

Neurology
Potpourri 2022



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Objectives

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

- describe recent studies on managing persons with sleep disturbances
- describe the management of persons with concussion
- describe the management of children with seizure disorders

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Sleep
Disturbances



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US DoD and VA guideline for OSA and insomnia (1)

- Diverse development group, limited COI, guided by SRs with focus on outcomes of importance to patients
 - 41 separate recommendations
- OSA
 - Screen for OSA with STOP (Snoring/Tiredness/Observed stopped breathing/blood Pressure)
 - Home testing for OSA
 - Use CPAP
- Chronic insomnia
 - Sleep hygiene
 - CBT
 - +/- auricular acupuncture
 - Last resort-low dose doxepin or nonbenzodiazepine hypnotic

Mysliwiec, Ann Int Med 2020

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Telephone-based cognitive behavioral therapy for insomnia is effective (2)

- Unblinded RCT with 327 adults with DJD and insomnia – average Insomnia Severity Index 15.5 (28 points; estimated MCID=3-4 points)
- Telephone-based CBT-I or education
 - CBT-I: in-bed restriction, cognitive strategies to reduce hyperarousal, and setting realistic sleep expectations
 - All were contacted via phone 6 times in 8 weeks
- 2 months after end of intervention
 - ISI decreased average 8.1 points in CBT-I and 4.8 in education
 - At least 30% improvement in ISI: 81% of CBT-I and 49% in education group (NNT=4)
- 12 months after end of intervention – between group differences persisted

McCurry, JAMA Int Med 2021

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Limited data suggest that music improves sleep quality in older adults (3)

- MA, 5 crappy little trials (288 adults) in community settings
 - Pittsburgh Sleep Quality Index (0-21; 5+ indicates poor quality; MCID=3)
- Wide range of interventions: live and recorded music, 30 to 60 minutes long, and the intervention periods ranged from 2 days to 3 months
- Results:
 - Music was better than no music: mean difference 1.96
 - Sedative music was better than rhythmic music: mean difference 2.35
 - Longer than 4 weeks more effective: mean difference 2.61
 - No data on adverse events
 - No data on responders vs. non-responders
- Overall, poor studies and differences not clinically important

Chen, JAGS 2021

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Medications for daytime sleepiness in individuals with idiopathic hypersomnia (4)

- Cochrane SR, 3 tiny trials (112 participants), but all low risk of bias!
- Modafanil
 - Epworth score improved by 5 points more than placebo
 - Ability to remain awake 4.74 minutes longer than with placebo
 - 1 study – improved ratings of exhaustion and effectiveness/performance
 - No difference in number of naps
- Clarithromycin – 1 study with 20 participants. No better than placebo
- Overall – not much data

Trotti, Cochrane Database 2021

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Concussion



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Duh (5)

- Natural experiment at Tennessee, Virginia, Kentucky border
 - KY is the only state without a law mandating helmet use by motor-bikers
 - Data from the level I trauma center serving the region
- 729 crash victims 2005-2015
- Helmet usage: KY 41%, TN 89%, VA 81%
- In-hospital fatality rate: KY 7.3% vs. 4.3% combined for TN & VA
- Un-helmeted vs. helmeted
 - Severe head injuries AdjOR 15.3
 - Death AdjOR 4.2

Testerman, South Med J 2018

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Clinical score to identify kids not needing imaging after head injury (6)

- PECARN, CHALICE, CATCH all accurate
- CATCH
 - High risk if present:
 - GCS score of less than 15 at 2 hours after injury;
 - suspected open or depressed skull fracture;
 - history of worsening headache;
 - irritability on examination;
 - Low risk if absent:
 - any sign of basal skull fracture;
 - a large, boggy hematoma of the scalp; and
 - dangerous mechanism of injury including motor vehicle accident, a fall from 3 or more feet or down 5 or more stairs, or a bicycle injury without a helmet
- CATCH2 added 4 or more episodes of vomiting

Osmond, CMAJ 2018

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CATCH vs. CATCH2 (6)

- Based on CT findings and 2-week follow-up

	CATCH				CATCH2			
	Se	Sp	LR+	LR-	Se	Sp	LR+	LR-
Brain Injury on CT	97.5	59.6	2.4	0.04	99.5	47.8	1.9	0.01
Neurosurgery	91.3	57.1	2.1	0.2	100	45.7	1.8	0

- Better at ruling out than ruling in
- Note-without a rule clinicians ordered CT in 35% of kids while the rules would have ordered them in more than half!

