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Recent Advances in Pharmacotherapy for Acute Ischemic Stroke: Emerging Neuroprotective and Regenerative Agents: A Comprehensive Narrative Review

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ABSTRACT

Background: One of the leading causes of death worldwide and long-term neurological impairment is acute ischemic stroke (AIS). Although intravenous thrombolysis and endovascular thrombectomy are reperfusion methods that are considered the standard of care, a significant number of patients are left without adequate treatment due to their limited therapeutic windows and eligibility restrictions.

With a focus on neuroprotective and neuroregenerative agents such as sovateltide, edaravone, dexborneol, butylphthalide, nerinetide, tenecteplase, stem cell-based therapies, and remote ischemic conditioning, this review summarizes the most recent research on new pharmacotherapeutic approaches for AIS.

Methods: PubMed/MEDLINE, Scopus, and PubMed Central databases were used to conduct an organized narrative review. Randomized controlled trials and Phase II/III studies were given priority, and only Scopus-indexed, publicly accessible original publications and clinical trials published between 2020 and 2025 were chosen.

Results: Sovateltide, an ETB receptor agonist, has been approved by Indian regulators after showing notable improvements in mRS and NIHSS at 90 days in Phase III trials. In comparison to a placebo, edaravone dexborneol (TASTE-SL study) considerably improved 90-day functional outcomes. At 90 days, butylphthalide (BAST trial) demonstrated greater functional independence. Tenecteplase showed logistical advantages and non-inferiority to alteplase. With encouraging preclinical findings, stem cell and exosome-based treatments are in the early phases of clinical development.

Conclusion: AIS's developing pharmacotherapeutic landscape is encouraging. Neuroregenerative biologics, combination approaches, and multi-target therapies may be able to get around the drawbacks of existing monotherapy. To definitively prove clinical utility, more extensive, global, randomized controlled trials are necessary.

Keywords: Stroke; Acute Ischemic Stroke; Neuroprotection; Sovateltide; Emerging Therapies; Neuroregeneration; Pharmacotherapy; Clinical Outcomes

1. INTRODUCTION

About 87% of all stroke episodes worldwide are acute ischemic stroke (AIS), which is characterized as a rapid localized neurological impairment brought on by cerebrovascular blockage leading to brain infarction [1]. It is a major contributor to long-term impairment and the second most common cause of death globally. The Global Burden of Disease (GBD) 2021 Study estimates that there were 69.9 million prevalent cases worldwide in 2021, with an age-standardized prevalence rate of 819.5 per 100,000 people [2]. Low- and middle-income countries (LMICs), which currently account for nearly 87% of stroke-related deaths and disability-adjusted life years (DALYs), were disproportionately affected by the significant increase in the absolute burden between 1990 and 2021, with a 70% increase in incident strokes and an 86% increase in prevalent stroke cases [3].

Excitotoxicity, oxidative stress, neuroinflammation, disruption of the blood–brain barrier (BBB), mitochondrial dysfunction, and apoptotic cell death in the ischemic penumbra—the salvageable peri-infarct zone that serves as the main therapeutic target—are all part of the complex pathophysiology of AIS [4]. Time-sensitive reperfusion therapy is justified since the penumbra may survive for several hours whereas the ischemic core experiences permanent necrosis within minutes.

Intravenous recombinant tissue plasminogen activator (rt-PA; alteplase), given within 4.5 hours of stroke onset, is currently the only approved pharmacological reperfusion treatment [5]. In certain patients with visible penumbra on imaging, mechanical thrombectomy has further extended the therapy window to 24 hours [6]. Despite these developments, reperfusion therapy is only available to 5–15% of AIS patients in the majority of healthcare systems because to stringent eligibility requirements, such as time frames, the absence of bleeding, and imaging requirements. Because effective recanalization may not always result in functional recovery due to ischemia-reperfusion injury, even among treated patients, results are still not ideal.

The search for supplemental medications that can (i) prolong the therapeutic window, (ii) enhance neuroprotection by reducing secondary injury cascades, and (iii) encourage neuroplasticity and neuroregeneration during the post-acute recovery phase has become more intense due to these limitations [7]. Hundreds of neuroprotective compounds have failed to show efficacy in pivotal trials despite encouraging preclinical data; this is primarily due to heterogeneous patient populations, insufficient preclinical models, and improper timing of intervention [8].

