated; ideally in – sufficiently powered – large randomized controlled trials.

KEY WORDS: Shoke - Recovery - Pharmacotherapy - Neurorehabilitation - Safety.

The concept of brain plasticity and the findings of experimental studies in animals as well as in humans indicate that pharmacological enhancement of recovery after stroke is feasible and that there is scope for benefit.[1, 2]

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The aim of rehabilitation after stroke is to aid reorganization of the ischemically damaged neuronal network structures.[3] This dynamic process of reorganization is also named neuronal plasticity of the central nervous system and occurs on different levels. It includes alterations of synaptic efficacy, unmasking of latent connections, axonal sprouting, synaptogenesis, neurogenesis and more.[2, 3] Some of which can be modulated pharmacologically.[2, 3] For many years the evidence for such treatment approach was mostly anecdotic or based on small, mostly uncontrolled observational data. During the last years more convincing studies have emerged. The current report provides a review across studies about pharmacological enhancement of stroke recovery and put a special focus on safety aspects.

Agents with a negative impact on brain plasticity and recovery

Experimental studies and clinical observations indicate that classical neuroleptics in particular butyrophenones like haloperidol have unfavorable effects on recovery and neuroplasticity. Likewise, benzodiazepines like lorazepam – sometimes used as tranquillizer or in patient with delirium – showed an unfavorable effect.[4, 5] Therefore, such agents should

be avoided if ever possible.[6] In agitated patients, an alternative to benzodiazepins could be clomethiazole: in a controlled randomized study (*i.e.*, CLASS-I) – clomethiazol was tested against placebo in order to reveal putative neuroprotective effects.[7] The study result was neutral, *i.e.*, there was no difference in recovery between the patient groups treated with clomethiazol and those treated with placebo. Thus, there was no safety concern about clomethiazol with regard to functional recovery after stroke. However, one should be aware that nearly half of the patients in the clomethiazol-group but only 30% of the placebo-group experienced some degree of somnolence during the treatment course.[7] As clomethiazol increases bronchial secretion, the agent should not be given to patients with asthma, or acute or chronic lung diseases.[8]

Older, classical antiepileptic agents such as phenytoin or phenobarbital also have an negative impact on recovery.[4] In patients with poststroke epileptic seizures, requiring antiepileptic treatment, the use of levetiracetam,[9] or lamotrigine [10, 11] may bereasonable alternative, as such unwanted effect were not reported at least in animal studies.

Agents with a potentially positive impact on brain plasticity and recovery

Levodopa

Animal studies showed that dopamine has a crucial role in motoric learning and for synaptic plasticity.[12] If rats had memory training together with levodopa, they had a better performance in memory tests four months later as compared with rats who had memory training without levodopa enhancement.[13] In healthy humans, the use of levodopa led to a faster and better word learning.[14] A beneficial effect was also reported for swallowing.[15] Likewise, in locomotion tasks healthy subjects with pretreatment of levodopa veered less than the placebo-treated subjects in the control group.[16] Interestingly, none of the levodopa treated subjects in the latter study had any recognizable side effects; in particularly neither nausea, nor vertigo was reported. In stroke patients, a randomized, placebo-controlled study showed that levodopa given in a dose of 100 mg per day for three weeks (six weeks after stroke onset), as add-on-treatment to physical therapy revealed a significant better motor recovery than physical therapy alone. This beneficial effect was present also three weeks after levodopa treatment had been stopped.[17] With regard to safety issues: one of the 26 patients randomized for levodopa had nausea at the beginning, which was absent in the 27 patients randomized for placebo. In the placebo group, two patients discontinued the trial for infection (N.=1) and early discharge (N.=1). In the levodopa-group, four patients terminated the trial early because of adverse events. These include pneumonia (N.=2), orthopedic complications (N.=1) and early discharge (N.=1).[17] However, the study population was small (N.=53) and the beneficial effect of levodopa on stroke recovery could not be reproduced later [18] indicating the possibility of chance findings. Still, levodopa appeared to be safe in this study too. Solely one patient in the levodopa-group (N.=11) and one patient in the placebo-group (N.=7) experienced confusions, while other adverse events were absent.[18]

