

Management of Trigeminal Neuralgia

History

- Aretaeus of Cappodocia provided one of the earliest descriptions in 2nd century- first account of TN.
- 1756, the French surgeon Nicholas Andre coined the term “tic douloureux” .
- 1773- Fothergill described typical features of TN.
- 1820’ s- Charles Bell attributed this to disease of V nerve.

Epidemiology

- Incidence: 4-5/100,000
- Also known as *Fothergill's disease*/*Tic Douloureux*/*Suicide Disease*
- Female predominance (M: F = 1:2 -2:3)
- Mean age: 50 yrs

Clinical features

- *A diagnosis of TN is always based on the patient's clinical history.*
- Hallmark pain is agonising, paroxysmal and lancinating along one/ more divisions of V nerve.
- Pain is virtually always *unilateral*, most commonly in V₂ distribution.
- *Triggered by activities* such as chewing, speaking, swallowing, touching the face, or brushing the teeth.
- Periods of remissions and exacerbations

- Pain typically more severe in morning and disappears during sleep
- Pain relief when treated with carbamazepine.
- Pain free intervals are common- weeks to as long as years
- Recurrences are common- at the site of initial complaint
- Neurological examination is essentially normal except a slight degree of sensory loss (usually ipsilateral nasolabial fold commonly)
- Burning, aching pain with no trigger points- Atypical TN

Distribution of trigeminal neuralgia

V1 – 4%

V2 – 35%

V3 – 30%

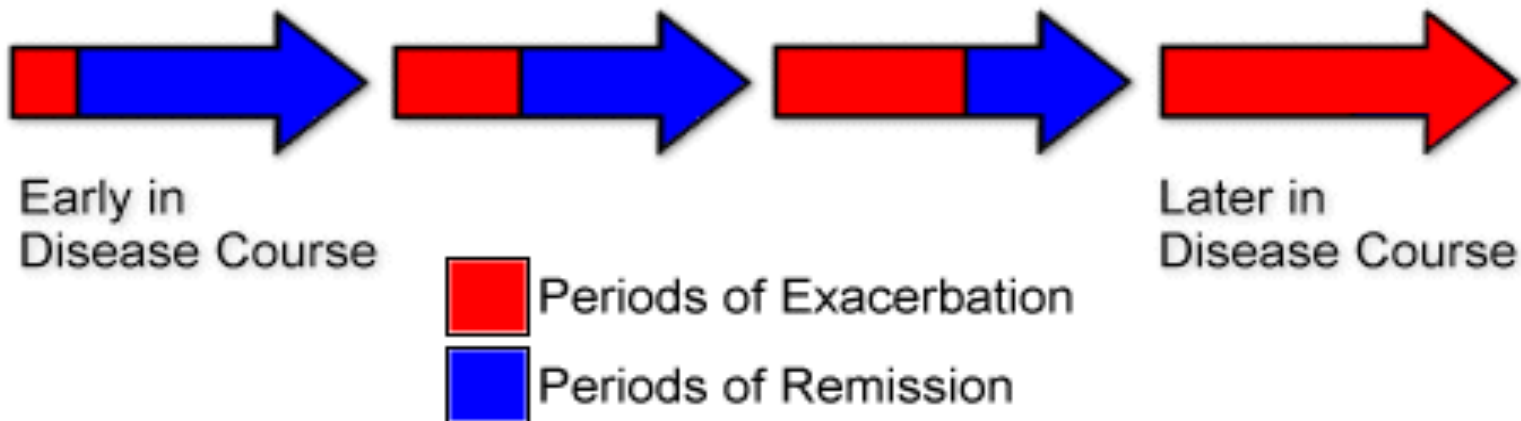
V1 AND V2 – 10%

V2 AND V3 – 20%

Pathophysiology

- Nerve injury
- Central and peripheral demyelination
- Ectopic action potentials in the sensory nerve root
- Paroxysmal, lancinating attacks

Progression of Trigeminal Neuralgia Over Time



- ***Etiology:***
- Idiopathic (Vascular loops)
- Tumours
- AVM, aneurysm
- Inflammatory- Multiple sclerosis, sarcoidosis, Lyme disease

- ***D/D***
- Glossopharyngeal neuralgia
- Post herpetic neuralgia
- Geniculate neuralgia (Hunt neuralgia)
- TM joint pain
- Cluster headache
- Dental, orbital pain or sinusitis



MANAGEMENT- *Investigations*

MR Imaging

- Most important imaging: Used to identify
 - Structural lesions (Cavernomas, V nerve schwannomas, meningiomas)
 - Vascular loops
 - White matter lesions in brain stem/ subcortical white matter(f/o MS)
 - If MS is suspected- then LP for oligoclonal bands and evoked potentials to be done.
- Good quality, thin (1 mm thick) section with contrast to be done.
- 3D CISS (Constructive interference in steady state)
- MR angio has 95% sensitivity and 100% specificity for identifying vascular compression .

