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

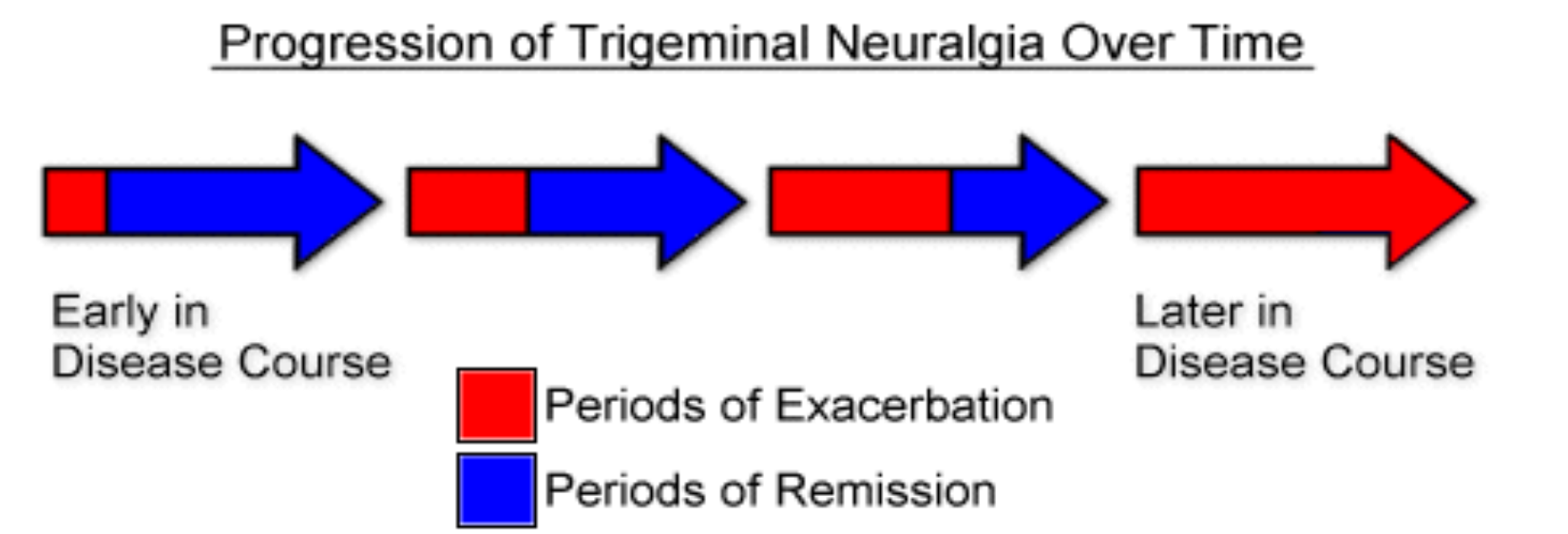
- Pain typically more severe in morning and disappears during sleep
- Pain relief when treated with carbamazepine.
- Pain free intervals are common- weeks to as long as years
- Recurrences are common- at the site of initial complaint
- Neurological examination is essentially normal except a slight degree 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



- ***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
  - Stuctural 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.
- ***3 D 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 ½ 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 ½ 3-4 hrs; renal elimination
- Synergism with CBZ/phenytoin
- 30% develop resistance in long term
- Dose: Start with 10 mg TDS, increase gradually; Typical maintainence 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
- Janetta-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/ V1,2)- 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

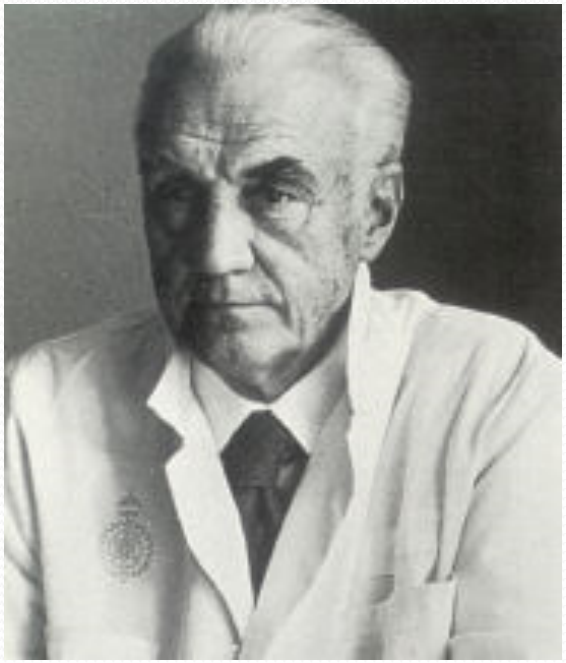
- Preserve petrosal vein
- Inspect the entire V nerve from brainstem to Meckel's cave
- ***No vessel is too small to cause trigeminal neuralgia***
- To inspect the ventral and distal portions- dental mirror/ endoscope can be used. (*Charles et al: Neurosurgery 2006 Oct)*
- Dissect arachnoid over the 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
- **<u>Advantages:</u>**
  - 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 alveloar 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
- **<u>Co-existent TN and hemifacial spasm</u>**
  - 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-HT2C 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

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