Surgical and Nonpharmacological Treatment of Epilepsy

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DEFINITION OF PHARMACORESISTANCE ................................................................. 2
EPIDEMIOLOGY OF PHARMACORESISTANCE ......................................................... 2
MECHANISM OF PHARMACORESISTANCE ............................................................ 3
INDICATION ........................................................................................................... 3
  Referral to Epilepsy Center ............................................................................. 4
  Timing of Surgery ........................................................................................... 4
CONTRAINDICATIONS ........................................................................................... 5
DEFINITIONS OF SURGICAL ZONES .................................................................... 6
  Node vs. Network disease .............................................................................. 7
PRESURGICAL EVALUATION (NON-INVASIVE) .................................................... 7
  SCALP (SURFACE) EEG .................................................................................... 7
  NEUROIMAGING ............................................................................................... 8
    CT ................................................................................................................... 8
    MRI ................................................................................................................. 8
    FDG-PET ......................................................................................................... 8
    SPECT (single-photon emission computerized tomography) ....................... 9
    Subtraction Ictal SPECT CO-registered to MRI (SISCOM) ......................... 9
    Magnetoencephalography (MEG) ............................................................... 10
NEUROPSYCHOLOGICAL TESTING (NEUROPSYCHOMETRY) ............................ 12
CONFERENCE ....................................................................................................... 12
PRESURGICAL EVALUATION (INVASIVE) ............................................................ 13
  INTRACAROTID AMOBARBITAL (WADA) TEST ................................................ 13
    UAMS protocol ............................................................................................ 14
  INTRACRANIAL EEG ....................................................................................... 16
ALGORITHM (TREATMENT) ................................................................................... 16
  FOCAL EPILEPSY ............................................................................................ 17
    Mesiotemporal ............................................................................................ 17
    Nonmesiotemporal (neocortical temporal, or extratemporal) ..................... 17
    Algorithm .................................................................................................... 18
  GENERALIZED EPILEPSY ............................................................................... 21
    Genetic (s. idiopathic, primary) generalized epilepsy ................................. 21
    Lennox–Gastaut type (s. symptomatic, cryptogenic generalized epilepsy) .... 21
    Algorithm .................................................................................................... 22
PREOPERATIVELY .................................................................................................. 22
  AED .................................................................................................................. 22
TYPES OF SURGERY ............................................................................................. 23
  TEMPORAL RESECTIONS .................................................................................. 24
  LESIONECTOMY ............................................................................................... 24
  LESIONING ....................................................................................................... 24
  TAILORED NEOCORTICAL RESECTION ......................................................... 24
  MULTILOBAR RESECTION ............................................................................ 24
  MULTIPLE SUBPIAL TRANSECTIONS (MST) .................................................... 25
  HEMISPHERECTOMIES (FUNCTIONAL, ANATOMICAL) .................................... 25
  CORPUS CALLOSO Tomy ............................................................................... 25
  DEEP BRAIN STIMULATION (DBS) .................................................................. 25
  VAGUS NERVE STIMULATION (VNS) .............................................................. 25
RESPONSIVE NEUROSTIMULATION (RNS) ........................................................................................................... 25
TRANSCRANIAL MAGNETIC STIMULATION (TMS) ........................................................................................... 25
TYPE OF TREATMENT ACCORDING TO SEIZURE TYPE .............................................................................. 26
  Generalized seizures (Lennox - Gastaut syndrome) ......................................................................................... 26
  Seizure localized to bilateral or non-resectable temporal lobe ......................................................................... 26
  Extratemporal seizures .................................................................................................................................... 26
POSTOPERATIVELY ........................................................................................................................................... 27
  AED .................................................................................................................................................................. 27
  Before discharge .............................................................................................................................................. 27
SURGERY OUTCOMES ......................................................................................................................................... 27

Reading
D.J. Englot. A modern epilepsy surgery treatment algorithm: incorporating traditional and emerging technologies. Epilepsy Behav, 80 (2018), pp. 68-74,

DEFINITION of pharmacoresistance

Drug-resistant ≠ Treatment-resistant

N.B. pharmacoresistance is diagnosed by history taking!

Medical intractability (pharmacoresistant epilepsy)

A. Failed 2 medications

  2 trials of AEDs at optimal doses with appropriate medications are sufficient to consider referral of patients with focal seizure disorder for presurgical evaluation

  – Commission on Therapeutic Strategies of the International League Against Epilepsy (ILAE) definition (officially adopted at the ILAE’s 2009 meeting in Budapest, Hungary):
    "DRUG-RESISTANT EPILEPSY - failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.” – i.e. complete epilepsy control!

B. Failed 3 medications – obsolete!!!

  – some advocate at least 3 regimens, including 2 trials of high-dose monotherapy + 1 trial of 2-drug therapy.

  • these therapeutic trials can be accomplished within 6-12 months - depending on frequency of seizures at baseline (i.e. how quickly can see treatment results).
  • no rationale to try different medications with the same mechanism of action.

EPIDEMIOLOGY of pharmacoresistance

20-30% patients are not controlled adequately with AED!
  (= ½ of them are potential surgery candidates)

Prevalence of pharmacoresistance: 17% (if count > 1 sz / month) or 26% if count > 1 sz / year)
• among all patients with epilepsy, 60-70% are expected to become seizure-free with AEDs:

  - 47% of patients respond to first AED
  - additional 14% respond to second AED
  - additional 3% respond to third AED
  - 36% of patients are refractory


N.B. development of new medications did not change these figures! (same numbers in 2008 Kwan and Brodie study)

Response to first AED is most important predictor of drug-resistant epilepsy!

• another study showed slightly more optimistic results: 18.5% and 16.5% were made seizure free with a third and fourth AED, respectively, and decreased to 0% after 5 or 6 previous AED failures.


• CRT (16 U.S. centers) of 38 patients with mesial temporal lobe epilepsy of < 2 years duration who failed 2 brand-name AEDs: 0 of 23 patients assigned to continued medical optimization achieved seizure freedom with drug adjustments alone during 2 years of follow up (vs. 11 of 15 in the surgical group became seizure free).


• positive therapeutic expectations of AEDs vary according to epileptic syndrome:
  - 80-90% of patients with idiopathic generalized seizures are expected to become seizure-free;
  - only 50% of patients with focal seizure disorders are expected to become seizure-free (seizure-freedom may decrease to 30% in cases of temporal lobe epilepsy secondary to mesial temporal sclerosis or be as high as 95% in cases of benign rolandic epilepsy of childhood).