Treatment

- Medical
- Surgical

Classes of drugs used in TN

- AED' s
 - Carbazepine/ Baclofen/ Phenytoin
- Antidepressants
 - Amitryptiline/ Nortryptiline
- Neuroleptics
 - Fluphenazine
- Opioids

Medical line

- **First line**

- Carbamazepine
- Phenytoin
- Valproate
- Baclofen
- Amitryptiline
- Nortryptiline

- **Second line**

- Gabapentin
- Oxcarbazepine
- Lamotrigine
- Topiramate
- Zonisamide
- Levetiracetam

AED's in TN

- Historically, potassium bromide used
- Later, phenytoin use described in 1942.
- Carbamazepine (1961)- ***Mainstay of medical therapy***
- Baclofen- only other effective first line drug.
- MOA- Enhance inhibitory neuronal activity in the trigeminal nucleus.
- No double blind RCT for drugs used in trigeminal neuralgia.

Carbamazepine (Tegretal/Mazetol)

- Use in TN first described in 1962.
- Shown to be effective in the treatment of TN in a number of studies
- Sodium-channel modulator
- *Initial response is virtually universal (If no response-then reconsider diagnosis)*
- Initial response rate- 80%; By 10 yrs it drops to 50%
- Dosing: Start at 200 mg/d. Add up to 200 mg in intervals of 4-5 days until pain relief. Typical dose 1200 mg/day
- Dose may need to be increased after several weeks because of auto-induction (as $t_{1/2}$ reduces)

Adverse effects- seen in 20-40% pts

- Neurologic- Ataxia, Dizziness, Diplopia, vertigo
- Systemic- GI irritation, hyponatremia, hypersensitivity, Asymptomatic elevation of liver enzymes , rarely severe hepatotoxicity
- Rare- **Aplastic anemia**, agranulocytosis, thrombocytopenia, and Stevens-Johnson syndrome.
- Drug interactions:
 - Level decreased by enzyme-inducing drugs
 - Level increased by erythromycin, propoxyphene, isoniazid, cimetidine, fluoxetine
- Monitoring: CBC, LFT, RFT
 - 2 weekly for 2 months
 - Later, 3 monthly

Baclofen

- Analogue of GABA
- Promotes segmental inhibition at the nucleus oralis of trigeminal brainstem complex.
- $t_{1/2}$ 3-4 hrs; renal elimination
- Synergism with CBZ/phenytoin
- 30% develop resistance in long term
- Dose: Start with 10 mg TDS, increase gradually; Typical maintenance dose: 50-60 mg/day
- Side effects: Somnolence/ dizziness/ GI distress
- Usually well tolerated- no life threatening A/E
- No known drug interactions
- Withdraw gradually (or else Seizures and hallucinations can occur)

Phenytoin

- Sodium channel blocker
- Also tried in TN but not that effective (25-60%)
- Dose 5-7 mg/kg/day
- Pain relief within 2 days of therapy

First generation drugs

- **Advantages:**
- Physician's familiarity with the drug
- Low cost
- Reasonable degree of efficacy
- These medications are present in most formularies
- **Disadvantages:**
- Complicated pharmacokinetics (often nonlinear)
- Higher levels of protein binding
- Narrow therapeutic indices
- Drug-drug interactions.

Second generation AED's

- Gabapentin
 - GABA analogue
 - Halts the formation of new synapses
 - Effective in cases resistant to traditional treatment modalities
 - Effective daily dose: upto 3 gm/day
 - Adverse effects: Dizziness, weight gain, peripheral edema, mood swings
- Pregabalin: Successor of Gabapentin
 - More potent, absorbs faster and greater bioavailability
 - 70% response rate within 6-8 weeks
 - Dose: 150-600 mg/day
 - *Obermann et al: Cephalgia 2008*

- Oxcarbazepine (Trileptal)-
 - Prodrug
 - As effective as CBZ
 - Less toxic, no hepatic enzyme induction, improved side effect profile
- Lamotrigine:
 - Acts presynaptically on voltage-gated sodium channels to decrease glutamate release.
 - Effective in refractory TN (as an add on drug to the combination)
 - Usually well tolerated
 - Most serious A/E- Stevens- Johnson syndrome

