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Novel Pharmacological Approaches for Neuroprotection in Acute Stroke

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Abstract

Acute stroke remains a leading cause of mortality and long-term disability worldwide, necessitating urgent advancements in neuroprotective strategies to mitigate brain damage and improve patient outcomes. Despite progress in reperfusion therapies, the translation of preclinical neuroprotective agents to clinical success has been limited by challenges such as narrow therapeutic windows, heterogeneity in stroke pathology, and safety concerns. This review critically examines the current landscape of neuroprotection in acute stroke, highlighting emerging pharmacological approaches and the barriers to their clinical implementation. The review explores novel pharmacological strategies, including targeted molecular therapies like nerinetide and repurposed drugs such as glibenclamide, which show promise in addressing excitotoxicity and cerebral edema. It also discusses innovative delivery methods, such as intranasal administration and nanotechnology-based systems, designed to enhance drug bioavailability and bypass the blood-brain barrier (BBB). Insights from clinical trials, including the ESCAPE-NA1 and EXTEND-IA TNK studies, underscore the potential of combining neuroprotection with reperfusion therapies. Additionally, the review evaluates non-pharmacological adjuncts like transcranial magnetic stimulation (TMS) and hypothermic neuroprotection, which may complement traditional drug treatments. The integration of multi-target therapeutics and temporal targeting approaches is emphasized as a means to address the dynamic pathophysiology of stroke. Finally, the review highlights the role of advanced technologies, such as artificial intelligence and systems biology, in accelerating the development of next-generation neuroprotective agents. Future research should focus on refining preclinical models to better mimic human stroke conditions and optimizing clinical trial designs to validate the efficacy of emerging therapies. The exploration of holistic approaches targeting the neurovascular unit and the combination of neuroprotection with rehabilitation techniques represents a promising frontier. By fostering interdisciplinary collaboration and leveraging cutting-edge innovations, the field can overcome existing challenges and realize the potential of neuroprotection as a cornerstone of comprehensive stroke care.

Keywords: Blood-brain barrier, Combinational therapy, Excitotoxicity, Neuroprotection, Reperfusion, Stroke, Targeted delivery

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Introduction

The pursuit of novel pharmacological approaches for neuroprotection in acute stroke has garnered significant attention, as evidenced by recent comprehensive reviews and experimental studies [1-3]. Paul and Candelario-Jalil [4] highlight the complexity of stroke pathology, emphasizing the need for innovative neuroprotective strategies that address both ischemic and hemorrhagic subtypes. Their overview underscores the challenges faced in translating preclinical neuroprotectants into clinical success, while also noting ongoing initiatives such as the stroke preclinical assessment network aimed at identifying promising candidates. Emerging pharmacological agents are being evaluated across various phases of stroke management. Safouris et al. [5] discuss several agents under clinical trial, including nerinetide, which shows promise as a neuroprotective agent, and tenecteplase, an alternative thrombolytic to alteplase. Additionally, glibenclamide is being investigated for its potential to reduce edema in malignant hemispheric infarction, illustrating a multifaceted approach to neuroprotection that extends beyond thrombolysis.

Preclinical studies have explored innovative molecular targets and compounds. Zhang et al. [6] introduced a novel metformin derivative, metformin threonate (SHY-01), which has demonstrated efficacy in improving functional recovery post-ischemia. Similarly, Ayuso-Dolado et al. [7] designed cell-penetrating peptides targeting calpain-mediated cleavage of PSD-95, a process implicated in excitotoxic neuronal damage, suggesting a targeted molecular approach to neuroprotection. Non-pharmacological strategies are also gaining traction as adjuncts or alternatives to traditional drug therapies. Buetefisch et al. [8] investigated low-frequency repetitive transcranial magnetic stimulation (rTMS), revealing its potential to confer neuroprotection when applied acutely after stroke. Complementing this, Chen et al. [9] demonstrated the efficacy of targeted hypothermic neuroprotection via autologous blood transfusion in a non-human primate model, highlighting a novel approach to mitigate ischemic injury during reperfusion.

Furthermore, the modulation of intracellular signaling pathways and neuroinflammation remains a promising avenue (Figure 1) [10]. Wolska et al. [11] reviews the role of long non-coding RNAs

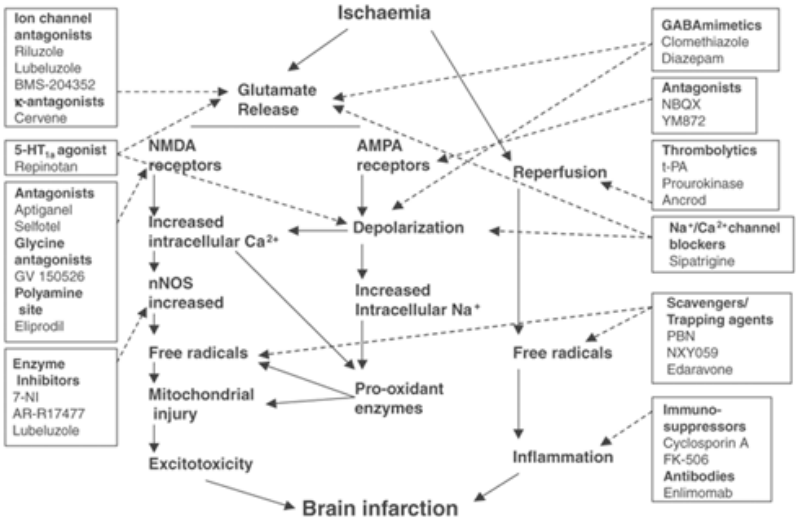

Figure 1: A simplified schematic illustrating the key steps in the ischemic cascade, alongside the neuroprotective agents designed to target specific pathways and mitigate neuronal damage [10].

