Developments in this area are now moving faster than ever before. It is evident that recovery drugs and techniques promoting recovery after brain ischemia deserve separate consideration and special efforts. A large number of trials are ongoing, and several new methods are being tested in single or combination mode. We have decided to report Cochrane data, meta-analyses, or (when both not available) to select 1 or 2 major papers representative for each area to illustrate the achieved results and to point to the many promising experimental, clinical, and field trials currently underway.

Drug Therapy Options Evolving to Enhance Motor Recovery

Several drugs have been tested for efficacy in motor recovery in recent years, but none has evolved with such clear significance as is the case for Fluoxetine for Motor Recovery in Acute Ischemic Stroke (FLAME) study. This study investigated whether fluoxetine enhances motor recovery if given to patients with motor deficits within the first 10 days after stroke.

One hundred eighteen patients with ischemic stroke and hemiplegia or hemiparesis had Fugl-Meyer motor scale (FMMS) scores of ≤55 and were randomly assigned to fluoxetine (n=59; 20 mg once per day, orally) or placebo (n=59) for 3 months starting 5 to 10 days after the onset of stroke. All patients had physiotherapy. The primary outcome measure was the change in the FMMS score between day 0 and day 90 after the start of the study drug. Two patients died before day 3 withdrew from the study. The remaining 113 showed that fluoxetine enhances motor recovery if given to patients with motor deficits within the first 10 days after stroke.

The main frequent adverse events in the fluoxetine versus placebo groups were transient and not severe. They included nausea, diarrhea, abdominal pain (14 [25%] versus 6 [11%]), and partial seizure (1 [<1%] versus 0).

Chollet et al. concluded that for patients with ischemic stroke and moderate-to-severe motor deficit, the early prescription of fluoxetine with physiotherapy enhances motor recovery after 3 months. They speculate that, although modulation of spontaneous brain plasticity by drugs is a promising pathway for treatment of patients with ischemic stroke, the mechanisms of action are not entirely clear and need to investigated further.

Early Mobilization

Testing early and very early mobilization is a promising concept in patients without severe complications or brain swelling. The A Very Early Rehabilitation Trial (AVERT phase 2) study showed that mobilization within the first 24 hours of stroke and at regular intervals is safe, feasible, and fast-track return to walking unassisted, increasing the likelihood of milder stroke patients being discharged home, and is independently associated with good functional outcomes at 3 and 12 months. Early mobilization is also advocated to prevent poststroke complications, such as contractures and deep vein thrombosis.

Currently, the optimal physical therapy dose in acute stroke care is unknown. The authors hypothesized that physical therapy would be significantly different between treatment arms in a trial of very early and frequent mobilization (VEM) and that immobility-related adverse events would be associated with therapy dose.

This study was a single-blind, multicenter, randomized control trial of acute stroke patients admitted to a stroke unit within 24 hours of onset. Patients were randomized to receive either standard care (SC) or SC plus additional early out-of-bed therapy (VEM). A total of 71 patients (SC n=33; VEM n=38) received 788 therapy sessions in the first 2 weeks of stroke. Schedules (hours to first mobilization, dose per day, frequency, and session duration) and nature (percentage out-of-bed activity) of therapy differed significantly between groups (P<0.001 for all components). Mobilization was earlier and happened on average 3x per day in those receiving VEM, with the proportion of out-of-bed activity double in VEM session (median SC 42.5%; VEM, 85.5%). SC consisted of 17 minutes of occupational and physiotherapy per day and was the same between groups. The number of immobility-related adverse events 3 months post-stroke was not associated with therapy dose or frequency.

The authors detailed the usual care and intervention therapy provided to patients from admission to 14 days after stroke. The therapy schedule was markedly different in the intervention arm, but whether this schedule reduces complications or improves outcome is still unclear until the main phase of the study is finished.
Ambulation With Body Weight Support Treadmill Training

Although timing of mobilization is an important issue, methods of mobilizing stroke survivors also remain an important issue. In only the second National Institutes of Health–funded trial of a rehabilitation intervention, Duncan et al. investigated the use of body weight support in treadmill stepping as an intervention to improve the ability to walk after stroke.

