



Enabling the Nervous System to Repair Itself

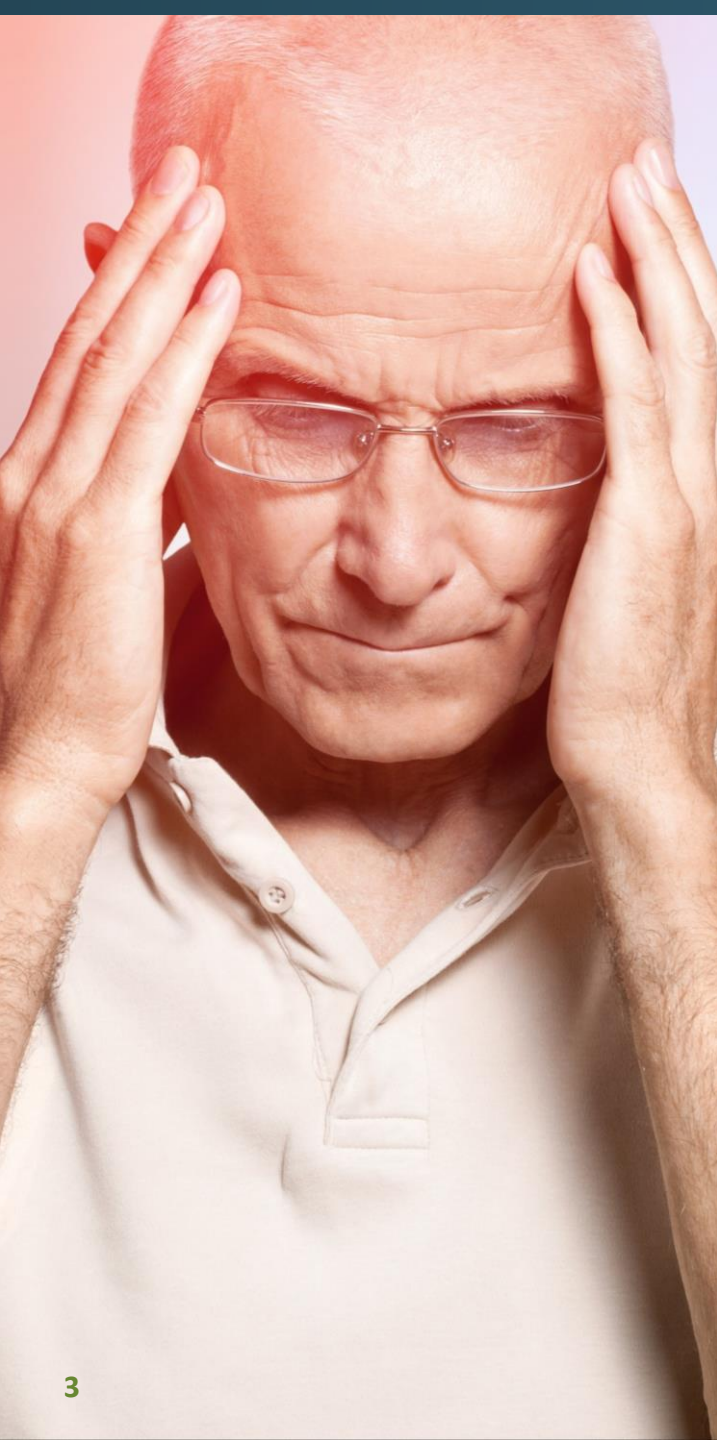
NVG-291 – Stroke Indication

JULY 2022

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Stroke Overview

There is **No FDA-Approved Drug** that Repairs Damage Caused by Stroke

- Stroke is a disease that affects the blood vessels leading to and within the brain
- There are two types of stroke:
 - Ischemic (~87% of strokes) – caused by a clot in a blood vessel supplying the brain
 - Hemorrhagic (~13% of strokes) – caused by a rupture of a blood vessel in the brain
- Currently there is only 1 FDA-approved drug for ischemic stroke – tPA (tissue plasminogen activator)
 - tPA does not repair damage, instead it can reduce damage by breaking down clots and restoring blood flow
 - only ~5% of stroke patients are given tPA as:
 - tPA must be administered within 4.5 hours of a stroke to be effective
 - tPA can only be administered for ischemic strokes, and
 - a brain image to exclude the possibility of a hemorrhagic stroke is required
- There are no pharmaceutical treatments for hemorrhagic stroke