in ischemic stroke, suggesting that these molecules could serve as therapeutic targets or biomarkers for neuroprotection. The integration of such molecular insights with pharmacological interventions could enhance the specificity and efficacy of future therapies. In summary, recent research underscores a diverse array of novel pharmacological and adjunctive approaches for neuroprotection in acute stroke. These include targeted molecular therapies, innovative drug derivatives, and non-invasive neuromodulation techniques, all aimed at reducing neuronal damage and improving functional outcomes. Continued interdisciplinary efforts and rigorous clinical evaluation are essential to translate these promising strategies into effective treatments for stroke patients [4, 5].

Stroke remains a leading cause of mortality and long-term disability worldwide, necessitating the exploration of innovative pharmacological strategies for neuroprotection. Acute ischemic stroke is characterized by the sudden blockage of blood flow to the brain, leading to neuronal death and functional impairment. Despite advancements in reperfusion therapies, the need for effective neuroprotective agents remains critical to mitigate brain damage and improve patient outcomes.

Current Challenges in Neuroprotection

The development of neuroprotective drugs has faced significant hurdles, with many promising candidates failing to translate from preclinical models to clinical practice [12-14]. A review by Paul et al. highlights the urgent need for therapeutic agents that can protect the brain during the critical period of ischemia and reperfusion, extending the therapeutic window for intervention and enhancing functional recovery [4]. The failure of forward translation in neuroprotection research raises questions about the relevance of existing preclinical models, suggesting that alternative approaches, such as reverse translational research, may be necessary to identify new therapeutic targets [15].

Another major challenge lies in the timing of neuroprotective interventions [16, 17]. The therapeutic window for effective neuroprotection is narrow, often requiring administration within hours of stroke onset [18, 19]. However, logistical delays in diagnosis and treatment initiation frequently hinder the timely delivery of these therapies. Additionally, the presence of comorbidities, such as hypertension or diabetes, further complicates treatment efficacy, as these conditions can alter drug metabolism and patient responsiveness [20-22]. These factors highlight the need for strategies that extend the therapeutic window or enhance the brain's resilience to ischemic injury.

Safety and tolerability concerns also pose significant barriers [23, 24]. Some neuroprotective agents, such as beta blockers and streptokinase, have been associated with increased early case fatality in clinical trials, raising questions about their risk-benefit profiles [25, 26]. Moreover, the heterogeneity of stroke subtypes and patient populations makes it difficult to identify universally effective therapies [27, 28]. Current guidelines provide clear recommendations for certain drugs, like Cerebrolysin and citalopram, but many others remain under investigation or are not recommended due to insufficient evidence or safety issues [29, 30]. Addressing these challenges will require rigorous clinical trial designs, personalized treatment approaches, and a deeper understanding of stroke mechanisms.

Early pharmacological support for post-stroke neurorehabilitation has seen an abundance of mixed results from clinical trials [31], leaving practitioners at a loss regarding the best options to improve patient outcomes. Cerebrolysin, this intervention is recommended for clinical use in early neurorehabilitation following acute ischemic stroke. The specific dosage and administration are 30 mL/day, intravenously, for a minimum of 10 days. Citalopram, at a dosage of 20 mg/day orally, is also recommended for clinical use in early neurorehabilitation after acute ischemic stroke. Several other pharmacological interventions were identified by the systematic search but are not recommended for clinical use. These include: amphetamine (5 x 10 mg/day, oral), citalopram (10 mg/day, oral), dextroamphetamine (10 mg/day, oral), Di-Huang-Yi-Zhi (2 x 18 g/day, oral), fluoxetine (20 mg/day, oral), lithium (2 x 300 mg/day, oral), MLC601 (3 x 400 mg/day, oral), and phosphodiesterase-5 inhibitor PF-03049423 (6 mg/day, oral). Interventions with no specific recommendations are: selegiline (5 mg/day, oral), the guideline provides no recommendation 'for' or 'against' its use. Issues related to safety and tolerability were identified for amphetamine, dextroamphetamine, fluoxetine, and lithium. The guideline provides clear recommendations for clinicians regarding pharmacological support in neurorecovery after acute ischemic stroke,

highlighting specific drugs that are recommended, not recommended, or for which no stance is taken, along with identified safety concerns for some interventions.