Recent developments in neuroimaging, the creation of multi-target drugs, and a better knowledge of stroke pathobiology have all contributed to a new wave of pharmacological innovation. These include the NMDA antagonist nerinetide, the next-generation thrombolytic tenecteplase, the endothelin-B receptor agonist sovateltide (a first-in-class neuroprogenitor-stimulating agent), the combination antioxidant edaravone dexborneol, the mitochondria-protective agent butylphthalide, and cell-based regenerative therapies [9, 10, 11].

In order to assess the effectiveness, safety, and potential for future translation of novel neuroprotective and neuroregenerative approaches, this review offers a critical evaluation of the present pharmacotherapeutic landscape for AIS by synthesizing the most recent Scopus-indexed clinical evidence. For physicians, neuropharmacologists, and translational researchers working on stroke treatments, it is meant to be a thorough scientific resource.

2. CURRENT STANDARD OF CARE: REPERFUSION STRATEGIES

Intravenous Thrombolysis with Alteplase

The most effective thrombolytic treatment for AIS within the 4.5-hour window is still intravenous alteplase (0.9 mg/kg). By changing plasminogen into plasmin and breaking up fibrin clots, it accomplishes recanalization. However, the majority of patients are ineligible due to exclusion criteria, a short treatment window, and the risk of symptomatic intracranial hemorrhage (sICH) [5]. Only 5–10% of stroke patients worldwide receive alteplase, and even among those who do, less than 50% of patients attain functional independence after 90 days [12].

Tenecteplase: A Next-Generation Thrombolytic

A possible substitute thrombolytic is tenecteplase (TNK), a bioengineered version of alteplase with increased fibrin selectivity, a longer plasma half-life, and resistance to plasminogen activator inhibitor-1 (PAI-1). TNK at 0.25 mg/kg was non-inferior to alteplase in 90-day functional outcomes, with a comparable safety profile regarding sICH, according to a systematic review and meta-analysis by Singh et al. (2024) that examined data from several randomized controlled trials (RCTs) comparing TNK and alteplase in AIS [13]. Additionally, TNK has practical benefits: its intravenous single-bolus delivery streamlines workflow and may shorten door-to-needle times, especially in drip-and-ship models.

TNK 0.25 mg/kg significantly boosted early vascular recanalization and was linked with excellent neurological recovery, without a significant increase in sICH risk, according to a 2024 updated meta-analysis by Li et al. that examined nine RCTs comparing TNK with alteplase in AIS [14]. In light of these findings, a number of national and international guidelines now suggest TNK as a suitable substitute for alteplase, particularly for patients having concomitant endovascular thrombectomy.

Endovascular Thrombectomy in Extended Therapeutic Windows

AIS treatment has been transformed by mechanical endovascular thrombectomy (EVT), especially for large vessel occlusion (LVO). With a generalized odds ratio of 1.51 (95% CI: 1.20–1.89; P<0.001), the SELECT2 trial (2023) showed that endovascular thrombectomy plus medical care produced significantly better 90-day functional outcomes than medical care alone in patients with large ischemic core volumes (ASPECTS 3–5 or ischemic core ≥50 mL) [15]. At the one-year follow-up, the advantage remained constant across subgroups. These results represent a paradigm change toward treating even large-core strokes and have broadened the eligibility criteria for EVT.

3. EMERGING NEUROPROTECTIVE PHARMACOTHERAPIES

Sovateltide: A First-in-Class Neuroregenerative Agent

The selective endothelin-B (ET-B) receptor agonist sovateltide (IRL-1620) offers a mechanistically innovative method of treating AIS. Activation of the ET-B receptor increases cerebral blood flow, angiogenesis, neuroprogenitor cell proliferation and differentiation, and mitochondrial protection to prevent apoptosis [16]. Because of these pleiotropic effects, sovateltide stands out from most other medications as a medication that promotes both acute neuroprotection and subacute neuroregeneration.

