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New drugs on the horizon for cerebral edema: what's in the clinical development pipeline?

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Abstract

Introduction: Research has advanced our understanding of the molecular and cellular mechanisms of cerebral edema and has propelled the development of novel anti-edema therapeutics. Current evidence supports aberrant neuro-glial ion transport as a central mechanism that underlies pathological fluid accumulation after central nervous system injury.

Areas covered: Novel agents in clinical development show potential in altering the natural history and treatment of cerebral edema. Using the PubMed and Google Scholar databases, we review recent advances in our understanding of cerebral edema and describe agents under active investigation, their mechanism, and their application in recent and ongoing clinical trials.

Expert Opinion: Pharmacotherapies that target molecular mechanisms underlying the compensatory post-injury response of ion channels and transporters that lead to pathological alteration of osmotic gradients, are the most promising therapeutic strategies. Repurposing of drugs such as glyburide that inhibit the aberrant upregulation of ion channels such as SUR1-TRPM4, and novel agents, such as ZT-a1, which re-establish physiological regulation of ion channels such as NKCC1/KCC, could be useful adjuvants to prevent and even reverse fluid accumulation in the brain parenchyma.

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1. Introduction

Cerebral edema, the pathological accumulation of fluid in the brain parenchyma, is caused by multiple traumatic and pathological insults, including traumatic brain injury (TBI), stroke (both hemorrhagic and ischemic), infection, primary and metastatic tumors, and inflammatory disease. Even some systemic diseases, including acute liver failure and diabetic ketoacidosis, can lead to brain swelling. Regardless of the inciting event, a common consequence of cerebral edema is the elevation of intracranial pressure (ICP). Swelling brain tissue and increasing ICPs result in compromised cerebral blood flow, ischemia, cell death, and neurological deficits.[1] Although the severity, location, and extent of swelling determine the specific downstream consequences, the side effects are often severe, frequently affecting functional outcome and increasing mortality to upwards of 80%.[1,2]

Here, we review recent advancements in our understanding of the pathology of cerebral edema and highlight novel or repurposed therapeutic agents that are being explored in animal models of edema, as well as preclinical and clinical human trials. This was accomplished through a comprehensive literature review using both PubMed and Google Scholar databases, limiting searches to include only studies published after the year 2000 so that the most up-to-date information was reported. Clinicaltrails.gov was utilized for all ongoing or recently completed clinical trials.

2. Management of Cerebral Edema

The Monro-Kellie doctrine, first described by Dr. Alexander Monro and Dr. George Kellie more than two centuries ago, is a well-accepted principle in neurological disease. This principle states that the sum of the volumes of intracerebral blood, cerebrospinal fluid, and brain tissue, consisting of interstitial and intracellular fluid, is constant given the constraints of a rigid skull.[3] An increase in one must cause a reciprocal decrease in one or more of the others. Therefore, current management of cerebral edema focuses on temporizing tissue swelling and decreasing ICPs to prevent brain herniation and ischemia resulting from high ICPs and loss of cerebral blood flow.

Osmotherapy, a common first line management, consists of intravenous administration of hypertonic solution (typically mannitol or hypertonic saline). Following Starling's principle, creating an osmotic gradient across blood vessels causes water to move from the intra- and extra-cellular compartments of the brain into the vasculature, decreasing parenchymal fluid volume. This movement of water along an imposed ionic gradient serves to decrease intracranial volume, and as a result, pressures. In addition to osmotherapy, the glucocorticoid Decadron is commonly used, especially in the setting of tumor-induced edema.[4] Other less commonly used medications for edema include loop diuretics (typically furosemide), anti-inflammatory agents, and barbiturates.[5]

Although often first-line, medical management is largely temporizing and exposes patients to significant side effects, as well as rebound swelling after therapy is discontinued. Surgical management with decompressive craniectomy is often required if medical therapy fails, or as initial management if the edema is too extensive, resulting in dramatically increased ICP,

and urgent intervention is needed. Interestingly, these strategies to reduce cerebral swelling and increasing ICP have been used for over a century.

