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Review article

The potential of drug repurposing combined with reperfusion therapy in cerebral ischemic stroke: A supplementary strategy to endovascular thrombectomy

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ABSTRACT

Stroke is the major cause of adult disability and the second or third leading cause of death in developed countries. The treatment options for stroke (thrombolysis or thrombectomy) are restricted to a small subset of patients with acute ischemic stroke because of the limited time for an efficacious response and the strict criteria applied to minimize the risk of cerebral hemorrhage. Attempts to develop new treatments, such as neuroprotectants, for acute ischemic stroke have been costly and time-consuming and to date have yielded disappointing results. The repurposing approved drugs known to be relatively safe, such as statins and minocycline, may provide a less costly and more rapid alternative to new drug discovery in this clinical condition. Because adequate perfusion is thought to be vital for a neuroprotectant to be effective, endovascular thrombectomy (EVT) with advanced imaging modalities offers the possibility of documenting reperfusion in occluded large cerebral vessels. An examination of established medications that possess neuroprotective characters using in a large-vessel occlusive disorder with EVT may speed the identification of new and more broadly efficacious medications for the treatment of ischemic stroke. These approaches are highlighted in this review along with a critical assessment of drug repurposing combined with reperfusion therapy as a supplementary means for halting or mitigating stroke-induced brain damage.

1. Introduction

Stroke is the leading cause of physical disability and intellectual impairment in adults and a leading cause of death in most developed countries. It is estimated that over 80% of strokes result from thrombotic or embolic events causing ischemic brain damage [70,144]. The treatment of choice for acute ischemic stroke is with rapid intravenous administration of recombinant tissue-type plasminogen activator (tPA) to eligible patients [81]; National Institute of Neurological and [119]. However, at most, only 8% of stroke victims are eligible for tPA because effective treatment must commence within 3 or 4.5 h of stroke onset [133]. Recently, endovascular thrombectomy (EVT) has become a treatment of choice for patients with acute stroke due to large-vessel occlusion [130]. Initially, to be performed within 6 h after stroke onset [16,22,63,85,139], now EVT may be of benefit when initiated as long as 16–24 h after a stroke, mainly to those who have large vessel occlusion in the anterior circulation with documented imaging mismatch [3,122,131].

It was acknowledged that full or partial reopening the occluded vessels up to 24 h after stroke onset is coupled with a better outcome than persistent occlusion after reperfusion therapy [88,167,172]. Approximately, 10% of patients with acute ischemic stroke are eligible for EVT within 6 h [23,39,42] and about 9% of patients in the 6 to 24 h time window may be eligible for EVT [80]. As patients with large vessels occlusion result in more disabled condition after stroke, to delineate the underlying molecular mechanisms and find a way to further lessen the neurological deficit and long-term disability maybe critical even with more advanced therapeutic option such as EVT.

Drug repurposing is gaining popularity as a new approach to drug discovery [11,83]. Various techniques for identifying new uses for existing medications are being employed in an attempt to reduce the time and cost of drug development [105]. Examples of repurposed drugs include aspirin [53,75,110], sildenafil (Viagra®, Pfizer) [18,59,103], and thalidomide [11,148,149,175]. This report focuses on the potential

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Abbreviation

AD	Alzheimer's disease
Aβ	beta-amyloid
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
β2AR	β2-adrenoreceptor
BBB	blood-brain barrier
DALYs	disability-adjusted life years
DM	diabetes mellitus
DMF	dimethyl fumarate
EVT	endovascular thrombectomy
IκB	inhibitor of NF-κB
IL-1β	interleukin-1β
IL-6	interleukin-6
iNOS	inducible nitric oxide synthases
NF-κB	nuclear factor-kappa B
NO	nitric oxide
NOSs	nitric oxide synthases
Nrf2	nuclear factor erythroid-2-related factor
MMP9	matrix metalloproteinase 9
MS	multiple sclerosis
NMDA	N-methyl-D-aspartate
PD	Parkinson's disease
PPARγ	Peroxisome proliferator-activated receptor gamma
ROS	reactive oxygen species
TNF- α:	tumor necrosis factor-α
tPA	recombinant tissue-type plasminogen activator

of drug repurposing after EVT. Topics covered include a brief review of the basic mechanisms of the tissue damage following a stroke, the identification potential targets for therapeutic intervention, and examples of approved drugs that could be candidates for repurposing for the management of stroke after EVT.

2. The cerebral-ischemic cascade and potential targets for therapeutic intervention

The pathophysiologic alterations in signaling pathways following cerebral ischemia are well characterized in various stroke models [24,33,67,100,117]. The resulting symptoms from ischemic stroke depend on the brain region affected. These include focal motor weakness, sensory impairment, speech difficultly, and mental dysfunction. The ischemic event reduces the levels of glucose, oxygen, and various nutrients in the affected brain tissue, leading to dysfunction in cellular homeostasis and ultimately neuronal cell death. Many of the cellular and molecular events leading to ischemia-induced neuronal death have been identified and characterized and could be targets for drug development (Fig. 1).

