Neuropsychiatry of Epilepsy and Stroke

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Classifying psychiatric symptoms in epilepsy

Peri-ictal Symptoms – transient, temporally associated with seizure

- pre-ictal (seizure prodrome)
- Ictal
- post-ictal

Interictal Symptoms

- Chronic or transient
- May occur secondary to epilepsy treatments (ASM or surgical adverse effect, forced normalization)

Pre-ictal psychiatric symptoms

- Prodrome/Pre-monitory Symptoms - Minutes to days before seizure
  - Non-specific funny feeling, anxiety/irritability, dysphoria
  - Not necessarily predictive of seizure, may reflect recall bias or provoking factors

- Not to be confused with Aura - Seconds to minutes before loss of consciousness or motor symptoms
  - Aura = early ictal symptoms

Ictal psychiatric symptoms

	Symptom	Proposed Localization
Visual	Elementary visual hallucinations (phosphenes, colored spheres)	Occipital lobe
	Complex visual hallucinations	Occipitotemporal cortex, limbic structures
	Visual distortions (micropsia, macropsia, metamorphopsia)	visual association cortex (occipitotemporal, occipitoparietal)
	Out of body experience, autoscopy	Temporal-parietal junction
Auditory	Elementary auditory hallucinations (simple tones, buzzing sounds)	Transverse temporal gyri of Heschl
	Complex auditory hallucinations (music, speech)	Lateral superior temporal cortex
Other Special Senses	Vertigo	Temporal-parietal junction
	Olfactory hallucinations	Mesial temporal cortex
	Gustatory hallucinations	Insula
Somatosensory	Paresthesias, numbness, pain, thermal sensations	Contralateral parietal lobe somatosensory cortex
	Sensation of a shrinking or swelling body part	Non-dominant temporo-parieto-occipital junction
Experiential (emotional/ autonomic)	Fear	Amygdala
	Gastrointestinal sensations, autonomic Symptoms (palpitations, piloerection, urinary urgency)	Insula or limbic structures such as cingulate cortex or amygdala
	Déjà vu or jamais vu, depersonalization, derealization	Hippocampus/mesial temporal cortex
Cognitive/ Behavioral	Forced Thinking	Frontal lobe
	Ictal laughter (gelastic seizure)	Hypothalamus (hamartoma)
	Motor automatisms	Anterior cingulate cortex; may be a release phenomenon during temporal lobe seizures

Psychiatric symptoms with non-convulsive status epilepticus

- Types of seizures (Rohr-LeFlock, 1988)
  - Absence (32 cases): indifference, perplexity, mutism, poverty or slowness of speech
  - Temporal (9 cases): ideas of persecution (30%), anxiety/fear (44%), negativism (22%), irritability/aggression (56%)
  - Frontopolar (19 cases): smiling, hilarity, confabulations

Ictal panic vs. non-epileptic panic attack

	Panic attack (interictal)	Focal seizure with fear (ictal)
Duration of attack	More than 5 min	1-2 minutes
Course of attack	Crescendo course that peaks within 10 min	Sudden onset and offset
Stereotypic presentation	Changes in symptoms may occur	Very stereotyped presentation
Awareness during attack	Usually preserved	May be impaired as seizure progresses
Anticipatory anxiety	Common	Uncommon
Agoraphobia	Common	Uncommon
Post-attack confusion	Very rare	Possible
Trigger	Possible, but unprovoked attacks also occur	Uncommon
Age of onset	20s-30s	Any age
Family history of panic disorder	Common	Uncommon

Postictal psychiatric symptoms

Postictal State

- period between end of ictus and return to baseline, associated with EEG suppression, slowing
- usually lasts 5–30 minutes, can be prolonged
- hallmark is confusional state
- can also include other cognitive, behavioral and motor symptoms
- aggression can occur, generally reactive to misperception of threat
    - important to calmly orient patient, particularly before approaching

