SEIZURES IN CANCER

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There are no conflicts of interest noted by presenter.

Objectives

- Understand the etiology of seizures in primary or metastatic cancer
- Review diagnosis of seizures, including imaging and lab work
- Discuss management of seizures in cancer patients
- Briefly review differential diagnosis leading to seizures

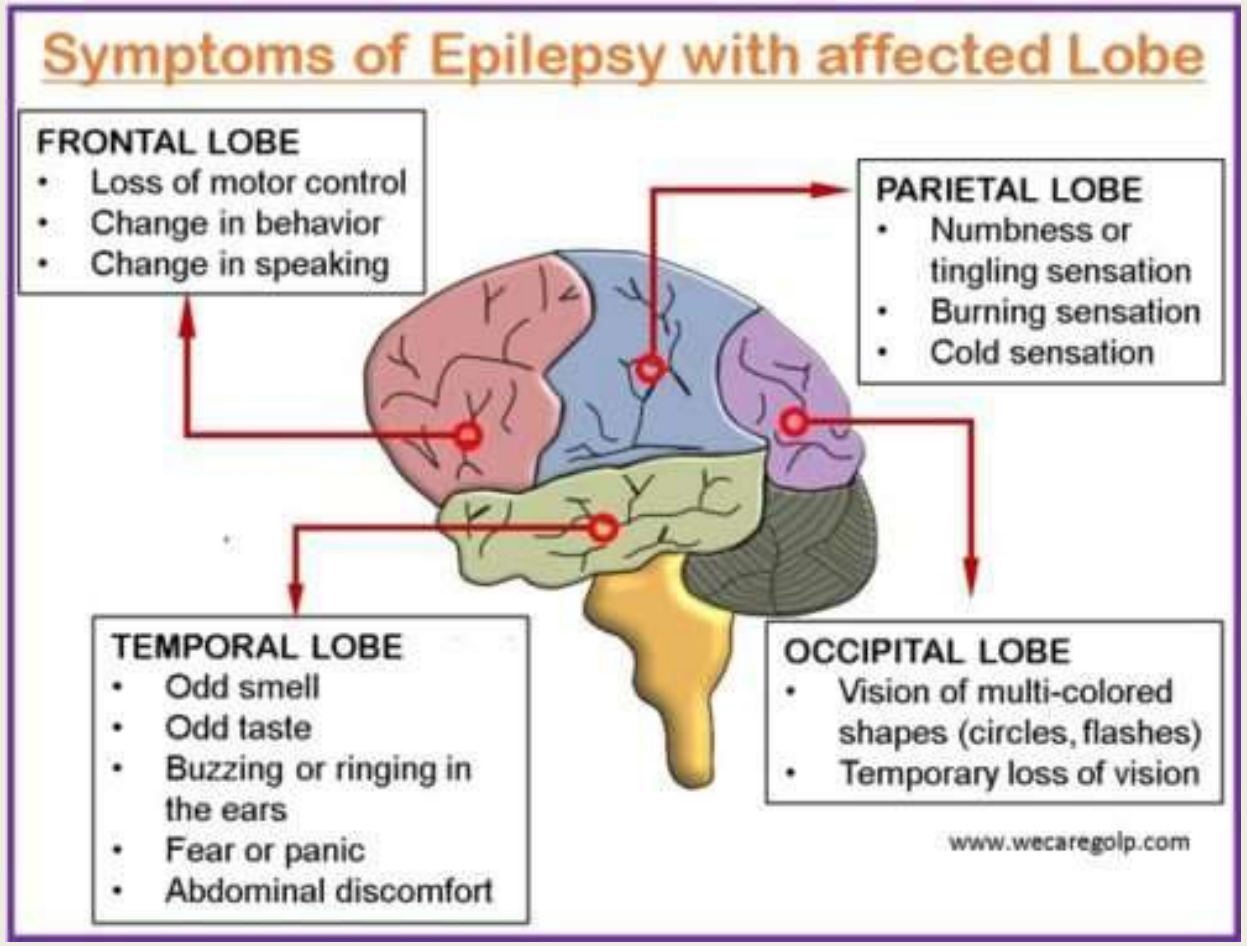
Case

