“What’s New in Neurology?”
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Outline

Stroke
- Acute treatment
- Prophylaxis
- Intracranial hemorrhage

Epilepsy
- First-line medications
- Epilepsy surgery

Multiple sclerosis
- New treatment options
- Avoiding progression

Potpourri
- Neuropathic pain
- Parkinson’s disease
- Cognitive decline
- Lyme disease

Acute stroke

DAWN Trial

Inclusion criteria
- ICA or proximal MCA occlusion
- Last known well 6–24 hours earlier
- Mismatch between clinical exam and infarct volume

Randomized intervention
- Thrombectomy + standard care
- Standard care alone

Results
- Terminated early due to efficacy
- Less disability and higher independence with thrombectomy

Relevant Disclosures
None
Acute stroke
DEFUSE-3 Trial
Inclusion criteria
◦ ICA or proximal MCA occlusion
◦ Last known well 6 – 16 hours earlier
◦ Perfusion: Small infarct size, high adjacent at-risk territory
Randomized Intervention
◦ Thrombectomy + standard care
◦ Standard care alone
Results
Terminated early due to efficacy
Lower mortality, less disability and higher independence with thrombectomy

Acute stroke
WAKE-UP Trial
Inclusion criteria
◦ Unknown time of onset
◦ Particular MRI appearance
◦ Ischemic lesion on diffusion without T2 hyperintensity
Randomized intervention
◦ Intravenous alteplase
◦ Placebo
Results
Terminated early due to cessation of funding
More favorable outcomes and lower disability with alteplase
More hemorrhage with alteplase

Acute stroke: Take-homes
➢ More options available > 6 hours into symptoms
➢ Send patients for emergent evaluation if < 24 hours
➢ Educate patients & families regarding symptoms of acute stroke and importance of emergent care

After the Stroke: Prophylaxis
POINT trial
Inclusion criteria
◦ Minor ischemic stroke or high-risk TIA
Randomized intervention
◦ Clopidogrel + Aspirin
◦ Aspirin alone
Results
Terminated early due to efficacy
Dual antiplatelet therapy (DAPT) with lower ischemic events and higher hemorrhage
Meta-analysis of RCTs suggested DAPT within 24 hours reduced risk of recurrent stroke primarily within the first 21 days.
After the Stroke: Risk factors

Post Hoc analysis of IRIS trial

Inclusion criteria
- Prior stroke or TIA + insulin resistance (not diabetes)
  - Prediabetes: 
    - Hgb A1c 5.7-6.4% or fasting BG 100-125 mg/dL

Randomized intervention
- Pioglitazone
- Placebo

Results
- Reduced risk of stroke, MI, progression to diabetes
- Increase in bone fractures, weight, edema

After the Stroke: Take-homes

- Dual antiplatelet therapy after minor stroke/TIA for 21-30 days (POINT Trial)
- Treat patients with prediabetes
  - Hgb a1c 5.7 – 6.4 or Fasting BG 100-125
  - Pioglitazone is one – but perhaps not the only – option

Hemorrhagic Stroke: Unruptured aneurysms

Risk of unruptured aneurysm repair: Meta-analysis of 74 studies

Endovascular therapy
- 30-day complications 4.96%
- Fatality 0.3%

Neurosurgical therapy
- 30-day complications 8.34%
- Fatality 0.1%

Management strategies for tiny incidental aneurysms

Decision model
- Comparing management strategies
  - Incidental ≤ 3mm aneurysms

Outcome
- Quality-adjusted life years (QALYs)

Results
- No follow-up was associated with highest number of QALYs
- MRA every 5 years had second highest number of QALYs
Hemorrhagic Stroke: DOAC reversal

**Inclusion criteria**
- Acute major bleeding
- Factor Xa inhibitor within 18 hours

**Intervention**
- Bolus + Infusion of Andexanet

**Results**
- Intracranial (64%), gastrointestinal (26%)
- Reductions in median anti-factor Xa activity
- Modestly predictive of hemostatic efficacy in patients with ICH
- Excellent or good hemostasis at 12 hours: 82%
- 30-day thrombotic events: 10%

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Hemorrhagic Strokes: Take-homes

- Small aneurysms have very low risk of growing and rupturing
- Repair is not benign
- Preferred no follow-up, or at the most MRA every 5 years

