ED Ischemic Stroke Patient Neuroprotection:
What neuroprotection strategies do we utilize and what might be the role of NXY-059?

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Emergency Medicine Associates

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Chicago, IL

Disclosures

- NovoNordisk, King Pharmaceuticals, UCB Pharma Advisory Boards
- Eisai Speakers' Bureau

- ACEP Clinical Policies Committee
- ACEP Scientific Review Committee
- Executive Board, Foundation for Education and Research in Neurologic Emergencies

Global Objectives

- Maximize patient outcome
- Utilize health care resources well

- Optimize evidence-based medicine
- Enhance ED practice

Sessions Objectives

- State key questions and concepts
- Why perform neuroprotection?
- What global neuroprotections?
- What specific therapies?
- What lies ahead?

Case Presentation…

- 64 year old presents to ED
- Trouble using L hand and speech
- Symptoms for last 90 minutes
- No headache or trauma
- History of TIA x 1, similar symptoms
- Hx DM, smoker
- No recent illness

ED Neuroprotection: *Key Concepts*

- Outcome related to infarct volume
- Need to limit infarct size
- Aggressively Rx ischemic penumbra
- ED MD is the best neuroprotectant
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ED Neuroprotection: *Key Concepts*

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Stroke Volume and Outcome

- Vessel occlusion
- Infarct core
- Ischemic penumbra

- How large is the core in the ED?
- What is the penumbra conversion?
- Do ED therapies limit infarct growth?

ED Neuroprotection: *Key Concepts*

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Limiting Stroke Volume

- Enhance perfusion
- Treat hypoxia, hypotension
- Limit ischemic cascade effects
- Prevent complications

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Aggressively Rx Ischemic Penumbra

- Maximize cerebral perfusion
- Provide optimal substrates, O2
- Avoid cell death
- Maintain intact blood brain barrier

Cerebral Perfusion

- CPP = MAP - ICP
- Cerebral perfusion pressure
- Mean arterial pressure
- Intracranial pressure

Cerebral Perfusion

- CPP = MAP - ICP
- If MAP = 110 mmHg, ICP 10 mmHg
- CPP then equals 100 mmHg
- Cerebral blood flow auto-regulation
- CPP maintained over range of MAPs
- Pathological ICP elevations limited

Mean Arterial Pressure

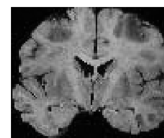
- 120 / 75 MAP = 90 mmHg
- 210 / 120 MAP = 150 mmHg
- 180 / 110 MAP = 97 mmHg
- How much MAP therapy is OK?
- What agents provide best Rx?
- How to avoid watershed infarct?

Watershed Infarct

wa·ter·shed _ (wô t r-sh d) *n.*

1. A ridge of high land dividing two areas that are drained by different river systems. Also called *water parting.*
2. The region draining into a river, river system, or other body of water.
3. A critical point that marks a division or a change of course; a turning point:

watershed infarction *n.*
Infarction of the cerebral cortex in an area of blood supply between two major cerebral arteries.



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- Know our limitations

ED MD: Best Neuroprotectant

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- Effectively able to diagnose infarct
- Systems expert; able to make things happen quickly
- Focus on acute interventions
- Know our limitations
- We can be trained

ED MD Neuroprotection

- Manage the airway

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- Manage the airway
- ETI, rapid sequence induction

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- Manage hypotension

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ED MD Neuroprotection

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- ETI, rapid sequence induction
- Manage hypotension
- Manage hypertension
- Treat metabolic abnormalities
- Diagnose and lower elevated ICP
- Prevent and treat seizures
- We first do no harm

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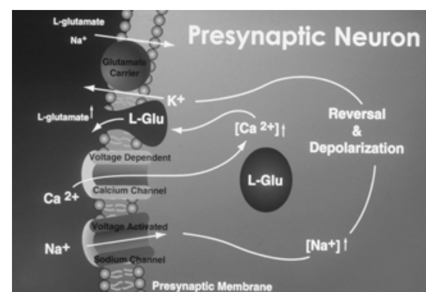
Stroke Pathophysiology, Neuroprotectants