While the average adult human brain represents about 2% of the body weight, it consumes 20% of the body's oxygen and calories [132]. Following a stroke, the occluded vessels reduce blood flow to the affected area, impede the transfer of substrates, impair the production of energy, and disrupt ion homeostasis [109]. Uncontrolled, anoxic neuronal depolarization occurs during brain ischemia [170]. The main features of anoxic depolarization are increased intracellular concentrations of Na^+ and Ca^{2+}, of extracellular K^+ and aspartate. Within minutes of an ischemia insult, there is an increase in the extracellular levels of excitatory neurotransmitters, particularly glutamate which binds a family of receptors, including the ionotropic N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) sites, thereby promoting an abnormally high influx of neuronal calcium. This calcium overload causes activation of various proteases and phospholipases, leading to the destruction of proteins and other essential membrane components [13,121].

Excessive production of reactive oxygen species (ROS) can cause extensive damage to the cell membrane, DNA structure, and proteins, and result in cell death. Brain ischemia and reperfusion may cause excessive production of ROS. Enzymatic antioxidants including catalase, glutathione peroxidase, superoxide dismutase, and peroxiredoxins can protect cells from excessive generation of ROS [90]. Brain ischemia also elicits the activation of different isoforms of nitric oxide synthases (NOSs) and cause excessive NO formation which may be toxic to cells. The toxic effects of NO might be ascribed to its affinity for thiol and iron groups [74,101]. Moreover, NO may react with ROS to form peroxynitrite anions, thereby contribute to the formation of the hydroxyl radical and superoxide anion, both of which are toxic to cells [92]. The pathological mechanisms of oxygen free radicals and oxidative stress in ischemic brain injury have been extensively reviewed before [30,174].

Stroke-induced ROS and NOS may directly or indirectly trigger innate immune-induced inflammation. Brain ischemia and reperfusion is known to activate the complement system and form complexes such as C5b-9. Circulating dendritic cells, lymphocytes, monocytes, monocyte-derived macrophages, and natural killer cells modulate inflammatory responses and thereby facilitate the thrombo-inflammatory response. This differentiates cerebral microvasculature dysfunction from interactions among leucocytes, the ischemic brain endothelium, and platelets [27]. The transcription factor nuclear factor-kappa B (NF-κB) is a crucial regulator of various genes involved in cell survival and inflammation. The NF-κB gene products, such as inducible NOS (iNOS), interleukin (IL)-1b, IL-6, matrix metalloproteinase 9 (MMP9), and tumor necrosis factor-α (TNF-α), influence the post-ischemic inflammatory reaction, the integrity of the blood-brain barrier (BBB), and

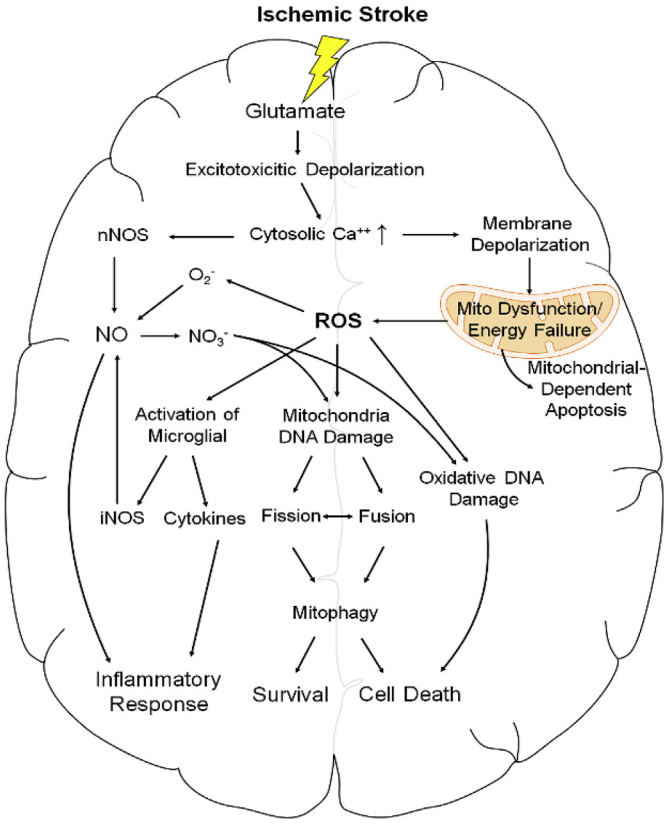

Fig. 1. Schematic illustration of brain cell death mechanisms triggered by ischemic stroke. Evidence is strong that oxidative stress (ROS) is a key component of these processes.

neuronal damage [134]. The immune-mediated inflammatory response that occurs following acute ischemic stroke is a major target for therapeutic intervention [28]. Mechanistic approaches used in these studies included activating retinoid X receptors, promoting macrophage (microglia) M2 transition, *activating Nrf2*, inhibiting MMP-2 or MMP-9, activating PPARγ, inhibiting calcium-activated potassium channels (K_{Ca} 3.1), and inhibiting calcineurin [25].