A review by Jha et al. [32] analyzed data from 32 trials involving 5,368 patients to assess the effects of vasoactive drugs on blood pressure and outcomes in acute stroke. Intravenous calcium channel blockers (CCBs) significantly lowered late blood pressure, with an average reduction of -8.2/-6.7 mm Hg (systolic/diastolic BP). Oral CCBs also significantly lowered late blood pressure, with an average reduction of -3.2/-2.1 mm Hg (systolic/diastolic BP). Beta blockers significantly lowered late diastolic blood pressure by -4.5 mm Hg but did not significantly lower late systolic blood pressure. Angiotensin converting enzyme inhibitors, non-significantly reduced late blood pressure by -5.4/-3.0 mm Hg. Prostacyclin, non-significantly reduced late blood pressure by -7.4/-3.9 mm Hg. Magnesium, naftidrofuryl, and piracetam had no significant effect on blood pressure. Oral CCBs, significantly reduced late heart rate by -2.8 beats per minute (bpm). Beta blockers significantly reduced late heart rate by -9.3 bpm. Prostacyclin significantly increased late heart rate by +5.6 bpm. There was insufficient evidence to reliably evaluate the effect of altering blood pressure on outcomes after acute stroke. Beta blockers and streptokinase drug classes were found to increase early fatality. Specifically, beta blockers had an odds ratio of 1.77 for increased early case fatality, and streptokinase had an odds ratio of 2.27. Significant imbalances in baseline blood pressure were observed across trials, particularly for intravenous CCBs and prostacyclin. Major imbalances in baseline blood pressure between treatment and control groups made the interpretation of results difficult. In summary, while several vasoactive drugs like CCBs and beta blockers effectively lowered blood pressure and heart rate in acute stroke patients, the review highlights a lack of clear evidence regarding their impact on overall patient outcomes, partly due to methodological challenges such as baseline blood pressure imbalances in the included trials. Some drugs, notably beta blockers and streptokinase, were associated with increased early case fatality.

While the challenges in neuroprotection for acute stroke are significant, ongoing research and technological advancements continue to offer hope for future breakthroughs. The complexity of the ischemic cascade and the narrow therapeutic window remain major hurdles, but innovative approaches and improved trial designs may eventually lead to effective neuroprotective therapies [33-35]. The integration of neuroprotection with existing reperfusion strategies could provide a more comprehensive approach to stroke treatment, potentially improving outcomes for patients worldwide.

Emerging Pharmacological Strategies

Recent studies have identified several novel pharmacological approaches that show promise for neuroprotection in acute stroke (Table 1). For instance, the use of cell-penetrating peptides targeting calpain-cleavage of PSD-95 has demonstrated improved neurological outcomes in stroke models by preserving synaptic integrity and reducing excitotoxicity [7]. Additionally, the inhibition of transient receptor potential M2 ion channels has been shown to restore synaptic function and memory in juvenile mice following global cerebral ischemia, indicating a potential avenue for neurorestoration [36].

Another innovative approach involves the combination of existing drugs to enhance neuroprotective effects. A study by Simats et al. explored the synergistic effects of ceruletide and alpha-1 antitrypsin, which significantly reduced infarct volume in a mouse model of stroke [37]. This drug repositioning strategy highlights the potential of combinational therapies to target multiple pathways involved in stroke pathology.

Another innovative avenue focuses on modulating ion channels, particularly transient receptor potential M2 channels, which play a critical role in post-ischemic synaptic dysfunction [38, 39]. Preclinical research shows that transient receptor potential M2 inhibition restores synaptic plasticity and memory in juvenile mice after global cerebral ischemia, suggesting its utility in promoting neurorestoration [40]. This approach not only addresses acute neuronal damage but also supports long-term recovery, bridging the gap between neuroprotection and neurorehabilitation. The ability to target specific ion channels opens new possibilities for developing drugs with fewer off-target effects compared to broad-spectrum neuroprotectants [41, 42].

Combinational therapies are also gaining traction as a means to enhance neuroprotection by simultaneously targeting multiple injury pathways [43, 44]. For example, the synergistic pairing of ceruletide (a cholecystokinin analog) and alpha-1 antitrypsin (an anti-inflammatory protein) have been shown to significantly reduce infarct volume in murine stroke models [45]. This strategy leverages the complementary mechanisms of different drugs to amplify therapeutic effects, potentially overcoming the limitations of single-agent treatments. Drug repositioning-repurposing existing medications for stroke-further accelerates this approach by utilizing compounds with established safety profiles, reducing the time and cost associated with traditional drug development [46, 47].

Non-pharmacological adjuncts, such as low frequency rTMS, are also being explored to augment neuroprotective interventions [48]. Early studies indicate that rTMS, when applied acutely after stroke, can reduce infarct volume and improve functional recovery, possibly by modulating neuronal excitability and enhancing neuroplasticity [49]. When combined with pharmacological agents, these neuromodulatory techniques may offer a multifaceted approach to optimize outcomes [50, 51]. As research progresses, the integration of novel drugs, targeted molecular therapies, and complementary non-invasive techniques could redefine the standard of care for acute stroke management.

While the focus remains on improving acute interventions, there

Table 1: Emerging pharmacological agents for neuroprotection in acute stroke.

Agent	Mechanism of action	Stage	Remarks
Nerinetide	Disrupts PSD-95/nNOS interaction, reduces excitotoxicity	Phase III clinical	Adjunct to thrombectomy shows functional improvement
Glibenclamide	Inhibits SUR1-TRPM4 channels, reduces cerebral edema	Clinical (Repurposed)	Originally for diabetes, promising brain swelling
SHY-01	Activates AMPK signaling, improves recovery post-ischemia	Preclinical	Derivative of metformin, better neuroprotective effect
Cell-penetrating peptides	Target calpain-cleavage of PSD-95, preserves synaptic integrity	Preclinical	Experimental, promising synaptic protection
Tenecteplase	Alternative thrombolytic agent	Phase II/III clinical	Potential alternative to alteplase
NXY-059	Free radical trapping agent	Population PK model	Failed late-phase trials, dosing strategy studied
Lovastatin	Statin, anti-inflammatory/neuroprotective properties	Phase I clinical	Dose-escalation for acute stroke

is also a growing interest in strategies that address the subacute and recovery phases of stroke. These include regenerative approaches aimed at enhancing neurobehavioral recovery and reducing long-term disability [52, 53]. The integration of pharmacological and mechanical strategies, along with advancements in imaging and patient selection, holds promise for significantly improving outcomes in acute ischemic stroke [54, 55]. However, the complexity of stroke pathophysiology and the variability in patient response necessitate continued research and innovation in this field.