Postictal Psychiatric Symptoms

- Follow resolution of the postictal state

Postictal psychosis

- self-limited period of psychosis (majority resolve within a week)
- occurs following resolution of postictal state and subsequent period of lucidity (2 hours – 1 week, mean 2.5 days)
- most often seen following cluster of tonic-clonic seizures
- may include aspects of…
  - thought disorder
  - hallucinations
  - delusions
  - paranoia
  - affective changes (including manic sxs)
  - aggression (including suicidal behavior)

Postictal psychosis

- symptoms often fluctuate over time, may include confusional component

- Risk factors include:
  - Long duration of epilepsy
  - Bilateral interictal epileptiform activity
  - Bilateral ictal foci on EEG
  - Intellectual Impairment
  - *Family history* of seizures, mood disorders, or psychosis

- can be treated with antipsychotic medication or benzodiazepines
  - decrease risk and suffering
  - possibly shorten duration of episode

Non-psychotic postictal psychiatric symptoms

In a retrospective survey, 74% of patients reported at least one postictal psychiatric symptom (Kanner et al, 2004). Only 7% of those were psychotic symptoms.

43% reported symptoms of depression

62% reported neurovegetative symptoms

45% reported symptoms of anxiety

22% reported hypomanic symptoms

82% reported cognitive symptoms, but only 14% reported only cognitive symptoms

POSTICTAL SYMPTOM	PREVALENCE	MEDIAN DURATION in hours (range)
Symptoms of depression, total	**43**	
Irritability	30	24 (0.5 – 108)
Poor frustration tolerance	36	24 (0.1 – 108)
Anhedonia	32	24 (0.1 – 148)
Hopelessness	25	24 (1.0 – 108)
Helplessness	31	24 (1.0 – 108)
Crying bouts	26	6 (0.1 – 108)
Suicide ideation	13	24 (1.0 – 240)
Active suicidal thoughts	8	
Passive suicidal thoughts	13	
Feelings of self deprecation	27	24 (1.0 – 120)
Feelings of guilt	23	24 (0.1 – 240)
Neurovegetative symptoms, total	**62**	
Early night insomnia	11	-
Middle night awakening	13	-
Early AM awakening	11	-
Excessive somnolence	43	24 (2 – 72)
Loss of appetite	36	24 (2 – 148)
Excessive appetite	10	15 (0.5 – 48)
Loss of sexual interest (not related to fatigue)	26	39 (6 – 148)
Symptoms of anxiety, total	**45**	
Constant worrying	33	24 (0.5 – 108)
Panicky feelings	10	6 (0.1 – 148)
Agoraphobic symptoms	29	24 (0.5 – 296)
Due to fear of seizure recurrence	20	-
Compulsions	10	15 (0.1 – 72)
Self Consciousness	26	6 (0.05 – 108)

Interictal neuropsychiatric symptoms

- memory complaints (20-50%)
- dysphoria/depression (13.2-36.5%)
- anxiety (14.8-30.9%)
- psychogenic nonepileptic seizures (functional neurologic symptom disorder) (17%)
- psychosis (2-10%)

Interictal depression

- bidirectional relationship
- suicide far more prevalent than in general population (standardized mortality ratio of 3.5-5)
- depression is the single most important predictor of reduced quality of life in patients with recurring seizures
- Clinicians must differentiate from postictal mood changes, ASM side effects
- Pharmacotherapy considerations include drug interactions, risk of epilepsy exacerbation

Putative Biological Factors	• hyperactive HPA axis • neuronal and glial cell loss in mesial temporal and frontal lobe regions • neuroinflammatory changes • Increased glutamatergic and decreased GABAergic and serotonergic activity
Putative Psychosocial factors	• learned helplessness • burden of chronic disease • impact on independence, career, personal life • social stigma