Cell death associated with brain ischemic may involve a transition between a detrimental pathway and a protective pathway over the course of hours or even days. Many features, including age- and gene-specific factors, ischemia duration and severity, energy failure, and metabolic disturbances all contribute to the type of cell death, such as apoptosis or necrosis, observed after an ischemic insult [107,179]. Following an ischemic event, the affected tissue is characterized by a necrotic core and surrounded by an area referred to as the "ischemic penumbra". The penumbra is a region of viable tissue that while experiencing reduced blood flow and compromised metabolic activity contains cells that can be rescued by immediate post-stroke therapy [61,69]. Because neurons in the ischemic penumbra may not experience apoptotic cell death until several hours or days after a stroke [20,97,164], it could be possible to salvage this tissue and mitigate the functional damage. With recent development of EVT therapy, to better understand the mechanisms of apoptosis may add a supplementary therapy and further lessen the neurological damage for patient with large vessel occlusion.

3. Drug repurposing approaches for the discovery of new therapies in acute ischemic stroke with EVT

Drug repurposing is a discovery approach for identifying new uses for agents approved for other indications [11] (Fig. 2). It is an attractive alternative to traditional drug discovery methodologies given its potential for more rapidly and less expensively developing new therapeutics, especially for conditions where this is a significant unmet need for effective treatments [11,83,116]. For pharmaceutical firms, factors influencing new drug development include increasing costs of development, especially for clinical trials, eventual generic competition, market size, degree of innovation, and regulatory demands. To medical professionals, the limitations of current medications is most troubling for age-related disorders and malignancies [89,98]. The source of agents in a repurposing program includes not only approved drugs, but also compounds found in clinical studies to have acceptable safety profiles but that were never launched because they failed to display sufficient efficacy for the intended indication [89].

Most drug repurposing successes were serendipitous. Several examples are well known such as aspirin [53,75,110], sildenafil (Viagra®, Pfizer) [18,59,103], and thalidomide [11,148,149,175] which are widely used now with new indications that are quite different as originally developed.

Drug repurposing has several advantages over conventional drug discovery, particularly with respect to cost and the time needed for approval and launch [11,83,116]. Drug repurposing also substantially lowers the number of risks associated with traditional drug discovery with respect to pharmacokinetics and safety of the candidate compound [11,124].

Human with chronic medical conditions are often due to combinations of genetic, environmental, and lifestyle factors that negatively influence biochemical pathways essential for normal cellular activity and function. Examples of such chronic conditions are Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), osteoporosis, connective tissue diseases, autoimmune diseases, and stroke [17,72,108]. Recent advances in genomics and proteomics have made it possible to begin defining the molecular modifications responsible for such conditions. When a molecular target is found, drug repurposing may be attempted by screening approved agents regardless of their known mechanism of action against the site on the chance the known compound may display efficacy in the condition under investigation. As indicated above, the new use for most current repurposed drugs was discovered by accident. Bupropion, which was originally marketed as an antidepressant, is now prescribed for smoking cessation [73].