NervGen's goal is to **repair damage** following stroke

Stroke Facts and Figures

Incidence and Prevalence of Stroke

In 2018, **1 in every 6 deaths** from cardiovascular disease was due to stroke¹

Every year, more than **795,000 people in the US have a stroke**. About 610,000 of these are first or new strokes²

Worldwide the **annual incidence** is estimated to be **16.9 million**³

The Cost of Stroke

Although 80% of patients suffering from stroke return home within a month, **patients often need nursing care**, presenting a burden for both them and their family

Stroke-related costs in the US came to nearly **\$46 billion** between 2014 and 2015²

The total costs of stroke in 2045 (in 2015 dollars) is **projected to be \$81.1 billion**¹

Cell Reports Publication on NVG-291-R and Stroke – Study Purpose & Design

Study Purpose

- This peer reviewed publication is composed of several *in vitro* and *in vivo* studies performed to **evaluate the pharmacodynamic, histological and functional effects** of administering NVG-291-R to rodents that experienced an ischemic stroke

Study Design

- Mice were given an ischemic stroke on one side of the motor-sensory cortex of the brain which resulted in motor, sensory and cognitive deficits
 - cognitive deficits assessed by the Barnes Maze Test which measures an animal's spatial learning & memory
- Animals were subcutaneously treated daily **starting either at 24 hours or 7 days after the stroke**, with either a placebo or 1 mg/kg of NVG-291-R
 - animals treated starting 24 hours after the stroke were treated for 4 weeks
 - animals treated starting 7 days after the stroke were treated for 3 weeks
- Assessments for the animal study included the following:
 - quantification of brain atrophy
 - measurement of axonal spouting
 - histology to track neuronal stem cell migration, proliferation and neurogenesis
 - neurobehavioral analysis, including locomotor function, sensory function, spatial learning and memory

Stroke Study Highlights

Treatment with NVG-291-R resulted in **significant improvement in cognitive function** when treated 24 hours - and **even 7 days** - after an ischemic stroke

Treatment with NVG-291-R resulted in a **significant increase in plasticity** - the creation of new connections between neurons