- 52-year-old male with a past medical history of metastatic oropharyngeal squamous cell carcinoma s/p palliative radiation and chemotherapy who presents for inpatient hospice due to worsening pain and altered mental status
- Worsening agitation, focal abnormal movements
- Progressed to general tonic-clonic seizure

What Are Seizures?

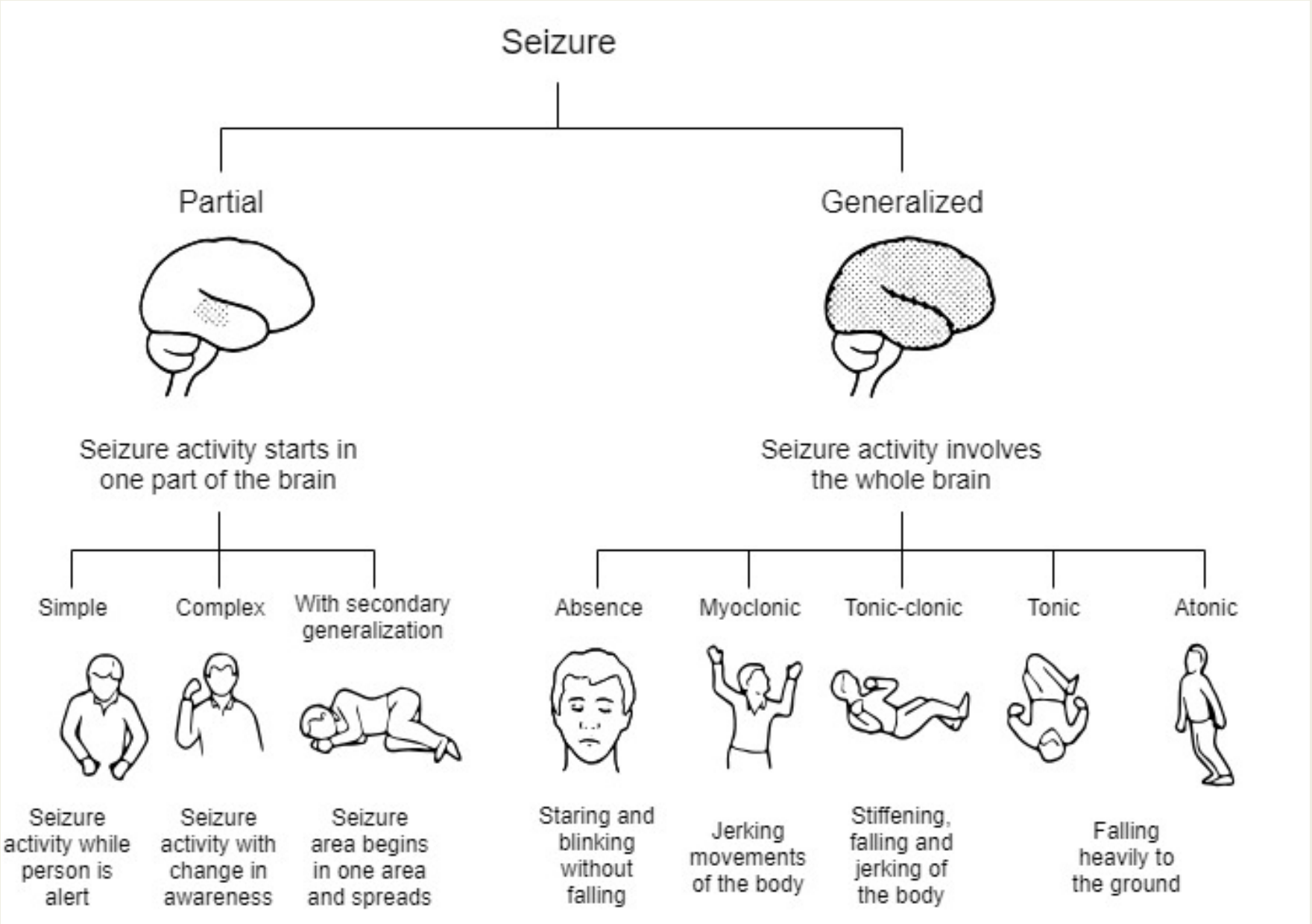
- Seizures result from an abnormal synchronous discharge of a group of neurons (seizure focus)
  - *Clinical manifestations of seizures depend on location in the brain*