3. Pathophysiology of Cerebral Edema

Cerebral edema is traditionally classified as cytotoxic or vasogenic, based on location of fluid accumulation.[6,7] Vasogenic edema causes increased extracellular fluid due to blood-brain barrier (BBB) breakdown, while cytotoxic edema occurs when water accumulates in the intracellular space, resulting in cell swelling.[6,7] Ionic cerebral edema, more recently defined as a subset of cytotoxic edema, consists of vessel leakage into the extracellular space through an intact BBB.[6]

While historical classifications remain useful, current research is advancing our understanding of the mechanisms underlying cerebral edema. Intracranial water balance is based on intra- and extra-cellular and vascular ionic gradients dictated primarily by cellular channels and transporters. Accordingly, current theories ascribe the pathophysiology of cerebral edema to alterations in intracranial ion transport, and new pharmacological targets in this framework are under investigation.[1]

4. Anti-edema Drugs in Development

As our understanding of the pathophysiology of cerebral edema increases, pharmacological treatments are being developed to target specific, underlying molecular mechanisms. New candidates are showing promise in attenuating tissue swelling and improving functional outcomes in *in vivo* models and clinical trials. Table 1 summarizes these novel therapeutic agents.

4.1 Cation-Chloride Cotransporter (CCC) Regulation

Intracranial ionic homeostasis is, in part, maintained by cation-Cl^- cotransporters (CCC), specifically NKCC1 and the KCCs. Through phosphorylation, SPAK (SPS1-related proline/alanine-rich kinase) is the master regulator of both, stimulating NKCC1 and inhibiting KCCs.[8] As electroneutral cotransporters, NKCC1 imports and KCC1–4 export Cl^- by utilizing the transmembrane gradients of Na^+ and/or K^+. Their coordinated regulation is required to effect appropriate cell volume changes while preventing pathological volume changes in response to altered osmotic gradients. SPAK, in combination with OSR1 (oxidative stress-responsive kinase 1), which functions similarly to SPAK in regard to modulating NKCC1 and KCCs activity, ensures control over cellular Cl^- concentrations, and consequently, water movement and cell volume.[8] In experimental models, enhanced SPAK activity has been found in ischemia-induced cerebral edema.[9]

A newly developed, selective SPAK inhibitor, ZT-1a (5-chloro-N-(5-chloro-4-((4-chlorophenyl)(cyano)methyl)-2-methylphenyl)-2-hydroxybenzamide), is a modulator of both NKCC1 and KCC, inhibiting and activating these cotransporters, respectively.[9] SPAK inhibition with ZT-1a stimulates K^+-dependent Cl^- export, and improves regulation of cellular volume after insult. In animal models, ZT-a1 reduces ischemia-induced CCC phosphorylation, and results in reduced infarct volume, decreased cerebral edema, and

improved functional outcomes.[9] Although further research and clinical trials are needed to better understand the therapeutic benefit and potential side effects, given the target specificity and promising *in vivo* results, ZT-1a has significant therapeutic potential for treatment of cerebral edema.

4.2 SUR1-TRPM4 Inhibition

The sulfonylurea receptor 1 (Sur1) is an ion channel important in cerebral ion homeostasis that is upregulated in neurons, astrocytes, microglia, oligodendrocytes, and microvascular endothelial cells under ischemic conditions in both humans[10,11] and animal models.[4,12–14] Sur1 associates with transient receptor potential melastatin 4 (Trpm4), which is concurrently upregulated with Sur1 after cerebral ischemia,[15] to create SUR1-TRPM4, a non-selective cation channel.[4] SUR1-TRPM4 can complex with AQP4, increasing influx of cations and water into cells, particularly astrocytes. In addition, SUR1 expression contributes to vascular damage that may play a role in vasogenic edema.[4] Glyburide, a second-generation sulfonylurea developed for type 2 diabetes mellitus, targets the SUR1-TRPM4 channel and inhibits its upregulation after central nervous system (CNS) injury. *In vivo* studies show that glyburide-mediated inhibition of SUR1/TRPM4 after ischemic injury reduces brain swelling and death.[12]

Glyburide, which is used clinically to lower blood glucose levels in diabetic patients, does not penetrate the intact blood-brain barrier. However, after ischemic, which results in BBB breakdown, significant levels of the drug accumulate in the injured brain tissue. Therefore, low doses of glyburide appear to allow therapeutic effects on ischemia-related edema. Although glyburide's system mechanism of action does present dose-limiting side effect of hypoglycemia, treatment with low doses appear to have therapeutic effects on the post-ischemic brain with minimal effect on blood glucose.[4] With the conclusion of phase 2 clinical trials, evidence supports administration of intravenous glyburide; the greatest benefit was observed in stroke patients with large hemispheric infarcts, where glyburide treatment resulted in reduced parenchymal swelling, improved functional outcomes, and reduced mortality (ClinicalTrials.gov Identifiers: NCT01268683; NCT01794182). A phase 3 clinical trial is currently underway (ClinicalTrials.gov Identifiers: NCT02864953).