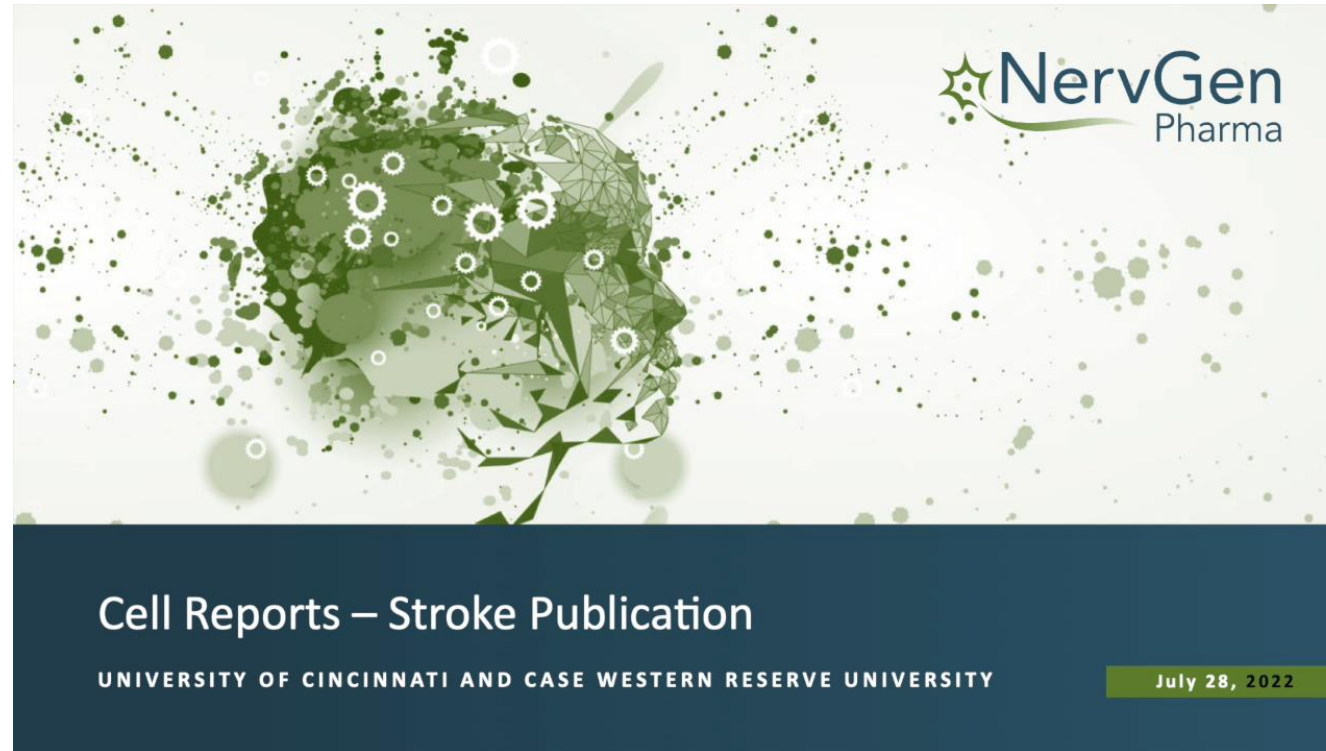
Treatment with NVG-291-R **significantly improved motor and sensory recovery**

Treatment with NVG-291-R **enhanced migration of newly created neurons derived from neuronal stem cells to the site of damage**

Dramatic and Unprecedented Recovery From a Stroke

STROKE MODEL

Play video →

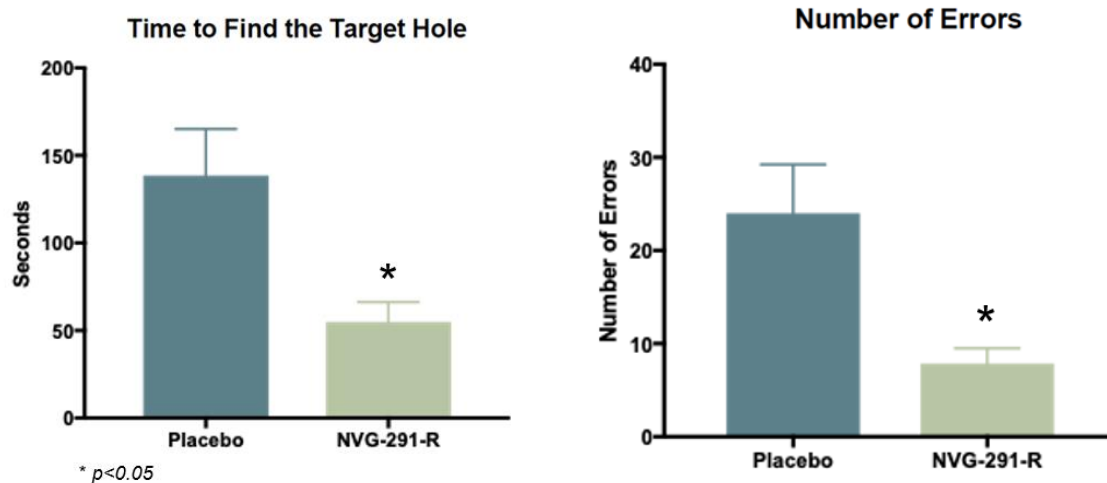


Significant improvement in cognitive function
when treated 24 hours - and even *7 days* - after a stroke