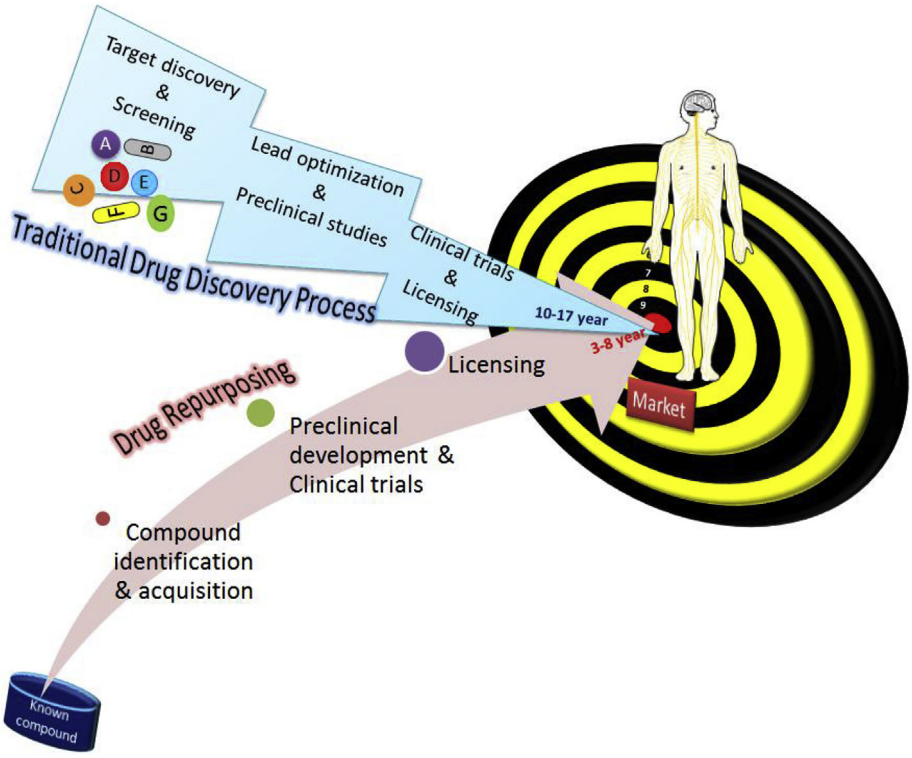

Fig. 2. Comparison between traditional drug discovery and drug repurposing. The traditional process of drug discovery requires 10–17 years of testing for before drug approval, whereas drug repurposing is accomplished, on average, within 3–8 years.

Moreover, side effects observed during clinical trials, such as penile erection with sildenafil and new hair growth with minoxidil, led to unanticipated indications for these agents [19,60,98].

More systematic approaches to drug repurposing include identifying novel actions of existing, approved products that can be exploited for treating other conditions [98]. A recent example involved an unbiased screen targeting endogenous gene expression [112]. The results of Mittal's study indicated that because the β2-adrenoreceptor (β2AR) is a regulator of the α-synuclein gene, β2AR ligands should be modulators of α-synuclein gene transcription. This was then demonstrated in cell culture and then in intact animals, and ultimately in a human study in Norway. The screening of 1126 compounds, including drugs approved by the U.S. Food and Drug Administration, found that salbutamol, a β2AR agonist approved for the treatment of asthma, is associated with a reduced risk of developing PD, and propranolol, a β2AR antagonist, with an increased risk for PD [112]. This report is a good demonstration of a drug repurposing discovery that may lead to changes in the management of PD [153].

Although drug-repurposing programs can involve high-throughput chemical screening to discover new drug-target interactions, the cost and technical demands of such an approach often preclude its general application. *In silico* methods represent another approach, utilizing modern, high-performance computing for virtual screening [78]. Various types of large data sets (e.g. chemical structural, clinical, genomic, and phenotypic data) are freely available for computational drug repurposing research. Integrative approaches for heterogeneous data facilitate the discovery of new indications for old drugs. Computational drug repurposing shows promise in accelerating drug discovery for various diseases [96].

Because of lack of effective treatments for neurodegenerative diseases such as AD, PD, Huntington disease (HD), and MS [45], drug repurposing strategies are being used to identify new therapeutics as an alternative to conventional drug development programs. For example, dimethyl fumarate (DMF), a drug approved for the treatment of MS was repurposed for use against PD-associated synucleinopathy, and riluzole, a medication for motor neuron disease, was repurposed to treat cerebellar ataxia [137]. Moreover, bioinformatics has been used in drug repurposing for the treatment of AD [146]. Candesartan, an approved antihypertensive agent, was found to inhibit toll-like receptor 2 (TLR2) expression and thereby reduce the inflammatory activation of primary microglia resulting from exposure to oligomeric α-synuclein. These findings suggest candesartan might be repurposed as a therapy for synucleinopathies [46].

A mechanism-based, drug-target interaction modeling approach was used to predict repositioning candidates for AD and amyotrophic lateral sclerosis [52]. This suggests that a standardized and systematic approach to candidate identification for drug repurposing trials has broad application for identifying candidates for the management of neurodegenerative disorders [165].

Combinations of various repurposed drugs, even agents with unrelated characteristics, could represent a new strategy for developing innovative treatments. For example, the combination of acamprosate, a treatment for alcohol dependence, and baclofen, a sedating muscle relaxant, yielded a potential approach for reducing the beta-amyloid (Aβ) oligomers associated with AD [41]. Also, miconazole, an antifungal, and clobetasol, a synthetic glucocorticoid, were found to promote precocious myelination when used in combination, suggesting this therapy might enhance remyelination in MS patients [118]. Inasmuch as ischemic stroke and neurodegenerative diseases share similar pathophysiological mechanisms, including oxidative stress, inflammation, and compromised neurovascularization [106,129], it has been suggested that the results of drug repurposing studies for neurodegenerative diseases could be applied to the treatment of brain ischemic as well.

It is reported that acute ischemic stroke accounts for 87% of all strokes [171]. Based on the TOAST classification, stroke results from vascular occlusion in atherosclerotic large artery disease, small artery disease, and cardioembolic events [1]. It was estimated that in 2013 there were 6.5 million stroke-related deaths and 10.3 million new strokes globally, with an overall cost of 113 million disability-adjusted life years (DALYs) [56]. These numbers are expected to increase because of socioeconomic factors and the aging population. If current trends continue, stroke will result in the loss of 200 million DALYs by 2030 [55], increasing dramatically the human and financial toll of this condition.