Novel Drug Candidates

The search for more effective neuroprotective agents has led to the development of innovative drug candidates with enhanced mechanisms of action and improved pharmacokinetic profiles. Among these SHY-01, a derivative of the widely used antidiabetic drug metformin, has emerged as a promising candidate [6]. Preclinical studies demonstrate that this compound exhibits superior neuroprotective effects compared to its parent drug, particularly in the acute phase of cerebral ischemia. Its rapid cellular uptake and potent activation of neuroprotective pathways, such as AMPK signaling, suggest its potential to limit neuronal damage and promote recovery in stroke patients. These findings highlight the value of modifying existing drugs to optimize their therapeutic potential for neurological applications [8, 56].

Another notable candidate is nerinetide, a peptide that disrupts the interaction between postsynaptic density protein-95 [57] and neuronal nitric oxide synthase [58], a key mediator of excitotoxic injury. Clinical trials, such as the ESCAPE-NA1 study by Hill et al. [59] have investigated its efficacy as an adjunct to endovascular thrombectomy, with results indicating improved functional outcomes in select patient populations. Nerinetide's targeted approach to mitigating excitotoxicity-while avoiding broad suppression of neuronal activity-positions is as a precision therapy for acute stroke [60]. Its success in trials underscores the potential of peptide-based drugs to address specific pathological mechanisms underlying ischemic injury.

Glibenclamide, an FDA-approved sulfonylurea used for diabetes, has also garnered attention for its neuroprotective properties in stroke [61, 62]. Research suggests that it reduces cerebral edema by inhibiting SUR1-TRPM4 channels, which are implicated in swelling and secondary injury following ischemia [63, 64]. This repurpose of an existing drug offers practical advantages, including established safety profiles and reduced development timelines. Ongoing studies are exploring its utility in malignant hemispheric infarction, where edema poses a significant threat to patient survival. The case of glibenclamide exemplifies how drug repositioning can yield viable neuroprotective strategies with relatively low barriers to clinical implementation [65].

In addition to small molecules and peptides, novel biologics such as cell-penetrating antibodies are being investigated for their ability to target intracellular proteins involved in stroke pathology [66]. For instance, antibodies designed to inhibit caspase-3-a key executor of apoptotic cell death-have shown promise in preclinical models by reducing infarct size and improving functional recovery [67, 68]. These biologics combine the specificity of antibody-based therapies with the ability to penetrate cells, addressing intracellular targets traditionally considered 'undruggable.' While challenges remain in delivery and stability, such advancements highlight the expanding toolkit for neuroprotection in stroke.

Finally, the exploration of natural compounds and their synthetic derivatives continue to yield potential candidates. Compounds derived from traditional medicines have demonstrated neuroprotective effects in early studies, though further validation is needed [69, 70]. Similarly, flavonoids and other polyphenols are being studied for their antioxidant and anti-inflammatory properties, which may complement existing therapies [71, 72]. As the field moves toward multimodal treatment approaches, the integration of these novel candidates-ranging from repurposed drugs to cutting-edge biologics-holds promise for overcoming the limitations of current neuroprotective strategies and improving outcomes for stroke patients.

Clinical Studies

Neuroprotection in acute stroke clinical studies has been a challenging area, with mixed results in terms of efficacy and safety. The integration of neuroprotective strategies with reperfusion therapies, such as intravenous thrombolysis (IVT) and endovascular therapy, has shown some promise in improving clinical outcomes. However, the heterogeneity in study designs and outcome measures has made it difficult to draw definitive conclusions.

Campbell et al. [73] study on EXTEND-IA TNK trial (NCT02388061) investigated the efficacy and safety of tenecteplase compared to alteplase in patients with ischemic stroke undergoing endovascular thrombectomy. This multicenter, randomized, controlled study aims to determine whether tenecteplase is non-inferior to alteplase in achieving reperfusion at the initial angiogram when administered within 4.5 h of stroke onset. EXTEND-IA TNK is an investigator-initiated, phase II, multicenter, prospective, randomized, open-label, blind-endpoint non-inferiority study. Patients are randomized to receive either intravenous alteplase (0.9 mg/kg, max 90 mg) or tenecteplase (0.25 mg/kg, max 25 mg) prior to thrombectomy. The primary measure is reperfusion on the initial catheter angiogram, defined as modified treatment in cerebral infarction 2b/3 or the absence of retrievable thrombus. Secondary outcomes, these include the modified Rankin scale (mRS) at day 90 and a favorable clinical response (reduction in National Institutes of Health Stroke Scale by ≥8 points or reaching 0 to 1) at day 3. In summary, the provided information details the methodological framework and objectives of the EXTEND-IA TNK trial, which investigates the comparative efficacy and safety of tenecteplase versus alteplase in acute ischemic stroke patients receiving endovascular thrombectomy.