4.3 Vascular Endothelial Growth Factor (VEGF) Inhibition

Intracranial malignancies, both primary and metastatic, cause significant peri-lesional edema. The chronic progression of tumor-associated edema can be difficult to manage and often causes significant morbidity and mortality. Vascular endothelial growth factor (VEGF), a glycoprotein upregulated in intracranial malignancies, contributes to tumor angiogenesis and formation of inter-endothelial gaps, fragmentations, and fenestrations in the brain endothelium; thus, overexpression and aberrant activity of VEGF may result in compromised BBB function.[16,17] Bevacizumab, a monoclonal immunoglobulin G humanized antibody against VEGF-A, and cediranib, a VEGFR tyrosine kinase antagonist, have emerged as promising anti-angiogenic and anti-edema therapies.[18,19] Although VEGF inhibition by these drugs does not improve overall patient survival, animal studies and clinical trials demonstrate normalization of tumor vasculature, reduction in the severity of

peritumoral edema, and improvement of progression-free survival in both animal studies and clinical trials (ClinicalTrials.gov NCT00943826; NCT00305656).[20–22]

VEGF inhibition has been investigated in stroke-induced cerebral edema as well, however, findings remain contradictory and time-dependent, including a possible protective effect of VEGF in the early post-stroke brain. Ongoing investigation may further clarify the role of VEGF and the consequences of its inhibition in a stroke setting, which may allow introduction of clinical trials in the future that are likely focused on delayed VEGF inhibiton.[23,24] However, researchers and physicians advocating for the use of antiangiogenic agents such as bevacizumab and cediranib in tumor or stoke pathology should be aware that they are not without risks and adverse events. Their use has been found to cause increased risk of thromboembolic complications, hypertension, hemorrhage, gastrointestinal perforation, rebound edema, and surgical wound dehiscence. Additionally, given an increased bleeding risk, once treatment is started, surgery is contraindicated for at least 28 days after last dose, preventing any further potentially necessary surgical intervention.[19,25]

4.4 Arginine Vasopressin (AVP) Receptor Inhibition

Arginine vasopressin (AVP), also known as antidiuretic hormone (ADH), a peptide produced in the posterior pituitary, has been implicated in intracerebral volume regulation. AVP exerts homeostatic effects via signaling through G protein-coupled receptors expressed on vasculature (V_{1A}), the anterior pituitary gland (V_{1B}/V_3), and in renal collecting duct principal cells (V_2), conferring integrated control of body fluid volume. Physiologically present in non-pathological CSF, AVP demonstrates an ability to increase brain water content,[1] and plasma concentrations can be significantly increased in stroke patients.[26] Indeed, the hyponatremia characteristic of the syndrome of inappropriate antidiuretic hormone secretion (SIADH) is present in a significant proportion of TBI and SAH patients, indirectly exacerbating brain edema.[27]

Vaptans, small-molecule vasopressin receptor inhibitors, can modestly ameliorate cerebral edema. Administration of the AVP A_{1A}/A_2 receptor inhibitor, conivaptan, demonstrated reduction of brain edema in a rodent model,[28] and is now being investigated in an ongoing phase 1 clinical trial (ClinicalTrials.gov Identifier: NCT03000283). However, while conivaptan effects on renal water excretion have been well characterized, the drug's mechanism of action in the brain remains poorly understood, warranting further molecular and clinical research. Furthermore, the side effect profile of conivaptan includes hypernatremia, dehydration, and infusion site reaction. Conivaptan may also precipitate renal failure and ischemic organ damage; thus, given the aforementioned considerations, it is classified as a category C drug in pregnancy, and it is contraindicated in lactating women. These risks will need to be taken into account if proven effective for cerebral edema in a clinical setting.[29]

4.5 Inflammatory Cascade Inhibition

Proinflammatory cascades induced by CNS injury often contribute to widespread cerebral edema in patients. Cyclooxygenase (COX) enzymes propagate this inflammatory signaling by converting arachidonic acid into proinflammatory prostaglandins.[30] This action plays a

key pathological role in amplifying tissue injury, especially in the setting of intracerebral hemorrhage (ICH). COX2 is upregulated in endothelium and leukocytes in rodent models of ICH, exacerbating progression of neuronal cell death, infarct volume, and brain edema.[1,31] In a retrospective study, ICH patients treated with the non-steroidal COX2 inhibitor, celecoxib, exhibited attenuated hematoma expansion and decreased edema.[32] A 2009 pilot clinical trial of 44 patients demonstrated similar findings, showing reduced hematoma expansion and less peri-hematomal edema in patients treated with celecoxib as compared with standard management (ClinicalTrials.gov Identifier: NCT00526214).[33] Although celecoxib treatment following cerebral hemorrhage failed to show sustained improvements in functional outcomes, COX inhibitors of increased specificity are being developed and investigated.[33]