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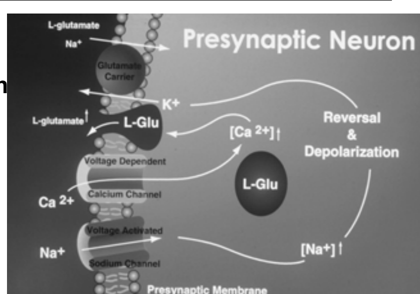
Stroke Pathophysiology, Neuroprotectants

Lubeluzole
Fosphenytoin
Sipatrigine
Riluzole
Lamotrigine
Lifarizine
Maxipost



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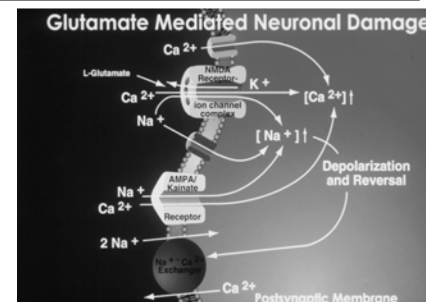
Stroke Pathophysiology, Neuroprotectants



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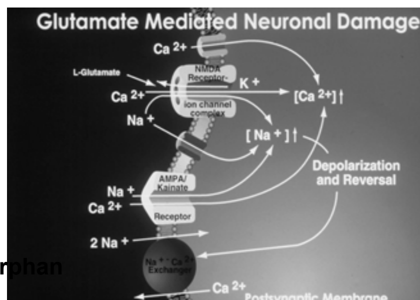
Stroke Pathophysiology, Neuroprotectants

Aptiganel
Selfotel
GV-150526
CP-101606
Eliprodil
ACPC
ACEA 1021
Dizocilpine
Dextromethorphan
NBQX
Magnesium



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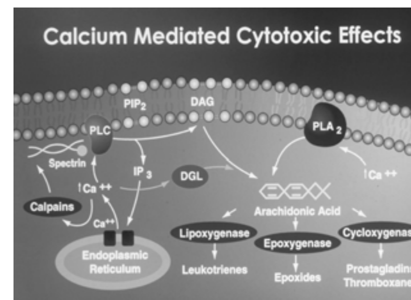
Stroke Pathophysiology, Neuroprotectants



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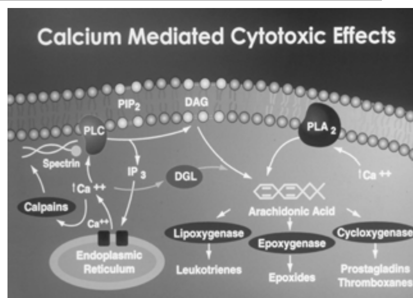
Stroke Pathophysiology, Neuroprotectants

- GM$_1$
- Piracetam
- Tirilizad
- PEG SOD
- PNA
- Enlimomab
- Citicoline
- CX295
- Ceresine



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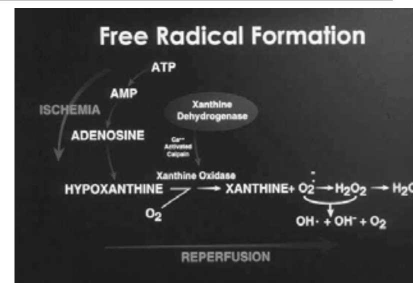
Stroke Pathophysiology: Free Radical Formation



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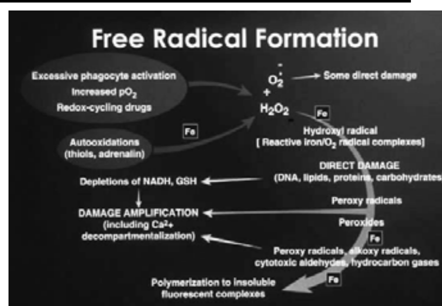
Stroke Pathophysiology: Free Radical Formation

- Tirilazad
- Citicoline
- Ebselen
- NXY-059



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Neuroprotection 1955-2000

Trials of Neuroprotection Agents in Stroke: 1955-2000

Neuroprotective Agents Tested	49
RCTs Performed	114
Patients Enrolled	21,445
Trials with Positive Results	0

This year, first positive primary endpoint trial

Kidwell CS et al. *Stroke* 32(6):1349-59.

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Why have neuroprotection agents failed in human trials?