Nogueira and Tsivgoulis [74] study on DIRECT-MT trial (NCT03469206), which included 656 acute ischemic stroke patients with specific large vessel occlusions treated within 4.5 h, assessed whether primary mechanical thrombectomy (MT) was noninferior to a bridging strategy of IVT followed by MT. Primary outcome, primary MT was found to be noninferior to combined IVT + MT regarding the primary outcome of 90 day mRS shift. The adjusted common odds ratio was 1.07 (95% confidence interval (CI): 0.81 to 1.40), with a p value of 0.04. Reperfusion rates, despite the noninferiority, the absence of IVT in the primary MT group was associated with lower rates of successful reperfusion before MT (extended Thrombolysis in Cerebral Infarction ≥2, 2.4% vs 7.0%; odds ratio, 0.33 (95% CI: 0.14 to 0.74)).

Suzuki et al. [75] study on SKIP (UMIN000021488) trial involved 204 acute ischemic stroke patients with internal carotid artery (ICA) or middle cerebral artery M1 occlusions, presenting within 4 h of stroke onset. This trial utilized a reduced dose of alteplase (0.6 mg/kg). Noninferiority, the SKIP trial was unable to demonstrate the noninferiority of primary MT over combined therapy. Functional independence, there was no significant difference in the rates of functional independence at 90 days (mRS ≤ 2) between the groups

(59.4% for primary MT vs 57.3% for combined therapy; p = 0.78). However, the prespecified noninferiority margin of 0.74 was not met for either the primary (90 day mRS ≤ 2: odds ratio, 1.09 (95% CI: 0.63 to 1.90); p = 0.17) or secondary (90 day mRS shift, 0.97 (95% CI: 0.60 to 1.56); p = 0.27) outcomes. Rates of successful reperfusion (modified thrombolysis in cerebral infarction ≥2b, 90% vs 92%; p = 0.78), symptomatic intracranial hemorrhage (ICH; 6% vs 8%; p = 0.78), and 90 day mortality (7.9% vs 8.7%; p = 1.00) did not differ significantly between the two groups. However, the incidence of any ICH was higher with the bridging strategy (34% vs 50%; p = 0.02). In summary, while DIRECT-MT found primary MT to be noninferior to bridging therapy, SKIP, using a lower alteplase dose, could not demonstrate noninferiority. Both trials contribute to understanding treatment strategies for large vessel occlusion strokes.

Hill et al. [59] study on ESCAPE-NA1 trial (NCT02930018.) is a significant study in the field of acute ischemic stroke treatment, focusing on the efficacy and safety of nerinetide, a neuroprotectant, in patients undergoing endovascular thrombectomy. The ESCAPE-NA1 trial investigated the outcomes and treatment strategies for patients with acute ischemic stroke and tandem cervical carotid occlusion. Out of 1105 patients in the trial, 115 (10.4%) were identified as having tandem occlusions. Tandem occlusions were defined as a complete occlusion of the cervical ICA on catheter angiography, along with a proximal ipsilateral intracranial large vessel occlusion. Among the 115 patients with tandem occlusions, 62 (53.9%) underwent stenting for the cervical ICA occlusion. Of those who received stenting, 46 patients (74.2%) were stented after intracranial thrombectomy, while 16 patients (25.8%) were stented before the intracranial thrombectomy. A mRS of 0 to 2 at 90 days, indicating a good functional outcome, was achieved by 82 out of 115 patients (71.3%) with tandem occlusions. In comparison, 579 out of 981 patients (59.5%) without tandem occlusions achieved an mRS of 0 to 2. Adjusted analysis revealed that tandem occlusion did not negatively impact on the functional outcome (Odds ratio 1.5, 95% CI: 0.95 to 2.4). Within the subgroup of patients with tandem occlusion, cervical carotid stenting was not associated with different outcomes compared to not stenting. Specifically, 75.8% of patients who received stenting achieved an mRS of 0 to 2, compared to 66.0% of patients who did not receive stenting. The adjusted odds ratio for stenting vs no stenting was 2.0 (95% CI: 0.8 to 5.1). In conclusion, the study found that tandem cervical carotid occlusion in patients with acute large vessel strokes did not reduce the likelihood of a good functional outcome. Furthermore, the functional outcomes were similar regardless of whether the cervical ICA occlusion was managed with stenting or not.

Bracard et al. [76] study on THRACE trial (NCT01062698) was a multicenter, randomized controlled trial involving 26 centers in France, targeting patients aged 18 to 80 years with acute ischemic stroke and proximal cerebral artery occlusion. Between June 1, 2010, and February 22, 2015, a total of 414 patients were randomly assigned in the THRACE trial. Of these, 208 were allocated to the IVT group, and 204 were assigned to the IVT + MT group. Four patients (two from each group) were lost to follow-up, and six patients (four in the IVT group and two in the IVT + MT group) had missing data. These patients were excluded from the analysis. Functional independence at 3 months, defined as a mRS score of 0 to 2, was achieved by 85 (42%) of 202 patients in the IVT group. In contrast, 106 (53%) of 200 patients in the IVT + MT group achieved functional independence in 3 months. The odds ratio for achieving functional independence in the IVT + MT group compared to the IVT group was 1.55 (95% CI: 1.05 to 2.30), with a statistically significant p-value of 0.028. There was no significant difference in mortality at 3 months between the two groups. 24 (12%) of 202 patients in the IVT group died, compared to 27 (13%) of 206 patients in the IVT + MT group (p = 0.70). The incidence of symptomatic intracranial hemorrhage at 24 h was similar, with four (2%) of 185 patients in the IVT group and three (2%) of 192 patients in the IVT + MT group experiencing it (p = 0.71). Common adverse events specifically related to the thrombectomy procedure included vasospasm in 33 (23%) patients and embolization in a new territory in nine (6%) patients. In summary, the THRACE trial demonstrated that adding MT to standard IVT significantly improves functional independence at 3 months for patients with acute cerebral ischemia, without increasing mortality or the risk of symptomatic intracranial hemorrhage.