- Prodrome → Seizure/Ictal → Post-Ictal



Schachter et al. Evaluation and management of the first seizure in adults. In: UpToDate, Wolters Kluwer. (Accessed May 2025.) Available at: https://www.uptodate.com/contents/evaluation-and-management-of-the-first-seizure-in-adults

Image credit https://wecaregolp.com/epilepsy/



Swaminathan, 2019. CORE EM: Approach to Adult First Time Seizure in the ED. Available at: https://www.emdocs.net/core-em-approach-to-adult-first-time-seizure-in-the-ed/

Post Ictal State

- Focal Seizure (with or without impaired awareness)
  - *Weakness (Todd's Paralysis)*
  - *Aphasia*
  - *Somnolence*
  - *Confusion*
  - *Headache*
- Generalized Seizure (Tonic-clonic)
  - *Deep sleep*
  - *Breathing deeply*
  - *Confusion or agitation*

Tradounsky 2013

Incidence

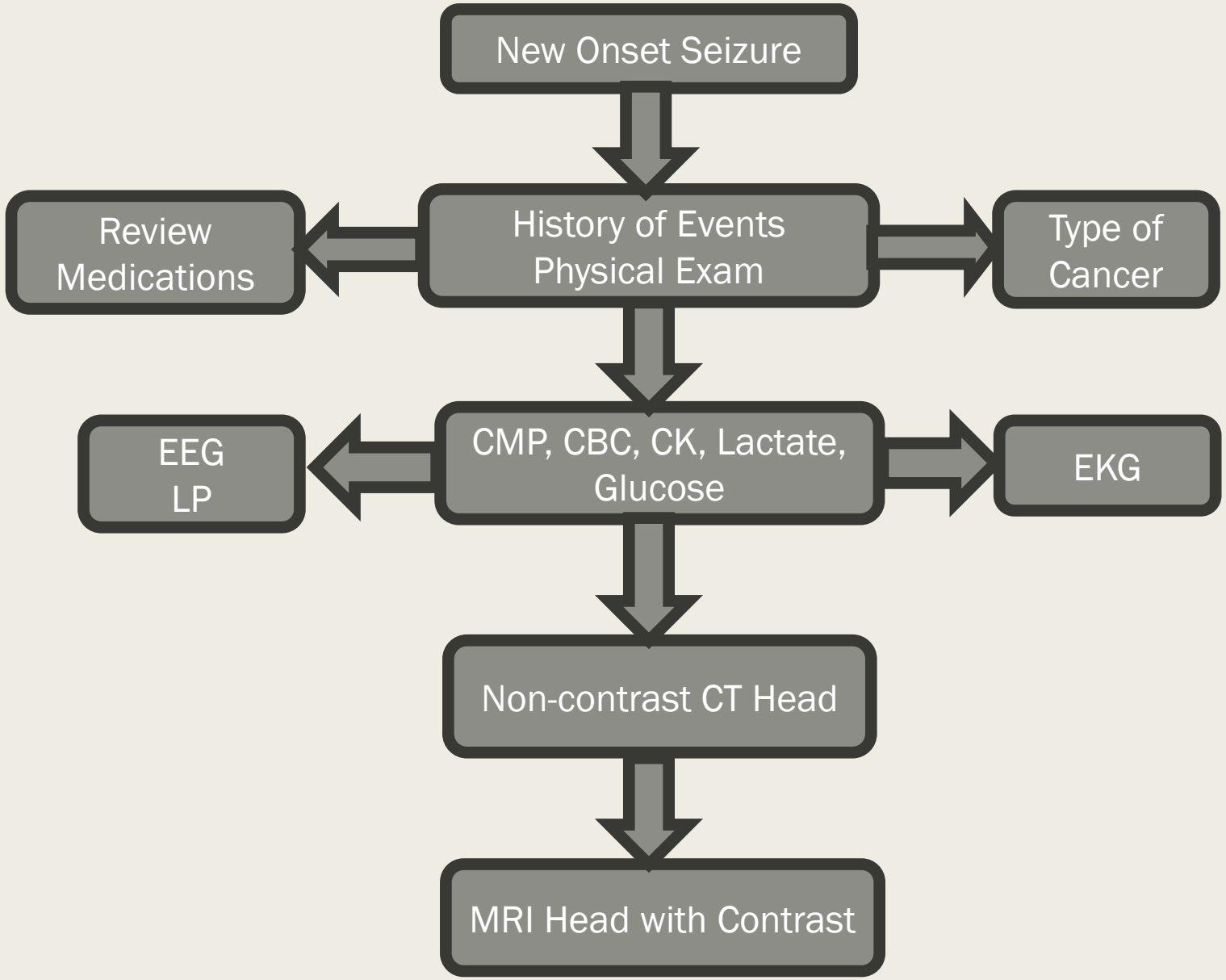
- 25 to 50% of palliative patients who develop seizures have brain metastasis
- 20 to 40% of patients with primary brain tumors present with convulsions
- Slow growing tumors more likely to cause seizures