The study was a multicenter, randomized clinical trial of 408 subjects who experienced stroke within 2 months. They were stratified by the extent of walking impairment: moderate (able to walk 0.4 to <0.8 m per second); or severe (able to walk <0.4 m per second). They were randomly assigned to 1 of 3 training groups: training on a treadmill with body weight support 2 months after the stroke (early locomotor training); training 6 months after the stroke (late locomotor training); or an exercise program at home 2 months after the stroke (home exercise program). Each intervention included thirty-six 90-minute sessions for 12 to 16 weeks. The primary outcome measure was the proportion of subjects in each group who improved in walking ability 1 year after the stroke.

The results were surprising. After 1 year, 52.0% of all participants had increased walking ability. No significant differences in improvement were found between early locomotor training and home exercise or between late locomotor training and home exercise. All groups had similar improvements in walking speed, motor recovery, balance, functional status, and quality of life. Neither the delay in starting late locomotor training nor the severity of the initial impairment affected any outcome. Each of the groups receiving locomotor training had a higher frequency of dizziness or faintness during treatment than that of the home exercise group. Most notably, multiple falls in subjects with severe impairment were more common in the early locomotor training group than in the other 2 groups. As a result, the use of body weight support treadmill training for locomotion was not shown to be superior to progressive exercise at home managed by a physical therapist. Furthermore, early training of locomotion using body weight support treadmill training carried a higher risk for falls.

Robotics

Despite notable variations between the trials investigating electromechanical and robot-assisted arm training after stroke, 1 Cochrane review concluded that this therapy is likely to improve generic activities of daily living. Paretic arm function may also improve, but not arm muscle strength.

This systematic review examined the effectiveness of electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength in patients after stroke and also assessed the acceptability and safety of the therapy.

This was found when evaluating 19 trials (involving 666 participants). Electromechanical and robot-assisted arm training did improve activities of daily living (standardized mean difference, 0.43; 95% CI, 0.11–0.75; P=0.009; I²=67%), as well as arm function (standardized mean difference, 0.45; 95% CI, 0.20–0.69; P=0.0004; I²=45%), but not arm muscle strength (standardized mean difference, 0.48; 95% CI, −0.06 to 1.03; P=0.08; I²=79%). Electromechanical and robot-assisted arm training did not increase the risk of patients to dropout (risk difference, 0.00; 95% CI, −0.04 to 0.04; P=0.82; I²=0.0%), and adverse events were rare.

Virtual Reality

Virtual reality and video game applications are novel and potentially useful technologies that can be combined with conventional rehabilitation for upper arm improvement after stroke. Saposnik et al. performed a meta-analysis to determine the added benefit of virtual reality technology on arm motor recovery after stroke. Twelve studies involving 195 participants, among them 5 randomized clinical trials and 7 observational studies with a preintervention/postintervention design, were identified. Eleven of 12 studies identified showed a significant benefit toward VR for the selected outcomes.

In the pooled analysis of all 5 randomized controlled trials, the effect of virtual reality on motor impairment (Fugl-Meyer score) was odds ratio=4.89 (95% CI, 1.31–18.3). No significant difference was observed for Box and Block Test or motor function. Among observational studies, there was a 14.7% (95% CI, 8.7%–23.6%) improvement in motor impairment and a 20.1% (95% CI, 11.0%–33.8%) improvement in motor function after virtual reality.

Transcranial Magnetic Stimulation

Hsu et al. performed a meta-analysis of studies that investigated the effects of repetitive transcranial magnetic stimulation (rTMS) on upper limb motor function in patients with stroke. Evaluating 18 randomized controlled trials published between 1990 and 2011 found that a significant effect size of 0.55 was for motor outcome (95% CI, 0.37–0.72). Subgroup analyses demonstrated more prominent effects for subcortical stroke (mean effect size, 0.73; 95% CI, 0.44–1.02) or studies applying low-frequency rTMS (mean effect size, 0.69; 95% CI, 0.42–0.95).