160 patients with confirmed AIS and NIHSS ≥6 who presented within 24 hours of symptom start were included in the pivotal Phase III multicenter, randomized, double-blind, placebo-controlled trial by Gulati et al. (2024), which was carried out across several locations in India [17]. In addition to usual care, three intravenous doses of 0.3 µg/kg of sovateltide were given over the first 72 hours. At 90 days, compared to controls, a substantially greater number of patients in the sovateltide group demonstrated improvement of ≥2 points on the modified Rankin Scale (mRS) (76.1% vs. 52.8%; P=0.005) and ≥6 points on the NIHSS

(82.1% vs. 64.3%; P=0.019). Importantly, an adequate safety profile was confirmed by the identical frequency of cerebral bleeding between groups (8.75% vs. 8.97%).

In September 2023, the Drug Controller General of India (DCGI) gave sovateltide (commercial name: TyvalziTM) regulatory approval based on these Phase III data, making it the first neuroprogenitor cell-stimulating medication for AIS licensed globally [18]. In order to assess sovateltide in a larger North American/European cohort with NIHSS ≥8, a follow-up global RESPECT-ETB experiment has been submitted for FDA approval. The endothelin-B axis is a promising therapeutic target that may be used to treat neurodegenerative diseases other than acute stroke.

Edaravone Dexborneol: Multi-Target Antioxidant Neuroprotection

Edaravone dexborneol (EDD) is a dual-mechanism agent combining edaravone—a potent hydroxyl radical scavenger—with dexborneol, a stereoisomer of borneol possessing antioxidant and anti-inflammatory properties, as well as BBB-enhancing effects. The TASTE-SL trial (2024), a Phase III, double-blind, placebo-controlled multicenter RCT conducted at 33 Chinese centers (n=914), evaluated sublingual EDD in AIS patients within 48 hours of onset [10]. The sublingual formulation enables rapid mucosal absorption, bypassing first-pass metabolism.

Compared to placebo, a far greater percentage of patients taking EDD had a good outcome (mRS ≤1) at 90 days (64.4% vs. 54.7%; risk difference 9.70%, 95% CI: 3.37%–16.03%; OR 1.50; P=0.003) [10]. There were no significant adverse drug-related events, and the rate of adverse events was similar among groups. These results were further supported by a real-world multicenter prospective cohort research (n=6,000+; 72 centers, China, 2023), which demonstrated that edaravone dexborneol was linked to noticeably improved 90-day mRS outcomes in ordinary clinical practice [19].

EDD's clinical adoption as an adjuvant to reperfusion therapy is supported by a 2025 systematic review and meta-analysis by Moghib et al. that evaluated EDD across multiple RCTs and confirmed significant reductions in NIHSS scores and improved 90-day functional outcomes when compared to edaravone monotherapy or placebo [20].

Butylphthalide (NBP): Mitochondria-Protective Neuroprotection

Celery seeds (Apium graveolens) are the source of DL-3-n-butylphthalide (NBP), a multi-mechanism neuroprotective drug that maintains mitochondrial function, suppresses oxidative stress, lowers neuroinflammation, and stimulates angiogenesis and neurogenesis. In China, it is authorized for the treatment of AIS. NBP was linked to a significantly higher proportion of patients achieving a favorable functional outcome at 90 days (56.7% vs. 44.0%; P<0.001) with an odds ratio of 1.7 when compared to placebo, according to the seminal Butylphthalide for Acute Ischemic Stroke Patients Receiving Thrombolysis (BAST) trial (2023), a multicenter double-blind RCT that enrolled 1,216 patients receiving reperfusion therapy [21]. All groups had similar rates of major adverse events.

Crucially, patients receiving IV thrombolysis alone, endovascular therapy alone, or both consistently benefited from NBP across predetermined categories. NBP significantly lowered NIHSS scores (mean difference -3.39; 95% CI: -3.76 to -3.03) and enhanced activities of daily living, confirming its role as a neuroprotective adjunct, according to a 2023 meta-analysis of 57 RCTs comprising 8,747 AIS participants [22]. Butylphthalide was also shown to enhance cerebral autoregulation in AIS patients with big artery atherosclerosis in the EBCAS randomized controlled study (2023), which may help improve perfusion of the ischemic penumbra [23].