- Wrong theoretical concept
- Treatment initiated too late
- Stroke heterogeneity
- Wrong drug action
- Doses too low
- Trials underpowered
- Wrong outcome measures
- Insensitive statistical techniques

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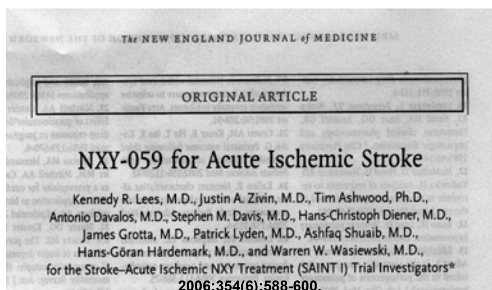
NXY-059 (Cerovive)


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

NXY-059 for Acute Ischemic Stroke

Kennedy R. Lees, M.D., Justin A. Zivin, M.D., Tim Ashwood, Ph.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., James Grotta, M.D., Patrick Lyden, M.D., Ashfaq Shuaib, M.D., Hans-Göran Härdemark, M.D., and Warren W. Wasiewski, M.D., for the Stroke–Acute Ischemic NXY Treatment (SAINT I) Trial Investigators*

2006;354(6):588-600.

NXY – 059 Characteristics

- NXY-059 (Cerovive) is an intravenous, nitrone-based, free radical trapping agent
- Preclinical trials positive in rats/primates
- Effective after 4 hours of ischemia
- Significant dose response

SAINT I Trial

(Stroke – Acute Ischemic – NXY-059 Treatment)

- RCT Design
  - 72 hr treatment window
  - NXY-059 vs placebo
  - Target plasma concentration ~260 μM
  - 158 centers across 24 countries
    - Europe, Asia, Australia, New Zealand, South Africa

Lees KR et L. *N Engl J Med* 2006;354(6):588-600.

SAINT I Trial

(Stroke – Acute Ischemic – NXY-059 Treatment)

- Eligibility
  - CT/MR consistent with AIS
  - Previous independence
  - NIHSS ≥6 including limb weakness
    - t-PA permitted
  - < 6hr ictus to treatment
    - Forced allocation to achieve mean time from onset to start of treatment ≤ 4 hrs

Lees KR et L. *N Engl J Med* 2006;354(6):588-600.

SAINT I Primary Outcome Variable: Change in Modified Rankin Scale

At 90 Days

Description	Score	Label
Symptom free	0	Symptom free
Symptomatic, but performing previous activities	1	Able to do all usual activities
Unable to do some previous activities, but independent	2	Able to look after self
Requires some help, but can walk without assistance	3	Able to walk without assistance
Needs assistance with walking and attending to bodily needs	4	Not bedridden
Bedridden, incontinent, requires constant care	5	Bedridden / Death

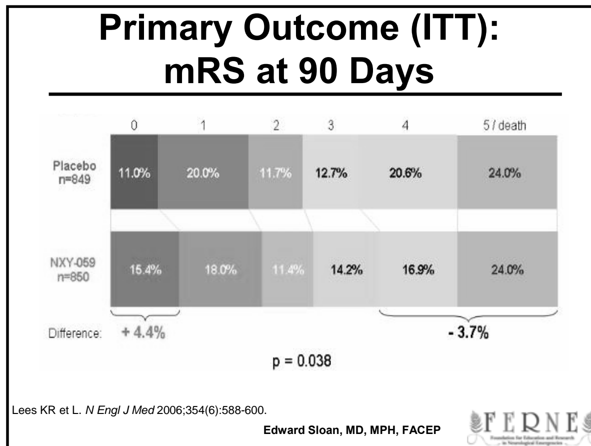
Lees KR et L. *N Engl J Med* 2006;354(6):588-600.

SAINT I Secondary Outcome Variables

- mRS at 7 and 30 days
- NIHSS change on days 7 and 90
- Barthel Index on days 7, 30, and 90
- Safety
- Day 90 SIS-16 and Four Domains
- Day 90 EQ-5D

Lees KR et L. *N Engl J Med* 2006;354(6):588-600.

Primary Outcome (ITT): mRS at 90 Days



Lees KR et L. *N Engl J Med* 2006;354(6):588-600.