Osmond, CMAJ 2018

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Return to play guidelines following concussion (7)

- Consensus statement (BOGSAT)
- 24-48 hours of physical and cognitive rest.
- Symptom limited activity.
- Light aerobic exercise, no resistance training.
- Sport-specific exercise.
- Noncontact training drills.
- Full contact training after medical clearance.
- Game play
- If post-concussion symptoms recur, drop back a level and try again after 24 hours

McCrory, Br J Sports Med 2017

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After concussion, subthreshold aerobic exercise returns teens to play sooner than stretching (8)

- Single-blind RCT, 13-18 year olds with sports-related concussion
- All participants had an ETT to the point of concussive symptoms and rated the severity of symptoms
- Randomized to daily aerobic program (n=52) or placebo stretching program (n=51)
 - Aerobic program: no stretching; 20 minutes on treadmill or bike to ETHR 80% of symptom exacerbation at baseline; to stop if symptoms increased by more than 2 points above baseline
 - Control: 20 minutes of gentle stretching designed to not increase HR
- Median time to recovery (ability to exercise to exhaustion without symptoms)
 - Exercise group: 13 days
 - Control group: 17 days

Leddy, JAMA Peds 2019

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Video screens after a head injury (9)

- Unblinded RCT in ER
 - 125 young people (12-25 years of age) within 24 hours of head injury
 - GCS = 15 and no abnormalities on imaging
 - Randomized to receive instructions to avoid use of videoscreens or not
- 30 (24%) did not complete the 10 days of follow-up 😞
- Recovery (based on Post-Concussive Symptom Scale of 3 or less)
 - 72% vs. 60% in controls (NNT=9)
 - Longer time to recovery in control group (8.0 vs. 3.5 days)
 - Women were less likely to recover than men (HR 0.34; 95% CI 0.19 - 0.60)

Macnow, JAMA Peds 2021

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Levetiracetam = second-line agents for status epilepticus (10)

- MA; 10 studies with 1907 children
 - 7 compared levetiracetam with phenytoin
 - 3 compared either fosphenytoin or valproic acid
 - Generally low risk of bias except for blinding
- Levetiracetam vs. phenytoin: rate of seizure cessation 83% vs. 80%
- No difference with the other comparators on rate of cessation
- No difference for other outcomes:
 - time to cessation of seizure activities,
 - seizure recurrence at 24 hours,
 - need for rapid sequence intubation,
 - need for intensive care,
 - all-cause mortality
 - adverse events
- Benzodiazepines remain first line, but levetiracetam is comparable to other second line agents

Abdelgadir, Arch Dis Child 2020

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Two RCTs: levetiracetam = phenytoin for status epilepticus but is easier to use and may be safer (11)

- 2 open-label RCTs (ECLIPSE and ConSEPT), in ERs with children with status epilepticus needing second-line treatment
 - Randomized to levetiracetam (40 mg/kg over 5 minutes; n [for the 2 studies] = 271) or phenytoin (20 mg/kg over 20 minutes; n = 248)
- ECLIPSE outcome: time to seizure cessation-35 vs. 45 minutes, respectively
 - 1/3 in each group needed second agent
 - 20% needed rapid sequence induction
- ConSEPT outcome: cessation of seizures within 5 minutes of completing infusion-60% vs. 50%
 - About 25% needed rapid sequence induction
- Harms were rare, stacked in the phenytoin-treated kids. Need more data to fully assess safety
 - 1 death in each study; but only occurred in phenytoin-treated
 - 1 phenytoin-treated child had life-threatening hypotension, increased focal seizures, and decreased consciousness
- Levetiracetam can be administered more quickly

Lyttle, Lancet 2019
Dalziel, Lancet 2019

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Prophylactic drug management for febrile seizures in children (12)