Nerinetide: Excitotoxicity Blockade

Nerinetide is a 20-amino acid cell-penetrating peptide derived from the PDZ1 domain of PSD-95 protein

that uncouples NMDA receptor activation from downstream excitotoxic signaling cascades, including nitric oxide synthase activation. Its mechanistic rationale is distinct from direct NMDA channel blockade, which has historically failed in clinical trials due to off-target CNS effects. A 2025 systematic review and meta-analysis pooling three RCTs encompassing 2,462 AIS patients demonstrated a modest but statistically significant reduction in mortality risk with nerinetide (RR=0.86; P=0.05), particularly in patients not receiving concomitant IV alteplase [24]. The ESCAPE-NEXT trial (2025) specifically evaluated nerinetide in EVT patients not receiving thrombolysis, reporting neuroprotective signals in infarct volume reduction and early neurological improvement [25].

However, a critical pharmacokinetic interaction was identified: alteplase appears to cleave nerinetide, reducing its effective concentration. This observation, if validated, has profound implications for trial design and may explain the negative results seen in alteplase-premedicated subgroups in earlier studies. Ongoing trials are evaluating nerinetide as monotherapy adjunct to EVT without thrombolysis.

Fingolimod: Immunomodulatory Neuroprotection

Fingolimod (FTY720), a sphingosine-1-phosphate (S1P) receptor modulator originally approved for multiple sclerosis, has demonstrated neuroprotective potential in AIS through its immunomodulatory mechanism—sequestering autoreactive lymphocytes in lymph nodes, reducing post-ischemic neuroinflammation, promoting microglial polarization toward anti-inflammatory M2 phenotypes, and stabilizing BBB integrity. A structured narrative review by Seidel et al. (2024) examining preclinical and clinical studies published between 2015 and 2024 concluded that fingolimod reduced infarct size and preserved BBB function in animal models, with preliminary clinical data supporting improved short- and long-term neurological outcomes when combined with IV thrombolysis or EVT [26]. Its safety profile in the stroke context appears manageable, though larger RCTs are required before clinical adoption.

Network Meta-Analysis: Comparative Efficacy of Neuroprotective Agents

A 2025 network meta-analysis by Wang et al., adhering to PRISMA guidelines and incorporating data from RCTs identified through comprehensive database searches (PubMed, Embase, Cochrane) up to September 2024, systematically compared the efficacy of multiple neuroprotective agents in AIS [7]. The analysis evaluated outcomes based on mRS and NIHSS scores and found that combination neuroprotective strategies (particularly multi-target agents like EDD and NBP) ranked highest in terms of improving neurological function and achieving favorable prognosis at 90 days, while single-mechanism agents showed more variable efficacy. The authors recommended that future trials adopt combination neuroprotective frameworks and standardized outcome measures.

Similarly, edaravone-based combinations and NBP were found to be among the most effective agents in a 2024 network meta-analysis by Li et al. (Frontiers in Pharmacology), which evaluated neuroprotective drugs in AIS patients using NIHSS and mRS endpoints from databases up to June 2024 [14]. These results offer a framework for evidence-based selection of adjunctive pharmacotherapy in AIS.

4. NEUROREGENERATIVE STRATEGIES

Neural Stem Cell Therapy

In AIS, neural stem cell (NSC) treatment signifies a paradigm change from neuroprotection to active neurorepair. In addition to having the ability to develop into neurons, astrocytes, and oligodendrocytes, NSCs also have paracrine effects by producing extracellular vesicles that alter the post-ischemic milieu, trophic factors (BDNF, VEGF, and IGF-1), and anti-inflammatory cytokines. In a thorough 2024 review published in Neural Regeneration Research, Wang et al. summarized the possible mechanisms of NSC

therapy in ischemic stroke, examined the findings of clinical trials, and emphasized NSC engineering techniques such as scaffold-supported delivery and gene-modified NSCs with improved post-transplant survival rates [27]. Intravenous administration, intranasal mucosal delivery, and stereotactic intracerebral injection are the main delivery methods.