Improved Spatial Learning and Memory

Barnes Maze Test

Treatment beginning 7 days post stroke

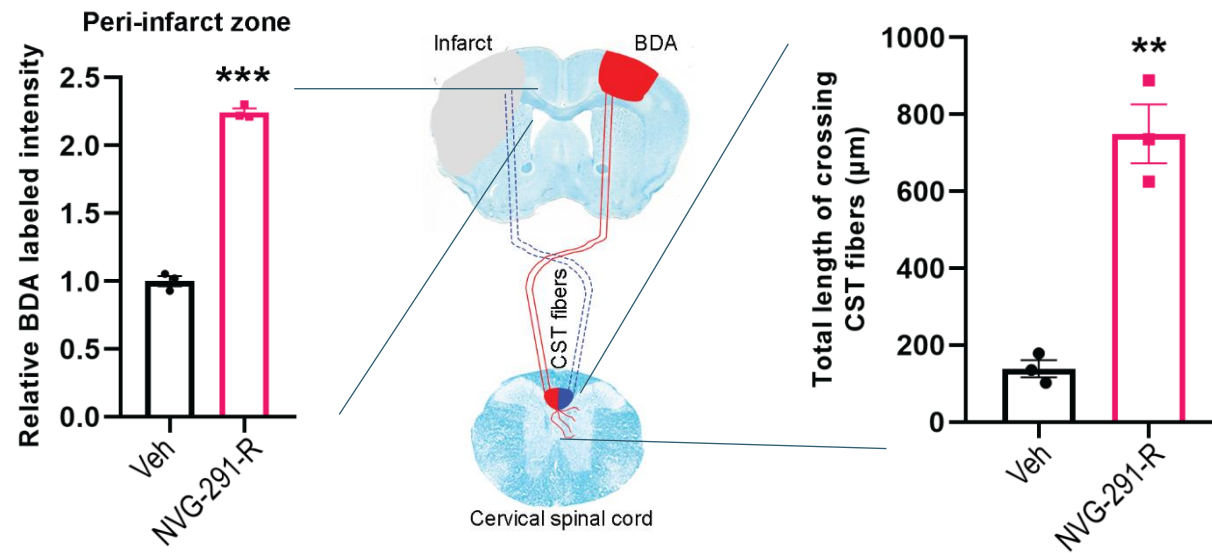


Treatment with NVG-291-R resulted in a **faster time** to identify the target holes compared to placebo treated animals

Animals treated with NVG-291-R made **fewer errors** to identify the target holes compared to placebo treated animals

Significant improvements observed when NVG-291-R was administered 24 hours or 7 days after an ischemic stroke

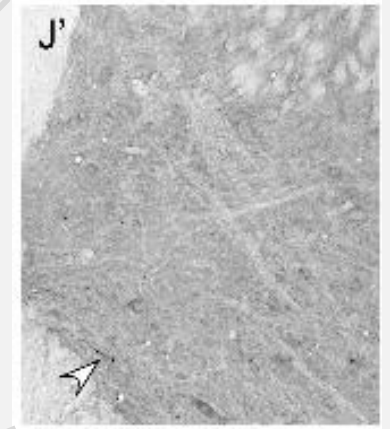
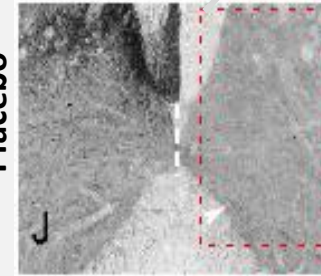
Enhances Plasticity



Once daily subcutaneous injection of either placebo or 1 mg/kg of NVG-291, starting 24 hours after the stroke for 4 weeks

Treatment with NVG-291-R resulted in a significant **increase in** plasticity, the creation of new connections between neurons

