PAIN
Pharmacology
MSME 709

Dr John Alchin, FAFOEM(RACP), FFPMANZCA

- **Pain Management Centre, Burwood Hospital, Christchurch**
- **Orthopaedic Surgery & Musculoskeletal Medicine, University of Otago Christchurch**

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Summary

Chronic Pain

1. Size of the problem
2. Severe limitations of most biomedical treatments
3. Evidence-Based Medications, 1st-line:
    1. Tricyclics, 25 – 150 mg nocte
    2. Gabapentinoids:
        - Gabapentin, 1.2 – 3.6 gm daily
        - Pregabalin, 300 – 600 mg daily *(not funded)*
    3. SNRIs
        - Venlafaxine, 150 – 225 mg mane
        - Duloxetine, 60 – 120 mg daily *(not funded)*

MANAGEMENT– KEY POINTS

- Empirical, N-of-1 trials
- Nor-adrenergic ADs & gabapentinoids
- Limited Role of Opioids
- Analgesic Report Card: C minus →
- Interdisciplinary pain self-management – CBT, exercise
- Ie, Biopsychosocial (socio-psycho-biomedical) model

Definition of pain

IASP, 1979

"Pain is an unpleasant sensory & emotional experience associated with actual or potential tissue damage, or described in terms of such damage"

Proposed new definition (*Pain* 157; 2016 2420–2423)

"Pain is a distressing experience associated with actual or potential tissue damage with sensory, emotional, cognitive, and social components"

Size of the Problem

- 195 countries & territories; 85 causes of disability (diseases, etc)
- Based on data til Nov 2015:

Conclusion (p 1545): "***Lower back & neck pain the leading global cause of disability in 2015 in most countries***" (158/195 countries):

GBD 2015 Disease & Injury Incidence & Prevalence Collaborators*:* "Global, regional, & national incidence, prevalence, & years lived with disability for 310 diseases & injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015"; *Lancet* 2016; 388: 1545–602; 8.10.16.

Table 2, p 1578: **Top 20 causes of YLD globally**, 2015.

1. **Low Back & Neck Pain**
2. Sense organ disease
3. **Depressive Disorders**
4. Fe deficiency anaemia
5. Skin Disease
6. Diabetes
7. **Migraine**
8. **Other Musculoskeletal Disorders**
9. **Anxiety Disorders**
10. Oral Disorders
11. Asthma
12. Schizophrenia
13. **Osteoarthritis**
14. COPD
15. Falls
16. Autistic Spectrum D
17. **Gynaecological Disease**
18. **Drug Use Disorders**
19. **Other Mental & Substance**
20. **Medication Overuse Headache**

Figure 3, page 1579: Top 10 causes of age-specific (5 year groupings from 12 months) YLD **globally**, 2015:

- Birth to age 14 – Fe Deficiency
- Age 15 to 19 – Skin
- **Age 20 to 24 – Depression**
- **Age 25 to 64 – Back & Neck Pain**
- Age 65 and over – sense organ loss

NZ (2015)

1. **Low Back & Neck Pain**
2. **Depressive Disorders**
3. Sense organ disease
4. **Anxiety Disorders**
5. Skin Diseases
6. Diabetes
7. **Other Musculoskeletal Disorders**
8. **Migraine**
9. Asthma
10. Oral Disorders

Figure 7 (p 1583 – 89): Top 10 causes of YLDs by Country, 2015 (NZ p 1583):

"**Topical Review: a classification of chronic pain for ICD-11**";
Treede R-D et al: *Pain*, June 2015; Volume 156·Number 6, pp 1003 – 07

Chronic pain = "persistent or recurrent pain lasting > 3 months"

1. Chronic primary pain

"*Chronic primary pain is pain in 1 or more anatomic regions that persists or recurs for longer than 3 months, is associated with significant emotional distress or significant functional disability (interference with activities of daily life and participation in social roles), & cannot be better explained by another chronic pain condition*."

- 1.1. Widespread chronic primary pain (including fibromyalgia)
- 1.2. Localized chronic primary pain (including nonspecific back pain, chronic pelvic pain)

Ie, "*chronic primary pain*" will include both somatic/musculoskeletal, & visceral pain.

Kosek E et al: "Do we need a third mechanistic descriptor for chronic pain states?"; *Pain*, July 2016; Volume 157, pp 1382–1386

Proposed new term be introduced to describe pain states characterized by clinical and psychophysical findings that suggest altered nociception, despite there being:

- No evidence of actual or threatened tissue damage causing the activation of nociceptors (ie*, not nociceptive or inflammatory pain*); or
- No evidence for disease or lesion of the somatosensory system causing the chronic pain (ie, *not neuropathic pain*).

Alternative suggested terms: Nociplastic/algopathic/nocipathic pain

- "Nociplastic" ("nociceptive plasticity," ie change in function of nociceptive pathways.)
- "Nocipathic" (from "nociceptive pathology," ie pathological [ie, not "normal"] nociception.)
- "Algopathic" ("algos" [Greek for pain] +"pathic" [from Greek "patheia" for suffering] = "a pathological perception/sensation of pain not generated by injury."

NB: Patients can have a combination of nociceptive & nociplastic/algopathic/nocipathic pain.

"**Topical Review: a classification of chronic pain for ICD-11**";
Treede R-D et al: *Pain*, June 2015; Volume 156·Number 6, pp 1003 – 07

2. Chronic cancer pain
3. Chronic postsurgical & post-traumatic pain
4. Chronic neuropathic pain
5. Chronic headache and orofacial pain
6. Chronic visceral pain (due to peripheral causes – subdivisions include persistent inflammation, vascular, obstruction/distension, traction/compression, referred)
7. Chronic musculoskeletal pain (due again to peripheral causes – subdivisions include persistent inflammation [eg RA], OA, neurological disease eg, muscle spasm)