Sphingosine-1-phosphate (S1P) and its G protein-coupled receptors S1P1–5 propagate inflammatory responses.[34] Expressed by all cell types in the CNS, S1P receptors are upregulated in neuroinflammatory conditions such as stroke.[35] Each receptor type demonstrates a unique function determined by its localization. S1P1, S1P2, and S1P3 are expressed on neuro-endothelial cells, where they regulate vascular and BBB permeability. The prominent role of S1P2 in disrupting intercellular adherens junctions and increasing vascular permeability makes it of particular interest as a potential therapeutic target in brain edema.[36] The S1P receptor modulator Fingolimod, originally approved to treat multiple sclerosis, is being repurposed for treatment of brain edema, with promising preliminary and clinical data. In rodent models of ICH, fingolimod mitigated onset and progression of cerebral edema.[37] Similarly, in a phase 2 clinical trial of patients with either ischemic or hemorrhagic stroke, fingolimod reduced peri-hematomal edema and lesional growth, and improved neurological outcomes (ClinicalTrials.gov Identifier: NCT02002390). However, the mechanism by which fingolimod exerts its effects via the S1Ps remains elusive and requires further research. Furthermore, the side effects associated with fingolimod include bradycardia and slowing of atrioventricular conduction, requiring close observation upon initiation, increase risk of infections due to its immunosuppressive effects, and has been associated with a few cases of progressive multifocal leukoencephalopathy.[38,39] Development of a specific S1P2 inhibitor may allow direct inhibition of vasogenic edema, mitigating the off-target effects responsible for adverse treatment outcomes.

4.6 Corticotrophin-Releasing Factor Therapy

Although corticosteroid therapy has proven effective for management of cerebral edema in some intracranial pathologies, and particularly in peritumor edema, the significant systemic side effect profile has prompted development of “steroid-sparing” therapies.[40] Of these, human corticotrophin-releasing factor (hCRF) has as shown promise clinically. Alternatively named Xerecept, this synthetic, modified hypothalamic peptide demonstrates protective effects on brain endothelium and a lower incidence of the severe side effects associated with corticosteroid treatment when given systemically. For example, administration of Xerecept in an RG2 cell-derived glioma rodent model significantly reduces vasogenic brain edema.[41] In humans, a completed phase I clinical trial demonstrated improved neurological outcomes and reduced peritumoral edema in 10 of 17 primary brain tumor patients treated with Xerecept.[42] A follow up phase 3 clinical trial of 200 brain tumor patients showed that

Xerecept was effective in reducing steroid requirements and steroid-related side effects such as myopathy and Cushing's Syndrome (ClinicalTrials.gov Identifier: NCT00088166).[43]

5. Conclusion

Cerebral edema is a significant contributor to the morbidity and mortality of many central nervous system pathologies, especially with acute injuries and disease. The currently limited options for standard of care management include temporizing intracranial pressures with the administration of hypertonic solutions, corticosteroids, and in the most severe cases, decompressive craniectomy. However, as our understanding of the molecular drivers of cerebral edema improves, several new therapeutic agents are being developed and tested in animal models and clinical trials with promising results. With novel and specific pharmacological targets to effectively treat, and even prevent brain swelling, future patients may be partially or completely spared of the brain damage associated with elevated ICP and cerebral ischemia.

6. Expert Opinion

As an underlying theme in most neurologic and neurosurgical disease, cerebral edema represents a common secondary pathology leading to increased mortality and neurological deficits in patients. Clinical management of edema largely centers on temporizing strategies to minimize consequences of acute fluid accumulation, specifically mass effect and elevated ICPs. Corticosteroids are used for longer term management; however, their side effect profile often limits their utility and chronic administration.

Fortunately, our growing understanding of the molecular and cellular mechanisms underlying the pathophysiology of cerebral edema is fostering development of targeted antiedema agents. The most promising candidates are those targeting specific molecular mechanisms controlling the compensatory post-injury response of ion channels and transporters that lead to pathological alteration of osmotic gradients. Although further clinical studies are needed, repurposing of drugs such as glyburide to inhibit the aberrant upregulation of ion channels such as SUR1-TRPM4, and novel agents, such as ZT-a1, which re-establish physiological regulation of ion channels like NKCC1/KCC, appear to restore ion gradient homeostasis to prevent and even reverse fluid accumulation in the brain parenchyma.

