Anti-epileptics

Update on use in neuropathic pain

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For neuropathic pain….

- What do you do if pain persists despite gabapentinoids and analgesic-antidepressants?
- Do you use other AEDs:
  - 1st line (i.e. *before* trying gabapentinoids)?
  - 2nd/3rd line (i.e. only if gabapentinoids *fail*)?

[NB: gabapentinoids = gabapentin and pregabalin; AED = anti-epileptic drugs]

Overview

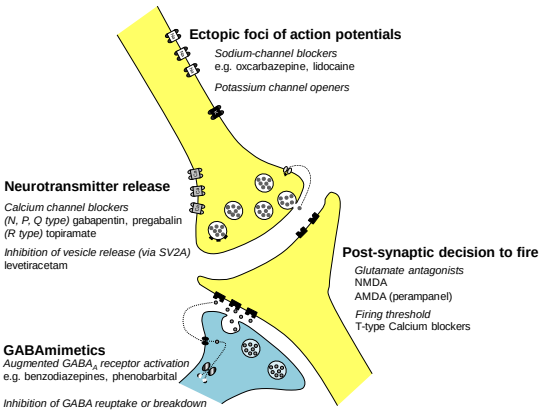
- Introduction
  - What's changed in the last 20 yrs?
  - Brief revision of AED pharmacology
- Where are we now?
  - Are gabapentin and pregabalin different?
  - Is there evidence for other AEDs?
  - Practical considerations? (esp. oxcarbazepine)
- Any new options on the horizon?

What's changed?

What's changed?

- Improved understanding of the biology and pharmacology
- New drugs
  - E.g. gabapentin, pregabalin, oxcarbazepine
- Cost
  - Pregabalin: from £70 to £3/month
- IV / SC options
  - Valproate, lacosamide, (levetiracetam – though not for pain)
- Regulatory
  - Gabapentinoids → CD3
  - Valproate teratogenicity precautions
- Alternatives to AEDs
  - Availability of interventional anaesthesia / implantable pumps
  - New concerns (e.g. ketamine and urotoxcity)
  - 'New' drugs (e.g. Sativex)
  - Simpler approaches for old drugs? (e.g. low dose methadone)

Not directly linked: nerve pain hasn't reached a "captopril" moment yet



Interactions and undesirable effects

- Pharmacokinetic interactions
  - Many (enzyme inducers) Carbamazepine, phenytoin, barbiturates
  - None clinically relevant Gabapentin, pregabalin, levetiracetam
- Adverse effects
  - Shared
    - CNS depression
    - A surprising number cause hepatitis, pancreatitis and skin reactions
  - More common with specific AEDs
    - Oxcarbazepine hyponatraemia
    - Topiramate kidney stones
    - Levetiracetam aggression

Where are we now?

Are gabapentin and pregabalin different?

Does the evidence support using other AEDs in nerve pain?

Are gabapentin / pregabalin different?

Efficacy and tolerability comparable

- 2 network analyses – comparable outcomes
  - NICE (appendix G of their neuropathic guidance)
  - Griebeler 2014 (Ann Intern Med 161: 639-649)
- 3 Head-to-head RCTs – comparable outcomes
  - Peripheral nerve injury (n=30) - comparable
  - Spinal cord injury (n=28) - comparable
  - Malignant nerve pain (n=120)*
    - Titrated up to gaba 600 tds or pregab 300 bd
    - Pain relief similar
    - Lower opioid use in pregab group

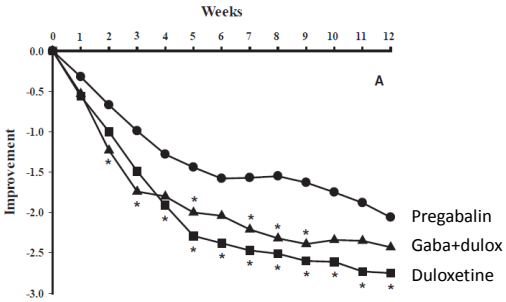
But I think this is a less pressing question now they're similar prices

* Mishra 2012; Am J of Hospice and Pall Med 29: 177-182

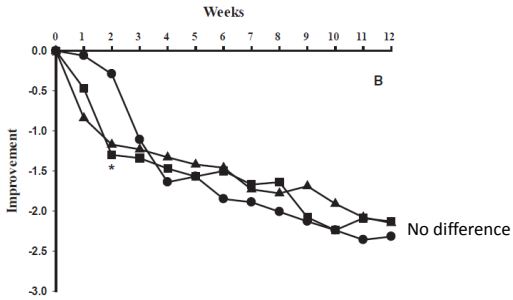
What about *switching* to pregabalin if gabapentin fails?

