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Drugs to Enhance Motor Recovery After Stroke

Steven C. Cramer, MD[1]

[1]Depts. Neurology, Anatomy & Neurobiology, and Physical Medicine & Rehabilitation, University of California, Irvine

Abstract

Among the therapeutic strategies under study to improve long-term outcome after stroke are drugs targeting events that underlie recovery. Drugs that enhance recovery are separate from those that promote neuroprotection or reperfusion in patients with stroke. Recovery-based drugs have distinct therapeutic targets that are related to plasticity and growth following stroke, and in general, improvements in behavioral outcome are not accompanied by a reduction in infarct volume. Interventions targeting recovery have a time window measured in days or sometimes weeks-months, suggesting potential utility for a large percentage of patients with stroke. Currently, among drugs that enhance motor recovery after stroke in humans, the strongest evidence exists for serotonergic and dopaminergic agents. Restorative therapies generally target the brain directly, in contrast to approved stroke therapeutics that target arteries, clots, platelets, glucose, or cholesterol. Targeting the brain has wide-ranging implications, for example, in relation to drug delivery. In addition, because restorative drugs aim to change brain structure and function, their effects are influenced by concomitant behavioral experience, a finding that informs selection of entry criteria, outcome measures, and biomarkers in a clinical trial setting. These points underscore the importance of a neural systems approach in studying stroke recovery.

Keywords

stroke; recovery; motor system; drugs; outcomes

Introduction

A new stroke activates several biological pathways, including those related to the ischemic cascade, immunological response, and restorative response. These constitute distinct therapeutic targets for stroke therapy. Reperfusion therapies are effective when given during the early hours following stroke onset, when regions of ischemic penumbra remain salvageable. As a result of this narrow therapeutic time window, a minority of patients with stroke currently receives a reperfusion-based therapy acutely post-stroke. Restorative therapies have a much wider time window, some being introduced during the days-weeks of spontaneous growth seen in the brain after stroke, and others introduced months later in an

FOR CORRESPONDENCE: Steven C. Cramer, MD, UC Irvine Medical Center, 200 S. Manchester Ave., Suite 206, Orange, CA 92868-4280, Phone: (714) 456-6876, Fax: (714) 456-8805, scramer@uci.edu.

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Dr. Cramer has served as a consultant for GlaxoSmithKline, MicroTransponder, Dart Neuroscience, Roche, and RAND Corporation.

effort to stimulate neuroplasticity. Because of this wider time window, a large fraction of patients with stroke could potentially be eligible to receive a restorative therapy.

The current review focuses on drugs, specifically small molecules, which are commonly used in neurologic practice and which have advantages compared to some treatment approaches in terms of drug delivery and access to the brain[1]. Many types of restorative therapy besides small drugs are under study, including large molecules such as growth factors or monoclonal antibodies, biological agents such as stem cells, brain stimulation, robotics, and activity-based therapies[2]; ultimately the value of any drug must be measured in relation to the risk/benefit performance of all candidate restorative therapies. The current focus is on a mono-therapy approach, but increasing evidence will likely foster studies evaluating poly-therapy approaches.

The current review is focused on the motor system. A systems approach is central to many aspects of restorative neuroscience. The brain is in many ways an amalgam of many different systems operating in parallel. For a stent retriever placed in the MCA, the therapeutic target is a hemisphere full of at-risk brain systems. For a restorative therapy, however, only one or a few neural systems are likely to be viable therapeutic targets, as many systems may be either decimated beyond repair or little affected. Adoption of a systems-level approach has immediate implications for clinical trials in relation to topics such as entry criteria, endpoints, biomarkers, and the concomitant training that is important to shaping the effects of a restorative therapy.

The current focus on the motor system reflects the fact that motor deficits are common after stroke (82% of patients[3]) and are linked with reduced quality of life[4, 5]. At 6 months after stroke, 65% of patients are unable to incorporate a paretic hand effectively into daily activities[6], which affects subjective well-being[7]. Moreover, even when neurological exam declares the patient wholly recovered, 71% of patients report persistent motor deficits when studied using patient-reported outcomes[8]. Lower extremity motor status is also linked with disability level[9]. Only 37% of persons with stroke can walk after the first week post-stroke, after which gait improvement is linked to better quality of life. Hemiplegic patients rank recovery of gait as their top priority[10, 11].

Current status

There are no drugs approved in the U.S. to enhance motor recovery after stroke.