**MECHANISM of pharmacoresistance**

- remains incompletely understood.

  **Target hypothesis** - changes in the AED targets, such as ion channels, lead to decreased drug efficacy.

  **Transporter hypothesis** - efflux pumps are thought to restrict AED movement into cells and to be overexpressed in patients resistant to AEDs; P-glycoprotein (Pgp) is one such multidrug transporter that has been implicated in drug-resistant epilepsy.

**INDICATION**

- seizures refractory to appropriate medical management + seizures seriously limit patient's activities* + well-defined epileptogenic focus not involving eloquent cortex**.

  * patients' quality of life must be included (e.g. even as few as 2-3 seizures year may be disabling to individual whose occupation requires transportation with motor vehicle; vs. homebound patients who are not physically harmed by their seizures).
Surgical Treatment of Epilepsy

**cortical resection must not intentionally produce significant neurologic deficit such as aphasia or hemiparesis; this is obsolete – RNS / DBS / VNS can treat those!**

N.B. pharmacoresistance per se is not an indication for surgery!

**DRUG-RESISTANT ≠ TREATMENT-RESISTANT**

Make sure it is epilepsy and not something else (once a while a mistake is made when cardiac arrhythmias mimic epilepsy)

- Complex partial seizures or partial seizures with secondary generalization are seizure types most amenable to surgical resection

Today, most “ideal” pathology for surgery is right-sided temporal lobe epilepsy.

N.B. temporal lobe epilepsy is most medical refractory but surgical results are the best!

- studies show that surgical results for frontal lobe epilepsy are also good.

**Referral to Epilepsy Center**

- given that individuals who have continued seizures after treatment with ≥ 2 AEDs has failed are very unlikely to achieve seizure freedom with medical treatment alone, guidelines recommend that these patients be referred to a comprehensive epilepsy center.


Patients in whom ≥ 2 AEDs (appropriately chosen and tolerated) have failed to completely control epilepsy (sustained seizure freedom) should be considered drug resistant and referred to a comprehensive epilepsy center for surgical evaluation

**National Association of Epilepsy Centers >>**

- if you see a family doctor, and you are continuing to have seizures, you should ask for another opinion after 3 months.

- if you are seeing a neurologist, and the seizures have not been brought under control after 9 to 12 months, then you should ask for a referral to a specialized epilepsy center.

- NAEC recommends that patients whose seizures are not fully controlled after treatment for one year be referred to a level 3 or 4 specialized epilepsy center. In addition, patients may benefit from the advanced care provided by epilepsy centers if they continue to have seizures despite treatment with two medications, experience unacceptable side effects or are pregnant or want to become pregnant.

**Timing of Surgery**
Surgery should be *performed as early as possible*!!! (surgery is no longer therapy of last resort)

Epilepsy is progressive disease! (kindling, new foci, network damage)

- intractable seizures, the longer they persist, portend poorer prognosis for seizure remission and psychosocial outcome (e.g. "mirror" foci can become established as independent foci).
- strategy of trying all combinations of drugs is not acceptable in syndromes known to have excellent chances of benefiting from surgery.
- it is especially important in *children*, when epileptogenic discharges interfere with normal development! (language can shift to opposite hemisphere if surgery is performed while patient is < 6 years).

N.B. even patients only few months of age are treated surgically if surgery is treatment of choice!

Despite reported success, surgery for pharmacoresistant seizures is often seen as a last resort. Patients are typically referred for surgery after 20 years of seizures, often too late to avoid significant disability and premature death.

- neurosurgery in patients’ minds is notorious for poor outcomes and mortality in severe TBI, malignant tumors, vascular pathology.
- patients don’t know that neurosurgery for epilepsy is very safe (made possible by technological advances and multidisciplinary team work).

Tell patients about the risk of SUDEP in uncontrolled epilepsy! It is not to scare your patient; it is your obligation (“I am obligated to tell you about SUDEP, the same as I tell my patients about diagnosis of cancer and life expectancy”)

Do not delay neuromodulation – involved networks may get damaged as time goes.

Given results of Brodie (2000) and Schiller (2008) studies, timing of surgery should be individualized:
- for MTS in which the seizure-free rate is high and the risk low after both ablative and resective surgery, surgery may be considered *earlier, that is, after 2 drug failures*.
- when the chance of seizure freedom after surgery is possibly lower, such as in the *absence of MTS*, and risk is correspondingly higher in the setting of preserved neurocognitive functions, ablative surgical treatment might be delayed until *after a more exhaustive regimen of AEDs or neuromodulation have been attempted*.

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**CONTRAINDICATIONS**

1) benign partial childhood epilepsy  
2) significant noncompliance  
3) progressive neurologic diseases  
4) severe concurrent medical illness  

Relative contraindications:  
1) generalized epilepsy (indication for corpus callosotomy or VNS or DBS)  
2) mental retardation / low IQ (< 70)  
3) psychiatric disease (psychosis or other serious psychiatric disorder)  
4) multiple seizure types arising from different brain regions (unless one seizure type is most frequent and disabling)  
5) coexistence of epileptic and nonepileptic seizures.

Not contraindications:
1) epileptogenic focus in dominant hemisphere  
2) epileptogenic focus in eloquent cortex  
3) bilateral or multifocal epileptogenic foci (although surgery is rarely considered for seizures arising from > 1 epileptogenic focus)  
4) neurological deficits on examination  

**DEFINITIONS of surgical zones**

**Epileptogenic lesion s. Seizure Onset Zone (SOZ)** – lesion / area able to produce seizures; needs to be included in resection.

**Epileptogenic zone (EZ) (ictal onset zone + ictal forming zone)** – cortical area that needs to be resected (in order to make patient seizure free); may be larger than lesion (includes lesion and surrounding margin, sometimes extends beyond brain lobe boundaries; e.g. cavernoma itself is not epileptogenic but adjacent hemosiderin-lade cortex is) – epileptogenic zone may be larger than lesions visible on MRI (H: intracranial EEG).  

N.B. it is essential to resect EZ and not just SOZ

**Irritative zone** – cortical area generating epileptiform discharges but whose resection is not necessary*; usually larger than epileptogenic zone.  

*irritative spikes cease after surgical resection of epileptogenic zone!