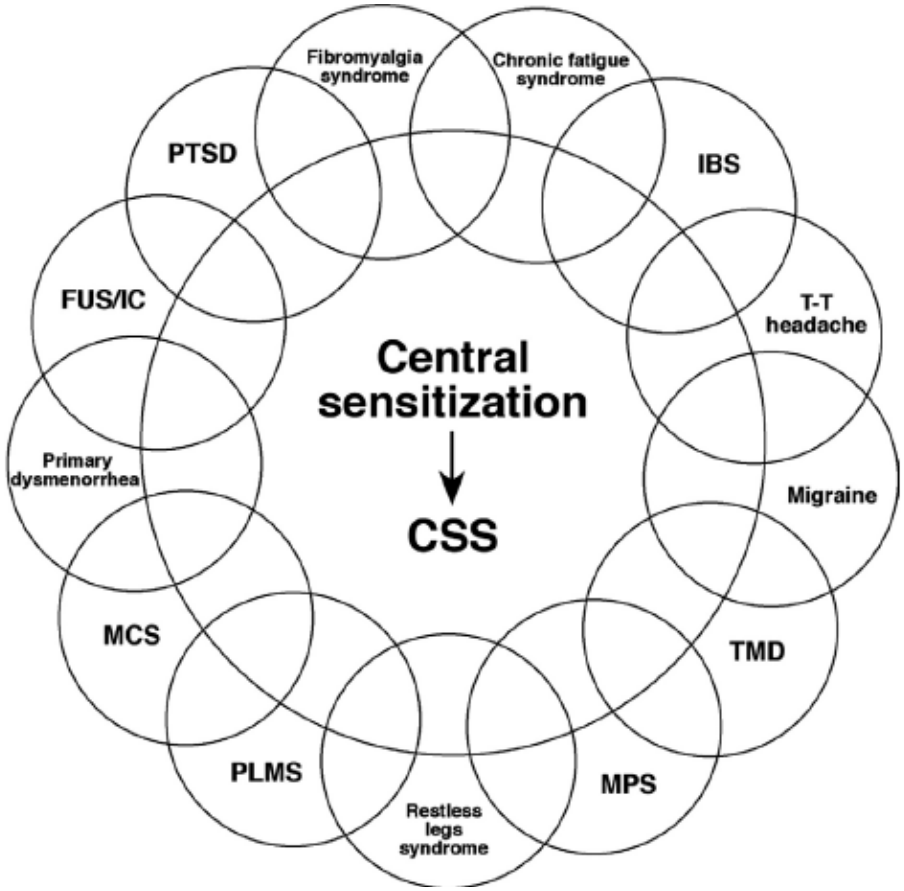
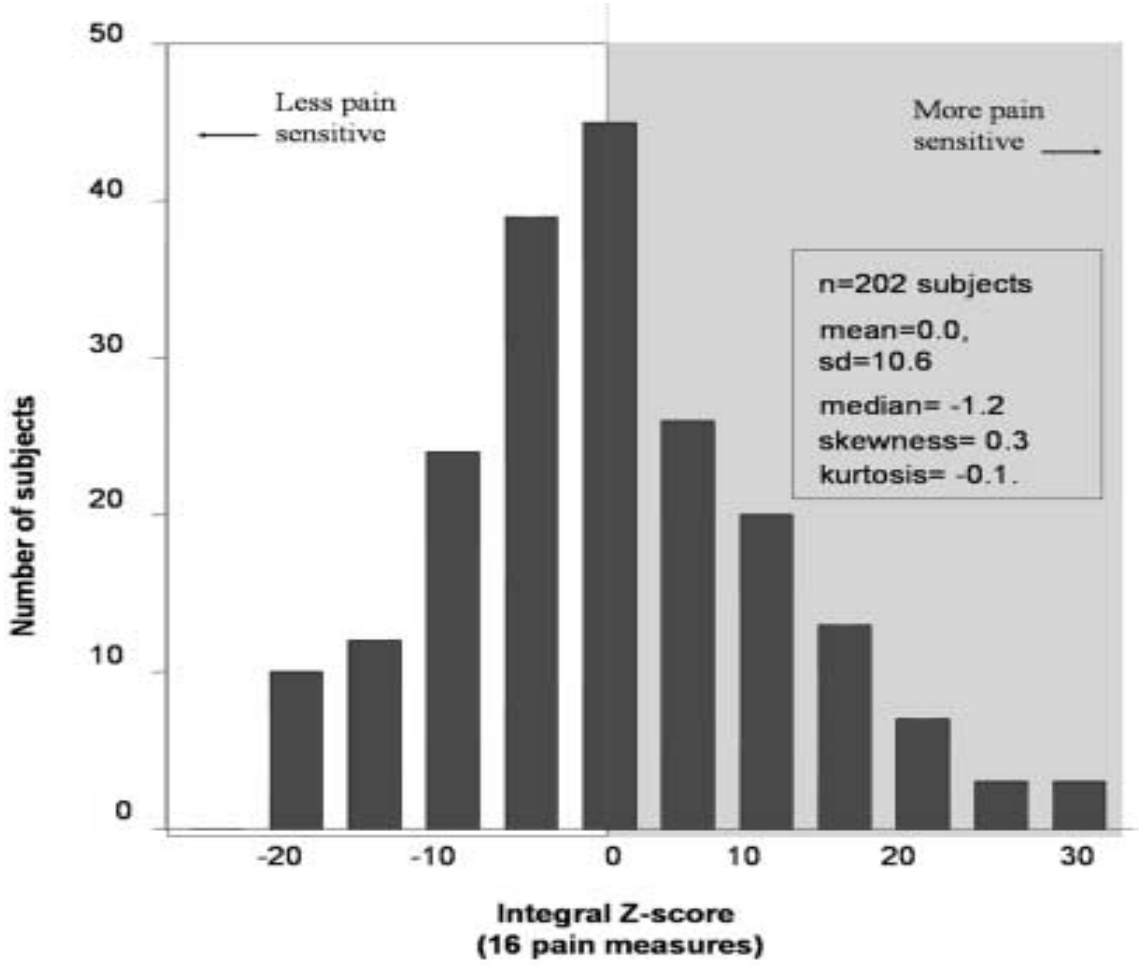


Figure 1 Currently proposed members of the CSS family with overlapping relationships and a common pathophysiological link of CS. IBS, irritable bowel syndrome; T-T headache, tension-type headache; TMD, temporomandibular disorders; MPS, myofascial pain syndrome; RSTPS, regional soft-tissue pain syndrome; PLMS, periodic limb movements in sleep; MCS, multiple chemical sensitivity; FUS, female urethral syndrome; IC, interstitial cystitis; PTSD, posttraumatic stress disorder. Depression may also be a member (see text). Modified from reference 198.

(Yunus, 2007, 341) Also – non-cardiac chest pain; chronic abdominal pain; vulvodynia

Pain Perception is Normally Distributed

Diatchenko et al: *Human Molecular Genetics*, 2005, Vol. 14, No. 1; pp 135–143



Genetics

Family members of patients with fibromyalgia may also have a history of chronic pain. Compared with relatives of those without fibromyalgia, **first-degree relatives of fibromyalgia patients are more likely (OR 8.5) to have fibromyalgia & other chronic pain states**. Genetic factors may explain the strong familial predisposition to fibromyalgia & many chronic pain conditions. Genes associated with increased or decreased frequency of chronic pain or pain sensitivity regulate the breakdown or binding of pain sensitivity–modulating neurotransmitters, and others of inflammatory pathways. Pain sensitivity is polygenic, and differential pain sensitivity between individuals may result from imbalances or altered activity of various neurotransmitters, explaining why centrally acting analgesics either help many co-occurring symptoms (pain, sleep, mood, fatigue), or do not help at all, in a given individual. **Twin studies show that about 50% of the risk of developing fibromyalgia, IBS & headache is genetic, and 50% is environmental**.

Clauw DJ: "Fibromyalgia: Clinical Review"; *JAMA*, 16.4.14 Vol 311, No 15, 1547 - 55

Genetics

- A genome-wide linkage study of people reported that siblings of patients with fibromyalgia have a **13.6-fold (95% CI 10.0 to 18.5) increased risk** of developing the condition compared with the general population.
- A single region on chromosome 17 was significantly linked to fibromyalgia in this population (P<0.001).

Arnold LM et al: "The fibromyalgia family study: a genome-wide linkage scan study." *Arthritis Rheum* 2013; 65:1122-8.

Ferreira PH et al: "Review: Nature or nurture in low back pain? Results of a systematic review of studies based on twin samples";

***Eur J Pain* 2013; 17; 957–71**

In this review:

- Estimates of LBP heritability ranged from 21% to 67%.
- Genetic component was higher for more chronic & disabling LBP than acute & less disabling LBP:
- More disabling LBP (measured as number of days with worst LBP symptoms, & LBP requiring hospitalization): genetic component 46%; vs
- Prevalence of "any" LBP: genetic component 27%.