- Tanenberg 2013
  - PDN failing on gaba were randomised to:
    - Switch to pregab
    - Switch to duloxetine
    - *Add* duloxetine to the gabapentin
  - NB
    - mean gaba dose ~400mg tds
    - 20% were already on an antidepressant

In those *not* already on an antidepressant……



But in those who *are* already on an antidepressant……



Are gabapentin / pregabalin different?

Conclusions

- Similarities
  - Same efficacy and tolerability (lessons re pharma influence?)
  - Both now cheap in capsule form (~£3/month)
  - Both expensive in liquid form (~£100 a bottle)

- Pregabalin
  - Absorption more reliable at high doses
  - Simpler to take? (1 capsule BD versus 1–2 TDS)

Pregabalin versus all gabapentinoid scripts

Adjacent CCGs/different hospital catchments [Jan'18]

"come back when you've got some evidence"

"specialists know best"

Do RCTs support using other AEDs in nerve pain?

Not effective
- Levetiracetam
- Lamotrigine
- Zonisamide

Data conflicting or methodological issues
- Topiramate
- Valproate
- Carbamazepine
- Lacosamide

No RCT evidence
- All others (incl. clonazepam)

Sensory profiling?
- Oxcarbazepine

Topiramate

Multiple actions (Na; Ca [R-type]; GABAmimetic)

- Versus placebo (mainly PDN)
  - 4 RCTs; 2 "+ve" (all either small or LOCF+high drop out)
  - ~25% drop out due to AEs (c.f. 5-10% placebo arm)
    - Psychotropic effects/drowsiness
- Versus gabapentin [Nazarbaghi 2017]
  - Painful neuropathies of mixed cause (n = 30)
  - Efficacy and tolerability comparable
- Case series in cancer (n=13)
  - Benefit in (heavily pre-treated) nerve pain

Topiramate

- Specific problems
  - Cognitive impairment (relates to dose/speed of titration)
  - Renal stones (dehydration may be a risk factor)
- Practicalities
  - Start low/go slow (25mg nocte; then ↑25mg per week)
  - Doses in open-label cancer series ≤200mg/day

Valproate

Multiple actions (Na, K, NMDA, Ca [T-type], GABAmimetic)

- 6 RCTs
  - 4 +ve; but mostly short and used completer analysis
  - <5% drop out due to AEs (c.f. gabapentin 10%; pregabalin 20–30%)
  - (open label series in cancer)
- Possible advantages
  - Once daily dosing; inexpensive; liquid preparation
  - SC syringe driver
    - 1:1 conversion (e.g. 200mg BD PO ≡ 400mg/day CSCI)
    - Separate pump – no data on mixing
    - Diluent is water (30ml syringe)
- Specific issues
  - Pancreatitis, liver reactions, thus:
    - IASP "weak recommendation against use"
    - FBC, U+E, LFT, coag at baseline and thereafter
  - Teratogenicity precautions

Carbamazepine

Sodium channel blocker

- Possible advantages
  - Rectal route if PO route lost
  - (NB licensed for trigeminal neuralgia)
- Specific issues
  - **Multiple drug interactions**
  - Rare-but-serious reactions:
    - liver and bone marrow
      - » FBC, U+E, LFT at baseline and thereafter (?freq)
    - skin
      - » HLA typing (Han Chinese, Hong Kong Chinese, Thai)