**Symptomatogenic zone** – cortical area that produces clinical symptoms but whose removal is not necessary (e.g. seizures may begin silently in frontal lobe and produce typical temporal lobe complex partial seizure when discharge has spread there); cortical stimulation studies have shown that often region producing auras is much larger than epileptogenic zone.

**Functional deficit zone** – cortical area showing hypometabolism on FDG-PET; much larger than epileptogenic zone (e.g. in medial TLE, hypometabolism involves both medial and lateral temporal lobe cortex ± subtle regions of hypometabolism in frontal lobe).
**Surgical Treatment of Epilepsy**

**Node vs. Network Disease**

There are proponent experts in each theory.

- **generalized epilepsy** – EZ (node) is entire brain *(meganode)*
- **why some patients become seizure free after callosotomy** if it is node disease - two nodes across corpus callosum **can no longer synchronize** oscillations.
- **focal epilepsy** – small local network *(mininet)*.

*Definition for focal epilepsy: seizure onset at ≤ 4 contiguous contacts*

**Presurgical Evaluation (Non-Invasive)**

- goal is to define **Epileptogenic Zone**.

*Surgical treatment is presently limited by our inability to localize epileptogenic focus.*

**Scalp (Surface) EEG**

All surgical candidates should begin presurgical evaluation with **EEG-audio-video monitoring** to record actual seizures *(weaning from anticonvulsants* may be necessary) – so called **Phase I Monitoring**.

N.B. **seizures** may begin in areas distant from (or even contralateral to) location of **interictal** epileptiform activity - **ictal discharges** are most reliable means of localization!

- since it is **impossible to record from all cortical & subcortical structures** from which seizures may arise, exact onset may not involve recording electrodes until spread of discharge has occurred (i.e. early ictal changes are often not identified in scalp recordings).
• foci in *mesial* or *basal* cortical areas are particularly apt to escape detection; *extratemporal seizures* are more difficult to localize (e.g. epilepsy of occipital or frontal lobe origin may have interictal activity at temporal region).

• **modified electrode placements, dense array, and semi-invasive techniques** increase yield.

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**NEUROIMAGING**

see also p. E1 >>, p. E9 >> (temporal lobe epilepsy, diagnosis)

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**CT**

- it is now replaced by MRI (only need for high-resolution CT is for intraoperative neuronavigation)

• seizure focus may enhance with IV contrast shortly following a seizure.

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**MRI**

*All patients* with partial epilepsy should undergo MRI without and with IV contrast.

• there is software (e.g. FreeSurfer) for automated cortical thickness analysis.

N.B. MRI and ictal EEG can be discordant or negative in up to 40% of potentially preoperative cases!

**Tractography**

- displays of optic radiations and pyramidal tracts are the most relevant for epilepsy surgery.

**Resting state fMRI** – network analysis; becoming popular for developing surgical strategies.

• TLE patients have different subcortical connectivity seen on rs-fMRI (“recovers” after successful surgery).

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**FDG-PET**

- determines *functional deficit zone* in some patients with partial epilepsy.

• shows hypometabolism lateralized to side of temporal lobe focus in 70% of patients.

  N.B. PET often shows hypometabolism in temporal lobes of pediatric patients – ignore it (esp. if symmetric)

• FDG is made in an expensive medical cyclotron and "hot-lab" (automated chemistry lab for radiopharmaceutical manufacture), and then delivered immediately to scanning sites because of the natural short (110-minute) half-life of Fluorine-18.

• *not necessary* in most surgical workups, because PET:
  - has highest accuracy for temporal lobe foci, which are diagnosed most easily with MRI and EEG.
  - is least reliable for extratemporal nonlesional foci, which also are most difficult to define with MRI and standard EEG.

• indications:
  a) discordant MRI and EEG findings
  b) normal MRI findings.

• PET can be combined with *simultaneous EEG* – helps to avoid false lateralizations from *hypermetabolism* due to unrecognized ictal / postictal events as well as frequent interictal epileptiform discharges.
SPECT (SINGLE-PHOTON EMISSION COMPUTERIZED TOMOGRAPHY)
- gamma-emitting tracer used is 99mTc-HMPAO (hexamethylpropylene amine oxime) - emits gamma rays that can be detected by a gamma camera.
  - HMPAO allows 99mTc to be taken up by brain tissue in a manner proportional to brain blood flow (i.e. SPECT is assessment of regional cerebral blood flow in 3D).
  - SPECT is more widely available (than PET), because the radioisotope is longer-lasting and far less expensive.

**Interictal SPECT** - shows hypoperfusion; resolution is inferior to that of PET.

**Ictal SPECT** - hyperperfusion during seizure - high localizing value* (only if ictal injection occurs within 20 seconds of ictal onset - then may scan within next several hours).

*accuracy is not sufficient to justify routine use

**Subtraction Ictal SPECT CO-REGISTERED TO MRI (SISCOM)**
- much higher accuracy than either ictal or interictal SPECT! (may provide alternative to depth electrode studies)
  - requires two SPECT scans (separated by ≥ 48 h to accommodate radionuclide washout) - during *interictal* period and *within seconds of seizure onset*.
  - using computer software, these scans are subtracted from each other.
  - subtracted scan then can be co-registered onto MRI to provide support for focus location.
N.B. in *MRI-negative* cases, reliability of functional neuroimaging is much reduced, and positive result from *functional imaging* generally requires verification by *depth electrode recordings*!

**Magnetoencephalography (MEG)**
- emerging method for 3D detection of deep epileptic foci; records magnetic fields produced by brain electrical activity; requires sophisticated suite (well isolated, far from highways).
Identifying Epileptic Spikes
(Merrifield et al., 2007)

Right Temporal Lobe Epilepsy
50,000 neurons need to fire to generate a Readable signal.

Neurons near the outside of the brain generate the strongest signals.