- Cochrane SR; 32 RCTs with 4431 participants
 - 15 interventions vs. control
 - Moderate to poor quality
- No benefit from
 - intermittent phenobarbital, phenytoin, valproate, pyridoxine, ibuprofen, or zinc sulfate
 - diclofenac versus placebo followed by ibuprofen, paracetamol, or placebo
 - continuous phenobarbital versus diazepam, intermittent rectal diazepam versus intermittent valproate, oral diazepam versus clobazam, intermittent diazepam vs. melatonin
- Reduction in recurrent seizures
 - intermittent diazepam vs. placebo or no Tx: 6 months RR 0.64; 12 months RR 0.69; 18 months RR 0.37; 24 months RR 0.73; 36 months RR 0.58; 48 months RR 0.36; none at 60-72 months
 - phenobarbital vs. placebo or no Tx: 6 months RR 0.59; 12 months RR 0.54; 24 months RR 0.69; none at 18 months and at 60-72 months
 - clobazam: 6 months RR 0.36; but only 1 study
 - levetiracetam vs. placebo: 12 months RR 0.27; but only 1 study
- Harms: no surprise but variably reported
 - phenobarbital 30%
 - benzodiazepines 36%

Offringa, Cochrane Database 2021

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Authors' conclusion (12)

- more data and better studies are needed

“Given the benign nature of recurrent febrile seizures, and the high prevalence of adverse effects of these drugs, parents and families should be supported with adequate contact details of medical services and information on recurrence, first aid management, and, most importantly, the benign nature of the phenomenon. “

Offringa, Cochrane Database 2021

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Ketogenic diets for drug-resistant epilepsy (13)

- Ketogenic diet (KD) high in fat and low in carbohydrates
- Cochrane SR; 13 RCTs with 711 children and 221 adults
 - Overall moderate to high risk of bias
- KD vs. usual care in children
 - 4 studies, 385 children, low to very low certainty evidence
 - Seizure-free RR 3.16; seizure reduction RR 5.8
- KD vs. usual care in adults
 - 2 studies, 141 adults, very low certainty evidence
 - Seizure-free never happened; seizure reduction RR 5.03
- Head-to-head comparison of KDs in children or in adults
 - Some differences but limited data and poor quality studies

Martin-McGill , Cochrane Database 2020

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AAN Guideline on Withdrawing Meds (14)

- Update of 1996 guideline
 - Partialist panel, no patients, no primary care
 - Tried to minimize financial COI
 - Guided by SRs
 - Seizure-free interval in studies varied from 12 to 60 months
 - Addressed time to recurrence, QOL, mortality, status epilepticus
- Adults who have been seizure-free for 24 months or longer
 - patient and clinician should engage in shared decision-making about the benefits and harms of continuing anticonvulsants
 - no conclusions as to the utility of electroencephalograms or imaging
- Children with abnormal EEG – does not recommend withdrawal
- Children who have been seizure-free for 18-24 months and have a normal EEG, the panel recommends shared decision-making as to the benefits and harms of continuing anticonvulsants

Gloss , Neurology 2021

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Miscellaneous



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Anticonvulsants, SNRIs, and rubefaciants for diabetic neuropathy or postherpetic neuralgia (15)

- MA of RCTs, needed to include a clinically meaningful response-at least 30% improvement
- Anticonvulsants - 40 RCTs, moderate certainty evidence
 - Mostly pregabalin and gabapentin
- Rubefaciants - 10 RCTs, low certainty evidence
 - Capsaicin
- SNRIs - 8 RCTs, moderate certainty
 - duloxetine, venlafaxine, and desvenlafaxine
- Opioids - 6 RCTs, low certainty
- Acupuncture – 3 RCTs, very low certainty
- TCAs – 2 RCTs, low certainty

Falk, Can Fam Phys 2021

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Medications for diabetic neuropathy or postherpetic neuralgia-Results (15)

- Acupuncture – no significant benefit
- TCAs – no significant benefit

Intervention	Studies (Participants)	NNT	NNTH	Quality
Anticonvulsants	40 (9575)	7	17-22	Moderate
SNRIs	8 (2746)	7	13	Moderate
Rubefaciants	10 (2344)	7	25	Low
Opioids	6 (1149)	8	12	Low

Falk, Can Fam Phys 2021

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Midodrine is worth a trial in people with frequent episodes of vasovagal syncope (16)