Drug	Dosage	Common side effect	Severe adverse reaction
Carbamazepine	Start with 100-300 mg/day Therapeutic range: 800-1200 mg/day	Dizziness/ somnolence/ nausea/ vomiting/ rash	Aplastic anaemia, Stevens- Johnson syndrome
Phenytoin	Start with 200-300 mg/day Therapeutic range: 5-7 mg/kg/day	Nystagmus/ Ataxia/ diplopia/ rash/ gingival hyperplasia/	Hepatitis/ Stevens- Johnson syndrome
Baclofen	Start with 30 mg/ day Therapeutic range: 50-60 mg/day	Lethargy/ Ataxia/ GI distress	Seizures/ hallucinations
Oxcarbazepine	Start with 300 mg/ day Therapeutic range: 800-1200 mg/day	Dizziness/ somnolence/ nausea/ vomiting	Unknown

Other drugs

- Sodium valproate
- Proparacaine eye drops
- Tocainide (LA)
- Caspaicin
- New drugs:
 - Dextromethorphan
 - NSAID- Misoprostol
 - Botulinum toxin

Assessment score

- ***BNI score***
- 1-no pain, no medications
- 2-occasional pain, no medications
- 3-some pain, adequately controlled with medications
- 4-some pain, not adequately controlled with medication
- 5-severe pain/ no relief

SURGICAL MANAGEMENT

- *Gasserian ganglion-level procedures*
 - Microvascular decompression (MVD)
 - Ablative treatments
 - Radiofrequency thermocoagulation (RFT)
 - Glycerol rhizolysis (GR)
 - Balloon compression (BC)
 - Stereotactic radiosurgery (SRS)
- *Peripheral procedures*
 - Peripheral neurectomy
 - Cryotherapy (cryonanlgesia)
 - Alcohol block

Microvascular decompression (Jannetta procedure)

- Dandy in 1934- Anatomic observations made during post. fossa exploration
- Gardner and Sava- 1959 first developed MVD
- Jannetta-1977 perfected and popularized the technique
- Indications: Relatively young pts with definite vascular loop and no other major co-morbidities
- Contraindications:
 - Only absolute C/I- Patients unfit for GA
 - Relative C/I- Multiple sclerosis
 - Elderly pts- not a C/I: equally good outcome as compared to young pts
 - *Gunther et al: Neurosurgery Sep 2009*

Offending vessels:

- Arterial: 85%: Venous-68%, sole venous- only- 12%; Both- 55%
- Arterial
 - SCA- 75%; AICA- 10%
 - Others: VA, Basilar (*more in elderly, males and HTN*), PICA and unnamed arteries
- Lower TN (V₃)- SCA commonly found compressing anterosuperiorly
- Upper TN (V₁/ V_{1,2})- Arterial compression caudo-laterally
- Isolated V₂- Medial/ lateral venous compression
- The most common site of venous compression- ant to V_n at DREZ.

Pre-op evaluation

- MR imaging with CISS sequences, CT
- PTA, BERA

Surgical technique:



- Lateral position on 3 pin with padding of pressure points
- Vertex placed parallel to the floor
- Small RMSOC
- C-shaped dural opening
- Retraction of cerebellum supero-medially to drain CSF

Continued

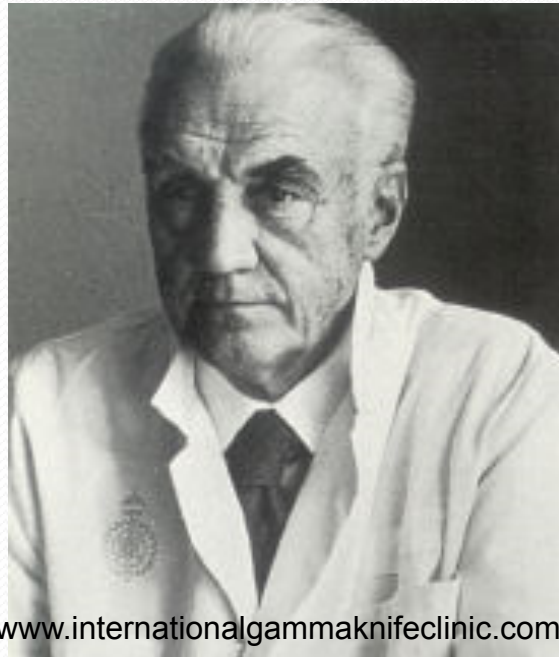
- Preserve petrosal vein
- Inspect the entire V nerve from brainstem to Meckel's cave
- **No vessel is too small to cause trigeminal neuralgia**
- To inspect the ventral and distal portions- dental mirror/ endoscope can be used. (*Charles et al: Neurosurgery 2006 Oct*)
- Dissect arachnoid over the nerve; free the nerve from tethering points
- Shredded teflon felt placed in between in proximal to distal fashion.
 - Other materials used previously- cotton, ivalon sponge, Dacron sponge, muscle, gelfoam, Gore-tex pad, fenestrated clips)
 - Teflon is used: Well tolerated, not reabsorbed, low complication rate
 - Arachnoid layer (lat ponto-mesencephalic membrane) is also used
 - *Miran Skrap et al: Operative Neurosurgery Mar 2010*
- Arteries to be never sacrificed.

