Trigeminal Neuralgia Association
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# Trigeminal Neuralgia Diagnosis and Medical Management


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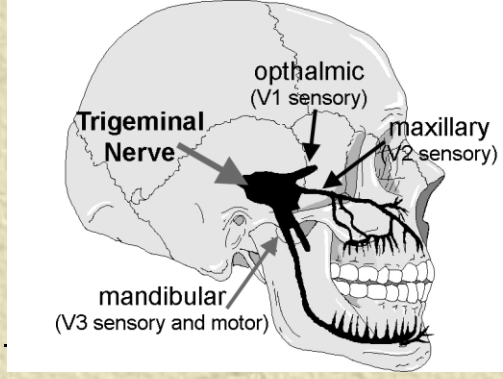
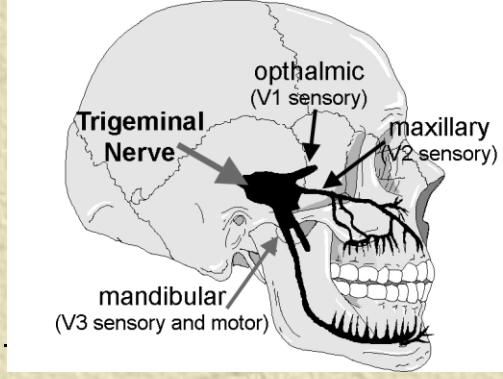
# Trigeminal Neuralgia



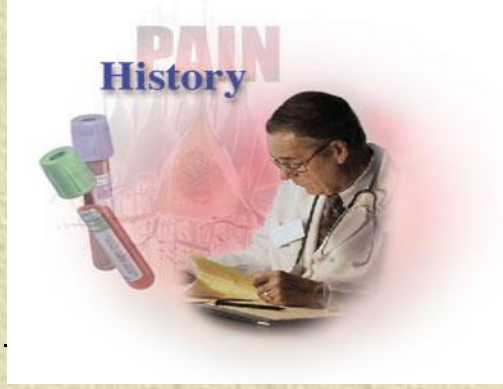

***IASP***

***"sudden, usually unilateral, severe brief stabbing recurrent pain in the distribution of one or more branches of the fifth cranial nerve"***

# Trigeminal Neuralgia




- Intense, paroxysms of sharp, stabbing pain
  - Lasting few seconds to 2 minutes
  - Pain free between attacks
  - Attacks are sterotyped
- Precipitated from trigger
  - Light touch of the face (washing, shaving)
  - Chewing, talking, swallowing, cold
- No clinical neurological deficit
- Not caused by another disorder




# Examination

- **Normal facial and cranial nerve examination**
  - Normal power
  - Normal sensation to touch and pain
  - Normal corneal reflex
  - Normal jaw jerk
  - Flushing of the skin, lacrimation and salivation may occur
- **Trigger zone**
  - Aggravates pain
- **Facial spasm**
  - Pain evokes reflex facial spasm – “tic douloureux”

# Burchiel TN Classification

- **TN, type 1**
  - >50% sharp, stabbing and intermittent
- **TN, type 2**
  - >50% constant pain
- **Trigeminal neuropathic pain**
  - Caused by unintentional injury (trauma, tooth extraction)
  - Associated sensory distrubance
- **Trigeminal deafferentation pain**
  - Caused by medical procedure (Anaesthesia dolorosa)
- **Symptomatic TN**
  - Secondary (MS, tumour)
- **Atypical facial pain**
  - No known physical cause (psychogenic)

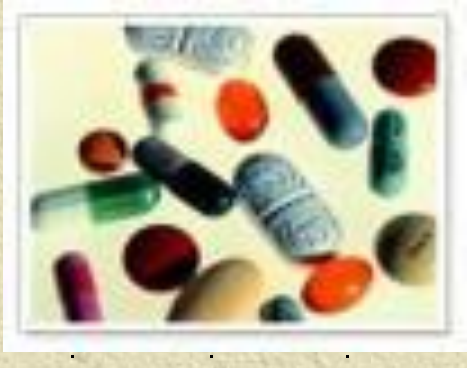
# MRI/MRA

- Should be obtained in all patients at the time of diagnosis, to **exclude** other causes of facial pain, **not to diagnosis TN**
  - Sensory loss
  - Under 40
  - Bilateral symptoms
  - Not responding to conservative therapy
- 1 mm (fine cuts) cuts through V nerve with contrast
  - Defines vascular anatomy at the REZ of V nerve
  - Ectatic blood vessel (neuro-vascular compression)
  - Neuro-radiologist to review films

# Differential Diagnosis

- Multiple sclerosis – plaque in pons or thalamus
- Posterior fossa tumour, Compression by aneurysm
- Central pathology – Syringobulbia or LMS
- Costen's syndrome (TMJ dysfunction)
- Post-herpetic neuralgia, Occipital neuralgia
- Frontal sinusitis, Maxillary sinusitis
- Nasopharygeal malignancy, Glaucoma, Dental caries
- Cluster headache, Episodic paroxysmal hemicrania
- SUNCT (Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing)
- Trigeminal sensory neuropathy
- Glossopharyngeal neuralgia, Sluder's sphenopalatine neuralgia
- Chronic neuropathic pain syndrome

# Medical Therapy



- **Variety of medications**
  - Tegretol (NNT 50% relief – Cook 1995 2.5)
  - Epilim, Dilantin, Rivotril
  - Neurontin, Lyrica, Lamictal, Topamax, Trileptal, Keppra
  - Endep, Allegron, Tofranil, Anafranil
  - Opioids –Tramal, Oxycontin, MS Contin, Norspan
  - Baclofen, Mexilitene, Clonidine
  - N-methyl-D-aspartate (NMDA) blockers - Ketamine
  - Botulinum Toxin, Capsaicin cream
- **Pain Clinics**