There has been significant progress in the treatment and prevention of acute stroke. Stroke occurrence and recurrence are reduced by the use of antiplatelet drugs such as aspirin or clopidogrel and by controlling modifiable risk factors such as hypertension, diabetes mellitus (DM), and dyslipidemia, and by treating patients in dedicated stroke units [81]. Recently, recanalization of the occluded artery through thrombolysis and/or EVT has gained popularity [130]. In contrast to treatment of intravenous tPA, the EVT procedure starts with the groin puncture and uses a device through the femoral artery to reach a documented occluded brain vessel such as in internal cerebral or middle cerebral artery and remove the blood clot [62,154]. Patients receiving EVT are those stroke groups with higher morbidity and mortality because of the involvement in main trunk of the intracranial vessels. These result in large area infarction and severe neurological deficits. It is estimated that EVT is indicated for approximately 7% to 10% of patients with ischemic stroke and approximately one-third of those who undergo thrombolysis [21]. However, this percentage is expected to increase based on the recent studies indicating that EVT may be effective up to 24 h after the initiation of an ischemic stroke [3,122,131].

Neuroprotection is sought by developing pharmacological agents that will lessen neurological deficits following acute or chronic neurological insults by slowing or preventing cell damage or death. Based on what is known about the ischemic cascade, there are a number of potential therapeutic targets for neuroprotective agents in acute ischemic stroke [30,33,35,86]. The most obvious are those related to oxidative stress, inflammation, and apoptosis. Although there are preclinical data demonstrating the efficacy of such agents in animal models of stroke [57,123], the clinical results were uniformly negative [65,115]. Because of the lack of success, The 2013 American Heart Association Stroke Guidelines list no Level 1 recommendations for neuroprotective agents in acute ischemic stroke [81]. Several reasons are given for these failures, such as differences in the populations between the experimental and clinical studies, including age and sex, the heterogeneity of stroke types in humans, the variable duration of ischemia, the limited time during which ischemia can be effectively treated, differences in drug efficacy in the target area, and different methods for measuring clinical outcomes [111,158].

Given these failures, it was suggested that neuroprotection alone without restitution of tissue perfusion or preservation of vascular integrity is insufficient for treating acute stroke [178]. The emerging concept of the neurovascular unit posits that cell-cell signaling events relevant for glial, neuronal, and vascular responses occur after an acute brain insult, with targeting of these multicellular connections being the best approach for developing therapeutics that will reduced acute brain injury and promote repair [48,104]. In terms of vascular protection, promising stroke targets include inhibition of endogenous mediators of vascular damage such as superoxide, endothelin, matrix metalloproteases, cytokines, and caspases, and the stimulation of endogenous protectors such as nitric oxide, angiopoietin-1, vascular endothelial growth factor, and superoxide dismutases. Some commonly off-label-used drugs, such as atorvastatin (angiotensin II receptor blockers), erythropoietin (glycoprotein cytokine), melatonin (neuronal hormone), and minocycline (tetracycline antibiotic) provide vascular protection [53]. The underlying pathophysiology of cerebral ischemia involves in various signaling pathway among different time frame and brain regions could be more emphasized as therapeutic targets, moreover, the medication with pleiotropic activities should be put on focus as a

Table 1
List of some clinical studies involving neuroprotectants with tPA or tPA/thrombectomy that were registered in clinical trials https://clinicaltrials.gov).