Lacosamide

Sodium channel blocker

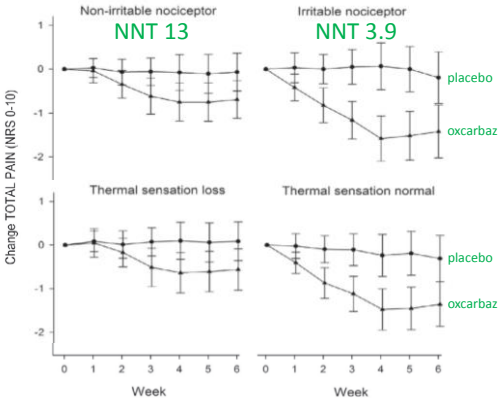
- 6 RCTs (n=1863) in PDN
  - NNT 10 – 12 (both 30% VAS drop or Global impression)
  - Even this may be over-estimate (LOCF + high drop out rate)
  - AEs: dizziness/nausea; NNH $11_{withdrawals}$
- Other considerations
  - SC administration
  - £86 to £144/month (though off-patent soon)

Oxcarbazepine

Sodium channel blocker

- 4 RCTs (mainly PDN) in unselected nerve pain
  - 2 +ve (NNT = 6.6 for 50%↓VAS; n = 229)
  - 1 equivocal (NNT = 12 for global impression of impr'v; n = 247)
  - 1 –ve (n = 141)
- But might clinical examination select responders?
  - allodynia, hyperalgesia, normal temperature sensation

Demant 2014 *Pain*. **155**: 2263-73



Oxcarbazepine

- Specific problems
  - Hyponatraemia
  - Cardiac conduction problems
- Practicalities
  - Check sodium at baseline, 2 wks, then monthly for 3 months
  - Start low: 75mg BD → 150mg BD → 300mg BD
    4-7 days 4-7 days

Do other AEDs have a place?

- I think so, yes, if
  - better evidenced alternatives have been exhausted
  - the uncertainties in evidence are carefully discussed
  - monitoring in place, mindful of other's (un)familiarity
- Little literature about patient views on poorly evidenced treatments

Do other AEDs have a place?
My current practice

- 1st line
  - Pregabalin *or* amitriptyline
- 2nd line
  - Switch or combine pregabalin *and* amitriptyline
  - Duloxetine if depressed or amitriptyline poorly tolerated
- 3rd line
  - Methadone – low dose parallel use
  - Oxcarbazepine – esp if longer prognosis or temp sensation intact
  - (Es?)ketamine – esp if short prognosis or rapid relief needed
- 4th line
  - Cannabis or valproate

What's on the horizon? (1/3)

- **Refined versions of our current approach….?**
  - Peripherally-acting Na blockers?
  - More selective? (though $Na_V1.7$ and $GABA_{\alpha 2/3/5}$ disappointing)
- **….or new targets from better understood pathophysiology?**
  - Glial cells / neuroinflammation?
  - Glial-neuronal communication?
  - Combinations of ion channels?

What's on the horizon? (2/3)

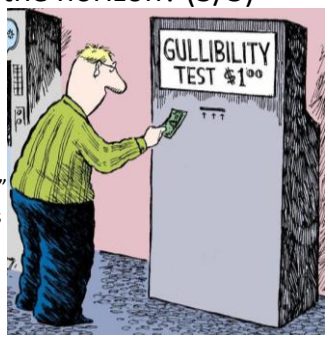
- More about sensory profiling
- Adapting to lengthening prognoses
  - Detrimental effects of opioids on pituitary, pain, mood
  - Other longer term risks (benzos, steroids etc)
  - Better at shared care monitoring and trying down-titrations

What's on the horizon? (3/3)

- New 'me-too's
  - "gaba and pregab are *non-selective* α2δ ligands
  - α2δ-1 = analgesia
  - α2δ-2 = side effects"

  Luckily, **mirogabalin** is α2δ-1 selective!!!

  (….but still seems to cause somnolence, dizziness, oedema)



In summary

- Oxcarbazepine may be of benefit
  - in selected patients (e.g. normal temperature sensation)
  - start low (75mg bd)
  - monitor sodium
- We're likely to hear more about
  - sensory profiling
  - glial cells and neuroinflammation