- Complications:
 - Mortality: < 0.5%
 - Facial weakness- < 1%; Hearing loss- 1-2% (because of stretching of VIII nerve during cerebellar retraction- can be reduced with high approach, use of lumbar drain, intra-op BEAR)
 - Facial numbness- 1.5%
 - Facial palsy, brainstem/ cerebellar infarct, CSF leak/ meningitis
- Pain free- > 75% pain relief
 - At 2 yrs: 75% 10 yrs: 70% 20 yrs: 63%
 - *Barker, Jannetta et al: N Eng J Med 1996 (series of 1204 pts)*
 - *Tronnier et al: Neurosurgery 2001 (series of 378 pts)*
- Prior ablative surgery and prolonged symptoms are predictors of poor outcome
- Typical v/s atypical TN:
 - *Immediate relief- 91% v/s 83%*
 - *5 year relief- 80% v/s 52%*
 - *Kabara EC et al: JNS 2002 Mar- Pre-op hypesthesia is a negative predictor for pain relief in atypical pain*

- Recurrence rates: 10-15%
- Factors associated with long term recurrence:
 - Female patients
 - Symptoms > 8 yrs
 - Venous compression
 - Failure of immediate post op pain relief
- **Advantages:**
 - Consistent long term success rates
 - Lower recurrence rates
 - Substantially lower incidence of facial dysesthesias
 - Ability to restore normal/ near normal function of the nerve itself
 - Improved neurophysiologic parameters immediately after MVD
 - If immediate recurrence- re-explore
 - Delayed recurrence- medical line; If fails- redo-MVD

STEREOTACTIC RADIOSURGERY-

- Attractive option for elderly patients and those who do not tolerate the more invasive surgical procedures available.



Gamma knife

- Developed by Lars Leksell
- First use of GK was for TN in 1971
- MOA: 2 step process
 - Immediate interruption of ephaptic transmission (Immediate relief)
 - Demyelination injury of nerve (sustained relief)
- Technical aspects:
 - Single 4 mm isocentre
 - 70-90 Gy, Brainstem receives < 20% of dose
 - Target- 2-4 mm from entry into pons (DREZ/ RGZ)

Results

- Initial response rates: 80%-90%
 - Median time to response: 2 wks-1 month
- Long term response rates:
 - 65-70% at 3 yrs; 50-55% at 5 yrs
 - Higher recurrences with secondary GKRS
- Response with dose:
 - Better response with 90 Gy than 70 Gy
- Adverse effects: Facial sensory loss (< 10%)
 - More with high doses (>90 Gy)
 - *Kondziolka et al: GKRS for TN: 1997*
 - *Young et al: GKRS for treatment of TN: 1998*
 - *Dhople et al: Long term outcomes of GKRS for TN: JNS 2009*

- *Target differences?*

- The RGZ targeting technique in the GKRS for TN had a better treatment success, with fewer bothersome complications compared to the DREZ target.

- *Park et al: Acta Neurochirur (Wien) 2010 Jul*

- *Primary/ Secondary GKRS:*

- GKRS can be offered both as a primary and as a secondary procedure with both offering durable pain relief.