Saver et al. [77] study on SWIFT PRIME trial (NCT01657461) investigated the efficacy and safety of stent-retriever thrombectomy in addition to intravenous tissue plasminogen activator (t-PA) compared to t-PA alone for acute ischemic stroke patients with proximal anterior intracranial circulation occlusions. The study was stopped early due to clear efficacy, demonstrating significant improvements in functional outcomes for the intervention group. Thrombectomy with the stent retriever plus intravenous t-PA significantly reduced disability at 90 days across the entire range of scores on the mRS, with a p < 0.001. The median mRS score at 90 days was 2 for the intervention group compared to 3 for the control group. The rate of functional independence (mRS score of 0 to 2) was substantially higher in the intervention group (60%) compared to the control group (35%), with a p < 0.001. This represents an absolute increase of 25% in functional independence. For every 2.6 patients treated, one additional patient achieved an improved disability outcome, and for every 4.0 patients treated, one additional patient was functionally independent at 90 days. In the intervention group, the median time from qualifying imaging to groin puncture was 57 min. The rate of substantial reperfusion (defined as 50 to 99% reperfusion or complete reperfusion) at the end of the procedure was 88%. Successful reperfusion (≥ 90%) of 27 h was also significantly higher in the intervention group (83%) compared to the control group (40%). There were no significant differences in 90 day mortality between the intervention group (9%) and the control group (12%), with a p = 0.50. No significant difference was observed in symptomatic intracranial hemorrhage, with 0% in the intervention group and 3% in the control group (p = 0.12). The rates of serious adverse events were also similar between groups (36% in intervention vs 31% in control, p = 0.54). The demographic and clinical characteristics of the two treatment groups were well-balanced at baseline. In the intervention group, the median time from symptom onset to groin puncture was 224 min (interquartile range, 165 to 275 min). The median time from qualifying brain imaging to groin puncture was 57 min (interquartile range, 40 to 80 min). In summary, the SWIFT PRIME trial concluded that for patients with acute ischemic stroke due to proximal anterior intracranial circulation occlusions who received intravenous t-PA, the addition of thrombectomy with a stent retriever within 6 h of symptom onset significantly improved functional outcomes at 90 days without increasing mortality or symptomatic intracranial hemorrhage.

A study by Jönsson et al. [78] study on aimed to develop a population pharmacokinetic model for NXY-059 and estimate individualized dosing strategies in acute stroke patients (Figure 2) [79]. The final population model, derived from data of 179 patients across two clinical studies, was a two-compartment model. This model showed unexplained interpatient variability for clearance (23% coefficient of variation (CV)) and central volume of distribution

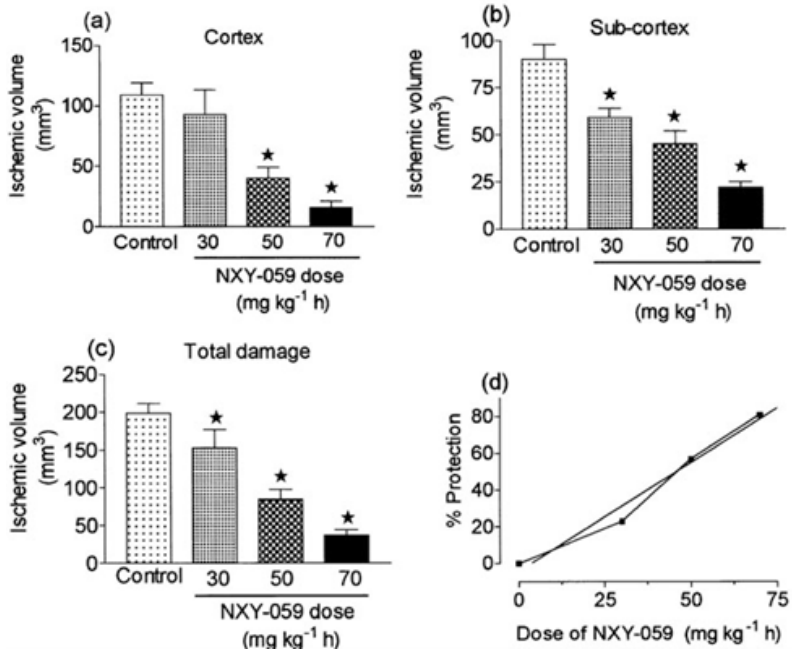

Figure 2: The effect of increasing doses of NXY-059 on the volume of ischaemic damage in the **(a)** cortex, **(b)** subcortex and **(c)** total brain volume, together with the **(d)** dose-response vs neuroprotection [79].

(40% CV). Variability in clearance and volume of distribution was partially explained by creatinine clearance (CLCR) and body weight, respectively. Typical clearance was estimated at 4.54 L/h for a patient with a CLCR of 70 mL/min. The preferred dosing strategy for NXY-059 included an initial loading infusion, which was the same for all patients. This was followed by an individualized maintenance infusion based on CLCR. The strategy involved three dosing categories with cut-off values for incrementing or decrementing infusion rates at 50 and 80 mL/min CLCR. These results demonstrate the successful optimization of an individualized dosing strategy for NXY-059, leveraging increasing pharmacokinetic and pharmacodynamic knowledge during clinical development to achieve target plasma concentrations early in acute stroke treatment.