(Livshits G et al: "Lumbar disc degeneration & genetic factors are the main risk factors for low back pain in women: the UK Twin Spine Study"; *Ann Rheum Dis* 2011; 70: 1740–45)

Odds Ratio of LBP in female twin if co-twin had LBP:

- approximately 6 in monozygotic twins,
- 2.2 in dizygotic twins.

Pathophysiology of Chronic Primary Pain – Recent Reviews

1. Chronic Primary Pain (in general)

- Sluka KA, Clauw DJ: "Review: Neurobiology of Fibromyalgia & Chronic Widespread Pain": *Neuroscience* 338 (Dec 2016); pages 114–129
- Brodal P: "Topical review: a neurobiologist's attempt to understand persistent pain"; *Scandinavian Journal of Pain* 15 (2017); 140–147
- Kuner R, Flor H: "Structural plasticity & reorganisation in chronic pain"; *Nature Reviews Neuroscience*, Jan 2017, Vol 18; pp 20-30

Pathophysiology of Chronic Primary Pain – Recent Reviews 2. Chronic LBP

- Marco L. Loggia ML et al: “Evidence for brain glial activation in chronic pain patients”; *Brain* 2015: 138; 604–15
- Hashmi JA et al: “Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits”; *Brain* 2013: 136; 2751–68
- Vachon-Presseau E et al: “Corticolimbic anatomical characteristics predetermine risk for chronic pain”; *Brain* 2016: 139; 1958–70
- Apkarian AV et al: “Review: Predicting transition to chronic pain”; *Curr Opin Neurol* 2013, 26:360–67
- Nijs J et al: “Low Back Pain: Guidelines for the Clinical Classification of Predominant Neuropathic, Nociceptive, or Central Sensitization Pain”; *Pain Physician* 2015; 18: E333-E46
- Gerhardt A et al: “Chronic Widespread Back Pain is Distinct From Chronic Local Back Pain”; *Clin J Pain* 2016;32:568–79
- Vardeh D, Mannion RJ, Woolf CJ: “Toward a Mechanism-Based Approach to Pain Diagnosis”; *The Journal of Pain*, Vol 17, No 9, Suppl. 2, 2016: pp T50-T69
- Huijnen IPJ et al: “Subgrouping of Low Back Pain Patients for Targeting Treatments: Evidence from Genetic, Psychological, & Activity-related Behavioral Approaches”; *Clin J Pain* 2015;31:123–132

Pain & Psychiatric Co-Morbidities

Crofford LJ: "Psychological aspects of chronic musculoskeletal pain";
Best Practice & Research Clinical Rheumatology, 29 (2015), pp 147-55

Chronic pain (eg FMS) strongly associated with:

- PTSD
- Major depressive disorder:
  - 30 – 60% chronic pain patients have comorbid depression;
  - Lifetime prevalence of major depression or other mood disorder even higher.
  - 50% prevalence of pain in patients whose primary diagnosis is depression.
  - Pain complaints are typically amplified in patients with depression.

  → concept of a bidirectional relationship between pain (presence & severity) & depression.
- bipolar disorder;
- anxiety disorders, including panic disorder, social phobia, OCD
- substance abuse disorder

Pain & Psychiatric Co-Morbidities

Chang M-H et al: "Bidirectional Association Between Depression and Fibromyalgia Syndrome: A Nationwide Longitudinal Study"; *Journal of Pain*, Vol 16, No 9 (September), 2015: pp 895-902

Taiwan National Health Insurance Research Database, between 2000 and 2008 enrolled:

- 25,969 patients with FMS, but no psychiatric disorder, vs
- 17,142 patients with depression, and without FMS
- age- and sex-matched (1:4) control groups, adjusted for demographic data and medical comorbidities

FMS patients who developed depression, and depressed pts who developed FMS, identified at follow-up (end of 2011):

- Patients with FMS: → increased risk of subsequent depression (HR 7.46, 95% CI 6.77–8.22)
- Patients with depression → increased risk of subsequent FMS (HR 6.28, 95% CI 5.67–6.96).

→ Bidirectional temporal association between depression & FMS.

Pain & Psychiatric Co-Morbidities

Burri A et al: "Chronic widespread pain: clinical comorbidities & psychological correlates"; *Pain*, August 2015: pp 1458-64

- 3266 female UK twins
- Considerable clinical overlap between chronic widespread pain (CWP) & depression
- Strong associations of CWP with a range of psychoaffective correlates
- Prevalence of CWP = 20.8%
- Heritability of CWP = 58%
- Genes & environmental stressors / factors equally important for development & maintenance of CWP
- High heritability of combined CWP + Depression = 86%

Drug Treatment of Chronic Pain – Principles

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) – **slides 37-47**

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

Drug Treatment of Chronic Pain – Principles

- starts by recalling a 2003 newspaper article by the chief of *Glaxo* entitled, "*Our drugs do not work on most patients*", stating that most drugs work in only 30-50% of people.
- "*While that surprised journalists and the public, it was not news to professionals*".

Evidence for analgesic efficacy

Evidence for analgesic efficacy (those with a 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

Message: Very sobering. No Triumphalism. Be realistic.
"Expect Analgesic Failure."

Analgesia not normally distributed

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

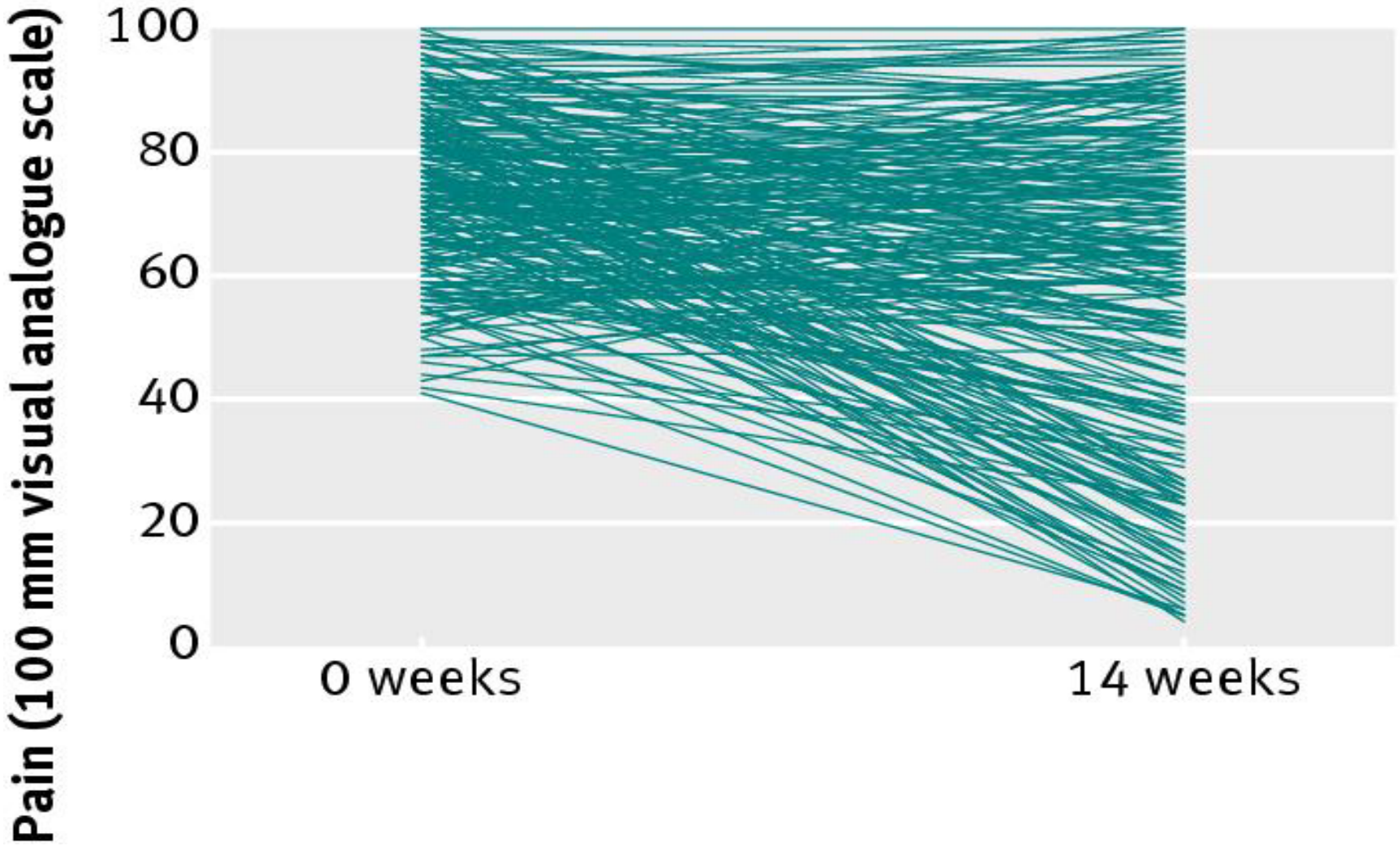
That is, any given analgesic tends to either:

- 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: recent individual patient analyses for chronic pain interventions have shown that 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."*

“Average benefits have no part in these discussions.”

- *“Using averages is unhelpful and misleading, because ‘average’ pain relief is actually experienced by few (if any) patients, and it tells us nothing about how many patients will experience clinically useful pain relief*.”

Explanation & Implications

These disappointing results not unexpected:

"*Chronic pain conditions are complex, and associated with considerable comorbidity. Coupled with the intricacies of pain modulation, central nervous system changes, and genetic influences, high failure rates with single interventions are unsurprising*."

The *"magnitude of the failure to achieve good pain relief, especially over the longer term in chronic pain, is sobering*"

Requiring

"a radical rethink of achievable analgesic effects".

Minimises 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*."

Medications need to have a ‘functional’ outcome

Pain scores are NOT enough

If pain reduction comes at the cost of medication side effects (“Zombie effect”), or avoidance of movement/ activity, then its not an effective treatment.

Long term chronic pain disability and depression is most highly predicted by fears and avoidance, rather than pain intensity (Rikard Wicksell: *Acta Anaesthesiologica Scandinavica*, Feb 2017).

Analgesics have a ‘very’ limited role

- “*The analgesic effects of many treatments for non-specific low back pain are small*”

(Machado LAC et al: “Analgesic effects of treatments for non-specific low back pain: a meta-analysis of placebo-controlled randomized trials”; *Rheumatology* 2009; 48:520–527)

- “*A common key finding in the literature on these interventions for CLBP is their disappointing magnitude of pain reduction & gain in functionality*”

(Morlion B: “Chronic low back pain: pharmacological, interventional & surgical strategies”; *Nat. Rev. Neurol*. 2013: 9, 462–473)

Analgesics have a ‘very’ limited role

“*from 1960 to 2009 … Very intensive research efforts directed at diverse molecular targets related to pain mechanisms produced thousands of publications, but those efforts have not yet yielded new analgesics with sufficient effectiveness … lack of real breakthroughs in analgesic drug development despite intense research efforts*.”

(Kissin, I: “SPECIAL ARTICLE: The Development of New Analgesics Over the Past 50 Years: A Lack of Real Breakthrough Drugs”; *Anesth Analg;* 2010;110:780 –9)

Analgesics have a ‘very’ limited role

“*Most existing analgesics for persistent pain are relatively ineffective … the number of patients who are needed to be treated (NNT) to achieve 50% reduction in neuropathic pain in one patient is more than four*”.

Woolf, C: “Review: Overcoming obstacles to developing new analgesics”; *Nature Medicine* (Supplement); 16,11: 1241 – 47; November 2010

Analgesics have a ‘very’ limited role

In terms of biomedical treatments to reduce pain intensity:

“If one were to review “effective” treatments for back pain, the picture would be rather large, but perhaps somewhat underwhelming. There is now a massive body of randomized controlled trials (RCTs), systematic reviews, and meta-analyses on treatments for back pain … *treatments that do exist, regardless of the discipline that offers them, & regardless of their provenance, offer on average a small benefit or no benefit at all, aside from the nonspecific effects of treatment*”.

(Moseley GL: “Innovative treatments for back pain”; *Pain Supplement* April 2017; pp 2–10)

Analgesics have a ‘very’ limited role

“Currently available analgesics — nonsteroidal anti-inflammatory drugs (NSAIDs), amine reuptake inhibitors, antiepileptic drugs and opioids — have varying but typically low levels of analgesic efficacy, which is generally coupled with deleterious effects.”

Nat Reviews Drug Discovery, August 2017; pp 545-564.

Medications need to have a 'functional' outcome

"*Overall, present treatment options result in modest improvements at best, & part of chronic pain management should include dialogue with the patient about realistic expectations of pain relief, & bring focus to improvement of function … Of all treatment modalities reviewed, the best evidence for pain reduction averages roughly 30% in about half of treated patients …*

Turk DC, Wilson HD, Cahana A: "Treatment of Chronic Non-Cancer Pain", *The Lancet* 2011; 377: 2226–35 (25.6.11)

Medications need to have a 'functional' outcome

. . . none of the most commonly prescribed treatment regimens are, by themselves, sufficient to eliminate pain & to have a major effect on physical & emotional function in most patients with chronic pain. This conclusion is hardly surprising in view of the complexity of chronic pain. … If there is no … improvement in patient pain, physical & emotional functioning, then an alternate treatment approach should be recommended."

Turk DC, Wilson HD, Cahana A: "Treatment of Chronic Non-Cancer Pain", *The Lancet* 2011; 377: 2226–35 (25.6.11)

Not only analgesia development has made little progress
1: Alzheimer's Disease

"Alzheimer disease (AD), first described more than a century ago, continues to challenge our generation. If we compare the therapeutic progress that modern science has made in this condition with that achieved in treating bacterial infectious diseases, we are unfortunately still in the pre-antibiotic era with respect to AD. Despite a huge leap in our understanding of the basic science and pathogenesis of this devastating neurodegenerative disease and the many clinical trials of various drugs with disease modifying potential, we have seen little real progress in achieving a cure."
(*JAMA Intern Med*. May 27, 2013, page 901)

Not only analgesia development has made little progress: 2: Depression

- "*We need more effective treatments for depression, because current treatments avert less than half of the considerable burden caused by the illness*." (*MJA*, 16 May 2016, page 348)

- "*Approximately 50% of patients do not respond to initial first-line anti-depressant treatment, while approximately one third fail to achieve remission following several pharmacological interventions*" (*Euro J Pharm*, 53 (2015) 32–50)

- "*Despite the tremendous personal agony and societal burden associated with major depressive disorder (MDD), we have not been able to significantly improve the effectiveness of our treatments for more than 5 decades. Large real-world studies … have presented us with humbling data on the relatively low rates of sustained remission associated with our current armamentarium of therapeutic options*" (*JAMA Psychiatry*, July 2016, page 651)

Not only analgesia development has made little progress
3: Cancer Chemotherapeutics