Placebo



NVG-291-R

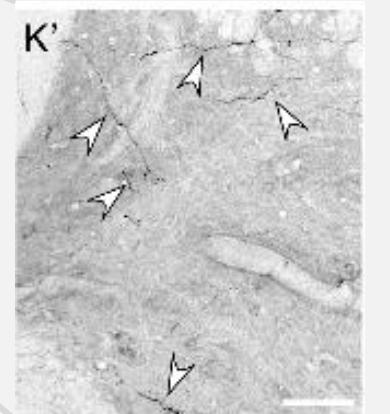
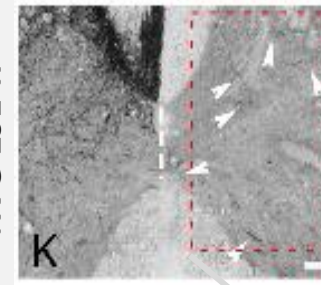
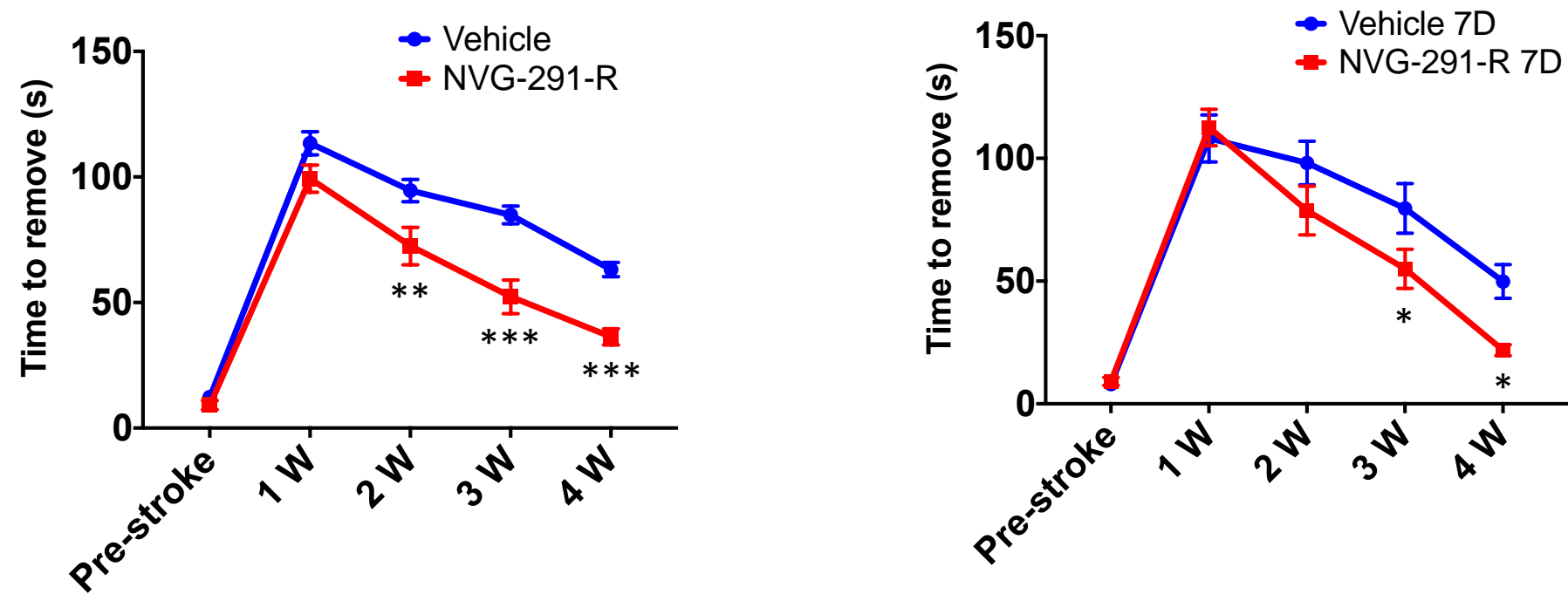