They conclude that rTMS has a positive effect on motor recovery in patients with stroke, especially for those with subcortical stroke, and that low-frequency rTMS over the unaffected hemisphere may be more beneficial than high-frequency rTMS over the affected hemisphere.

Disclosures

None.

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**Key Words:** brain recovery ◼ mobilization ◼ neurological rehabilitation ◼ stroke rehabilitation
Advances in Stroke Recovery and Rehabilitation

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Running title: Advances Recovery and Rehabilitation

Conflict of interest: the authors declare that they do not have a conflict of interest

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Word count: 1860
Advances Recovery and Rehabilitation

Developments in this area are now moving faster than ever before. It is evident that recovery drugs and techniques promoting recovery after brain ischemia deserve separate consideration and special efforts. A large number of trials are ongoing and several new methods are being tested in single or combination mode. We have decided to report Cochrane data, metanlyses, or (when both not available) to select one or two major paper representative for each area to illustrate the achieved results and to point to the many promising experimental, clinical and field trials currently under way.

**Drug therapy options evolving to enhance motor recovery**

Several drugs have been tested for efficacy in motor recovery in recent years but none has evolved with such clear significance as is the case for fluoxetine in the FLAME study (1). This study investigated whether fluoxetine enhances motor recovery if given to patients with motor deficits within the first 10 days following stroke.

118 patients with ischaemic stroke and hemiplegia or hemiparesis had Fugl-Meyer motor scale (FMMS) scores of 55 or less and were randomly assigned to fluoxetine (n=59; 20 mg once per day, orally) or placebo (n=59) for 3 months starting 5-10 days after the onset of stroke. All patients had physiotherapy. The primary outcome measure was the change on the FMMS between day 0 and day 90 after the start of the study drug. Two patients died before day 90 and three withdrew from the study. The remaining 113 showed FMMS improvement at day 90 significantly greater in the fluoxetine group (adjusted mean 34.0 points [95% CI 29.7-38.4]) than in the placebo group (24.3 points [19.9-28.7]; p=0.003).

The main frequent adverse events in the fluoxetine versus placebo groups were transient and not severe. They included nausea, diarrhoea, and abdominal pain (14 [25%] vs six
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[11%]), and partial seizure (one [<1%] vs 0).

The authors (1) concluded that for patients with ischaemic stroke and moderate to severe motor deficit, the early prescription of fluoxetine with physiotherapy enhances motor recovery after 3 months. They speculate that, while modulation of spontaneous brain plasticity by drugs is a promising pathway for treatment of ischaemic stroke patients, the mechanisms of action are not entirely clear and need to investigated further.

**Early mobilization**

Testing early and very early mobilization is a promising concept in patients without severe complications or brain swelling. The A Very Early Rehabilitation Trial (AVERT Phase 2) study (2,3) showed that mobilization within the first 24 hours of stroke and at regular intervals is safe, feasible, and fast-track return to walking unassisted increasing the likelihood of milder stroke patients being discharged to home and is independently associated with good functional outcomes at 3 and 12 months. Early mobilization also is advocated to prevent post-stroke complications such as contractures and deep vein thrombosis.

The optimal physical therapy dose in acute stroke care currently is unknown. The authors hypothesized that physical therapy would be significantly different between treatment arms in a trial of very early and frequent mobilization (VEM) and that immobility-related adverse events would be associated with therapy dose.

This study (2) was a single-blind, multicenter, randomized control trial of acute stroke patients admitted to a stroke unit <24 hours of onset. Patients were randomized to receive
either standard care (SC) or SC plus additional early out-of-bed therapy (VEM). A total of 71 patients (SC n = 33, VEM n = 38) received 788 therapy sessions in the first 2 weeks of stroke. Schedules (hours to first mobilization, dose per day, frequency and session duration) and nature (percentage out-of-bed activity) of therapy differed significantly between groups (P ≤ .001 for all components). Mobilization was earlier, happened on average 3 times per day in those receiving VEM, with the proportion of out-of-bed activity double in VEM session (median SC 42.5%, VEM 85.5%). SC consisted of 17 minutes of occupational and physiotherapy per day and was the same between groups. Number of immobility-related adverse events 3 months poststroke was not associated with therapy dose or frequency.