- *Park et al: Clin Neurol Neurosurg 2011 Jul*

- *Dose differences with changes in V nerve*

- 60-70 Gy: very less impact
 - 80-90Gy: Loss of axons and demyelination
 - 100 Gy: Necrosis of some neurons

- *Zhao et al: JNS 2010 Jul (experimental study on rhesus monkeys)*

Predictive factors for success of GKRS

- Development of post-GKRS facial numbness positive factor
- Previous RFA/ longer cisternal nerve length/ DM- negative factors
 - *Marshall et al: Neurosurgery Aug 2011*
- High-dose (80-90Gy) retrogasserian (7-8mm from the brainstem) GKS provides the patient with a better chance of long-term pain relief and a lower risk of trigeminal nerve functional disturbance.
- Patient selection (typical versus atypical, age, past surgery, multiple sclerosis) and details of operative technique (maximum dose, volume of nerve treated, target location, etc.) have a major influence on the probability of pain relief and toxicity risk
 - *Regis et al: Neurochirurgie 2009 Apr*
- For recurrent TN
 - Patients who developed sensory loss after GKRS had better long term pain control
 - Factors associated with better long-term pain relief included no relief from the surgical procedure preceding GKRS, pain in a single branch, typical TN, and a single previous failed surgical procedure
 - *Kano et al: Neurosurgery 2010 Dec*

Cyberknife

- Also called non isocentric radiosurgical rhizotomy
- It dynamically tracks skull position and orientation during treatment using noninvasive head immobilization and advanced image-guidance technology
- It offers the ability to deliver non isocentric, conformal and homogeneous radiation doses to nonspherical structures such as the trigeminal nerve.
- Median maximal dose of 78 Gy (range, 70-85.4 Gy)
- Median length of the nerve treated of 6 mm (range, 5-12 mm).
- Initial pain relief 67-92% at median response delay of 7-14 days
- Around 50% pain relief at 2 yrs
 - *Lim M et al: Neurosurg Focus 18:E9, 2005*
 - *Villavicencio et al: Neurosurgery: Mar 2008*
- Appears to be a cost-effective option for recurrent TN
 - *Tarricone et al: Neuropsychiatr Dis Treat 2008*

Linear accelerator (LINAC)

- Another option for TN
- Produces radiation that is referred to as high energy X-ray.
- Similar to the one used in Radiotherapy (IMRT)
- Good outcome in TN- 80% pain relief with a mean f/u of 28 months
- Mean duration of initial relief- 2weeks to 2 months
- Increased dose (90Gy v/s 70 Gy), increased isodose to brainstem (30% v/s 50%) had better pain relief but with increased risk of numbness (35% v/s 50%)
 - *Smith ZA et al: Int J Radiat Onco Biol Phy 2011 Sep*
 - *Chen et al: Minim Invasive Neurosurg 2010 Oct*

PERCUTANEOUS TECHNIQUES

- Under LA/ short GA on outpatient basis
- Commonly are performed in debilitated persons or those older than 65 years.
 - Thermal ablation
 - Glycerol rhizolysis
 - Balloon compression
- Standard landmarks for foramen ovale
 - 2.5 cm lat to angle of lip, 3 cm ant to EAM, just below the medial aspect of pupil

Percutaneous retrogasserian glycerol rhizotomy (PRGR)

- Hakanson introduced in 1981.
- 0.3 ml injected into the trigeminal cistern
- Outcomes:
 - Initial pain relief: 90%
 - Recurrence rates: 30-70% after 2 yrs
 - Mild hypesthesia: 10-70%

Percutaneous thermal rhizotomy

- Thermocoagulation probe is used.
- Benefits depends upon how much numbness is created
- Dense hypalgesia rather than analgesia is recommended
- Outcomes:
 - 90% initial pain relief; 50% at 2 yrs, 25% at 4 yrs.
 - Complications: Dysesthesia, motor weakness, keratitis

Percutaneous balloon compression

- Under short GA
- Balloon catheter directed towards f.ovale
- Balloon is inflated 1.3 to 1.5 atmospheres using insufflation syringe
- Compression for not > 1.5 min
- Outcome:
 - Initial success rate: 95%
 - Recurrence: 25% at 2 yrs

PERIPHERAL PROCEDURES

- Goal is to denervate the trigger zone region in contrast to denervating the area of pain distribution.
- Both chemical and surgical
- Supraorbital, supratrochlear, infraorbital and inferior alveolar nerves are targeted.
- Have been superseded by other safe and effective methods
- Indications:
 - Elderly patients, cognitively impaired pts who cannot co-operate with physicians to undergo percutaneous procedures.
- Drawbacks:
 - High incidence of recurrence
 - Near total/ total anaesthesia in distribution of ablated nerves.