- Direct Oral Anticoagulants now have an FDA-approved reversal agent: Andexanet

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Epilepsy: History

Prior to 2004, only 6 major antiepileptic drugs (AEDs) available for epilepsy treatment
- Carbamazepine
- Phenytoin
- Valproic acid
- Phenobarbital
- Primidone
- Ethosuximide (absence seizures)

Significant drawbacks associated with these AEDs
- Enzyme-inducers
- Side-effect ridden

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Epilepsy: History continued

In 2004, AAN investigated 7 new AEDs for treatment of new-onset epilepsy, adding 4 options
- Lamotrigine
- Gabapentin
- Oxcarbazepine
- Topiramate

Insufficient evidence to recommend
- Levetiracetam
- Tiagabine
- Zonisamide
### Epilepsy: First-line update

**New 2018 AAN guidelines**
- Lamotrigine: Probably effective
  - Including in patients aged > 60 years
- Levetiracetam: Possibly effective
- Zonisamide: Possibly effective
- Gabapentin: Possibly effective age > 60 years
- No change
  - Oxcarbazepine: Established as effective

### Epilepsy: First-line take-homes

**Established options**
- Carbamazepine: prior to '04
- Phenobarbital: prior to '04
- Valproic acid: prior to '04
- Oxcarbazepine: in 2004
- Topiramate: in 2004
- (Phenobarbital): (prior to '04)

**2018: New option**
- Lamotrigine

**Less certain options include**
- Levetiracetam
- Zonisamide
- Gabapentin

### Epilepsy surgery: Works in children

**Inclusion criteria**
- < 18 years
- Drug-resistant epilepsy

**Randomized Intervention**
- Epilepsy surgery
- Medical therapy

**Results**
- Seizure freedom higher in surgical group
- Better scores in behavior and quality of life in surgical group

### Epilepsy surgery: Works in adults

**Inclusion criteria**
- Anterior temporal lobectomy
- 5 years of follow up

**Intervention**
- Antiepileptic drug (AED) withdrawal

**Results**
- 84.9% attempted to withdrew at least one AED
  - 72.8% of these remained seizure-free
  - After recurrence, 86% of these later achieved seizure freedom
- AED-free, seizure-free in 54% of the entire population
Epilepsy surgery: When to refer

- Medically refractory epilepsy: Traditional
  - Therapeutic failure of 3 antiseizure drugs

- Medically refractory epilepsy: Currently
  - Therapeutic failure of 2 antiseizure drugs
  - Seizures uncontrolled at 12 months

- Encourage epilepsy center evaluation

Relapsing-Remitting Multiple Sclerosis: Disease-modifying therapy (DMTs)

<table>
<thead>
<tr>
<th>Class of DMT</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable</td>
<td>Established safety profile</td>
<td>Less effective injection route</td>
<td>Flu-like symptoms, injection site necrosis, transaminases</td>
</tr>
<tr>
<td>Oral</td>
<td>Self-administered, *highly effective</td>
<td>*Safety</td>
<td>Dimethyl fumarate: GI symptoms, lymphopenia, LFTs, teriflunomide: Teratogen, hair loss, GI symptoms, LFTs, fingolimod: Arrhythmia, macular edema, skin cancer, LFTs, PML, other infections</td>
</tr>
<tr>
<td>Infusion</td>
<td>*Highly effective</td>
<td>Safety, New</td>
<td>Natalizumab: PML, sx rebound, ocrelizumab: HBV activation, alemtuzumab: Infections, autoimmune disease, rituximab: PML</td>
</tr>
</tbody>
</table>

Primary progressive Multiple sclerosis

ORATORIO Trial

- Inclusion criteria
  - Primary progressive multiple sclerosis patients

- Randomized Intervention
  - Ocrelizumab
  - Placebo

- Results
  - Reduced disability progression at 12 and 24 weeks
  - Reduced brain lesions and volume loss on MRI
  - More infusion reactions, URIs, oral herpes infections
Secondary progressive Multiple sclerosis

**EXPAND Trial**

**Inclusion criteria**
- Secondary progressive multiple sclerosis patients

**Randomized Intervention**
- Simponimod
- Placebo

**Results**
- Reduced risk of disability progression
- More lymphopenia, transaminase elevation, bradycardia, bradyarrhythmia, macular edema, hypertension, varicella zoster reactivation, convulsions