The authors detailed usual care and intervention therapy provided to patients from admission to 14 days after stroke. The therapy schedule was markedly different in the intervention arm, but whether this schedule reduces complications or improves outcome is still unclear until the main phase of the study is finished.

**Ambulation with Body-Weight-Support Treadmill Training**

While timing of mobilization is an important issue, methods of mobilizing stroke survivors also remains an important issue. In only the second NIH-funded trial of a rehabilitation intervention, Duncan and colleagues (4) investigated the use of body-weight support in treadmill stepping as an intervention to improve recovery of the ability to walk after stroke.

The study was a multi-center, randomized clinical trial of 408 subjects who suffered a stroke within 2 months. They were stratified by the extent of walking impairment: moderate (able to walk 0.4 to <0.8 m per second); or severe (able to walk <0.4 m per second). They were randomly assigned them to one of three training groups: training on a treadmill with body-weight support 2
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months after the stroke (early locomotor training); training 6 months after the stroke (late locomotor training); or an exercise program at home 2 months after the stroke (home-exercise program). Each intervention included 36 90-minute sessions for 12 to 16 weeks. The primary outcome measure was the proportion of subjects in each group who improved in walking ability 1 year after the stroke.

The results were surprising. After 1 year, 52.0% of all participants had increased in walking ability. No significant differences in improvement were found between early locomotor training and home exercise, or between late locomotor training and home exercise. All groups had similar improvements in walking speed, motor recovery, balance, functional status, and quality of life. Neither the delay in starting late locomotor training nor the severity of the initial impairment affected any outcome. Each of the groups receiving locomotor training had a higher frequency of dizziness or faintness during treatment than that of the home-exercise group. Most notably, multiple falls in subjects with severe impairment were more common in the early locomotor training group than in the other two groups. As a result, the use of body-weight support treadmill training for locomotion was not shown to be superior to progressive exercise at home managed by a physical therapist. Furthermore, early training of locomotion using body-weight support treadmill training carried a higher risk for falls.

Robotics

In spite of notable variations between the trials investigating electromechanical and robot-assisted arm training after stroke, one Cochrane review (5) concluded that this therapy is likely to improve generic activities of daily living. Paretic arm function may also improve, but not arm muscle strength.
This systematic review examined the effectiveness of electromechanical and robot-assisted arm training for improving generic activities of daily living, arm function, and arm muscle strength in patients after stroke and also assessed the acceptability and safety of the therapy. This was found when evaluating 19 trials (involving 666 participants). Electromechanical and robot-assisted arm training did improve activities of daily living (standardized mean difference, 0.43, 95% CI, 0.11-0.75; P=0.009; I²=67%) as well as arm function (standardized mean difference, 0.45; 95% CI, 0.20-0.69; P=0.0004; I²=45%), but arm muscle strength did not improve (standardized mean difference, 0.48, 95% CI, -0.06 to 1.03; P=0.08; I²=79%). Electromechanical and robot-assisted arm training did not increase the risk of patients to dropout (risk difference, 0.00; 95% CI, -0.04 to 0.04; P=0.82; I²=0.0%), and adverse events were rare.

**Virtual reality**

Virtual reality and video game applications are novel and potentially useful technologies that can be combined with conventional rehabilitation for upper arm improvement after stroke. Saposnik et al. (6) performed a meta-analysis to determine the added benefit of virtual reality technology on arm motor recovery after stroke. 12 studies involving 195 participants, among them 5 randomized clinical trials and 7 observational studies with a pre-/postintervention design were identified. Eleven of 12 studies identified showed a significant benefit toward VR for the selected outcomes.