# Tegretol CR

- **First-line agent**
  - 200mg nocte increasing slowly to 400mg bd
  - Response within a week in 65-80%
  - t ½ 4-24 hrs - steady state attained within 1-2 weeks
  - Minor SE: sedation, dizziness, nausea, unsteadiness, rash
  - Major SE: bone marrow suppression, liver function abnormalities, hyponatremia
  - safest AED during pregnancy
- Serum therapeutic ranges are irrelevant
- 4 placebo controlled trials

# Campbell 1966

| Study | Campbell 1966 |
|---|---|
| Methods | Multicentre crossover 8 weeks, ( 4 two week periods; 2 on each of carbamazepine and placebo). 36 started on carbamazepine, 34 (report says 35 in one place) started on placebo. Active and control had same appearance |
| Participants | 77 patients with trigeminal neuralgia, but 7 excluded, 6 for logistic problems, one for a rash. Age range 20 to 84 (mean 59 years) . 34% were males |
| Interventions | Carbamazepine 100 mg 4x daily to 200 mg 3x daily (1 centre) or 200 mg 4x daily (2 centres)<br>In order C,P,C,P where C = carbamazepine, P= placebo<br>Placebo order P,C,P,C |
| Outcomes | Mean % maximum possible pain intensity fell 58% with carbamazepine, 26% with placebo. Paroxysms and triggers significantly reduced on carbamazepine |
| Notes | 7 withdrawals (1 rash, other logistic) . 50% had 1 or more adverse event on carbamazepine. 26% on placebo<br>Placebo controlled<br>QS = 5 |

Decrease in pain 58% c.f 26% for placebo

# Killian 1968

| Study | Killian 1968 |
|---|---|
| Methods | Double blind.<br>Placebo controlled crossover study 10 days (2 5-day periods); open follow-up , range 2 weeks to 36 months<br>Randomised , double blind (identical tablets) |
| Participants | Trigeminal neuralgia 30 participants, PHN 6; other chronic neuralgia 6;<br>36/42 studied double blind. (24/32 TN)<br>Age range 36-83 (mean 52) |
| Interventions | Carbamazepine dose titration 400 mg to 1g /day<br>Placebo |
| Outcomes | 19/27 TN complete or very good response. Placebo responses 'minimal or absent in all cases'. |
| Notes | 3/30 TN withdrawn (ADRs). ADRs in 23/36 on active, placebo not reported.<br>QS =4 |

19/27 complete or very good response

# Nicol 1969

| Study | Nicol 1969 |
|---|---|
| Methods | Partial crossover (successful first treatment period stayed on same treatment)<br>20 had carbamazepine only, 7 had placebo only. 17 had placebo then carbamazepine. Follow up 46 months.<br>Double blind, randomised (method not stated) |
| Participants | 64 facial pain recruited. 54 with trigeminal neuralgia.<br>Results presented on 44 TN only due to insufficient follow up.<br>Males 21; Females 23 |
| Interventions | Carbamazepine dose titration 100 mg to 2.4 g/day<br>Placebo<br>Patients started on one treatment and increased dose until 8 tablets a day. At two weeks if no satisfactory results the second treatment was substituted. |
| Outcomes | 15/20 starting on carbamazepine had good or excellent response (four point pain relief scale). 12/17 switched from placebo to carbamazepine and 6/7 placebo had good or excellent response. |
| Notes | 2/37 carbamazepine withdrawn (ADRs); 4/37 on carbamazepine died (other causes)<br>Placebo controlled<br>QS = 3 |

15/20 excellent or good response

# Rockliff 1966

| Study | Rockliff 1966 |
|---|---|
| Methods | Crossover two 3-day periods |
| Participants | Trigeminal neuralgia (9). Duration 2 weeks to 30 years. Male 1 Female 8, Mean age 65 (37-81) |
| Interventions | Carbamazepine 200 mg or placebo 3x a day for 3 days, then crossover. No washout |
| Outcomes | Patient preference. 8/9 patients expressed preference for carbamazepine. 1/9 found both treatments equally effective. No evaluable data |