In stroke-related aphasia levodopa had been tested in a randomized controlled setting: 20 patients received 100 mg levodopa per day (N.=20) or placebo (N.=19) eight weeks after stroke onset. Study medication was given 30 minutes before language therapy. Treatment has lasted for three weeks. Patients with levodopa experienced greater improvement in verbal fluency and repetition. Serious adverse events were absent.[19] No significant adverse were reported in the levodopa-group. One patient in the placebo group had a hemorrhagic stroke.[19] In another study, 10 chronic stroke patients received levodopa or placebo in a double-blind placebo-controlled crossover study.[20] Levodopa-treatment had no benefit with regard to dexterity, force and functionality of the paretic arm. Therefore, there is still uncertainty about the effectiveness of levodopa in enhancing stroke rehabilitation. At least levodopa appears to be relatively safe: In an observational study focused on safety of pharmacological enhancement of rehabilitation after stroke, only 4 of 36 patients treated with levodopa had any kind of adverse events. None were serious, all were relatively mild and transient and comprised of diarrhea (n=1), nausea (n=1), and hallucinations (N.=2).[21]

Dopamine agonists

Ropinirol (0.25-4 mg once a day) or placebo was given in addition to physical therapy in a small study

of 33 stroke patients with moderate motor deficits 1 to 12 months after stroke onset.[22] The primary outcome was gait velocity after 12 weeks. After a treatment duration of nine weeks, ropinirol treatment did not result in a benefit compared to placebo. In five patients, serious adverse events occurred. One (*i.e.*, falling) occurred in the placebo-group. Four other serious adverse events (new stroke, urinary tract infection, aphasia and sensory motor symptoms, death from bile duct cancer) occurred in the ropinirol group, but were thought to be unrelated to the study medication. None-serious adverse events in the ropinirol-group included sleepiness (N.=8), fatigue (N.=6) and dizziness (N.=3) of the 17 patients treated with ropinirol and physical therapy.[22]

For post-stroke aphasia, case reports and small observational, uncontrolled studies have been published. With regard to safety, in one series several patients developed dystonia (*i.e.*, 5 out of 7 patients in one study; overview in Bakheit 2004).[23]

Selective serotonin reuptake inhibitors

A small placebo-controlled study of eight patients with pure motor stroke showed that the application of fluoxetine (20 mg) have improved motor performance.[24] In 2011, a relatively large randomized placebo-controlled trial testing fluoxetine for enhancement of motor recovery after stroke was published.[25] The 57 patients treated with fluoxetine (20 mg once a day) had a significantly better motor recovery as measured with the Fugl-Meyer motor scale than 56 placebo-treated patients. Both groups had comparable amounts of usual rehabilitation therapies. Furthermore, the rate of patients who reached independence in the activities of daily living (modified Ranking Scale (mRS) score 0-2) were significantly larger in the fluoxetine group than in the placebo-group (after adjustment for potential confounders [*i.e.*, the variables "study center", "prior stroke" and "initial mRS-score")]. The main adverse events in the fluoxetine- and placebo-groups were hyponatremia (4% in both groups), transient digestive disorders including nausea, diarrhea and abdominal pain (25% for fluoxetine, 11% for placebo), hepatic enzyme disorders (9% for fluoxetine, 18% for placebo), psychiatric disorders (5% for fluoxetine for 7% placebo), insomnia (33% fluoxetine, 36% placebo) and partial epileptic seizures (2% for fluoxetine *vs.* 0% for placebo). Two of the adverse events in the fluoxetine group were serious (1 hyponatremia and 1 partial epileptic seizure) and two patients died (1 in each group). Interestingly, the rate of newly encountered depression during the treatment period was significantly greater in the placebo group (29%) than in the fluoxetine group (7%).[25] Therefore, SSRI seem to have a positive influence on the occurrence of "post stroke depression", which may contribute to the favorable effect on the functional outcome. A beneficial effect has also been shown for escitalopram [26, 27] and citalopram.[28, 29] Thus, the benefit in motor recovery associated with the use of SSRIs in addition to neurorehabilitative therapies seems to reflect a class effect rather than a characteristic restricted to a distinct agent.