However, the recent approval by the U.S. FDA of a 4-aminopyridine preparation as a treatment to improve walking in patients with multiple sclerosis[12] sounds a hopeful note for stroke.

Drugs with strongest evidence to date

For at least two classes of drug, serotonergic and dopaminergic, both of which are monoaminergic, existing evidence from human studies supports the possibility for enhancing motor outcome after stroke.

Serotonergic drugs—Serotonin normally plays in a role in modulating multiple cognitive functions, particularly response inhibition and memory consolidation, and modulates the impact of punishment-related signals on learning and emotion[13–15]. Recent reports suggest potential clinical utility of selective serotonin reuptake inhibitor (SSRI) drugs for promoting improved motor outcome after stroke. Building on several prior smaller studies[16–19], the Fluoxetine for Motor Recovery After Acute Ischemic Stroke (FLAME) study[20] was a double blind, placebo-controlled trial that enrolled non-depressed hemiplegic/hemiparetic patients within 10 days of ischemic stroke onset. Patients were randomized to 3 months of oral fluoxetine (20 mg/day) or placebo. Patients randomized to fluoxetine showed significantly greater gains on the primary endpoint, change in the arm/leg Fugl-Meyer motor score to day 90 ($p=0.003$), a remarkable difference of 9.7 points on this 100-point scale. Other human trials have reported favorable effects of SSRI drugs on recovery of non-motor behaviors after stroke [21–23], increasing confidence in the results of the FLAME study. The importance of these findings is underscored by the substantial clinical experience with SSRI drugs (hundreds of millions of humans have been treated) and their generally strong safety record, in the broad population as well as in patients with cerebrovascular disease[24, 25].

Several different mechanisms might account for these findings. The central mechanism of action for SSRI drugs in the treatment of major depression is via their high affinity for the serotonin transporter; drug binding to the transporter inhibits serotonin removal from the synaptic cleft, with long-term SSRI administration down-regulating and desensitizing key serotonin receptors thereby dampening negative feedback on serotonin release[26]. While it is true that the FLAME study excluded subjects with depression, these SSRI mechanisms might nonetheless have contributed to the findings in the FLAME study. Although depression is often classified dichotomously, i.e., as present or absent, evidence suggests that depressive symptoms impact brain function along a continuum, with increasing levels of depressive symptoms associated with larger effects even when restricting analysis to subjects who do not meet criteria for major depression[27, 28], including after stroke[29, 30]. Consistent with this, better functional recovery after stroke is associated with lower depressive symptoms and with greater improvement of depressive symptoms over time[31].

Other suggested mechanisms of action for SSRI drugs include reducing neural inflammation[32], enhancing neurotrophin activity[33], and increasing neurogenesis[34]. Chronic SSRI dosing increases intra-cortical facilitation[35] and reduces intra-cortical inhibition[36], and these changes have been compared to reinstating conditions of developmental critical periods[36, 37]. In addition, serotonin modulates spinal motor control through multiple effects on spinal motor circuits, including regulation of rhythmic activity and control of excitability, by acting on intrasynaptic and extrasynaptic receptors; this may help locomotor function but can also worsen spasticity[38].

Dopaminergic drugs—Dopamine regulates many aspects of neural functioning, including excitability, synaptic transmission, plasticity, protein trafficking, and gene transcription[39]. Not surprisingly, therefore, dopamine has a key role in wide-ranging brain processes such as movement, reward, learning, and plasticity[40]. The role of this neurotransmitter is movement is well established: dopaminergic terminals in motor cortex contribute to cortical plasticity and indeed are necessary for motor skill learning[41, 42]. A

randomized, double blind, placebo-controlled study of 53 patients within 6 months of stroke onset found that 100 mg L-Dopa/day, given as Sinemet and combined with physical therapy, was significantly better than placebo plus physical therapy on motor recovery after three weeks measured using the Rivermead Motor Assessment[43]. These effects were very likely attributable to dopamine, as studies in rodents, sub-human primates, and humans indicate that systemic administration of L-Dopa increases the brain concentration of dopamine but not norepinephrine--dopamine is the predominant brain metabolite formed from systemic L-Dopa[44–47].

Large studies of drugs that modulate dopamine neurotransmission after stroke continue to be needed but lacking[48]. Smaller studies that have examined a range of dopaminergic drugs in patients with stroke at varying time points post-onset have been inconsistent, with motor learning and plasticity improved in some studies[49] but not others[50–52]. For example, a placebo-controlled, double-blind study of 33 patients 1–12 months post-stroke did not find a difference between a 9 week course of ropinirole + physiotherapy compared to placebo + physiotherapy on gait velocity[50]. These differences might reflect small sample sizes. Some evidence suggests that genetic factors may be relatively important in modulating dopamine neurotransmission in humans[53–55].