Title	Clinical Trial Gov Identifier	Status	Intervention	Study Result
Ginkgolide With Intravenous Alteplase Thrombolysis in Acute Ischemic Stroke Neurological Improving Trial	NCT03772847	Recruiting	Ginkgolide with iv tPA	No Result Available
Efficacy and Safety of Butylphthalide for Acute Ischemic Stroke Patients Receiving Intravenous Thrombolysis or Endovascular Treatment	NCT03539445	Recruiting	Butylphthalide with iv tPA and/or endovascular thrombectomy	No Results Available
Butyphthalide in Combination with Recombinant Tissue Plasminogen Activator for Acute Ischemic Stroke	NCT03394950	Recruiting	Butylphthalide with iv tPA and/or endovascular thrombectomy	No Results Available
Safety and Efficacy of Glibenclamide Combined with Rt-PA in Acute Cerebral Embolism	NCT03284463	Recruiting	Glibenclamide with iv tPA	No Results Available
Combinating Fingolimod with Alteplase Bridging with Mechanical Thrombectomy in Acute Ischemic Stroke	NCT02956200	Unknown [a]	Fingolimod with iv tPA with endovascular thrombectomy	No Results Available
Safety and Efficacy of Two Doses of SP-8203 in Patients with Ischemic Stroke Requiring rtPA	NCT02787278	Unknown [a]	SP-8203 with iv tPA and/or endovascular thrombectomy	No Results Available
Ketamine for Thrombolysis in Acute Ischemic Stroke	NCT02258204	Unknown [a]	Ketamine with iv tPA	No Results Available
THR-18's Pharmacokinetics and Pharmacodynamics in Subjects with Acute Ischemic Stroke Treated with tPA	NCT01957774	Completed	THR-18 with iv tPA	No Results Available
Stroke Treatment with Acute Reperfusion and Simvastatin	NCT01073007	Completed	Simvastatin with iv tPA	Published [114]:
Efficacy Study of Combined Treatment With Uric Acid and rtPA in Acute Ischemic Stroke	NCT00860366	Completed	Uric Acid with iv tPA	Published [8,26]:
Combined Treatment with Alteplase (Rt-PA) and Cerebrolysin® in Acute Ischemic Hemispheric Stroke	NCT00840671	Completed	Cerebrolysin with iv tPA	Published [94]:
Thrombolysis and Deferoxamine in Middle Cerebral Artery occlusion	NCT00777140	Completed	Deferoxamine with iv tPA	No Results Available
Study of a Neuroprotective Drug to Limit the Extent of Damage From an Ischemic Stroke	NCT00630396	Completed	Minocycline with iv tPA	Published [54]:
Multicenter Efficacy Study of Recombinant Human Erythropoietin in Acute Ischemic Stroke	NCT00604630	Completed	Erythropoietin with iv tPA	Published [51]:
A Study to Evaluate the Effects of YM872 on Brain Function and Disability When Administered in Combination With Alteplase (Tissue Plasminogen Activator)	NCT00044057	Completed	YM872 (zonampanel) with iv tPA	No Results Available
Super-Selective Intra-Arterial Administration of Verapamil for neuroprotection After Intra-Arterial Thrombolysis for Acute Ischemic Stroke Phase I Study	NCT02235558	Completed: phase 1	Verapamil with ia tPA or endovascular thrombectomy	Published [58]:
Safety and Efficacy of NA-1 in Subjects Undergoing Endovascular Thrombectomy for Stroke (ESCAPE-NA1) (ESCAPE-NA1)	NCT02930018	Recruiting	NA-1 with endovascular thrombectomy	No Results Available

iv: intravenous ia: intra-arterial.

[a] Study has passed its completion date and status has not been verified in more than two years.

repurposed drugs adding to reperfusion therapy. With the advent of EVT and the ability to validate reperfusion therapy through advanced imaging modalities, it is time to reinvestigate vascular- or neuroprotectants as adjunct therapies with reperfusion [120]. In a recent update of management guidelines for acute ischemic stroke, EVT is said to represent a true reperfusion therapy with documentation in neuroimaging studies [16,22,63,85,139].

Although the results for patients with large vessel occlusion receiving EVT are better than conventional treatment including intravenous tPA [16,22,63,85,139], physical disability is still a major problem. Results of a meta-analysis of EVT after large vessel ischemic stroke, though EVT can significantly reduce disability at 90 days compared with control, revealed only 46% of them were functionally independent [64]. In a recent review article concerning combining neuroprotection with EVT of acute stroke, it appeared that there still has much room for improvement even with EVT [163]. To maximize the treatment effect of neuroprotection is thus critical in this clinical setting. Several rules are crucial to conduct a clinical trial effectively, such as successful intervention in animal studies, minimizing heterogeneity of enrolling subjects, enrolling subjects within optimal therapeutic window and maximizing the treatment effect size to detect the therapeutic benefit [163]. Patients with EVT are subjects with large vessel occlusion on neuroimaging documentation and treated within optimal therapeutic time window [16,22,63,85,139]. The treatment effect size could be maximized due to poor prognosis in patients with large vessel occlusion even with EVT [64]. The combining drug should be given soon after the subject with EVT and the device and reperfusion rate should achieve a standard level if conduct a clinical trial of EVT with neuroprotectant. Searching from *Clinicaltrials.gov* with term of tPA with neuroprotectant, or EVT with neuroprotectant yields some results which were shown in Table 1. Only limited EVT study ongoing were noted. The Trial numbers put in Table 1 are for readers to track further results if it is interested to them.

Although results from previous clinical trials with neuroprotectants were disappointing [123], there is reason to believe that combination therapy involving EVT and neuroprotectants could be of benefit for these patients [27]. The potential benefit of drug repurposing with tPA or EVT is shown in Fig. 3. In contrast with tPA, EVT representes a real reperfusion therapy because it is obligatory to show large vessel occlusion before treatment and reopening of the occluded vessel after treatment with neuroimaging documentation. It was proposed before for the possibility of combination therapy of neuroprotectants plus thrombolytics for ischemic stroke which can either enhance thrombolytic efficacy or extend therapeutic window of tPA [33,127]. Several clinical trials have been conducted before with various results (see Table 1). The co-administration after EVT of medications with anti-oxidative stress, anti-inflammatory, and anti-apoptosis characteristics may be warranted because reperfusion therapy can enhance drug delivery effect and further decrease unwanted reperfusion injury such as excessive ROS and inflammatory responses [77,138].