Reboxetine

In a double-blind placebo-controlled crossover study chronic hemiparetic stroke patients (N.=10) received a single dose of reboxetine or placebo, before they participated in a one-hour physical therapy session focused on the function of the paretic hand. Compared with placebo reboxetine-treated patients had an increase of tapping-speed and grip-strength of the paretic hand. In the reboxetine group one patient reported a short lasting period of nausea, but was able to complete the investigation. No other adverse events were reported.[30]

Acetylcholinesterase inhibitors

Acetylcholinesterase inhibitors (AchEi) are known to improve cognition in Alzheimer's disease. Impairment of cognition is also common after stroke and predicts poor functional recovery. A placebo-controlled double-blind study of 26 patients with post-stroke aphasia at a chronic stage (*i.e.*, more than one year after stroke onset) showed a beneficial effect on the degree of severity of aphasia effect if treated with 10 mg donepezil as add on treatment.[31] The same authors reported also a positive effect of donepezil on the sensomotor function in chronic stroke patients with marked hemiparesis.[32] In the study of aphasic patients, adverse events were more frequent in the donepezil group (61%) than in the placebo group (23%).[31] Irritability (4 patients [30%]), insomnia and tiredness (2 patients [15%]) were seen only during donepezil titration. Recurrent post-stroke seizures (2 patients [15%]) were seen during

donepezil maintenance without relapse after dose reduction. Adverse events in the placebo-group included headaches (N.=1), abnormal dreams (N.=1) and anorexia (N.=1).[31]

In a 12 week-open label study, donepezil was compared to galantamine in stroke survivers aged >60 years with cognitive impairment. Study patients treated with donepezil (max. dose 10 mg per day) had greater improvement in activities of daily living (as measured with the functional independence measure) compared to 13 galantamine-treated participants. Among the originally 40 participants, 14 (7 on donepezil, 7 on galantamine) dropped out prior to week 12. Reasons for dropping out included gastroenterological side effects (N.=5), concurrent medical profiles (N.=3), and new onset agitation (N.=1), which might be drug-related adverse events. Four other study patients withdrew consent and one patient was relocated.[33]

Donepezil was also studied in a randomized double-blind, placebo-controlled trial among CADASIL patients with subcortical vascular cognitive impairment. While some improvements were noted on measures of executive functions, there was not difference between Donepezil-treated (N.=86) or placebo-treated (N.=62) CADASIL- patients in the primary endpoint (*i.e.*, the change of the vascular Alzheimer disease assessment scales cognitive [V-ADAS-cog] at 18 weeks). With regard to safety, 10 donepezil-treated patients discontinued treatment due to adverse events compared to 7 placebo-treated patients.[34]

Piracetam

Piracetam has been considered to have potentially neuroprotective effects, though the exact mechanism has yet to be explored in detail.[35] Piracetam has been studied in the rehabilitation of stroke-related aphasia in doses up to 4.8 g per day. A systematic meta-analysis reported weak evidence, that patients might improve in language measures if treated with piracetam.[36] Patients who were treated with piracetam had no statistically significantly higher risk than those who took a placebo to experience adverse events (Odds ratio 1.29, 95% Confidence interval 0.9 to 1.7). However, the higher death rates among piracetama treated patient "gave rise to some concerns that there may be an increased risk of death from taking piracetam".[36] The authors concluded therefore "more research is needed for exploring the effect of drugsfor (stroke-related) aphasia in particular piracetam. If a trial is done, this must be large enough to have adequate statistical power. The safety of the drug should be of primary interest".[36] Another systematic review summarized the effects of piracetam on acute ischemic stroke. Piracetam was associated with a statistically non-significant increase in death at one month. However, this insignificantly higher rate of death might simply reflect imbalances in the clinical deficit in stroke severity between piracetam-treated patients and those of the control group. Despite data on more than 1000 patients, the issue of safety and effectiveness of piracetam is still unclear.