Randomized controlled clinical trials on stem cell therapy for ischemic stroke were assessed in a systematic review and network meta-analysis by Zhang et al. (BMC Neurology, 2025), which included data from the Cochrane Library, PubMed, Web of Science, and other databases from inception to December 2024 [28]. Although variation in cell type, dosage, time, and route of administration prevented decisive findings, the research revealed functional gains with stem cell transplantation, especially with mesenchymal stem cells (MSCs) and bone marrow-derived stem cells. The unfavorable ischemia microenvironment, which is marked by oxidative stress, inflammation, and decreased cerebral blood flow and hinders the survival and integration of transplanted cells, continues to be the primary obstacle.

Exosome-Based Cell-Free Therapy

In comparison to whole-cell transplantation, extracellular vesicles (EVs) and exosomes produced from MSCs provide a number of useful benefits, including increased stability, less immunogenicity, simpler large-scale production, and the ability to pass the blood-brain barrier. Non-coding RNAs (miRNAs), growth factors, and proteins that support angiogenesis, neurogenesis, and anti-inflammatory signaling in the post-ischemic brain are carried by MSC-derived exosomes. In the Asian Journal of Pharmaceutical Sciences, Sun et al. (2024) thoroughly examined stem cell-based modifications and clinical difficulties in ischemic stroke therapy, emphasizing exosome engineering techniques like surface functionalization and drug loading that may significantly enhance targeted delivery to ischemic tissue [29]. Although exosome treatment for stroke is still in its early phases of clinical studies, Phase I findings indicate a satisfactory safety profile.

5. NON-PHARMACOLOGICAL ADJUNCTS AND COMBINATION STRATEGIES

Remote Ischemic Conditioning (RIC)

In order to trigger endogenous neuroprotective pathways mediated by humoral factors (adenosine, bradykinin), neurogenic signaling, and anti-inflammatory gene expression, remote ischemic conditioning (RIC) entails short, repeated cycles of limb ischemia-reperfusion (usually via upper arm cuff inflation/deflation). When compared to conventional therapy alone, adjuvant RIC significantly improved NIHSS scores and short-term functional prognosis, according to a 2025 prospective controlled trial by Huang et al. (Frontiers in Neurology) that included 266 AIS patients [30]. Mechanistically, RIC enhances the benefits of pharmaceutical neuroprotection by lowering oxidative stress, reducing pro-inflammatory cytokine cascades, and attenuating microglial activation.

Additionally, RIC was noted as a promising adjunct to EVT in a 2024 review of neuroprotective strategies during thrombectomy (Zhao et al., Brain Circulation). Preliminary clinical evidence supports improved early neurological outcomes when RIC is applied prior to or during endovascular procedures [31]. Ongoing trials are evaluating RIC's synergy with pharmaceutical medicines, and its non-invasive, low-cost nature makes it particularly useful in situations with limited resources.

Intra-Arterial Selective Hypothermia

Another supplementary neuroprotective approach that aims to lower metabolic demand and attenuate ischemia-reperfusion damage in real-time is intra-arterial local therapeutic hypothermia (IA-LTH), which is administered via infusion of 4°C saline during EVT. IA-LTH plus standard therapy versus standard care

alone in anterior circulation LVO patients was examined in a 2024–2025 multicenter pilot RCT that was carried out across 18 stroke hospitals in China (n=100) [32]. Although the primary 90-day mRS results in this underpowered pilot did not approach statistical significance, the biological plausibility is still strong and the safety findings were comforting. There are continuing larger definitive trials.

6. PATHOPHYSIOLOGICAL TARGETS AND FUTURE DIRECTIONS

A number of methodological and biological issues have historically contributed to the failure of many neuroprotective compounds in clinical translation: (i) inadequate patient stratification by infarct location, size, and penumbral extent; (ii) delayed or suboptimal drug delivery in relation to the evolution of ischemic injury; (iii) single-mechanism agents unable to address the multifactorial injury cascade; and (iv) poor recapitulation of human stroke pathophysiology in rodent models.

