Headache and Neurology Update 2025

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Objectives

At the end of this session, the participant will be able to:

- Describe thunderclap headaches and their serious underlying causes
- Summarize recent research on treating and preventing migraine headaches
- Summarize recent approaches to diagnosing and managing adults with Alzheimer's disease

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Thunderclap Headache (1)

- Sudden, maximum severity at onset
- 10 years of EMR data – excluded those referred for evaluation
- 932 adults
  - 393 (42.1%) had aneurysmal SAH
  - 275 had other serious findings
    - Cerebral vasoconstriction syndrome
    - Non-aneurysmal SAH
    - Nontraumatic intracerebral hemorrhage
    - Ischemia, tumors, encephalitis, meningitis, etc.
- Bottom line: 72% had a serious condition, most if which could be identified with imaging

Zorko Garbajs, Am J Emerg Med 2024

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Migraine

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Overarching themes

- Most of the newer studies are industry sponsored
- Generally have high internal validity
- Common definitions
  - Episodic migraine: 4-14 per month
  - Chronic migraine: more than 14 per month
- Common outcome measures (International Headache Society)
  - Clinically meaningful outcomes
  - 50% reduction in headache frequency
  - Pain-free 2 hours after acute treatment

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Ubrogepant during migraine prodrome (2)

- Crossover RCT
  - adults with well-defined warning signs of impending headache
  - At least 75% accurate as demonstrated with a 60-day headache diary
  - 1087 initially recruited, only 518 were enrolled
- Randomized to 1 of 2 sequences
  - Sequence A: placebo during first prodrome and ubrogepant during the next
  - Sequence B: ubrogepant for first prodrome then placebo for the next
- 90% had at least one episode
- Outcome: absence of moderate to severe HA within 24 hours
  - 28.6% with placebo vs. 45.5% with ubrogepant (NNT=6)
  - More adverse effects with ubrogepant (NNTH=21) but no difference in discontinuation rates
- ???any better than triptans???

Dodick, Lancet 2023

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NMA of medications for acute migraine (3)

- Network MA of 137 DBRCTs (n=89,445)
  - Excluded patients seen in ER
  - 2/3 of the data were unpublished!
  - 17 different medications: triptans, acetaminophen, NSAIDs, gepants
  - Methodologic quality variable
- Does not report absolute event rates (no NNT)
- All agents were more effective than placebo after 2 and 24 hours
- Triptans were more effective and better tolerated than gepants

Karlsson, BMJ 2024

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Migraine prevention in children & adolescents (4)

- Network MA of 45 RCTs (n=3771)
  - Variety of agents, including propranolol, calcium channel blockers, anticonvulsants, antidepressants, vitamins, supplements
  - Low to medium risk of bias
- Does not report absolute event rates (no NNT/NNTH)
- Decreased HA frequency: Pregabalin, topiramate + vitamin D3, flunarizine, levetiracetam, riboflavin
- At least 50% reduction in HA frequency: flunarizine+ α-lipoic acid, flunarizine, pregabalin
- None improved QOL or attack duration
- 365 had adverse events (mild); 24 stopped treatment
  - highest with amitriptyline, topiramate, and valproate

Gargari, JAMA Network Open 2024

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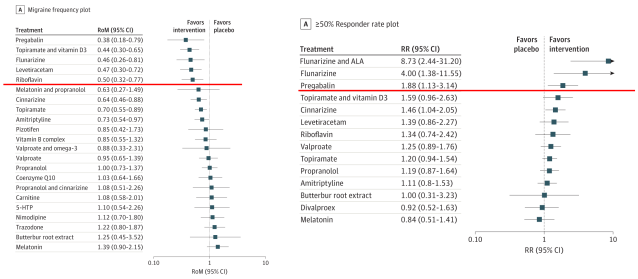

Gargari, JAMA Network Open 2024

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ACP Guideline for preventing episodic migraines in adults(5)

- ACP does guidelines well
  - Explicit evidence base and assessment
  - Comparative effectiveness (i.e., NMAs)
  - Well-constituted panels, COI
  - Practical (although their PubMed abstract is almost useless)
- Episodic migraines: 1 to 14 headache days per month
- Evaluated multiple classes of drugs but **only** drugs

