Gabapentinoids in Chronic Pain

NZPS, ASM

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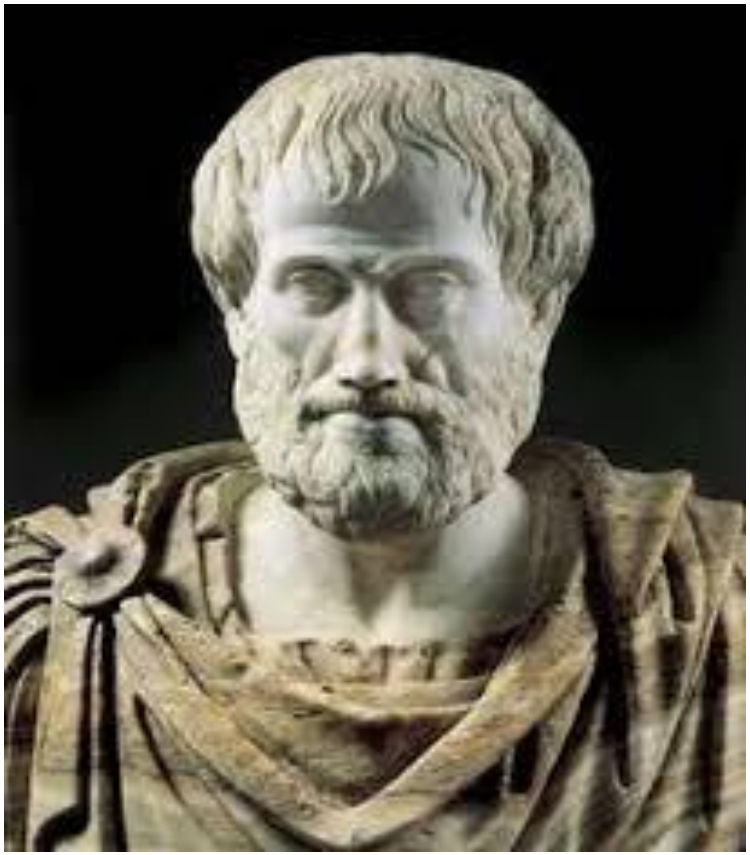


5 Things Clinicians and Consumers Should Question. FPMANZCA & Choosing Wisely February 2018

1. Avoid prescribing opioids (particularly long-acting opioids) as first-line or monotherapy for chronic non-cancer pain (CNCP)
2. Do not continue opioid prescription for chronic non-cancer pain (CNCP) without ongoing demonstration of functional benefit, periodic attempts at dose reduction, & screening for long-term harms
3. **Avoid prescribing pregabalin & gabapentin for pain which does not fulfil the criteria for neuropathic pain**. *"Pregabalin has a restricted PBS authority for 'neuropathic pain' … As with any pharmacotherapy used in pain medicine, the outcome of a trial of pregabalin or of gabapentin should be judged by improvement in everyday physical, emotional and cognitive functioning, including activity, sleep, absence of adverse effects, and improvement in quality of life*".
4. Do not prescribe benzodiazepines for low back pain
5. Do not refer axial lower lumbar back pain for spinal fusion surgery

Pharmacotherapy

Moore A, Derry S, Eccleston C, Kalso E: **"Expect Analgesic Failure; Pursue Analgesic Success".** *British Medical Journal*; BMJ 2013;346:f2690 (Published on-line 3 May 2013; print edition 08.06.13) – Doi: http://dx.doi.org/10.1136/bmj.f2690

See also R. Andrew Moore:

- **"Review. What works for whom? Determining the efficacy and harm of treatments for pain"; *Pain*** 154 (2013) S77–S86
- **"Review. Treating chronic non-cancer pain in older people – More questions than answers?"** *Maturitas*, 79 (2014), pp 34–40

Evidence for analgesic efficacy (success rate > 50%) in 4 types of pain

("success" = *50% or more pain reduction in 50% or more of those randomised to active drug*)

- Acute postoperative pain – only 4 of 10 analgesics.
- Acute migraine – only 1 of 6 medications
- Chronic musculoskeletal pain (osteoarthritis, chronic low back pain, fibromyalgia, ankylosing spondylitis) – none of 19 medications
- Neuropathic pain (painful diabetic neuropathy, post-herpetic neuralgia) – none of 9 medications

Analgesia not normally distributed

"Pain relief is not normally distributed, but usually bimodal, being either very good (> 50%) or poor (< 15%)."