In the pooled analysis of all 5 randomized controlled trials, the effect of virtual reality on motor impairment (Fugl-Meyer) was OR=4.89 (95% CI, 1.31 to 18.3). No significant difference was observed for Box and Block Test or motor function. Among observational studies, there was a 14.7% (95% CI, 8.7%-23.6%) improvement in motor impairment and a
20.1% (95% CI, 11.0%-33.8%) improvement in motor function after virtual reality.

**Transcranial magnetic stimulation**

Hsu et al. (7) performed a meta-analysis of studies that investigated the effects of repetitive transcranial magnetic stimulation (rTMS) on upper limb motor function in patients with stroke. Evaluating 18 randomized controlled trials published between 1990 and 2011 found a significant effect size of 0.55 was for motor outcome (95% CI, 0.37-0.72). Subgroup analyses demonstrated more prominent effects for subcortical stroke (mean effect size, 0.73; 95% CI, 0.44-1.02) or studies applying low-frequency rTMS (mean effect size, 0.69; 95% CI, 0.42-0.95).

They conclude that rTMS has a positive effect on motor recovery in patients with stroke, especially for those with subcortical stroke and that low-frequency rTMS over the unaffected hemisphere may be more beneficial than high-frequency rTMS over the affected hemisphere.

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脳卒中領域の進歩：回復とリハビリテーション

この分野の進歩は以前より早まっており、脳虚血後の回復においては薬物療法とリハビリテーション技法がそれぞれ研究されている。多くの試みが進行中で、新しい手法が単一もしくは複数の組み合わせで試されている。

運動機能の回復強化のための薬物治療：ここ数年、いくつかの薬剤で運動回復の効果が検討された。

FLAME研究では運動障害を持つ発症10日以内の患者へのfluoxetineの運動機能回復効果について、中等度から高度の運動障害を示す患者でfluoxetineの早期投与が3カ月後の運動機能の改善を示したとの結果が得られた1。薬物による脳可塑性の調節は期待できる作用であるが、メカニズムはまったく不明で研究する必要がある。

早期の運動：高度合併症や脳浮腫のない患者への早期・極早期の運動療法は効果が期待できる。AVERT研究では、脳卒中発症24時間以内の定期的な運動は安全に実行でき、早期に介助なしに歩行が可能となり、軽症患者では自宅退院の頻度が増し、3、12カ月後には機能良好な転帰が示された2。早期の運動は拘縮や静脈血栓症の予防にも推奨される。今や通常の運動量は不明である。

体重補助を用いた歩行トレッドミル訓練：脳卒中患者を動かす方法も重要な問題として残っている。Duncanらは、脳卒中後の歩行能力の改善目的に体重を補助したトレッドミルの利用について調べたが、1年後に理学療法士による自宅訓練と比べて同訓練の優位性は示されず、逆に転倒リスクが高かった3。

ロボット工学：Cochrane総説では、延べ666人の参加者で19試験が評価された。電動機械的ロボット補助アーム訓練では上肢機能改善に日常生活活動も明らかに改善したが、上肢筋力は改善しなかった4。同訓練は患者脱落のリスクを増大させ、副作用もまれであった。

仮想現実：仮想現実やビデオゲームの応用は斬新で潜在的に役立つ技術であり、新たな理学療法の開発につながる可能性がある。Saposnik等は、上肢の運動機能回復に対する仮想現実技術の有効性を調べた。延べ195人が参加した12の研究（5つの無作為臨床試験と7つの観察研究）があった。そのうち11の研究で仮想現実技術の十分な有用性が示された。

経頭蓋磁気刺激（rTMS）：Hsuらは脳卒中患者の上肢運動機能に対するrTMSの効果を調査するメタ解析研究を行った。rTMSは特に皮質下障害患者の運動回復に有益であり、脳卒中のある半球への低頻度rTMSは脳卒中のある半球への高頻度rTMSより有用性があるかもしれないとしている。

（文責：福山 秀直）