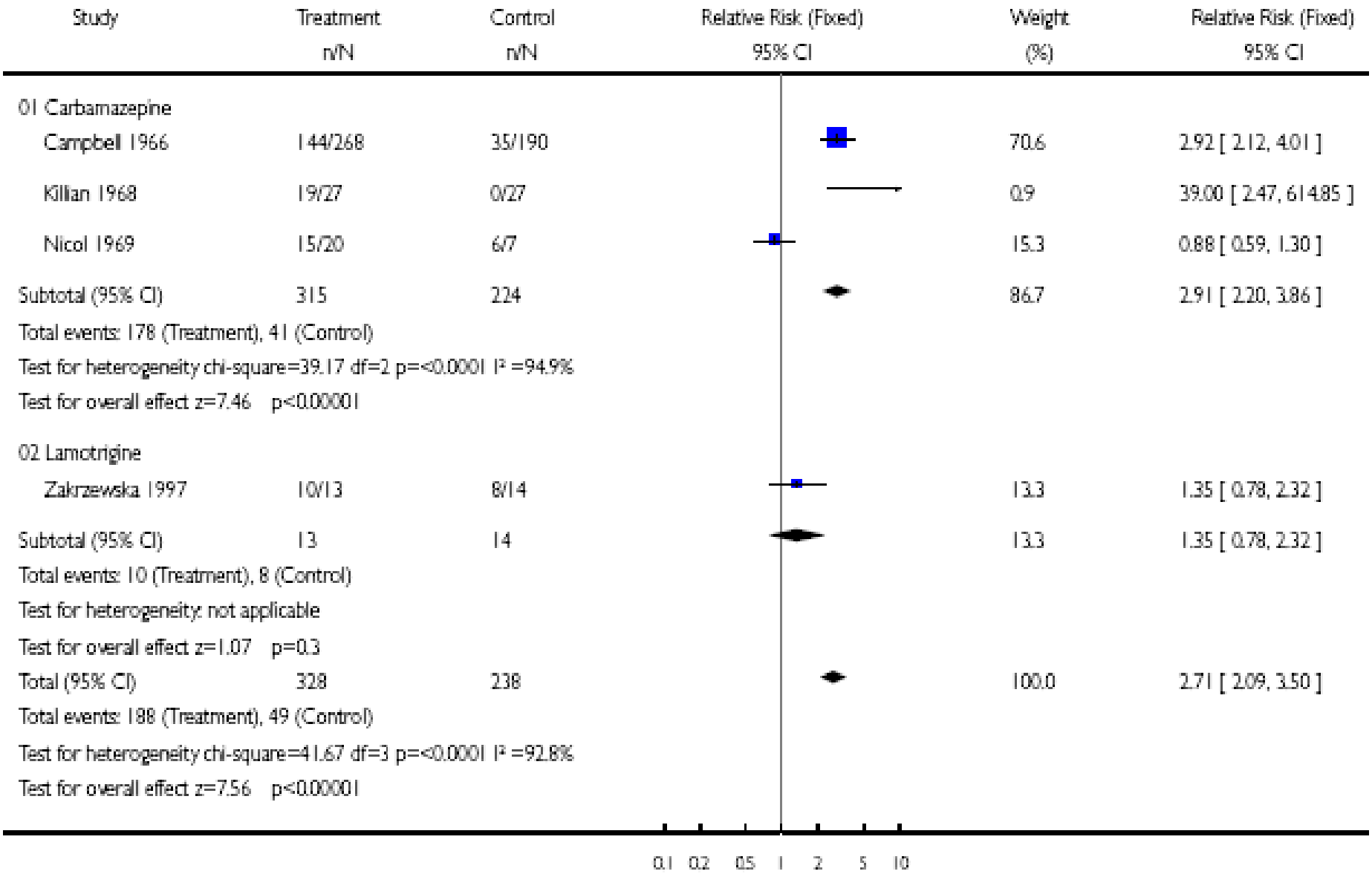
8/9 preferred Tegretol (3 days)

# Analysis 01.01. Comparison 01 Neuropathic Pain, Outcome 01 Trigeminal neuralgia

Review: Anticonvulsant drugs for acute and chronic pain

Comparison: 01 Neuropathic Pain

Outcome: 01 Trigeminal neuralgia




# Gabapentin

- Used in a variety of neuropathic pain conditions
  - Prevent allodynia and hyperalgesia
  - Improves pain and sleep
- Designed as an analogue of GABA
  - Acts also on NMDA receptors
  - t ½ 5-7 hrs – renal excretion
- Dose
  - 300mg nocte titrating up to 1800mg/day
- SE's
  - Drowsiness, dizziness, ataxia

# Gabapentin (Neuropathic pain)

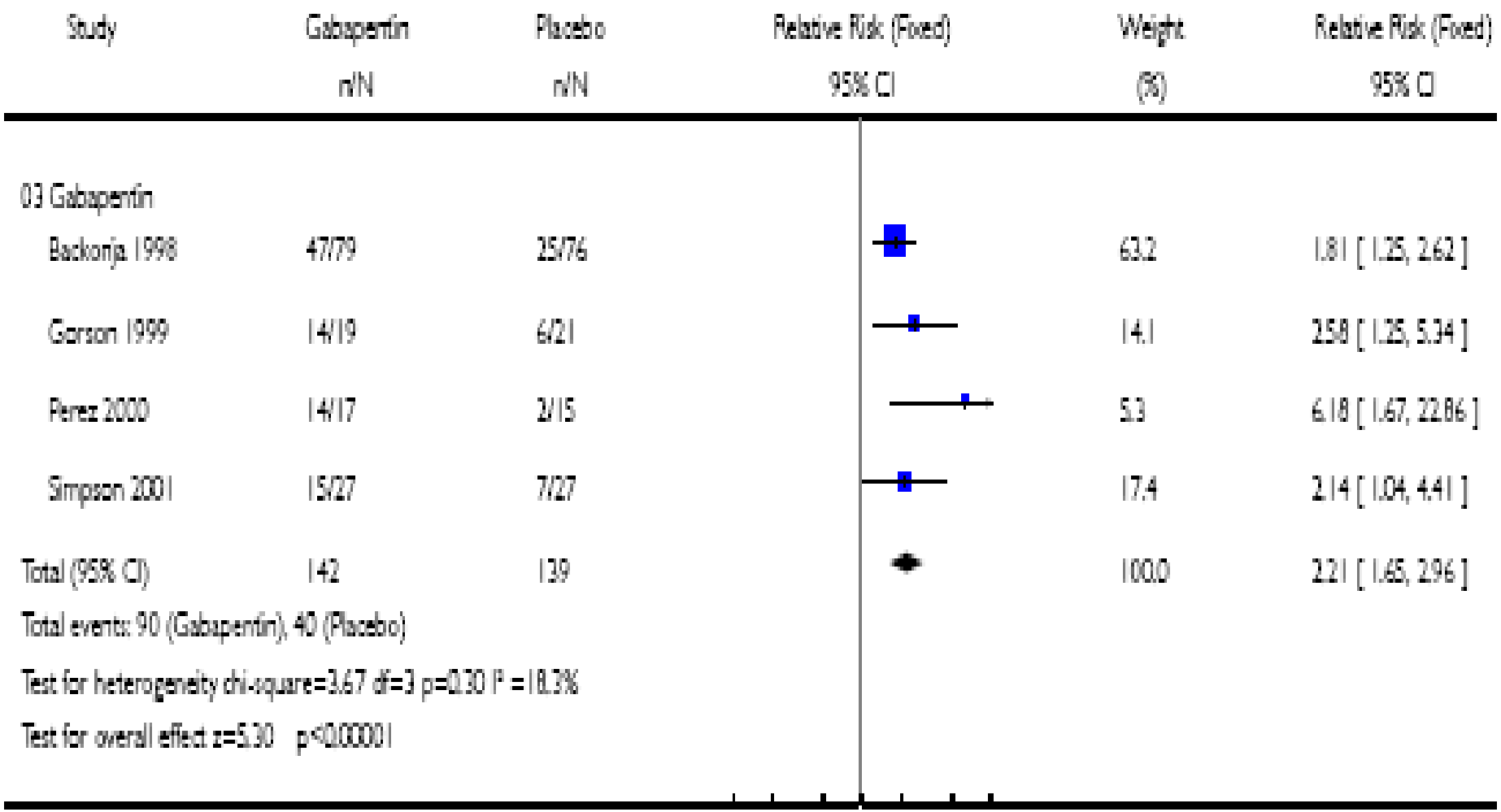
- Backonja 1998
  - 165 patients, up to 3600 mg / day - 60% improvement after 4 weeks
    - 25/79 placebo and 47/79 on Gabapentin
- Gorson 1999
  - 40 patients, up to 900 mg / day in a crossover study
    - Not effective
- Perez 2000
  - 32 patients, up to 1200 mg / day
    - 14/17 >50% reduction at 1 month
- Simpson 2001
  - 64% compared to 28% on placebo improved - NNT 3.4