- Growing economic burden of cancer: cost of cancer drugs rising most rapidly: new cancer therapies cost > $US 10,000 a month.
- **71 new therapies approved by US FDA for solid tumour Rx 2002-14 → median gain in overall survival = only 2.1 months.**

Fojo et al: "Unintended Consequences of Expensive Cancer Therapeutics – The Pursuit of Marginal Indications & a Me-Too Mentality That Stifles Innovation & Creativity"; *JAMA Otolaryngol Head Neck Surg*. Published 28/7/14 doi:10.1001/jamaoto.2014.1570

NP - MEDICATION MANAGEMENT

Lancet Neurology, Feb 2015; 162-73

- Finnerup NB et al: "Pharmacotherapy for neuropathic pain in adults: a systematic review & meta-analysis", for NeuPSIG, IASP
- (Edit comment: Bennett DL; 129-30)

Previous iterations:

- *Pain* December 2007, 237-51
- *Arch Neurol* November 2003, 1524-34

MEDICATION MANAGEMENT
Lancet Neurology, Feb 2015; 162-73
MAIN CONCLUSION (page 169)

- "*Based mainly on moderate or high quality of evidence and efficacy in most trials*", TCAs, gabapentinoids, & SNRIs, are recommended "*for use in neuropathic pain, and are proposed as first-line treatments*"

Strong Recommendations – 1st-Line

	Dose (mg/day)	NNT
• **Tricyclic ADs**	25-150	3.6

Nortriptyline (fewer side-effects than amitriptyline)

• **Gabapentin**	1200-3600	7.2
• **Pregabalin**	300-600	7.7 *(not funded)*
• **Duloxetine**	60-120	6.4 *(not funded)*
• **Venlafaxine**	150-225	6.4

Ie, 3 classes of 1st-line pharmacotherapy for NP:

- TCAs, gabapentinoids, SNRIs

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

Medication Combinations

TCA + Gabapentinoid:

- Nortriptyline + gabapentin (*The Lancet*; 10.10.09, pp 1252 – 61)
- Imipramine + pregabalin (*Pain*, May 2015, pp 958-66)

SNRI + Gabapentinoid:

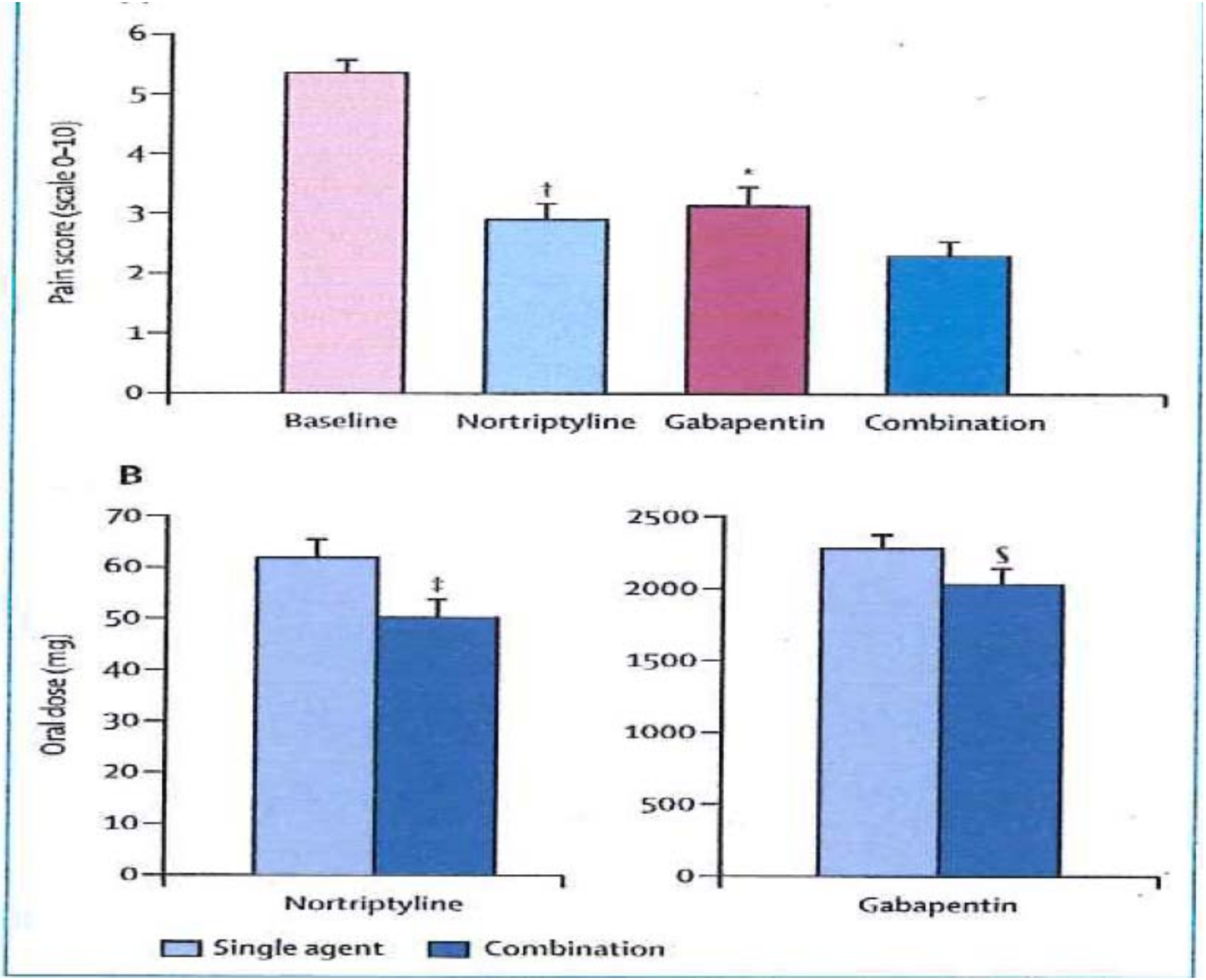
- Venlafaxine + gabapentin (*J Clin Neuromuscul Dis*; 2001; 3: 53–62)
- Duloxetine + Pregabalin (*Pain*, July 2016, pp 1532–1540)

Opioid +

- Morphine + gabapentin (*N Engl J Med*; 2005; 352: 1324–34)
- Morphine + nortriptyline (*Pain*, August 2015, pp 1440-48)

See also:

- Mao et al: *J Pain*, Feb 2011, 157-66
- Gilron et al: *Lancet Neurology*, Nov 2013, 1084-95


Pain score (scale 0–10)
6
5
4
3
2
1
0
†
*
Baseline
Nortriptyline
Gabapentin
Combination
B
Oral dose (mg)
70
60
50
40
30
20
10
0
‡
Nortriptyline
2500
2000
1500
1000
500
0
§
Gabapentin
Single agent
Combination