Interictal anxiety

- bidirectional relationship

- PWE are at increased risk for
  - GAD (OR 1.5-4.7)
  - social anxiety disorder (OR 2.1-13.1)
  - agoraphobia (OR 1.2-8.7)

- Clinicians must differentiate from ictal and postictal anxiety, and ASM effect

Putative Biological Factors	• Amygdala kindling • Long-term potentiation of excitatory amygdala efferents • Neurotransmitter effects
Putative Psychosocial factors	• Unpredictable nature of seizures • Social rejection • Stigma • Fear of seizure/seizure phobia • Dispersed locus of control

Chronic interictal psychosis

- Epilepsy associated with almost 3-fold increased risk for schizophrenia-like psychosis *in the absence of a family history of schizophrenia.* Family hx of epilepsy and Fam hx of psychosis are both risk factors schizophrenia-like psychosis
- typically follows onset of epilepsy by a decade or more
- May exhibit a greater degree of affective symptomatology than is typical in schizophrenia, less likely to have negative symptoms
- Neurocognitive deficits similar to schizophrenia
- Postictal psychosis can progress to chronic interictal psychosis (10-15%?), not clear that this is evidence of causation
- More common in TLE than extra-temporal lobe epilepsy

Putative Biological Factors

- Focal and widespread structural abnormalities (e.g. dysplasias)
- Microstructural abnormalities in the limbic system (e.g. misguidance of mossy fiber projection in the hippocampus)
- Genetic factors (e.g. 15q11.2 BP1-BP2 microdeletion , LGI-1 gene loci)

Psychiatric effects of epilepsy treatment

- Forced normalization/alternate psychosis
- Positive and negative cognitive and behavioral effects of ASMs

Forced normalization

- In 1953, Landolt described a series of 107 patients with epilepsy and psychosis
    - In 47 of them, psychosis developed as EEG normalized
- Alternate Psychosis: psychosis emerges when seizures stop (Tellenbach)
- Must be distinguished from ASM side effect and postictal psychosis

Figure 1. Heinrich Landolt (1917–1971).

Pharmacotherapy considerations

- Antiseizure medications may have positive or negative cognitive and psychiatric effects
- Psychotropic medications may impact the seizure threshold (e.g. clozapine, bupropion)
- There may be interactions between ASMs and psychiatric medications
- Whenever possible, choose medications that may provide benefit for both seizures and psychiatric symptoms
- Whenever possible, choose ASMs that are less likely to worsen the patient's existing psychiatric problems and choose psychotropic medications that are less likely to worsen a patient's seizures

Potential psychiatric benefits from particular anti-seizure medications

Drug	Potential psychiatric benefit
Valproic acid	Acute manic and mixed episodes in bipolar I disorder* Maintenance in bipolar I disorder Impulsive aggression
Carbamazepine	Acute manic episodes in bipolar I disorder* Maintenance in bipolar I disorder Impulsive aggression
Oxcarbazepine	Acute manic episodes
Lamotrigine	Maintenance in bipolar I disorder* Acute depressive episodes in bipolar disorder Anger, affective instability in borderline personality disorder
Gabapentin	Insomnia Anxiety Alcohol dependence/alcohol use disorder
Pregabalin	Anxiety

*FDA approved indication

Psychiatric and cognitive adverse effects of anti-seizure medications

Lower Likelihood of Psychiatric Side Effects	Higher Likelihood of Psychiatric Side Effects	Lower Likelihood of Cognitive Side Effects	Higher Likelihood of Cognitive Side Effects
Lamotrigine* Lacosamide Eslicarbazepine Gabapentin Pregabalin Oxcarbazepine Carbamazepine Valproic acid*	Topiramate* Zonisamide* Levetiracetam* Perampanel* Phenobarbital Vigabatrin	Lamotrigine* Levetiracetam* Lacosamide Gabapentin Tiagabine Vigabatrin Rufinamide Perampanel* Eslicarbazepine	Phenobarbital Primidone Topiramate* Zonisamide*