# Analysis 01.01. Comparison 01 Neuropathic Pain, Outcome 01 Diabetic neuropathy

Review: Gabapentin for acute and chronic pain

Comparison: 01 Neuropathic Pain

Outcome: 01 Diabetic neuropathy



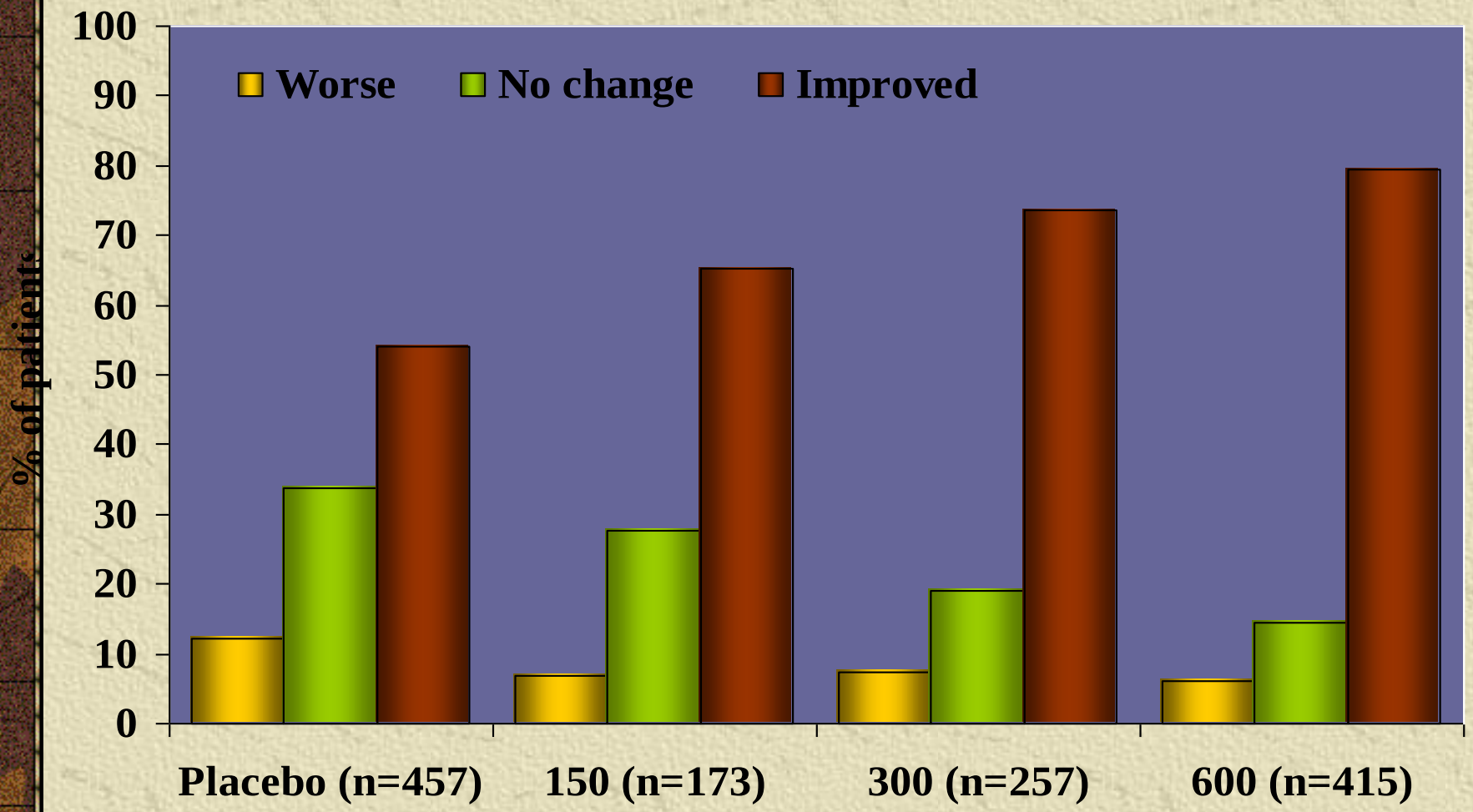
# Pregabalin - Lyrica

- **TGA approved for neuropathic pain, but not funded for use in PAIN (only epilepsy)**

- Works on alpha-2-delta ligand
  - t ½ 2.5 hrs – reaches steady state within 24-48 hours
- Analgesic, anxiolytic and anti-convulsant

- SE's
  - Dizziness and somnolence, blurred vision
  - Weight gain and peripheral oedema
- Dosage
  - 75mg nocte increasing slowly to 300mg bd