	Combination studied	Trial comparisons			
		Placebo-controlled	Combination vs only one component	Combination vs both components	Combination vs other treatment
Agrawal et al (2009)[67]	Oral valproate + topical glyceryl trinitrate	Yes	..	Yes	..
Amr (2010)[68]	Intravenous ketamine + oral gabapentin	..	Yes	..	..
Caraceni et al (2004)[69]	Oral opioid + oral gabapentin	..	Yes	..	..
Eichenberger et al (2008)[39]	Intravenous calcitonin + intravenous ketamine	Yes	..	Yes	..
Freeman et al (2007)[70]	Oral paracetamol + oral tramadol	Yes	..	..	Yes
Gilron et al (2005)[62]	Oral gabapentin + oral morphine	Yes	..	Yes	..
Gilron et al (2009)[63]	Oral nortriptyline + oral gabapentin	..	..	Yes	..
Gomez-Perez et al (1985)[71]	Oral nortriptyline + oral fluphenazine	Yes	..	..	Yes
Gomez-Perez et al (1996)[72]	Oral nortriptyline + oral fluphenazine	..	..	..	Yes
Graff-Radford et al (2000)[40]	Oral amitriptyline + oral fluphenazine	Yes	..	Yes	..
Hanna et al (2008)[37]	Oral oxycodone + oral gabapentin	..	Yes	..	..
Khoromi et al (2007)[38]	Oral nortriptyline + oral morphine	Yes	..	Yes	..
Lynch et al (2003)[73]	Topical amitriptyline + topical ketamine	Yes	..	Yes	..
Lynch et al (2005)[74]	Topical amitriptyline + topical ketamine	Yes	..	Yes	..
McCleane (2000)[75]	Topical doxepin + topical capsaicin	Yes	..	Yes	..
McCleane (2003)[76]	Oral morphine + oral L-365,260 (cholecystokinin blocker)	..	Yes	..	..
Mercadante et al (2002)[77]	Oral morphine + oral amitriptyline	..	Yes	..	..
Tonet et al (2008)[78]	Oral ketamine + oral amitriptyline + oral carbamazepine	..	Variant*	..	..
Zin et al (2010)[79]	Oral oxycodone + oral pregabalin	..	Yes	..	..

Adapted from Chaparro et al,[5] with permission of the Cochrane Collaboration. *Comparison of amitriptyline + carbamazepine + ketamine vs amitriptyline + carbamazepine; all other studies listed assessed only two-drug combinations.

Table 3: **Methodology of combination therapy trials in neuropathic pain**

Weak Recommendations – 2nd-Line

	Dose (mg/day)	NNT
• Capsaicin (PNP)	8% patch (30-60 mins every 3 months)	10.6
• Lignocaine (PNP)	5% patch (Max: 3 patches, up to 12 hours/day)	
• Tramadol	200-400	4.7

(Demoted from 1st-line due to “weak quality of evidence”)

Weak Recommendations – 3rd-Line

	Dose (mg/day)	NNT
• Strong Opioids	SR 180 mg Meq individual titration	4.3

(*13 trials in PNP used 10-120 oxycodone or 90-240 morphine; 10/13 +ve; max effectiveness 180mg morphine equivalent*)

(*demoted from 1st or 2nd line – abuse potential, & deaths, etc*)

• Botulinum A (PNP)	50-200 units (Sub-cut every 3 months)	1.9*

(*4 small RCTs; but one large unpublished RCT –ve)

Recommendations against use:

(Negative Trials &/or Safety Concerns)

1. Weak recommendations against use:

- Cannabinoids ("negative results, potential misuse, diversion, & long-term mental health risks")
- Valproate

2. Strong recommendations against use:

- Levetiracetam
- Mexiletine

Other comments

- “efficacy of systemic drug treatments is generally” independent of aetiology of “underlying disorder”
- “generally no evidence of efficacy of particular drugs in specific disorders” → “recommendations apply to neuropathic pain in general”
- “might not be applicable to trigeminal neuralgia” – only 1 x RCT meeting inclusion criteria (→ see Review, *BMJ* 28.3.15)

No Evidence in Neuropathic Pain for:

- Anti-inflammatories

  Vo, T et al: “Topical review: Non-steroidal anti-inflammatory drugs for neuropathic pain: How do we explain continued widespread use?” *Pain*; 143 (2009) 169–71

- Paracetamol

NB: WHO Analgesic Ladder does **not** apply to chronic non-malignant pain, including neuropathic pain.

Other comments

- Publication Bias → previous meta-analyses overestimated Effect Sizes by about 10%
- “for individual drugs … NNT for 50% pain relief ranging from about 4 to 10 for most positive trials emphasise the modest overall study outcomes … Inadequate response to drug therapy constitutes a substantial unmet need” … & “might have important consequences in terms of psychological or social adjustment”

1st-Line Drugs for **Fibromyalgia**

Level 1 Evidence:

- Amitriptyline – Tricyclic

- Duloxetine) – SNRIs
- Milnacipran)

- Pregabalin) – Gabapentinoids
- Gabapentin)

Summer C: “Fibromyalgia: A Clinical Update”; *IASP*, June 2010

Treatment of Chronic Pain – Summary

For both Neuropathic Pain & Dysfunctional Pain:

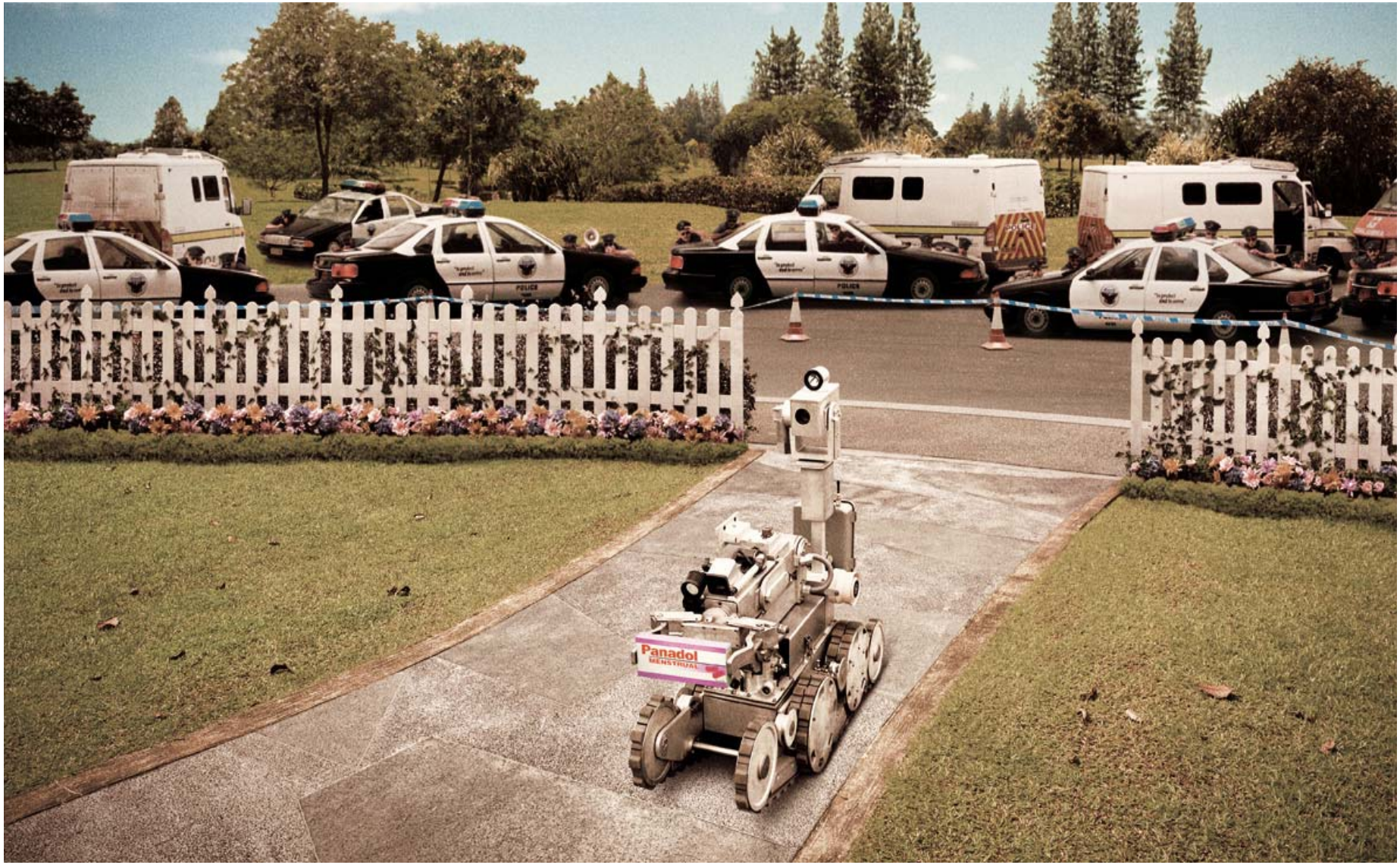
- Pharmacological
  - **TCAs** (nortriptyline, a secondary amine). Titrate to therapeutic dose (plasma range: 200-600 nmol/L)
  - **Gabapentin / Pregabalin**
  - **SSNRIs (venlafaxine)**
- Non-Pharmacological:
  - Graduated aerobic Exercise
  - CBT