*Broad spectrum

Suicide and suicidal ideation with ASMs: FDA alert

- FDA Alert in 2008 about increased risk of SI, suicide attempts, and completed suicides with ASMs
  - based on meta-analysis of 199 RPCT of 11 ASMs (FDA, 2008) showing risk of suicidality elevated for pts on ASMs (0.37%) compared to PCB (0.24%). Interpreted as a class effect
  - 27,863 patients in the drug arms and 16,029 patients in the placebo arms
  - When considered individually, only **LTG** and **TPM** showed a statistically significantly increased risk

Table 12: Events by Type and Treatment Arm, Placebo-Controlled Trials.

Event	Drug	Placebo	Total
Completed suicide	4	0	4
Suicide attempt	30	8	38
Preparatory acts	3	1	4
Suicidal ideation	67	29	96
Total	104	38	142

Notes: Events include only the most critical event for each patient.

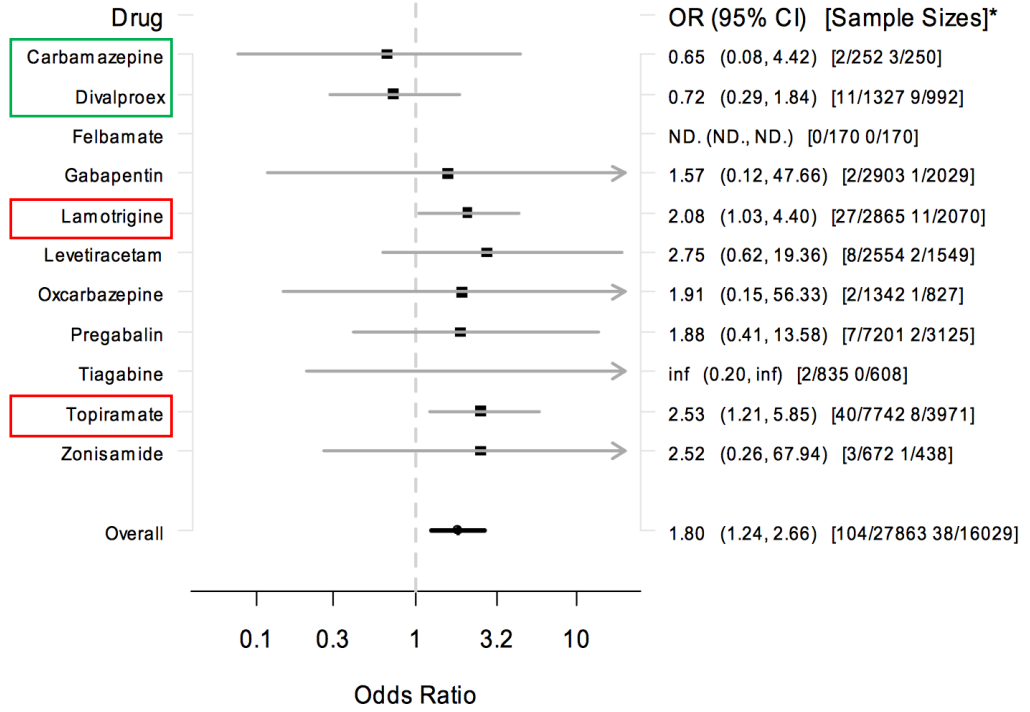

Figure 2: Suicidal Behavior or Ideation Odds Ratio Estimates, Placebo-Controlled Trials.