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<tr>
<th><strong>NEUROPSYCHOLOGICAL TESTING (NEUROPSYCHOMETRY)</strong></th>
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<td>• routinely, all surgical candidates undergo extensive neuropsychological testing.</td>
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<td>• testing is not standardized between centers.</td>
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<td>• test battery contains:</td>
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<td>1) <strong>personality</strong> inventory (e.g. Minnesota Multiphasic Personality Inventory)</td>
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<td>2) tests of <strong>memory</strong> and <strong>language</strong></td>
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<td>3) tests for <strong>interhemispheric transfer</strong> (before callosotomy) - cross-retrieval and naming of objects, cross-replication of hand postures, cross-localization of fingertips.</td>
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<td>4) other tests, depending upon interests of neuropsychologist.</td>
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<td>• goals of testing:</td>
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<td>1) to help <strong>localize epileptogenic focus</strong> (subtle deficits in cognitive functioning might provide additional localization that neurologic examination misses); it is not reliable because very few tests reliably measure frontal and temporal lobe function.</td>
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<tr>
<td>2) identification of <strong>significant cognitive problems</strong> (e.g. memory problems - might not be a candidate for temporal lobectomy).</td>
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<tr>
<td>3) predicting <strong>postoperative cognitive deficits</strong>.</td>
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<td>4) formulating <strong>postoperative vocational goals</strong>.</td>
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<th><strong>CONFERENCE</strong></th>
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<td>• final results of noninvasive testing (phase I) are presented to <strong>multidisciplinary epilepsy surgery conference</strong> (neurologist specializing in epilepsy, epilepsy neurosurgeon, neuropsychologist, epilepsy nurse, speech pathologist, neuroradiologist, and psychiatrist).</td>
</tr>
</tbody>
</table>
Conference decides on:
1) need for WADA test (phase II)
2) need for intracranial EEG (phase III)
3) surgical plan

- in most scenarios, there are several reasonable options, which are not mutually exclusive, and some differences among centers, and even among epileptologists, are expected - this is why all comprehensive epilepsy centers make decisions after discussions at multidisciplinary conferences.

PRESURGICAL EVALUATION (INVASIVE)

**Intracarotid Amobarbital (Wada) test**

- so called **PHASE II TESTING**
- injection of 100-150 mg SODIUM AMOBARBITAL (AMYTAL®) / PROPOFOL into carotid artery - to temporarily anesthetize (inactivate) hemisphere in ipsilateral carotid artery distribution (includes amygdala and anterior hippocampus) - allows independent testing function of contralateral hemisphere.

Clinical uses (once epileptogenic focus has been identified) - injection ipsilateral to epileptogenic zone:

1. Which hemisphere contains **LANGUAGE function** (dominant hemisphere inactivation → aphasia; nondominant → dysarthria); fMRI is much less useful here.
2. Functional adequacy of contralateral hippocampus to **sustain MEMORY** (before anterior temporal lobectomy to avoid permanent amnesia).
   - N.B. failure of memory function is contraindication to resection of hippocampus and parahippocampal structures on injected side!
   - Some experts believe that WADA is more important for temporal neocortical resections (and not so much for SAH).
3. Prognosing **seizure-free OUTCOME**.

- instruct patient as to what is expected.
- catheter is passed from femoral artery (as for standard carotid arteriograms).
- **4-vessel arteriography** must verify that blood flows to corresponding hemisphere (not to brainstem or contralateral side – i.e. no cross flow, no persistent trigeminal artery – will cause brainstem failure)

N.B. fetal PComA is not contraindication but will cause cortical blindness.
N.B. significant cross-flow is relative contraindication to anesthetizing side of dominant supply (patient goes to sleep).

- start on side of lesion.
- have patient hold both arms in air and count loudly - **contralateral hemiparesis** and **ipsilateral EEG slowing** (> 50%) must appear (confirmed adequacy of injection); if not add 25 mg more of drug.
- inject Amytal rapidly; effect starts almost instantaneously, begins to subside after ≈ 8 minutes.
- patient is monitored to make certain that **recirculation** has not affected both sides simultaneously during testing.
• assess **language** by showing patient pictures of objects and ask them to name each one out loud and remember each one.
• assess **memory** by asking patient to name as many of pictures as they can 15 minutes after test: if they have difficulty, ask them to pick out pictures from a group that contains additional ones not shown to patient.
• may repeat procedure on other side (use lower Amytal doses with each subsequent injection).
• never has been standardized, but many centers insist on Wada tests even when clearly right-handed patient is diagnosed with right temporal focus.
• **possible future alternatives to Wada test** – fMRI, magnetoencephalography, H$_2^{15}$O-PET.
• **caveats:**
  — Wada test may be grossly inaccurate with high flow AVM.
  — portions of hippocampus may be supplied by posterior circulation (not anesthetized by ICA injection).

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**UAMS PROTOCOL**

**Prerequisites:**
Providers-Neurology, Neuropsychology and Interventional Neuroradiology
Location: IR suite
Ancillary: EEG tech with vEEG setup (full montage)
Medication: Amytal (amobarbital sodium preparation) (at least 1 vial for each side)

**Team member specific considerations**

**EEG tech**
1. Must be vEEG (live) with patient’s face and hand in clear unobstructed view
2. Audio recording should be ON with appropriately placed microphone
3. EEG tech at the machine side annotating the record
   a. Injection times
   b. Delta slowing
   c. 50% delta-theta reduction
   d. Strength assessment by MD
   e. EEG return to baseline
4. EEG screen should also be clearly visible to the Epilepsy MD
5. Perform a baseline at least 15 min recording before the start of the procedure (during baseline assessment by Neuropsychology, prepping etc)

**Nursing**

**Amytal (amobarbital sodium preparation)**
1. Needed 20 cc of sterile water and 500 mg of amobarbital for EACH side
2. Reconstitute **MAXIMUM** 30 min before use
3. Add 5 cc of sterile water to amobarbital vial.
4. **Do not shake.** Only rotate vial.
5. The dose should also be mixed and allowed to **dissolve for > 5 minutes.**
6. Withdraw solution into a 25 cc syringe
7. Wash amobarbital vial with additional 5 cc of sterile water. Withdraw into 25 cc syringe containing first 5 cc or amobarbital solution
8. Add another 10 cc sterile water to 25 cc syringe containing amobarbital solution. Mix
9. **Final concentration:** 25 mg/cc
10. Carefully note and label the syringe with the time the medication was mixed.
11. Discard if not clear in 5 minutes and discard if a precipitate forms.
12. Attach **0.22 micron filter (yellow disc)** to Amytal syringe. **Give 6 ml (150 mg) Amytal to IR MD by pushing** it through the 0.22 micron filter (not pulling up through filter) into 12 ml sterile syringe MD is holding.

13. Amytal once mixed it must be used within 30 minutes. Be prepared to mix a second dose.
   - The time gap between two sides injection must be minimum 30 min and preferably 40 min so the previously reconstituted via CANNOT be used for the other side.