Qaseem, Ann Int Med 2025

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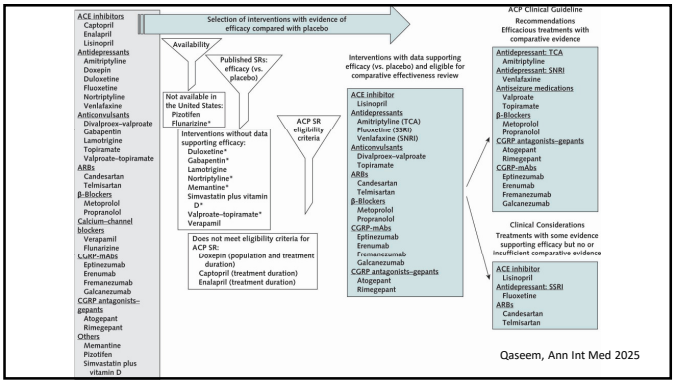

Qaseem, Ann Int Med 2025

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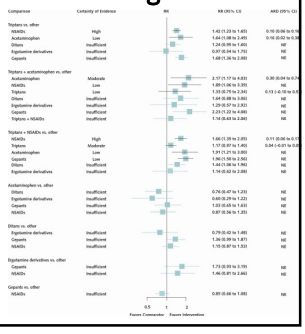
ACP SR and NMA of meds for acute migraines in adults

- Searched multiple databases and gray literature
  - 21 head-to-head RCTs (18 industry-funded); 8 low ROB, 2 hi ROB; n=43-1700
  - 164 placebo-controlled RCTs; 59 low ROB, 8 hi ROB; n=40-3331
  - **Multiple** meds and combos available in the US
- Pain-free after 2 hours (124 trials, n=64,572)
  - Triptan+NSAID better than acetaminophen, gepants, monotherapy
- Adverse effects – greatest with triptans
- BL: start with NSAID or acetaminophen; add a triptan



Gartlehner, Ann Int Med 2025

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Medication Overuse Headaches

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Erenumab for reducing nonopioid medication overuse headaches (6)

- DBRCT of 582 adults with nonopioid medication overuse headaches (separate cohort of adults with opioid medication overuse headaches)
- Monthly injections for 6 months: placebo, 70 mg erenumab, 140 mg erenumab
  - No requirement for detoxification
  - Allowed other interventions
- Outcome: remission = ***<10 headache days during months 4 to 6 of the study***
  - Placebo: 52.6%
  - 70 mg erenumab: 60.3% (NS)
  - 140 mg erenumab: 69.1% (NNT=7; 95% CI 4 – 15)
- Adverse events leading to discontinuation: 1.5% for placebo, 2.1% for erenumab

Tepper, JAMA Neurol 2024

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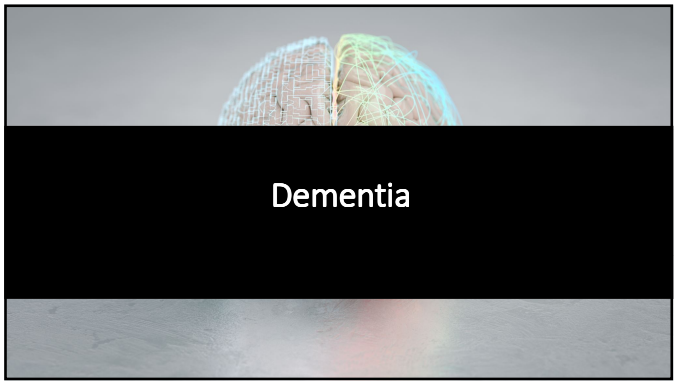

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Revised criteria for diagnosis of Alzheimer's disease: Alzheimer's Association Workgroup

"We define Alzheimer's disease (AD) to be a biological process that begins with the appearance of AD neuropathologic change (ADNPC) while people are asymptomatic."

Rationale:
"Defining diseases biologically, rather than based on syndromic presentation, has long been standard in many areas of medicine (e.g., oncology), and is becoming a unifying concept common to all neurodegenerative diseases, not just AD."