Tradounsky 2013, Hauff et al 2023

Etiology of Seizures

Structural Damage	Systemic Insult
Primary Brain Tumors	Electrolyte Abnormalities
Brain/Leptomeningeal Metastasis	TTP
Abscesses	Hepatic Failure
TIA/Stroke	Hypoxia
Hemorrhage	Uremia/TLS
PRES or RPLS	Infections
Encephalitis	Withdrawal – Alcohol & Benzodiazepines
Radiation Necrosis	Medications (discussed later)

Tradounsky 2013, Hauff et al 2023



Drappatz et al. Seizures in patients with primary and metastatic brain tumors. In: UpToDate, Wolters Kluwer. (Accessed May 2025.) Available at: https://www.uptodate.com/contents/seizures-in-patients-with-primary-and-metastatic-brain-tumors

Drugs that lower seizure threshold

Medication class	Examples
Opioids	Tramadol, Meperidine
Antibiotics	Penicillin, cephalosporins, Fluoroquinolones
Anti-Cancer drugs	Busulfan, Cytarabine, Doxorubicin, Etoposide, Fluorouracil, Interferon alfa, Methotrexate, Cisplatin, Vincristine
Hypoglycemic agents	Any antidiabetic agent
Immunosuppressant agents	Cyclosporine, Mycophenolate, Tacrolimus
Psychiatric medications	Antipsychotics, Bupropion, Buspirone, Lithium, MAO-I, SSRI, SNRI, TCA

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Antipsychotics

Drug	EPS	↑ Prolactin levels	↑ Weight	Dyslipidaemia	PHT[a]	↑ QTc interval	Antimuscarinic effects	Sedation[a]	Seizures
Conventional antipsychotic agents									
Haloperidol	+++	+++	+	+	+	+	+	+	+
Thioridazine	+	++	++	++	++	+++	+++	+	+
Atypical antipsychotics									
Amisulpride	+	+++	+	?	+	+	–	+	+
Aripiprazole	+	↓	–	–	+	+	–	–	+
Clozapine	–	–	+++	+++	+++	+	+++	+++	+++
Olanzapine	+	+	+++	+++	+	+	+	++	+
Quetiapine	–	–	++	++	++	+	+	++	+
Risperidone	++[b]	+++	++	–	++	+	–	+	+
Ziprasidone	+	+	–	–	+	++	–	+	+
Zotepine	+	++	++	?	+	+	–	++	++

a Tolerance often develops.

b Largely relates to dosages >6 mg/d.