14. Usual injection Amount
   - First injection (either side); 3 ml (75 mg)
   - Repeat injections in 1 ml (25 mg) bolus up to 3 ml (75 mg)

15. Patient’s both hands should be out of the sterile field and freely accessible to Epilepsy MD for testing

IR MD
1. Baseline assessment by Neuropsychology before catheter placement
2. Patient’s both hands should be out of the sterile field and freely accessible to Epilepsy MD for testing
3. Side planned as the surgical side to be injected first.
4. Pre (amytal)-injection contrast run-through
   - Cross-filing?: Yes/ No
   - Fetal PCOM?: Yes/ No
5. Pre-injection assessment by Neuropsychology (please see below)
6. Re-explanation of strength testing to the patient by Neurology MD
7. Patient to raise both hands in air and count from 1 to 20 at a paced rate
8. Inject at cue of Epilepsy MD around Count ~ #5-6
9. Inject 3 cc (75 mg) over 3-4 seconds
   - If flaccid contralateral hemiparesis does not occur after 5 secs, inject additional 1 cc (25 mg – total 100 mg)
   - If flaccid contralateral hemiparesis still does not occur after 5 secs, inject additional 1 ccs (25 mg – total 125 mg).
   - If flaccid contralateral hemiparesis still does not occur after 5 secs, inject remaining 1 ccs (25 mg – total 150 mgs).
   - If flaccid contralateral hemiparesis still does not occur, stop procedure and check catheter position.
     - If the lack of hemiparesis was due to inappropriate catheter placement, wait 45 minutes from initiation of injection, then repeat the original injection sequence.
     - If catheter placement is appropriate, wait 45 minutes from initiation of injection.
       1. Draw up 175 mg (7 cc) in 10 ccs sterile water. Hand inject 6 cc (150 mg) over 4 seconds. If flaccid contralateral hemiparesis still does not occur after 5 secs, inject the final 1 cc (25 mg).

- Usual range of Amytal dose 75-125 mg
- Preferred maximum dose: 150 mg
- Absolute maximal dose: 175 mg
- Time difference between two side injections, minimum 30 min (or complete recovery, whichever is later) preferably 40 min.

Neurology MD
1. Baseline strength or arm, sensation, vision AND grip
2. Contralateral hemiparesis achieved? Yes/ No __/5
3. Check grip strength
4. Speech arrest? Yes/ No
5. Amytal effect on EEG
SURGICAL TREATMENT OF EPILEPSY

a. Delta/theta slowing (ipsilateral)?
b. 50% reduction of EEG delta/theta ipsilateral to injection (or primarily theta background): for memory item presentation by Neuropsychology

6. Regularly check strength (may need repeat dose if strength improving fast)
7. No items presented after strength had recovered to three-fifths in the hand contralateral to injection.
8. Repeat Neuro exam between side injections

- Time difference between two side injections, minimum 30 min (or complete recovery, whichever is later) preferably 40 min.

Neuropsychology
1. Once the patient is arrived and prior to beginning of procedure (catheter placement) approximately 5-10 minutes of baseline testing
2. Rule out cross-filing and fetal PCOM before Amytal injection
3. Two minutes prior to injection the first test stimulus is shown
4. One minute prior to injection the second test stimulus is shown
5. Re-explanation of strength testing to the patient by Neurology MD
6. Patient to raise both hands in air and count from 1 to 20 at a paced rate
7. Inject Amytal at cue to Epilepsy MD ~ at Count #5-6
   a. Neurology MD to assess and confirm
      i. Hemiparesis
      ii. EEG ipsilateral delta slowing
8. Neuropsychology and neurology run Wada protocol (Neurology monitors strength and EEG; Neuropsychology does language/memory testing per Emory Clinic protocol).
   - 50% reduction of EEG delta/theta ipsilateral to injection (or primarily theta background),
   - Per Neurology MD: Memory item presentation
9. No items presented after strength had recovered to three-fifths in the hand contralateral to injection.
10. Assessment of both spontaneous and recognition memory:
    a. After full motor recovery and return of a 10-s epoch of the patient’s usual baseline EEG frequencies.
    b. At 12 minutes post injection recognition memory testing occurs
- Time difference between two side injections, minimum 30 min (or complete recovery, whichever is later) preferably 40 min.

INTRACRANIAL EEG
(subdural strips and grids, depth electrodes) – so called PHASE III MONITORING – only when noninvasive studies fail to adequately delineate epileptogenic zone. see p. E13 >>
• it may include Stimulation Cortical Mapping - determines areas of eloquent cortex that should not be encroached upon at time of operation. see p. E13 >>

ALGORITHM (TREATMENT)
Seizure semiology is extremely important in diagnosing ictal zone and seizure propagation network!
FOCAL EPILEPSY

- key dichotomies: temporal vs. extratemporal
  ↓
  mesial vs. neocortical
  – distinguishing mesial vs neocortical temporal may at times require intracranial EEG, but once that is done, the neocortical temporal group generally follows the same course as extratemporal.

MESIOTEMPORAL

Unilateral
- resective surgery or ablation is by far the treatment of choice.
- traditionally, en bloc resection of anterior lateral and mesial temporal lobes structures has been performed. However, the potential for neuropsychological decline (especially in dominant temporal lobe surgery) has led to the development of selective amygdaohippocampectomy (LITT of the mesial structures is an effective option).
- very rarely, neurostimulation may be preferable if memory is superior on that side, but this should be exceptional because a minor verbal memory decline is usually offset by seizure freedom.

Bilateral
- the issue is “how bilateral is it?” (continuum from minimal or weak evidence on one side, to definitely and clearly bilateral):
  a) high concern for bilateral disease (independent seizures on surface EEG, bilateral mesial temporal sclerosis (MTS) on MRI, conflicting lateralizing findings)
  b) low concern for bilateral disease (very rare interictal spikes on the opposite site)
  c) most often - anywhere in between high and low concern.
- options:
  a) straight unilateral resection
  b) bitemporal intracranial EEG
  c) high concern for bilateral disease* → neurostimulation with RNS (data may allow an eventual resection should there be a strong unilateral predominance).

* RNS is preferred over short-term intracranial EEG in order to ascertain lateralization based on a larger sample of seizures (hundreds), rather than on a limited number of seizures obtained in EMU (and usually on reduced doses of AEDs).