Memantine

Memantine is an N-Methyl-D-Aspartat (NMDA) antagonist with proven efficacy in severe Alzheimer disease. Experimental data suggest that memantine might also be effective in recovery after brain ischemia.[37] Observational data on 17 patients with posttraumatic cognitive impairment and serial PET suggest also a positive effect of memantine.[38] The combined application of memantine and "constrained induced treatment" lead to a beneficial effect in patients with aphasia.[39] With regard to safety, more recently findings in a murine model suggest that memantine may improve the safety of thrombolysis for acute ischemic stroke by prevention of noxious effects of tissue-plasminogen activator.[40]

Amphetamines

Amphetamines (*i.e.*, d,l-amphetamine, dexamphetamine, and methamphetamine) have been tried to enhance recovery after stroke; dexamphetamine is considered the most powerful central nerve system stimulant of the three.[41] The beneficial effect is likely mediated by Noradrenaline. Common side effects of Amphetamines are nervousness, insomnia, loss of appetite and addiction.[41] A systematic meta-analysis (Cochrane Review) [41] which involved 10 studies with 287 patients showed that – despite improved motor recovery after stroke – there was no evidence of a beneficial effects regarding dependency or death associated with amphetamine treatment. Due to a - non-significant - trend for more deaths at the end of follow-up among amphetamine allo-

cated patients (Peto Odds ratio 2.8, 95%-Confidence interval from 0.9 to 8.6), amphetamines should, if at all, exclusively be used in sufficiently designed and powered research studies.[41]

A more recent double-blind placebo-controlled randomized trial showed a significant gain in activities of daily living and arm function.[42] Interestingly, just 16 patients from 918 which were screened could be randomized to either dexamphetamine (10 mg orally, twice per week) plus physiotherapy or placebo (plus physiotherapy).[42] More importantly, adverse events were absent. Nevertheless, one patient in the amphetamine-group, but none on the placebo group, died during follow-up ("not related to the study").[42] In addition, one amphetamine-treated patient, but none of the placebo-treated patients, had to be "transferred to acute care during the intervention period because of health problems not related to the study".[42] Thus, any potential benefit of dexamphetamine in stroke rehabilitation is likely to be limited to a highly selected subgroup of stroke patients. Due to open questions about safety the use should be limited to patients participating in adequately powered and controlled studies.

Amantadine

Amantadine is considered an NMDA antagonist and indirect Dopamine antagonist.[43] Amantadine has been studied in smaller studies about traumatic brain injury. A meta-analysis across three retrospective and two randomized controlled double-blind studies concluded that the use of 200 to 400 mg amantadine per day is relatively safe and may influence consciousness and cognition positively.[44] Due to the large heterogeneity of the data more prospective controlled studies in a homogeneous population of patients are required according to Sawyer and colleagues.[44] More recently a randomized, placebo-controlled study in 184 patients with vegetative state or minimally-conscious state for 16 weeks after traumatic brain injury has been published. During a 4-week-treatment period recovery was significantly faster in the amantadine-group than in the placebo-group as measured by the Disability Rating Scale.[45] Medical complications in this – severely affected – patient population were frequent. However, significant differences in the incidence of adverse events between both groups were absent. The adverse events which were, just numerically but not significantly, more frequent in the amantadine-group than in the placebo-group were vomiting (11% *vs.* 8%), agitation (14% *vs.* 11%), hypertonia or spasticity (21% *vs.* 14%). One patient in the amantadine-group died from cardiac arrest.[45]

Methylphenidat

Due to its catecholamine-stimulating characteristics, Methylphenidate had been tested in enhancing stroke rehabilitation. In a prospective randomized double-blind placebo-controlled study 21 stroke patients were either treated with Methylphenidate (5 mg, increased to 30 mg per day) a placebo. Study medication was used in combination with physical therapy for three weeks. Patients treated with methylphenidate had less depression, greater achievements in activities of daily living and better motor recovery. There was no difference in the number of side effects; however, details were not given.[46] More recently, a beneficial effect of methylphenidate (with or without additional levodopa) had been reported with regard to mood, cognitive and motor recovery.[47, 48] No adverse events were observed in Methylphenidate- as well as placebo-treated patients. However, 15 of 100 participants were lost to follow-up because of death. The cause of death was reported to be related to initial stroke and not considered to be a result of the study participation. Interestingly, just 100 stroke patients out of 1043 met all inclusion criteria in the aforementioned study. It is likely that contraindications - especially the cardiovascular ones - limit the use of methylphenidate, in particular in older stroke patients.