Image of axon fibers crossing the midline of the cervical spinal cord (marked with arrows). Note significantly more fibers are crossing the spinal cord in the NVG-291-R treated animals compared to placebo treated animals

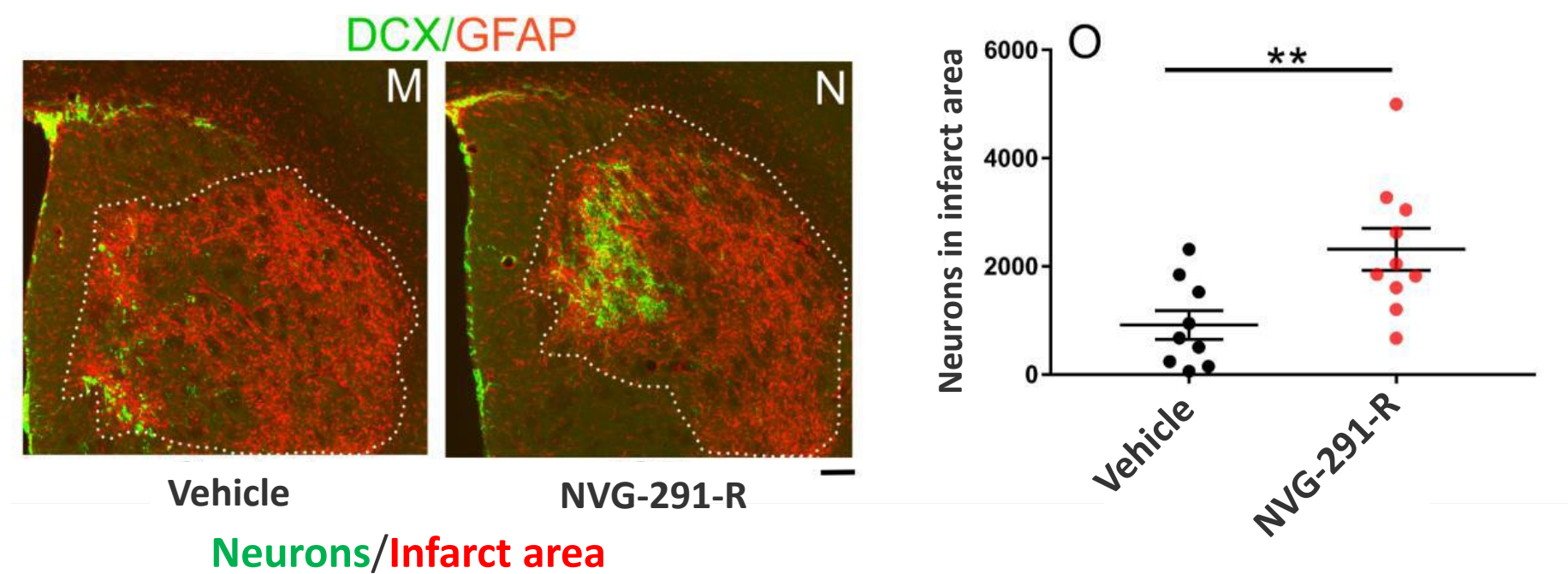
Improved Sensory and Motor Recovery



Once daily subcutaneous injection of either placebo or 1 mg/kg of NVG-291, starting 24 hours (left graph) or 7 days (right graph) after the stroke until 4 weeks

Treatment with NVG-291-R significantly improved motor and sensory recovery measured by the time required to remove an adhesive tape from the animal's paw

Enhanced Stem Cell Migration and Neurogenesis



Treatment with NVG-291-R promotes migration of newly created neurons derived from neuronal stem cells to the site of damage, differentiate into neurons and engraft into the lesion

More about Stroke

Stroke – Long Term Complications

- The impact of a stroke can range from transient to devastating to fatal, depending on the location, size, and duration of the infarct
- A stroke with widespread impact can leave an individual in a vegetative state, while focal strokes leave damage that varies by location