NONMESIOTEMPORAL (NEOCORTICAL TEMPORAL, OR EXTRATEMPORAL)

Lesional
Here, much of the approach depends on the nature of the lesion and, specifically, its suspected nature (tumor, vascular malformation, cortical dysplasia, etc.), size, location (with respect to eloquent cortex), and the degree of certainty (based on semiology and EEG) that the lesion is indeed causing the seizures. If the lesion is a suspected neoplasm, then its potential for evolution into higher grades becomes part of the equation, favoring resection for tumor reasons rather than epilepsy reasons. If the lesion itself is static and not concerning for a neoplasm, then lesionectomy has the highest probability of seizure freedom and will usually be preferred, with neurostimulation being a distant second choice, and probably only appropriate if the resection would involve critical eloquent cortex. Here, a partial resection can be combined with neurostimulation, though RNS can interfere with serial MRI surveillance of lesions. Another complicating factor in lesional focal epilepsy is the potential for dual pathology. Resection can be done with or without
intra cranial EEG or ECoG. Hemispherectomy represents an extreme example of lesional resection (e.g., hemimegalencephaly, Rasmussen’s Syndrome) and also belongs in this category.

**Nonlesional**
This scenario (neocortical + nonlesional) is the most challenging and a very common scenario at level-4 epilepsy centers.

A. Strongly lateralized (hemisphere known) Strong lateralization can be based on interictal discharges, ictal EEG, or seizure semiology (e.g., consistent head version prior to secondarily generalized convulsions). This scenario, most commonly frontal, will require intracranial EEG to cover the area in question (frontal, frontotemporal, parietal, occipital, etc.). Since the area is usually extensive, sEEG is increasingly preferred to subdural grids and strips, but both can be used.

B. Not confidently lateralized (hemisphere unclear) Such cases have often been referred to as “fishing expeditions.” In the past, they could only be pursued with abundant amounts of hardware (bilateral strips and grids), resulting in a higher rate of complications and a relatively poor outcome. For that reason, many centers have tended to not pursue these cases for possible resective surgery. The advent of sEEG, and especially frameless robot-assisted sEEG, allows better surveying both in space (numerous depth electrodes on both sides) and time (electrodes can remain in place for weeks with little morbidity). Therefore these cases can now be reasonably pursued, “displacing” palliative neurostimulation treatments. One approach here is initially bilateral frontotemporal sEEG, which after the first few seizures can be focused by adding depth electrodes on the confirmed side of seizure onset once clarified [24]. Subdural electrodes and sEEG can also be combined. In this scenario, neurostimulation is also a reasonable option, since it carries less morbidity and the chances of seizure freedom with resective surgery are lower than in temporal or lesional cases.

**Algorithm**
Medically refractory disabling focal seizures

\[
\begin{align*}
\text{Focus can be localized} & \rightarrow \text{NO} \rightarrow \text{VNS or DBS} \\
\text{How many foci} & \rightarrow 2 \rightarrow \text{RNS; more than 2 } \rightarrow \text{VNS or DBS} \\
\text{Safe to resect and cognitive risk is low} & \rightarrow \text{NO} \rightarrow \text{RNS (or multiple subpial transections?)} \\
\text{Will it be curative} & \rightarrow \text{NO} \rightarrow \text{RNS} \\
\text{Ablation (resection, laser, SRS, RF, FUS)} & \rightarrow \text{YES} \\
\end{align*}
\]

N.B. RNS data (in bitemporal epilepsy) may support later resection / laser ablation
Alternative algorithm
Alternative algorithm (fig. 60-2)
GENERALIZED EPILEPSY

GENETIC (S. IDIOPATHIC, PRIMARY) GENERALIZED EPILEPSY

- this group is usually not medically intractable, but it can be.
- occasionally, when bifrontal epileptiform discharges mimic generalized spike–wave complexes (“secondary bilateral synchrony”), distinguishing a GGE from a frontal lobe epilepsy can be challenging, and it is generally safer to err on the side of GGE and only pursue surgically if there is strong evidence for a focal onset.

LENNOX–GASTAUT TYPE (S. SYMPTOMATIC, CRYPTOGENIC GENERALIZED EPILEPSY)

- usually with cognitive impairment (developmental intellectual disability), neurologic abnormalities such as cerebral palsy, and characteristic EEG abnormalities.
- cause may be genetic, structural, or metabolic but is often unknown.
- this group can also be considered multifocal rather than “generalized” (epilepsy with ≥ 3 “foci” is equivalent to “generalized”).
Resective surgery and RNS are never options for the generalized epilepsies, but corpus callosotomy, VNS, and DBS can be. Technically, VNS for generalized epilepsy is off label in the US but is nonetheless one of the most common uses of VNS (endorsed by AAN guidelines). Corpus callosotomy is almost never performed in patients with GGE since they are usually mentally and neurologically healthy, but is a viable option for LGS type and while it is most often used in children, it can be performed in adults [45]. Corpus callosotomy can be partial initially and completed in a second phase. Compared with neurostimulation, corpus callosotomy is more invasive, more ambitious, and may have more immediate effects. Neurostimulation is less invasive than callosotomy (VNS less than DBS), and the therapeutic effect is delayed, taking weeks to months. Preferences to use callosotomy or VNS first vary, and both are acceptable strategies that are not mutually exclusive. Additionally, since both are palliative procedures, some patients will benefit from both sequentially. Very rarely, patients with LGS-type of generalized epilepsy with a lesion can benefit from a focal (lesional) resection.

Lastly, patients with true multifocal epilepsy, i.e., related to truly multifocal discrete lesions such as tubers or cavernomas, can be considered for resection if it is confidently proven that one lesion is the source of a majority of the seizures.

**Algorithm**

**PREOPERATIVELY**

**AED**

- **Valproate** can cause bleeding disorders - routinely check coags and bleeding time - if values are abnormal, decrease or discontinue* valproate and recheck values before surgery!
  * at least 3 weeks prior to surgery (replace with another medication).
- on surgery morning, patient receives usual medication dosage with few sips of water.
• some centers taper anticonvulsants, and completely D/C 1 day before surgery (???).