# Pregabalin – Patient rated improvement – 6 trials



# Pregabalin – Adverse Events

| | Placebo (n=764) | Pregabalin dose (mg/day) | | | All Pregabalin doses pooled | |
|---|---|---|---|---|---|---|
| | | 150 (n=427) | 300 (n=509) | 600 (n=459) | Incidence (n=1556) | Discontinued (n=1556) |
| Dizziness | 6.4 | 13.3 | 25.5 | 29.6 | 21.7 | 3.1 |
| Somnolence | 3.8 | 9.8 | 15.9 | 17.6 | 13.8 | 2.6 |
| Peripheral oedema | 1.8 | 5.2 | 12.0 | 13.5 | 9.5 | 0.8 |
| Dry mouth | 1.8 | 4.7 | 5.3 | 8.1 | 5.9 | 0.3 |

# Pregabalin - Lyrica

- 65 yo TN since 1980
  - Lyrica 75mg bd 50 % improvement in pain
  - Ceased Gabapentin 600mg bd, Tramadol SR 200mg bd
  - Less drowsy, managing better
- 35 yo TN since 1997
  - Gabapentin 300mg tds
  - Keppra 1000mg bd
  - Found Lyrica 300mg bd better – no SE's

# Lamotrigine

| Study | Zakrzewska 1997 |
|---|---|
| Methods | Crossover 2 weeks, one week washout then 2 weeks, no follow-up |
| Participants | Trigeminal neuralgia (14) Duration 1-23 years). Male 8, female 6, mean age 60 ( 44 to 75 yrs) |
| Interventions | All patients on carbamazepine or phenytoin.<br>Lamotrigine or placebo added. Dose increment over 4 days to 400 mg. Rescue medication of carbamazepine or phenytoin |
| Outcomes | Gloabal scale<br>10/13 improved on lamotrigine, 8/14 placebo |
| Notes | 1 withdrawal (placebo) reason not stated. 7/13 reported side effects on lamotrigine and 7/14 on placebo<br>QS = 4 |

10/13 improved on Lamotrigine

# Oxcarbazepine

- Tegretol without the side effects
  - Less Na, dizziness, drowsiness and lethergy
- Slightly less potent
  - Higher doses needed
- 4 studies in Canada and Europe
  - As effective as Tegretol (70-80% response)
- Cost
  - Not covered by PBS
  - Approx $90 per month

# Anti-convulsants in TN

- 4 placebo controlled trials of Tegretol
  - NNT 2.5 (2.0-3.4)
  - Loss of effect or tolerability - 50% after 10 years
- 1 randomised trial of Lamotrigine
  - Effective as add-on therapy
- Little evidence to support
  - Epilim, Gabapentin, Phenytoin, Clonazepam or Pregabalin, at this stage

# Analysis 01.01. Comparison 01 Neuropathic Pain, Outcome 01 Trigeminal neuralgia

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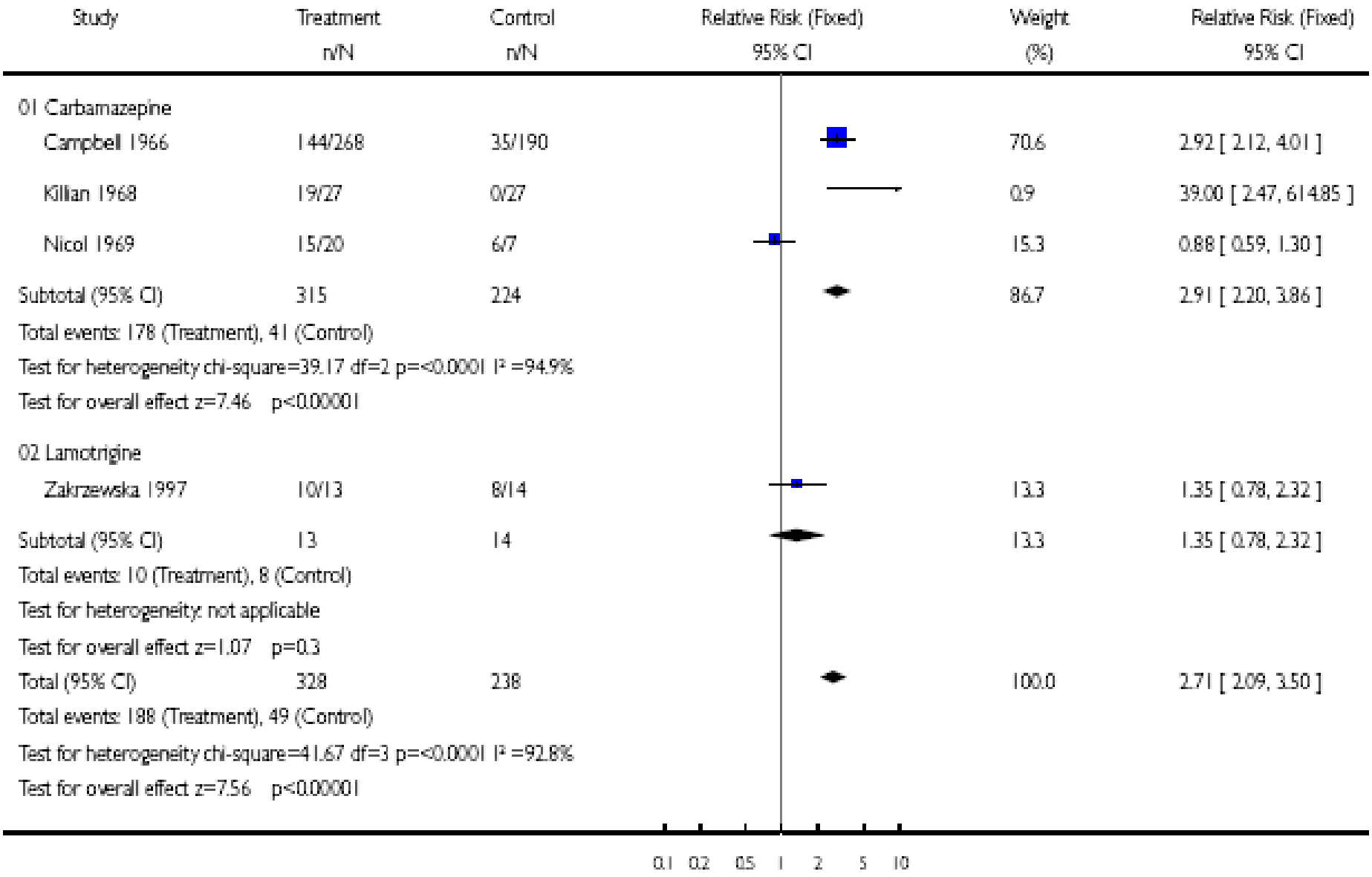