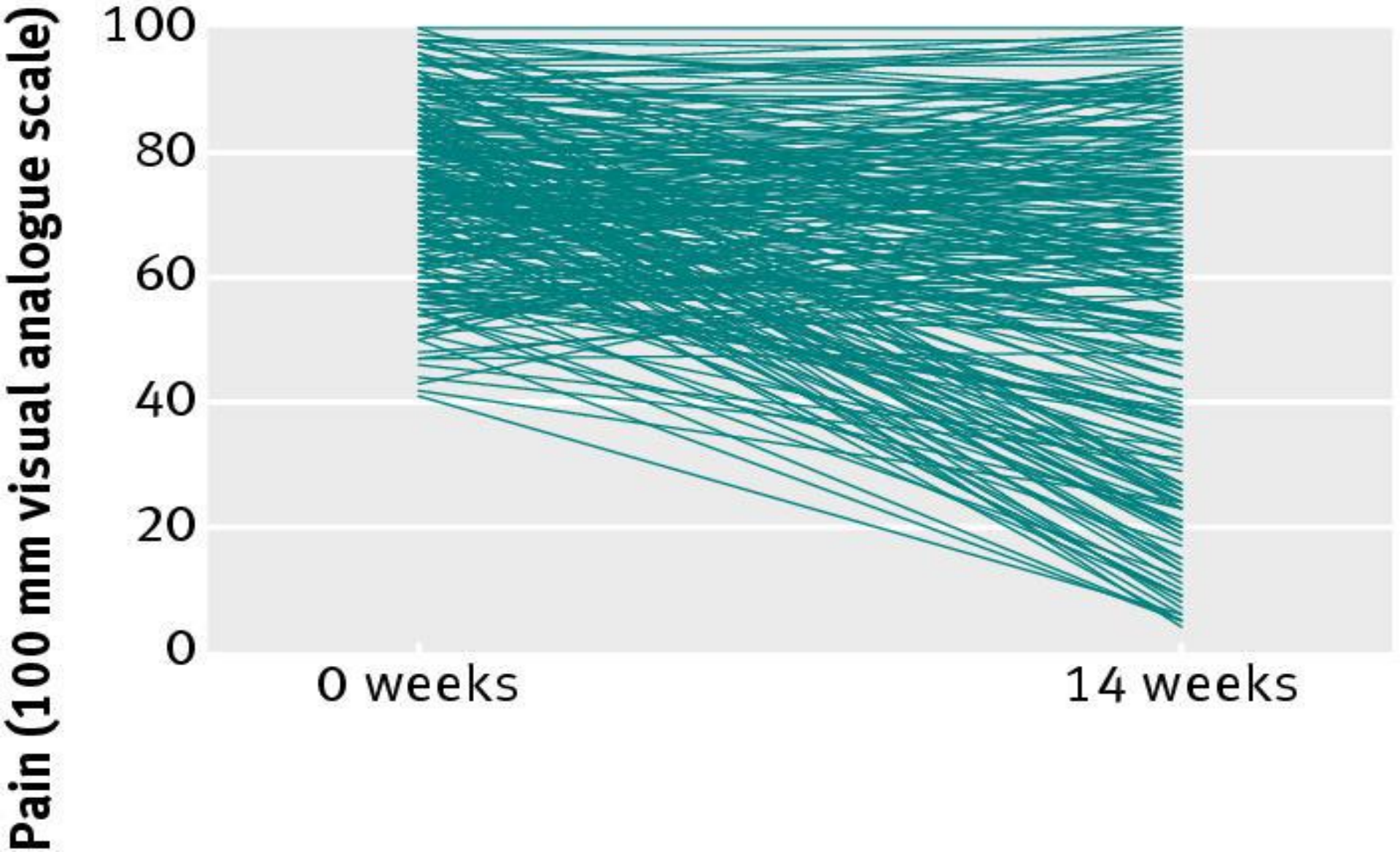
That is, any given analgesic tends to either:

- Work quite well (but only in a small minority of patients – 10-15%);

or

- Not work at all (in 85-90% of patients).