### TYPES OF SURGERY

**ABLATIONS S. RESECTIONS** *(curative)* - resection of seizure focus (up to entire hemisphere):
- 2) lesionectomy
- 3) neocortical resections

**DISCONNECTIONS** *(palliative)* - used when eloquent brain is involved to disconnect seizure focus from other functional parts of brain:
- 1) callosotomy
- 2) hemispherectomy
- 3) multiple subpial transections

**STIMULATION S. NEUROMODULATION**
- 1) RNS
- 2) DBS
- 3) VNS

Only 10-30% of pharmacoresistant patients are candidates for **resective** surgery (rest of patients – **neuromodulation**)

**Nodes vs. Networks** – biggest debate about *pathophysiology of epilepsy* and may affect *surgical philosophy* (lesion resection or stimulation with RNS vs. network disconnection by lesioning or stimulation with DBS / VNS).

Comparison of Neuromodulations:

<table>
<thead>
<tr>
<th>Feature</th>
<th>VNS</th>
<th>DBS</th>
<th>RNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed-loop</td>
<td>Partially (newer models may detect tachycardia)</td>
<td>No</td>
<td>Yes (detects electrographic activity)</td>
</tr>
<tr>
<td>Generalized or multifocal epilepsy</td>
<td>Yes (probably limited evidence)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Invasiveness (intracranial)</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Recording capability</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Indication for depression</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Positive effects on mood &amp; cognition</td>
<td>Yes</td>
<td>Unknown</td>
<td>Probably</td>
</tr>
<tr>
<td>Children</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>MRI (brain)</td>
<td>Yes (up to 3 T)</td>
<td>Yes (up to 1.5 T)</td>
<td>No (pending)</td>
</tr>
<tr>
<td>Side effects during stimulation</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Regulatory approval</td>
<td>The whole world (FDA in 1997)</td>
<td>USA (FDA in 2018),</td>
<td>USA (FDA in 2013) only</td>
</tr>
<tr>
<td>(2018 December)</td>
<td></td>
<td>Europe (CE mark),</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Canada, Australia</td>
<td></td>
</tr>
</tbody>
</table>
**Temporal Resections**

see p. E15 >>

**Lesionectomy**

– for **structural lesions** delineated by MRI ± **electrocorticography**.
  - most often in frontal lobe.
  - all larger arteries or veins adjacent to or crossing gyri should be preserved.
  - avoid resection of deep fiber pathways in white matter.
  - most common mistake is to remove only gross tumor and not immediate surrounding tissue (leaving epileptogenic tissue and clinical seizures).
    - e.g. small vascular abnormalities surrounded by hemosiderin can be extremely epileptogenic.
  - unilateral **insular** resection – no deficits to anticipate.

**Lesioning**

a) for **structural lesions** delineated by MRI ± **electrocorticography**.

b) for **disconnecting** (e.g. callosotomy)

Available modalities:

1. Laser ablation (LITT)
2. RF-ablation (e.g. guided by SEEG)
3. Stereotactic radiosurgery (SRS)
4. Focused ultrasound (FUS)

**Tailored Neocortical Resection**

– for **nonlesional extratemporal epilepsy** – resection guided by SEEG and/or intraoperative **electrocorticography**.

  Tailored - no two operations are identical!
  - epileptiform discharges recorded acutely during surgery define boundaries of cortical resection.
  - **eloquent cortical regions** are spared.
    *Brazilians call intraop ECoG as an alternative to SEEG in poor countries: ECoG uncovers (interictal spikes) and guides resection of “dormant” EZs that would emerge later if only “active” EZ was removed.

**Multilobar Resection**

a) corticectomy (resection of grey matter)

b) lobe excision (resection of grey and white matter)

c) lobe disconnection

d) combination.

  - usually involves **frontoparietal**, **parieto-occipito-temporal**, or **parieto-occipital lobes**.
• indications as for functional hemispherectomy.

**Multiple Subpial Transections (MST)**
see p. E17 >>

**Hemispherectomies (functional, anatomical)**
see p. E19 >>

**Corpus Callosotomy**
see p. E21 >>

**Deep Brain Stimulation (DBS)**
see p. E27 >>

**Vagus Nerve Stimulation (VNS)**
see p. E23 >>

**Responsive Neurostimulation (RNS)**
see p. E25 >>

**TRANSCRANIAL MAGNETIC STIMULATION (TMS)**
- cortical stimulation
  • results vary (some studies show ne efficacy).

Randomized Double Blind Sham Controlled Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Theodore (NIH) 2002 Neurology</th>
<th>Fregni (Sao Paulo) 2006 Ann Neurol</th>
<th>Cantello (Multicenter Italy) 2007 Epilepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>24</td>
<td>21</td>
<td>43</td>
</tr>
<tr>
<td>Sz Type /Location</td>
<td>Mesial TLE 10</td>
<td>Lateral TLE 10</td>
<td>Frontal 3</td>
</tr>
<tr>
<td>MRI</td>
<td>all lesions except MS were excluded</td>
<td>all malformation of cortical development (MCD)</td>
<td>Posttraumatic 6 MTS 5 Hemiatrophy 4 Cortical dysplasia 2 Tuberous Sclerosis 1</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------------------------------------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Stim Target</td>
<td>EEG identified seizure focus</td>
<td>MRI abnormality in 17, vertex in 4 with diffuse MCD</td>
<td>Vertex</td>
</tr>
<tr>
<td>Stim Parameters</td>
<td>1 Hz, 120% MT, 900 stim bid x 7 days</td>
<td>1 Hz, 70% max coil output, 1,200 stim/day x 5 days</td>
<td>0.3Hz, 120% MT, 1,000 stim/day x 5 days</td>
</tr>
<tr>
<td>Outcome</td>
<td>No sig diff in stim vs sham, trend for better results in neocortical</td>
<td>Stimulated 2 weeks 72% p=0.003 4 weeks 53% p= 0.002 8 weeks 58% p=0.001 Sham – no change</td>
<td>No effect</td>
</tr>
</tbody>
</table>

**TYPE OF TREATMENT ACCORDING TO SEIZURE TYPE**

**GENERALIZED seizures (LENNOX - GASTAUT syndrome)**

1. VNS – 44-67% response  
2. ANT DBS – Sante trial limited to CPE  
3. CM DBS – 0-100% response  
4. RNS – by definition excluded  
5. Hippocampal DBS - by definition excluded  
6. STN DBS- N/A  
7. TMS – N/A

**Seizure localized to BILATERAL or NON-RESECTABLE TEMPORAL LOBE**

1. VNS – 60-62.5% response  
2. ANT DBS – Sante trial - 44.2% response  
3. RNS - 74 % response in hippocampal epilepsy  
4. Hippocampal DBS – 25-100% response in hippocampal epilepsy  
5. CM DBS – not as effective on focal epilepsy  
6. STN DBS – too limited data  
7. TMS – probably ineffective for mesial TLE

**EXTRATEMPORAL seizures**

1. VNS – efficacy in focal epilepsy does not appear to be limited to temporal lobe  
2. RNS – 37% response rate in neocortical epilepsy  
3. CM DBS – not as effective on focal epilepsy  
4. ANT DBS – Sante trial did not demonstrate efficacy in this subgroup  
5. STN DBS – was efficacious in small #'s tested and FLE was main target  
6. TMS – may be effective for MCD  
7. Hippocampal DBS - N/A
Surgical Treatment of Epilepsy

POSTOPERATIVELY

- Patient is returned to seizure monitoring room in epilepsy unit (vs. overnight ICU).