Jack, Alzheimers Dement 2024

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Working group response to updated Alzheimer's disease diagnostic criteria (7)

- International working group with concerns about a purely biological definition of AD being applied clinically
  - Guided by systematic literature review
- majority of biomarker-positive cognitively normal individuals will not become symptomatic
- disclosing a diagnosis of AD to cognitively normal people with only core 1 AD biomarkers represents the most problematic implication of a purely biological definition of the disease
- Adults who are cognitively normal but amyloid-positive or other biomarker-positive, should ***not*** be labeled as having AD. Rather, they should be considered as being ***at risk*** for AD

Dubois, JAMA Neurol 2024

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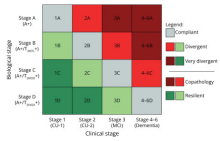
New criteria "correct" in only 1 in 3 (8)

- Neuroimaging cohort of 256 adults undergoing serial imaging and neurocognitive testing
  - 51% female; mean 73 years of age
- Developed a 4x4 matrix based on the amyloid cascade and on clinical stages of cognition (ranging from no impairment to dementia)
- 5 different statistical models
  - Concordance 31-36%
  - Resilience 6-52%
  - Copathology 17-63%



Mendes et al. Neurology 2025
https://pubmed.ncbi.nlm.nih.gov/40359457/

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Italian guideline on diagnosing and managing adults with dementia or MCI (9)

- Panel of experts plus representatives of families and caregivers
  - Structured set of questions answered by explicit process
  - Addressed pharmacologic, nonpharmacologic, and system approaches
- Full guideline (in English) is 423 pages
  - Specific recommendations for primary care clinicians, dementia care experts, families, caregivers, social care
  - Practical
  - Interactive tools for clinicians, families, and caregivers

Fabrizi, Age Ageing 2024

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Italian guideline on diagnosing and managing adults with dementia or MCI (9)

- **Keep the patient and family involved in the decision-making**
- Hx, PE, tests to evaluate for reversible or secondary causes
- Use validated tests (e.g., MoCA, MMSE, etc.); referral if abnormal
- No recommendations for or against screening or case finding
- Aerobic and nonaerobic exercise
- Music and art therapy
- MCI: no meds
- Dementia:
  - Nuanced guidance on use of cholinesterase inhibitors
  - ***Strongly*** recommends ***against*** amyloid-directed monoclonal antibodies

Fabrizi, Age Ageing 2024

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MAbs and dementia (10)

- MA of 13 RCTs (n=18,826) with over 200 participants
- Some evidence for publication bias
- Outcomes
  - Scores of cognition: better but tiny effect sizes and heterogeneous data
  - All-cause mortality: no difference
  - ARIA-edema: 16.6% vs. 1.4%; NNTH 7
  - ARIA-hemorrhage: 18.4% vs. 9.2%; NNTH 10
  - Headache: 12.8% vs. 9.9%; NNTH 54
- Similar to analysis published a year earlier by Ebell and Barry

Tonegawa-Kuji; PLoS 2025
https://pubmed.ncbi.nlm.nih.gov/40163534/

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Pot Pourri

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New-onset seizures following SARS-CoV-2 vaccine (11)

- MA of 6 RCTs (118,440 participants)
  - 4 only included adults; 2 children
  - All used placebo and reported 28-day outcomes
  - All low risk of bias
- Only 10 (0.008%) had a new onset seizure
  - 9 received active vaccine
  - OR 2.70 (95% CI 0.76-9.57)

Rafati, JAMA Neurol 2024

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Anticonvulsants following mild or moderate traumatic brain injury (12)

- MA of 8 cohort studies (n=5637)
  - low risk of bias
  - Most widely used: levetiracetam, phenytoin, and valproic acid
- Post-traumatic seizures ranged from 0 to 4%
- Anticonvulsants decreased rate: ARR 0.6% (95% CI 0.1%-1.2%)
- Low rate of seizures, small degree of benefit to be balanced against cost and adverse effects

Pease, JAMA Neurol 2024

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Botulinum toxin for essential or isolated head tremor (13)

- Medical tx for hand tremor not effective for head tremor
- DB RCT (117 adults)
- 2 injections 12 weeks apart: placebo or botulinum toxin type A
- Outcome: improved or much improved on a global rating scale
  - Week 6: 44% vs. 7%; NNT=3
  - Week 18: 31% vs. 9%; NNT=5
  - Week 24: 23% vs. 13%; NS
- Adverse effects were mild and self-limited, although 1 was hospitalized

Marques, NEJM 2023

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Bottom Lines

- Thunderclap headaches are serious business
- Ubrogepant during migraine prodrome prevents moderate or severe headaches (but so do triptans)
- Triptans are the most effective drugs for acute migraine abortive therapy
- Cognitively intact adults who are amyloid-positive should not be labeled as having Alzheimer's disease but should be considered as being at risk for AD.
- Medications should not be used in adults with mild cognitive impairment

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