From the standpoint of drug repurposing, current approved medications such as statins, ARBs, minocycline, and erythropoietin are

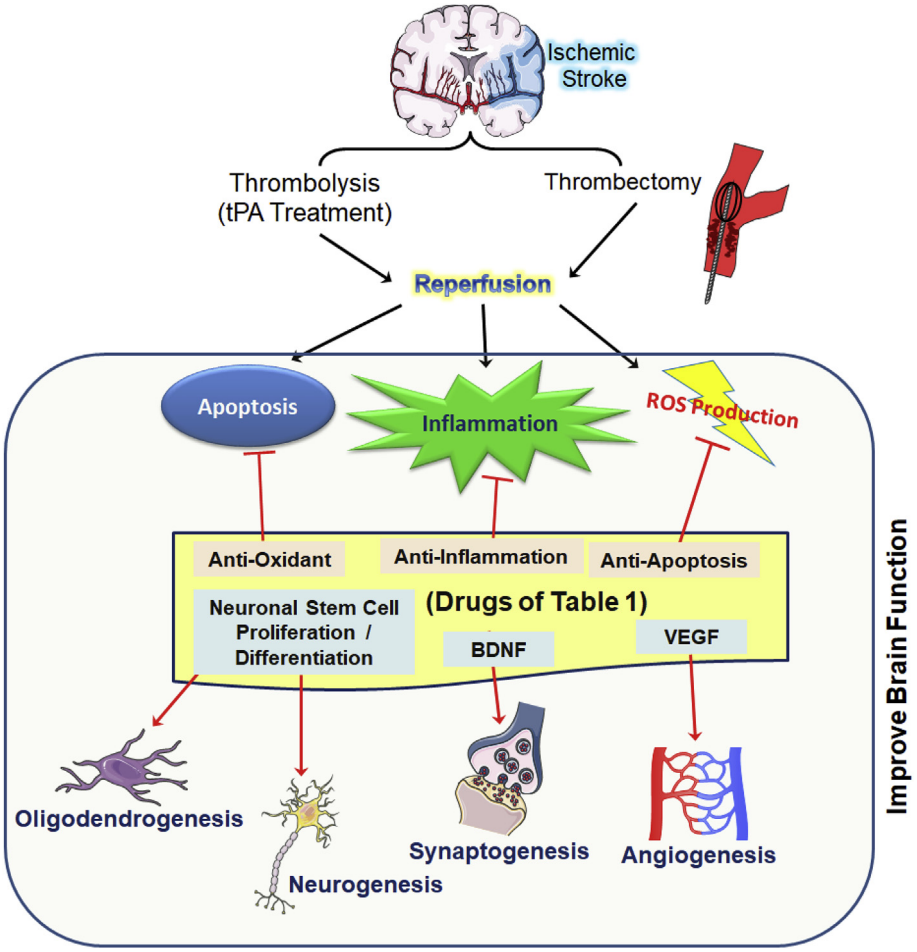

Fig. 3. The schematic cartoon illustrates that the proposed repurposing drugs of "Table 1" ameliorate the reperfusion-accompanied pathological symptoms and enhance neuronal survival. Post-procedure of thrombolysis thrombectomy, the restoration of oxygen and nutrient supply commonly induce oxidative stress, inflammation, and apoptosis. The clinic-used drugs of Table 1 are potentially able to cope with the reperfusion injury, moreover, enhance neurogenesis, synaptogenesis, oligodendrogenesis, and angiogenesis.

among those that may have value in the treatment of acute ischemic stroke based on their demonstrated neuroprotective or vascular-protective effects [53,66]. Candesartan, an angiotensin II receptor antagonist, has been shown the vascular protective effect in patients with acute ischemic stroke [53]. Innate immune cells may play a dual role in the progress of ischemic brain damage, one way to promote injury, and the other way to activate M2 microglia/macrophages and provide tissue repair and remodeling ability [4]. Several examples showed the promise in repurposing drugs with immunomodulatory properties for stroke therapy such as minocycline or azithromycin [6,66,176]. There is also a paper reviewed the topic about small vessels disease and drug repurposing which is quite different from large vessel occlusive disease and irrelevant to EVT but has significant clinical importance for lacunar infarct and vascular dementia [14]. Currently, EVT offers an unprecedented opportunity for vascular or neuroprotectant trial design, though, only limited trials are ongoing. It is critical to search ideal adjunctive therapy and augment the treatment both for EVT and various drug effects to preserve neurovascular functions and at the end to lessen the physical or intellectual disability. Drug repurposing approach may speed this process and we believe more targets will be dug out with the potential need and with the promotion of some program such as Drug Repurposing Hub (www.broadinstitute.org/repurposing) [43], or from NIH (https://ncats.nih.gov/preclinical/repurpose) [71]. Through drug repurposing approach, choosing patients with EVT would greatly reduce the time and cost for a drug trial to conduct. A list of some approved medications with the potential for repurposing as treatment for acute ischemic stroke is provided in Table 2. This list demonstrates that there are common medications that have a potential for repurposing as therapies for acute stroke. Most of these drugs were shown to display anti-oxidant, anti-inflammatory, and anti-apoptosis characteristics either in pre-clinical or clinical studies (Table 2). Mechanisms involving vascular protection/angiogenesis, gliogenesis, and neurogenesis are also included to highlight the emerging importance the neurovascular unit as a targeting strategy in ischemic stroke [31,32,49,68,91,102,136,161,169,177] (also see Table 2). It is believed that with contemporary technological approaches, including computational drug repositioning supplemented with various types of large data sets such as chemical structural, clinical, and genomic information, more indications may be found for current medications. With the development of reperfusion therapy in acute ischemic stroke using EVT, these drugs could be viable candidates for testing the beneficial effect of their co-administration in the treatment of large cerebral ischemic infarcts.