- **Alcohol injections:**

- Absolute alcohol is highly neurotoxic.
- Under LA; needles oriented for the respective foramina
- 0.5-1.5 ml injected
- Average duration of pain relief: 8-16 months

- **Surgical neurectomy**

- For V₁ distribution: Supraorbital and supratrochlear
- For V₂: Infraorbital neurectomy
- For V₃: Inferior alveolar neurectomy
- Pain relief: 26-30 months
- Recurrence rates: 30% at 5 yrs



Special circumstances

Pediatric onset TN

- Extremely uncommon: 0.2/100000
- Onset before 18 yrs
- 1% of all pts with TN
- Pathogenesis different
- MVD is an effective option: (venous compression more)
 - Lower outcome rates than adults-
 - 55% at a mean f/u of 105 months
 - 30% recurrence in 1 year
- **Co-existent TN and hemifacial spasm**
 - MVD is an effective option

Recurrent TN

- Management dilemma
- Depends on the primary treatment modality
- Multiple options:
 - Repeat MVD (in pts who had previous MVD)
 - Intra-op findings: None/ vessel/ compressed teflon
 - Secondary GKRS/ repeat GKRS
 - Repeat GKRS provides similar rates of pain relief as primary GKRS
 - Median retreatment dose 45 Gy with a median cumulative dose of 125 Gy
 - *Toshinori Hasegawa et al: Neurosurgery 2002*

TN with multiple sclerosis-

Symptomatic TN

- 2% of pts with MS, earlier onset, more atypical pain, frequently B/L
- Pathology is one of demyelination rather than isolated compression.
- Multiple treatment options as for idiopathic TN
- Recurrences are high
- GKS is an effective treatment for refractory TN in MS
 - Lower retreatment rates and
 - Longer pain-free intervals between procedures compared with radiofrequency lesioning or MVD.
 - *Jason Cheng et al: Neurosurgery Focus 2005*
- Percutaneous procedures also tried.
- MVD also performed
 - 50-75% good outcome at f/u of 50 months
 - Neurovascular conflict found in 58% in MRA and 90% intra-op
 - Veins more common
 - High rate of hearing dysfunction (13%)
 - *Sandell et al: Neurosurgery Sep 2010*

TN in elderly

- Medical line of treatment preferred.
- Points to be considered for MVD
 - Duration of disease: Longer disease duration inversely proportional to outcome
 - Prior ablative procedures which is often used in these pts: outcome rate drops from 85% to 50%
 - Effectiveness: good relief rates as compared to young pts
 - Safe procedure in otherwise fit pts.
 - Ashkan et al: Neurosurgery Oct 2004
- For GKRS:
 - MVD provides immediate relief while GK has delayed pain relief over 2 yrs. No significant differences present between the two groups.
 - Considering treatment complications for elderly patients, GKRS is a better treatment method.
 - Oh et al: J Korean Neurosurg Soc 2008
- SRS and MVD are viable options with both possessing good efficacy rates.

Experimental studies


- Neuropathic pain mediated by nociceptive neurons which express vanilloid receptor 1 (VR1)
- Resiniferatoxin (RTX)- excitotoxic VR1 agonist that causes destruction of VR1-positive neurons
- Selective ablation of nociceptive neurons can be done by intraganglionic RTX infusion
- It results in the elimination of high-intensity pain perception and neurogenic inflammation while maintaining normal sensation and motor function.
- Study conducted in monkeys
 - *Tender C et al. Neurosurgery focus 18 (11) 2005*
- 5-HT_{2C} receptor agonists attenuate pain-related behaviour in a rat model of trigeminal neuropathic pain.
 - Nakai et al: European J of pain. 2010 Nov

Epidural bupivacaine HCl

- Continuous **administration** of 60mL of 0.5% bupivacaine HCl at 1mLh(-1) with a pain pump and epidural catheter can be used as a transition treatment for patients with side effects from high-dose antiepileptic drugs and for patients awaiting neurosurgery or individuals who refuse cranial surgery.
 - *Dergin G et al: J Craniomaxillofacial surg 2011 May*

Choice of surgical treatment

- Relatively young patients with no co-morbidities:
MVD
- Patients unable to tolerate GA:
 - Percutaneous procedures
 - Stereotactic radiosurgery
- Multiple sclerosis: SRS/ Percutaneous techniques/
MVD
- Final choice based on patient's preference and ability
to tolerate GA

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- MVD remains gold standard for TN
 - SRS and percutaneous techniques- an important adjunct in the treatment but with relatively high recurrence rates.