# Anti-depressants

- **Tricyclic anti-depressants**
  - Amitriptyline (Endep)
  - Nortripyline (Allegron)
  - Doxepin (Deptran)
  - Clomipramine (Anafranil)
- **Selective seretonin reuptake inhibitors (SSRI)**
  - Paroxetine (Aropax)
  - Fluoxetine (Prozac / Lovan)
  - Citalopram (Cipramil)
  - Seretaline (Zoloft)
- **Mixed (SNRI)**
  - Mirtazapine (Avanza)
  - Venlafaxine (Efexor)
  - Reboxetine (Edronax)

# Tricyclic Anti-depressants

- Direct analgesic effect
  - Also relieve other symptoms, such as sleep disorder
  - Lower doses (10-25mg) required c.f 100-150mg for mood
  - Occurs faster (3-4 days) than anti-depressive effects
- SE's:
  - Anticholingeric effects
    - sedation, dry mouth, blurred vision, urinary retention
  - Life-threatening cardiovascular effects - arrhthymias
- **McQuay** - systematic review 1996
  - NNT 3 in DN, NNH 2.8

# Anti-depressants in TN

- **Tri-cyclic anti-depressants**
  - Single blind randomised trial (Carasso 1979) 18 patients
    - Moderate improvement in 7/9 Clomipramine c.f 3/9 Amitriptyline
- **SSRI's**
  - Fluoxetine, citalopram and paroxetine
    - Effective in 3 studies in diabetic PN, but none in TN
  - St.John's wart and venlafaxine
    - Studies too small for any firm conclusions
- **SNRI's (PN)**
  - 50% reduction in 50% of patients within 1 week
  - SE's: somnolence, nausea, constipation

# Carasso 1979

| Study | Carasso 1979 |
|---|---|
| Methods | Randomized (methods not described). Single-blind (patient "blind").<br>No dropouts.<br>No ITT analysis. Length of the trial and baseline time of observation unclear. |
| Participants | 18 patients (9 and 9).<br>Age 35 to 70 years.<br>61% females. Duration of illness unreported.<br>No inclusion or exclusion criteria. |
| Interventions | Treatment group: clomipramine 20 mg to 75 mg daily, (divided into three doses), orally 3 months.<br>Control group: amitriptyline 30 mg to 110 mg daily (divided into three doses), taken orally.<br>No description of steady dose period. |
| Outcomes | Clomipramine group: 7/9 moderate to marked improvement. Amitriptyline group: 3/9 moderate to marked improvement.<br>No report of adverse effects. |

7/9 Clomipramine, 3/9 Amitriptyline

# Non-Epileptic drugs for TN

- Aspirin, Codeine and NSAID's - Not helpful
- **Baclofen -** GABA b receptor agonist
  - Lacinating pains primarily through inhibitory effect
  - Initiate slowly, 5mg bd (increase up to 40-60mg/day)
- Side effects:
  - CNS depression
    - sedation, confusion, dizziness
  - Nausea
  - Postural hypotension

# Fromm 1984

| Study | Fromm 1984 |
|---|---|
| Methods | No clear randomization.<br>Double-blind crossover study. No dropouts. No ITT analysis. Length of the trial unclear.<br>No baseline time of observation. |
| Participants | 10 patients.<br>Age 59 to 78 years. Proportion of females unclear. Duration of illness from 1 month to 15 years.<br>Baseline paroxysms/day of pain from 3 to 50. Diagnosis according to the usual criteria. Typical patients enrolled.<br>No exclusion criteria. |
| Interventions | Patients were given baclofen or placebo for 1 week. The initial dosage of baclofen was 10 mg three times a day and was increased by 10 mg/day. At the end of phase A the patients were given the other tablet. The duration of each phase was one week.<br>No washout phase.<br>No description of max dose and steady dose period. |
| Outcomes | Baclofen period: 7/10 decrease in daily frequency of pain.<br>Placebo period: 0/10 decrease in daily frequency of pain.<br>No major adverse effects or abnormal laboratory findings. |
| Notes | Patients had classical trigeminal neuralgia. |

7/10 improved by 50% c.f 0/10 on placebo

# Analysis 02.01. Comparison 02 Baclofen versus carbamazepine, Outcome 01 Number of patients with a 75% reduction in attacks on the 10th day

Review: Non-antiepileptic drugs for trigeminal neuralgia

Comparison: 02 Baclofen versus carbamazepine

Outcome: 01 Number of patients with a 75% reduction in attacks on the 10th day

| Study | Baclofen n/N | Carbamazepine n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Parekh 1989 | 5/7 | 3/10 | | 100.0 | 2.38 [ 0.83, 6.85 ] |
| Total (95% CI) | 7 | 10 | | 100.0 | 2.38 [ 0.83, 6.85 ] |

Total events: 5 (Baclofen), 3 (Carbamazepine)