Additional insight into divergent findings across studies of dopaminergic drugs might stem from the fact that a large number of environmental, cognitive, psychological, and other factors are important cofactors in the expression of dopamine effects. Dopamine is a central player in the limbic reward system, where, adding to the complexity, its neurotransmission is under the influence of numerous other transmitters[56]. Reward significantly influences long-term motor learning[57]. Dopamine is also important to motivation[58], action learning[59], action selection[60], and in the control of voluntary exercise[61]. Thus, as with serotonergic drugs, dopaminergic drugs might influence motor recovery after stroke indirectly, through their action on any of several different non-motor neural systems.

Other drugs that might have important effects on recovery

Noradrenergic drugs

Noradrenergic neurotransmission broadly amplifies neuronal activity, increases the general level of excitability, and selectively amplifies activities evoked by unexpected inputs[62]. This effect of norepinephrine on regulating overall arousal levels has a modulatory effect on executive function[14]. To date there has been only a handful of studies of noradrenergic drugs to promote stroke recovery. These have been small in size but show promising results[63–65].

Cholinergic drugs

In the cortex, acetylcholine inputs positively enable plasticity by (a) selectively amplifying only anticipated (“selectively attended”) and (b) selectively weakening non-anticipated inputs[62]. Modulation of nicotinic cholinergic neurotransmission alters attention, while muscarinic receptors play a greater role in cognitive flexibility[14]. Luria long ago advocated for cholinergic therapies to enhance recovery[66], yet very few controlled studies in humans with stroke have been published to date. Limited data in non-motor aspects of stroke

recovery are promising[67–69], and a recent study in 33 patients found that donepezil to be safe when initiated within 24 hours of stroke onset[68].

Amphetamine

Amphetamines increase neurotransmission in several monoamine systems. Initial studies of amphetamine to enhance post-stroke motor[70, 71] or language [72] recovery were small but promising. A subsequent randomized, double blind, placebo-controlled trial of amphetamine in 71 patients with sub-acute stroke did not show a drug-related benefit[73]. At 5–10 days after stroke onset, patients were randomized to 10 sessions of either physiotherapy + amphetamine (10 mg) or physiotherapy + placebo, twice per week for five weeks. No difference between treatment groups was found for the primary outcome, Fugl-Meyer motor score. The subgroup with milder deficits might have derived the greatest drug-related gain, a possibility that requires further study. The optimal dose and administration schedule for amphetamine has not been rigorously studied and it remains to be definitively evaluated in human patients with stroke[74].

Drugs that impede recovery

For a number of drugs, particularly neuroleptic or antiepileptic drugs, some evidence suggests that administration after stroke can impede motor recovery and thereby reduce motor outcome [75–78]. Such findings could potentially provide insights into the mechanisms of stroke recovery, and might also inform strategic planning in the design of pharmacological approaches to improving motor recovery after stroke.

Experiences such as those summarized above have identified a number of important issues in the design of clinical trials of brain repair after stroke[79]. These are considered below.

How does time since stroke onset affect a restorative therapy?—Time is a major factor. As with many CNS diseases, stroke evolves over time, and biological targets shift. The initial hyper-acute injury period is followed by a several week period throughout which repair-related events spontaneously increase in the brain[80–82], and during which the brain is galvanized for growth in a manner resembling normal development[83]. A critical window for therapeutic effectiveness has been defined during this period for several restorative interventions in preclinical studies[84–86]. Drugs that promote recovery one week may be inert or even harmful the next[87–90]. Importantly, because restorative therapies are generally introduced at a time when stroke injury is fixed, behavioral outcomes are improved after stroke without affecting final infarct volume. The period of spontaneous growth resolves over the ensuing weeks-months, but even in the chronic phase, clinically important gains may be seen for some therapies that aim to promote neural repair[91, 92].