EPS = extrapyramidal symptoms, **PHT** = postural hypotension; **QTc** = QT interval corrected for heart rate; ↓ indicates decrease; ↑ indicates increase; – indicates minimal risk; + indicates small risk; ++ indicates moderate risk; +++ indicates high risk; ? indicates unclear risk.

There are important differences between atypical antipsychotics in the relative risk of adverse effects. Drugs Ther. Perspect 24, 19–22 (2008). https://doi.org/10.2165/00042310-200824100-00006

Differential diagnosis

- Syncope/convulsive syncope
- Arrythmia
- Cerebrovascular Disease
- Migraine
- Psychiatric disturbances
- Parasomnias
- Delirium

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Chemotherapy Induced Seizures

- Can be seen in regimens for bone marrow transplantation
- Some medications can cross blood-brain barrier to provoke seizures
- Some cause electrolyte abnormalities
- Chemotherapy can have medication interactions with certain AEDs
  - *Busulfan*
  - *Cisplatin*
  - *Vincristine*

Tradounsky 2013

Cerebrovascular Disease

- Risk factor for seizures secondary to coagulation abnormalities

- Ischemic stroke due to
  - *Tumor cell embolization*
  - *Endocarditis (bacterial and nonbacterial)*
  - *Head, neck and skull cancer compression to large vessels*

- Hemorrhagic stoke due to
  - *Coagulation disorders – liver dysfunction*
  - *Thrombocytopenia*
  - *Direct vessel infiltration*

Tradounsky 2013

RPLS or PRES

- Reversible posterior leukoencephalopathy syndrome
- Posterior reversible encephalopathy syndrome
- Seizures are typically generalized
- Can lead to status epilepticus

Treatment

- Must always weigh the risk of recurrent seizures vs side effects
- Patients without history of seizure do not benefit from prophylaxis
- Start AEDs once patient has experienced a seizure
- Use non CYP450 enzyme inducing AEDs – Keppra, Lamotrigine, Pregabalin, Gabapentin
- About one third of patients will have recurrent seizures requiring more than one AED