Test for heterogeneity: not applicable

Test for overall effect z=1.61 p=0.1

# Miscellaneous Agents -Mexilitene

- Blocks sodium channels
  - Reducing abnormal baseline and inducible nerve discharges
- Difficult to initiate
  - 50 mg daily increasing slowly to 200 mg tds
- Poorly tolerated
  - Anorexia, nausea, vomiting
  - Drowsiness, confusion

# Sympatholytics - Clonidine

- Alpha 2 adrenergic agonist in dorsal horn and brainstem
  - Transdermal, intravenous, oral, and epidural
  - Suppress CNS noradrenergic activity and peripheral sympathetic tone
- Opiate analgesia may be potentiated
  - Dual effects on opiate receptors
- Non-addictive
  - Useful for weaning opioid-dependent patients by blocking withdrawal effects

# Topical agents - Capsaicin

- Naturally occurring alkaloid
  - works on small cutaneous c-fiber afferents
  - stimulating then blocking fibres
  - depleting substance P
  - reducing membrane excitability
  - blocking axon transport
- Low concentration, 0.075% topical cream
- May burn for the first several weeks

# Opioids

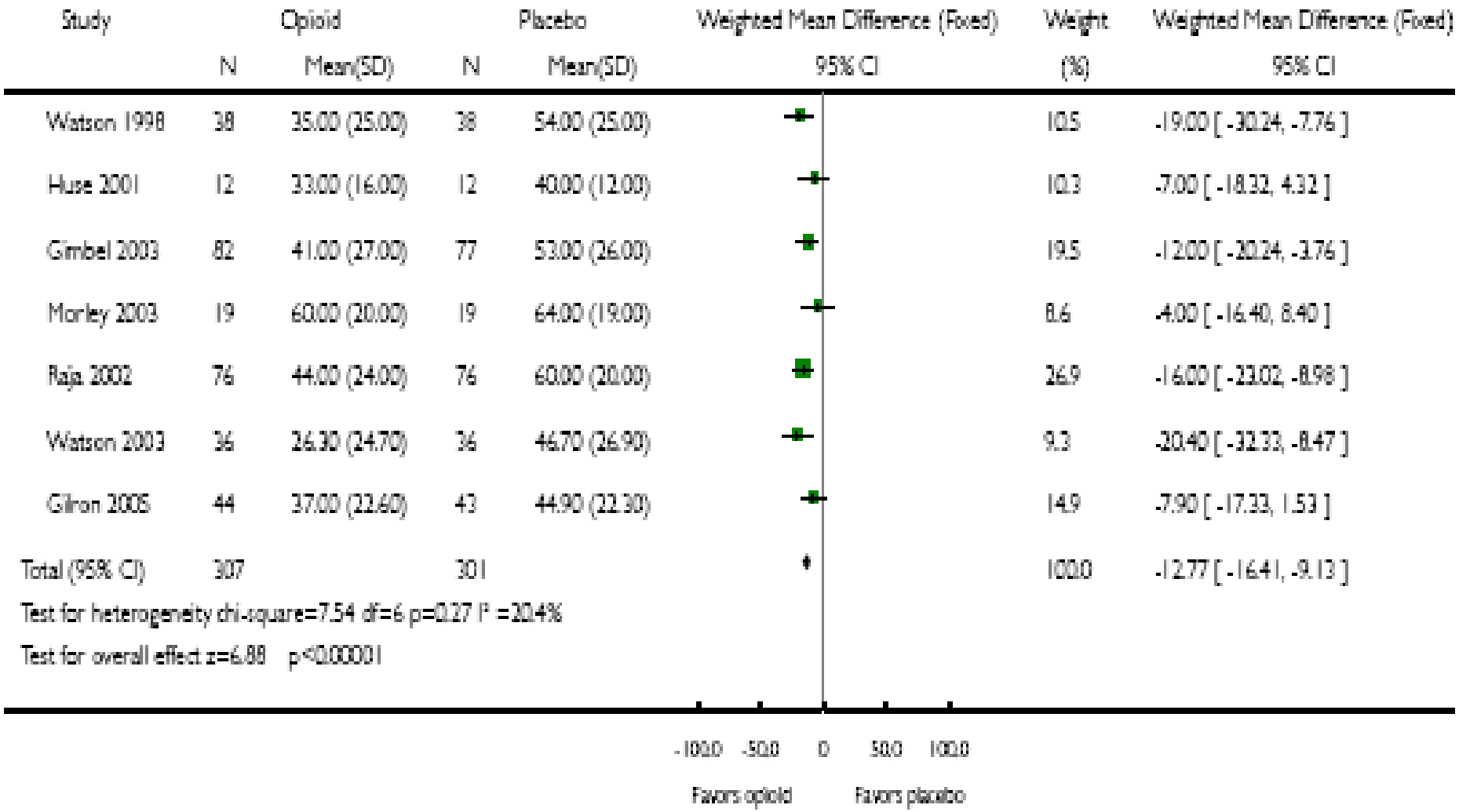
- Lack of evidence
- 2 trials in neuropathic pain c.f other drugs
  - Gilron 2005
    - Non-significant superiority of Morphine to Gabapentin
  - Raja 2002
    - Non-significant superiority of morphine and methadone to nortriptyline - 4.4 vs 5.1 - low numbers 120
- Concerns:
  - Adverse effect profiles
  - Potential for abuse, addiction and hormonal changes
- Generally, discourage use in neuropathic pain

# Analysis 02.01. Comparison 02 Intermediate-term Efficacy Studies: Opioid vs. Placebo, Outcome 01 Pain intensity post opioid/placebo

Review: Opioids for neuropathic pain

Comparison: 02 Intermediate-term Efficacy Studies: Opioid vs. Placebo

Outcome: 01 Pain intensity post opioid/placebo



# Tramadol

- **Opioid** (mu-opioid) analgesic activity
- **Non-opioid** analgesic activity
  - Inhibition of noradrenaline reuptake
  - Stimulation of serotonin release at the spinal level
- Quick acting, slow release and IV or IM forms
- Side effects:
  - CNS (somnolence, confusion, dizziness) & GIT (nausea)
- Moderate post-operative pain - NNT 100mg 4.7