4. Conclusions

Although neuroprotectants have failed repeatedly as treatments for acute ischemic stroke, the establishment of EVT as a standard treatment for main trunk occlusion offer the opportunity to document the success of reperfusion through advanced imaging modalities. Given the urgent need for decreasing the mortality and morbidity associated with stroke and large vessel occlusion, the repurposing of approved medications for this purpose is a means for the rapid and relatively inexpensive achievement of this goal. It is conceivable that neuroprotective and vascular protective agents will reveal their efficacy as stroke therapies when they are combined with modern reperfusion therapy. Through an understanding of the underlying pathogenesis of ischemic stroke and the identification of potential drug targets to minimize neuronal damage, the testing of approved medications with known anti-oxidant, anti-inflammatory, and anti-apoptosis properties could hasten the discovery of effective treatments. The hypothesis that drug repurposing may provide a complementary therapy to EVT in this devastating disorder awaits testing in controlled clinical trials.

Declaration of competing interest

The authors declare no conflict of interest.

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Table 2
List of some potential neuroprotective drugs may be applied for repurposing in acute ischemic stroke with endovascular thrombectomy.

Name of Drug	Mechanism	Reference
Azithromycin	Macrolide antibiotic, immunomodulatory and anti-inflammatory effects, drug-induced polarization of migratory macrophages towards a protective, non-inflammatory M2 phenotype	[5–7,128]
Bexarotene	Retinoid X receptor agonist, immunomodulatory effects,	[25]
Candesartan	angiotensin II type 1 receptor blocker, pleiotropic activities (including anti-oxidation, anti-apoptosis, and proangiogenic growth factors), increasing VEGF, enhancement of early angiogenic remodeling	[15,46,66,91,143,166]
Dimethyl fumarate	Nicotinic acid receptor agonist, Nrf2 activator, increasing autophagy, anti-inflammation	[95]
Eplerenone, Spironolactone	Mineralocorticoid receptor antagonist, suppressing superoxide production, anti-oxidation, angiogenic factors, upregulating bFGF and VEGF, improvement of cerebral blood flow	[79,125]
Erythropoietin	Red blood cell production, anti-apoptosis, neuroprotective, neural stem cell proliferation/differentiation	[50,151,161]
Exenatide	Glucagon-like receptor 1 agonist, anti-ROS, anti-inflammation	[47,173]
Granulocyte colony stimulating factor	Hematopoietic growth factor, neurotrophic factor, neurogenesis, anti-apoptosis, increasing neuroplasticity, arteriogenic factor	[2,113,135,140–142,155]
Metformin	Treatment for type 2 diabetes, anti-inflammatory, induces autophagy by activation of brain AMPK	[9,82,84]
Melatonin	Regulator of sleep and wakefulness, antioxidant, free radical scavenging, neuroprotection, anti-inflammatory	[10,31,126,150]
Minocycline	Broad-spectrum tetracycline antibiotic, anti-inflammatory, antioxidant, anti-apoptotic, inhibitor of microglia, MMP-2 and MMP-9 inhibitor	[29,36,66,83,93,99,160,176]
Rosiglitazone and Pioglitazone	Peroxisome proliferator-activated receptor gamma (PPARγ) agonists, anti-ROS, anti-inflammation, promoting oligodendrogenesis and facilitating microglial polarization	[34,40,44,68]
Senicapoc	Anti-inflammatory, calcium activated potassium channel (K_{Ca} 3.1) inhibitor	[156]
Sildenafil	Phosphodiesterase 5 inhibition, increasing local blood flow, upregulating synaptophysin, PSD-95/nNOS, BDNF/TrkB, and NGF/TrkA	[38,49,147]
Simvastatin, Atorvastatin	Pleiotropic activities, HMG-CoA reductase inhibitors	[12,32,66,87,114,136,152,159,162,177]
Tacrolimus	Macrolide calcineurin inhibitor, anti-inflammatory, anti-apoptosis	[76,145]
Terazosin	Adrenergic receptor antagonist, activates phosphoglycerate kinase 1, anti-apoptosis	[37]
Valproic acid	Inhibitor of MMP-9, degradation of tight junction proteins, and nuclear translocation of NF-κB, histone deacetylase inhibitor, anti-inflammation, anti-oxidation, angiogenesis, neurogenesis	[102,157,168,169]

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