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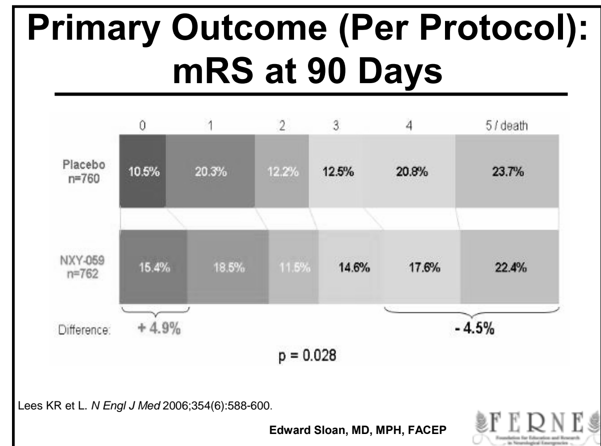
Primary Outcome (Per Protocol): mRS at 90 Days



Lees KR et L. *N Engl J Med* 2006;354(6):588-600.

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NXY-059 Number Needed to Treat: Benefit Using mRS Shift Analysis

Lowest Possible	7.9
Highest Possible	16.7
Expert Panel	9.8
Expert Panel	8.7 – 10.9

Saver J. *UCLA Stroke Center*

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NXY-059 Number Needed to Treat: Benefit Using Outcome Dichotomy

mRS	NNT
0 vs 1-6	23
0-1 vs 2-6	42
0-2 vs 3-6	48
0-3 vs 4-6	28

Saver J. *UCLA Stroke Center*

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SAINT I Clinical Endpoints

Endpoint	P Value
Rankin shift	0.038
Rankin dichotomized	0.17
Improvement in NIHSS	0.86
Barthel Index dichotomized	0.14
Stroke Impact Scale	0.08
Euro QOL Index	0.06
QOL Visual Analogue Scale	0.05

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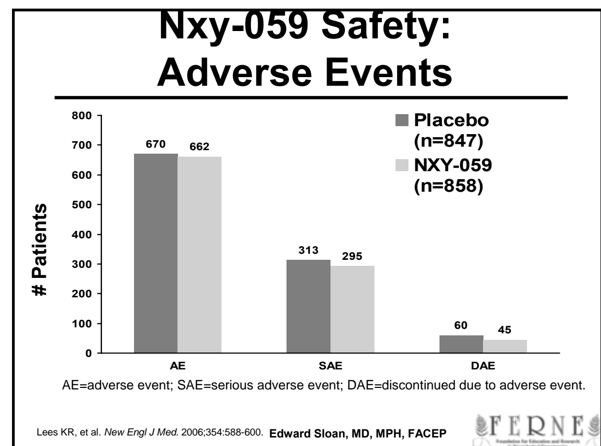
Nxy-059 Safety: Adverse Events



AE=adverse event; SAE=serious adverse event; DAE=discontinued due to adverse event.

Lees KR, et al. *New Engl J Med.* 2006;354:588-600.

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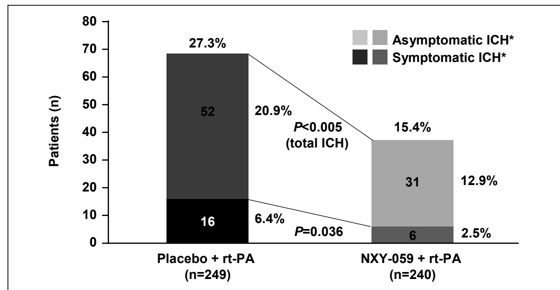
ICH After IV tPA Thrombolysis: (SAINT –I Post Hoc Analysis)



*NINDS definition; ICH=intracerebral hemorrhage

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Neuroprotectant Questions

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- How to explain BBB information?

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Neuroprotectant Questions

- Will SAINT-II reproduce results?
- Will the NNT be comparable?
- Will safety data be comparable?
- Will the tPA / ICH data compare?
- How to explain BBB information?
- What cost will the results justify?

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Conclusions

- We provide neuroprotection
- Neuroprotection reduces infarct volume, complications
- New neuroprotection data
- Interesting data related to IV tPA
- Ischemic stroke care enhanced
- Patient outcomes improved

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Questions?

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