How do a patient's activity, training, and experience after stroke affect a restorative therapy?—These are key considerations. When introducing a drug to promote plasticity after neural injury, the best behavioral recovery requires rehabilitation in order to mold new connections[93] --neural repair after stroke occurs on the basis of experience-dependent plasticity[94]. In a landmark study, Feeney et al[75] found that in rodents with an experimental stroke, amphetamine improved motor outcome, but only if drug dosing

was paired with training. Subsequent studies have confirmed this principle across many other classes of post-stroke restorative therapy[95–99]. This issue is not a consideration in acute stroke and preventative stroke studies, where treatment generally targets clots, platelets, arteries, the heart, or serum glucose or cholesterol levels. However, in stroke recovery studies, treatment often directly targets the brain, and retraining the brain is dependent on repeated behavioral reinforcement. Thus the patient need not engage in any particular behavioral regimen to enable tPA effectiveness, but available data indicate that such activity is central to realizing maximal effects of restorative drugs after stroke. These data are largely from preclinical studies, and so further studies in humans are needed to better understand the impact of post-stroke activity and training as adjuvants to recovery drugs. Similarly, evidence suggests that the psychosocial milieu in which patients experience post-stroke recovery is also a critically important experiential covariate[100].

Given these many influences on stroke recovery, how can the target patient population be defined for a drug designed to enhance recovery after stroke?—Several techniques show promise to identify target populations. Stroke is a very heterogeneous condition. Just as no single drug is appropriate to treat all patients with cancer or pneumonia, so it is that no one therapy is likely to be useful to enhance recovery across all patients with stroke. Patients differ tremendously before the stroke, and infarcts are highly variable across subjects. Numerous measures have been studied for their ability to understand and to measure variance in behavioral recovery after stroke. Results have implications for patient selection and stratification in clinical trials of drugs targeting recovery. For example, in a study of 23 patients with chronic stroke undergoing robotic therapy to improve arm motor deficits, extent of stroke injury to the corticospinal tract accounted for approximately one third of the variance in treatment response[101]. These results remain to be confirmed in a study using a drug to enhance motor recovery after stroke, but likely results will generalize across treatment categories. This is an example of an imaging-based approach to identify the target population--extent of corticospinal tract injury substantially informs which patients are most likely to benefit from a recovery-based intervention. Further work remains to maximize the robustness of this approach, and this is a fervent area of investigation. Recent models emphasizing an interaction between neural function and neural injury[102, 103]. For some therapies, including serotonergic[104, 105] and dopaminergic[53] drugs, measures of genetic variability might also inform the likelihood that a patient will benefit from a drug.

For some therapies, preclinical findings may provide specific guidance for defining the target human population. For example, in a phase III clinical trial of epidural motor cortex stimulation in patients with chronic stroke, rodent and primate studies showing efficacy required preserved motor evoked responses[98, 106–108] but the trial[109] did not did not. A post-hoc analysis found that trial enrollees randomized to epidural motor cortex stimulation who (like preclinical subjects) had preserved motor evoked responses were 2.5 times more likely ($p<0.05$) to achieve the primary efficacy endpoint as compared to enrollees lacking such responses[110].

How do these issues affect selection of endpoints in trials of drugs aiming to enhance recovery after stroke?—As above, a systems approach is often important to therapeutic studies of stroke recovery. A therapy that improves outcome by promoting neuroplasticity might have maximum effect in a neural system that has sustained subtotal injury, but show no effect in a system that has been utterly obliterated by stroke. As such, a restorative drug given to a patient with dense aphasia but moderate hemiparesis might provide useful gains in motor function but not in language function. In such a context, drug effects would likely be more apparent using an outcome measure that has the granularity to detect differential effects across neural systems of the brain.

These points suggest the potential utility of modality-specific outcome measures to capture effects of treatments that target stroke recovery[111]. Global endpoints that capture many aspects of human behavior and summarize a person's outcome using a single number (often a single digit) have established value in stroke clinical trials, but their value may be greatest for acute treatments that aim to salvage a large volume of threatened brain. On the other hand, for drugs that aim to enhance stroke recovery by improving function in specific neural systems that have been injured by survived, global endpoints might lack granularity and thus be insensitive; endpoints that are linked to the target neural system might provide a more accurate measure of drug effects. For example, a restorative therapy that significantly improves the modality-specific outcome measure "gait velocity" may or may not have a significant effect on the global outcome measure "modified Rankin scale score," but improved gait might nonetheless be associated with improved quality of life[112] and social participation[113].