Although cerebral edema across all CNS pathologies has a likely common underlying pathophysiology, it is important to consider the unique characteristics of these lesions. TBI, an acute and global CNS injury, likely involves different molecular drivers than peritumoral edema or peri-lesional edema in hemorrhagic or ischemic stroke territories. Timing of drug administration is also a consideration. Injuries such as TBI and ICH stimulate processes contributing to a pro-edema environment, including upregulation of SUR1-TRPM4 channels and enhancement of peri-lesional SPAK activity. However, in chronic and evolving oncological lesions, upregulation of the VEGF pathway and inflammatory cascades through both aberrant CNS signaling, as well as pathological signaling from the tumor itself, offer alternative pathways for drug targeting. Conversely, however, the role of VEGF in post-

ischemic cerebral edema remains controversial. Some studies suggest a beneficial role of VEGF inhibition post-stroke; however, many also show a beneficial and neuroprotective effect of active VEGF signaling. These apparent inconsistencies in the literature are likely a result of experimental timing and targeting of VEGF in the ischemic brain and will likely become clearer and better defined as pre-clinical and clinical research advances and elucidates further the underlying mechanism of VEGF-mediated response.

As our understanding of the molecular mechanism and pathways underlying the development and propagation of cerebral edema improve, more signaling pathways and channels/transporters will emerge as potential targets. A recently published study showing improvement in spinal cord edema using an antipsychotic drug, trifluoperazine (TFP), identifies targeting of aquaporin water channels as a possible strategy to combat development of CNS edema.[44]

One important challenge that remains is how to determine when a drug target effectively reduces cerebral ischemia in the clinical population. Most studies rely on data such as imaging findings, neurological symptoms, and need for decompressive hemicraniectomy to determine drug effect and reduction in cerebral edema. However, given the complex patient presentation and clinical course that varies based on underlying pathology and progression of disease, defined and consistent endpoints would be valuable in evaluating the drug targets. Once such scoring system has been recently proposed as a standardized mechanism for determining the effect of corticosteroid use in peritumoral edema (The Response Assessment in Neuro-Oncology (RANO) proposal).[45] A consistent and broadly used criteria that takes into consideration findings from previously successful clinical trials would allow more thorough evaluation of current and future drug targets and their ability to improve the neurological outcomes in this patient population.

In vivo and clinical trials are gaining momentum. Repurposing current drugs will be beneficial in shortening the translational timeline between *in vivo* preclinical research and eventual clinical application. Agents such as COX2 inhibitors and the VEGF inhibitor bevacizumab offer important avenues for expansion of the range of anti-edema agents available for the clinic. Although hurdles remain to be overcome in developing effective and novel therapeutics for cerebral edema, promising targets are being identified, driving new pharmaceutical development. As we identify the molecular drivers of cerebral edema and leverage these discoveries to create novel treatment strategies, clinical management of cerebral edema will become more targeted and effective.

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Declaration of interest

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Article Highlights

- Cerebral edema is the pathological accumulation of fluid in the brain and a potentially life-threatening complication of many central nervous system insults, including traumatic brain injury, stroke, infection, tumor, and inflammatory disease.
- Due to the constraints of a rigid skull, cerebral edema often leads to increased intracranial pressure (ICP) and compromised cerebral blood flow, resulting in cell death and neurological dysfunction. Current strategies to reduce cerebral edema and ICPs have been used for over a century and rely on osmotic agents and surgery.
- Historically, cerebral edema has been classified as either cytotoxic, vasogenic, or ionic, depending on location of water accumulation and blood brain barrier integrity. As our understanding of the underlying pathological mechanisms of cerebral edema expands, these classifications are being redefined to reflect the molecular mediators involved and allow development of more specific treatment targets.
- Cerebral edema is dynamic and time dependent, factors that must be considered when developing and administering targeted therapies. Ongoing research is exploring the temporal expression and regulation of proteins and transporters and their role in cerebral protection and development of cerebral edema. This will guide timing and indications for newly developed targeted therapies.
- Development of new drugs, and repurposing of currently used drugs, to target recently discovered pathways, such as cation-chloride cotransporters and *SUR1-TRPM4*, will provide more effective treatment, and potentially prevention, of cerebral edema resulting from multiple intracranial pathologies.
- Given the heterogenous presentation, progression, and etiology of cerebral edema, a standardized mechanism to assessment of efficacy of treatment is needed to guide clinical implementation and further treatment development.