Some Exceptions

- Trigeminal Neuralgia
  - Carbamazepine the drug of choice

- Migraine
  - 1st-line preventatives:
    - Tricyclics
    - Beta-Blockers
    - Valproate
    - Topirimate

Paracetamol



Paracetamol – References

- *Williams CM et al: "*Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial"; *Lancet* 2014; 384: 1586–96
- Brune K: "Review: Acetaminophen/paracetamol: a history of errors, failures and false decisions"; *Eur J Pain* 19 (2015), 953—965
- *da Costa BR: "*Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis"; *Lancet* 2017; 390: e21–33
- Machado GC et al: *"*Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials"; *BMJ* 2014;350:h1225doi: 10.1136/bmj.h1225
- Roberts E et al: "Extended Report: Paracetamol: not as safe as we thought? A systematic literature review of observational studies"; *Ann Rheum Dis*. 2016;75:552–559.

R Andrew Moore RA, Moore N: "**Paracetamol & pain: the kiloton problem**"; *Eur J Hosp Pharm.* published online April 27, 2016

- Discovered in the 1950s
- European paracetamol sales: from < 200 tons in Greece & Portugal, to 6300 tons in UK and 10 000 tons in France
- Per capita range: 4–5 tons to 30–50 tons per million
- Considerable uncertainty over how it works. Only recently accepted that it "*inhibits COX-1 and COX-2 isoenzymes, and is in fact a weak NSAID*"
- "*considerable evidence that, as well as not being particularly effective, neither is it particularly safe*"

R Andrew Moore RA, Moore N: "**Paracetamol & pain: the kiloton problem**"; *Eur J Hosp Pharm.* published online April 27, 2016. **Efficacy**:

- 500 to 1000 mg: in the least effective quartile of drugs for acute post-op pain
- 1000 mg: modest efficacy in migraine & TTH
- Up to 4000 mg daily ineffective in back pain
- Up to 4000 mg daily practically ineffective in OA: marginally better than placebo, but little chance of achieving clinically meaningful benefit in osteoarthritis
- No review evidence for neck pain, cancer pain, dysmenorrhoea, rheumatoid arthritis

R Andrew Moore RA, Moore N: "**Paracetamol & pain: the kiloton problem**"; *Eur J Hosp Pharm.* published online April 27, 2016. **Safety**:

Systematic review of observational studies: vs people not taking it, paracetamol use, especially at higher doses, is associated with:

- Increased mortality,
- Cardiovascular adverse events:
  - Fatal or non-fatal myocardial infarction,
  - stroke,
- Gastrointestinal adverse events: Gastroduodenal ulcers and complications (upper GI haemorrhage)
- Estimated glomerular filtration rate decrease of at least 30 mL/ min/1.73 sq m.

R Andrew Moore RA, Moore N: "**Paracetamol & pain: the kiloton problem**"; *Eur J Hosp Pharm.* published online April 27, 2016. **Safety**:

- Chronic pain RCTs: vs placebo, patients on paracetamol four times as likely to have abnormal liver function tests
- Large case-population study: non-overdose paracetamol (vs NSAIDs): Acute liver failure needing transplantation twice as common.
- Paracetamol had very similar adverse event rates to ibuprofen over 3 months in patients with arthritis, and was not better tolerated than ibuprofen for short-term relief of common pain
- Any adverse event in acute pain studies were the same for paracetamol (up to 1000 mg) and placebo.

R Andrew Moore RA, Moore N: "**Paracetamol & pain: the kiloton problem**"; *Eur J Hosp Pharm.* published online April 27, 2016. **Remaining uses**:

- "*There may of course be circumstances where paracetamol might be useful, in paediatric pain, for treating patent ductus arteriosus, or for intravenous use during surgery*."
- "*If paracetamol were an unimportant and little-used drug, none of this might amount to much. But it is not. It is a drug whose use is measured in thousands of tons, has little or no effect in many conditions, and has significant adverse events. Maybe it is time to consider the evidence again, and think about the possibility of change*."

Enthoven WTM et al: “NSAIDs for Chronic Low Back Pain”; *JAMA* 13.6.17 2327 – 28 (Cochrane Review)

- NSAIDs (vs placebo) associated with a small but significant improvement in pain and disability
- But this difference became nonsignificant when studies with high risk for bias were excluded.
- The benefits were smaller than the minimal clinically important difference.

Moore RA et al: “Oral nonsteroidal anti-inflammatory drugs for neuropathic pain.” *Cochrane Review*; 2015

- third tier evidence, very low quality.
- No indication of any significant pain reduction with NSAIDs.
- no good evidence whether oral NSAIDs are helpful to treat neuropathic pain
- Adverse event rates were low, with insufficient events for any analysis

Limited Role of Opioids

- Lack of evidence of long term efficacy in Chronic pain
- Tolerance and Physiological Dependence
- Risks of accidental overdose (US “opioid epidemic”)
- Substance Use Disorder
- Opioid induced hyperalgesia
- Withdrawal from Opioids

BPMC Opioid Guidelines

National Academies of Sciences, Engineering, & Medicine. "*Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits & Risks of Prescription Opioid Use*". Washington, DC: National Academies Press; 2017. (393 pages) https://www.nationalacademies.org/opioidstudy

- envisions a path leading to reduced reliance on opioids for chronic pain, while counselling against arbitrary regulatory restriction of responsible prescribing for patients whose pain has not been alleviated by alternative treatments
- Summarizes the state of the science on the harms associated with opioid misuse, and the effects of strategies aiming to reduce those harms.

Suggests actions that the US FDA, the study sponsor, could undertake "*to balance the needs of pain patients and the need to address opioid misuse*":

- a proactive approach by the US FDA and state regulators regarding opioid approval and prescription monitoring;
- a commitment to funding basic and translational research to develop non-opioid paradigms for pain management;
- better access to treatment for opioid use disorder (OUD) and to medication (naloxone) for preventing overdose deaths
- prescription opioids must be viewed by patients, Drs, nurses, etc as part of a larger ecosystem that encompasses the illicit use and sale of prescribed opioids diverted from the legal market, as well as the use and sale of illegally manufactured opioid products, including potent synthetics.