Complications from stroke may include¹:

- Paralysis or loss of muscle movement. You may become paralyzed on one side of your body, or lose control of certain muscles, such as those on one side of your face or one arm.
- Difficulty talking or swallowing. A stroke might affect control of the muscles in your mouth and throat, making it difficult for you to talk clearly, swallow or eat. You also may have difficulty with language, including speaking or understanding speech, reading, or writing.
- Memory loss or thinking difficulties. Many people who have had strokes experience some memory loss. Others may have difficulty thinking, reasoning, making judgments and understanding concepts.
- Emotional problems. People who have had strokes may have more difficulty controlling their emotions, or they may develop depression.
- Pain, numbness or other unusual sensations may occur in the parts of the body affected by stroke. For example, if a stroke causes you to lose feeling in your left arm, you may develop an uncomfortable tingling sensation in that arm.
- Changes in behavior and self-care ability. People who have had strokes may become more withdrawn. They may need help with grooming and daily chores.

Stroke – Acute Treatments

Therapy for stroke can be divided into two components:

- **Acute** - where the goal is to limit the damage, and to rescue the penumbra
 - The penumbra is the brain tissue surrounding the center of the stroke, and vulnerable to permanent damage if the infarct evolves
- **Chronic** - where the goal is to regain function, predominately through physiotherapy, and to prevent a recurring stroke

In the acute setting, the therapy that should be applied depends on the type of stroke that has occurred (i.e., ischemic vs hemorrhagic). Thus, the first course of action in treating a stroke patient is to perform a CT scan, or MRI, to determine the type of stroke.

Acute Therapy for Ischemic Stroke

- In eligible patients
 - Thrombolytic (clot busting) and clot-preventing pharmaceuticals such as t-PA, aspirin, warfarin, heparin or clopidogrel*
 - Endovascular thrombectomy to remove clots

Acute Therapy for Hemorrhagic Stroke

- Endovascular procedures (ex. coils, stents) to repair damage
- Surgical treatment to prevent bleeding and relieve pressure build-up

Issues with Thrombolytic (Clot Busting) Drugs for Ischemic Stroke

Tissue plasminogen activate (t-PA), aspirin, warfarin, heparin or clopidogrel, also known as “clot busters” are used in the case of ischemic stroke

- t-PA is the only FDA approved treatment for stroke

To be effective, **t-PA must be used within 3 - 4.5 hours of the onset of a stroke**

- FDA labelling states t-PA must be used within 3 hours; however, benefit has been demonstrated to be beneficial in a select group patients up to 4.5 hours post onset¹

There are several contraindications to using t-PA and other thrombolytics, including using t-PA in patients with hemorrhagic stroke

- The thrombolytic effects of t-PA can make a hemorrhagic stroke worse, and can be lethal
- As a result, patients must have a CT scan or MRI prior to treatment with t-PA

Given (i) the very narrow treatment time, (ii) the contraindication in hemorrhagic stroke, and (iii) the requirement for a patient to have a brain scan prior to treatment, very few patients are eligible to receive t-PA within the 3 - 4.5-hour time window

- **Less than 10% of all stroke patients receive t-PA²**

¹ American Stroke Association (ASA) 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke)

² Messe et al., Neurology 2016

Stroke – Impact on Society

Stroke is third only to Alzheimer's and Parkinson's in its scale as a neurodegenerative disease

- Estimate of the annual incidence in the US is 800,000 (600,000 new patients, and 200,000 with repeat strokes)¹
- Worldwide the annual incidence is estimated to be 16.9 million¹

20% of individuals suffering a stroke die within a week, while another 13% die within a year

Although 80% of patients suffering from stroke return home within a month, **patients often need nursing care**, presenting a burden for both them and their family

- The economic burden of Stroke in the US in 2015 was estimated by the CDC to be \$34 billion¹
- The total cost of stroke in 2035 (in 2015 dollars) is projected to be \$81.1 billion¹



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