Table 1:

Summary of novel therapeutics with promising preclinical and clinical findings in brain edema

Drug	Target	Experimental Investigation	Preclinical Findings	Clinical Trials	Clinical Trial Patient Population	Clinical Trial Results
ZT-1a	SPAK	Zhang et al. 2020[4]	ZT-1a reduced NKCC1 and KCC2 phosphorylation, mitigating cerebral edema and improving functional outcomes in a rat model of stroke	N/A	N/A	N/A
Glyburide	SUR1-TRPM4	Simard et al. 2006[5]	Glyburide attenuated brain water volume and decreased 7-day mortality from 65% to 24% in a rat model of middle cerebral artery occlusion	NCT01268683; Phase 2a; Completed in 2013	10 patients with a 82–210 mL acute MCA or MCA/ACA ischemic stroke	Improved clinical outcomes and attenuated vasogenic edema
				NCT01794182; Phase 2; Completed in 2016	83 patients with a 82–300 mL acute MCA ischemic stroke	Attenuated NIH stroke scale scores and reduced 30-day mortality rates, however, the primary and secondary outcome goals were not met
				NCT02864953; Phase 3; Ongoing	Aims to recruit 680 patients with 80–300 mL acute MCA ischemic stroke	N/A
Bevacizumab	VEGF-A	Folkins et al. 2007[8]	Bevacizumab reduced BBB permeability and normalized tumoral and peritumoral vasculature	No identifier; Phase 2; Completed in 2007	32 patients with progressive or recurrent grade III/IV gliomas who were treated with radiation and not surgical intervention	Reduced tumor size and edema resulting in improved neurological outcomes
				NCT00943826; Phase 3; Completed in 2015	921 patients with stable or decreasing glucocorticoid use and a newly diagnosed, untreated glioblastoma	Improved length of progression-free survival and maintenance of baseline performance, but failed to improve overall survival
Cerdiranib	VEGFR	Kamoun et al. 2009[16]	Cerdiranib reduced tumor vasculature permeability and size, as well as expansion of edema	NCT00305656; Phase 2; Completed in 2012	31 patients with a confirmed diagnosis of glioblastoma	More typical vascular development around the tumor and mitigated development of cerebral edema
Celecoxib	COX2	Chu et al. 2004[11]	Celecoxib treatment in rats with induced cerebral hemorrhage reduced edema, inflammation, and cell death, leading to increased functional recovery	NCT00526214; Pilot Trial; Completed in 2009	44 patients with diagnosed intracerebral hemorrhage not caused by trauma, aneurysmal bleeding, or anticoagulation	Mitigated hematoma and perihematomal edema progression and expansion
Fingolimod	S1P Receptors	Wei et al. 2011[13]	Fingolimod reduced infarct volume, neuronal cell death, edema, and neurological dysfunction in a mouse model of middle	NCT02002390; Phase 2; Completed in 2014	22 patients with ischemic stroke or intracerebral hemorrhage not caused by coagulopathy, trauma, or thrombocytopenia	Reduced edema and improved neurological outcomes in hemorrhage patients and reduced lesional

Drug	Target	Experimental Investigation	Preclinical Findings	Clinical Trials	Clinical Trial Patient Population	Clinical Trial Results
			cerebral artery occlusion			expansion and improved neurological functioning in stroke patients
Conivaptan	AVP A_{1A}/A_2	Can et al. 2019[17]	Conivaptan was shown to be a more potent diuretic than mannitol in a rat model of ischemic brain injury	NCT03000283; Pilot Trial; Ongoing	Goal of 7 patients with an intracerebral hemorrhage of >20 mL not due to thrombolysis, infection, trauma, or tumor	N/A
Xerecept	Unknown	Tjuvajev et al. 1996[14]	Xerecept directly acted on tumor microvasculature, reducing permeability and vasogenic edema in rats with RG2 cell-derived gliomas	No identifier; Phase 1; Completed in 1998	17 patients with primary brain tumors and radiographic evidence of edema	10 of 17 patients in the clinical trial had improved neurological outcomes
				NCT00088166; Phase 3; Completed in 2008	200 patients with a brain tumor and complications from prior steroid use	Reduced steroid requirements and steroid-associated side effects such as Cushing's Syndrome and myopathy