Modafinil

Modafinil, which is usually used in the treatment of narcolepsy or idiopathic hypersomnia, seems to have a positive influence on wakefulness and awareness by positive impact on excitatory transmission processes. In mixed population of patients with stroke and multiple sclerosis, modafinil reduced the severity of fatigue.[49]

Subgroup analysis showed a beneficial effect of modafinil (50-200 mg per day) in the 10 patients with vertebrobasiläre stroke, while such an effect was absent among 9 patients with carotidal cortical stroke. The tolerability of the starting dose of 50 mg was good. However, the frequency of adverse events increased

with advancing dosages. Headache, increased irritability, and aggressiveness were the most common adverse events. One out of four study patients stopped the study prematurely due to of adverse events.[49]

Conclusions

The reviewed data indicate that the evidence for the use of pharmacological enhancement of stroke recovery is currently rather weak. Positive studies, those showing a beneficial effect, were usually based on a small study population with narrow eligibility criteria. Furthermore, they were usually focused on a distinct clinical symptom (*e.g.*, motor recovery). Heterogeneity was also frequent with regard to the timing of the start of pharmacological enhancement. For some agents, (*e.g.*, amphetamines and piracetam) the safety is still questionable, at least for the majority of stroke patients. In several studies, agents (*e.g.* methyphenidate or amphetamines) were applicable just to a small minority of patients. Nevertheless, the approach of pharmacological enhancement of stroke rehabilitation applied as add-on-treatment to conventional rehabilitation therapies – seems to be attractive. A recent observational study in Switzerland about pharmacological aid of recovery in the clinical practice of in-hospital stroke rehabilitation revealed that 257 (55.4%) of 464 patients had agents potentially enhancing recovery. In 159 (34.3%) patients such agents were exclusively used to aid recovery (*i.e.*, without an otherwise established indication).[50] The distribution of agents used is shown in Figure 1. Interestingly, the utilization rates of pharmacological enhancement differed largely across centers. Thus, this observation suggests uncertainty about usefulness and safety of this approach and indicates the need for additional studies.[50] Future randomized controlled and adequately powered trials are strongly encouraged. Some studies are indeed ongoing or planned. These include, a multicenter randomized double-blinded placebo-controlled trial about dopamine augmented rehabilitation in stroke (DARS) in the United Kingdom,[51] the LIFE-study, in which a new SSRI is going to be tested in several centers across Europe,[52] or the ESTREL Study (Enhancement of Stroke Rehabilitation with Levodopa) in Switzerland.[53] If ever possible, the participation of patients in such trials is strongly encouraged.

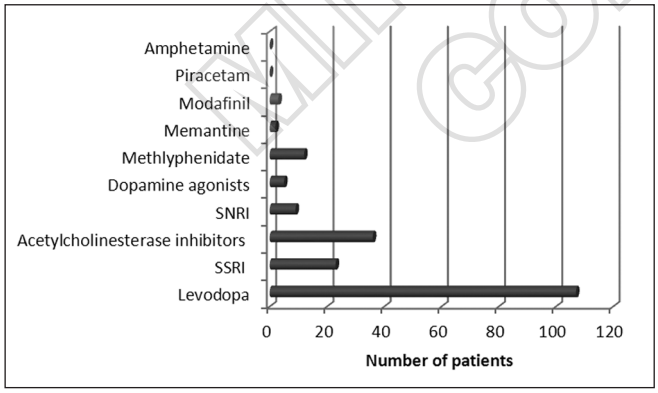

Figure 1.—Distribution of agents used for pharmacological enhancement of stroke rehabilitation. Modified from Engelter ST *et al.*[50]

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