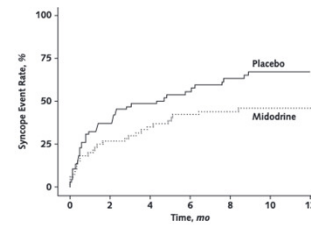
- DB RCT, 133 adults without orthostatic hypotension who had fainted at least twice (median 6 times) in the previous year
- Randomized to midodrine 5mg 3 times daily (increased to 10 mg 3 times daily if tolerated) or placebo
- After one year
 - Midodrine had more syncope-free participants (58% vs. 39%; NNT=5)
 - Longer time to first faint
 - Subset of those who fainted, the rates were similar between groups (3.6-3.8 episodes)
- Looks like an all or none response

Sheldon, Ann Int Med 2021

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Midodrine is worth a trial in people with frequent episodes of vasovagal syncope (16)

Figure 2. Syncope recurrence rates.



Sheldon, Ann Int Med 2021

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Anticoagulants for acute ischemic stroke (17)

- Cochrane SR of 28 trials with 24,025 participants
 - variable quality
 - unfractionated heparin, low-molecular-weight heparins, heparinoids, oral anticoagulants, and thrombin inhibitors
 - 90% administered within first 48 hours
- Outcomes
 - All-cause mortality OR 0.98 (95% CI 0.92 to 1.03)
 - Recurrent stroke OR 0.75; NNT = 112
 - Symptomatic intracranial hemorrhage OR 2.47; NNTH = 143
 - Symptomatic pulmonary emboli OR 0.60; NNT = 334
 - Major extracranial hemorrhage OR 2.99; NNTH = 143

Wang, Cochrane Database 2021

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Resuming antiplatelet therapy after intracranial hemorrhage: RESTART (18)

- Single blind RCT with 576 adults who survived at least 24 hours after intracranial hemorrhage and whose antiplatelet tx was stopped
- Randomized to resumption or antiplatelet avoidance
- Median 7 years of follow-up
 - Subsequent ICH similar between groups: 9.3% vs. 8.2%
 - Similar rate of major vascular events: 26.8% vs 32.5%
- Designed to recruit 720; however, the rate of ICH in those back on antiplatelet tx was lower than control group
- Similar to findings from observational studies

Al-Shahi Salman, JAMA Neurol 2021

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Fewer strokes, more bleeding with aspirin + either clopidogrel or ticagrelor than with monotherapy in secondary stroke prevention (19)

- Strange network MA of dual antiplatelet therapy versus monotherapy
 - RCTs **had** to include ticagrelor in at least one wing
 - Could include aspirin, clopidogrel, or prasugrel
 - 26 trials with 124,495 participants with cerebrovascular, coronary, or peripheral artery disease
 - Low risk of bias
 - Focused exclusively on stroke prevention
- Compared with aspirin monotherapy
 - aspirin plus clopidogrel: RR 0.77; 95% CI 0.62 - 0.96
 - aspirin plus ticagrelor: RR 0.80; 95% CI 0.72 - 0.89
 - monotherapy and prasugrel + aspirin did not decrease stroke risk
- Dual therapy doubled the risk of bleeding compared with aspirin or with monotherapy
- None decreased all-cause mortality
- Data not reported so as to facilitate estimates or NNT or NNTH

Balint, Stroke 2021

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Bottom Lines

- Regardless of age or the presence of underlying medical or psychiatric conditions, nonpharmacologic approaches are the preferred approach to managing sleep disorders
- Clinical features can accurately identify which children do not need imaging following head injury.
- After concussion, graded symptom-limited activities can facilitate return to activity.
- The primary approach to managing febrile seizures is in reassurance, education and fever control and to minimize the use of anticonvulsants.
- Seizure-free adults and children are candidates for withdrawing anticonvulsants, however, this requires shared decision-making about the potential benefits and harms.
- Anticoagulation after acute ischemic stroke prevents recurrent stroke and VTE, but increases the risk of symptomatic intracranial hemorrhage and major extracranial bleeding
- The rate of events after resuming antiplatelet therapy after intracranial hemorrhage is similar to the event rate in those not resuming it – this is a place of shared decision-making
- Dual antiplatelet therapy for secondary stroke prevention in high-risk adults is more effective than monotherapy but doubles to risk of bleeding.

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