AED

Patients generally need to remain on AED therapy (for ≈ 2 years); some continue to require AED therapy to remain seizure free (e.g. if pathology showed heterotopia, then other foci of heterotopia likely exist).

N.B. surgery is not indicated if patient expects to be AED-free!

60% of patients are able to stop all AEDs
- If patient is taking 2 AEDs, least effective drug is tapered after 1 year.
- If patient is seizure free at 2 years, remaining drug can be tapered.
- One seizure during or after withdrawal → resume single medication therapy.
- Postoperative seizures:
  - Seizures within first 24 hours ("honeymoon seizures") do not correlate with poor long-term seizure outcome - may be due to irritation and edema of tissues adjacent to resection (neighborhood seizures).
  - Convulsions in immediate postop phase are common in first 3-5 days, if they are stereotypic of seizures prior to surgery, they may indicate lower changes of success and seizure freedom, but otherwise, they are not of huge concern unless they do not stop.
  - Acute postoperative seizures (up to 1 week after surgical resection) are not counted as evidence of recurrent epilepsy
  - Seizures after 48 hours (with adequate serum AED levels) do not bode well for eventual outcome.

N.B. many patients may continue to have components of preoperative auras;
- Some may have occasional seizures for few years which then cease (wind down);
- Others may be seizure-free for few years, then have recurrence.

Alternative view – early withdrawal of AEDs - safe and does not affect long-term seizure outcome or cure, might unmask incomplete surgical success sooner (identifying patients who need continuous drug treatment and preventing unnecessary continuation of AEDs in others).
- If seizures recur postop, only minority do recur during AED withdrawal.
- If seizures recur, restarting AED helps regain control.

BEFORE DISCHARGE

1) Neuropsychiatric evaluation? (usually delayed for 6-12 months)
2) Serum anticonvulsant levels
3) EEG

SURGERY OUTCOMES

The only reliable predictor of seizure-free outcome – resection of lesional focus! (unclear if laser ablation qualifies for that)

- Goal of epilepsy surgery:
  - Palliative epilepsy surgery - seizure reduction (still can be very desirable for some patients, e.g. getting rid of convulsive seizures)
  - Radical epilepsy surgery - seizure freedom
• in medical therapy, > 50% reduction in seizures = success
• seizure control is assessed at 1, 3 & 6 most post op, and then annually.
  – 90% of seizures that recur do so within 2 years; per Dr. R. Gross – if seizures recur, they do it within 6 months (therefore, outcomes are measured earliest at 12 months).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Seizure Free (%)</th>
<th>Improved* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior temporal lobectomy</td>
<td>76</td>
<td>24.0-27.2</td>
</tr>
<tr>
<td>Amygdala-Hippocampectomy</td>
<td>68.8</td>
<td>22.3</td>
</tr>
<tr>
<td>Extratemporal cortical resection</td>
<td>25.0-60</td>
<td>18.2-35.2</td>
</tr>
<tr>
<td>Lesionectomy</td>
<td>66.6</td>
<td>21.5</td>
</tr>
<tr>
<td>Hemispherectomy</td>
<td>67.4-77.3</td>
<td>18.2-21.1</td>
</tr>
<tr>
<td>Corpus callosotomy</td>
<td>7.6-8.0</td>
<td>60.9-80.0</td>
</tr>
</tbody>
</table>

*50% reduction of seizure frequency

Long-term (> 5 years) outcome combining all kinds of epilepsy surgeries – 22% seizure free and no AEDs

• ablative surgery is associated with IMPROVEMENT in intelligence, in psychiatric and behavioral disorders, in social and vocational function (abnormal brain tissue resection may remove undesirable functional effects which are interfering with function of other cortical areas).

  N.B. cognitive function starts to improve after successful surgery but after the lag period
• parents often wonder whether their child's personality will change or if he / she will become more depressed or anxious after undergoing resection of temporal or frontal lobe surgery – surgery doesn't appear to have major effect on mood or anxiety in children, and some kids even do better.
• **RUNNING DOWN phenomenon** - gradual decline of seizures over several months or years until seizure freedom is achieved after surgery.

---

**Jerome Engel's classification of postoperative outcome:**

**Class I: Free of disabling seizures**
  A. Completely seizure free since surgery
  B. Nondisabling simple partial seizures only since surgery
  C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
  D. Generalized convulsions with AED discontinuation only
• class 1 includes patients with **residual auras**.
  1) auras do not bother patient if they are infrequent.
  2) depending on nature of auras (e.g. intense fear), they can affect quality of life.

**Class II: Rare disabling seizures** (“almost seizure free”)
  A. Initially free of disabling seizures but has rare seizures now
  B. Rare disabling seizures since surgery
  C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years
  D. Nocturnal seizures only

**Class III: Worthwhile improvement** (> 90% reduction)
  A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not < 2 years

Class IV: No worthwhile improvement (< 90% reduction)
   A. Significant seizure reduction
   B. No appreciable change
   C. Seizures worse

**ILAE classification of postoperative outcome:**

1. Completely seizure free; no auras
2. Only auras; no other seizures
3. 1-3 seizure days per year; ± auras
4. 4 seizure days per year to 50% reduction of baseline seizure days; ± auras
5. Less than 50% reduction of baseline seizure days; ± auras
6. More than 100% increase of baseline seizure days; ± auras

Factors predictive of freedom from seizures:

1. MRI-detectable lesion (unless functional constraints limit extent of resection); better temporal than extratemporal.
2. Concordant interictal epileptiform discharges.
3. More extensive resections.

**BIBLIOGRAPHY** for ch. “Epilepsy and Seizures” → follow this Link