Dosing & Side Effects

Table 3. Anticonvulsant doses and side effects

ANTICONVULSANT	STARTING DOSE	USUAL EFFECTIVE DOSE	SIDE EFFECTS
Phenytoin	NA	200-500 mg/d in single or divided doses	Drug-drug interactions including dexamethasone, CNS (ataxia), liver, GI, dermatologic, hirsutism, anemia, osteoporosis
Carbamazepine	200 mg/d; increase by 200 mg/wk	300-1600 mg/d in 3-4 divided doses or 2 divided doses if long-acting	Drug-drug interactions, SIADH, CNS (sedation, vertigo, ataxia, diplopia), myelotoxicity
Valproic acid	15 mg/kg daily; 250-500 mg/d, increased weekly by 250 mg/wk	1000-3000 mg/d, up to 60 mg/kg daily (check serum levels) in 3 divided doses or 2 divided doses if long-acting; decrease dose if hepatic failure occurs	Drug-drug interactions, CNS (ataxia, tremors, sedation), weight gain, hair loss, GI, thrombocytopenia, liver toxicity
Oxcarbazepine	300-600 mg/d	900-2400 mg/d; decrease dose if renal failure occurs	Hyponatremia, dizziness, somnolence, nausea, ataxia, diplopia
Phenobarbital	NA	60-250 mg/d, maximum 600 mg/d (1-5 mg/kg in adults) in single or divided doses; decrease dose if renal or hepatic failure occur	Drug-drug interactions, CNS depressor, respiratory depression, somnolence, rash
Gabapentin	NA	300-3600 mg/d as monotherapy; up to 1800 mg/d as adjuvant therapy, in 3-4 divided doses; decrease dose if renal failure occurs	Interaction with antacids; decrease in memory and concentration; somnolence, ataxia, dizziness, edema, weight gain
Lamotrigine	50 mg/d for 2 wk, then increase by 25-50 mg/wk	100-500 mg/d in 2 divided doses; decrease dose if renal or hepatic failure occur	Rash, especially if dose escalation is rapid
Topiramate	25 mg/d; increase by 25-50 mg/wk	75-400 mg/d in 2 divided doses; decrease dose if renal failure occurs	Drug-drug interactions, somnolence, confusion, weight loss, metabolic acidosis, angle-closure glaucoma
Levetiracetam	750-1000 mg/d	1000-3000 mg/d in 2 divided doses; decrease dose if renal failure occurs	Anxiety, aggressivity, somnolence, asthenia, dizziness
Clobazam	10 mg/d	10-30 mg/d, maximum 60-80 mg/d in 2 divided doses	Same as for benzodiazepines; rash
Clonazepam	NA	1-6 mg/d in 2-3 divided doses	Same as for benzodiazepines; paradoxical excitation

CNS—central nervous system, GI—gastrointestinal, NA—not applicable, SIADH—syndrome of inappropriate antidiuretic hormone secretion.
Data from Beaulieu and Nadeau,[3] and Caraceni et al.[5]

Drappatz et al. UpToDate

Status Epilepticus

- Mortality is nearly three times higher in patients with brain tumors
- Treat with benzodiazepines as first line therapy
  - *Second line therapy – Levetiracetam, Phenytoin, Valproic Acid*

Dosing and routes for commonly used AEDs

Parenteral AED Dosing and Routes.

Drug	Status loading dose	Maintenance dose
Diazepam	0.2 mg/kg or 10-20 mg PR	20 mg PR nightly
Lorazepam	0.1 mg/kg IV, IM, or SC	
Midazolam	0.1-0.3 mg/kg IV or SC	Titrate to control refractory seizures if needed
Clonazepam	1 mg IV or SC	
Phenytoin	20 mg/kg IV	4-5 mg/kg/day IV divided TID
Fosphenytoin	20 mg/kg IV or IM	4-5 mg/kg/day IV or IM divided TID
Phenobarbital	10-15 mg/kg	1-3 mg/kg/day IV or IM 1200 mg/day SC (2)

Ariguzo, 2014. Treating Seizures. Available at: https://www.pdcrx.com/articles/treatingseizures

End of Life

- Seizures occur in 35 to 50% of brain tumor patients in last month of life.
- Consider dysphagia
- Change route of administration
- Use benzodiazepines as abortive medication

Drappatz et al. UpToDate

Case

- Abnormal movements aborted with Ativan 2 mg every 5 min for 2 doses and Keppra load of 3g.
- Labs all within normal limits
- Family did not want to continue further workup
- Concern for metastasis to brain
- Started on Clonazepam 0.5 mg daily and 1 mg nightly
- Discharged home with hospice on Clonazepam

Tumor Markers & Future Studies

- IDH 1 and 2 driver mutation
  - *IDH1 inhibitor – Ivosidenib*
  - *mTOR inhibitors – Rapamycin, Everolimus, Temserolimus*

- MGMT promoter methylation status

Hauff et al, 2023

Discussion

- What diagnostic and management strategies do you employ in your practice for patients with cancer having seizures?
- What seizure management challenges have you faced in patients at end of life?
- What are your preferences for first-line medications?

Resources

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