A study by Elkind et al. [80] describes the objective and design of the NeuSTART trial. The study outlines the trial's goals, methodology, and statistical design, indicating it is an early phase trial designed to determine the maximal-tolerated dose of lovastatin for acute stroke therapy. The primary objective of this early phase trial is to determine the maximal-tolerated dose of lovastatin for short-term acute stroke therapy. The primary safety outcome is the occurrence of myotoxicity or hepatotoxicity, defined by clinical and laboratory criteria. The study aims to identify the highest dose of lovastatin that can be administered with less than 10% risk of myotoxicity or hepatotoxicity. This is a multicenter phase 1B dose-escalation and dose-finding study. It utilizes an adaptive design called the continual reassessment method, which is novel for stroke trials, to find optimal dosage. The dose-toxicity model is calibrated to select a dose causing 7 to 13% dose-limiting toxicity (within 3% of target). Thirty-three patients with acute ischemic stroke will be administered lovastatin. Doses will increase from one to 10 mg/kg daily for 3 days, beginning within 24 h after symptom onset. A sample size of 33 ensures that estimates of any binary variables will have a 95% CI of width less than or equal to 0.34. This sample size also enables the detection of unexpected toxicity occurring at a 5% rate (non-dose-dependent) with a probability of 0.82. The probability of choosing a dose for further trials with 25% or higher likelihood of toxicity is no more than 23%. In summary, the provided text details the experimental design and objectives of the NeuSTART trial, specifically focusing on dose-escalation and safety assessment for lovastatin in acute ischemic stroke.

A study by Minina et al. [81] investigated the effectiveness of neuroprotective therapy with Cellex in patients experiencing an acute period of ischemic stroke. By the end of the study, between days 14 and 21, both the study group (receiving Cellex) and the control group demonstrated significant improvements across various clinical scales, including NIHSS, mRS, and RMI. Patients in the study group exhibited a more significant recovery of motor function compared to the control group. FMA 'A to D', the study group scored 54 [53, 62] compared to the control group's 42 [34, 51] ($p = 0.03$). FMA 'E to F', the study group scored 29 [28, 33] compared to the control group's 25 [18, 27] ($p = 0.03$). ARAT, the study group scored 47 [48, 57] compared to the control group's 32 [24, 48] ($p = 0.046$). By the study's conclusion, 67% of patients in the study group had mild stroke severity, significantly higher than the 11% observed in the comparison group ($\chi 21df = 6.48$; $p = 0.01$). The application of Cellex neuroprotective therapy positively influenced both the prognostic score and the long-term assessment according to the SSS scale. This positive effect was attributed to the regression of motor disorders affecting both the upper and lower extremities. In summary, the study concluded that neuroprotective therapy with Cellex is effective in treating movement disorders in acute ischemic stroke patients, leading to reduced stroke severity and an improved disease prognosis.

Innovative Delivery Methods

The challenge of delivering neuroprotective agents effectively to the brain has led to the exploration of novel delivery methods (Table 2). Intranasal administration of mitochondria-targeted compounds has shown promise in bypassing the BBB and enhancing drug bioavailability [82]. This non-invasive approach could facilitate the treatment of acute stroke and other central nervous system disorders, providing a significant advantage over traditional delivery methods.

Table 2: Innovative delivery methods for neuroprotective agents.

Method	Description	Advantages	Limitations
Intranasal administration	Direct nasal delivery bypassing BBB	Non-invasive, rapid central nervous system access	Limited by formulation constraints
Nanoparticle-based delivery	Engineered carriers (liposomes, polymeric nanoparticles)	Targeted delivery, enhanced bioavailability	Complex manufacturing, regulatory hurdles
Stem cell-based delivery	Mesenchymal stem cells engineered to release neuroprotective factors	Dual role: delivery + endogenous repair	Delivery route, immunogenicity, scalability issues
Focused ultrasound with microbubbles	Temporarily opens BBB to allow drug penetration	Precise spatial targeting, non-invasive	Requires specialized equipment, safety monitoring
Gene therapy (Viral vectors)	Delivers genes encoding neuroprotective proteins (e.g., BDNF, VEGF)	Sustained protein expression, long-term effect	Immunogenicity, off-target effects, regulatory

Nanotechnology-based delivery systems represent another breakthrough in overcoming the limitations of conventional drug administration [83]. Engineered nanoparticles, such as liposomes and polymeric nanocarriers, can be designed to cross the BBB selectively, releasing their payloads at the site of ischemia [84]. These carriers can be further functionalized with targeting ligands, such as antibodies or peptides, to enhance their specificity for injured brain tissue. Preclinical studies have shown that nanoparticle-delivered neuroprotective agents, including antioxidants and anti-inflammatory drugs, achieve higher concentrations in the brain and exhibit prolonged therapeutic effects compared to free drug formulations [85].

Cell-based delivery systems are also being explored as a means to enhance the precision and durability of neuroprotection [86]. Mesenchymal stem cells, for example, can be engineered to secrete neuroprotective factors and then administered intravenously or directly into the brain [87]. These cells naturally migrate to sites of injury, where they release therapeutic molecules in a sustained manner. Additionally, mesenchymal stem cells have inherent anti-inflammatory and tissue-repair properties, making them dual-function vehicles for both drug delivery and endogenous repair. Early-phase clinical trials are investigating the safety and efficacy of this approach, with encouraging preliminary results.