Fig. 1 Individual changes in pain over 14 weeks of treatment with pregabalin 450 mg in 200 patients with fibromyalgia



Responders vs Non-Responders

Responders (a minority)

- *"success is often achieved within the first 2 weeks or so of treatment or not at all, & … tends to last."*

- *"Those who get better (responders) do well: . . . people who respond experience improvements in fatigue, depression, and sleep … & general measures of function and quality of life, including ability to work."*

Non-responders (the majority)

"have none of these benefits."

Minimise Side-Effects

An important advantage of this "responder analysis" approach to assessing analgesic efficacy is that it **minimises patient exposure to adverse drug effects**:

- In the (likely) event of analgesic trial failure, "*patients without benefit should be exposed to no risk, because the drug is stopped; only effective drugs should continue to be prescribed*."

- On the other hand, "*With success, considerable benefits in terms of pain relief, sleep, fatigue, depression, function, and quality of life, are balanced against rare risk of serious harm*."

NP – Strong Recommendations – 1st-Line

	Dose (mg/day)	NNT
• **Tricyclic ADs**	25-150	3.6
Nortriptyline (fewer side-effects than amitriptyline)		
• **Venlafaxine**	150-225	6.4
• **Duloxetine**	60-120	6.4 *(not funded)*
• **Gabapentin**	1200-3600	7.2
• **Pregabalin**	300-600	7.7

(Finnerup NB et al: "Pharmacotherapy for neuropathic pain in adults: a systematic review & meta-analysis". *Lancet Neurol*, Feb 2015; 162–73)

Pregabalin in NP - 2019

- reduces pain in neuropathic pain – statistically significant in peripheral pain, but not in central neuropathic pain.
- Pregabalin significantly reduces sleep interference scores compared with placebo.
- significantly increases the risk of adverse events, including: weight gain, somnolence, dizziness, dry mouth, peripheral oedema, fatigue, visual disturbances, ataxia, non-peripheral oedema, vertigo and euphoria.
- Quality of the included studies rated as low or very low according to the GRADE framework

Onakpoya IJ et al: "Benefits & harms of pregabalin in the management of neuropathic pain: a rapid review & meta-analysis of randomised clinical trials"; *BMJ Open* 2019;9:e023600. doi:10.1136/bmjopen-2018-023600

Treatment of Fibromyalgia Syndrome – Medications

Goldenberg DL, Burckhardt C, Crofford L: "Management of Fibromyalgia Syndrome"; *JAMA*, 17.11.04; pp 2388-95: *American Pain Society* reviewed 505 trials

Strong Evidence for Efficacy

- **Tricyclics – amitriptyline,** cyclobenzaprine

Modest Evidence for Efficacy

- **Tramadol**
- **SNRIs: Venlafaxine, Milnacipran, Duloxetine**
- **Pregabalin**
- Serotonin reuptake inhibitors (SSRIs)

Weak Evidence for Efficacy

- Growth hormone
- 5-Hydroxytryptamine (serotonin)
- Tropisetron
- S-adenosyl-methionine

No Evidence for Efficacy

- **Opioids**,
- corticosteroids,
- **nonsteroidal anti-inflammatory drugs,**
- **benzodiazepine and non-benzodiazepene hypnotics,**
- melatonin,
- calcitonin,
- thyroid hormone,
- guaifenesin,
- dehydroepiandrosterone,
- magnesium.

Treatment of Fibromyalgia Syndrome – Non-Medication

Goldenberg DL, Burckhardt C, Crofford L: "Management of Fibromyalgia Syndrome"; *JAMA*, 17.11.04; pp 2388-95

Strong Evidence for Efficacy (Wait-List or Flexibility Controls But Not Blinded Trials)

- **Cardiovascular exercise**
- **CBT**
- **Patient education: group format with lectures, written materials, demonstrations;**
- **Multidisciplinary therapy, eg exercise + CBT, or education + exercise.**

Moderate Evidence for Efficacy

- Strength training
- Acupuncture
- Hypnotherapy
- biofeedback
- balneotherapy

Weak Evidence for Efficacy

- Chiropractic,
- manual, and massage therapy;
- electrotherapy,
- ultrasound

No Evidence for Efficacy

- Tender (trigger) point injections
- flexibility exercise.