# Buprenorphine - Norspan

- Transdermal patch - weekly
  - Partial opioid agonist
  - SE's
    - Application site skin irritation (rotate sites)
    - Headaches
    - Dizziness, drowsiness, nausea, constipation
  - Doses
    - 5 mcg/hr / 10 / 20

# ‘Wind Up’

- Prolonged response to a noxious stimulus
  - Dramatic increase in duration and magnitude of cell responses, but input into spinal cord remains the same
- Activation of:
  - Neurotransmitters (glutamate, substance P, NO)
  - Receptors ( NMDA)
  - Inflammation and chemicals (neurotropin)
  - Genes (Cfos)

# NMDA receptor antagonists

- **Ketamine**
  - Non-competitive NMDA antagonist - dorsal horn of SC
  - Inhibits binding of excitatory amino acids (glutamate) to NMDA receptor, blocking transmission of pain
  - Highly lipid soluble – crosses BBB rapidly

- **Oral NMDA receptor antagonists**
  - Dextromethorpan and Amantadine
  - Higher dosages required
    - e.g. for Dextromethorpan as a cough suppressant - 40-80mg c.f pain - 400mg/day

# Ketamine – ‘Special K’


- Developed in 1963 as safer alternative to PCP
- **Anaesthetic** with:
  - Dissociative (separates perception from sensation)
  - Analgesic, sedative and amnesic properties
  - Used in veterinary medicine
  - Odorless, tasteless, undetectable in drinks
- 80% hepatic metabolism to active Norketamine
  - Orally as only 1/3 analgesic potency of ketamine)
  - Cognition side effects and hallucinations at high doses

# Ketamine

- **Ketamine infusion**
  - 200mg in 50ml plus
  - **Lignocaine 10%** (sodium channel blocker) 2000mg in 20 ml
  - Generally run at 2ml/hr initially over 3-5 days
  - If effective
    - **Ketamine lozenges** – 25mg three times a day initially
- **Ketamine drops** – not available yet
- **Oral Ketamine** – poorly absorbed
- **Topical Ketamine gel -** 0.093 mg/kg – 9.33 mg/kg

# Mrs CH

- 52yo Registered Nurse
  - Right TN Dx 1997
    - Lacinating pain in 2nd and 3rd division
  - Responded well to Tegretol and Epilim
    - Developed drug induced hepatitis
  - Microvascular Decompression 1998
    - Pain free for next 4-5 years (normal facial sensation)
- Dec 2003, pain recurred
  - Commenced on Gabapentin – no response
  - 2nd microvascular decompression Aug 2004
    - No evidence of vascular compression, nerve “pinched”
    - Pain free for 3 months then recurred

# Mrs CH

- R facial pain in all divisions of V nerve
  - Sharp, shooting, knife-like lasting for seconds
  - Attacks of pain brought on by touching face, chewing, talking, smiling, blinking, blowing nose
  - Increased sensitivity to touch over face
- Canberra hospital in Dec 2004
  - 5 day Lignocaine infusion revealed pain but recurred once infusion ceased
- Subsequently tried:
  - Endone, MS Contin, Baclofen, Mexilitine
  - Stereotactic Radiotherapy in March 2005

# Mrs CH

- Initial Consultation:
  - Considered palliative rhizolysis or radiofrequency abalation
    - Permanent sensory loss and pain relief for 2-3 years only
  - Gabapentin 600 mg  and Lamotrigine 150 mg 6 times a day
- Admitted to RPAH in February 2006
  - Ketamine and Lignocaine infusion
    - Improved pain within 24 hours
  - Able to reduce Gabapentin and Lamotrigine within 3 days
    - 50% to 3 times a day
- Discharged home pain free
  - Ketamine lozenges 25 mg three times a day

# Mrs CH

- Follow up March 2006 (4 weeks post)
  - Remains pain free and now able to touch face, rub cream, blow nose (unable to do for over 2 years)
    - Ceased Gabapentin and reduced Lamictal to 100mg tds
    - Feels less drowsy and has more energy
- July 2006
  - Pain very well controlled – ceased Lamotrigine
    - Wearing make-up and no pain with wind blowing on face
- December 2006 – (nearly 12 months post infusion)
  - Leading a completely normal life, without pain worry
    - Ketamine 25 mg three times a day only

# Botulinum Toxin


- Turk et al Aug 2005 - Clin NeuroPharm
  - 8 patients with TN
  - 100 u of Botox in 2 ml N saline
  - 50 u injected just above and below the zygomatic arch at a depth of 1.5 to 2 cm

- Reduction in pain within hours or days in all after the injection – 3.2 +/- 2 days

| • Time | 0 | 1 week | 2 month | 6 month |
|---|---|---|---|---|
| • VAS | 4.0 | 2.9 | 1.9 | 1.2 |

# Vitamin B12

- Used by the body in the production of myelin
- Gross deficiencies
  - Lead to nerve damage (pain and inflammation)
  - Vegetarians as found in beef, lamb, eggs, liver, oysters
- Replace with 1000 micrograms daily
  - Help regenerate myelin and nerve cells
  - Even in non-deficient
- Initial studies (1940's) -promising results

# Pain Clinics

- **Does not** imply "**Pain is not Real**"
  - When pain persists beyond healing or with no cause, it is often assumed patient is willingly aggravating the pain

    **This is rarely the case**
  - Pain is a perception, which is filtered through the brain

- **Multidisciplinary treatment**
  - 1st pain clinic to include psychological component –1976
  - Cognitive components are crucial to the treatment
    - Reduce pain but also improve mood and decrease disability
  - Medical, physical, behavioural, emotional, vocational, social

# Why Medications Fail?