Focused ultrasound combined with microbubbles is a cutting-edge technique that temporarily disrupts the BBB, allowing systemically administered drugs to penetrate the brain [88]. This method provides precise spatial and temporal control, enabling targeted delivery to the ischemic region while sparing healthy tissue. Preclinical studies have demonstrated that focused ultrasound enhanced delivery of neuroprotective agents, such as growth factors or small-molecule inhibitors, significantly reduces infarct volume and improves functional recovery [89]. As technology advances, its potential for clinical translation in acute stroke continues to grow, offering a versatile platform for enhancing drug delivery.

Gene therapy approaches are also being investigated to provide long-term neuroprotection by modulating the expression of key proteins involved in stroke pathology [90]. Viral vectors, such as adeno-associated viruses, can deliver genes encoding neuroprotective factors (e.g., BDNF or VEGF) directly to the brain [91]. These vectors offer the advantage of sustained protein production, potentially providing weeks to months of therapeutic benefit after a single administration. While challenges related to immune responses and vector distribution remain, ongoing research aims to optimize these systems for safe and effective use in stroke patients. Together, these innovative delivery methods are expanding the horizons of neuroprotection, offering new hope for more effective and targeted treatments.

Future Directions

Despite these promising developments, the translation of neuroprotective strategies from animal models to human clinical trials has been fraught with challenges. The complexity of human stroke syndromes and the variability in patient conditions have contributed to the limited success of past trials [10]. Additionally, the need for rapid administration and the presence of comorbidities complicate the clinical application of these therapies [92]. Future research should focus on refining animal models to better mimic human conditions and exploring the neurovascular unit's role in stroke pathology [10]. Moreover, integrating neuroprotective strategies with existing reperfusion therapies could enhance overall treatment efficacy [93]. As the understanding of stroke pathophysiology evolves, so too does the potential for innovative pharmacological approaches to neuroprotection. The integration of advanced technologies, such as artificial intelligence and systems biology, may further enhance the identification and development of novel therapeutic agents [33]. Additionally, the exploration of cellular dynamics and efferocytosis presents new avenues for improving post-stroke recovery [94].

A particularly promising avenue involves targeting the neurovascular unit as an integrated system rather than focusing solely on neuronal protection [95]. This holistic approach recognizes that stroke affects not just neurons but also endothelial cells, astrocytes, pericytes, and microglia in a complex interplay. Novel therapeutics are being developed to preserve BBB integrity, regulate cerebral blood flow, and modulate neuroinflammatory responses simultaneously. Compounds that can maintain this delicate cellular ecosystem during and after ischemia may offer more comprehensive protection than agents targeting single pathways [96].

The development of multi-target therapeutics represents another important frontier in neuroprotection. Rather than relying on single-mechanism drugs, researchers are designing compounds and combination therapies that address multiple injury cascades simultaneously - including excitotoxicity, oxidative stress, apoptosis, and inflammation [97]. This approach mirrors the success seen in other complex diseases like cancer and HIV, where combination therapies have dramatically improved outcomes. High-throughput screening and computational drug design are accelerating the identification of such multi-functional agents.

There is growing recognition that effective neuroprotection may require different strategies at various stages of stroke injury and recovery. The concept of 'temporal targeting' involves administering specific therapies at optimal time points - acute phase interventions to limit initial damage, subacute treatments to prevent secondary injury, and chronic-phase therapies to enhance plasticity and repair. This paradigm shift acknowledges that the pathophysiological processes

evolve over time and require careful coordination of interventions across the care continuum.

Finally, the integration of neuroprotective strategies with advanced rehabilitation techniques offers exciting possibilities for optimizing functional recovery. Combining pharmacological agents with neuromodulation technologies like TMS or brain-computer interfaces may create synergistic effects that enhance neuroplasticity. Similarly, pairing drug therapies with task-specific training during critical recovery windows could maximize the brain's innate repair mechanisms. These combinatorial approaches represent the next generation of stroke treatment, moving beyond simple neuroprotection to active neurorestoration.

Conclusion

The field of neuroprotection in acute stroke has entered a transformative phase, marked by innovative pharmacological strategies, advanced delivery systems, and a deeper understanding of stroke pathophysiology. While challenges remain in translating preclinical success to clinical practice, recent breakthroughs-such as targeted molecular therapies, drug repositioning, and multimodal approaches-offer renewed hope for effective interventions. The integration of precision medicine, artificial intelligence, and novel technologies is paving the way for more personalized and effective treatments tailored to individual patient needs and stroke subtypes.

Future progress will depend on addressing key limitations, including the narrow therapeutic window, heterogeneity of stroke presentations, and the complexity of human stroke pathology compared to animal models. Collaborative efforts across disciplines-combining insights from neuroscience, pharmacology, bioengineering, and data science-will be essential to overcome these hurdles. Additionally, optimizing clinical trial designs to better capture the benefits of neuroprotective agents, particularly when combined with reperfusion therapies, will be critical for demonstrating efficacy in human studies.

As research continues to evolve, the ultimate goal remains clear: to develop neuroprotective treatments that significantly improve outcomes for stroked patients worldwide. By building current advancements and fostering innovation in drug development, delivery methods, and combination therapies, the next decade may finally realize the long-awaited promise of effective neuroprotection. The convergence of scientific and technological progress positions the field at the threshold of a new era in stroke care, one where neuroprotection becomes an integral and impactful component of comprehensive stroke management.

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None.

Conflict of Interest

None.

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