FDA Approved Treatment of Fibromyalgia Syndrome

- June 2007 – pregabalin became the first FDA-approved drug for specifically treating fibromyalgia;
- June 2008 – duloxetine became the second;
- January 2009 – milnacipran became the third.

SR of Gabapentinoids in Fibromyalgia Syndrome

Häuser W et al: "Treatment of fibromyalgia syndrome with gabapentin and pregabalin – a meta-analysis of randomized controlled trials"; *Pain*, 145 (2009), 69–81

- 6 x RCTs selected: 5 of pregabalin, 1 of gabapentin

Strong evidence for:

- Reduced pain,
- improved sleep,
- improved health-related quality of life,
- non-substantial reduction of fatigue and of anxiety.

- NNT for at least 30% pain reduction = 8
- Small effect sizes, 0.2 – 0.4
- 150 mg pregabalin / day no difference from placebo
- 300 = 450 = 600 mg /day

No evidence of improvement in depressed mood.

SR of Pregabalin in Fibromyalgia Syndrome

Derry S, et al. "Pregabalin for pain in fibromyalgia in adults". *Cochrane Database Syst Rev. 2016;9:CD011790.*

- 8 RCTs
- 150 mg pregabalin / day no difference from placebo
- 300 mg/d,
  - ≥ 30% pain relief: NNT 10
  - ≥ 50% pain relief: NNT 14
- 450 mg/d,
  - ≥ 30% pain relief: NNT 8
  - ≥ 50% pain relief: NNT 10
- 600 mg/d,
  - ≥ 30% pain relief: NNT 10
  - ≥ 50% pain relief: NNT 11

Conclusion

- In patients with fibromyalgia, pregabalin reduces pain, but increases adverse events.

EULAR 2017 FMS Treatment Recommendations

Recommendation	Pharmacological treatment	Non-pharmacological treatment
Strong for	None	Aerobic &strengthening exercise
Weak for	**TCAs** (amitriptyline, cyclobenzaprine) **SNRIs** (duloxetine, milnacipran) **tramadol** **pregabalin**	CBT meditative movement therapy mindfulness: mind/ body therapy
Weak against	NSAIDs, SSRIs, MAOIs	
Strong against	Growth hormone, sodium oxybate, strong opioids, glucocorticoids	

Macfarlane GJ et al: “EULAR revised recommendations for the management of fibromyalgia”; *Ann Rheum Dis*; 2017;76:318–328.

Gabapentinoids in CLBP 1

- Evidence on gabapentinoids in CLBP is limited, with significant risk of adverse effects without demonstrated benefit
- Compared with placebo, AEs more commonly reported with gabapentin:
  - dizziness (NNH 7);
  - fatigue (NNH 8);
  - difficulties with mentation (NNH 6);
  - visual disturbances (NNH 6).

Shanthanna H et al: “Benefits & safety of gabapentinoids in chronic low back pain: a systematic review & meta-analysis of randomized controlled trials”; PLoS Med 14(8): e1002369. August 15.08.2017

Gabapentinoids in CLBP & Radicular Pain 2

- moderate- to high-quality evidence that anticonvulsants are ineffective treatment of low back pain or lumbar radicular pain.
- There is high-quality evidence that gabapentinoids have a higher risk for adverse events.

Enke O et al: "Anticonvulsants in the treatment of low back pain & lumbar radicular pain: a systematic review & meta-analysis"; *CMAJ* 2018 July 3; 190:E786-93

Conclusions

1. Gabapentinoids have some effect against both peripheral neuropathic pain and fibromyalgia, although:
2. it is not a large effect overall,
3. the evidence base is weak,
4. Increased risk of AEs.
5. No evidence of benefit in other common chronic pain conditions, eg CLBP, radicular pain, visceral pain.
6. As with any medication, only persist if benefits are very significant, & well outweigh any adverse effects