Avoiding Secondary Progression

**Inclusion criteria**
- Relapsing-remitting MS patient
- Beginning disease-modifying therapy
- 4+ years of follow-up

**Exposures**
- Interferon beta
- Glatiramer acetate
- Fingolimod
- Natalizumab
- Alemtuzumab

**Results**
- Conversion to SPMS lower with early highly-effective therapy

New MS therapies: Stem Cell Transplant

**Inclusion criteria**
- Relapsing-remitting MS
- At least 2 relapses on DMT
- Disability score 2-6

**Randomized Intervention**
- Stem cell transplant + cyclophosphamide + ATG
- DMT of higher efficacy or different mechanism than prior

**Results**
- Dramatically reduced disease progression in SCT
- More short-term infections in SCT

Multiple Sclerosis: Take-homes

- Expanding armamentarium for Relapsing-Remitting multiple sclerosis
  - B-cell therapies are promising
- New approved therapies exist for:
  - Primary progressive multiple sclerosis
  - Secondary progressive multiple sclerosis
- Use (or escalate to) highly effective therapy early in disease to reduce progression to SPMS
- Stem cell transplant: emerging therapy but not ready for prime time
**Outline**

- Stroke
  - Acute treatment
  - Prophylaxis
  - Intracranial hemorrhage
- Epilepsy
  - First-line medications
  - Epilepsy surgery
- Multiple sclerosis
  - New treatment options
  - Avoiding progression

**Potpourri**

- Neuropathic pain
- Parkinson’s disease
- Cognitive decline
- Lyme disease

**Neuropathic Pain**

- Gabapentinoid use markedly increasing → Review of placebo-controlled RCTs

**FDA approved indications**

- Gabapentin: postherpetic neuralgia
- Pregabalin: postherpetic neuralgia, diabetic neuropathy, spinal cord injury, fibromyalgia

**Minimal or no evidence for**

- Low back pain
- Sciatica
- Acute zoster pain
- Traumatic nerve injury
- Complex regional pain syndrome
- Burn injury
- Sickle cell

**Gabapentinoids: Take-homes**

- Few FDA-approved indications
  - Modestly effective
- Side effects
  - Dizziness, somnolence, gait disturbance
  - Use with opioids associated with increased odds of opioid-related death
- Alternative therapies to opioids needed, but gabapentinoids likely not the answer
  - Comprehensive pain management program

**Parkinson’s disease**

- Inclusion criteria
  - Early Parkinson’s disease
- Randomized intervention
  - Levodopa + Carbidopa
  - Placebo → Levodopa + Carbidopa (delayed start)
- Outcome
  - Score on Parkinson’s disease rating scale (UPDRS)
- Results
  - No significant difference after 80 weeks
  - But Levodopa was safe → motor complications not accelerated
Deep brain stimulation indications

Movement-disorder approved indications
- Essential tremor
- Parkinson’s disease
- Isolated dystonia

Off label indications
- Tardive dystonia
- Secondary dystonia
- Tourette syndrome
- Orthostatic tremor
- Holmes tremor
- Musician’s dystonia

- Other approved indications
- Obsessive compulsive disorder
- Epilepsy

Cognition

Inclusion criteria
- Cognitively normal adults
- Aged 20-67 years

Randomized Intervention
- 4 x weekly aerobic exercise to target HR
- 4 x weekly stretching / toning

Results
- Aerobic exercise associated with increase in aerobic capacity, cortical thickness, executive function (moderated by age)
- Aerobic exercise associated with reduction in BMI

Lyme disease

PLEASE study secondary analysis

Inclusion criteria
- B. burgdorferi antibodies OR linked to proven symptomatic Lyme
- Persistent symptoms (pain, sensory or cognitive symptoms)

Randomized Intervention
- Two weeks IV ceftriaxone and then ...
- 12 weeks of doxycycline
- 12 weeks of clarithromycin/hydroxychloroquine
- 12 weeks of placebo

Results
- No difference in cognitive performance at 14, 26, or 40 weeks

Potpourri: Take-homes

- No need for “Levodopa sparing” in Parkinson’s disease
- Indications for deep brain stimulation slowly expanding
- Further evidence for benefit of aerobic exercise in cognitive functioning
- Prolonged antibiotics of no benefit in cognitive symptoms after Lyme disease
Summary of Key Points

Stoke
- Acute interventions within 24 hours
- Treat prediabetes
- Dual antiplatelet therapy x 21-30 days
- Reversal agent for DOACs
- Aneurysms ≤ 3mm are benign

Epilepsy
- First-line medications (+ Levetiracetam)
- Epilepsy surgery works

Multiple sclerosis
- Emerging B-cell therapies
- New treatment options for PPMS, SPMS

References (1 of 2)

References (2 of 2)