FDA, 2008

Suicide and suicidal ideation with ASMs

- BUT…
  - based on spontaneously reported AEs (not systematically collected data)
  - Lumped together drugs with different mechanisms and markedly different psychiatric profiles
  - LTG data surprising given its positive mood profile. Three additional LTG trials subsequently submitted including 9 suicidal events, 8 of which were in the PCB arm – when integrated with other data, LTG finding no longer significant

- More important risk factors for SI than ASM use include: history of psychiatric disorders and especially suicide attempts (30% risk for recurrence in an 8 year period)

Psychotropic medications that lower seizure threshold

- worst antipsychotic: clozapine
- worst antidepressant: bupropion, especially IR form
- worst TCA: clomipramine
- worst mood stabilizer: lithium
- worst benzodiazepine: alprazolam

- SSRIs are first line for anxiety and depression

Interactions between ASMs and psychotropic medications

- Beware of synergistic adverse effects, for example…
  - potential hematological toxicity from carbamazepine and clozapine
  - Potential for hyponatremia from SSRIs and carbamazepine, oxcarbazepine
  - Potential for weight gain on valproate and atypical antipsychotics

- Beware of pharmacokinetic interactions, for example…
  - Potential for fluoxetine to decrease clearance of carbamazepine
  - Potential for carbamazepine to increase clearance of olanzapine

Neuropsychiatry of Stroke

- Post-stroke Depression
- Post-stroke Apathy
- Post-stroke Psychosis
- Post-stroke Mania
- Post-stroke Pseudobulbar Affect

Post-stroke Depression

- Affects about 1/3 of stroke survivors, greatest risk in first year
- Phenomenology: Similar to primary depression, but diagnosis can be more challenging
- Most consistent predictor: physical/cognitive disability
- For left-sided strokes, may correlate with proximity of stroke to left frontal pole
- Prognosis
  - Early PSD usually remits by 1 year.
  - Late PSD (onset after 2 mo) tends to have a more protracted course
- Usually treated off label with SSRIs (fluoxetine may aid motor recovery)
  - Nortriptyline > fluoxetine > placebo
  - ECT

Post-stroke Apathy

- Must be distinguished from PSD.
  - Emotional indifference rather than low mood/sadness
  - Low motivation, decreased motor, verbal, behavioral output, anhedonia
- Pathophysiology: disruption of frontal-subcortical circuits connecting ACC and basal ganglia
- Rx: dopamine agonists, stimulants (but caution re cardiovascular s/e), cholinesterase inhibitors

Post-stroke psychosis

- Hallucinations and/or delusions after stroke in the absence of delirium.
- 12-year incidence 6.7%. Mean onset 6 months following stroke
- Risk factors: previous psych history, esp. depression, AUD, right hemisphere lesion, preexisting subcortical atrophy
- Typically presents as delusional disorder
- Rx: antipsychotics, but special considerations regarding side effects. Avoid, if possible, in elderly pts with dementia

Post-Stroke Mania

- Incidence: rare (0.4-1.6% of stroke patients)
- Heterogeneous lesion locations, but may be associated with right OFC, other limbic areas
- Rx: similar to primary manic episode, but caution with side effects of meds

Post-stroke pseudobulbar affect (A.K.A. Pathological laughing and crying)

- Frequent, brief, and intense bouts of uncontrollable crying and/or laughing
  - Mood incongruent or exaggerated response
- Associated with stroke, Alzheimer's disease, ALS, MS, PD, and TBI
- Caused by lesions that disrupt the neurocircuitry of emotional regulation and expression (frontal, parietal lobes, descending pathways to brainstem, subcortical cerebellar tracts)
  - Disruption of corticopontine projections/circuits
  - Release of subcortical systems mediating affect expression (i.e. hypothalamus, amygdala, PAG)

Summary

- Neuropsychiatric symptoms are an important aspect of epilepsy and stroke and may include affective symptoms, anxiety, or psychosis.

- Neuropsychiatric symptoms may be linked to seizures, seizure treatments or structural brain lesions. Biological as well as psychosocial factors are likely important mediators of these symptoms.

- Neuropsychiatric symptoms should be addressed as part of the comprehensive care of patients with epilepsy and stroke. This may require interdisciplinary collaboration between neurologists, psychiatrists, psychologists, nurses, and social workers.

Thank you!