How do these issues affect interpretation of animal models and translation of preclinical stroke recovery studies?—The limits of preclinical models for stroke recovery remain to be completely defined. For studies focused on molecular responses to specific perturbations, rodent models offer great potential. Humans and rodents shared a common ancestor approximately 80–100 million years ago. Most genes are shared, and tissue-specific transcriptional responses have been highly conserved[114, 115]. However, as a human recovers during the weeks-months following a stroke, psychological issues such as mood, hopelessness, resilience, anxiety, and caregiver support may have important effects on outcomes, as might marital, religious, occupational, fiscal, litigational, and other social issues. Many patients at my institution struggle with insurance copayments, alcoholism, adjustments in retirement plans, power of attorney, and immigration status. Such factors of human life after stroke may be incompletely modeled in a study of rodents housed in an 18" cage with solitary (or single cellmate) confinement. A rat brain weighs 2 gm, has one third the proportional white matter volume of a human brain, is perfused by a pulse >250 beats/min, and has had a distinct trajectory of psychosocial and cultural evolution since the common mammalian ancestor, as compared to humans[116]. Thus for studies focused on the net effect of a drug on behavioral recovery after stroke, rodent models may have critical limitations. Given that regulatory agencies emphasize the importance of clinically meaningful endpoints in human trials[117], rodent studies might be seen as providing the greatest insight at the molecular or tissue level rather than at the behavioral level.

Is there a role for biomarkers?—Definitely--this is a major unmet need that when robustly addressed could massively impact this field. A biomarker is an indicator of disease state[118] that provides information on key molecular/cellular events that may be difficult to measure directly. Examples of biomarkers commonly used in clinical practice include plasma RNA levels in the setting of HIV infection, and intraocular pressure in the setting of glaucoma. A good biomarker must be in the causal pathway of the disease process and fully capture the net effect of treatment on the clinical outcome[119, 120]. Biomarkers are particularly useful in phase II trials, for example, to probe biological activity of a proposed therapy or to inform the decision whether or not to proceed to phase III[119]. A valid biomarker for a drug aiming to enhance stroke recovery could improve decision-making regarding timing, duration, frequency, or intensity with which treatment is prescribed for individual subjects, and could generate an improved understanding as to how findings in rodents relate to findings in humans[121]. There have been important advances in the study of biomarkers of stroke recovery in humans. Evidence suggests that the optimal choice of biomarker likely varies according to degree of injury and may differ across neural systems. Numerous candidate biomarkers have been proposed including blood-based tests, measures of brain structure and injury, and functional neuroimaging measures[77, 122, 123]. However, valid biomarkers of motor recovery after stroke in human, and the effects of drug targeting motor recovery, remain to be established.

How do current systems of care affect the study of drugs to enhance motor recovery after stroke?—Current patterns of care delivery may be important in several regards. Concomitant experience and training is a key factor when studying stroke recovery (see above). Provision of healthcare, including post-stroke rehabilitation therapy, differs substantially across countries and insurance plans and should be considered in the design of restorative trials. Even in optimal settings the dose of rehabilitation therapy may be lower than desired[124]. In the absence of approved therapies, clinicians prescribe unapproved drugs in the hopes that they can give patients some potential advantage, a fact that adds complexity to trials and so is worthy of note in the study of recovery-related drugs[125]. In many U.S. healthcare systems, a patient may be transferred to several care settings, under the care of several different physicians, during the critical month of brain repair following stroke onset, a fact that can also complicate clinical trials in stroke recovery.

Are there data that a restorative therapy can enhance motor outcome after stroke in humans, and are such effects clinically meaningful?—Several key trials have described effects that readily meet the definition of clinically meaningful. The 9.7 point Fugl-Meyer motor scale score found with fluoxetine in the FLAME study[20] readily meets most definitions of minimum clinically important difference for this scale in patients recovering from stroke[126]. The same can be said for the 51.8% reduction in time to complete the Wolf Motor Function Test found one year after constraint induced therapy in the “Extremity Constraint Induced Therapy Evaluation” study[91], a prospective, single-blind, randomized, clinical trial of 222 patients with arm motor deficits 3–9 months after stroke. Similarly, the “Locomotor Experience Applied Post-Stroke” trial[92] found that 52% of enrollees receiving locomotor training shifted up an entire category of functional walking ability at one year post-stroke, a remarkable therapeutic achievement.

Conclusions

In selected instances, solid evidence exists that a restorative therapy, introduced long after injury is fixed, can improve behavioral outcome after stroke[127]. The largest trials to date have examined behavioral interventions such as constraint induced therapy or locomotor training. Regarding trials of drugs to enhance motor recovery, exciting results have been found in phase II studies of SSRI's and of L-Dopa. This review considered several factors important to stroke recovery trials.

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