Annual US opioid overdose deaths:

- Nearly tripled from 1999 (8048) to 2011 (22,784)
- (from illicit opioids): nearly tripled 2011 (7019) to 2015 (19,884).
- 2015: each day 90 US overdose deaths involving an opioid
- Annual US opioid prescribing (per 10,000 population) quadrupled from 1.8kg (1999) to 7.1kg (2010)

Hoffman EM et al: "Association of Long-term Opioid Therapy With Functional Status, Adverse Outcomes, & Mortality Among Patients With Polyneuropathy"; *JAMA Neurol*. doi:10.1001/jamaneurol.2017.0486
Published online May 22, 2017.

2892 patients with polyneuropathy (1364 women); mean age, 67.5 years; vs 14,435 controls (6827 women); mean age, 67.5 years:

- Polyneuropathy patients received long-term opioids more often (545 [18.8%] vs 780 [5.4%]).
- Polyneuropathy patients on long-term opioids had multiple functional status markers modestly poorer, even after adjusting for medical comorbidity, including increased reliance on gait aids (adjusted odds ratio, 1.9);
- No functional status markers improved by long-term opioid use.
- Adverse outcomes were more common among with polyneuropathy patients on long-term opioids, including depression (adjusted HR 1.53), opioid dependence (adjusted HR 2.85), and opioid overdose (adjusted HR 5.12).

Frank JW et al: "Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy: A Systematic Review"; *Ann Int Med*, doi:10.7326/M17-0598. published at Annals.org on 18 July 2017

- 67 studies (11 RCTs & 56 observational studies) examining 8 interventions (interdisciplinary pain programs, buprenorphine assisted dose reduction, and behavioral interventions)
- Study quality good for 3 studies, fair for 13 studies, and poor for 51 studies.
- Among 40 studies examining patient outcomes after dose reduction (very low overall quality of evidence), improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).
- "*Among the higher-quality studies evaluating pain, function, and quality of life, all found improvements in all outcomes evaluated after opioid dose reduction*." (Editorial Comment)

Opioids

- "The use of added short-acting opioids for "breakthrough pain" ("rescue" dosing) is controversial. Although occasionally taking an extra pill for a pain spike is unlikely to harm, too many patients end up with daily or near-daily use of "rescue" opioids, obviating their purpose, and encouraging tolerance to what is effectively a higher daily dose."

R. Norman Harden et al: "Special Article. Complex Regional Pain Syndrome: Practical Diagnostic & Treatment Guidelines, 4th Edition"; *Pain Medicine* 2013; 14: 180–229

Burwood Hospital PMC Opioid Guidelines (1999):

1. Generally don't use strong opioids in CNMP
2. If we do, it is normally methadone
3. We do not use strong opioids in CNMP pts with co-morbid addiction ("dual pathology")
4. We do not give an opioid script at the first appointment. We do so only after discussion with colleagues, eg at weekly case conference.

Opioid Contract

Consider a signed opioid contract with the patient:

1. It is a **trial** – if it is not effective, it will be stopped. *Starting* a patient on morphine does not morally oblige us to *continue* it:
2. Patients don't tell us what drug, & how many mg, to prescribe – the law specifies that that is our job.
3. **Evidence of diversion / abuse → stop**
4. **"Effectiveness" normally needs an objective measure**, eg improved function. Eg a patient reporting that their pain "*is much better, but it's not good enough yet, because I'm still in agony & disabled by pain. So I need more*" – is not evidence of efficacy, & thus not grounds for *perpetual* dose escalation
5. **100mg Morphine Equivalent / day** will not be exceeded – risks, & lack of efficacy
6. **No replacements** for lost, eaten, stolen, or transmigrated scripts.
7. **Random Urine Drug Screens** – to see what is, & isn't, present
8. One prescriber, one dispensing pharmacy

Fallacies, often implicit / sub-conscious, driving opioid prescribing & escalation: "If all else fails, use morphine" because:

1. **It is our strongest analgesic, our gold standard**. **Wrong**: it is the gold standard for severe nociceptive or inflammatory pain (eg, post-op, post-traumatic), & for terminal malignant pain. But, as we have seen, it is not the gold standard for neurogenic pain.
2. Related to the above – **it must be nociceptive or inflammatory pain, so morphine must be effective, because the nociceptive system, alone of bodily organ systems, is infallible** (except neuropathic pain). Nociceptive *exceptionalism* → nociceptive *fundamentalism*. **Wrong**: the nociceptive system is not an exception; but, like every other organ system, it can also malfunction, mislead; so it must not always be read literally (fundamentalism). Primary pain disorders Eg, CRPS-1; primary headaches (migraine): in these cases, pain does not = severe & life-threatening intra-cranial pathology. The pain is misleading. A malfunctioning fire alarm, not a fire.
3. **The Fairy-Tale Fallacy** ("*they all lived happily ever after*"): "There must be a fix." **Wrong**: Need to grapple with the Problem of Evil.

Yekkirala, Roberson, Bean, Woolf CJ:

"**Breaking barriers to novel analgesic drug development**";

Nat Reviews Drug Discovery, August 2017; pp 545-564.

(285 references)

"Cannabis for Pain and Posttraumatic Stress Disorder: More Consensus Than Controversy or Vice Versa?" Ed. *Ann Int Med*, on-line 15.8.17

- These 2 "*systematic reviews highlight an alarming lack of high-quality data from which to draw firm conclusions about the efficacy of cannabis for these conditions, for which cannabis is both sanctioned and commonly used*."

Pain SR:

- "limited, low-strength evidence that cannabis alleviates neuropathic pain, and insufficient evidence for other types of pain."
- Heavily based on studies using nabiximols (oral mixture of THC & cannabidiol), not smoked cannabis.
- Most available studies are small, have methodological pitfalls, and are of relatively short duration.
- largest clinical trial reviewed: only 28% of participants showed a clinical response to nabiximols, vs 16% to placebo; ie, most participants in the intervention group did not have clinically meaningful benefit
- "These conclusions seem at odds with the fact that pain is one of the most common medical conditions for which cannabis is used and approved in many states. So, why the discrepancy?"

"Cannabis for Pain and Posttraumatic Stress Disorder: More Consensus Than Controversy or Vice Versa?" Ed. *Ann Int Med*, on-line 15.8.17

PTSD SR:

- Reviewed studies of cannabis or purified cannabis constituents (but not synthetic cannabinoids) on PTSD.
- Evidence "insufficient to draw firm conclusions".
- "In fact, one of the largest observational studies of veterans with PTSD found small but significant worsening of symptoms in patients who continued or started cannabis use, compared with patients who had never used or stopped using cannabis during the study."
- "Most currently available evidence is limited by small samples, weak experimental designs, and lack of adjustment for potential confounding factors."

"Cannabis for Pain and Posttraumatic Stress Disorder: More Consensus Than Controversy or Vice Versa?" Ed. *Ann Int Med*, on-line 15.8.17

Conclusions

- "Most available studies are small, have methodological pitfalls, and are of relatively short duration."
- Little high-quality evidence from which to draw firm conclusions about the efficacy of cannabis and cannabinoid products for treating pain and PTSD.
- "Although several well-designed trials are under way to address this critical issue, to some degree the horse is out of the barn – and unlikely to return. Even if future studies reveal a clear lack of substantial benefit of cannabis for pain or PTSD, legislation is unlikely to remove these conditions from the lists of indications for medical cannabis."
- "These conclusions seem at odds with the fact that pain is one of the most common medical conditions for which cannabis is used and approved in many states. So, why the discrepancy?"