Multi-target combination regimens, temporally optimized delivery (e.g., pre-hospital thrombolysis + early neuroprotection + post-reperfusion neuroregenerative therapy), and personalized medicine approaches incorporating neuroimaging biomarkers and genomic data are likely to be the direction of future pharmacotherapeutic approaches in AIS. To increase the accuracy of pharmacotherapy in AIS, artificial intelligence-driven patient selection and trial design are being used more often [33]. The most physiologically consistent and clinically developed areas include the endothelin-B axis (sovateltide), mitochondrial protection (NBP), and exosome-based neuroregeneration.

Moreover, regulation of the blood-brain barrier is yet an unexplored therapeutic target. An intriguing area of convergence for translational study is agents that maintain barrier integrity against hemorrhagic transformation while selectively increasing BBB permeability in the therapeutic setting, enabling improved drug penetration [34]. To get around the BBB problem in AIS, nanomedicine-based drug delivery methods, such as liposomal formulations and nanoparticle-conjugated neurotrophic factors, are being studied as vectors [35].

There is growing recognition of the significance of the post-acute neuroregeneration period. The subacute (days 3–14) and chronic (weeks 2–24) phases provide separate windows for neuromodulation, circuit rewiring, and synaptic plasticity beyond the hyperacute window (0–6 hours). These processes may be pharmacologically aided by substances like sovateltide, stem cell-derived exosomes, and erythropoietin analogs [36]. Synergistic functional improvements may result from the combination of organized rehabilitation and pharmaceutical neuroregeneration.

7. EMERGING BIOMARKERS AND CLINICAL OUTCOME MEASURES

The almost ubiquitous use of the modified Rankin Scale (mRS) and NIHSS as primary and secondary endpoints has enhanced the standardization of outcome measurements among AIS studies. These global metrics, however, could overlook minute functional improvements. A growing number of co-primary or secondary goals include patient-reported outcomes, health-related quality of life evaluations (EQ-5D, PROMIS), and measurements specialized to the cognitive domain. Diffusion-weighted imaging (DWI) lesion volume, penumbra-to-core ratio, and functional MRI connectivity are examples of neuroimaging biomarkers that offer objective surrogates for neuroprotective effectiveness and may be more sensitive to treatment effects at earlier time periods [20]. As pharmacodynamic indicators for neuroprotective medication trials, plasma biomarkers (GFAP, NfL, and S100B) are now being investigated.

8. CONCLUSION

Beyond proven reperfusion techniques, acute ischemic stroke continues to be a catastrophic neurological emergency with substantial unmet treatment needs. A rich and quickly changing treatment landscape has been shown by this study, which has compiled the most recent Scopus-indexed clinical evidence on novel pharmacological and neuroregenerative techniques.

As the first neuroprogenitor-stimulating medication for AIS to be authorized worldwide, sovateltide stands out as a groundbreaking discovery. It has shown strong Phase III effectiveness in considerably improving mRS and NIHSS results at 90 days with a respectable safety profile. By actively boosting neurorepair rather than just slowing the course of damage, its mode of action—ET-B receptor-mediated neurogenesis and angiogenesis—addresses the basic shortcoming of existing treatments.

The most clinically validated neuroprotective adjuncts are butylphthalide and edaravone dexborneol, which are backed by multicenter RCT evidence showing better functional results at 90 days. Tenecteplase's practical benefits and similar effectiveness to alteplase are making it the favored thrombolytic. Although nerinetide and fingolimod have mechanistic promise, further validation in well planned subgroup studies is necessary. Neuroregeneration based on stem cells and exosomes is at the forefront of biological treatment, and within the next ten years, clinical translation is anticipated.

Precision neuroimaging and validated biomarkers are guiding the movement in therapy philosophy toward a multi-phase, multi-mechanism treatment model: acute reperfusion + early neuroprotection + subacute neuroregeneration. To significantly enhance clinical outcomes for the millions of AIS patients, combination pharmacotherapy, improved delivery methods, and individualized stroke care must be integrated.

Large-scale, globally coordinated prospective RCTs with pre-specified biomarker-stratified subgroup analyses should be given top priority in future directions. They should also investigate synergistic combinations and the best times to use newly developed neuroprotective and neuroregenerative drugs. There is great potential for improving stroke recovery results worldwide if this therapy portfolio is developed further.

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